16 September 2021
EMA/CHMP/563896/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Keytruda

International non-proprietary name: pembrolizumab

Procedure No. EMEA/H/C/003820/II/0099

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

1L	First-line
AE	Adverse event(s)
AEOSI	Adverse event(s) of special interest
ALT	Alanine aminotransferase
ASaT	All Subjects as Treated
AST	Aspartate aminotransferase
AUC	Area under the curve
BICR	Blinded independent central radiology review
Cavg	Average concentration over the dosing interval
CD8+	Cluster of differentiation 8 positive
cHL	Classic Hodgkin lymphoma
CI	Confidence interval
Cmax	Observed maximum (peak) concentration
Cmin	Minimal (trough) plasma concentration
CNS	Central nervous system
CPS	Combined positive score
CR	Complete Response
CRC	Colorectal cancer
CSR	Clinical Study Report
cSSC	Cutaneous squamous cell carcinoma
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data monitoring committee
dMMR	Mismatch repair deficient
DOR	Duration of response
ECOG PS	Eastern Cooperative Oncology Group performance status
EMA	European Medicines Agency
E-R	Exposure-response
ER	Estrogen receptor
ESMO	European Society for Medical Oncology
EU	European Union
FAS	Full analysis set
FDA	US Food and Drug Administration

FoxP3	Forkhead box P3
gBRCAm	Germline breast cancer susceptibility gene-mutated
GCP	Good Clinical Practice
HCC	Hepatocellular carcinoma
HER2	Human epidermal growth factor receptor 2
HNSCC	Head and neck squamous cell carcinoma
HR	Hazard ratio
IA1	First interim efficacy analysis
IA2	Second interim efficacy analysis
IC	PD-L1 stained tumor-infiltrating immune cells
IFNγ	Interferon gamma
IgG4	Immunoglobulin G4
IHC	Immunohistochemistry
IL-2	Interleukin-2
ITT	Intent-to-treat
IV	Intravenous
KM	Kaplan-Meier
mAb	Monoclonal antibody
MCC	Merkel cell carcinoma
MSI-H	Microsatellite instability-high
NAC	Neoadjuvant chemotherapy
NCCN	National Comprehensive Cancer Network
NKC	Natural killer cells
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PARP	Poly (ADP-ribose) polymerase
PD	Progressive disease
PD-1	Programmed cell death 1
PD-L1	Programmed cell death 1 ligand 1
PD-L2	Programmed cell death 1 ligand 2
PFS	Progression-free survival
PgR	Progesterone receptor

PI	Prediction interval
PK	Pharmacokinetic(s)
PMBCL	Primary mediastinal B-cell lymphoma
PR	Partial Response
PRO	Patient-reported outcome
PTs	Preferred terms
Q2W	Every 2 weeks
Q3W	Every 3 weeks
Q6W	Every 6 weeks
QoL	Quality of life
RCC	Renal cell carcinoma
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RSD	Reference Safety Dataset
SAE	Serious adverse event(s)
SAP	Statistical Analysis Plan
sBLA	Supplemental Biologics License Application
SCLC	Small cell lung cancer
SD	Stable Disease
SmPC	Summary of product characteristics
SOC	System Organ Class
sPMA	Supplemental Premarket Approval
sSAP	Supplemental Statistical Analysis Plan
TILs	Tumor-infiltrating lymphocytes
TMB	Tumor mutational burden
TNBC	Triple negative breast cancer
TNFα	Tumor necrosis factor alpha
US	United States
USPI	United States prescribing information
WBC	White blood cells

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Merck Sharp & Dohme B.V. submitted to the European Medicines Agency on 19 November 2020 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication for Keytruda to include in combination with chemotherapy, treatment of locally recurrent unresectable or metastatic triple negative breast cancer in adults whose tumours express PD L1 with a CPS ≥ 10 and who have not received prior chemotherapy for metastatic disease; as a consequence, sections 4.1, 4.2 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 31.1 of the RMP has also been submitted.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included EMA Decision P/0043/2018 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP (EMEA-001474-PIP01-13-M01) covering the condition 'Treatment of all conditions included in the category of malignant neoplasms (except nervous system, haematopoietic and lymphoid tissue)' was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Armando Genazzani Co-Rapporteur: Jan Mueller-Berghaus

Timetable	Actual dates
Submission date	19 November 2020
Start of procedure:	26 December 2020
CHMP Rapporteur Assessment Report	26 February 2021
CHMP Co-Rapporteur Assessment Report	19 February 2021
PRAC Rapporteur Assessment Report	25 February 2021
PRAC Outcome	11 March 2021
CHMP members comments	15 March 2021
Updated CHMP Rapporteur(s) (Joint) Assessment Report	20 March 2021
Request for supplementary information (RSI)	25 March 2021
CHMP Rapporteur Assessment Report	28 May 2021
CHMP members comments	14 June 2021
Updated CHMP Rapporteur Assessment Report	17 June 2021
Request for supplementary information (RSI)	24 June 2021
CHMP Rapporteur Assessment Report	1 September 2021
CHMP members comments	6 September 2021
Updated CHMP Rapporteur Assessment Report	9 September 2021
Opinion	16 September 2021

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

The claimed therapeutic indication is: *"KEYTRUDA, in combination with chemotherapy, is indicated for the treatment of locally recurrent unresectable or metastatic triple negative breast cancer in adults whose tumours express PD-L1 with a CPS ≥ 10 and who have not received prior chemotherapy for metastatic disease."*

Epidemiology

Breast cancer is the most common cancer and the leading cause of cancer mortality in women. In Europe, the expected number of new cases and deaths from breast cancer is 522,500 and 137,700, respectively[1]. TNBC represents 15% to 20% of all breast cancers[2].

Biologic features

TNBC is phenotypically defined by a lack of ER and PgR expression and the absence of HER2 overexpression and/or amplification[4] [3]. TNBC is overlapping, but not synonymous, with the basal-like subtype defined by gene expression, as about 70% of TNBCs have basal-like characteristics according to gene-expression profiling[4]. TNBC is a heterogeneous entity that encompasses several subtypes with distinct molecular characteristics (basal-like 1 and 2, mesenchymal, mesenchymal stem-like, immunomodulatory, luminal androgen receptor)[5]. Actionable somatic mutations are generally low-frequency events in TNBC[6]. TNBCs are significantly associated with BRCA1-germline mutations and high levels of genomic instability, TP53 (82%) and PIK3CA (10%) being the two most frequently mutated somatic genes[7]. Approximately 15% of subjects with TNBC carry deleterious BRCA mutations[8].

TNBC is characterized by the presence of TILs and gene signatures enriched for cytotoxic CD8+ T cell and NKC activity, suggesting that this cancer subtype may be an immunoreactive disease and may be amenable to immune modulation of the tumor microenvironment[9]. Published studies report PD-L1 positivity ranging from 20% to 60% in all breast cancers[10] [11], which have been associated to good or bad prognosis in different studies[12]. In addition, PD-L1 positivity in breast cancer is often associated with TILs or TIL activity[9] and the presence of other immune regulators[13], although there is a noteworthy heterogeneity between breast tumors even within the same molecular subtype[14].

Clinical presentation, diagnosis and stage/prognosis

TNBC occur more frequently in younger patients and it is associated with higher tumor grade at diagnosis, a higher risk of distant disease recurrence, occurring earlier with a peak of recurrence within 1

[1] Ferlay J, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries and 25 major cancers in 2018. Eur J Cancer. 2018;103:356-87.
[2] Bauer KR, et al. Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype: a population-based study from the California cancer Registry. Cancer. 2007 May 1;109(9):1721-8.
[3] Arnedos M, Bihan C, Delaloge S, Andre F. Triple-negative breast cancer: are we making headway at least? Ther Adv Med Oncol. 2012 Jul;4(4):195-210.
[4] Badve S, et al. Basal-like and triple-negative breast cancers: a critical review with an emphasis on the implications for pathologists and oncologists. Mod Pathol. 2011 Feb;24(2):157-67.
[5] Lehmann BD, et al. Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. J Clin Invest. 2011;121(7):2750–67.
[6] Bareche Y, et al. Unravelling triple-negative breast cancer molecular heterogeneity using an integrative multiomic analysis. Ann Oncol 2018;29:895-902.
[7] Lehmann BD, Pietenpol JA. Clinical implications of molecular heterogeneity in TNBC. Breast 2015;24:S36–S40.
[8] Sharma P, et al. Germline *BRCA* mutation evaluation in a prospective triple-negative breast cancer registry: implications for hereditary breast and/or ovarian cancer syndrome testing. Breast Cancer Res Treat. 2014;145:707–714.
[9] Stagg J, Allard B. Immunotherapeutic approaches in triple negative breast cancer: latest research and clinical prospects. Ther Adv Med Oncol. 2013 May;5(3):169-81.
[10] Mittendorf EA, et al. PD-L1 expression in triple-negative breast cancer. Cancer Immunol Res. 2014 Apr;2(4):361-70.
[11] Ghebeh H, et al. FOXP3+Tregs and B7-H1+/PD-1+ T lymphocytes co-infiltrate the tumor tissues of high-risk breast cancer patients: Implication for immunotherapy. BMC Cancer. 2008 Feb 23;8:57.
[12] Solinas C, et al. Targeting PD-1 in cancer: Biological insights with a focus on breast cancer. Crit Rev Oncol Hematol. 2019 Oct;142:35-43.
[13] Basu GD, et al. Expression of novel immunotherapeutic targets in triple-negative breast cancer. 2014 ASCO (American Society of Clinical Oncology) Annual Meeting; 2014 May 30-June 3; Chicago, IL.
[14] Solinas C, et al. Immune Checkpoint Molecules on Tumor-Infiltrating Lymphocytes and Their Association with Tertiary Lymphoid Structures in Human Breast Cancer. Front Immunol. 2017 Oct 30;8:1412.

to 3 years after initial diagnosis, more likely develop of visceral and CNS metastases, and poorer OS compared to other breast cancer subtypes[15].

Management

Treatment of TNBC is challenging, as these tumors lack therapeutic targets, such as ER and HER2. Chemotherapy is considered the standard of care, although become rapidly resistant to chemotherapy upon local recurrence and/or metastasis, even though they are often sensitive to cytotoxic drugs at initial presentation[5].

When KEYNOTE-355 started in 2016, recommendations for advanced TNBC included sequential monotherapy as the preferred choice, reserving combination chemotherapy to patients with rapid clinical progression, life-threatening visceral metastases, or need for rapid symptom and/or disease control. Anthracyclines and taxanes were the preferred option. Anthracyclines and taxanes were also suggested as rechallenge regimens in patients with 6–12 months of disease free survival following completion of neoadjuvant or adjuvant chemotherapy, whichever was completed last. In patients with advanced HER2-negative breast cancer, who were pre-treated in the adjuvant or metastatic setting with anthracycline and taxane and not in need of combination chemotherapy, single agent capecitabine, vinorelbine or eribulin were possible choices. As TNBC was a putatively BRCA-deficient population, platinum doublets were studied with some evidence of activity[16] [17].

According to the latest European treatment guidelines[18], for most patients with advanced TNBC, chemotherapy remains the only available non-investigational systemic treatment option for non-BRCA-mutated, with no specific recommendations regarding types of agents, with the possible exception of platinum compounds for patients with BRCA-mutated.

Based on the results of IMpassion130 study, atezolizumab in combination with nab-paclitaxel may be considered an option in the 1L setting for de-novo advanced/metastatic disease or disease that has developed at least 12 months after completion of (neo)adjuvant ChT in tumours that have PD-L1 expression≥1% on immune cells. This treatment was approved in EU in 2019 based on PFS advantage [updated PFS analysis in PD-L1 positive population: median PFS 7.46 (95%CI 6.7, 9.23) vs 5.29 (95%CI 3.81, 5.55), HR 0.63 (95%CI 0.5, 0.8), p<0.0001] and positive OS trend [not formally tested; median OS in the PD-L1 positive population 25.03 (95%CI 19.55, 30.65) vs 17.97 months (95%CI 13.63, 20.07), HR 0.71 (95%CI 0.54, 0.93)][19].

In contrast, atezolizumab + paclitaxel did not improve PFS or OS in participants with a recurrence-free interval of ≥12 months and PD-L1 positive tumors (IC ≥1%) enrolled in IMpassion131.

In patients with germline BRCA mutation, a PARP inhibitor is a preferred treatment option. Olaparib and talazoparib were approved in EU in 2019 for the treatment of germline BRCA1/2-mutations HER2 negative locally advanced or metastatic breast cancer; patients should have been previously treated with an anthracycline and a taxane in the (neo)adjuvant or metastatic setting unless not suitable for these treatments.

[15] Dent R, et al. Triple-negative breast cancer: clinical features and patterns of recurrence. Clin Cancer Res. 2007 Aug 1;13(15 Pt 1):4429-34.
[16] Andre F, Zielinski CC. Optimal strategies for the treatment of metastatic triple-negative breast cancer with currently approved agents. Ann Oncol. 2012 Aug;23 Suppl 6:vi46-51.
[17] Cardoso F, et al. ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). Breast 2014 Oct;23(5):489-502.
[18] Cardoso F, et al. 5th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 5). Ann Oncol 2020;31:1623-49.
[19] EPAR Tecentriq X-17, EMA/CHMP/425313/2019.

Table: Efficacy of Chemotherapy as 1L Treatment for mTNBC

Study/Breast Cancer Subtype/Reference	Line	Drug	ORR%/PFS_{mo}/OS_{mo}
Metanalysis of 3 Phase III trials: E2100, AVADO, RIBBON 1 – MCB TNBC subgroup analysis Miles et al. 2013 [78]	1L	Paclitaxel or docetaxel or capecitabine or (A/EC, FA/EC)	**23/5.4/17.5**
E2100-Phase III – MCB TNBC subgroup analysis Gray et al. 2009 [79]	1L	Paclitaxel	**22/5.3/16.3**
Phase III – TNBC 1L subgroup analysis O'Shaughnessy et al. 2014 [71]	1L	Gemcitabine + carboplatin	NR/**4.6/13.9**
Phase III – MBC TNBC subgroup analysis Rugo et al. 2015 [77]	1L	Paclitaxel + bevacizumab	NR/**6.5**/NR
		Nab-paclitaxel + bevacizumab	NR/**7.4**/NR
Note: In all studies included in Table 1, paclitaxel and nab-paclitaxel were both given on Days 1, 8, and 15 every 28 days.			

Table from KEYNOTE-355 study protocol

2.1.2. About the product

Keytruda (pembrolizumab) is a humanized mAb IgG4/kappa isotype directed against PD-1. By blocking the interaction between PD-1 and its ligands PD-L1/2, pembrolizumab enhances T cell lymphocyte activity with consequent stimulation of the immune-mediated anti-tumour activity. Pembrolizumab also modulates the level of IL-2, TNFα, IFNγ, and other cytokines. The antibody potentiates existing immune responses in the presence of antigen only; it does not non-specifically activate T cells.

Pembrolizumab is currently EU approved as monotherapy and in combination with chemotherapy or other agents for the treatment of melanoma, NSCLC, RCC, HNSCC, urothelial cancer, cHL and MSI-H mCRC.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The MAH for Keytruda applied for an extension of indication of pembrolizumab in combination with chemotherapy for the 1L treatment of patients with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 (CPS ≥10). This application is based on the efficacy and safety results of IA2 (data cutoff date 11-DEC-2019) of the pivotal phase III double-blind randomized KEYNOTE-355 study which evaluated pembrolizumab plus chemotherapy compared with placebo plus chemotherapy as treatment for locally recurrent inoperable or metastatic TNBC who had recurrence-free interval of ≥6 months from completion of treatment with curative intent. In both arms, chemotherapy was a physician's choice between paclitaxel, nab-paclitaxel, or gemcitabine plus carboplatin. During the procedure, the MAH submitted also the results of the final analysis for overall survival of KEYNOTE-355 (data cut-off date 15-JUN-2021).

No scientific advice was requested to CHMP on the design of the pivotal study KEYNOTE-355, which was obtained from the US FDA. A pre-submission TC meeting was held with Rapporteurs and EMA on 26 October 2020 regarding content and format of the submission.

2.1.4. General comments on compliance with GCP

The MAH stated that all studies were conducted according to current standard research approaches and following appropriate GCP standards and considerations for the ethical treatment of human participants that were in place at the time the studies were performed.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

According to the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00) proteins are exempted from the submission of ERA studies because they are unlikely to result in significant risk to the environment. Pembrolizumab is a protein, therefore an ERA has not been submitted by the MAH. This is acceptable.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study ID	Phase	Country / Region	Study Title	Study design	Dosing regimen	Study population	Participant exposure
P355V01MK3475 [Ref. 5.3.5.1: P355V01 MK3475]	3	USA Canada Brazil Mexico Argentina Chile Colombia Spain Belgium UK Ireland France Italy Germany Netherlands Denmark Ukraine Hungary Russia Poland Czech Republic Turkey Japan Taiwan South Korea Malaysia Hong Kong Australia New Zealand	A Randomized, Double-Blind, Phase III Study of Pembrolizumab (MK-3475) plus Chemotherapy vs Placebo plus Chemotherapy for Previously Untreated Locally Recurrent Inoperable or Metastatic Triple Negative Breast Cancer	Randomized, double-blind, parallel-group, placebo-controlled	**Pembrolizumab**: 200 mg Q3W **Placebo**: normal saline or dextrose Q3W **Paclitaxel**: 90 mg/m^2 on Days 1, 8, and 15 of every 28-day cycle **Nab-paclitaxel**: 100 mg/m^2 on Days 1, 8, and 15 of every 28-day cycle **Gemcitabine and carboplatin**: 1000 mg/m^2 and AUC 2 on Days 1 and 8 of every 21-day cycle.	Adult male and female participants (≥18 years of age) with locally recurrent inoperable or metastatic TNBC, not previously treated with chemotherapy	Pembrolizumab + chemotherapy: 562 Placebo + chemotherapy: 281

Trial ID	Phase	Country / Region	Trial Title	Trial design	Dosing regimen	Trial population	Subject exposure
3475-119 [Ref. 5.3.5.1: P119V01 MK3475]	3	Argentina Australia Belgium Brazil Colombia France Germany Guatemala Hong Kong Ireland Italy Japan Malaysia Mexico Netherlands New Zealand Peru Philippines Poland Russia Singapore South Africa South Korea Spain Sweden Switzerland Tarwan Thailand Turkey United Kingdom USA	A Randomized Open-Label Phase III Study of Single Agent Pembrolizumab versus Single Agent Chemotherapy per Physician's Choice for Metastatic Triple Negative Breast Cancer (mTNBC) – (KEYNOTE-119) Efficacy and safety in participants receiving second line (2L) or third line (3L) intervention for metastatic triple negative breast cancer (mTNBC)	Randomized, unblinded, open-label, active controlled	Arm 1: Pembrolizumab 200 mg IV Q3W, 35 administrations (approximately 2 years) Arm 2: Capecitabine Or Eribulin Or Gemcitabine Or Vinorelbine (local standard of care)	Male and female participants ≥18 years with Stage IV/M1 mTNBC	Arm 1: 309 participants Arm 2: 292 participants

Study ID	Phase	Country	Study Title	Study design	Dosing regimen	Study population	Participant exposure
P086V01 [Ref. 5.3.5.2: P086V01 MK3475]	2	Cohort A Australia Belgium Canada France, Germany Israel Italy Japan New Zealand South Africa Spain, United Kingdom, United States Cohort B Australia Belgium Canada Germany Israel Italy Japan South Africa Spain United Kingdom United States	A Phase 2 Clinical Trial of Pembrolizumab (MK-3475) as Monotherapy for Metastatic Triple-negative Breast Cancer (mTNBC) – (KEYNOTE-086) A safety and efficacy study of pembrolizumab as second line or above (2L+) monotherapy in tumors with programmed cell death receptor-ligand 1 (PD-L1) positive (+) expression and independent of PD-L1 expression; and as first line (1L) monotherapy in tumors with PD-L1 (+) and PD-L1 strong (+) expression	Open-label, nonrandomized, single-arm, 2-part, multicenter, multicohort Part 1: Cohort A participants with PD-L1 (+) tumors and all comers, and Cohort B participants with PD-L1 (+) tumors; Cohorts A and B enrolled in parallel; 2 interim analyses (IA 1 and IA 2) for Cohort A IA-1: Futility analysis on the PD-L1 negative (-) subpopulation of Cohort A IA-2: Efficacy analysis of responses in at least 10 participants with PD-L1 strong (+) tumors in Cohort A Part 2: Cohort C participants comprising at least 1 responder in 10-15 participants with PD-L1 strong (+) tumors from Cohort A and ~40-45 participants with PD-L1 strong (+) tumors	Pembrolizumab 200 mg IV Q3W for up to 24 weeks from the date of the first dose	Females/males ≥18 years of age mTNBC participants previously treated with at least 1 systemic treatment for metastatic breast cancer and documented progression after the most recent therapy; and previously treated with an anthracycline and a taxane in the (neo)adjuvant or metastatic setting	~285 participants Cohort A (2L+) ~160 participants Cohort B (1L) ~80 participants Cohort C (2L+) ~45 participants

2.3.2. Pharmacokinetics

Comprehensive review of the key clinical pharmacology findings for pembrolizumab as monotherapy (200 mg Q3W dosing regimen) from melanoma, NSCLC, HNSCC, HL, UC, GEJ adenocarcinoma, HCC, MSI-H mCRC and HL indications have been discussed extensively in previous submissions. The key clinical pharmacology characteristics are summarized in the SmPC.

Absorption

Pembrolizumab is dosed via the intravenous route and therefore is immediately and completely bioavailable.

Distribution

Consistent with a limited extravascular distribution, the volume of distribution of pembrolizumab at steady state is small (6.0 L; coefficient of variation [CV]: 20%). As expected for an antibody, pembrolizumab does not bind to plasma proteins in a specific manner.

Elimination

Pembrolizumab CL is approximately 23% lower (geometric mean, 195 mL/day [CV%: 40%]) after achieving maximal change at steady state compared with the first dose (252 mL/day [CV%: 37%]); this decrease in CL with time is not considered clinically meaningful. The geometric mean value (CV%) for the terminal half-life is 22 days (32%) at steady-state.

Pharmacokinetic in target population

A substantial characterization of the key clinical pharmacology and immunogenicity findings of pembrolizumab as monotherapy has been provided in previous submissions.

The updated clinical pharmacology results pertaining to the current submission include:

- PK data from subjects with from subjects with previously untreated locally recurrent inoperable or metastatic triple negative breast cancer (TNBC) (KEYNOTE-355)
- A comparison of KEYNOTE-355 observed PK data with reference model (TDPK) predicted PK.
- A comparison of KEYNOTE-355 observed PK concentrations with observed PK concentrations from subjects from historical data.

Pembrolizumab PK data from KEYNOTE-355 study

PK samples with a 15-June-2020 visit cut-off date were measured for a total of 221 subjects in KEYNOTE-355. The PK analysis dataset was constructed from the final locked SDTM datasets using SAS version 9.4 and contains observed MK-3475 serum concentrations and actual elapsed blood sampling times relative to the corresponding time of dose.

Summary statistics were calculated based on nominal time after first dose. Safety follow up and discontinuation visits, as well as PK results from subjects dosed with placebo instead of pembrolizumab were omitted from the PK analysis.

PK sampling schedule in KEYNOTE-355 for pembrolizumab: pre infusion pembrolizumab serum concentrations (Ctrough) were obtained within 24 hours prior to dosing at Cycle 1, 2, 4, and 8 and every 8 cycles (6 months) thereafter.

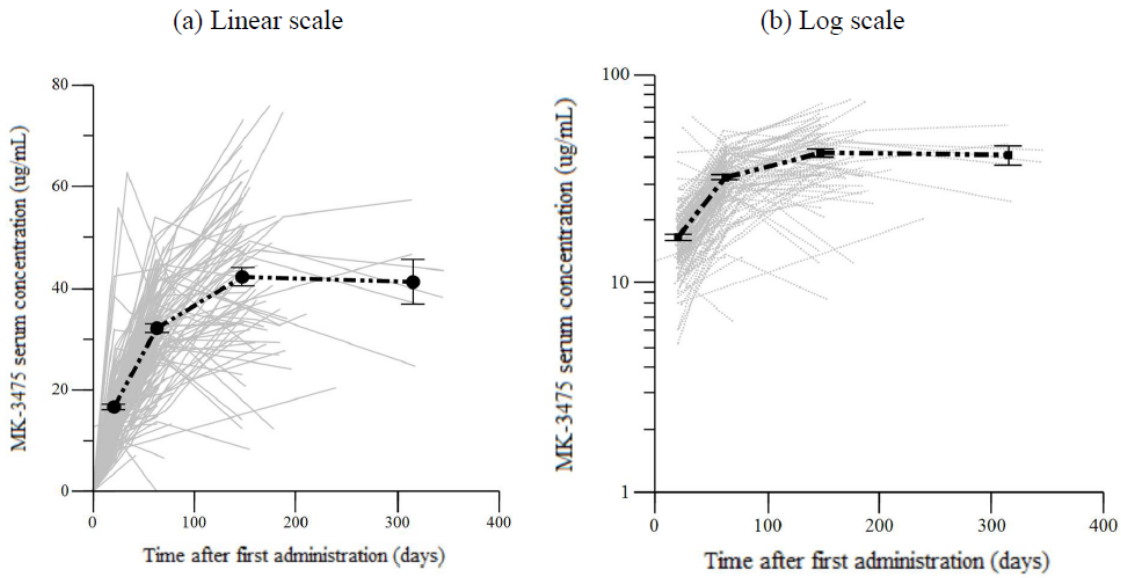
PK samples were also collected at discontinuation and at 30 days after discontinuation of trial treatment.

Phoenix™ WinNonlin® (Version 8.1.0.3530) software was used for pharmacokinetic analysis.

RESULTS

Individual predose serum pembrolizumab concentration-time profiles with mean ± SE profile overlaid are shown in [Figure 1], mean predose serum pembrolizumab concentration-time profile is shown in [Figure 2].

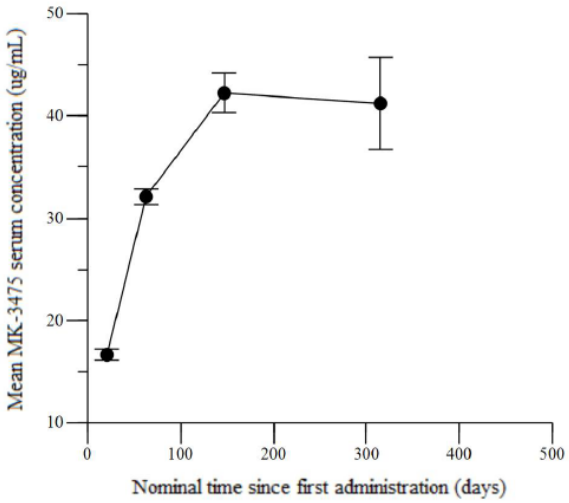
Figure 1 **Individual and Arithmetic Mean Predose Serum Concentrations of Pembrolizumab Following Administration of Multiple I.V. doses of 200 mg Q3W Pembrolizumab in KEYNOTE-355 (a) Linear scale, (b) Log scale**



Note: Grey lines represent individual concentration observations. Black dashed lines represent arithmetic mean concentrations and error bars are associated +/- SE. Actual times were used for this analysis.

Data Source: [05M6YJ: analysis-adpc]

Figure 2 **Arithmetic Mean (±SE) Predose Serum Concentrations of Pembrolizumab Following Administration of Multiple I.V. doses of 200 mg Q3W Pembrolizumab in KEYNOTE-355, Linear scale**



Data Source: [05M6YJ: analysis-adpc]

Summary descriptive statistics of the predose concentrations by Cycle are presented in the following table:

Table 2 **Summary Statistics of Pembrolizumab Predose (Ctrough) Serum Concentration Values Following Administration of Multiple I.V. doses of 200 mg Q3W Pembrolizumab in KEYNOTE-355**

Cycle	NOMTAFD (day)	N	GM (%CV)	GM (SD)	AM (SD)	Min	Median	Max
			(µg/mL)					
Predose (C_{trough})								
Cycle 2 (Week3)	21.0	195	--	--	16.7 (7.6)	0.00	15.8	62.7
Cycle 4 (Week9)	63.0	148	--	--	32.1 (9.5)	0.00	32.5	54.0
Cycle 8 (Week21)	147	64	38.9 (46.4)	38.9 (15.3)	42.2 (15.3)	8.31	42.0	75.9
Cycle 16 (Week45)	315	6	39.9 (29)	39.9 (10.9)	41.2 (10.9)	24.7	40.9	57.4

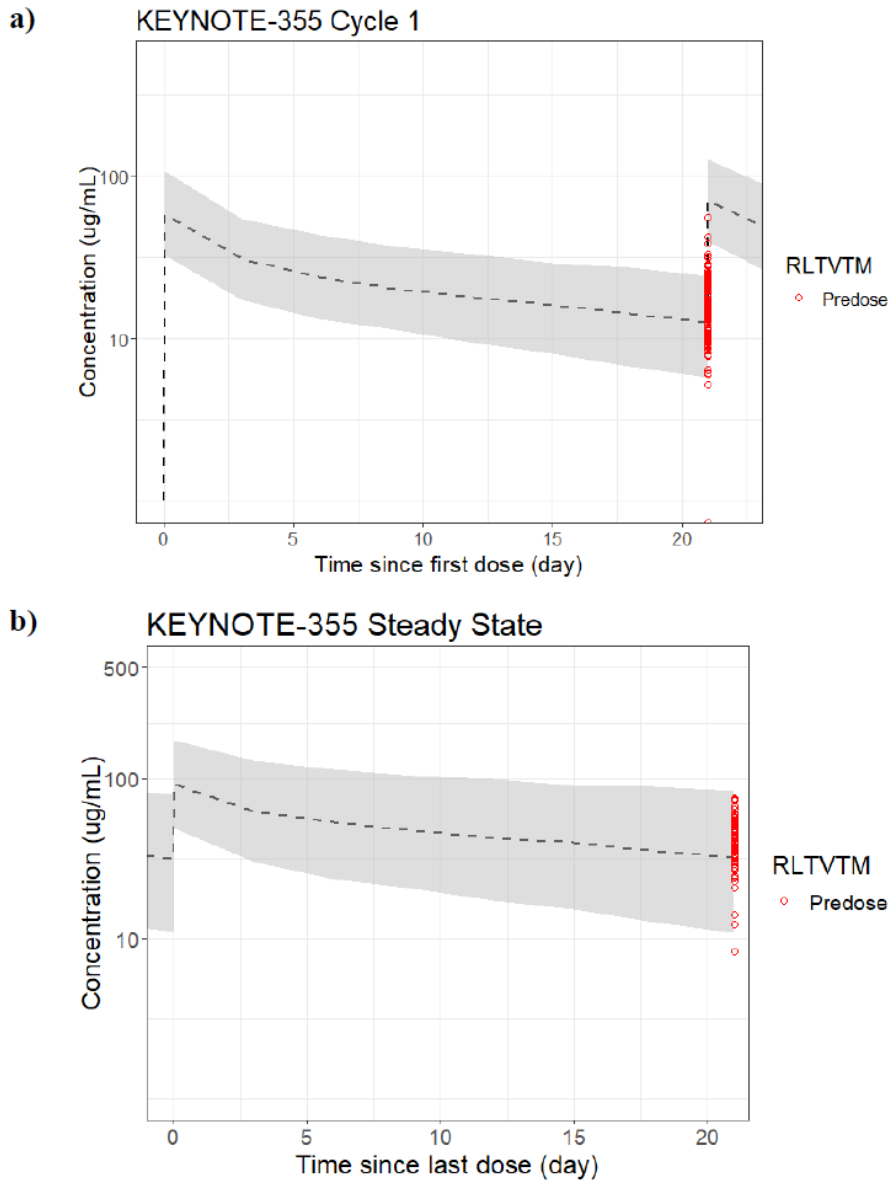
NOMTAFD = Nominal time after first pembrolizumab administration;
GM = Geometric Mean;
CV% = Geometric Coefficient of Variation;
SD = Standard Deviation;
AM = Arithmetic Mean;
Results reported for time points with N > 5.

Data Source: [05M6YJ: analysis-adpc]

Over the course of clinical development of pembrolizumab, PK has been robustly characterized. Using a dataset with sample size of 2993 participants, a time-dependent PK model was created to describe the PK profile as indicated in the USPI and EU SmPC. This model is used as the reference PK model to support pembrolizumab submissions across indications worldwide.

Observed pembrolizumab concentration data in KEYNOTE-355 for pembrolizumab + Chemotherapy group are overlaid on the simulated profile using the reference PK model as shown in [Figure 3]. While the majority of the observed serum concentration values in KEYNOTE-355 are above the median of the predicted interval, most are contained within the boundaries of the predicted interval using the reference PK model.

Figure 3 **Observed Concentration Data in KEYNOTE-355 Subjects Receiving 200 mg Q3W Pembrolizumab with Reference Model-Predicted Pharmacokinetic Profile for 200 mg Q3W Dose Regimen**



a) after 1st dose on log scale; b) at and after dose number 8 (21 weeks) on log scale;

Symbols are individual observed data (nominal time) from KEYNOTE-355 200 mg Q3W subjects; black line is median predicted concentrations from the model for a regimen of 200 mg Q3W and the grey shaded area represents the 90% prediction interval.

Data Source: [05M6YJ: analysis-adpc]

COMPARISON KEYNOTE-355

Tabular summaries of descriptive statistics and boxplots from Cycle 2 and steady-state dosing at Cycle 8, comparing observed pembrolizumab concentrations of 200 mg every 3 weeks (Q3W) from participants with previously untreated locally recurrent inoperable or metastatic triple negative breast cancer (TNBC) KEYNOTE-355 and monotherapy trials in non-small cell lung cancer (NSCLC, KEYNOTE-024), urothelial

cancer (UC, KEYNOTE-045 and KEYNOTE-052), melanoma (MEL, KEYNOTE-054), head and neck squamous cell cancer (HNSCC, KEYNOTE-055), gastric cancer (GC, KEYNOTE-059), classical Hodgkin Lymphoma (HL, KEYNOTE-087), microsatellite instability-high cancer (MSI-H, KEYNOTE-164), primary mediastinal large B-cell lymphoma (PMBCL, KEYNOTE-170) and hepatocellular carcinoma (HCC, KEYNOTE-224), are presented for all subjects in [Table 3] and [Figure 4]. In addition, the comparison of observed PK data is also shown across studies/indications by gender in [Table 3] and for female subjects only in [Figure 5], to provide a more balanced comparison across studies, considering KEYNOTE-355 has only female subjects due to the breast cancer indication, as gender was a significant covariate in the PK model.

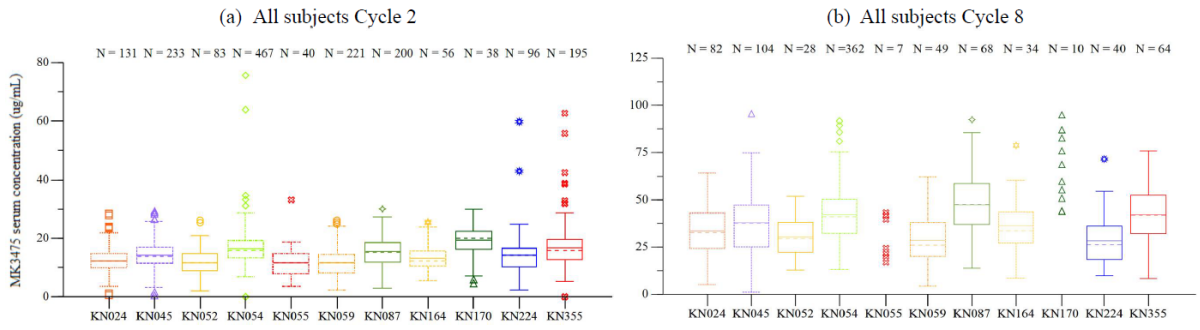
Table 3 **Summary Statistics of Observed Pembrolizumab Trough Concentrations at Cycle 2 and Cycle 8 (Steady-state) in Various Trials (KEYNOTE-024, -045, -052, -054, -055, -059,-087, -164, -170, -224 and -355)**

			Total			Female			Male		
CYCLE	STUDYID	Indication	N	GM (%CV) (ug/mL)	AM (SD) (ug/mL)	N	GM (%CV) (ug/mL)	AM (SD) (ug/mL)	N	GM (%CV) (ug/mL)	AM (SD) (ug/mL)
2	MK3475-024	NSCLC	131	11.1 (54)	12.2 (4.7)	52	13.5 (51)	14.6 (5.1)	79	9.80 (52)	10.7 (3.7)
8			82	30.6 (50)	33.6 (13)	30	37.2 (43)	40.0 (14)	52	27.4 (49)	29.9 (11)
2	MK3475-045	UC	233	13.1 (47)	14.2 (4.9)	60	16.0 (42)	17.1 (5.7)	173	12.3 (47)	13.2 (4.2)
8			104	33.4 (64)	37.8 (17)	26	47.7 (37)	50.5 (17)	78	29.7 (66)	33.6 (14)
2	MK3475-052	UC	83	10.9 (44)	11.8 (4.4)	20	14.4 (37)	15.3 (4.9)	63	9.93 (42)	10.6 (3.6)
8			28	28.8 (35)	30.4 (9.7)	5	36.6 (35)	38.1 (11)	23	27.3 (33)	28.7 (8.6)
2	MK3475-054	MEL	467	n.c.	16.5 (5.8)	170	n.c.	19.1 (4.8)	297	n.c.	15.0 (5.8)
8			362	40.2 (34)	42.3 (13)	130	47.8 (32)	50.0 (14)	232	36.5 (30)	38.0 (11)
2	MK3475-055	HNSCC	40	10.7 (47)	11.8 (5.2)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
8			7	27.8 (41)	29.6 (11)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
2	MK3475-059	GC	221	10.6 (46)	11.6 (4.6)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
8			49	25.3 (62)	28.7 (13)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
2	MK3475-087	HL	200	14.4 (40)	15.4 (5.1)	93	17.7 (29)	18.3 (4.8)	107	12.1 (38)	12.8 (3.9)
8			68	43.9 (43)	47.4 (17)	37	49.5 (38)	52.5 (16)	31	38.1 (45)	41.3 (16)
2	MK3475-164	MSI-H	56	12.5 (35)	13.2 (4.6)	22	15.8 (29)	16.5 (4.7)	34	10.7 (29)	11.1 (3.0)
8			34	33.6 (43)	36.2 (14)	16	42.3 (34)	44.4 (14)	18	27.4 (39)	29.0 (8.7)
2	MK3475-170	PMBCL	38	17.9 (45)	19.3 (6.3)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
8			10	64.1 (29)	66.4 (18)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
2	MK3475-224	HCC	96	13.0 (45)	14.2 (7.1)	17	15.9 (31)	16.5 (4.6)	79	12.4 (46)	13.7 (7.4)
8			40	25.9 (46)	28.5 (13)	6	30.8 (56)	34.6 (20)	34	25.2 (44)	27.4 (12)
2	MK3475-355	TNBC	195	n.c.	16.7 (7.6)	195	n.c.	16.7 (7.6)	0		
8			64	38.9 (46)	42.2 (15)	64	38.9 (46)	42.2 (15)	0		

GM = Geometric Mean; CV% = Geometric Coefficient of Variation; SD = Standard Deviation; AM = Arithmetic Mean; n.c. = not calculated; n.a.= information not available;
TNBC = triple negative breast cancer; NSCLC = non-small cell lung cancer; UC = urothelial cancer; MEL = melanoma; HNSCC = head and neck squamous cell cancer; GC = gastric cancer, HL = classical Hodgkin Lymphoma; MSI-H = microsatellite instability-high cancer; PMBCL = primary mediastinal large B-cell lymphoma; HCC = hepatocellular carcinoma.

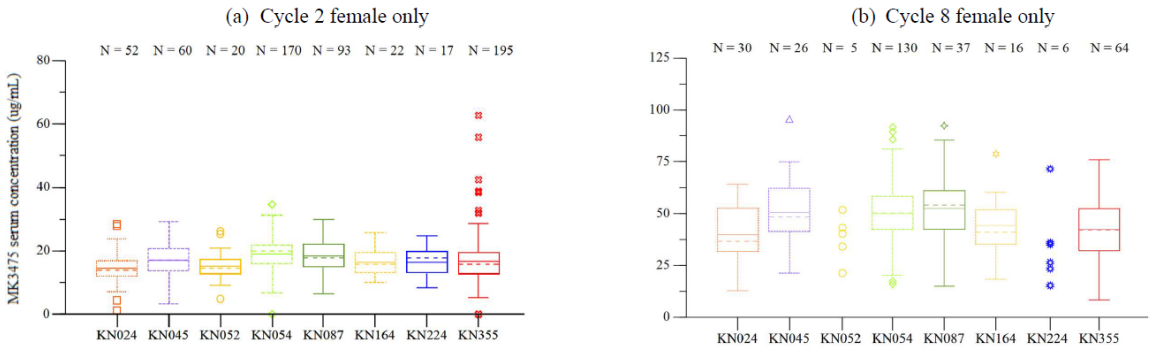
Data Source: [05M6YJ: analysis-adpc]

Figure 4 **Observed Trough Pembrolizumab Concentrations at Cycle 2 and Cycle 8 (Steady-state) Across Studies/Indications, All Subjects**



Data Source: [05M6YJ: analysis-adpc]

Figure 5 **Observed Trough Pembrolizumab Concentrations at Cycle 2 and Cycle 8 (Steady-state) Across Studies/Indications, Female Subjects Only**



Data Source: [05M6YJ: analysis-adpc]

2.3.3. Pharmacodynamics

Mechanism of action

KEYTRUDA is an antibody that binds to the programmed death-1 (PD-1) receptor and blocks its interaction with ligands PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. KEYTRUDA potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment.

Dose regimen

Pembrolizumab is approved at a 2 mg/kg or 200 mg Q3W dosing regimen for multiple indications as monotherapy and in combination with small molecule or chemotherapy worldwide (e.g., melanoma, NSCLC, HNSCC, HL, UC, gastric cancer, MSI-H cancer, HCC and RCC).

Pembrolizumab is also approved at 400 mg Q6W in the EU for monotherapy and combination indications.

A dosing regimen of 200 mg Q3W or 400 mg Q6W is recommended for pembrolizumab in the treatment of adult subjects with TNBC in combination with chemotherapy. The 200 mg Q3W dosing regimen is approved for use in multiple indications globally as monotherapy as well as in combination with small molecule or chemotherapy based on a large, integrated body of evidence at this dose level across indications.

2.3.4. PK/PD modelling

No new information regarding PK/PD modelling for pembrolizumab is available within this extension of indication.

Immunogenicity

The existing immunogenicity assessment for pembrolizumab for the monotherapy setting is based on a sufficiently large dataset of patients across several indications, with very low observed rates of total treatment ADA across different pembrolizumab regimens (1.4 – 3.8%) as well as of neutralizing antibodies (0.4 – 1.6%). This analysis has not demonstrated impact on efficacy or safety, as currently summarized in the SmPC. This low rate of immunogenicity has been shown to be consistent across tumor

type and no clinically meaningful consequences have been observed in the subjects with a positive immunogenicity reading. Based on the existing robust characterization of immunogenicity potential, alignment has been obtained with the US FDA and EMA that the current assessment of immunogenicity for pembrolizumab is adequate for non-adjuvant monotherapy settings.

No new ADA data are provided in this submission based on the robust characterization of immunogenicity potential with trials in non-adjuvant monotherapy setting.

2.3.5. Discussion on clinical pharmacology

Clinical pharmacology results in support of the current extension of indication of pembrolizumab in combination with chemotherapy for the treatment of locally recurrent inoperable or metastatic TNBC derive from study KEYNOTE-355. Data were collected on a total of 221 subjects with a visit cut-off date of 15-June-2020.

The MAH presented a descriptive PK analysis based on predose pembrolizumab serum concentrations (Ctrough) obtained within 24 hours prior to dosing at Cycles 1, 2, 4, 8 and every 8 cycles (6 months) thereafter. The observed pembrolizumab serum concentration values at cycle 2 and cycle 8 are consistent with other globally approved studies in different cancer indications.

A comparison was conducted between the observed PK of pembrolizumab for the current indication and the predictions from the reference PK model developed with pembrolizumab monotherapy data (KEYNOTE-001, -002, -006, -010, and -024). The observed concentrations in patients with advanced/metastatic TNBC with Pembrolizumab 200 mg Q3W generally fall within the 90% CI of the model predicted median concentration, both after first dose and at steady state.

In a comparative exercise with prior conducted clinical studies of pembrolizumab in monotherapy, the PK data at both Cycle 2 and Cycle 8 from KEYNOTE-355 show consistency with the established PK profile observed across the different clinical settings for which approval has been granted. Similarity in PK profile between KEYNOTE-355 and other clinical trials has also been confirmed in an analysis restricted to female subjects only.

Overall, the PK in participants with metastatic TNBC in KEYNOTE-355 after combination therapy of pembrolizumab with chemotherapy is generally consistent with monotherapy PK, as previously established. This refers also to the comparison of female patients only.

2.3.6. Conclusions on clinical pharmacology

Pharmacokinetics and immunogenicity of pembrolizumab has been sufficiently investigated for the extension of the indication of pembrolizumab 200 mg every 3 weeks in combination with chemotherapy for the treatment of TNBC. The PK profile that emerges from KEYNOTE-355 testing pembrolizumab 200 mg Q3W in combination with chemotherapy in patients with locally recurrent inoperable or metastatic TNBC is consistent with the established pharmacology of pembrolizumab as observed across different cancer subtypes.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

No specific dose response study have been performed. Pembrolizumab dose and regimen used in the pivotal KEYNOTE-355 study 200 mg Q3W IV is one of the dosages currently approved in combination with chemotherapy for other indications (NSCLC, HNSCC).

2.4.2. Main study

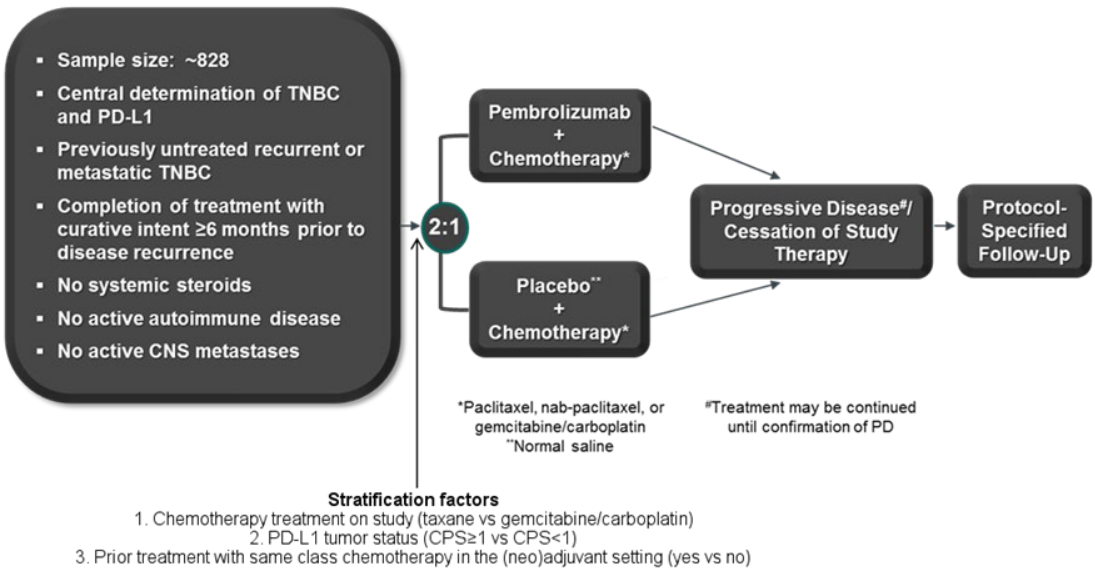
A Randomized, Double-Blind, Phase III Study of Pembrolizumab (MK-3475) plus Chemotherapy vs Placebo plus Chemotherapy for Previously Untreated Locally Recurrent Inoperable or Metastatic Triple Negative Breast Cancer – (KEYNOTE-355)

The study included 2 parts:

- **Part 1 – safety run-in**: unblinded, open-label, safety run-in that monitored participants (N=35) for unacceptable toxicities to study treatment (pembrolizumab + chemotherapy). Participants were assigned by forced randomization to ensure at least 10 participants were included in each treatment group (pembrolizumab + gemcitabine/carboplatin or pembrolizumab + taxane [paclitaxel or nab-paclitaxel]).
- **Part 2 – phase 3 study**: double-blind, placebo-controlled study on a background of chemotherapy, with 847 eligible participants randomly assigned in a 2:1 ratio to receive pembrolizumab + chemotherapy or placebo + chemotherapy, respectively.

The efficacy data are based on Part 2 results (all data described in the efficacy section below are related to Part 2).

Figure: Study Design for KEYNOTE-355 Part 2



Methods

Study participants

Key inclusion criteria:

- Have previously untreated metastatic TNBC or locally recurrent inoperable breast cancer which could not be treated with curative intent.
- Have centrally confirmed TNBC, as defined by the most recent ASCO/CAP guidelines.
- Have completed treatment for Stage I-III breast cancer, if indicated, and ≥6 months elapsed between the completion of treatment with curative intent and first documented local or distant disease recurrence. *(Note: Subjects who received taxane, gemcitabine, or platinum agents in the (neo)adjuvant setting can be treated with same class of chemotherapy (taxane or gemcitabine/carboplatin), if ≥12 months have elapsed between the completion of treatment with curative intent (e.g., date of primary breast tumor surgery or date of last adjuvant chemotherapy administration, whichever occurred last) and first documented local or distant disease recurrence).*
- Have been treated with (neo)adjuvant anthracycline, if they had received systemic treatment in that setting, unless anthracycline was contraindicated or not considered the best treatment option for the participant in the opinion of the treating physician. (*Note: Subjects presenting with de novo metastatic TNBC are eligible for the study, if anthracycline is contraindicated or not considered the best treatment option for the subject in the opinion of the treating physician).*
- Have measurable disease based on RECIST 1.1 as determined by local radiology review.
- Have at least 18 years of age.
- Have ECOG PS of 0 or 1, as assessed within 10 days prior to the start of study treatment.
- Have predicted life expectancy ≥12 weeks from randomization.
- Have provided recently or newly obtained core or excisional biopsy from a locally recurrent inoperable or metastatic tumor lesion for central determination of TNBC status and PD-L1 expression, unless contraindicated due to site inaccessibility and/or subject safety concerns.
- Demonstrate adequate organ function, within 10 days prior to the start of study treatment, as defined in the protocol
- Female subjects of childbearing potential must have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study treatment.

Key exclusion criteria:

- Had an active autoimmune disease that had required systemic treatment in the past 2 years. Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.
- Had a diagnosis of immunodeficiency or was receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to randomization.
- Had a known active CNS metastases and/or carcinomatous meningitis. Participants with known brain metastases may have participated provided the brain metastases had been previously treated (except with chemotherapy) and were radiographically stable. *(Note: Known brain metastases are considered active, if any of the following criteria are applicable: a. Brain imaging during screening demonstrates progression of existing metastases and/or appearance of new lesions compared to brain imaging*

performed at least 4 weeks earlier. b. Neurological symptoms attributed to brain metastases have not returned to baseline c. Steroids were used for management of symptoms related to brain metastases within 28 days of randomization).

- Had a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.
- Had active, or a history of, interstitial lung disease.
- Had a history of class II-IV congestive heart failure or myocardial infarction within 6 months of randomization.
- Had received prior therapy with an anti–PD-1, anti–PD-L1, or anti–PD-L2 agent or with an agent directed to another co-inhibitory T cell receptor (such as CTLA-4, OX-40, CD137) or has previously participated in Merck pembrolizumab clinical studies.
- Has a known additional malignancy that progressed or required active treatment within the last 5 years. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy, and in situ cervical cancer.
- Has a known history of human immunodeficiency virus (HIV), known active hepatitis B or C, history of active TB.
- Has received a live vaccine within 30 days prior to randomization.
- Has a known history of hypersensitivity or allergy to pembrolizumab and any of its components and/or to any of the study chemotherapies.
- Is pregnant or breastfeeding.

Treatments

Table: study treatments

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Treatment Period	Use
Pembrolizumab	200 mg	Day 1	IV infusion	Every 21 days	Experimental
Placebo (normal saline)	N/A	Day 1	IV infusion	Every 21 days	Placebo for pembrolizumab
Nab-paclitaxel	100 mg/m^2	Days 1, 8, and 15	IV infusion	Every 28 days	Chemotherapy background intervention
Paclitaxel	90 mg/m^2	Days 1, 8, and 15	IV infusion	Every 28 days	
Gemcitabine/ Carboplatin	1000 mg/m^2 AUC 2	Days 1 and 8	IV infusion	Every 21 days	
AUC=area under the concentration-time curve; IV=intravenous; N/A=not applicable.					

Chemotherapy was administered unblinded. Participants, investigators, other study site staff (except for an unblinded pharmacist), and the Sponsor were blinded to pembrolizumab/placebo administration.

Objectives

Primary objectives:

The combination of pembrolizumab and chemotherapy was compared to placebo and chemotherapy for the treatment of previously untreated locally recurrent inoperable or metastatic centrally confirmed TNBC:

- To compare progression-free survival (PFS) based on RECIST 1.1 as assessed by a blinded central imaging vendor (CIV) in all subjects.
- To compare PFS based on RECIST 1.1 as assessed by a blinded CIV in subjects with PD-L1 positive tumors (CPS≥1).
- To compare PFS based on RECIST 1.1 as assessed by a blinded CIV in subjects with PD-L1 positive tumors (CPS≥10).
- To compare overall survival (OS) in all subjects.
- To compare OS in subjects with PD-L1 positive tumors (CPS≥1).
- To compare OS in subjects with PD-L1 positive tumors (CPS≥10).

The study is considered to have met its primary objective if the combination of pembrolizumab and chemotherapy is superior to placebo and chemotherapy in either PFS or OS in either all subjects or in subjects with PD-L1 positive tumors (CPS≥1 or CPS≥10) at either an interim analysis or the final analysis (OS only).

Secondary objectives:

- To compare objective response rate (ORR) based on RECIST 1.1 as assessed by a blinded CIV in all subjects and in subjects with PD-L1 positive tumors (CPS≥1 and CPS≥10).
- To evaluate duration of response (DOR) based on RECIST 1.1 as assessed by a blinded CIV in all subjects and in subjects with PD-L1 positive tumors (CPS≥1 and CPS≥10).
- To compare DCR based on RECIST 1.1 as assessed by a blinded CIV in all subjects and in subjects with PD-L1 positive tumors (CPS≥1 and CPS≥10).
- To evaluate the safety and tolerability of 3 pembrolizumab + chemotherapy combinations.
- To evaluate changes in health-related quality-of-life (QoL) assessments from baseline in all subjects and in subjects with PD-L1 positive tumors (CPS≥1 and CPS≥10) using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and EORTC Breast Cancer–Specific Quality of Life Questionnaire (EORTC QLQ-BR23).

Exploratory Objectives:

- To characterize utilities in all subjects and in subjects with PD-L1 positive tumors (CPS≥1 and CPS≥10) using EuroQol-5 Dimension Questionnaire (EQ-5D™).
- To investigate association(s) between anti-tumor activity of study treatments and efficacy/resistance biomarkers, utilizing tumor and blood specimens obtained before randomization, during treatment, and at disease progression.
- To identify molecular (genomic, metabolic, and/or proteomic) determinants of response or resistance to pembrolizumab and other treatments in this study, so as to define novel predictive and pharmacodynamic biomarkers and understand the mechanism of action of pembrolizumab.

Outcomes/endpoints

The dual primary endpoints, evaluated for all participants and for those participants whose tumors express PD-L1 (CPS≥1 and CPS≥10), were the following:

- PFS, defined as the time from randomization to the first documented disease progression as measured by BICR per RECIST 1.1 or death due to any cause, whichever occurred first.
- OS, defined as the time from randomization to death due to any cause.

Secondary efficacy and PRO endpoints, evaluated for all participants and for those participants whose tumors express PD-L1 (CPS≥1 and CPS≥10), were as follows:

- ORR, defined as the proportion of participants in the analysis population who had a response (CR or PR) as measured by BICR per RECIST 1.1.
- DOR, defined as the time from the first documented evidence of CR or PR until disease progression as measured by BICR per RECIST 1.1 or death due to any cause, whichever occurred first.
- DCR, defined as the percentage of participants who had achieved CR or PR or had demonstrated SD for at least 24 weeks, as measured by BICR per RECIST 1.1.
- QoL, defined as changes from baseline using the EORTC QLQ-C30 and EORTC QLQ BR23 questionnaires.

Imaging assessment:

Tumor imaging were acquired by computed tomography (CT, strongly preferred). Brain imaging (MRI preferred) was required at screening and during the study for subjects with known brain metastases and those with worsening and/or new neurological symptoms. A bone scan was required prior to study entry if a subject had a history of bone metastases and/or suggestive symptoms/signs, and during the study if clinically indicated or if the site believed a subject attained a CR.

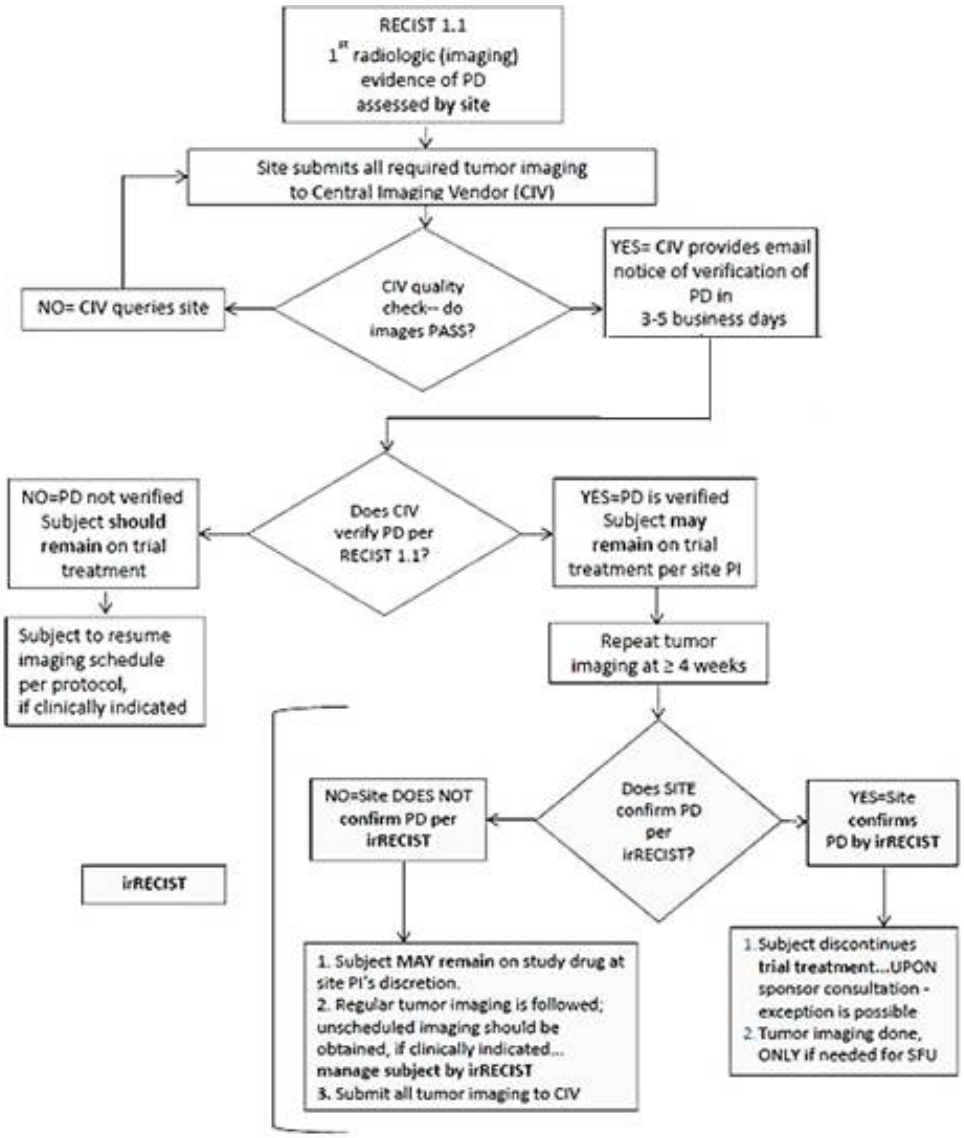
Baseline tumor imaging were performed during the 28-day screening window prior to randomization to confirm measurable disease based on RECIST 1.1 as assessed by local radiology review, then submitted to central imaging vendor (CIV) for retrospective review. Post-baseline imaging assessments were be performed at 8, 16, and 24 weeks post randomization, and then every 9 weeks during the first year. After 1 year, imaging were performed every 12 weeks. Imaging were not discontinued until PD verified by CIV or start of new anti-cancer treatment, consent withdrawal, death, or end of study, whichever occurs first.

RECIST 1.1 were applied by local radiology for assessing subject eligibility and by CIV as the primary measure for assessing efficacy parameters, allowing a maximum of 10 target lesions in total and 5 per organ. irRECIST, adapted to account for the unique tumor response seen with immunotherapeutic drugs, were used by site/investigator to assess tumor response and make treatment decisions both before and after PD is verified by CIV.

Based on RECIST 1.1, PRs and CRs were confirmed by repeat tumor imaging studies at ≥4 weeks from the date response was first documented.

Site/investigator-assessed first radiologic evidence of PD was also evaluated by the CIV in real time, and the results of central imaging review were expeditiously communicated to the study site and the Sponsor. Imaging flow algorithm for verification of PD by CIV for clinically stable subjects is illustrated in figure below.

Figure: Imaging and Treatment for Clinically Stable Subjects After First Radiologic Evidence of PD Based on RECIST 1.1 and as Assessed by Site/Investigator



Note: Verified refers to centrally verified.

PD-L1 status assessment: PD-L1 expression status was determined from a core or excisional biopsy and assessed centrally using the investigational PD-L1 IHC 22C3 pharmDx kit.

Sample size

Part 1: Approximately 30 subjects will be enrolled.

Part 2: It was expected that ~ 664 OS events among all subjects, ~ 482 OS events among subjects with CPS ≥1, and ~ 240 OS events among subjects with CPS ≥10 have been observed at the FA. The planned sample size was approximately 828 subjects:

(1) PFS in all subjects: at IA2 the analysis has ~ 89% power at a one-sided 0.111% alpha level, if the true HR is 0.70. At IA2, with ~ 634 events the HR at boundary for success is ~ 0.77 (~ 1.6 months

improvement over control median PFS of 5.5 months). At IA2, PFS in all subjects can only be tested if both hypotheses of PFS in subjects with CPS ≥10 and PFS in subjects with CPS ≥1 are supported.

(2) PFS in subjects with CPS ≥1: at IA2 the analysis has ~ 97% power at a one-sided 0.111% alpha level, if the true HR is 0.62. At IA2, with ~ 463 events the HR at boundary for success is ~ 0.74 (~ 1.9 months improvement over control median PFS of 5.5 months). At IA2, PFS in all subjects with CPS ≥1 can only be tested if the hypothesis of PFS in subjects with CPS ≥10 is supported.

(3) PFS in subjects with CPS ≥10: at IA2 the analysis has ~ 86% power at a one-sided 0.411% alpha level, if the true HR is 0.60. At IA2, with ~ 235 events the HR at boundary for success is ~ 0.69 (~ 2.4 months improvement over control median PFS of 5.5 months).

(4) OS in all subjects: the trial has ~ 60% power at a one-sided 0.75% alpha level, if the true HR is 0.80. With ~ 664 events, the HR at boundary for success at FA is ~ 0.81 (~ 4.0 months improvement over control median OS of 17.5 months). After IA1, OS in all subjects can be tested if hypothesis of OS in subjects with CPS ≥1 is supported.

(5) OS in subjects with CPS ≥1: the trial has ~ 87% power at a one-sided 0.75% alpha level, if the true HR is 0.71. With ~ 482 events, the HR at boundary for success at FA is ~ 0.78 (~ 4.8 months improvement over control median OS of 17.5 months).

(6) OS in subjects with CPS ≥10: the trial has ~ 79% power at a one-sided 1.011% alpha level, if the true HR is 0.65. With ~ 240 events, the HR at boundary for success at FA is ~ 0.72 (~ 6.8 months improvement over control median OS of 17.5 months).

Randomisation

Treatment allocation/randomization occurred centrally using an interactive voice response system / integrated web response system (IVRS/IWRS).

Part 1 used partial randomization with forced allocation depending on prior (neo)adjuvant treatment and disease-free interval, to stop enrollment into a specific treatment once ≥10 subjects are enrolled in that treatment.

In **Part 2** randomization was stratified for:

- chemotherapy on study (paclitaxel or nab-paclitaxel vs gemcitabine/carboplatin),
- tumor programmed cell death-ligand 1 (PD-L1) status (combined positive score [CPS]≥1 vs CPS <1),
- prior treatment with same class of chemotherapy in the (neo)adjuvant setting (yes vs no).

Blinding (masking)

Part 1 was open label.

Part 2 was double-blinded. Details regarding trial blinding/unblinding including unblinding required for operational purposes (e.g., unblinded pharmacist) were described in Protocol and Statistical analysis plan.

Statistical methods

Part 1 and part 2 were planned to be analysed separately.

Part 1:

The efficacy population were all subjects as treated (ASaT), who received at least one dose of study treatment. Patients were analysed in the treatment group correspondingly to the study treatment they actually received. The primary objective of safety and tolerability were addressed by performing descriptive summary statistics for safety endpoints by treatment. One interim analysis was planned for safety evaluation after the last subject have completed the first 21 or 28 days of study treatment, which was approximately 3 months after the first subject randomized reviewed by the DMC. Continuous safety monitoring were performed by the study team. No multiplicity correction was performed. Efficacy endpoints were secondary endpoints and analysed descriptively.

Part 2:

There are three planned interim analyses (IA) in addition to the final analysis for this study. The trial continues until the number of death is approximately equal to the targeted number for the final analysis, irrespective of the outcome from the interim analyses. The analyses planned, endpoints evaluated, and drivers of timing are summarized in the table below.

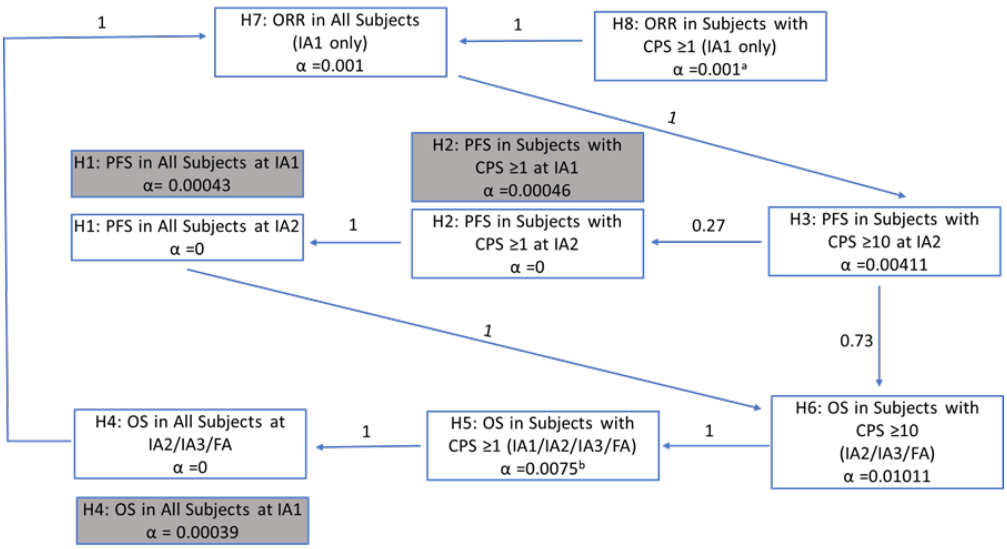
Analysis	Criteria	Endpoint	Time after last Subject Randomized	Primary Purpose of Analysis
IA1	IA1 was to be conducted when: (1) enrolment is completed, and (2) ~ 9 months after first 640 subjects are randomized in Part 2	• ORR • PFS • OS	~ 4 months (Actual LPLV: 18Oct2018)	Final ORR Interim PFS Interim OS
IA2	**IA2 was to be conducted after ~ 185 OS events among subjects with CPS ≥10 have been observed**	• **PFS** • **OS**	**~ 18 months (Actual LPLV: 11Dec2019)**	**Interim OS** **Final PFS**
IA3*	IA3 was to be conducted after ~ 210 OS events among subjects with CPS ≥10 have been observed	• OS	~24 months (Actual LPLV: 15Jun2020)	Interim OS
FA	FA will be conducted after : ~ 664 OS events among all subjects, ~ 482 OS events among subjects with CPS ≥1, and ~ 240 OS events among subjects with CPS ≥10 have been observed.	• OS	~ 31-36 months (Actual LPLV: 15Jun2021)	Final OS

IA2 was performed after approximately 185 OS events had been observed among participants with PD-L1 positive tumors (CPS≥10). A multiplicity strategy was applied to the 6 primary hypotheses (superiority of pembrolizumab + chemotherapy with respect to PFS and OS in All Participants, and in the PD-L1 positive subgroups [CPS≥1 and CPS≥10]), and the 2 secondary hypotheses of superiority of pembrolizumab + chemotherapy in ORR in All Participants and in the PD-L1 positive subgroup (CPS≥1). The family-wise Type-I error rate over the 6 primary hypotheses and 2 secondary hypotheses was strongly controlled at 2.5% (1-sided). The OS hypotheses were tested following a group sequential approach, with 3 IAs and a final analysis planned. The PFS hypotheses were tested with an interim analysis performed at IA1 and a final analysis at IA2. The ORR hypotheses were tested with a single analysis each at IA1.

Based on emerging biomarker data external to this study, the initial alpha allocation among the 6 primary hypotheses and 2 secondary hypotheses was revised in Protocol Amendment 05. The revision of the alpha

allocation occurs after the conduct of efficacy IA1. The family-wise Type-I error rate for this study was strongly controlled at 2.5% (one-sided) across all 6 primary hypotheses on PFS and OS as well as 2 secondary hypotheses on ORR. Figure below displays the revised multiplicity strategy diagram of the study. The initial one-sided alpha allocation for each hypothesis is shown in the rectangle representing the hypothesis. The weights for re-allocation from each hypothesis to the others are represented in the numbers along the lines connecting hypotheses. Overall, a total of 0.5% alpha was allocated to PFS endpoints, a total of 1.8% alpha was allocated to OS endpoints, and a total of 0.2% alpha was allocated to ORR endpoints.

Figure: multiplicity strategy (protocol 05)



a) Nominal alpha for testing will be calculated based on Spiessens and Debois method accounting for correlation between ORR in all subjects and ORR in subjects with CPS ⩾1. Of note, while the nominal alpha will be calculated and used for testing, the allocated alpha (0.001) will be passed to H7 when applicable.

b) H5 α=0.0075 which includes 0.00036 already spent at IA1. Note: The shaded boxes in this figure represent alpha that has already been spent at IA1 and will be considered lost for future analyses. These alphas will no longer be re-allocated to other hypotheses under the graphical approach, nor can they be used to account for correlation among group sequential tests within each endpoint across different time points.

The study uses the graphical method of Maurer and Bretz to control multiplicity for multiple hypotheses as well as interim analyses. According to this approach, study hypotheses may be tested more than once, and when a particular null hypothesis is rejected, the alpha allocated to that hypothesis can be reallocated to other hypothesis tests.

The boundary properties for each of these alpha-levels for the OS interim analyses were derived using a Lan-DeMets O'Brien-Fleming spending function.

Further details of statistical analyses were described in the SAP.

The Part 2 ITT population served as the population for the primary efficacy analyses. All randomly assigned participants were included in this population. The efficacy analyses in this submission were based on IA2, which was the final analysis of PFS and second interim analysis for OS. Participants enrolled in Part 1 were excluded from the efficacy analyses.

A summary of the analysis strategy for key efficacy endpoints is presented in the following table:

Endpoint/Variable (Description, Time Point)	Statistical Method[a]	Analysis Population	Missing Data Approach
Primary Hypothesis 1			
PFS based on RECIST 1.1 assessed by BICR in all participants	Test: Stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	See Table 11 of the study protocol
Primary Hypothesis 2			
PFS based on RECIST 1.1 assessed by BICR in participants with tumors that express PD-L1 with CPS ≥1	Test: Stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	See Table 11 of the study protocol
Primary Hypothesis 3			
PFS based on RECIST 1.1 assessed by BICR in participants with tumors that express PD-L1 with CPS ≥10	Test: Stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	See Table 11 of the study protocol
Primary Hypothesis 4			
OS in all participants	Test: Stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored at last known alive date
Primary Hypothesis 5			
OS in participants with tumors that express PD-L1 with CPS ≥1	Test: Stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored at last known alive date
Primary Hypothesis 6			
OS in participants with tumors that express PD-L1 with CPS ≥10	Test: Stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored at last known alive date
Key Secondary Hypothesis 1 (Hypothesis 7)			
ORR based on RECIST 1.1 assessed by BICR in all participants	Stratified M & N method[b]	The first ~ 640 participants randomized in Part 2 (a subset of ITT, IA1 only)	Participants with relevant data missing are considered non-responders.
Key Secondary Hypothesis 2 (Hypothesis 8)			
ORR based on RECIST 1.1 assessed by BICR in participants with tumors that express PD-L1 with CPS ≥1	Stratified M & N method[b]	The first ~ 640 participants randomized in Part 2 (a subset of ITT, IA1 only)	Participants with relevant data missing are considered non-responders.
Other Secondary Endpoints			
ORR based on RECIST 1.1 assessed by BICR in participants with tumors that express PD-L1 with CPS ≥10	Stratified M & N method[b]	ITT	Participants with relevant data missing are considered non-responders.
DCR based on RECIST 1.1 assessed by BICR in all participants and in participants with tumors that express PD-L1 (CPS ≥1 and CPS ≥10)	Stratified M & N method[b]	ITT	Participants with relevant data missing are considered non-responders.

Endpoint/Variable (Description, Time Point)	Statistical Method[a]	Analysis Population	Missing Data Approach
DOR based on RECIST 1.1 assessed by BICR in all participants and in participants with tumors that express PD-L1 (CPS ≥1 and CPS ≥10)	Summary statistics using Kaplan-Meier method	All responders in ITT	See Table 12 of the study protocol.

BICR=blinded independent central review; CPS=combined positive score; DCR=disease control rate; DOR=duration of response; IA1 = Interim Analysis 1; ITT=intention-to-treat; M & N=Miettinen and Nurminen; ORR=objective response rate; OS=overall survival; PD-L1=programmed cell death ligand 1; PFS=progression-free survival; RECIST 1.1= Response Evaluation Criteria in Solid Tumors version 1.1.

a. Statistical models are described in further detail in Section 8.6 of the protocol [Ref. 5.3.5.1: P355V01MK3475: 16.1.1]. For stratified analyses, the stratification factors used for randomization were used as stratification factors for analysis.

Table 11 Censoring Rules for Primary and Sensitivity Analyses of PFS

Situation	Primary Analysis	Sensitivity Analysis 1	Sensitivity Analysis 2
No PD and no death; and new anticancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment	Progressed at treatment discontinuation due to reasons other than complete response; otherwise censored at last disease assessment if still on study treatment or completed study treatment.
No PD and no death; new anticancer treatment is initiated	Censored at last disease assessment before new anticancer treatment	Censored at last disease assessment	Progressed at date of new anticancer treatment
PD or death documented after ≤1 missed disease assessment, and before new anti-cancer therapy, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death	Progressed at date of documented PD or death
PD or death documented immediately after ≥2 consecutive missed disease assessments or after new anti-cancer therapy, if any	Censored at last disease assessment prior to the earlier date of ≥2 consecutive missed disease assessment and new anti-cancer therapy, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death

Table 12 Censoring Rules for DOR

Situation	Date of Progression or Censoring	Outcome
No progression nor death, no new anti-cancer therapy initiated	Last adequate disease assessment	Censor (non-event)
No progression nor death, new anti-cancer therapy initiated	Last adequate disease assessment before new anti-cancer therapy initiated	Censor (non-event)
Death or progression immediately after ≥2 consecutive missed disease assessments or after new anti-cancer therapy, if any	Earlier date of last adequate disease assessment prior to ≥2 missed adequate disease assessments and new anti-cancer therapy, if any	Censor (non-event)
Death or progression after ≤1 missed disease assessments and before new anti-cancer therapy, if any	PD or death	End of response (Event)
A missed disease assessment includes any assessment that is not obtained or is considered inadequate for evaluation of response.		

PRO analyses were based on the PRO FAS population, defined as all randomized participants who received at least 1 dose of study intervention and had completed at least 1 PRO assessment. Participants were included in the treatment arm to which they were randomly assigned in the PRO analyses.

The safety analyses were based on the ASaT populations.

The non-parametric Kaplan-Meier method was used to estimate the PFS and OS curve in each treatment group. The treatment difference in PFS and OS was assessed by the stratified log-rank test. For PFS and OS a stratified Cox proportional hazard model with Efron's method of tie handling was used to assess the magnitude of the treatment difference between the treatment arms. The hazard ratio and its 95% confidence interval from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate was reported. The same stratification factors used for randomization were applied to both the stratified log-rank test and the stratified Cox model. The PFS and OS HRs were estimated for several subgroups based on baseline prognostic variables and demographic characteristics.

In order to evaluate the robustness of the PFS endpoint per RECIST 1.1 by a blinded independent central imaging vendor, sensitivity analyses with a different set of censoring rules was applied.

The stratified Miettinen and Nurminen method was used for the comparison of the ORR and DCR between the two treatment groups. The difference in ORR/DCR and its 95% confidence interval from the stratified Miettinen and Nurminen method with strata weighting by sample size with a single treatment covariate was reported. The stratification factors used for randomization were applied to the analysis.

If sample size permits, it was planned to summarize DOR descriptively using Kaplan-Meier medians and quartiles. Only the subset of patients who show a complete response or partial response were to be included in this analysis.

The analysis of safety results followed a tiered approach. There were no Tier 1 endpoints in this study, and Tier 2 parameters were assessed via point estimates with 95% confidence intervals (CIs) provided for between-group comparisons; only point estimates by intervention arm were provided for Tier 3 safety parameters. The 95% CIs for the between-treatment differences in percentages were provided using the Miettinen and Nurminen method.

Results

Note: Efficacy analyses to support this extension of indication are based on the Part 2 ITT population (N = 847). Participants enrolled in Part 1 (safety run-in; n=35) were excluded from the efficacy analyses. Therefore, the following sections are focused on the presentation of Part 2 results.

Participant flow (all subjects)

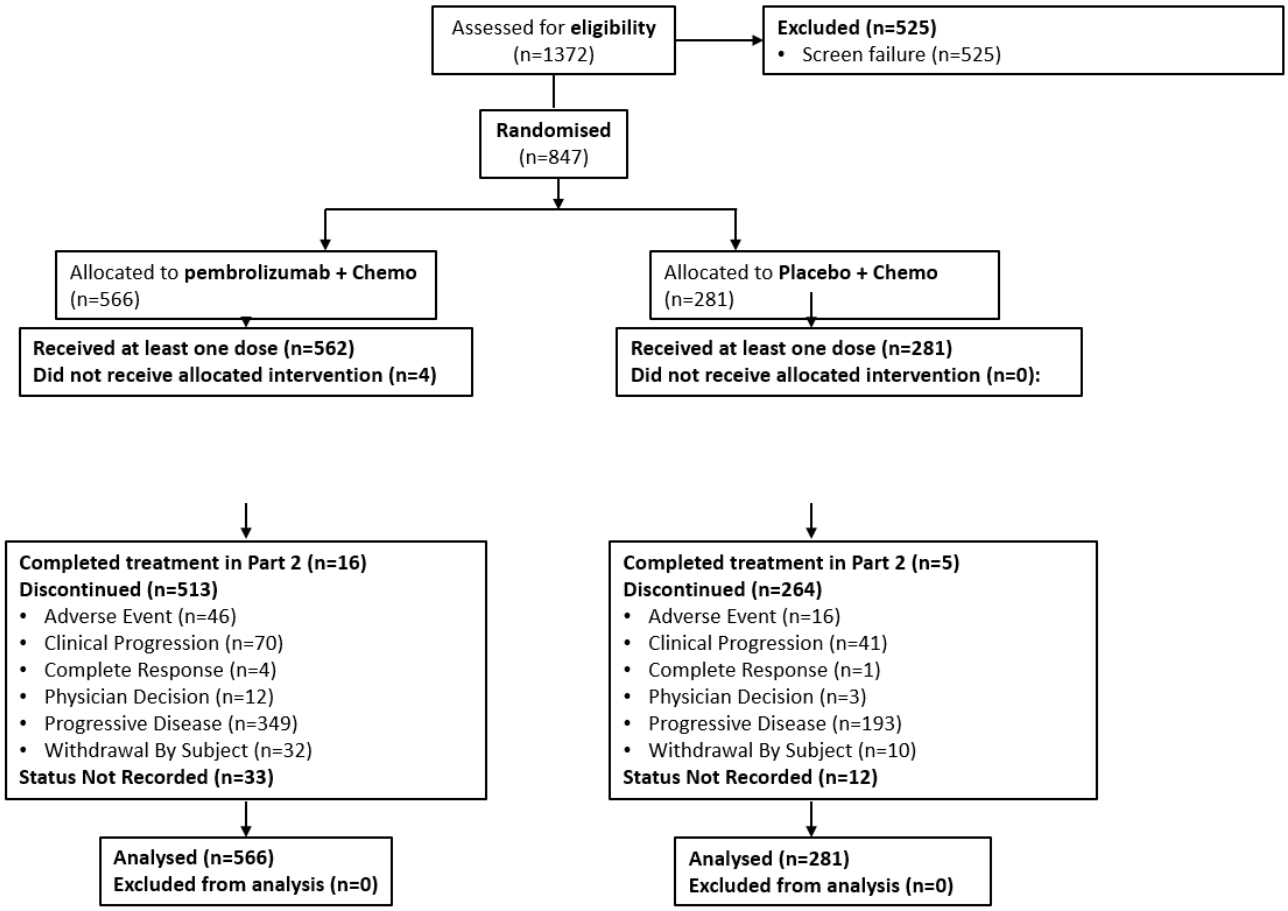


Table: Disposition of Subjects (Part 2 <u>All Subjects</u>) (ITT Population)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	566		281		847	
Status for Study Medication in Trial Segment of First Course Treatment						
Started	562		281		843	
Completed	16	(2.8)	5	(1.8)	21	(2.5)
Discontinued	513	(91.3)	264	(94.0)	777	(92.2)
Adverse Event	46	(8.2)	16	(5.7)	62	(7.4)
Clinical Progression	70	(12.5)	41	(14.6)	111	(13.2)
Complete Response	4	(0.7)	1	(0.4)	5	(0.6)
Physician Decision	12	(2.1)	3	(1.1)	15	(1.8)
Progressive Disease	349	(62.1)	193	(68.7)	542	(64.3)
Withdrawal By Subject	32	(5.7)	10	(3.6)	42	(5.0)
Status Not Recorded	33	(5.9)	12	(4.3)	45	(5.3)
Status for Trial						
Discontinued	386	(68.2)	203	(72.2)	589	(69.5)
Death	367	(64.8)	197	(70.1)	564	(66.6)
Withdrawal By Subject	19	(3.4)	6	(2.1)	25	(3.0)
Status Not Recorded	180	(31.8)	78	(27.8)	258	(30.5)
Clinical Progression and Progressive Disease are based on Investigator´s assessment and may be different from the data used in the primary analysis.						
Progressive Disease refers to disease progression based on RECIST 1.1 and does not include Clinical Progression.						

Study medication discontinuation refers to discontinuation of all study medications.

Status Not Recorded: Subjects without a completed study medication discontinuation form or without a completed study disposition form.

Database Cutoff Date: 11DEC2019

Table: Disposition of Subjects (Part 2 Subjects with PD-L1 CPS≥10) (ITT Population)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	220		103		323	
Status for Study Medication in Trial Segment of First Course Treatment						
Started	219		103		322	
Completed	14	(6.4)	2	(1.9)	16	(5.0)
Discontinued	190	(86.8)	95	(92.2)	285	(88.5)
Adverse Event	20	(9.1)	5	(4.9)	25	(7.8)
Clinical Progression	21	(9.6)	12	(11.7)	33	(10.2)
Complete Response	3	(1.4)	1	(1.0)	4	(1.2)
Physician Decision	7	(3.2)	3	(2.9)	10	(3.1)
Progressive Disease	125	(57.1)	70	(68.0)	195	(60.6)
Withdrawal By Subject	14	(6.4)	4	(3.9)	18	(5.6)
Status Not Recorded	15	(6.8)	6	(5.8)	21	(6.5)
Status for Trial						
Discontinued	128	(58.2)	72	(69.9)	200	(61.9)
Death	119	(54.1)	70	(68.0)	189	(58.5)
Withdrawal By Subject	9	(4.1)	2	(1.9)	11	(3.4)
Status Not Recorded	92	(41.8)	31	(30.1)	123	(38.1)

Clinical Progression and Progressive Disease are based on Investigator´s assessment and may be different from the data used in the primary analysis.

Progressive Disease refers to disease progression based on RECIST 1.1 and does not include Clinical Progression.

Study medication discontinuation refers to discontinuation of all study medications.

Status Not Recorded: Subjects without a completed study medication discontinuation form or without a completed study disposition form.

Database Cutoff Date: 11DEC2019

Recruitment

This study was conducted at 251 centers in 29 countries. First subject in part 2 was randomized on 9-Jan 2017, last subject randomized was on 12 Jun 2018.

A total of 525 patients were not randomized due to screen failure, the most common being not having centrally confirmed TNBC (38%) and not having measurable disease based on RECIST 1.1 as determined by local radiology review (10.5%). About 7% of subjects were not included due to ECOG ≥2 and about 6% due to symptomatic/unstable CNS disease.

A total of 847 participants were randomly assigned in a 2:1 ratio to pembrolizumab + chemotherapy (566 participants) or placebo + chemotherapy (281 participants). Enrolment in Part 2 of the study was from 09-JAN-2017 to 12-JUN-2018.

Conduct of the study

Protocol amendments: a total of 5 protocol amendments were released. Main changes are summarised below:

Original protocol (21-Apr-2016)

Amendment 1 (06-Dec-2016)

- Update of pneumonitis exclusion criterion and permanent discontinuation of subjects with Grade 2 pneumonitis
- Clarifications regarding visit schedule, review of safety labs and washout period for prior radiation therapy
- Clarification that adjuvant radiation therapy is not considered treatment with curative intent for the purpose of calculating the ≥6 month interval requirement between completion of surgery or adjuvant chemotherapy (whichever occurred last) and first disease recurrence. Therefore, a subject who was treated with adjuvant radiation therapy within the 6-month interval requirement may be eligible for study participation.

Amendment 2 (05-Feb-2018)

- Added guidelines for dose modification in the event of myocarditis and updated guidelines for several other conditions to align with the most current label and safety information for pembrolizumab.
- Clarification regarding the imaging assessments required to demonstrate stable brain metastases
- Clarification for requirements of non-emergent unblindings, imaging assessments and survival FU

Amendment 3 (31-Aug-2018)

- To allow testing of the hypotheses for ORR at IA1 independent of the outcome of the other hypotheses, the allocation of alpha was adjusted over the dual primary and key secondary endpoints.
- The timing of Interim analysis 1 (IA1) was changed from being driven by PFS events to occur ~9 months after 640 subjects were randomly assigned in Part 2 to ensure adequate follow-up time for the ORR analysis.
- Updated the censoring rules for PFS and DOR, to closely follows recent regulatory guidance (primary PFS analysis), and the "intent-to-treat complete follow-up principle" (first PFS sensitivity analysis).
- Interim analysis 2 (IA2) was changed from OS event driven (estimated ~28 months after the first subject randomized) to calendar time driven (~12 months after the last subject randomized) to allow IA2 be conducted at a pre-specified time point so that subjects will have sufficient follow-up time for analysis.
- The final analysis timing was changed from "~39.5 months after the first subject randomized" to "~23 months after the last subject randomized" to accommodate the new assumptions for the enrollment period.
- To prevent alpha over-spending at interim, alpha and beta-spending were updated to use the time spending approach.
- Power for ORR, PFS and OS have been updated to be in alignment with the updated multiplicity strategy, and to accommodate the new assumptions for the enrollment duration and the prevalence of PD-L1 positivity (from 60% to 75%) in mTNBC subjects updated based on recent available data.
- QoL evaluation has been promoted from an exploratory to a secondary objective.
- Removal of exploratory evaluation of efficacy endpoints based on irRECIST.

Amendment 4 (20-Mar-2019)

- The timing of the final analysis was changed from OS event driven to both OS event and follow-up time driven to ensure adequate follow-up duration at time of the final analysis.

- Addition of a third efficacy interim analysis (IA3) between IA2 and FA. The added IA3 also matched the timing of a periodical safety interim analysis.

Amendment 5 (04-Oct-2019)

- Data from external studies, including other indications of pembrolizumab monotherapy, demonstrated an enriched treatment effect with increasing PD-L1 expression. To identify an enriched population of subjects that could potentially benefit more from pembrolizumab plus chemotherapy in metastatic TNBC, the objectives, hypotheses, and statistical analysis plan was revised to include primary and secondary endpoints in participants with PD-L1 positive tumors with CPS≥10.
- Revised efficacy interim analyses plan, and updated multiplicity strategy to allocate initial alpha to PFS and OS in subjects with CPS≥10 to allow testing of added primary endpoints.
- Extended trial follow-up time, to ensure adequate power for the testing of OS and PFS endpoints in the smaller CPS≥10 population.
- Revised multiplicity strategy to allocate initial alpha to PFS and OS in subjects with CPS ≥10, to allow testing of added primary endpoints.
- Revised hazard ratio, trial follow-up duration, and PFS dropout rate assumptions for power calculations to reflect information from latest external data and updated statistical analysis plan and strategy. Revised power calculation based on the revised statistical analysis plan.
- Added subgroup analysis to examine different CPS cutoffs, and to align with the updated analysis strategy.

Additional information regarding protocol amendment 5 and the choice of the PD-L1 CPS≥10 cut-off:

Amendment 05 (4-Oct-2019) was initiated and finalized after efficacy IA1 had occurred (actual LPLV: 18 Oct 2018). Following review and recommendation by an independent, external DMC at IA1, the study continued to IA2. Per protocol, the Sponsor remained blinded to IA1 efficacy and safety study results, including individual treatment assignment and CPS scores. A conservative Bonferroni approach was implemented for Type-I error control in amendment 05 by eliminating alpha spent at IA1. The MAH stated that the timing of amendment 05 had no impact on the results or integrity of the study.

To minimize bias, all images for PFS (primary endpoint) evaluation were assessed by independent central reviewer who was blinded to both treatment assignment and PD-L1 status. Therefore, the MAH stated that the integrity of the study was preserved.

The MAH stated that the DMC decision, based on IA1, did not drive the decision to proceed with amendment 05. Amendment 05 was based on the totality of scientific evidence from emerging clinical data from studies in metastatic TNBC external to KEYNOTE-355, namely KEYNOTE-119 and IMpassion130, which were not fully available to the Sponsor until June 2019. Both studies demonstrated an enriched treatment effect of PD-1/L1 inhibition in a PD-L1-enriched patient population.

An enriched treatment effect in OS with increasing PD-L1 level was seen in other indications (HNSCC, urothelial carcinoma, gastric cancer). KEYNOTE-355 prospectively included the CPS cut-off ≥1 based on preliminary evidence from KEYNOTE-086 (Cohort B, 1L mTNBC CPS≥1). The addition of the additional cut-off CPS≥10 was related to data from 2 studies in the metastatic setting becoming available while KEYNOTE-355 was being conducted. KEYNOTE-119 demonstrated that pembrolizumab monotherapy provided a trend for improved OS with enrichment of tumor PD-L1 expression levels (CPS≥1 to CPS≥10) in recurrent locally advanced or metastatic TNBC tumors. In addition, as noted above, IMpassion130 demonstrated that atezolizumab + nab-paclitaxel significantly prolonged PFS in PD-L1 positive tumors,

defined as PD-L1 stained tumor-infiltrating immune cells of any intensity covering ≥1% of the tumor area by the VENTANA PD-L1 (SP142) assay. The PD-L1 IHC 22C3 pharmDx assay used in KEYNOTE-355 uses the combined score of tumor and immune cells that stain positive for PD-L1 expression. Previous studies have shown that the VENTANA PD-L1 (SP142) assay produces lower PD-L1 numerical scores compared with the PD-L1 IHC 22C3 pharmDx assay[20] [21] [22], expected based on differences in the antibodies and IHC platforms as well as intrinsic differences in the definitions of the scores (IC vs CPS) themselves; therefore, it is not possible to substitute cut-offs across assays. The prevalence of participants identified as PD-L1 positive (IC≥1%) in IMpassion130 by the VENTANA PD-L1 (SP142) assay and the prevalence of participants with tumors that express PD-L1 with CPS≥10 by the PD-L1 IHC 22C3 pharmDx assay in KEYNOTE-355 was similar between the 2 studies.

Protocol deviations:

Important protocol deviations (i.e. "those that may significantly impact the quality or integrity of key study data or that may significantly affect a participant's rights, safety, or well-being") were reported for 83 (9.8%) participants in Part 2 of the study (10.6% vs 8.2% in the pembrolizumab + chemo vs chemo arm). Seven participants received incorrect study intervention (pembrolizumab or placebo); 6 participants received the incorrect study invention for 1 cycle and 1 participant for 6 cycles.

Of the important protocol deviations, 27 (3.2%) participants had deviations that were considered to be clinically important (i.e. "deviations that may compromise critical data analyses pertaining to primary efficacy and/or safety endpoints or the participant's safety") (see table below).

Table: Summary of Important Protocol Deviations Considered to be Clinically Important (Part 2 All Subjects) (ITT Population)

[20] Buttner R, et al. Programmed death-ligand 1 immunohistochemistry testing: a review of analytical assays and clinical implementation in non-small-cell lung cancer. J Clin Oncol. 2017 Dec 1;35(34):3867-76.
[21] Hirsch FR, et al. PD-L1 immunohistochemistry assays for lung cancer: results from phase 1 of the blueprint PD-L1 IHC assay comparison project. J Thorac Oncol. 2017 Feb;12(2):208-22.
[22] Rugo HS, et al. Performance of PD-L1 immunohistochemistry (IHC) assays in unresectable locally advanced or metastatic triple negative breast cancer (mTNBC): post-hoc analysis of IMpassion130 [abstract]. Presented at: ESMO Congress; 2019 Sep 27-Oct 1; Barcelona (Spain). Ann Oncol. 2019 Oct;30(suppl 5):v858-9. Abstract no. LBA20.

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	566		281		847	
With one or more clinically important protocol deviations	20	(3.5)	7	(2.5)	27	(3.2)
With no clinically important protocol deviations	546	(96.5)	274	(97.5)	820	(96.8)
Inclusion/ Exclusion Criteria	**17**	**(3.0)**	**5**	**(1.8)**	**22**	**(2.6)**
Participants who do not have centrally confirmed TNBC, as defined by the most recent ASCO/CAP guidelines.	3	(0.5)	1	(0.4)	4	(0.5)
Participants who do not have completed treatment for Stage I-III breast cancer, if indicated, and greater than or equal to 6 months elapsed between the completion of treatment with curative intent (date of primary breast tumor surgery or date of last adjuvant chemotherapy administration, whichever occurred last) and first documented local or distant disease recurrence. Note: Subjects who received taxane, gemcitabine, or platinum agents in the (neo)adjuvant setting can only be treated with same class of chemotherapy, if greater than or equal to 12 months have elapsed between the completion of treatment with curative intent (date of primary breast tumor surgery or date of last adjuvant chemotherapy administration, whichever occurred last) and first documented local or distant disease recurrence.	11	(1.9)	3	(1.1)	14	(1.7)
Participants who do not have locally recurrent inoperable breast cancer not previously treated with chemotherapy and which cannot be treated with curative intent OR do not have metastatic breast cancer not previously treated with chemotherapy. Note: Some subjects with a history of locally recurrent breast cancer, which was previously treated with curative intent, may be eligible.	3	(0.5)	1	(0.4)	4	(0.5)
Informed Consent	**2**	**(0.4)**	**1**	**(0.4)**	**3**	**(0.4)**
Participant had no documented initial consent to enter the trial.	2	(0.4)	1	(0.4)	3	(0.4)
Safety Reporting	**1**	**(0.2)**	**1**	**(0.4)**	**2**	**(0.2)**
Participant had a reportable Safety Event and/or follow up Safety Event information that was not reported per the timelines outlined in the protocol.	1	(0.2)	1	(0.4)	2	(0.2)
Every subject is counted a single time for each applicable row and column. Database Cutoff Date: 11DEC2019						

No participant's data were excluded from the Part 2 analyses due to an important protocol deviation.

Overall, in the PD-L1 CPS ≥10 subgroup 9.6% of patients had an important protocol deviation, and 3.6% had a clinically important protocol deviation, which were similarly distributed in both treatment arms and were similar to the ITT population,

No important protocol deviations that occurred during Part 2 of the study were classified as a serious GCP compliance issue.

Premature unblinding

A total of 125 participants were prematurely unblinded during Part 2, as follows:

- Sponsor-approved non-emergency unblinding requests for discontinued participants to determine subsequent therapy in participants failing study intervention; N = 102
- Inadvertent unblinding; N = 11
- Emergency unblinding through the call centre; N = 12.

Baseline data

Note: Baseline characteristics data are presented below for the PD-L1 positive population CPS≥10 (sought indication), CPS≥1, and all patients (ITT population).

Table: Subject Characteristics (Part 2 Subjects with PD-L1 CPS≥10) (ITT Population)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	220		103		323	
Gender						
Female	220	(100.0)	103	(100.0)	323	(100.0)
Age (Years)						
< 65	178	(80.9)	79	(76.7)	257	(79.6)
>= 65	42	(19.1)	24	(23.3)	66	(20.4)
Mean	52.5		53.3		52.7	
SD	12.5		13.2		12.7	
Median	52.0		55.0		53.0	
Range	25 to 83		22 to 77		22 to 83	
Race						
American Indian Or Alaska Native	2	(0.9)	0	(0.0)	2	(0.6)
Asian	44	(20.0)	20	(19.4)	64	(19.8)
Black Or African American	9	(4.1)	6	(5.8)	15	(4.6)
Multiple	6	(2.7)	3	(2.9)	9	(2.8)
White	153	(69.5)	70	(68.0)	223	(69.0)
Missing	6	(2.7)	4	(3.9)	10	(3.1)
Ethnicity						
Hispanic Or Latino	37	(16.8)	21	(20.4)	58	(18.0)
Not Hispanic Or Latino	174	(79.1)	76	(73.8)	250	(77.4)
Not Reported	6	(2.7)	4	(3.9)	10	(3.1)
Unknown	2	(0.9)	2	(1.9)	4	(1.2)
Missing	1	(0.5)	0	(0.0)	1	(0.3)
Geographic Region						
Asia	38	(17.3)	18	(17.5)	56	(17.3)
Europe	108	(49.1)	52	(50.5)	160	(49.5)
Australia	5	(2.3)	2	(1.9)	7	(2.2)
North America	33	(15.0)	12	(11.7)	45	(13.9)
Rest of the World	36	(16.4)	19	(18.4)	55	(17.0)
Chemotherapy on Study (IVRS)						
Nab-Paclitaxel	63	(28.6)	36	(35.0)	99	(30.7)
Paclitaxel	33	(15.0)	11	(10.7)	44	(13.6)
Gemcitabine/Carboplatin	124	(56.4)	56	(54.4)	180	(55.7)
Chemotherapy on Study (Actual)						
Nab-Paclitaxel	61	(27.7)	36	(35.0)	97	(30.0)
Paclitaxel	33	(15.0)	11	(10.7)	44	(13.6)
Gemcitabine/Carboplatin	125	(56.8)	56	(54.4)	181	(56.0)
Missing	1	(0.5)	0	(0.0)	1	(0.3)

Prior Treatment with Same Class Chemotherapy in the Neoadjuvant or Adjuvant Setting (IVRS)						
Yes	46	(20.9)	19	(18.4)	65	(20.1)
No	174	(79.1)	84	(81.6)	258	(79.9)
Prior Treatment with Same Class Chemotherapy in the Neoadjuvant or Adjuvant Setting (Actual)						
Yes	44	(20.0)	17	(16.5)	61	(18.9)
No	175	(79.5)	86	(83.5)	261	(80.8)
Missing	1	(0.5)	0	(0.0)	1	(0.3)
Disease Status						
Metastatic, De Novo	68	(30.9)	35	(34.0)	103	(31.9)
Metastatic, Recurrence	144	(65.5)	62	(60.2)	206	(63.8)
Locally Recurrent Inoperable	7	(3.2)	6	(5.8)	13	(4.0)
Missing	1	(0.5)	0	(0.0)	1	(0.3)
ECOG						
0	134	(60.9)	62	(60.2)	196	(60.7)
1	86	(39.1)	41	(39.8)	127	(39.3)
HER2 Status						
0-1+ by IHC	153	(69.5)	80	(77.7)	233	(72.1)
2+ by IHC	67	(30.5)	23	(22.3)	90	(27.9)
History of Brain Metastasis						
Yes	5	(2.3)	6	(5.8)	11	(3.4)
No	215	(97.7)	97	(94.2)	312	(96.6)
Menopausal Status						
Pre-menopausal	74	(33.6)	34	(33.0)	108	(33.4)
Post-menopausal	146	(66.4)	69	(67.0)	215	(66.6)
Disease Free Interval						
de novo metastasis	68	(30.9)	35	(34.0)	103	(31.9)
< 12 months	49	(22.3)	17	(16.5)	66	(20.4)
>= 12 months	102	(46.4)	51	(49.5)	153	(47.4)
Unknown	1	(0.5)	0	(0.0)	1	(0.3)
Baseline Lactate Dehydrogenase (LDH)						
Normal	115	(52.3)	51	(49.5)	166	(51.4)
> ULN and < 2 x ULN	75	(34.1)	35	(34.0)	110	(34.1)
>= 2 x ULN	25	(11.4)	12	(11.7)	37	(11.5)
Missing	5	(2.3)	5	(4.9)	10	(3.1)
Sum of Target Lesion Size at Baseline (Central) (mm)						
Subjects with data	199		98		297	
Mean	69.2		72.4		70.2	
SD	47.6		51.4		48.9	
Median	57.0		59.5		59.0	
Range	11.0 to 290.0		15.0 to 271.0		11.0 to 290.0	
Sum of Target Lesion Size at Baseline (Investigator) (mm)						
Subjects with data	217		103		320	
Mean	77.3		78.1		77.6	
SD	59.9		47.8		56.2	
Median	60.0		66.0		60.0	
Range	10.0 to 352.0		10.0 to 237.1		10.0 to 352.0	
Database Cutoff Date: 11DEC2019						

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Subjects in Population	220		103		323	
No. of Metastatic Organ Sites						
0	7	(3.2)	6	(5.8)	13	(4.0)
1	39	(17.7)	21	(20.4)	60	(18.6)
2	76	(34.5)	35	(34.0)	111	(34.4)
≥3	97	(44.1)	41	(39.8)	138	(42.7)
Missing	1	(0.5)	0	(0.0)	1	(0.3)
Metastatic Organ Sites[†]						
Subjects with metastatic disease	212		97		309	
Bone	52	(23.6)	22	(21.4)	74	(22.9)
Brain	5	(2.3)	6	(5.8)	11	(3.4)
Breast	17	(7.7)	7	(6.8)	24	(7.4)
Chest Wall	56	(25.5)	15	(14.6)	71	(22.0)
Liver	62	(28.2)	32	(31.1)	94	(29.1)
Lung	120	(54.5)	55	(53.4)	175	(54.2)
Lymph Nodes	169	(76.8)	79	(76.7)	248	(76.8)
Other Metastasis	46	(20.9)	17	(16.5)	63	(19.5)
Visceral Disease						
Non-Visceral Only	13	(5.9)	9	(8.7)	22	(6.8)
With brain metastasis	0	(0.0)	0	(0.0)	0	(0.0)
Without brain metastasis	13	(5.9)	9	(8.7)	22	(6.8)
Any Visceral	206	(93.6)	94	(91.3)	300	(92.9)
With brain metastasis	5	(2.3)	6	(5.8)	11	(3.4)
Without brain metastasis	201	(91.4)	88	(85.4)	289	(89.5)
Missing	1	(0.5)	0	(0.0)	1	(0.3)
Prior Neoadjuvant or Adjuvant Chemotherapy						
Yes	131	(59.5)	62	(60.2)	193	(59.8)
Taxanes	107	(48.6)	50	(48.5)	157	(48.6)
Platinum	13	(5.9)	6	(5.8)	19	(5.9)
Anthracyclines	115	(52.3)	50	(48.5)	165	(51.1)
Other	118	(53.6)	55	(53.4)	173	(53.6)
No	89	(40.5)	41	(39.8)	130	(40.2)

[†] Breast, chest wall and lymph node also include locally recurrent lesions.
Database Cutoff Date: 11DEC2019.

Table: Subject Characteristics (Part 2 Subjects with PD-L1 CPS≥1) (ITT Population)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	425		211		636	
Gender						
Female	425	(100.0)	211	(100.0)	636	(100.0)
Age (Years)						
< 65	337	(79.3)	168	(79.6)	505	(79.4)
>= 65	88	(20.7)	43	(20.4)	131	(20.6)
Mean	52.8		52.6		52.8	
SD	12.9		12.8		12.9	
Median	52.0		52.0		52.0	
Range	25 to 83		22 to 77		22 to 83	
Race						
American Indian Or Alaska Native	7	(1.6)	0	(0.0)	7	(1.1)
Asian	89	(20.9)	41	(19.4)	130	(20.4)
Black Or African American	16	(3.8)	10	(4.7)	26	(4.1)
Multiple	9	(2.1)	7	(3.3)	16	(2.5)
White	291	(68.5)	146	(69.2)	437	(68.7)
Missing	13	(3.1)	7	(3.3)	20	(3.1)
Ethnicity						
Hispanic Or Latino	81	(19.1)	36	(17.1)	117	(18.4)
Not Hispanic Or Latino	324	(76.2)	163	(77.3)	487	(76.6)
Not Reported	12	(2.8)	8	(3.8)	20	(3.1)
Unknown	7	(1.6)	4	(1.9)	11	(1.7)
Missing	1	(0.2)	0	(0.0)	1	(0.2)
Geographic Region						
Asia	81	(19.1)	36	(17.1)	117	(18.4)
Europe	204	(48.0)	111	(52.6)	315	(49.5)
Australia	10	(2.4)	7	(3.3)	17	(2.7)
North America	54	(12.7)	25	(11.8)	79	(12.4)
Rest of the World	76	(17.9)	32	(15.2)	108	(17.0)
Chemotherapy on Study (IVRS)						
Nab-Paclitaxel	130	(30.6)	74	(35.1)	204	(32.1)
Paclitaxel	62	(14.6)	22	(10.4)	84	(13.2)

Gemcitabine/Carboplatin	233	(54.8)	115	(54.5)	348	(54.7)
Chemotherapy on Study (Actual)						
Nab-Paclitaxel	129	(30.4)	74	(35.1)	203	(31.9)
Paclitaxel	61	(14.4)	22	(10.4)	83	(13.1)
Gemcitabine/Carboplatin	231	(54.4)	115	(54.5)	346	(54.4)
Missing	4	(0.9)	0	(0.0)	4	(0.6)
Prior Treatment with Same Class Chemotherapy in the Neoadjuvant or Adjuvant Setting (IVRS)						
Yes	91	(21.4)	45	(21.3)	136	(21.4)
No	334	(78.6)	166	(78.7)	500	(78.6)
Prior Treatment with Same Class Chemotherapy in the Neoadjuvant or Adjuvant Setting (Actual)						
Yes	92	(21.6)	42	(19.9)	134	(21.1)
No	329	(77.4)	169	(80.1)	498	(78.3)
Missing	4	(0.9)	0	(0.0)	4	(0.6)
Disease Status						
Metastatic, De Novo	135	(31.8)	65	(30.8)	200	(31.4)
Metastatic, Recurrence	274	(64.5)	135	(64.0)	409	(64.3)
Locally Recurrent Inoperable	13	(3.1)	11	(5.2)	24	(3.8)
Missing	3	(0.7)	0	(0.0)	3	(0.5)
ECOG						
0	253	(59.5)	134	(63.5)	387	(60.8)
1	171	(40.2)	77	(36.5)	248	(39.0)
Missing	1	(0.2)	0	(0.0)	1	(0.2)
HER2 Status						
0-1+ by IHC	309	(72.7)	159	(75.4)	468	(73.6)
2+ by IHC	116	(27.3)	52	(24.6)	168	(26.4)
History of Brain Metastasis						
Yes	14	(3.3)	8	(3.8)	22	(3.5)
No	410	(96.5)	203	(96.2)	613	(96.4)
Missing	1	(0.2)	0	(0.0)	1	(0.2)
Menopausal Status						
Pre-menopausal	146	(34.4)	76	(36.0)	222	(34.9)
Post-menopausal	278	(65.4)	135	(64.0)	413	(64.9)
Missing	1	(0.2)	0	(0.0)	1	(0.2)
Disease Free Interval						
de novo metastasis	135	(31.8)	65	(30.8)	200	(31.4)
< 12 months	92	(21.6)	37	(17.5)	129	(20.3)
>= 12 months	195	(45.9)	109	(51.7)	304	(47.8)
Unknown	3	(0.7)	0	(0.0)	3	(0.5)
Baseline Lactate Dehydrogenase (LDH)						
Normal	202	(47.5)	99	(46.9)	301	(47.3)
> ULN and < 2 x ULN	142	(33.4)	75	(35.5)	217	(34.1)
>= 2 x ULN	70	(16.5)	29	(13.7)	99	(15.6)
Missing	11	(2.6)	8	(3.8)	19	(3.0)
Sum of Target Lesion Size at Baseline (Central) (mm)						
Subjects with data	394		193		587	
Mean	70.1		71.6		70.6	
SD	50.7		52.9		51.4	
Median	56.0		55.0		56.0	
Range	11.0 to 352.0		12.0 to 271.0		11.0 to 352.0	
Sum of Target Lesion Size at Baseline (Investigator) (mm)						
Subjects with data	420		211		631	
Mean	78.6		75.5		77.6	
SD	60.0		57.2		59.1	
Median	62.4		58.0		60.0	
Range	10.0 to 352.0		10.0 to 410.0		10.0 to 410.0	
Database Cutoff Date: 11DEC2019						

Table: Subject Characteristics (Part 2 <u>All Subjects</u>) (ITT Population)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	566		281		847	
Gender						
Female	566	(100.0)	281	(100.0)	847	(100.0)
Age (Years)						
< 65	443	(78.3)	224	(79.7)	667	(78.7)
>= 65	123	(21.7)	57	(20.3)	180	(21.3)
Mean	53.5		53.0		53.3	
SD	12.7		12.7		12.7	
Median	53.0		53.0		53.0	
Range	25 to 85		22 to 77		22 to 85	
Race						
American Indian Or Alaska Native	11	(1.9)	1	(0.4)	12	(1.4)
Asian	123	(21.7)	52	(18.5)	175	(20.7)
Black Or African American	20	(3.5)	17	(6.0)	37	(4.4)
Multiple	11	(1.9)	8	(2.8)	19	(2.2)
White	384	(67.8)	195	(69.4)	579	(68.4)
Missing	17	(3.0)	8	(2.8)	25	(3.0)
Ethnicity						
Hispanic Or Latino	116	(20.5)	48	(17.1)	164	(19.4)
Not Hispanic Or Latino	423	(74.7)	218	(77.6)	641	(75.7)
Not Reported	17	(3.0)	10	(3.6)	27	(3.2)
Unknown	9	(1.6)	5	(1.8)	14	(1.7)
Missing	1	(0.2)	0	(0.0)	1	(0.1)
Geographic Region						
Asia	113	(20.0)	47	(16.7)	160	(18.9)
Europe	263	(46.5)	144	(51.2)	407	(48.1)
Australia	13	(2.3)	8	(2.8)	21	(2.5)
North America	68	(12.0)	40	(14.2)	108	(12.8)
Rest of the World	109	(19.3)	42	(14.9)	151	(17.8)
Chemotherapy on Study (IVRS)						
Nab-Paclitaxel	173	(30.6)	95	(33.8)	268	(31.6)
Paclitaxel	82	(14.5)	32	(11.4)	114	(13.5)

Gemcitabine/Carboplatin	311	(54.9)	154	(54.8)	465	(54.9)
Chemotherapy on Study (Actual)						
Nab-Paclitaxel	172	(30.4)	95	(33.8)	267	(31.5)
Paclitaxel	81	(14.3)	32	(11.4)	113	(13.3)
Gemcitabine/Carboplatin	309	(54.6)	154	(54.8)	463	(54.7)
Missing	4	(0.7)	0	(0.0)	4	(0.5)
PD-L1 Status (CPS Cutoff of 1)						
PD-L1 CPS >=1	425	(75.1)	211	(75.1)	636	(75.1)
PD-L1 CPS <1	141	(24.9)	70	(24.9)	211	(24.9)
PD-L1 Status (CPS Cutoff of 5)						
PD-L1 CPS >=5	312	(55.1)	140	(49.8)	452	(53.4)
PD-L1 CPS <5	254	(44.9)	141	(50.2)	395	(46.6)
PD-L1 Status (CPS Cutoff of 10)						
PD-L1 CPS >=10	220	(38.9)	103	(36.7)	323	(38.1)
PD-L1 CPS <10	346	(61.1)	178	(63.3)	524	(61.9)
PD-L1 Status (CPS Cutoff of 15)						
PD-L1 CPS >=15	160	(28.3)	73	(26.0)	233	(27.5)
PD-L1 CPS <15	406	(71.7)	208	(74.0)	614	(72.5)
PD-L1 Status (CPS Cutoff of 20)						
PD-L1 CPS >=20	140	(24.7)	64	(22.8)	204	(24.1)
PD-L1 CPS <20	426	(75.3)	217	(77.2)	643	(75.9)
Prior Treatment with Same Class Chemotherapy in the Neoadjuvant or Adjuvant Setting (IVRS)						
Yes	124	(21.9)	62	(22.1)	186	(22.0)
No	442	(78.1)	219	(77.9)	661	(78.0)
Prior Treatment with Same Class Chemotherapy in the Neoadjuvant or Adjuvant Setting (Actual)						
Yes	124	(21.9)	56	(19.9)	180	(21.3)
No	438	(77.4)	225	(80.1)	663	(78.3)
Missing	4	(0.7)	0	(0.0)	4	(0.5)
Disease Status						
Metastatic, De Novo	167	(29.5)	84	(29.9)	251	(29.6)
Metastatic, Recurrence	383	(67.7)	185	(65.8)	568	(67.1)
Locally Recurrent Inoperable	13	(2.3)	12	(4.3)	25	(3.0)
Missing	3	(0.5)	0	(0.0)	3	(0.4)
ECOG						
0	332	(58.7)	173	(61.6)	505	(59.6)
1	232	(41.0)	108	(38.4)	340	(40.1)
2	1	(0.2)	0	(0.0)	1	(0.1)
Missing	1	(0.2)	0	(0.0)	1	(0.1)
HER2 Status						
0-1+ by IHC	414	(73.1)	214	(76.2)	628	(74.1)
2+ by IHC	152	(26.9)	67	(23.8)	219	(25.9)
History of Brain Metastasis						
Yes	19	(3.4)	9	(3.2)	28	(3.3)
No	546	(96.5)	272	(96.8)	818	(96.6)
Missing	1	(0.2)	0	(0.0)	1	(0.1)
Menopausal Status						
Pre-menopausal	178	(31.4)	92	(32.7)	270	(31.9)
Post-menopausal	387	(68.4)	189	(67.3)	576	(68.0)
Missing	1	(0.2)	0	(0.0)	1	(0.1)
Disease Free Interval						
de novo metastasis	167	(29.5)	84	(29.9)	251	(29.6)
< 12 months	126	(22.3)	50	(17.8)	176	(20.8)
>= 12 months	270	(47.7)	147	(52.3)	417	(49.2)
Unknown	3	(0.5)	0	(0.0)	3	(0.4)
Baseline Lactate Dehydrogenase (LDH)						
Normal	261	(46.1)	135	(48.0)	396	(46.8)
> ULN and < 2 x ULN	195	(34.5)	94	(33.5)	289	(34.1)
>= 2 x ULN	98	(17.3)	42	(14.9)	140	(16.5)
Missing	12	(2.1)	10	(3.6)	22	(2.6)
Sum of Target Lesion Size at Baseline (Central) (mm)						
Subjects with data	524		253		777	
Mean	70.1		70.9		70.3	
SD	52.9		53.8		53.2	

Median	55.0	54.0	55.0
Range	11.0 to 368.0	11.0 to 289.0	11.0 to 368.0
Sum of Target Lesion Size at Baseline (Investigator) (mm)			
Subjects with data	561	281	842
Mean	77.1	72.6	75.6
SD	59.3	55.4	58.0
Median	61.0	56.0	59.8
Range	10.0 to 406.8	10.0 to 410.0	10.0 to 410.0
Database Cutoff Date: 11DEC2019			

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Subjects in Population	566		281		847	
No. of Metastatic Organ Sites						
0	13	(2.3)	12	(4.3)	25	(3.0)
1	109	(19.3)	59	(21.0)	168	(19.8)
2	191	(33.7)	95	(33.8)	286	(33.8)
≥3	250	(44.2)	115	(40.9)	365	(43.1)
Missing	3	(0.5)	0	(0.0)	3	(0.4)
Metastatic Organ Sites†						
Subjects with metastatic disease	550		269		819	
Bone	169	(29.9)	85	(30.2)	254	(30.0)
Brain	17	(3.0)	9	(3.2)	26	(3.1)
Breast	35	(6.2)	18	(6.4)	53	(6.3)
Chest Wall	132	(23.3)	45	(16.0)	177	(20.9)
Liver	171	(30.2)	78	(27.8)	249	(29.4)
Lung	324	(57.2)	162	(57.7)	486	(57.4)
Lymph Nodes	417	(73.7)	206	(73.3)	623	(73.6)
Other Metastasis	110	(19.4)	51	(18.1)	161	(19.0)
Visceral Disease						
Non-Visceral Only	31	(5.5)	23	(8.2)	54	(6.4)
With brain metastasis	0	(0.0)	0	(0.0)	0	(0.0)
Without brain metastasis	31	(5.5)	23	(8.2)	54	(6.4)
Any Visceral	532	(94.0)	258	(91.8)	790	(93.3)
With brain metastasis	17	(3.0)	9	(3.2)	26	(3.1)
Without brain metastasis	515	(91.0)	249	(88.6)	764	(90.2)
Missing	3	(0.5)	0	(0.0)	3	(0.4)
Prior Neoadjuvant or Adjuvant Chemotherapy						
Yes	357	(63.1)	181	(64.4)	538	(63.5)
Taxanes	290	(51.2)	156	(55.5)	446	(52.7)
Platinum	41	(7.2)	24	(8.5)	65	(7.7)
Anthracyclines	318	(56.2)	155	(55.2)	473	(55.8)
Other	329	(58.1)	169	(60.1)	498	(58.8)
No	209	(36.9)	100	(35.6)	309	(36.5)

† Breast, chest wall and lymph node also include locally recurrent lesions.
Database Cutoff Date: 11DEC2019.

BRCA mutations: Of the 847 enrolled subjects, 100 have known BRCA mutational status assessed locally (12%), of whom 17 were BRCA positive. Most of the BRCA mutant patients have PD-L1 positive tumors. BRCA mutational status is under investigation as part of the planned exploratory biomarker research, which is due to be completed and provided in 2023.

Concomitant treatments:

The reported concomitant interventions were generally balanced between the 2 treatment groups, except for the following that were higher (≥5% point difference) in the pembrolizumab + chemotherapy group:

- Antidiarrheals, intestinal anti-inflammatory/anti-infective medications (16.9% vs 9.3%)
- Medications for constipation (30.4% vs 24.6%)

• Systemic antibacterial medications (55.2% vs 47.3%)

• Topical corticosteroids (18.1% vs 12.5%)

Subsequent anticancer treatments:

Subsequent anticancer treatments were received by 57.5% vs 66.2% of participants in the pembrolizumab + chemotherapy group vs placebo + chemotherapy group, respectively. The most common type of therapy administered in both treatment groups were antineoplastic agents, including capecitabine (29.4% vs 33.8%), carboplatin (10.7% vs 13.2%), cyclophosphamide (13.0% vs 15.3%), eribulin mesylate (13.7% vs 16%), gemcitabine (8.9% vs 12.1%), and paclitaxel (13.3% vs 12.8%). More participants in the placebo + chemotherapy group received subsequent immunotherapy, including atezolizumab (0.4% vs 2.1%), pembrolizumab (1.1% vs 4.3%) and nivolumab (0% vs 1.1%).

Numbers analysed

Efficacy analyses were based on the Part 2 ITT population (**n=847**), which included participants in the treatment arm to which they were randomly assigned, regardless of whether they received treatment. Participants enrolled in Part 1 were excluded from the efficacy analyses. According to PD-L1 expression, CPS≥1 patients were **n=636**, and CPS≥10 patients were **n=323**.

PRO analyses were based on the PRO FAS population, defined as all randomized participants who received at least 1 dose of study intervention and had completed at least 1 PRO assessment.

Outcomes and estimation

The efficacy analyses were based on IA2, which was the final analysis of PFS and the second interim analysis of OS. Data cut-off date was 11-Dec-2019, approximately 18 months after the last participant was randomized. Median follow-up duration was 16.8 months (range 0.2, 35) in the ITT population (n=847) and 19.2 months (range 0.3, 35) in the CPS≥10 population (n=323).

For the dual primary endpoints PFS and OS, PFS in the CPS≥10 population was statistically significant. OS in CPS≥10, as well as PFS and OS in CPS≥1 did not cross the prespecified efficacy boundary at IA2. PFS and OS in the ITT population were not statistically tested at the IA2 per the prespecified multiplicity strategy.

For the secondary endpoint ORR, ORR in all participants and in the CPS≥1 population were only tested at IA1 and the success criterion were not met. ORR in all the three populations was not formally tested at IA2 per the prespecified multiplicity strategy.

During the procedure, the MAH submitted the results of the final analysis for Overall Survival with data cut-off date 15-JUN-2021 (summarised at the end of this section).

PD-L1 with CPS ≥10

Table: Summary of Efficacy Results in Participants with CPS≥10 (ITT Population)

Endpoint	Pembrolizumab + Chemotherapy (N=220)	Placebo + Chemotherapy (N=103)
PFS[a]		
Number of Events (%)	136 (61.8)	79 (76.7)
Median PFS, months (95% CI)	9.7 (7.6, 11.3)	5.6 (5.3, 7.5)
HR (95% CI), p-value	0.65 (0.49, 0.86) p=0.0012	
PFS at 6 months (95% CI)	65.0 (58.1, 71.2)	46.9 (36.5, 56.6)
PFS at 9 months (95% CI)	53.0 (45.8, 59.8)	36.6 (26.9, 46.4)
PFS at 12 months (95% CI)	39.1 (32.0, 46.0)	23.0 (14.7, 32.3)
OS		
Number of Events (%)	121 (55.0)	71 (68.9)
Median OS, months (95% CI)	23.0 (18.8, 27.5)	16.1 (12.6, 18.8)
HR (95% CI), p-value	0.69 (0.51, 0.93) p=0.0066[b]	
OS at 12 months (95% CI)	70.5 (64.0, 76.1)	64.1 (54.0, 72.5)
OS at 18 months (95% CI)	58.1 (51.2, 64.3)	44.7 (34.9, 53.9)
OS at 24 months (95% CI)	49.1 (42.2, 55.7)	32.4 (23.3, 41.8)
Objective Response[c]		
ORR % (95% CI)[a]	53.2 (46.4, 59.9)	39.8 (30.3, 49.9)
ORR Difference % (95% CI), p-value	13.6 (1.9, 24.8) p=0.0115	
CR, n (%)	37 (16.8)	13 (12.6)
PR, n (%)	80 (36.4)	28 (27.2)
DCR, n (%)	143 (65.0)	56 (54.4)
DOR (months), median (range)[a, d, e]	19.3 (1.6+ – 29.8)	7.3 (1.5 – 32.5+)

Abbreviations: BICR = blinded independent central review; CI = confidence interval; CPS = combined positive score; CR = complete response, DCR = disease control rate; DOR = duration of response; HR = hazard ratio; IA2 = Interim Analysis 2; ITT = intent-to-treat; ORR = objective response rate; OS = overall survival; PD = progressive disease; PD-L1 = programmed cell death 1 ligand 1; PFS = progression-free survival; PR = partial response RECIST 1.1 = Response Evaluation Criteria in Solid Tumors version 1.1.

a. Response assessed by BICR per RECIST 1.1; only confirmed responses are included.
b. The observed p-value of p=0.0066 did not cross the prespecified efficacy boundary at IA2 (the multiplicity adjusted, one-sided nominal alpha level was 0.00472).
c. ORR was not formally tested at IA2 per the prespecified multiplicity strategy.
d. From product-limit (Kaplan-Meier) method for censored data.
e. "+" indicated there is no PD by the time of last disease assessment.

One-sided p-values based on stratified log-rank test (PFS and OS) or stratified Miettinen & Nurminen method (ORR).

Data cutoff: 11DEC2019

PFS - Dual primary endpoint

Pembrolizumab + chemotherapy demonstrated a statistically significant improvement in PFS compared with placebo + chemotherapy in participants with tumors that express PD-L1 with CPS ≥10. With about 67% of events/patients, the PFS HR was 0.65 (95%CI 0.49, 0.86), p=0.0012 [pre-specified boundary 0.00411]; median PFS was 9.7 (95%CI 7.6, 11.3) vs 5.6 (95%CI 5.3, 7.5) months in the pembrolizumab + chemotherapy vs placebo + chemotherapy, respectively.

Table: Analysis of PFS by BICR per RECIST 1.1 (Subjects with PD-L1 CPS ≥10) (ITT)

	Pembrolizumab + Chemotherapy (N=220)	Placebo + Chemotherapy (N=103)
Number of Events (%)	136 (61.8)	79 (76.7)
Kaplan-Meier Estimates (Months)[†]		
Median (95% CI)	9.7 (7.6, 11.3)	5.6 (5.3, 7.5)
[Q1, Q3]	[3.9, 31.4]	[3.6, 11.8]
Person-Months	2232.5	821.7
Event Rate / 100 Person-Months	6.1	9.6
vs Placebo + Chemotherapy		
Hazard Ratio (95% CI)[‡]	0.65 (0.49, 0.86)	
p-value[§]	0.0012	
PFS Rate at Month 3 (%) (95% CI)	81.8 (76.0, 86.4)	80.2 (71.0, 86.8)
PFS Rate at Month 6 (%) (95% CI)	65.0 (58.1, 71.2)	46.9 (36.5, 56.6)
PFS Rate at Month 9 (%) (95% CI)	53.0 (45.8, 59.8)	36.6 (26.9, 46.4)
PFS Rate at Month 12 (%) (95% CI)	39.1 (32.0, 46.0)	23.0 (14.7, 32.3)

[†] From product-limit (Kaplan-Meier) method for censored data.

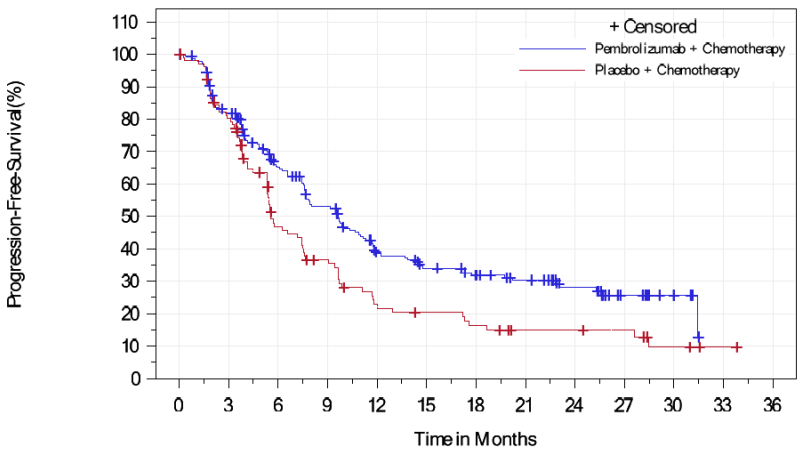
[‡] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by chemotherapy on study (taxane vs gemcitabine/carboplatin) and prior treatment with same class of chemotherapy in the (neo)adjuvant setting (yes vs no).

[§] One-sided p-value based on log-rank test stratified by chemotherapy on study (taxane vs gemcitabine/carboplatin) and prior treatment with same class of chemotherapy in the (neo)adjuvant setting (yes vs no).

BICR = Blinded Independent Central Review.

Database Cutoff Date: 11DEC2019

Kaplan-Meier Estimates of Progression-Free Survival Based on BICR Assessment per RECIST 1.1
(Part 2 Subjects with PD-L1 CPS ≥10) (ITT Population)



Number of subjects at risk

Pembrolizumab + Chemotherapy	220	173	122	96	63	52	44	37	25	12	5	0	0
Placebo + Chemotherapy	103	80	41	30	18	15	12	8	8	7	3	1	0

Database Cutoff Date: 11DEC2019

Additional analyses of PFS:

- PFS based on investigator assessment per RECIST 1.1: HR 0.71 (0.54, 0.93), median PFS 8.0 months vs. 5.6 months
- Sensitivity Analysis 1: HR 0.69 [0.53, 0.90], median PFS 9.5 months vs. 5.7 months

- Sensitivity Analysis 2: HR 0.78 [0.61, 1.0], median PFS 8.0 months vs. 5.7 months

OS – Dual Primary Endpoint

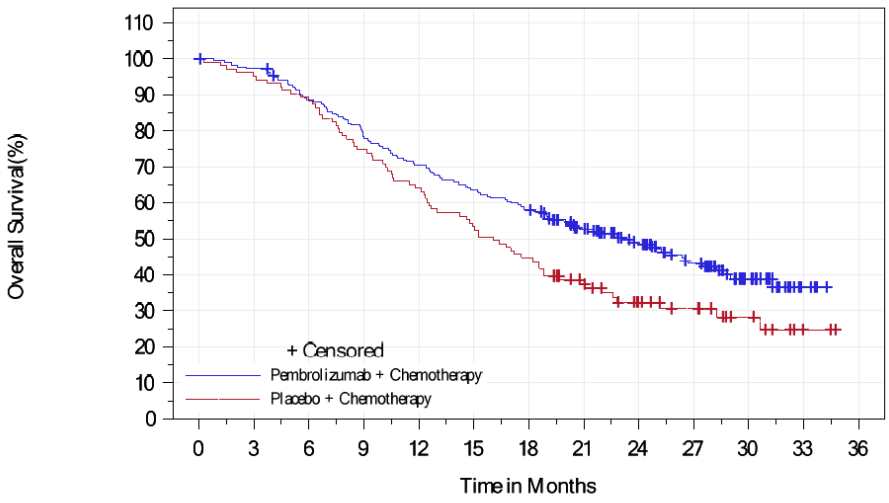
Pembrolizumab + chemotherapy showed a numerical improvement in OS compared with placebo + chemotherapy in participants with PD-L1 positive tumors (CPS≥10): HR 0.69 (95%CI 0.51, 0.93), median OS 23 months (95%CI 18.8, 27.5) vs 16.1 (95%CI 12.6, 18.8), number of events 55% vs 68.9% in the pembrolizumab + chemotherapy vs placebo + chemotherapy arm. However, the observed p-value of p=0.0066 did not cross the prespecified efficacy boundary at IA2 (the multiplicity adjusted, one-sided nominal alpha level was 0.00472).

Table: Analysis of Overall Survival (Subjects with PD-L1 CPS ≥10) (ITT Population)

	Pembrolizumab + Chemotherapy (N=220)	Placebo + Chemotherapy (N=103)
Number of Events (%)	121 (55.0)	71 (68.9)
Kaplan-Meier Estimates (Months)[†]		
Median (95% CI)	23.0 (18.8, 27.5)	16.1 (12.6, 18.8)
[Q1, Q3]	[10.3, NR]	[8.6, 30.6]
Person-Months	4074.4	1680.9
Event Rate / 100 Person-Months	3.0	4.2
vs Placebo + Chemotherapy		
Hazard Ratio (95% CI)[‡]	0.69 (0.51, 0.93)	
p-value[§]	0.0066	
OS Rate at Month 6 (%) (95% CI)	88.5 (83.5, 92.1)	88.3 (80.4, 93.2)
OS Rate at Month 12 (%) (95% CI)	70.5 (64.0, 76.1)	64.1 (54.0, 72.5)
OS Rate at Month 18 (%) (95% CI)	58.1 (51.2, 64.3)	44.7 (34.9, 53.9)
OS Rate at Month 24 (%) (95% CI)	49.1 (42.2, 55.7)	32.4 (23.3, 41.8)

[†] From product-limit (Kaplan-Meier) method for censored data.
[‡] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by chemotherapy on study (taxane vs gemcitabine/carboplatin) and prior treatment with same class of chemotherapy in the (neo)adjuvant setting (yes vs no).
[§] One-sided p-value based on log-rank test stratified by chemotherapy on study (taxane vs gemcitabine/carboplatin) and prior treatment with same class of chemotherapy in the (neo)adjuvant setting (yes vs no).
NR = Not reached.
Database Cutoff Date: 11DEC2019

Kaplan-Meier Estimates of Overall Survival (Part 2 Subjects with PD-L1 CPS ≥10) (ITT Population)



Number of subjects at risk

Pembrolizumab + Chemotherapy	220	213	192	170	153	138	126	99	76	53	26	4	0
Placebo + Chemotherapy	103	98	91	77	66	55	46	32	21	16	9	2	0

Database Cutoff Date:11DEC2019

Secondary endpoints

- **ORR**

Pembrolizumab + chemotherapy provides an improvement in ORR (per RECIST 1.1 by BICR) compared with placebo + chemotherapy (53.2% vs 39.8%) in participants with tumors that express PD-L1 with CPS ≥10 (difference 13.6% [1.9, 24.8]; p=0.0115). ORR was only tested at IA1 and not formally tested at IA2 per the prespecified multiplicity strategy, therefore the results of IA2 data may only be interpreted in exploratory manner.

Table: Summary of Best Overall Response by BICR per RECIST 1.1 (Subjects with PD-L1 CPS ≥ 10)

Response Evaluation	Pembrolizumab + Chemotherapy (N=220)			Placebo + Chemotherapy (N=103)		
	n	(%)	95% CI†	n	(%)	95% CI†
Complete Response (CR)	37	(16.8)	(12.1, 22.4)	13	(12.6)	(6.9, 20.6)
Partial Response (PR)	80	(36.4)	(30.0, 43.1)	28	(27.2)	(18.9, 36.8)
Objective Response (CR+PR)	**117**	**(53.2)**	**(46.4, 59.9)**	**41**	**(39.8)**	**(30.3, 49.9)**
Stable Disease (SD)	62	(28.2)	(22.3, 34.6)	45	(43.7)	(33.9, 53.8)
Disease Control (SD ≥ 24 Weeks+CR+PR)	**143**	**(65.0)**	**(58.3, 71.3)**	**56**	**(54.4)**	**(44.3, 64.2)**
No Evidence of Disease (NED)††	2	(0.9)	(0.1, 3.2)	0	(0.0)	(0.0, 3.5)
Progressive Disease (PD)	31	(14.1)	(9.8, 19.4)	12	(11.7)	(6.2, 19.5)
Not Evaluable (NE)‡	2	(0.9)	(0.1, 3.2)	0	(0.0)	(0.0, 3.5)
No Assessment§	6	(2.7)	(1.0, 5.8)	5	(4.9)	(1.6, 11.0)

† Based on the binomial exact confidence interval method for binomial data.
†† No Evidence of Disease (NED) includes subjects without evidence of disease at baseline and at least one post-baseline time point.
‡ Not Evaluable (NE) includes subjects with insufficient data for assessment of response per RECIST 1.1.
§ No Assessment includes subjects without post-baseline assessment on the data cutoff date.
Stable Disease (SD) includes both SD and Non-CR/Non-PD.
Confirmed responses are included.
BICR = Blinded Independent Central Review
Database Cutoff Date: 11DEC2019.

The results by Investigator assessment per RECIST 1.1 for confirmed responses were similar (ORR 53.2% vs. 34.0% in the pembrolizumab + chemotherapy group vs. the placebo + chemotherapy group; difference 19.1%); however reported ORR rates in the placebo + chemotherapy arm were numerically lower compared to the independent assessment.

- **DOR**

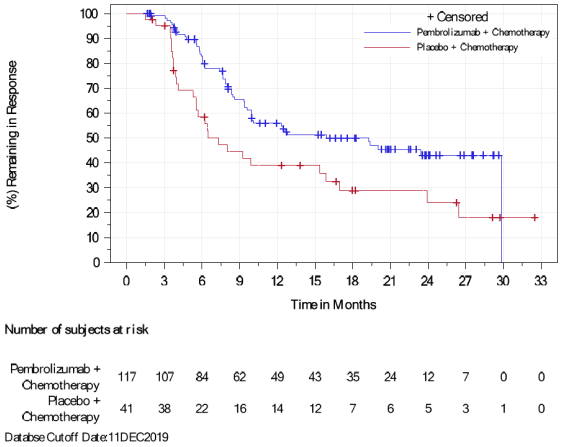
In responders with tumors that express PD-L1 with CPS ≥10, the responses in the pembrolizumab + chemotherapy group were durable relative to those observed in the placebo + chemotherapy group (median DOR, 19.3 months vs 7.3 months).

Summary of Time to Response and Duration of Response
Based on BICR Assessment per RECIST 1.1 in Subjects with Confirmed Response
(Part 2 Subjects with PD-L1 CPS ≥10)
(ITT Population)

	Pembrolizumab + Chemotherapy (N=220)	Placebo + Chemotherapy (N=103)
Number of subjects with response[†]	117	41
Time to Response (months)		
Mean (SD)	2.4 (1.5)	2.7 (1.5)
Median (Range)	1.9 (1.2-11.7)	1.9 (1.3-7.9)
Response Duration[‡] (months)		
Median (Range)	19.3 (1.6+ - 29.8)	7.3 (1.5 - 32.5+)
Number (%[‡]) of Subjects with Extended Response Duration:		
≥6 months	84 (82.8)	22 (58.5)
≥12 months	49 (55.9)	14 (39.0)

[†] Includes subjects with confirmed complete response or partial response.
[‡] From product-limit (Kaplan-Meier) method for censored data.
"+" indicates there is no progressive disease by the time of last disease assessment.
BICR = Blinded Independent Central Review.
Database Cutoff Date: 11DEC2019

Kaplan-Meier Estimates of Duration of Response in Subjects with Confirmed Response Based on BICR Assessment per RECIST 1.1 (Part 2 Subjects with PD-L1 CPS ≥10) (ITT Population)



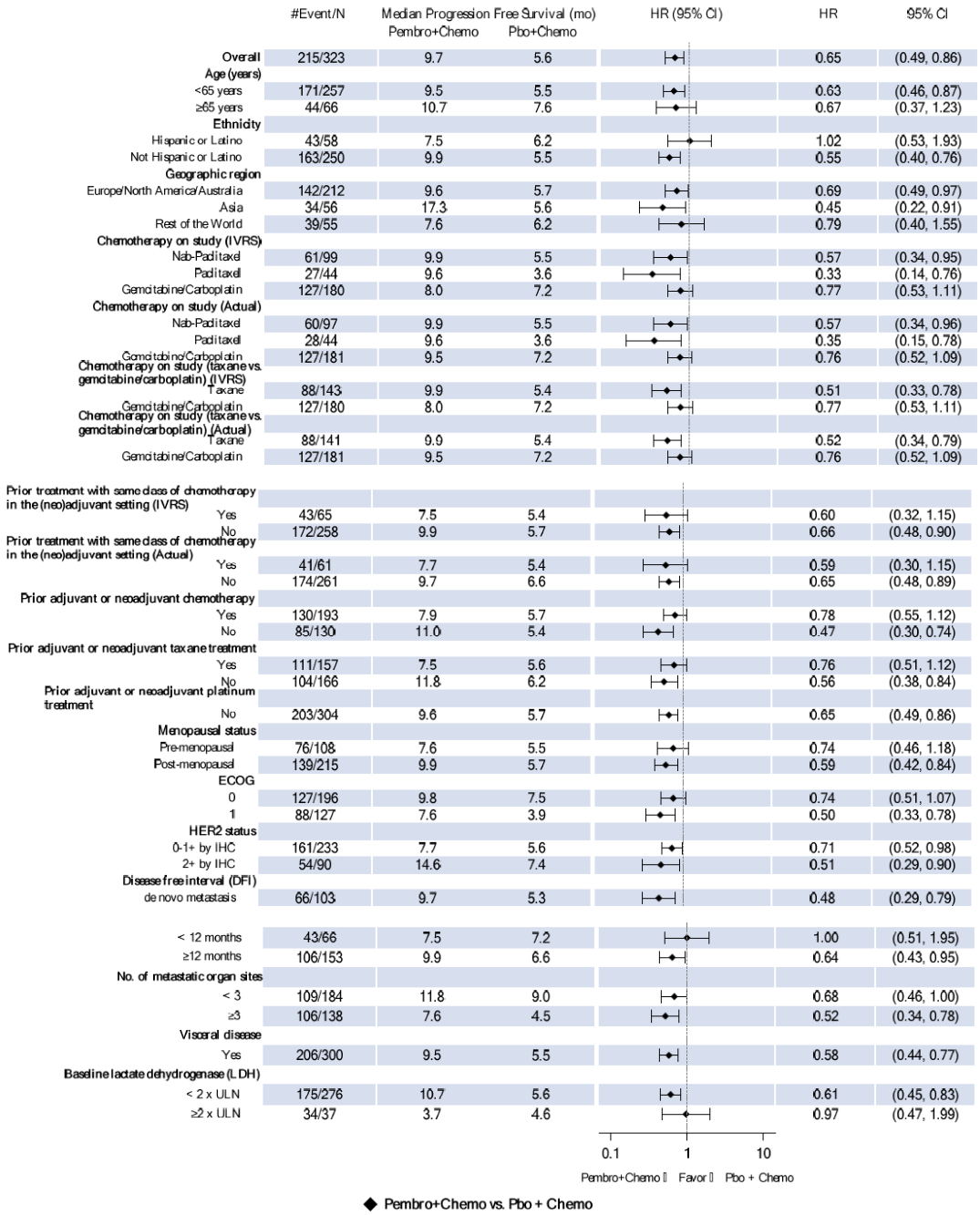
The results for DOR based on investigator assessment per RECIST 1.1 for confirmed responses in participants with PD-L1 positive tumors (CPS ≥10) showed the same trend as the primary results for DOR by BICR (median response duration 11.3 months vs. 8.0 months in the pembrolizumab + chemotherapy group vs. the placebo + chemotherapy group), but the difference between the treatment arms were smaller.

Subgroup analyses

- **PFS**

Figure: Forest Plot of PFS HR by BICR per RECIST 1.1 by Subgroup Factors (PD-L1 CPS ≥10)

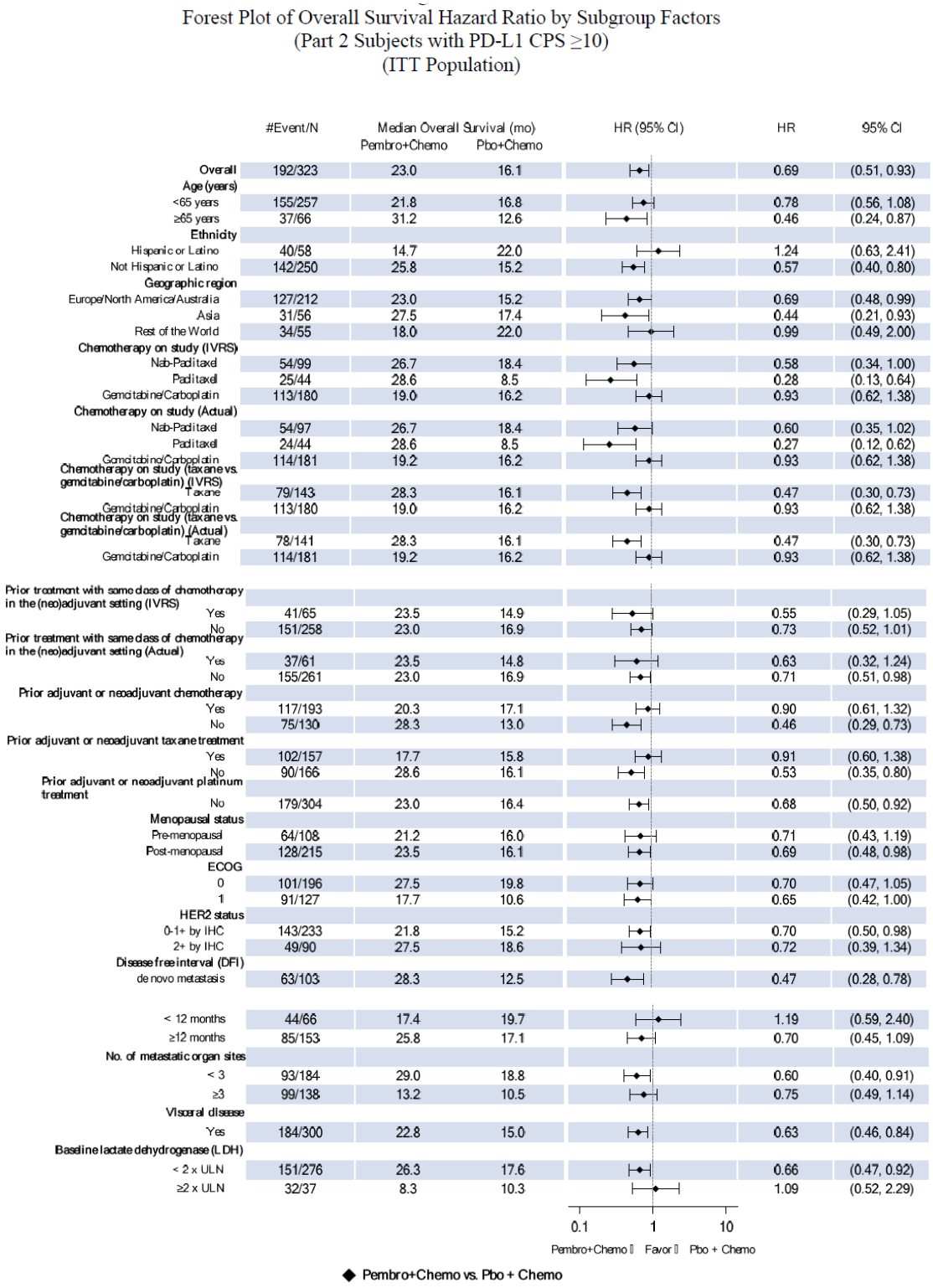
Forest Plot of Progression-Free Survival Hazard Ratio Based on BICR Assessment per RECIST 1.1 by Subgroup Factors
(Part 2 Subjects with PD-L1 CPS ≥10)
(ITT Population)



Analysis (HR and 95% CI) in the overall population is based on the stratified Cox regression model with Efron's method of tie handling stratified by chemotherapy on study (taxane vs gemcitabine/carboplatin) and prior treatment with same class of chemotherapy in the (neo)adjuvant setting (yes vs no); analysis in the subgroups is based on the unstratified Cox model. If any level of a subgroup variable has fewer than 30 subjects, subgroup analysis is not performed in that level of the subgroup variable. Database Cutoff Date: 11DEC2019

- **OS**

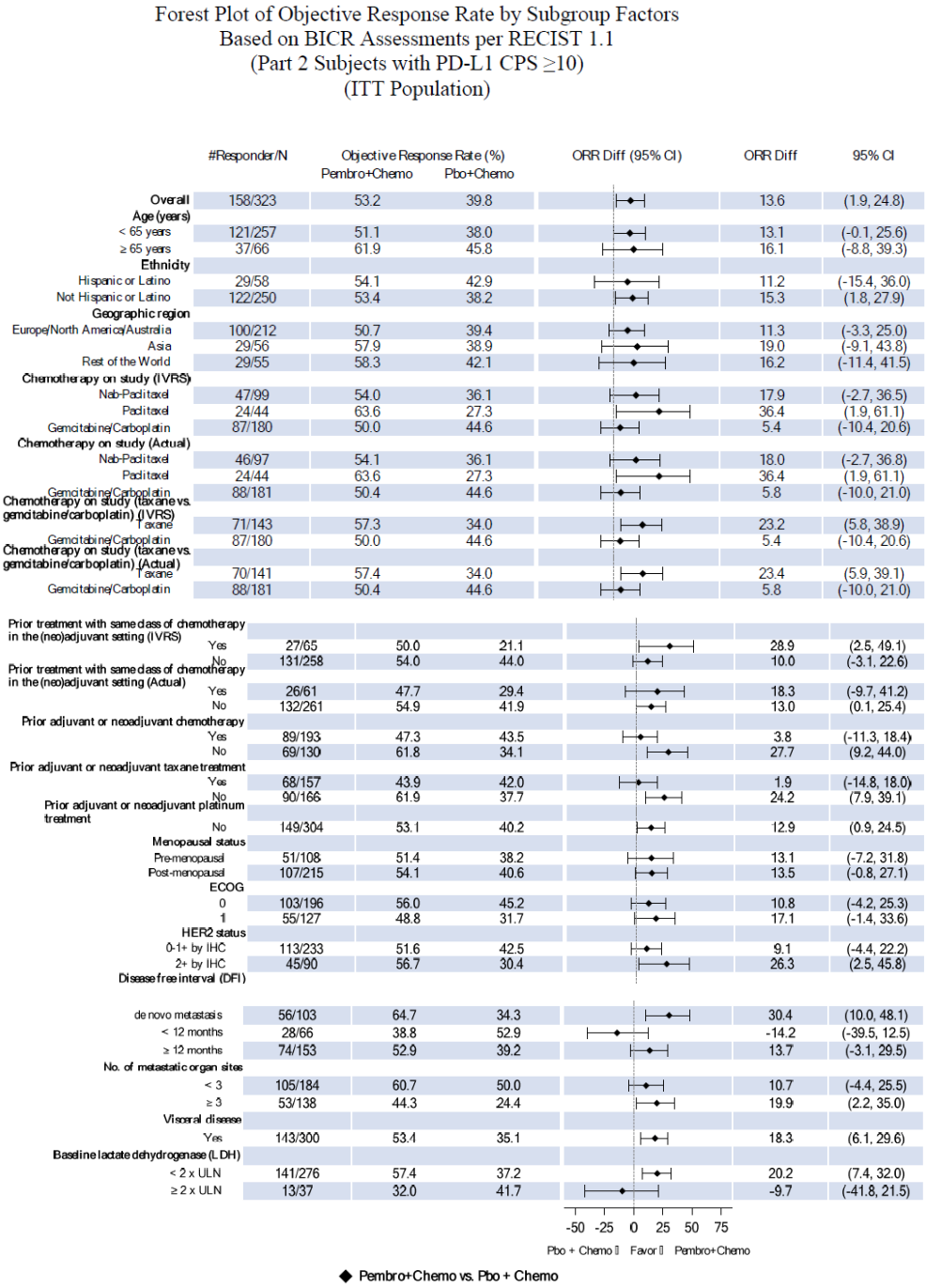
Figure: Forest Plot of OS HR by Subgroup Factors (Subjects with PD-L1 CPS ≥10) (ITT)



Analysis (HR and 95% CI) in the overall population is based on the stratified Cox regression model with Efron's method of tie handling stratified by chemotherapy on study (taxane vs gemcitabine/carboplatin) and prior treatment with same class of chemotherapy in the (neo)adjuvant setting (yes vs no); analysis in the subgroups is based on the unstratified Cox model. If any level of a subgroup variable has fewer than 30 subjects, subgroup analysis is not performed in that level of the subgroup variable. Database Cutoff Date: 11DEC2019

- **ORR**

Figure: Forest Plot of ORR by Subgroup Factors by BICR per RECIST 1.1 (PD-L1 CPS ≥10)



Analysis (ORR difference and 95% CI) in the overall population is based on the Miettinen and Nurminen method stratified by chemotherapy on study (taxane vs gemcitabine/carboplatin) and prior treatment with same class of chemotherapy in the (neo)adjuvant setting (yes vs no); analysis in the subgroups is based on the unstratified Miettinen & Nurminen method. If any level of a subgroup variable has fewer than 30 subjects, subgroup analysis is not performed in that level of the subgroup variable. Database Cutoff Date: 11DEC2019

PD-L1 with CPS ≥1

Numerical improvements in PFS, OS and ORR for pembrolizumab + chemotherapy compared with placebo + chemotherapy in the PD-L1 CPS ≥1 population were **not statistically significant**.

Table: Summary of Efficacy Results in Participants with PD-L1 CPS≥1 (ITT Population)

Endpoint	**Pembrolizumab + Chemotherapy (N=425)**	**Placebo + Chemotherapy (N=211)**
PFS[a]		
Number of Events (%)	288 (67.8)	162 (76.8)
Median PFS, months (95% CI)	7.6 (6.6, 8.0)	5.6 (5.4, 7.4)
HR (95% CI), p-value	0.74 (0.61, 0.90) p=0.0014[b]	
OS		
Number of Events (%)	273 (64.2)	155 (73.5)
Median OS, months (95% CI)	17.6 (15.5, 19.5)	16.0 (12.8, 17.4)
HR (95% CI), p-value	0.82 (0.68, 1.00) p=0.0263[c]	
Objective Response[d]		
ORR % (95% CI)[a]	45.2 (40.4, 50.0)	37.9 (31.3, 44.8)
ORR Difference % (95% CI), p-value	7.3 (-0.9, 15.2) p=0.0408	
CR, n (%)	53 (12.5)	18 (8.5)
PR, n (%)	139 (32.7)	62 (29.4)
DOR (months), median (range)[a, e, f]	10.1 (1.0+ – 29.8)	6.5 (1.5 – 32.5+)

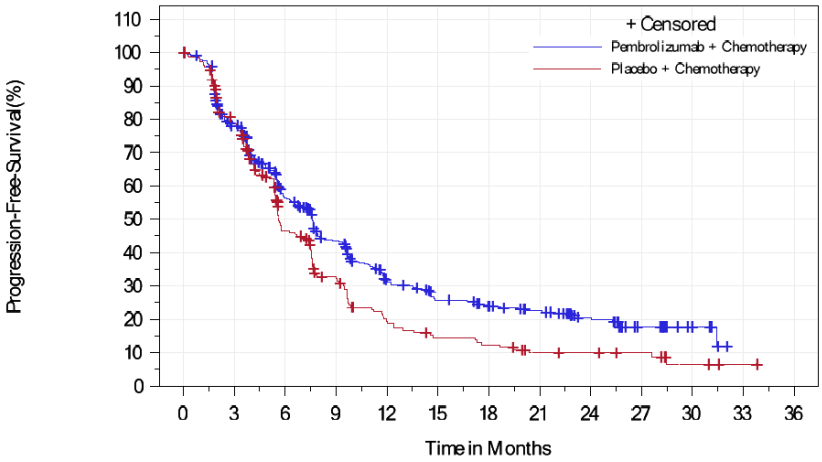
Abbreviations: BICR = blinded independent central review; CI = confidence interval; CPS = combined positive score; CR = complete response, DOR = duration of response; HR = hazard ratio; IA2 = Interim Analysis 2; ITT = intent-to-treat; ORR = objective response rate; OS = overall survival; PD = progressive disease; PD-L1 = programmed cell death 1 ligand 1; PFS = progression-free survival; PR = partial response; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors version 1.1.

a. Response assessed by BICR per RECIST 1.1; only confirmed responses are included.
b. The observed p-value of p=0.0014 did not cross the prespecified efficacy boundary at IA2 (the multiplicity adjusted, one-sided nominal alpha level was 0.00111).
c. The observed p-value of p=0.0263 did not cross the prespecified efficacy boundary at IA2 (the multiplicity adjusted, one-sided nominal alpha level was 0.00221).
d. ORR was not formally tested at IA2 per the prespecified multiplicity strategy.
e. From product-limit (Kaplan-Meier) method for censored data.
f. "+" indicated there is no PD by the time of last disease assessment.

One-sided p-values based on stratified log-rank test (PFS and OS) or stratified Miettinen & Nurminen method (ORR).

Data cutoff: 11DEC2019

Kaplan-Meier Estimates of Progression-Free Survival Based on BICR Assessment per RECIST 1.1
(Part 2 Subjects with PD-L1 CPS ≥1) (ITT Population)

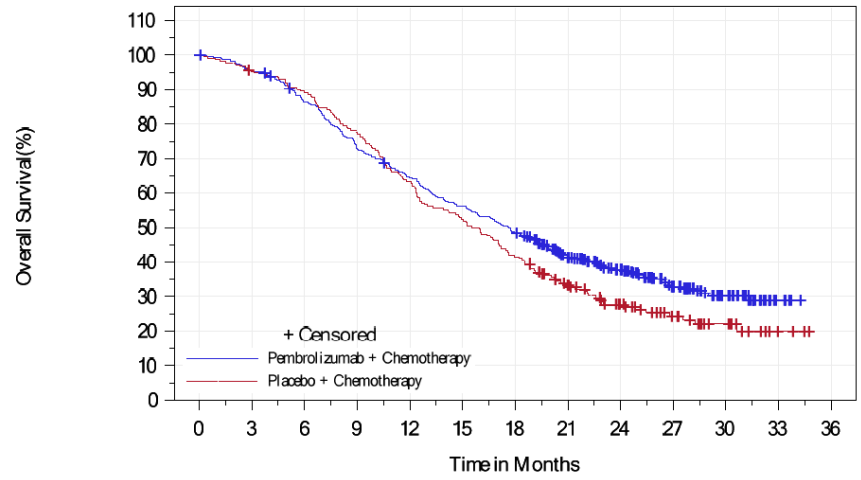


Number of subjects at risk

Pembrolizumab + Chemotherapy	425	315	202	143	94	72	60	51	32	16	6	0	0
Placebo + Chemotherapy	211	158	81	51	28	20	17	11	10	8	3	1	0

Database Cutoff Date:11DEC2019

Kaplan-Meier Estimates of Overall Survival (Part 2 Subjects with PD-L1 CPS ≥1) (ITT Population)



Number of subjects at risk

Pembrolizumab + Chemotherapy	425	405	364	307	270	235	203	148	111	68	33	5	0
Placebo + Chemotherapy	211	200	187	163	133	110	87	58	38	24	14	3	0

Database Cutoff Date:11DEC2019

All subjects

Per the multiplicity schema, the primary hypotheses pertaining to PFS and OS in All Participants were not formally tested because the success criteria for the primary hypotheses of PFS and OS in participants with tumors that express PD-L1 with CPS ≥1 were not met.

Table: Summary of Efficacy Results in All Participants (ITT Population)

Endpoint	Pembrolizumab + Chemotherapy (N=566)	Placebo + Chemotherapy (N=281)
PFS[a, b]		
Number of Events (%)	391 (69.1)	211 (75.1)
Median PFS, months (95% CI)	7.5 (6.3, 7.7)	5.6 (5.4, 7.3)
HR (95% CI), p-value	0.82 (0.69, 0.97) p=0.0112	
OS[b]		
Number of Events (%)	374 (66.1)	201 (71.5)
Median OS, months (95% CI)	17.2 (15.3, 19.0)	15.5 (13.9, 17.2)
HR (95% CI), p-value	0.87 (0.73, 1.03) p=0.0579	
Objective Response		
ORR % (95% CI)[a, c]	41.0 (36.9, 45.2)	35.9 (30.3, 41.9)
ORR Difference % (95% CI), p-value	5.1 (–1.9, 11.8) p=0.0768	
CR, n (%)	60 (10.6)	20 (7.1)
PR, n (%)	172 (30.4)	81 (28.8)
DOR (months), median (range)[a, d, e]	10.1 (1.0+ – 29.8)	6.4 (1.5 – 32.5+)

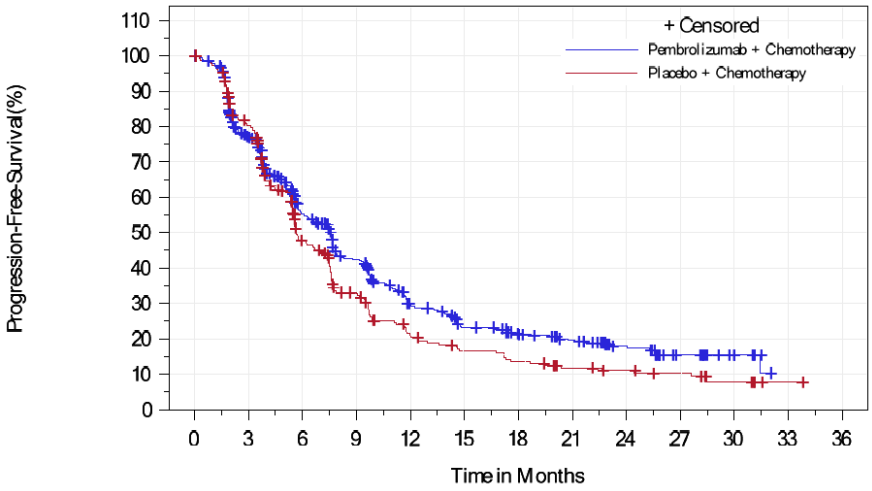
Abbreviations: BICR = blinded independent central review; CI = confidence interval; CPS = combined positive score; CR = complete response, DOR = duration of response; HR = hazard ratio; IA2 = Interim Analysis 2; ITT = intent-to-treat; ORR = objective response rate; OS = overall survival; PD = progressive disease; PD-L1 = programmed cell death 1 ligand 1; PFS = progression-free survival; PR = partial response; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors version 1.1.

a. Response assessed by BICR per RECIST 1.1; only confirmed responses are included.
b. Per the prespecified multiplicity strategy, the primary hypotheses pertaining to PFS and OS in All Participants were not formally tested because the success criterion for the primary hypotheses of PFS and OS in participants with tumors that express PD-L1 with CPS ≥1 were not met.
c. ORR was not formally tested at IA2 per the prespecified multiplicity strategy.
d. From product-limit (Kaplan-Meier) method for censored data.
e. "+" indicated there is no PD by the time of last disease assessment.

One-sided p-values based on stratified log-rank test (PFS and OS) or stratified Miettinen & Nurminen method (ORR).

Data cutoff: 11DEC2019

Kaplan-Meier Estimates of Progression-Free Survival Based on BICR Assessment per RECIST 1.1
(Part 2 All Subjects) (ITT Population)

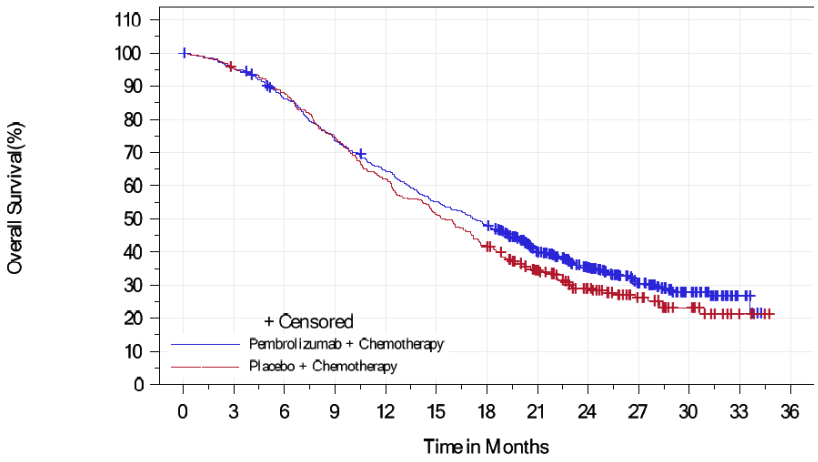


Number of subjects at risk

Pembrolizumab + Chemotherapy	566	408	260	184	118	86	70	57	32	16	6	0	0
Placebo + Chemotherapy	281	214	108	68	39	29	24	17	14	11	5	1	0

Database Cutoff Date:11DEC2019

Kaplan-Meier Estimates of Overall Survival (Part 2 All Subjects) (ITT Population)



Number of subjects at risk

Pembrolizumab + Chemotherapy	566	538	484	413	361	308	268	191	132	76	36	7	0
Placebo + Chemotherapy	281	267	246	209	174	144	116	78	50	30	16	4	0

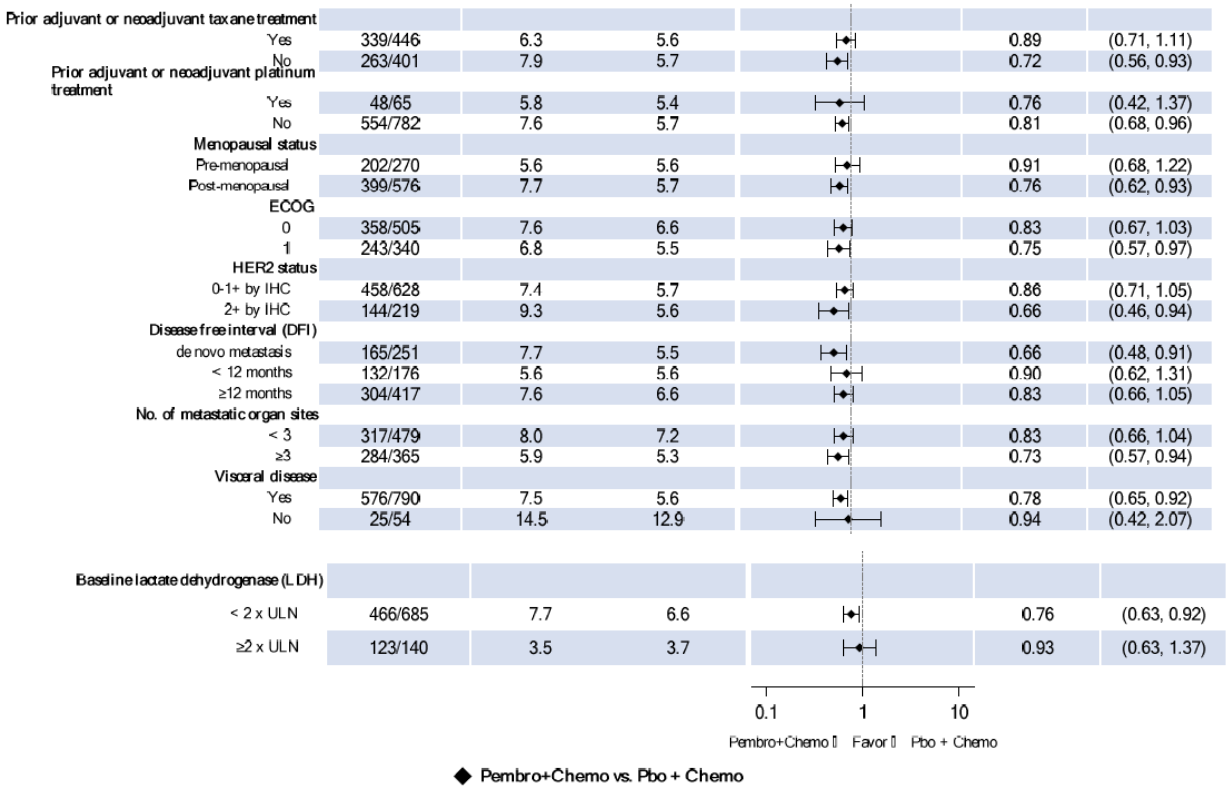
Database Cutoff Date:11DEC2019

Subgroup analyses for all participants

Figures: forest plot of PFS based on BICR assessment per RECIST 1.1 by subgroup factors

Forest Plot of Progression-Free Survival Hazard Ratio Based on BICR Assessment per RECIST 1.1 by Subgroup Factors
(Part 2 All Subjects)
(ITT Population)

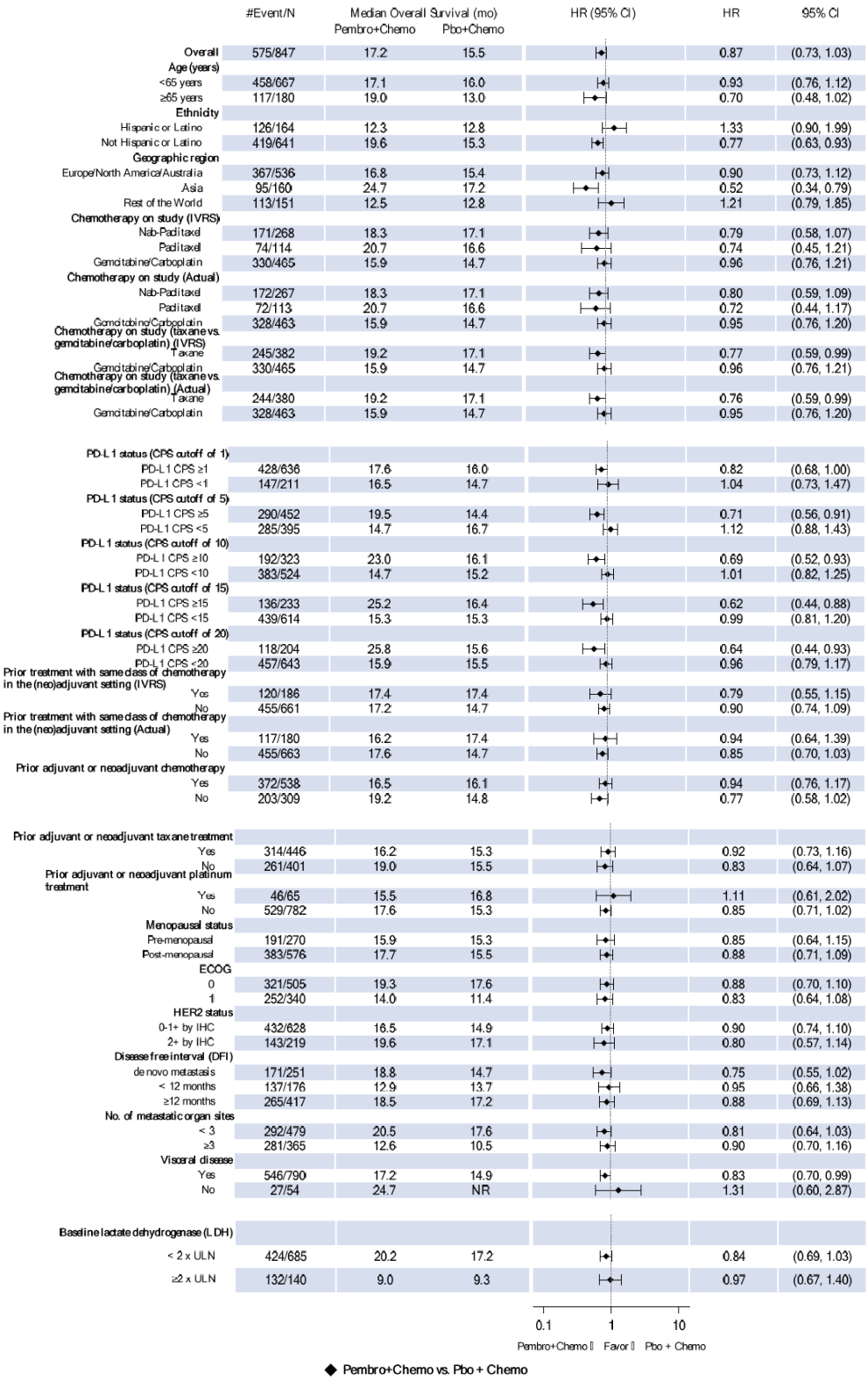
	#Event/N	Median Progression Free Survival (mo) Pembro+Chemo	Pbo+Chemo	HR (95% CI)	HR	95% CI
Overall	602/847	7.5	5.6		0.82	(0.69, 0.97)
Age (years)						
<65 years	485/667	7.3	5.6		0.83	(0.69, 1.00)
≥65 years	117/180	9.2	6.2		0.72	(0.49, 1.05)
Ethnicity						
Hispanic or Latino	125/164	5.6	5.6		1.25	(0.83, 1.87)
Not Hispanic or Latino	448/641	7.7	5.6		0.70	(0.58, 0.85)
Geographic region						
Europe/North America/Australia	376/536	7.5	5.7		0.83	(0.67, 1.02)
Asia	111/160	8.8	6.7		0.61	(0.41, 0.90)
Rest of the World	115/151	5.8	5.4		1.01	(0.67, 1.54)
Chemotherapy on study (IVRS)						
Nab-Paclitaxel	182/268	7.5	5.4		0.69	(0.51, 0.93)
Paclitaxel	76/114	8.0	3.8		0.57	(0.35, 0.93)
Gemcitabine/Carboplatin	344/465	7.4	7.4		0.93	(0.74, 1.16)
Chemotherapy on study (Actual)						
Nab-Paclitaxel	182/267	7.5	5.4		0.69	(0.51, 0.93)
Paclitaxel	76/113	8.0	3.8		0.58	(0.35, 0.94)
Gemcitabine/Carboplatin	343/463	7.4	7.4		0.92	(0.73, 1.15)
Chemotherapy on study (taxane vs. gemcitabine/carboplatin) (IVRS)						
Taxane	258/382	7.6	5.3		0.66	(0.51, 0.86)
Gemcitabine/Carboplatin	344/465	7.4	7.4		0.93	(0.74, 1.16)
Chemotherapy on study (taxane vs. gemcitabine/carboplatin) (Actual)						
Taxane	258/380	7.6	5.3		0.67	(0.52, 0.86)
Gemcitabine/Carboplatin	343/463	7.4	7.4		0.92	(0.73, 1.15)
PD-L1 status (CPS cutoff of 1)						
PD-L1 CPS ≥1	450/636	7.6	5.6		0.74	(0.61, 0.89)
PD-L1 CPS <1	152/211	6.3	6.2		1.08	(0.77, 1.53)
PD-L1 status (CPS cutoff of 5)						
PD-L1 CPS ≥5	311/452	7.7	5.6		0.73	(0.57, 0.92)
PD-L1 CPS <5	291/395	6.1	5.7		0.93	(0.73, 1.19)
PD-L1 status (CPS cutoff of 10)						
PD-L1 CPS ≥10	215/323	9.7	5.6		0.65	(0.49, 0.86)
PD-L1 CPS <10	387/524	5.8	5.7		0.94	(0.76, 1.16)
PD-L1 status (CPS cutoff of 15)						
PD-L1 CPS ≥15	159/233	9.6	5.4		0.60	(0.43, 0.83)
PD-L1 CPS <15	443/614	6.6	5.8		0.92	(0.75, 1.11)
PD-L1 status (CPS cutoff of 20)						
PD-L1 CPS ≥20	135/204	9.5	5.4		0.61	(0.43, 0.87)
PD-L1 CPS <20	467/643	6.6	5.8		0.89	(0.73, 1.07)
Prior treatment with same class of chemotherapy in the (neo)adjuvant setting (IVRS)						
Yes	137/186	7.5	5.4		0.56	(0.39, 0.80)
No	465/661	7.6	6.6		0.89	(0.73, 1.07)
Prior treatment with same class of chemotherapy in the (neo)adjuvant setting (Actual)						
Yes	133/180	6.3	5.4		0.67	(0.47, 0.96)
No	468/663	7.6	6.6		0.83	(0.69, 1.01)
Prior adjuvant or neoadjuvant chemotherapy						
Yes	402/538	6.3	5.7		0.92	(0.75, 1.13)
No	200/309	8.0	5.5		0.62	(0.47, 0.83)



Analysis (HR and 95% CI) in the overall population is based on the stratified Cox regression model with Efron's method of tie handling stratified by chemotherapy on study (taxane vs gemcitabine/carboplatin), tumor PD-L1 status (CPS ≥1 vs CPS <1) and prior treatment with same class of chemotherapy in the (neo)adjuvant setting (yes vs no); analysis in the subgroups is based on the unstratified Cox model. If any level of a subgroup variable has fewer than 30 subjects, subgroup analysis is not performed in that level of the subgroup variable. Database Cutoff Date: 11DEC2019

Figures: forest plot of <u>OS</u> by subgroup factors

Forest Plot of Overall Survival Hazard Ratio by Subgroup Factors
(Part 2 All Subjects)
(ITT Population)



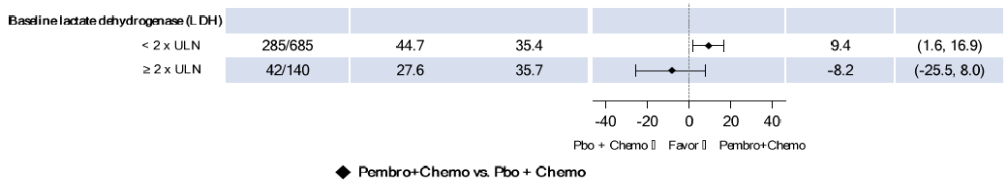
Analysis (HR and 95% CI) in the overall population is based on the stratified Cox regression model with Efron's method of tie handling stratified by chemotherapy on study (taxane vs gemcitabine/carboplatin), tumor PD-L1 status (CPS ≥1 vs CPS <1) and prior treatment with same class of chemotherapy in the (neo)adjuvant setting (yes vs no); analysis in the subgroups is based on the unstratified Cox

model. If any level of a subgroup variable has fewer than 30 subjects, subgroup analysis is not performed in that level of the subgroup variable. Database Cutoff Date: 11DEC2019

Figures: forest plot of ORR based on BICR per RECIST 1.1 by subgroup factors

Forest Plot of Objective Response Rate by Subgroup Factors
Based on BICR Assessments per RECIST 1.1
(Part 2 All Subjects)
(ITT Population)

	#Responder/N	Objective Response Rate (%) Pembro+Chemo	Objective Response Rate (%) Pbo+Chemo	ORR Diff (95% CI)	ORR Diff	95% CI
Overall	333/847	41.0	35.9		5.1	(-1.9, 11.8)
Age (years)						
< 65 years	259/667	40.0	36.6		3.3	(-4.5, 11.0)
≥ 65 years	74/180	44.7	33.3		11.4	(-4.2, 25.7)
Ethnicity						
Hispanic or Latino	56/164	31.9	39.6		-7.7	(-24.1, 7.9)
Not Hispanic or Latino	259/641	43.5	34.4		9.1	(1.1, 16.8)
Geographic region						
Europe/North America/Australia	204/536	40.4	33.9		6.6	(-2.1, 14.8)
Asia	76/160	48.7	44.7		4.0	(-12.9, 20.4)
Rest of the World	53/151	34.9	35.7		-0.9	(-18.3, 15.2)
Chemotherapy on study (IVRS)						
Nab-Paclitaxel	97/268	40.5	28.4		12.0	(-0.0, 23.2)
Paclitaxel	46/114	45.1	28.1		17.0	(-3.2, 34.2)
Gemcitabine/Carboplatin	190/465	40.2	42.2		-2.0	(-11.6, 7.4)
Chemotherapy on study (Actual)						
Nab-Paclitaxel	96/267	40.1	28.4		11.7	(-0.4, 22.9)
Paclitaxel	46/113	45.7	28.1		17.6	(-2.7, 34.8)
Gemcitabine/Carboplatin	191/463	40.8	42.2		-1.4	(-11.0, 8.0)
Chemotherapy on study (taxane vs. gemcitabine/carboplatin) (IVRS)						
Taxane	143/382	42.0	28.3		13.6	(3.4, 23.1)
Gemcitabine/Carboplatin	190/465	40.2	42.2		-2.0	(-11.6, 7.4)
Chemotherapy on study (taxane vs. gemcitabine/carboplatin) (Actual)						
Taxane	142/380	41.9	28.3		13.6	(3.3, 23.1)
Gemcitabine/Carboplatin	191/463	40.8	42.2		-1.4	(-11.0, 8.0)
PD-L1 status (CPS cutoff of 1)						
PD-L1 CPS ≥1	272/636	45.2	37.9		7.3	(-0.9, 15.2)
PD-L1 CPS <1	61/211	28.4	30.0		-1.6	(-15.2, 10.9)
PD-L1 status (CPS cutoff of 5)						
PD-L1 CPS ≥5	205/452	47.1	41.4		5.7	(-4.3, 15.3)
PD-L1 CPS <5	128/395	33.5	30.5		3.0	(-6.8, 12.3)
PD-L1 status (CPS cutoff of 10)						
PD-L1 CPS ≥10	158/323	53.2	39.8		13.4	(1.7, 24.6)
PD-L1 CPS <10	175/524	33.2	33.7		-0.5	(-9.2, 7.9)
PD-L1 status (CPS cutoff of 15)						
PD-L1 CPS ≥15	107/233	52.5	31.5		21.0	(7.3, 33.4)
PD-L1 CPS <15	226/614	36.5	37.5		-1.0	(-9.2, 6.9)
PD-L1 status (CPS cutoff of 20)						
PD-L1 CPS ≥20	95/204	52.9	32.8		20.0	(5.3, 33.4)
PD-L1 CPS <20	238/643	37.1	36.9		0.2	(-7.8, 8.0)
Prior treatment with same class of chemotherapy in the (neo)adjuvant setting (IVRS)						
Yes	70/186	43.5	25.8		17.7	(3.0, 30.9)
No	263/661	40.3	38.8		1.5	(-6.5, 9.2)
Prior treatment with same class of chemotherapy in the (neo)adjuvant setting (Actual)						
Yes	66/180	40.3	28.6		11.8	(-3.6, 25.5)
No	267/663	41.6	37.8		3.8	(-4.2, 11.5)
Prior adjuvant or neoadjuvant chemotherapy						
Yes	201/538	37.3	37.6		-0.3	(-9.1, 8.2)
No	132/309	47.4	33.0		14.4	(2.6, 25.3)
Prior adjuvant or neoadjuvant taxane treatment						
Yes	170/446	39.0	36.5		2.4	(-7.1, 11.7)
No	163/401	43.1	35.2		7.9	(-2.5, 17.8)
Prior adjuvant or neoadjuvant platinum treatment						
Yes	23/65	36.6	33.3		3.3	(-21.3, 25.8)
No	310/782	41.3	36.2		5.1	(-2.2, 12.2)
Menopausal status						
Pre-menopausal	105/270	38.8	39.1		-0.4	(-12.8, 11.6)
Post-menopausal	228/576	42.1	34.4		7.7	(-0.8, 15.9)
ECOG						
0	202/505	41.9	36.4		5.5	(-3.6, 14.2)
1	130/340	39.7	35.2		4.5	(-6.7, 15.1)
HER2 status						
0-1+ by IHC	242/628	38.9	37.9		1.0	(-7.1, 8.9)
2+ by IHC	91/219	46.7	29.9		16.9	(2.7, 29.6)
Disease free interval (DFI)						
de novo metastasis	106/251	46.1	34.5		11.6	(-1.4, 23.8)
< 12 months	56/176	31.7	32.0		-0.3	(-16.1, 14.1)
≥ 12 months	171/417	42.6	38.1		4.5	(-5.4, 14.1)
No. of metastatic organ sites						
< 3	213/479	47.6	38.6		9.0	(-0.3, 18.1)
≥ 3	120/365	33.2	32.2		1.0	(-9.6, 11.0)
Visceral disease						
Yes	315/790	41.7	36.0		5.7	(-1.6, 12.8)
No	18/54	32.3	34.8		-2.5	(-28.0, 22.2)



Analysis (ORR difference and 95% CI) in the overall population is based on the Miettinen and Nurminen method stratified by chemotherapy on study (taxane vs gemcitabine/carboplatin), tumor PD-L1 status (CPS ≥1 vs CPS <1) and prior treatment with same class of chemotherapy in the (neo)adjuvant setting (yes vs no); analysis in the subgroups is based on the unstratified Miettinen & Nurminen method. If any level of a subgroup variable has fewer than 30 subjects, subgroup analysis is not performed in that level of the subgroup variable. Database Cutoff Date: 11DEC2019

A tabular summary of the overall data presented by the MAH according to PD-L1 expression at various cut-offs is presented below:

Endpoint	CPS	Number of subjects		Median (95%CI, months)		HR (95%CI)
		Pembro	Placebo	Pembro	Placebo	
PFS	≥ 20	140	64	9.5 (7.6, 11.8)	5.4 (3.9, 7.2)	0.61 (0.43, 0.87)
	≥ 15	160	73	9.6	5.4	0.60 (0.43, 0.83)
	≥ 10	220	103	9.7 (7.6, 11.3)	5.6 (5.3, 7.5)	0.65 (0.49, 0.86)
	≥ 5	312	140	7.7	5.6	0.73 (0.57, 0.92)
	≥ 1	425	211	7.6 (6.6, 8.0)	5.6 (5.4, 7.4)	0.74 (0.61, 0.90)
	< 1	141	70	6.3	6.2	1.08 (0.77, 1.53)
	< 5	254	141	6.1	5.7	0.93 (0.73, 1.19)
	< 10	346	178	5.8	5.7	0.94 (0.76, 1.16)
	< 15	406	208	6.6	5.8	0.92 (0.75, 1.11)
	< 20	426	217	6.6 (5.7, 7.6)	5.8 (5.5, 7.5)	0.89 (0.73, 1.07)
	ALL	566	281	7.5 (6.3, 7.7)	5.6 (5.4, 7.3)	0.82 (0.69, 0.97)
OS	≥ 20	140	64	25.8 (18.8, 31.2)	15.6 (12.3, 20.8)	0.64 (0.44, 0.93)
	≥ 15	160	73	25.2	16.4	0.62 (0.44, 0.88)
	≥ 10	220	103	23.0 (18.8, 27.5)	16.1 (12.6, 18.8)	0.69 (0.51, 0.93)
	≥ 5	312	140	19.5	14.4	0.71 (0.56, 0.91)
	≥ 1	425	211	17.6 (15.5, 19.5)	16.0 (12.8, 17.4)	0.82 (0.68, 1.00)
	< 1	141	70	16.5	14.7	1.04 (0.73, 1.47)
	< 5	254	141	14.7	16.7	1.12 (0.88, 1.43)
	<10	346	178	14.7	15.2	1.01 (0.82, 1.25)
	<15	406	208	15.3	15.3	0.99 (0.81, 1.20)
	<20	426	217	15.9 (14.0, 17.7)	15.5 (12.6, 17.6)	0.96 (0.79, 1.17)

	ALL	566	281	17.2 (15.3, 19.0)	15.5 (13.9, 17.2)	0.87 (0.73, 1.03)

The analyses of PFS and OS with CPS as a continuous score (after square root transformation) in a Cox regression model using IA1 data suggest that CPS score is a strong predictive factor in the pembrolizumab + chemotherapy group, while there is no evidence suggesting CPS affects the efficacy in the placebo + chemotherapy group (tables not shown).

Ancillary analyses

Patients reported outcomes

Completion rates of the EORTC QLQ-C30 were above 93% in both the pembrolizumab + chemotherapy and placebo + chemotherapy groups at baseline among participants with PD-L1 positive tumors (CPS≥10 and CPS≥1) and in All Participants, and remained high at Week 15 (between 70 and 77%).

Compliance rates of the EORTC QLQ-C30, defined as the percentage of participants completing the measure among those expected to complete the measure (i.e. not missing by design) were similar at baseline in both arms among participants with CPS≥10 and CPS≥1 and in All Participants (above 93%) and remained high at Week 15 (between 81% and 88%). In the PD-L1 CPS≥10 population, at week 51 compliance rate was approximately 90% in both arms.

Similar rates of completion and compliance were observed for the EORTC QLQ-BR23 and EQ-5D.

The time frame of 15 weeks for the change from baseline analysis was selected based on a prespecified required minimum completion rate of 60% and compliance rate of 80% to minimize the impact of missing data.

EORTC QLQ-C30 Analysis

- Change from Baseline

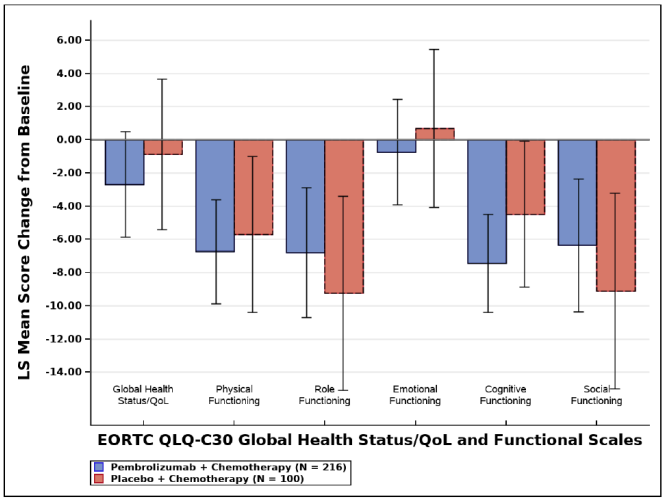
Baseline EORTC QLQ-C30 global health status/QoL scores were similar between the 2 treatment groups among participants with PD-L1 positive tumors (CPS ≥10 and CPS ≥1) and in All Participants. Over 15 weeks of follow-up, there was either no decrease or a similar decrease in the pre-specified global health status/QoL, Physical Functioning and Emotional Functioning scores observed for both treatment groups.

Analysis of Change from Baseline in EORTC QLQ-C30 Global Health Status/QoL at Week 15
(Part 2 subjects with PD-L1 CPS ≥10)
(FAS Population)

	Baseline		Week 15		Change from Baseline at Week 15		
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)†	
Pembrolizumab + Chemotherapy	201	67.54 (21.865)	166	66.32 (19.318)	216	-2.69 (-5.86, 0.48)	
Placebo + Chemotherapy	94	64.54 (21.514)	70	66.07 (22.085)	100	-0.88 (-5.41, 3.64)	
Pairwise Comparison						Difference in LS Means (95% CI)	p-Value
Pembrolizumab + Chemotherapy vs. Placebo + Chemotherapy						-1.81 (-6.92, 3.30)	0.4865

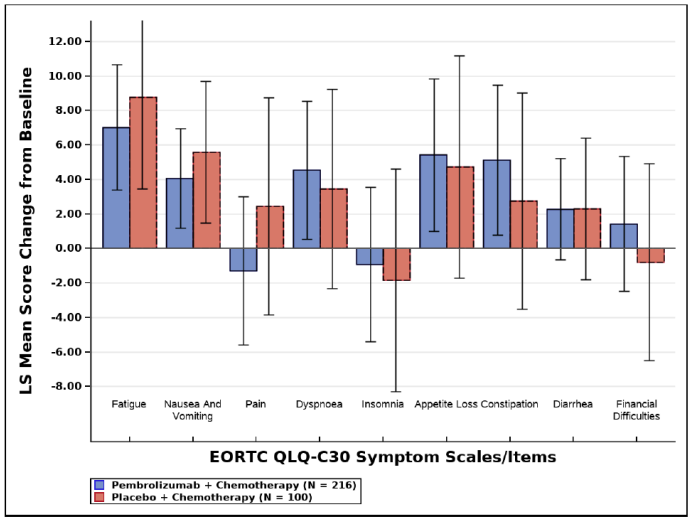
† Based on cLDA model with the PRO scores as the response variable, and treatment by timepoint interaction, and stratum (defined by stratification factors of chemotherapy on study [taxane vs gemcitabine/carboplatin] and prior treatment with same class of chemotherapy in the (neo)adjuvant setting [yes vs no]) as covariates.
For baseline and Week 15, N is the number of subjects in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of subjects in the analysis population in each treatment group.
Two-sided p-value.
Database Cutoff Date: 11DEC2019

Change from Baseline for EORTC QLQ-C30 Global Health Status/QoL and Functional Scales
at Week 15
(LS Mean Change and 95% CI)
(Part 2 Subjects with PD-L1 CPS ≥10)
(FAS Population)



For global health status/quality of life score and all functional scales, a higher score denotes better health related quality of life (HRQOL) or function. For symptoms scales/items, a higher score denotes worse symptoms.
N is the number of subjects in the analysis population in each treatment group.
Database Cutoff Date: 11DEC2019.

Change from Baseline for EORTC QLQ-C30 Symptom Scales/Items
at Week 15
(LS Mean Change and 95% CI)
(Part 2 Subjects with PD-L1 CPS ≥10)
(FAS Population)



For functional scales/items, a higher score denotes better function. For symptom scales/items, a higher score denotes worse symptom.
N is the number of subjects in the analysis population in each treatment group.
Database Cutoff Date: 11DEC2019.

- Time to Deterioration (TTD)

In participants with PD-L1 positive tumors (CPS ≥10), there were no differences in TTD in the EORTC QLQ-C30 global health status/QoL [median TTD 6.4 vs. 5.6 months, HR 0.99] and Physical Functioning scores [median TTD 5.6 vs. 6.2 months, HR 1.27] between the pembrolizumab + chemotherapy and placebo + chemotherapy groups. A directional difference in favor of the placebo + chemotherapy group was observed for the TTD in the Emotional Functioning score [median TTD 9.6 vs. 15.3 months, HR 1.26 [0.86, 1.84]; however, the 95% CI for the HR includes 1.

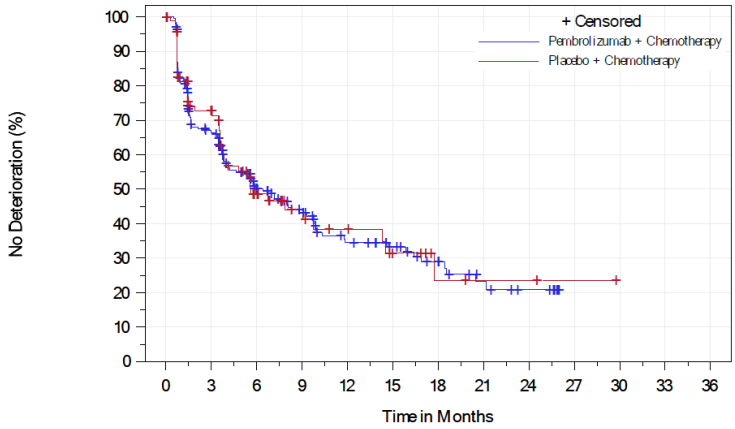
TTD analyses in participants with PD-L1 positive tumors using the cutoff of CPS ≥1 and in All Participants showed similar trends for global health status/QoL, Physical Functioning, and Emotional Functioning scores.

Analysis of Time to Deterioration for EORTC QLQ-C30 Global Health Status/QoL
(Part 2 Subjects with PD-L1 CPS ≥10)
(FAS Population)

	Pembrolizumab + Chemotherapy (N=217)	Placebo + Chemotherapy (N=100)
Number of Events (%)	116 (53.5)	47 (47.0)
Kaplan-Meier Estimates (Months)[†]		
Median (95% CI)	6.4 (3.8, 9.3)	5.6 (3.7, 14.3)
[Q1, Q3]	[1.4, 20.5]	[1.4, 17.7]
vs Placebo + Chemotherapy		
Hazard Ratio (95% CI)[‡]	0.99 (0.70, 1.39)	
p-value[§]	0.4834	

[†] From product-limit (Kaplan-Meier) method for censored data.
[‡] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by chemotherapy on study (taxane vs. gemcitabine/carboplatin) and prior treatment with same class of chemotherapy in the (neo)adjuvant setting (yes vs. no).
[§] One-sided p-value based on log-rank test stratified by chemotherapy on study (taxane vs. gemcitabine/carboplatin) and prior treatment with same class of chemotherapy in the (neo)adjuvant setting (yes vs. no).
Time to deterioration (event) is defined as time to first onset of 10 points or more worsening from baseline.
Database Cutoff Date: 11DEC2019

Kaplan Meier Estimate of Time to Deterioration for EORTC QLQ-C30 Global Health Status/QoL (Part 2 Subjects with PD-L1 CPS ≥10) (FAS Population)



n at risk

Pembrolizumab + Chemotherapy	217	116	69	50	34	26	17	10	6	0	0	0	0
Placebo + Chemotherapy	100	53	27	16	12	7	3	2	2	1	0	0	0

EORTC QLQ-BR23

In participants with PD-L1 positive tumors (CPS ≥10 and CPS ≥1) and in All Participants, the LS mean change from baseline to Week 15 in scores for EORTC QLQBR23 functional scales/items (Body Image, Sexual Functioning, Sexual Enjoyment and Future Perspective) and in symptom scales (Systemic Therapy Side Effects, Breast Symptoms, Arm Symptoms and Upset by Loss of Hair) were similar between the 2 treatment groups.

Exploratory Subgroup Analyses– EU Region

The prespecified subgroups for geographic region was North America/Europe/New Zealand + Australia vs Asia vs Rest of World. Post-hoc analyses of the EU subpopulation are presented to further examine the treatment effect in this group. EU participants in the CPS≥10 population were n=64 in the pembrolizumab

+ chemotherapy group vs n=28 in the placebo + chemotherapy group; the results of these exploratory analyses should be interpreted with caution.

Demographics and Other Baseline Characteristics

For participants with tumors that express PD-L1 with CPS ≥10 enrolled in the EU, intervention groups were generally balanced for most baseline characteristics and prognostic factors and were generally similar to the overall population of participants with tumors that express PD-L1 with CPS ≥10. Some differences are noted for participants enrolled in the EU:

- More participants in the pembrolizumab + chemotherapy group received paclitaxel (14.1%) compared with the placebo + chemotherapy group (7.1%)
- Fewer participants in the pembrolizumab + chemotherapy group received gemcitabine/carboplatin (43.8%) compared with the placebo + chemotherapy group (57.1%)
- More participants in the pembrolizumab + chemotherapy group had de novo metastatic disease (25.0% vs 17.9%) whereas more participants in the placebo + chemotherapy group had recurrent metastatic disease (68.8% vs 75.0%)
- More participants in the pembrolizumab + chemotherapy group had an ECOG of 1 (37.5%) compared with the placebo + chemotherapy group (28.6%)
- Fewer participants in the pembrolizumab + chemotherapy had an LDH level within normal limits at baseline (45.3%) compared with the placebo + chemotherapy group (60.7%)
- Fewer participants in the pembrolizumab + chemotherapy group received prior neoadjuvant or adjuvant chemotherapy (60.9%) compared with the placebo + chemotherapy group (75%).

Efficacy Results in the EU Subgroup

Table: Summary of Efficacy Results in Participants with PD-L1 CPS ⩾10 – EU Participants

Endpoint	Pembrolizumab + Chemotherapy (N=64)	Placebo + Chemotherapy (N=28)
PFS[a]		
Median PFS, months (95% CI)	5.7 (3.7, 11.0)	7.4 (3.9, 11.1)
HR (95% CI)	1.02 (0.60, 1.72)	
OS		
Median OS, months (95% CI)	15.8 (11.7, 22.8)	19.3 (16.1, NR)
HR (95% CI)	1.41 (0.80, 2.48)	
Objective Response		
ORR % (95% CI)[a]	40.6 (28.5, 53.6)	46.4 (27.5, 66.1)
ORR Difference % (95% CI)	–5.8 (–27.4, 15.5)	
CR, n (%)	8 (12.5)	3 (10.7)
PR, n (%)	18 (28.1)	10 (35.7)
DOR (months), median (range)[a, b, c]	12.6 (1.6+ to 29.6+)	6.5 (2.3 to 26.3+)

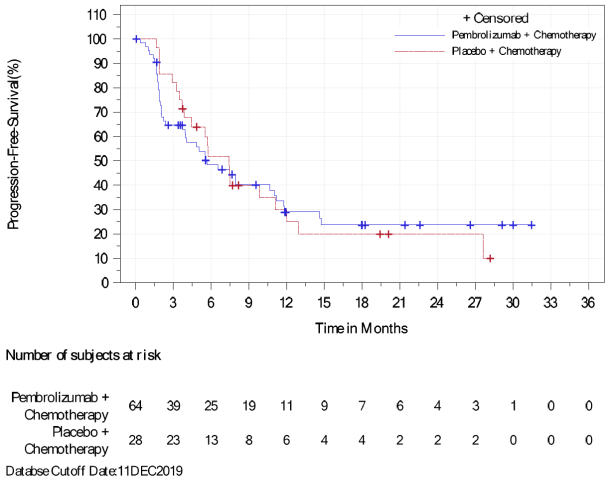
Abbreviations: CI = confidence interval; CR = complete response, DOR = duration of response; NR = not reached; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response.

a. Response assessed by BICR per RECIST 1.1; only confirmed responses (CR or PR) are included.
b. From product-limit (Kaplan-Meier) method for censored data.
c. "+" indicated there is no PD by the time of last disease assessment.

Data cutoff: 11DEC2019

Figure: KM Estimates of PFS and OS (Subjects with PD-L1 CPS ⩾10 - EU Subjects)

KM of **PFS** (CPS ≥10 - EU)



KM of **OS** (CPS ≥10 - EU)

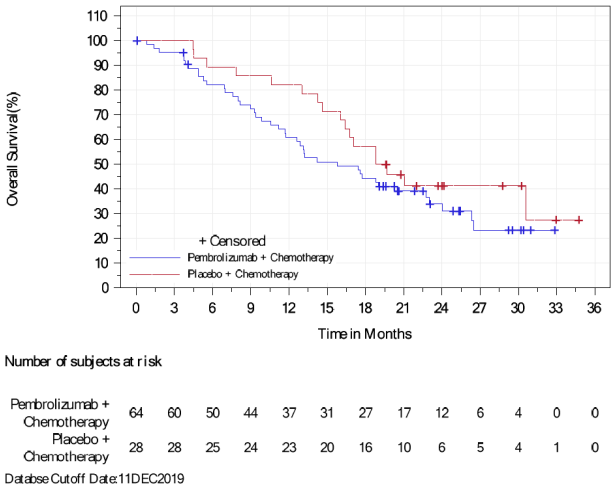


Table: Summary of Efficacy Results in All Participants - Participants Enrolled in EU and non-EU Countries (ITT Population)

Endpoint	EU Participants		Non-EU Participants	
	Pembrolizumab + Chemotherapy (N=165)	Placebo + Chemotherapy (N=94)	Pembrolizumab + Chemotherapy (N=401)	Placebo + Chemotherapy (N=187)
PFS[a]				
Median PFS, months (95% CI)[b]	5.8 (5.1, 7.7)	5.7 (5.1, 7.5)	7.6 (7.4, 8.0)	5.6 (5.4, 7.5)
HR (95% CI)[c]	1.01 (0.75, 1.36)		0.73 (0.60, 0.89)	
PFS rate at 6 months, % (95% CI)	47.0 (38.7, 54.9)	47.9 (36.9, 58.0)	58.7 (53.5, 63.6)	47.9 (40.2, 55.2)
PFS rate at 9 months, % (95% CI)	37.1 (29.0, 45.2)	36.2 (25.9, 46.5)	44.3 (39.0, 49.5)	31.8 (24.6, 39.2)
PFS rate at 12 months, % (95% CI)	25.3 (18.0, 33.2)	26.8 (17.3, 37.2)	31.6 (26.6, 36.6)	18.2 (12.3, 25.0)
OS				
Median OS, months (95% CI)[b]	14.2 (12.9, 17.4)	18.0 (14.6, 20.4)	18.3 (16.0, 20.4)	14.7 (12.4, 16.6)
HR (95% CI)[c]	1.18 (0.87, 1.61)		0.76 (0.62, 0.93)	
OS rate at 12 months, % (95% CI)	62.2 (54.2, 69.2)	64.9 (54.3, 73.6)	65.5 (60.6, 69.9)	60.8 (53.4, 67.4)
OS rate at 18 months, % (95% CI)	40.2 (32.6, 47.7)	50.0 (39.5, 59.6)	51.0 (46.0, 55.8)	37.6 (30.7, 44.6)
OS rate at 24 months, % (95% CI)	28.9 (21.7, 36.4)	33.3 (23.6, 43.2)	37.9 (32.9, 42.8)	27.1 (20.6, 34.0)
Objective Response				
ORR % (95% CI)[a]	38.8 (31.3, 46.7)	35.1 (25.5, 45.6)	41.9 (37.0, 46.9)	36.4 (29.5, 43.7)
ORR Difference % (95% CI)[d]	3.7 (–8.7, 15.5)		5.5 (–3.0, 13.8)	

Abbreviations: BICR = blinded independent central review; CI = confidence interval; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors version 1.1.

a. Response assessed by BICR per RECIST 1.1; only confirmed responses are included.

b. From product-limit (Kaplan-Meier) method for censored data.
c. Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.
d. Based on Miettinen & Nurminen method

Data cutoff: 11DEC2019

Source: Table 1, Table 3, and Table 5 of [Annex 6] [Ref. 5.3.5.1: P355V01MK3475: Table 14.2-37] [Ref. 5.3.5.1: P355V01MK3475: Table 14.2-66] [Ref. 5.3.5.1: P355V01MK3475: Table 14.2-111]

Efficacy by chemotherapy backbone

A summary of the most notable differences in baseline characteristics of subjects treated with each chemotherapy backbone is presented in the table below:

Table: differences in baseline characteristics by backbone chemotherapy

	Treatment with Carboplatin/Gemcitabine	Treatment with Nab-Paclitaxel	Treatment with Paclitaxel
De novo metastatic disease	22%	35.6%	46.9%
Prior (neo)adjuvant chemotherapy	72.8%	58.1%	40.7%
Prior Treatment with Same Class Chemotherapy (Actual)	6.3%	45.3%	26.5%
Disease free interval < 12 months	29.6%	10.1%	10.6%
LDH ≥2 x ULN	18.1%	14.2%	15.0%
No. of metastatic organ sites ≥3	46.4%	37.1%	44.2%
Median target lesion size (central)	53 mm	57 mm	61.5 mm
Median age (years)	50	55	59

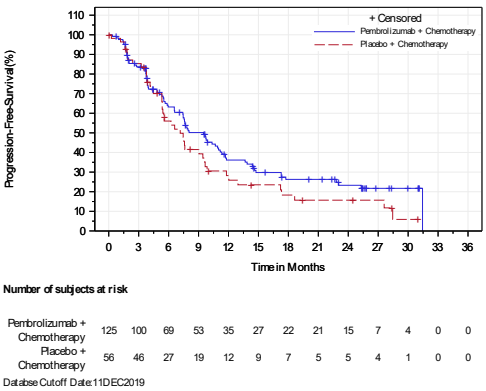
Summary table prepared by the assessment team

The subgroups by backbone chemotherapy were not individually powered to demonstrate treatment effect. The results of these exploratory analyses should be interpreted with caution.

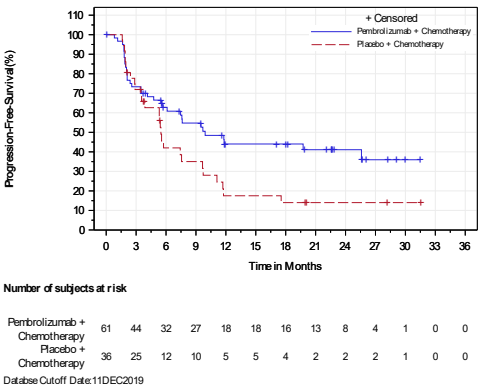
Efficacy in the Placebo + Carboplatin/Gemcitabine Group

Figures: Kaplan-Meier Estimates of PFS Based on BICR Assessment per RECIST 1.1 (Part 2 Subjects with PD-L1 CPS≥10 by Actual Chemotherapy Treatment (ITT Population)

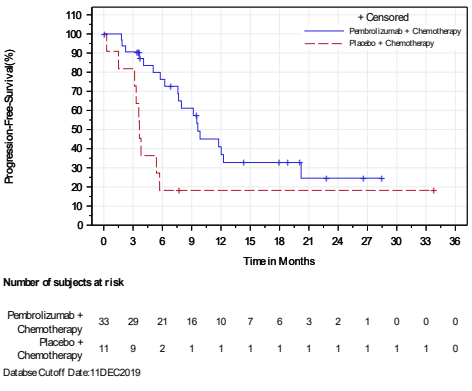
Carboplatin/gemcitabine



Nab-paclitaxel

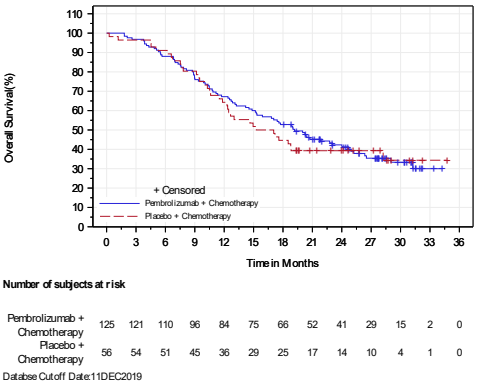


Paclitaxel

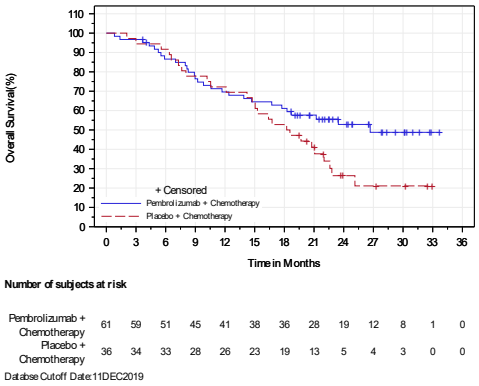


Figures: Kaplan-Meier Estimates of Overall Survival (Part 2 Subjects with PD-L1 CPS ≥ 10 by Actual Chemotherapy Treatment (ITT Population)

Carboplatin/gemcitabine



Nab-paclitaxel



Paclitaxel

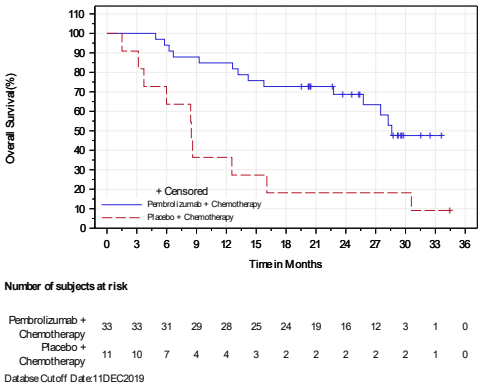


Table: Summary of Efficacy Results for Carboplatin/Gemcitabine as a First-line Treatment for Metastatic TNBC

Treatment (Study)	Median PFS, Months	Median OS, Months	ORR, %
Placebo + carboplatin/ gemcitabine (KEYNOTE-355)	7.2	16.2	44.6
Carboplatin/gemcitabine (tnAcity)	6.0	12.6	44.0
Carboplatin/gemcitabine (BSI-201)[a]	4.6	13.9	NR
Carboplatin/gemcitabine (Phase 2 study)			
HER2- (no taxane)[b]	NR	21.7	27.0

HER2- (prior taxane)[c]	NR	11.0	30.6

Abbreviations: DOR = duration of response, NR = not reported; ORR = objective response rate; OS = overall survival; PFS = progression-free survival.
a. Results from the subgroup analysis of patients receiving first-line treatment.
b. Patients had not received prior treatment for metastatic breast cancer but could have received prior treatment (docetaxel or paclitaxel ≥2 years prior) in the adjuvant setting.
c. Patients could had received <2 prior treatment for metastatic breast cancer and received prior treatment (docetaxel or paclitaxel <2 years prior) in the adjuvant setting.

Table: Summary of Efficacy Results for Paclitaxel as a First-line Treatment for Metastatic TNBC

Treatment (Study)	Median PFS, Months	Median OS, Months	ORR, %
Placebo + paclitaxel (KEYNOTE-355)	3.6	8.5	27.3
Paclitaxel alone (Phase 2 study)	3.5	13.1	32.0
Placebo + paclitaxel (LOTUS)	4.9	18.4	20.0
Placebo + Paclitaxel (PAKT)	4.2	12.6	28.8

Abbreviations: DOR = duration of response, ORR = objective response rate; OS = overall survival; PFS = progression-free survival.

Efficacy by prior (neo) adjuvant therapy

Table: subgroup analysis of PFS (subjects with PD-L1 CPS≥10)

Prior adjuvant or neoadjuvant chemotherapy							
Yes	131	84	(64.1)	62	46	(74.2)	0.78 (0.55, 1.12)
No	89	52	(58.4)	41	33	(80.5)	0.47 (0.30, 0.74)
Prior adjuvant or neoadjuvant taxane treatment							
Yes	107	72	(67.3)	50	39	(78.0)	0.76 (0.51, 1.12)
No	113	64	(56.6)	53	40	(75.5)	0.56 (0.38, 0.84)
Prior adjuvant or neoadjuvant platinum treatment							
No	207	128	(61.8)	97	75	(77.3)	0.65 (0.49, 0.86)

Table: subgroup analysis of OS (subjects with PD-L1 CPS≥10)

Prior adjuvant or neoadjuvant chemotherapy							
Yes	131	78	(59.5)	62	39	(62.9)	0.90 (0.61, 1.32)
No	89	43	(48.3)	41	32	(78.0)	0.46 (0.29, 0.73)
Prior adjuvant or neoadjuvant taxane treatment							
Yes	107	69	(64.5)	50	33	(66.0)	0.91 (0.60, 1.38)
No	113	52	(46.0)	53	38	(71.7)	0.53 (0.35, 0.80)
Prior adjuvant or neoadjuvant platinum treatment							
No	207	112	(54.1)	97	67	(69.1)	0.68 (0.50, 0.92)

Table: Subgroup Analysis of Objective Response Based on BICR Assessment per RECIST 1.1 (subjects with PD-L1 CPS≥10)

Prior adjuvant or neoadjuvant chemotherapy									
Yes	131	62	(47.3)	(38.5, 56.2)	62	27	(43.5)	(31.0, 56.7)	(3.8)	(-11.3, 18.4)
No	89	55	(61.8)	(50.9, 71.9)	41	14	(34.1)	(20.1, 50.6)	(27.7)	(9.2, 44.0)
Prior adjuvant or neoadjuvant taxane treatment									
Yes	107	47	(43.9)	(34.3, 53.9)	50	21	(42.0)	(28.2, 56.8)	(1.9)	(-14.8, 18.0)
No	113	70	(61.9)	(52.3, 70.9)	53	20	(37.7)	(24.8, 52.1)	(24.2)	(7.9, 39.1)
Prior adjuvant or neoadjuvant platinum treatment									
No	207	110	(53.1)	(46.1, 60.1)	97	39	(40.2)	(30.4, 50.7)	(12.9)	(0.9, 24.5)

PFS by Investigator and PFS sensitivity analyses

Table: PFS results in all populations *(table prepared by assessment team)*

PFS primary analysis by BICR per RECIST 1.1 HR (95%CI)	**PFS by Investigator per RECIST 1.1** HR (95%CI)	**PFS Sensitivity analysis 1*** HR (95%CI)	**PFS Sensitivity analysis 2**** HR (95%CI)	**PFS Sensitivity analysis with actual stratum** HR (95%CI)
All subjects				
0.82 (0.69, 0.97)	0.83 (0.71, 0.97)	0.84 (0.71, 0.98)	0.90 (0.77, 1.04)	0.81 (0.69, 0.96)
PD-L1 CPS≥1				
0.74 (0.61, 0.90)	0.79 (0.66, 0.95)	0.77 (0.64, 0.92)	0.84 (0.71, 1.00)	0.73 (0.60, 0.89)
PD-L1 CPS≥10				
0.65 (0.49, 0.86)	0.71 (0.54, 0.93)	0.69 (0.53, 0.90)	0.78 (0.61, 1.00)	0.64 (0.49, 0.85)

*Sensitivity analysis 1: PD or death after ≥2 consecutive missed disease assessments or after new anticancer therapy is an event.

** Sensitivity analysis 2: treatment discontinuation if no PD, no death and no new anticancer treatment is an event; if no PD, no death, start of new anticancer treatment is an event; PD or death after ≥2 consecutive missed disease assessments or after new anticancer therapy is an event.

EFFICACY RESULTS - FINAL ANALISIS (data cut-off 15-JUN-2021)

The MAH presented during the procedure the Final Analysis (FA) for overall survival with a data cutoff date of 15-JUN-2021, with a median follow-up of 16.7 months (range 0.2, 53.1) in the ITT population (n=847) and 20.2 months (range 0.3, 53.1) in the CPS≥10 population (n=323).

The testing of the primary hypotheses of PFS was completed at interim analysis 2 (FA of PFS) and was met at the IA2; PFS was not tested at the FA, although updated descriptive PFS analyses have been also provided. The key secondary hypotheses of ORR were only tested at IA1.

Per protocol, this event-driven FA was triggered by ~240 OS events in participants with CPS≥10, ~482 OS events in participants with CPS≥1, and ~664 OS events in All Participants.

The overall type I error over the primary endpoints PFS and OS and the secondary endpoint ORR was strongly controlled at 2.5% (one-sided), with initially 0.5% allocated to the PFS hypothesis, 1.8% to the OS hypothesis, and 0.2% to the ORR hypothesis.

At the FA, the primary endpoint of OS in participants with CPS≥10 was met. OS in the CPS≥1 population was not met at the FA, while OS in the ITT population was not statistically tested per multiplicity strategy.

Table: Outcomes of the Primary Endpoints of OS at FA

Endpoint	Number of Events/N	HR (95% CI)	p-value Boundary	p-value	Success Criterion for OS Hypothesis
OS in Participants with CPS ≥10	239/323	0.73 (0.55, 0.95)	0.0113	0.0093	Met
OS in Participants with CPS ≥1	513/636	0.86 (0.72, 1.04)	0.0172	0.0563	Not met
OS in All Participants	698/847	0.89 (0.76, 1.05)	N/A	0.0797	Not tested
Abbreviations: CPS = combined positive score; FA = final analysis; HR = hazard ratio; OS = overall survival. Database Cutoff Date: 15JUN2021.					

Table: participant disposition - subjects with PS-L1 CPS≥10 (data cut-off 15 Jun 2021)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	220		103		323	
Status for Study Medication in Trial Segment of First Course Treatment						
Started	219		103		322	
Completed	27	(12.3)	5	(4.9)	32	(9.9)
Discontinued	189	(86.3)	95	(92.2)	284	(88.2)
Adverse Event	21	(9.6)	5	(4.9)	26	(8.1)
Clinical Progression	17	(7.8)	11	(10.7)	28	(8.7)
Complete Response	3	(1.4)	1	(1.0)	4	(1.2)
Physician Decision	7	(3.2)	3	(2.9)	10	(3.1)
Progressive Disease	127	(58.0)	71	(68.9)	198	(61.5)
Withdrawal By Subject	14	(6.4)	4	(3.9)	18	(5.6)
Status Not Recorded	3	(1.4)	3	(2.9)	6	(1.9)
Status for Trial						
Discontinued	160	(72.7)	84	(81.6)	244	(75.5)
Death	151	(68.6)	82	(79.6)	233	(72.1)
Withdrawal By Subject	9	(4.1)	2	(1.9)	11	(3.4)
Status Not Recorded	60	(27.3)	19	(18.4)	79	(24.5)

Clinical Progression and Progressive Disease are based on Investigator's assessment and may be different from the data used in the primary analysis.
Progressive Disease refers to disease progression based on RECIST 1.1 and does not include Clinical Progression.
Study medication discontinuation refers to discontinuation of all study medications.
Status Not Recorded: Subjects without a completed study medication discontinuation form or without a completed study disposition form.
Database Cutoff Date: 15JUN2021

Overall survival (final analysis)

Pembrolizumab + chemotherapy was statistically superior to chemotherapy alone with respect to OS in participants with PD-L1 positive tumors (CPS ≥10). The observed p-value of p=0.0093 successfully crossed the prespecified efficacy boundary at the FA (the multiplicity adjusted, one-sided nominal alpha level was 0.0113); the OS HR was 0.73 (95% CI: 0.55, 0.95), with longer median OS in the pembrolizumab + chemotherapy group compared with the placebo + chemotherapy group (23.0 vs 16.1 months), and OS rates by KM estimation at month 18 and 24 favouring the experimental arm.

Table: Analysis of Overall Survival (Part 2 Subjects with PD-L1 CPS ≥10) (data cut-off 15 Jun 2021)

	Pembrolizumab + Chemotherapy (N=220)	Placebo + Chemotherapy (N=103)
Number of Events (%)	155 (70.5)	84 (81.6)
Kaplan-Meier Estimates (Months)†		
Median (95% CI)	23.0 (19.0, 26.3)	16.1 (12.6, 18.8)
[Q1, Q3]	[10.3, NR]	[8.6, 30.3]
Person-Months	5430.4	2091.1
Event Rate / 100 Person-Months	2.9	4.0
vs Placebo + Chemotherapy		
Hazard Ratio (95% CI)‡	0.73 (0.55, 0.95)	
p-value§	0.0093	
OS Rate at Month 6 (%) (95% CI)	88.6 (83.5, 92.1)	88.3 (80.4, 93.2)
OS Rate at Month 12 (%) (95% CI)	70.7 (64.1, 76.2)	64.1 (54.0, 72.5)
OS Rate at Month 18 (%) (95% CI)	58.3 (51.4, 64.5)	44.7 (34.9, 53.9)
OS Rate at Month 24 (%) (95% CI)	48.2 (41.4, 54.6)	34.0 (25.0, 43.1)

† From product-limit (Kaplan-Meier) method for censored data.

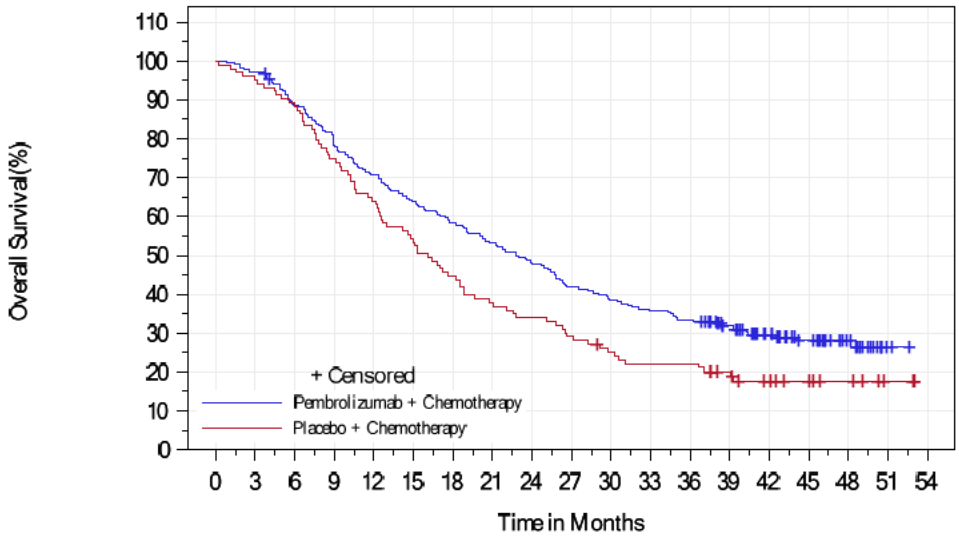
‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by chemotherapy on study (taxane vs gemcitabine/carboplatin) and prior treatment with same class of chemotherapy in the (neo)adjuvant setting (yes vs no).

§ One-sided p-value based on log-rank test stratified by chemotherapy on study (taxane vs gemcitabine/carboplatin) and prior treatment with same class of chemotherapy in the (neo)adjuvant setting (yes vs no).

NR = Not reached.

Database Cutoff Date: 15JUN2021

Figure: Kaplan-Meier Estimates of Overall Survival (PD-L1 CPS ≥10) (data cut-off 15 Jun 2021)

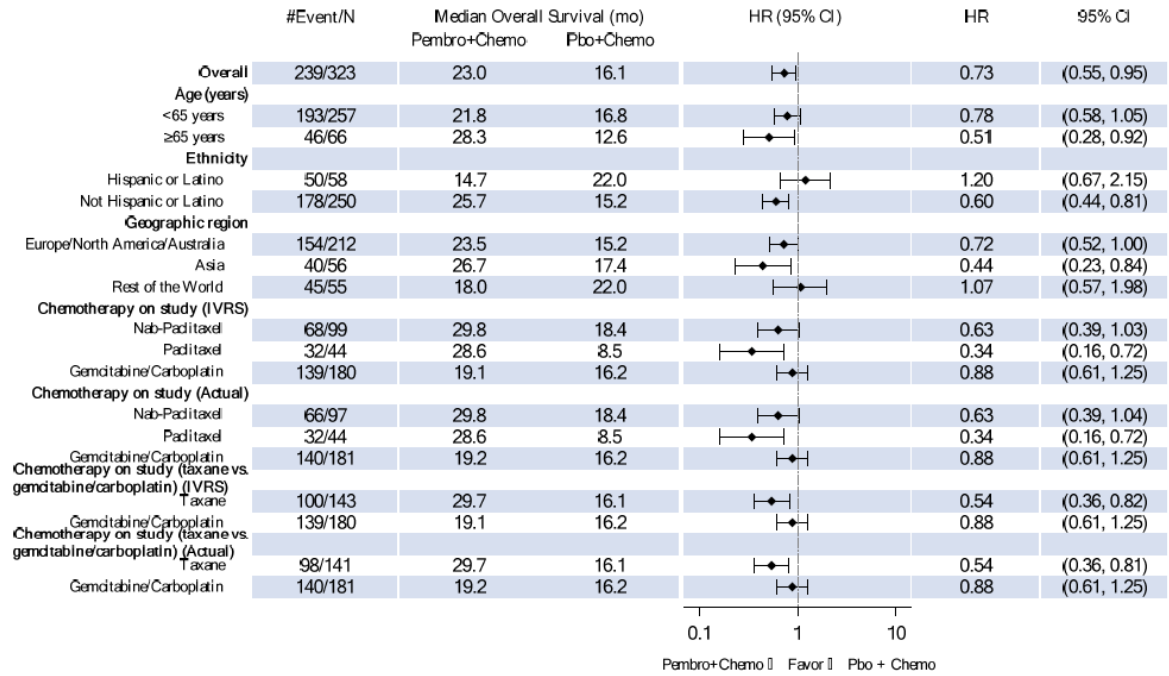


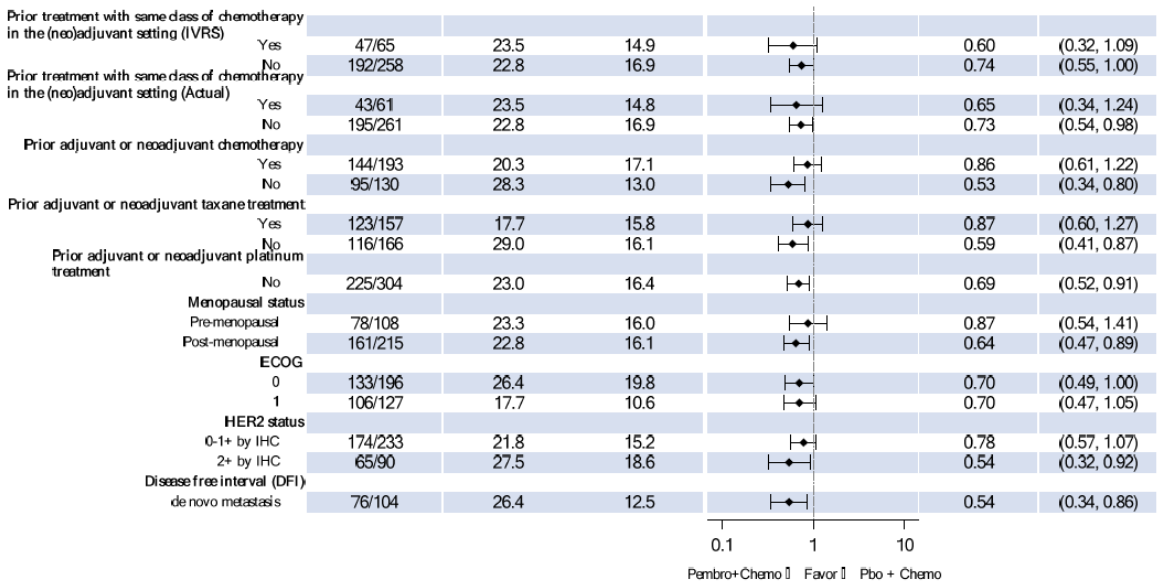
Number of subjects at risk

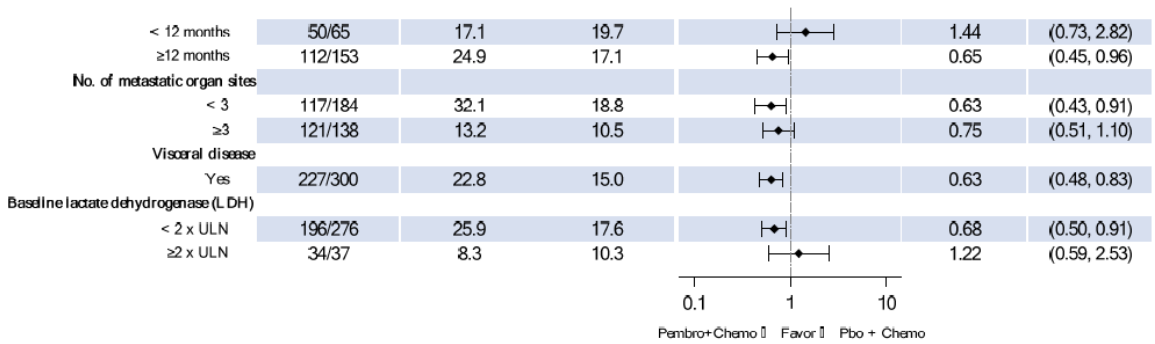
Pembrolizumab + Chemotherapy	220	214	193	171	154	139	127	116	105	91	84	78	73	59	43	31	17	2	0
Placebo + Chemotherapy	103	98	91	77	66	55	46	39	35	30	25	22	22	17	12	8	6	2	0

Database Cutoff Date:15JUN2021

Figure: Forest Plot of Overall Survival Hazard Ratio by Subgroup Factors (PD-L1 CPS ≥10) (data cut-off 15 Jun 2021)



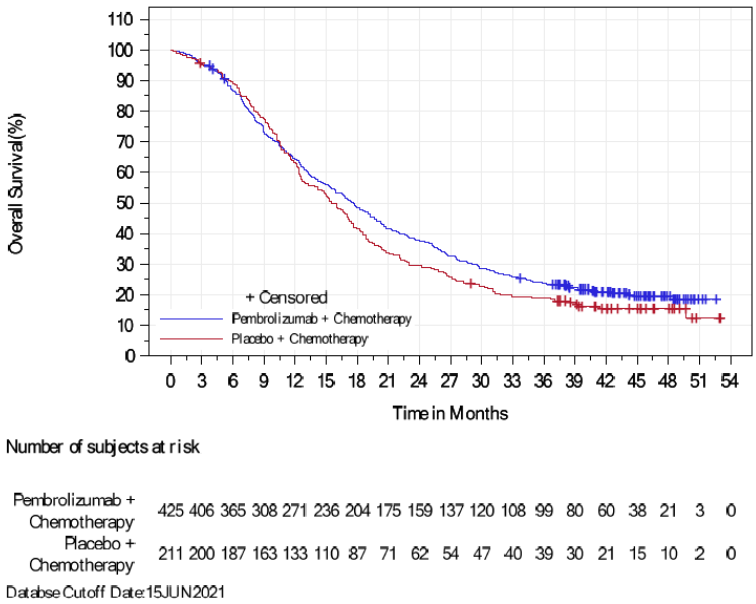




Analysis (HR and 95% CI) in the overall population is based on the stratified Cox regression model with Efron's method of tie handling stratified by chemotherapy on study (taxane vs gemcitabine/carboplatin) and prior treatment with same class of chemotherapy in the (neo)adjuvant setting (yes vs no); analysis in the subgroups is based on the unstratified Cox model. If any level of a subgroup variable has fewer than 30 subjects, subgroup analysis is not performed in that level of the subgroup variable. Database Cutoff Date: 15JUN2021.

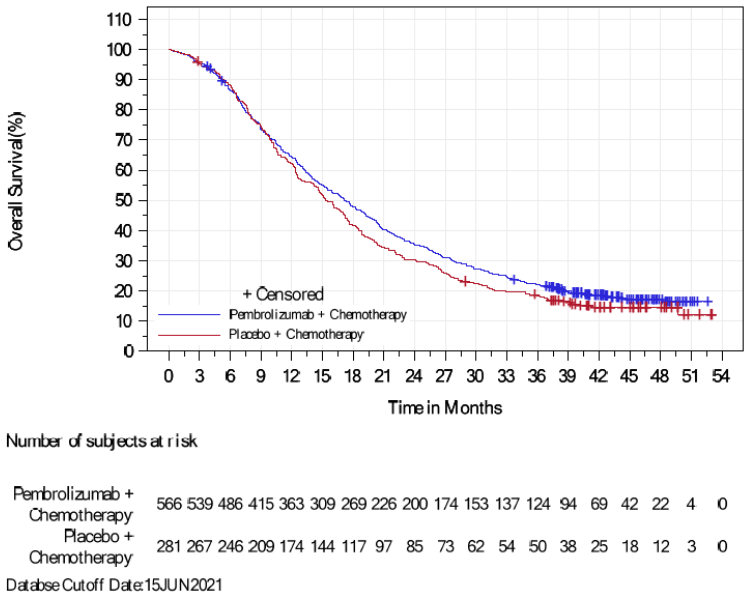
There was a directional improvement in the OS HR that favored the pembrolizumab + chemotherapy group in participants with PD-L1 CPS≥1; however, the observed p-value of p=0.0563 did not cross the prespecified efficacy boundary at FA (the multiplicity adjusted, one-sided nominal alpha level was 0.0172). OS HR was 0.86 (95% CI: 0.72, 1.04) in CPS≥1.

Figure: Kaplan-Meier Estimates of Overall Survival (PD-L1 CPS ≥1) (data cut-off 15 Jun 2021)



The primary hypothesis pertaining to OS in All Participants was not formally tested as per multiplicity strategy because the success criterion for the primary hypothesis of OS in participants CPS ≥1 was not met. The OS HR in all participants was 0.89 (95% CI: 0.76, 1.05).

Figure: Kaplan-Meier Estimates of Overall Survival (All Subjects) (data cut-off 15 Jun 2021)



Progression free survival (final analysis)

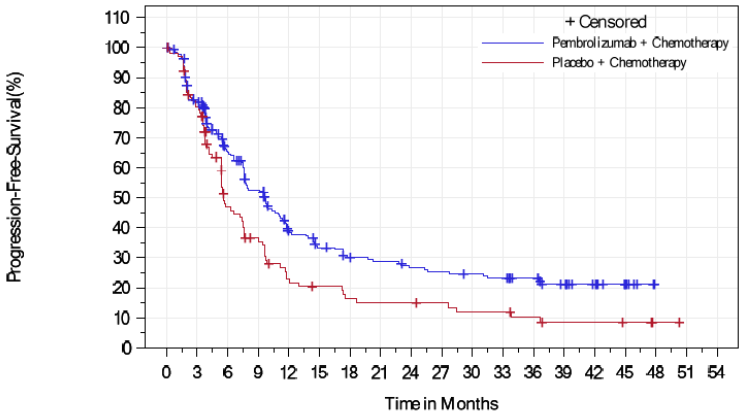
The analyses performed at IA2 were the final prespecified analyses for PFS. Updated data for PFS at the FA, with nominal p-values, are provided herein.

Table: Analysis of Progression-Free Survival Based on BICR Assessment per RECIST 1.1 (CPS ≥10) (data cut-off 15 Jun 2021)

	Pembrolizumab + Chemotherapy (N=220)	Placebo + Chemotherapy (N=103)
Number of Events (%)	144 (65.5)	81 (78.6)
Kaplan-Meier Estimates (Months)†		
Median (95% CI)	9.7 (7.6, 11.3)	5.6 (5.3, 7.5)
[Q1, Q3]	[3.9, 27.8]	[3.6, 11.8]
Person-Months	2714.5	940.6
Event Rate / 100 Person-Months	5.3	8.6
vs Placebo + Chemotherapy		
Hazard Ratio (95% CI)‡	0.66 (0.50, 0.88)	
p-value§	0.0018	
PFS Rate at Month 3 (%) (95% CI)	81.8 (76.0, 86.4)	80.2 (71.0, 86.8)
PFS Rate at Month 6 (%) (95% CI)	65.0 (58.1, 71.2)	46.9 (36.5, 56.6)
PFS Rate at Month 9 (%) (95% CI)	52.5 (45.2, 59.2)	36.6 (26.9, 46.4)
PFS Rate at Month 12 (%) (95% CI)	39.1 (32.0, 46.1)	23.0 (14.7, 32.3)

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by chemotherapy on study (taxane vs gemcitabine/carboplatin) and prior treatment with same class of chemotherapy in the (neo)adjuvant setting (yes vs no).
§ One-sided p-value based on log-rank test stratified by chemotherapy on study (taxane vs gemcitabine/carboplatin) and prior treatment with same class of chemotherapy in the (neo)adjuvant setting (yes vs no).
BICR = Blinded Independent Central Review.
Database Cutoff Date: 15JUN2021

Figure: Kaplan-Meier Estimates of Progression-Free Survival Based on BICR Assessment per RECIST 1.1 (CPS ≥10) (data cut-off 15 Jun 2021)



Number of subjects at risk

Pembrolizumab + Chemotherapy	220	173	122	95	63	52	44	42	38	36	34	32	27	19	13	6	0	0	0
Placebo + Chemotherapy	103	80	41	30	18	15	12	11	11	10	8	8	6	4	4	3	1	0	0

Database Cutoff Date:15JUN2021

Objective response rate (final analysis)

The endpoints of ORR were only tested at IA1 and not formally tested at the FA. Updated data for ORR at the FA, with nominal p-values, are provided herein.

Table: Analysis of Objective Response Based on BICR Assessment per RECIST 1.1 (CPS ≥10) (data cut-off 15 Jun 2021)

Treatment	N	Number of Objective Responses	Objective Response Rate (%) (95% CI)	Difference in % vs. Control	
				Estimate (95% CI)†	p-Value‡
Pembrolizumab + Chemotherapy	220	116	52.7 (45.9, 59.5)	12.1 (0.4, 23.4)	0.0213
Placebo + Chemotherapy	103	42	40.8 (31.2, 50.9)		

† Based on Miettinen & Nurminen method stratified by chemotherapy on study (taxane vs gemcitabine/carboplatin) and prior treatment with same class of chemotherapy in the (neo)adjuvant setting (yes vs no).
‡ One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.
Confirmed responses are included.
BICR = Blinded Independent Central Review.
Database Cutoff Date: 15JUN2021

The median DOR for responders with PD-L1 positive tumors (CPS ≥10) was 12.1 months (range: 1.6+ to 45.9+ months) in the pembrolizumab + chemotherapy group and 7.3 months (range: 1.5 to 46.6+ months) in the placebo + chemotherapy group.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 1. Summary of Efficacy for trial KEYNOTE-355

Title: A Randomized, Double-Blind, Phase III Study of Pembrolizumab (MK-3475) plus Chemotherapy vs Placebo plus Chemotherapy for Previously Untreated Locally Recurrent Inoperable or Metastatic Triple Negative Breast Cancer – (KEYNOTE-355)	
Study identifier	EudraCT: 2016-001432-35; IND: 124,442; NCT: 02819518
Design	Phase 3 (with safety run-in), two-arm, multicenter, international, randomized 2:1, double blind

	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		01-AUG-2016 (first patient, first visit) 15-JUN-2021 (last patient, last visit) Study is ongoing. NA NA
Hypothesis	Superiority		
Treatments groups	Pembrolizumab + chemotherapy (paclitaxel, nab-paclitaxel, carboplatin/ gemcitabine)		Pembrolizumab 200 mg IV Q3W, IV infusion Nab-paclitaxel 100 mg/m^2 Days 1,8, and 15, every 28 days Paclitaxel 90 mg/m^2 Days 1,8,and 15, every 28 days Gemcitabine/Carboplatin 1000 mg/m^2 and AUC 2, respectively, Days 1,8 every 21 days
	Placebo + chemotherapy (paclitaxel, nab-paclitaxel, carboplatin/ gemcitabine)		Placebo (normal saline) Q3W Nab-paclitaxel 100 mg/m^2 Days 1,8, and 15, every 28 days Paclitaxel 90 mg/m^2 Days 1,8,and 15, every 28 days Gemcitabine/Carboplatin 1000 mg/m^2 and AUC 2, respectively, Days 1,8 every 21 days
Endpoints and definitions	Dual Primary endpoint	PFS (per RECIST 1.1 by CIV) In the ITT, CPS≥1 and in the CPS≥10 populations	Time from randomization to the first documented disease progression or death due to any cause, whichever occurs first
	Dual primary endpoint	OS In the ITT, CPS≥1 and in the CPS≥10 populations	Time from randomization to death due to any cause.
	Secondary endpoint	ORR (per RECIST 1.1 by CIV) In the ITT, CPS≥1 and in the CPS≥10 populations	Proportion of the participants in the analysis population who have a complete response (CR) or partial response (PR)
	Secondary endpoint	DOR, AEs, PRO	
Data cut-off	11 Dec 2019 (IA2) 15 Jun 2021 (FA)		

Results and Analysis

Analysis description	**Interim analysis 2 (i.e. final analysis for PFS, interim analysis for OS)**		
Analysis population and time point description	Intent to treat, CPS≥1, CPS≥10 (only the CPS≥10 subpopulation is shown below, as this is the sought indication)		
Descriptive statistics and estimate variability	Treatment group	Pembrolizumab + chemotherapy	Placebo + chemotherapy
	CPS≥10		
	Number of subject	220 (ITT: 566)	103 (ITT: 281)
	PFS (median in months)	9.7	5.6
	95%CI	(7.6, 11.3)	(5.3, 7.5)
	OS (median in months)	23	16.1
	95%CI	(18.8, 27.5)	(12.6, 18.8)
	ORR	53.2 %	39.8 %

	95%CI	(46.4, 59.9)	(30.3, 49.9)
	DOR (median in months)	19.3	7.3
	range	(1.6+ – 29.8)	(1.5 – 32.5+)
Effect estimate per comparison	Dual Primary endpoint	Pembrolizumab + chemo vs placebo + chemo	PFS
		HR	0.65
		95%CI	(0.49, 0.86)
		P-value	0.0012
	Dual Primary endpoint	Pembrolizumab+ chemo vs placebo + chemo	OS
		HR	0.69
		95%CI	(0.51, 0.93)
		P-value	0.0066
	Secondary endpoint	Pembrolizumab+ chemo vs placebo + chemo	ORR
		Difference in %	13.6
		95%CI	(1.9, 24.8)
		P-value	0.0115 (nominal)
Notes	Only hypothesis H3 (PFS in the CPS≥10) can be rejected under the type-I-error control. This hypothesis was added to the type-I-error control with amendment 5 after interim analysis 1. P-values were one sided based on log-rank test. Hazard ratios based on Cox regression model with Efron's method of tie handling with treatment as covariate. Log-rank test and Cox-regression was stratified by chemotherapy on study (taxane vs. gemcitabine/carboplatin), tumor PD-L1 status (CPS≥1 vs CPS <1 for ITT), and prior treatment with same class of chemotherapy in the (neo)adjuvant setting (yes vs no).		
Analysis description	**Final Analysis (i.e. final analysis for OS)**		
Analysis population and time point description	Intent to treat, CPS⩾1, CPS⩾10 (only the CPS⩾10 subpopulation is shown below, as this is the sought indication)		
Descriptive statistics and estimate variability	Treatment group	Pembrolizumab + chemotherapy	Placebo + chemotherapy
	CPS⩾10		
	Number of subject	220 (ITT: 566)	103 (ITT: 281)
	PFS (median in months)	9.7	5.6
	95%CI	(7.6, 11.3)	(5.3, 7.5)
	OS (median in months)	23	16.1
	95%CI	(19, 26.3)	(12.6, 18.8)
	ORR	52.7 %	40.8 %
	95%CI	(45.9, 59.5)	(31.2, 50.9)
	DOR (median in months)	12.8	7.3
	range	(1.6+ – 45.9)	(1.5 – 46.6+)
Effect estimate per comparison	Dual Primary endpoint	Pembrolizumab + chemo vs placebo + chemo	PFS
		HR	0.66
		95%CI	(0.50, 0.88)
		P-value	0.0018 (nominal)
	Dual Primary endpoint	Pembrolizumab+ chemo vs placebo + chemo	OS
		HR	0.73
		95%CI	(0.55, 0.95)
		P-value	0.0093
	Secondary endpoint	Pembrolizumab+ chemo vs placebo + chemo	ORR

		Difference in %	12.1
		95%CI	(0.4, 23.4)
		P-value	0.0213 (nominal)
Notes	Updated PFS and ORR data with nominal p-values only		

Clinical studies in special populations

No data in special populations have been provided. Efficacy data of KN355 by age in the subgroup of patients with PD-L1 CPS ≥10 are summarized in the following table.

Approximately 20% of patients in KEYNOTE-355 were aged ≥65 years, of those 16% were ≥65-<75 years and about 5% were ≥75-<85 years. There was only one 85 years old patient in the pembrolizumab + chemotherapy arm. No patients aged over 77 years of age was enrolled in the control arm. Efficacy results in patients <65 and ≥65 years were overall consistent.

Table: Efficacy by age, Subjects with PD-L1 CPS ⩾10 (table prepared by the assessment team)

	Age < 65 years		**65 ≤ Age < 75 years**		**75 ≤ Age < 85 years**	
Endpoint	Pembro+C (N=178)	Placebo+C (N=79)	Pembro+C (N=35)	Placebo+C (N=21)	Pembro+C (N=7)	Placebo+C (N=3)
PFS						
Median PFS, months	9.5	5.5	10.7	7.6	9.6	3.5
HR (95% CI)	0.63 (0.46, 0.87)		0.70 (0.37, 1.36)		0.14 (0.01, 1.62)	
OS						
Median OS, months	21.8	16.8	28.3	13.0	NR (7.5, NR)	5.0
HR (95% CI)	0.78 (0.56, 1.08)		0.59 (0.29, 1.18)		0.00	
Objective Response						
ORR %	51.1	38	60	47.6	71.4	33.3
ORR Difference %	13.1		12.4		38.1	

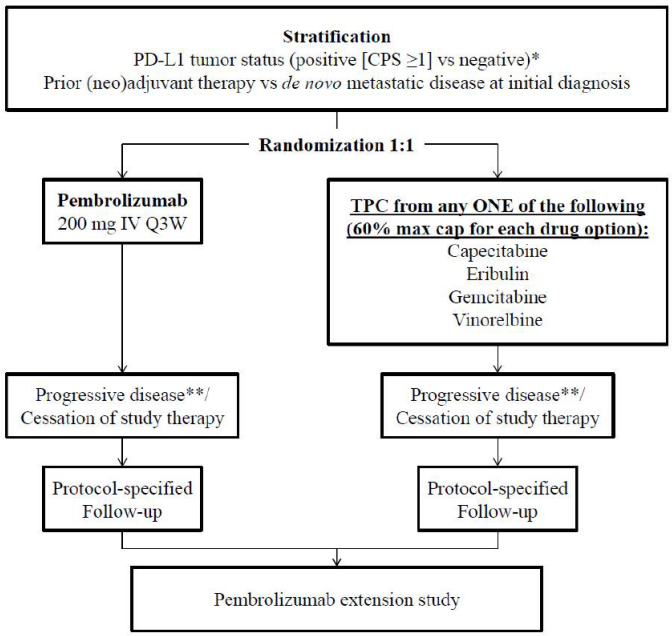
Supportive studies

Note: The MAH did not present any studies as supportive for the sought indication, although the clinical study reports of KEYNOTE-119, KEYNOTE-086 and KEYNOTE-012 in metastatic TNBC were included in the dossier. Brief summaries of these studies are presented below.

KEYNOTE-119

KEYNOTE-119 is a Phase 3 randomized, multicenter, open-label study of pembrolizumab versus single agent chemotherapy per physician's choice [TPC] (capecitabine, eribulin, vinorelbin, gemcitabine) for participants receiving 2L or 3L treatment for mTNBC.

Figure: Study Design Schematic KEYNOTE-119



Primary objectives were OS in subjects with PD-L1 positive tumors CPS≥10, CPS≥1 and in all subjects. PFS, ORR and DOR were secondary endpoints. 622 participants were enrolled (312 in the pembrolizumab arm, 310 in the TPC arm). First participant first visit was on 27 Oct 2015; the CSR included results as of the 11-APR-2019 data cutoff. Approximately 65% of patients had CPS≥1 and 30% had CPS≥10 tumors. Pembrolizumab monotherapy as 2/3L treatment for metastatic TNBC did not demonstrate a statistically significant improvement in OS compared to TPC in all participants or in participants with PD-L1 positive tumors (CPS≥1 or CPS≥10). Main results are summarized below:

OS HRs: ITT 0.97; CPS≥1 0.86; CPS≥10 0.78.

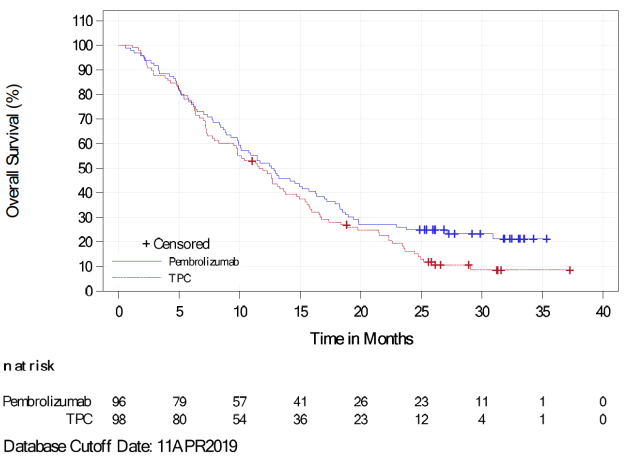
PFS HRs: ITT 1.60; CPS≥1 1.35; CPS≥10 1.14.

ORR: ITT 9.6% vs 10.6%; CPS≥1 12.3% vs 9.4%; CPS≥10 17.7% vs 9.2%.

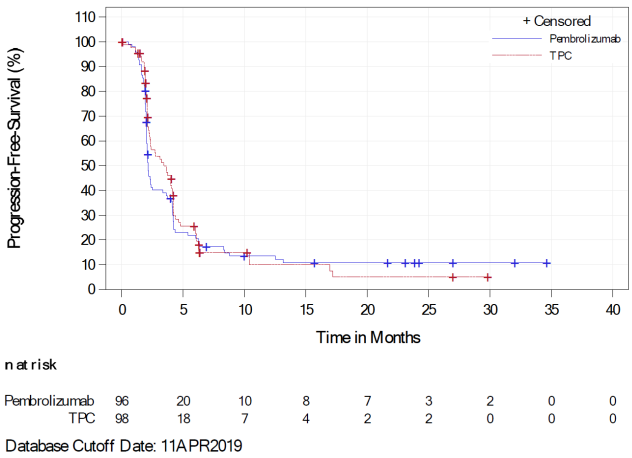
DOR: ITT 12.2 vs 8.3 months; CPS≥1 12.2 vs 6.5 months; CPS≥10 NR vs 7.1 months.

Figure: KM Estimates of PFS and Overall Survival (Subjects with PD-L1 CPS ⩾10)

KM of **OS** (**CPS ≥10**)



KM of **PFS** (**CPS ≥10**)



KEYNOTE-119 study failed to demonstrate superiority of pembrolizumab monotherapy over chemotherapy

as **2L or 3L** treatment of patients with **mTNBC** in its primary endpoint OS; a short overview is presented since KN119 results might support an association between PD-L1 expression status and efficacy outcomes (with the largest treatment effect in the not prespecified subgroup of patients whose tumors express PD-L1 CPS ≥20). Data further provide indirect evidence that monotherapy with pembrolizumab in the 1L TNBC setting would not be considered appropriate.

KEYNOTE-086

KEYNOTE-086 was planned as an open-label, nonrandomized, single-arm, multicenter, multicohort, Phase 2 study conducted in participants with centrally confirmed mTNBC, evaluating the efficacy and safety of pembrolizumab monotherapy as second line or above (2L+) in mTNBC with PD-L1 expression CPS≥1 and independent of PD-L1 expression (Cohort A), and as first line (1L) in mTNBC with PD-L1 expression CPS≥1 (Cohort B). ORR was the primary endpoint. Overall, 170 participants and 84 participants were allocated to treatment in Cohort A and Cohort B, respectively.

Cohort A (2L+): in the total population, ORR was 5.3% (95%CI 2.7%, 10%), Median DOR was not reached (range 1.2+ - 21.5+). Median PFS was 2.0 months, and median OS was 9.0 months. Results were similar regardless of PD-L1 status.

Cohort B (1L): ORR of 21.4% (95%CI 13.9%, 31.4%). Median DOR was 10.4 months (range: 4.2 – 19.2+ months). Median PFS was 2.1 months and median OS was 18.0 months.

KEYNOTE-012

KEYNOTE-012 is a Phase Ib Multi-Cohort Study of pembrolizumab (10 mg/kg Q2W) in subjects with advanced solid tumors. The CSR presented the results of 32 subjetcs from Cohort A, where patients with TNBC were enrolled. Safety and tolerability was the primary objective of this study. Of the 32 TNBC Cohort subjects in the ASaT population, 15.6% (5/32) had either a CR or PR as measured by RECIST 1.1 by BICR. Of the 5 responders, 3 had 5 or more prior lines of therapy for metastatic breast cancer, 1 had 3 prior lines, and 1 had 1 prior line. Median DOR was not reached as of the data cutoff.

2.4.3. Discussion on clinical efficacy

This is an extension of indication for Keytruda in combination with chemotherapy for patients with locally recurrent unresectable or metastatic triple negative breast cancer (TNBC) with PD-L1 CPS≥10 and who have not received prior chemotherapy for metastatic disease, based on the IA2 (final analysis for PFS and IA2 for OS) results of Part 2 of the pivotal study KEYNOTE-355, with data cut-off date 11-Dec-2019 (approximately 18 months after the last participant was randomized). Median follow-up duration was 16.8 months in the ITT population and 19.2 months in the CPS≥10 population. During the procedure, the MAH submitted also the final analysis for overall survival, with data cut-off date 15-Jun-2021 (3 years after last participant randomised), with median follow-up of 16.7 months. Part 1 of the study was an unblinded, open-label, safety run-in with 35 participants.

Design and conduct of clinical studies

Study KEYNOTE-355 is a randomized 2:1, double-blind, phase III study in previously untreated locally recurrent inoperable or metastatic TNBC comparing pembrolizumab (200 mg q3w) plus chemotherapy

(paclitaxel, nab-paclitaxel or carboplatin/gemcitabine) vs placebo plus chemotherapy. The double-blind, placebo-controlled, add-on design of KEYNOTE-355 is endorsed.

Adult patients with PS 0-1 and measurable disease by RECIST 1.1 were eligible. The diagnosis of TNBC was centrally confirmed in line with most recent ASCO/CAP guidelines. If previously treated with curative intent, such treatment should have been completed ≥6 months earlier (12 months if retreated with the same class of chemotherapy within the study), and if treated with (neo)adjuvant systemic treatment, anthracycline should have been given unless not indicated. The study allowed re-treatment with same class of chemotherapy (taxane or gemcitabine/carboplatin), if ≥12 months had elapsed between the completion of treatment with curative intent and first documented local or distant disease recurrence. If chemotherapy options included more than one regimen, choice of study chemotherapy was at physician's discretion. Patients with early recurrences (i.e. between 6 and 12 months following completion of definitive treatment for early disease) were allowed. Other key eligibility criteria accounted for the known safety profile of pembrolizumab. Overall inclusion/exclusion criteria are considered acceptable and reflect the intended target population. The diagnosis of TNBC was centrally confirmed in line with most recent ASCO/CAP guidelines.

The comparator, and backbone chemotherapy administered with pembrolizumab, was an investigator's choice between **3 different chemotherapy options** (paclitaxel, nab-paclitaxel or carboplatin plus gemcitabine). The dosing regimens proposed of the chemotherapy drugs can be considered acceptable. Chemotherapy on study (taxane vs gemcitabine/carboplatin) was one of the stratification factors as was prior treatment with same class of chemotherapy in the (neo)adjuvant setting and PD-L1 status (CPS cut off 1). Overall, stratification factors are considered appropriate, however the randomization was not stratified according to PD-L1 positive tumors CPS≥10 (see below).

Patients received treatment until confirmed disease progression, unacceptable toxicity, withdrawal of consent, or physician's decision, with up to 35 cycles (2 years) for pembrolizumab/placebo.

The MAH justified the inclusion of two different taxane options based on differential availability and clinical use worldwide and similar efficacies in terms of OS in mBC. Nab-paclitaxel is however not formally approved in EU as 1L treatment for metastatic breast cancer, although it was recently authorized in combination with atezolizumab in the same setting.

Overall, 55% of KN355 study patients received gemcitabine/carboplatin and 45% received taxane as chemotherapy regimen. ESMO and NCCN guidelines recommend use of combination chemotherapy only for patients with "high tumor burden, rapidly progressing disease, and visceral crisis" and "taxane-based therapy would usually be considered as treatment of choice" for taxane-naïve and anthracycline non-eligible patients according to ESMO guidance. Since nearly half of the study population were taxane-naïve (47%) and only 21% of patients had an early disease recurrence <12 months, the low proportion of patients treated with taxane (and the high proportion of patients treated with combination chemotherapy) does not appear in line with current guidelines. It was noted, however, that it was the sole responsibility of the physicians to choose between the different chemotherapy options.

The choice of OS and PFS as primary objectives can be considered appropriate. Assessments of PFS, ORR and DOR were measured independently by BICR per RECIST 1.1 which is endorsed.

The primary objectives/endpoints of KEYNOTE-355 were modified while the study was ongoing. Patients were enrolled regardless of PD-L1 biomarker status but were required to provide tumor tissue sample (unless contraindicated) for central testing and stratified according to PD-L1 tumor status (CPS ≥1 vs. CPS <1) in line with the biomarker plan of the original protocol that determined PD-L1 positive vs PD-L1 negative subpopulation by a PD-L1 CPS cutoff of 1. The addition of a higher **PD-L1 CPS** cut-off of **≥10** and the inclusion of subjects with PD-L1 CPS ≥10 in the primary analysis plan was introduced with amendment 5 (Oct 2019); it needs to be noted that Amendment No. 5 was finalised one year after the

first interim analysis had occurred (18 Oct 2018). Although KEYNOTE-355 is a double-blind trial, the late changes in an ongoing study raise concern over the risk of a data driven approach, taking also into account that this study would have been negative based on the initial hypotheses. The MAH provided a justification that the selection of the CPS cut-off of 10 was not driven by any knowledge of IA1 results (IA conducted by independent DMC while the sponsor remained blinded to study results per protocol, including individual treatment assignment and CPS scores; the statistical criterion for success at IA1 was not met and the DMC recommended study continuation). The MAH documented that they did not have access to the IA1 DMC at the time point where the primary hypotheses testing was modified (Amendment 5), and that the choice of the additional cut-off of CPS≥10 was based on external results from studies KEYNOTE-119 and IMpassion130, showing improved benefit with enrichment of tumor PD-L1 expression levels in TNBC. Meeting minutes of the eDMC from 3 Dec 2018 and the DMC recommendation form of IA1 show that there was no content-related communication with the MAH. The DMC charter provides information about the DMC members and unblinded study statistician, and their confidential agreement about the obligation to keep all information related to the eDMC confidential and not to discuss information to anyone other than DMC members. The results of IA2 using the SAP specified in Amendment 4 versus that specified in Amendment 5 confirmed that without the inclusion of OS and PFS hypotheses for the PD-L1 positive CPS≥10 population with amendment 5 none of the primary endpoints would have been met under amendment 4. Regarding KEYNOTE-119, a trend toward numerically better results for pembrolizumab was seen in a PD-L1 enriched population of recurrent locally advanced or metastatic TNBC tumors in (2L+), not reaching statistical significance though. IMpassion130 study demonstrated that atezolizumab + nab-paclitaxel significantly prolonged PFS in participants with PD-L1 positive tumors, defined as PD-L1 stained tumor-infiltrating immune cells of any intensity covering ≥1% of the tumor area by the VENTANA PD-L1 (SP142) assay. It is acknowledged that the timing the external results were publicly available is compatible with the date of Amendment 5 (IMpassion130 data were first publicly presented in Oct 2018[23], KEYNOTE-119 data cut-off was 11 Apr 2019). It is also acknowledged that published studies indicated that the VENTANA PD-L1 SP142 assay (used for atezolizumab) detects lower PD-L1 expression compared to the PD-L1 IHC 22C3 pharmDx assay (used in pembrolizumab studies), although there is no exact correspondence between score and cut-offs. In particular, literature suggests that there is greater variability in immune-cell staining between the two assays. The prevalence of participants identified as PD-L1 positive (IC ≥1%) in IMpassion130 by the VENTANA PD-L1 (SP142) assay and the prevalence of participants with tumors that express PD-L1 with CPS ≥10 by the PD-L1 IHC 22C3 pharmDx assay in KEYNOTE-355 was similar between the two studies (41% and 38%, respectively). In addition to the consideration regarding the choice of the PD-L1 cut-off, it is noted that the target magnitude of PFS and OS improvements was reduced in Amendment 5 compared to the original protocol success criteria (e.g. success criteria for PFS in the ITT population was 0.70 in the latest amendment, compared to 0.64 in prior protocol version).

The explanation for adding the CPS≥10 population as a confirmatory hypothesis seems reasonably justified by external studies and biological rationale. The results of PFS and OS with CPS as a continuous score show that CPS is a strong predictive factor for the pembrolizumab + chemotherapy group, but not for the placebo + chemotherapy group. Therefore, the treatment effect increases with increasing CPS values. Beneficial treatment effect for subgroups with CPS values lower than 10 is currently not proven and the treatment effect does not improve meaningfully for patients with CPS values higher than 10. With the given results it is comprehensible to set the cutoff at CPS = 10.

[23] Abstract LBA1_PR ESMO Congress 2018 'IMpassion130: Results from a global, randomised, double-blind, phase 3 study of atezolizumab (atezo) + nab-paclitaxel (nab-P) vs placebo + nab-P in treatment-naive, locally advanced or metastatic triple-negative breast cancer (mTNBC)' Annals of Oncology, Volume 29 Supplement 8 October 2018

The assumptions for median PFS of 5.5 months and OS of 17.5 months in the control arm were appropriately based on literature data available at the time of study initiation [24] [25].

The change in the multiplicity approach after interim analysis 1 was considered in the power calculation. For OS only the power calculation for the final analysis was described, not for the interim analyses. However, the provided power calculations are acceptable. Statistical methods were well reported in the protocol section and in the SAP, and considered appropriate.

Efficacy data and additional analyses

Part 1 of KEYNOTE-355 was open-label safety run-in, where a total of 34 subjects received pembrolizumab + one of the three chemotherapy options (paclitaxel, nab-paclitaxel, carboplatin/gemcitabine). Safety was the primary objective of this part: no new safety concerns were identified in part 1. Overall, the data can be considered in line with what observed in part 2, however efficacy results of part 1 are descriptive in nature and based on a limited number of subjects.

Part 2 was the phase 3 study, on which efficacy data are based. At the data cut-off for IA2, more than 90% of patients in both arms have discontinued treatment, mostly due to PD. In the ITT population, a higher number of patients discontinued pembrolizumab combination due to AE compared to chemotherapy alone, as well as due to patient or physician decision, while in the control arm more patients stopped study medication due to radiological and clinical progression. Similar trends are observed in the CPS≥10 population.

Patients in the ITT population (566 vs 281 in the pembro+chemo vs placebo+chemo arm) were well balanced with regard to **baseline characteristics** in the two arms. All patients were female with median age of 53 (about 20% >65 years), approximately 70% were post-menopausal. About 60% had ECOG 0 and 40% ECOG 1. Overall, 30% had de-novo metastatic disease. Of the remaining patients who received prior treatment for early disease, 20% had disease free interval between 6 and 12 months (i.e. early progressors), and about 20% received treatment with the same class chemotherapy used in the study in the (neo)adjuvant setting. Only few patients (3%) had history of brain metastases, therefore it is not possible to make any conclusion on efficacy/safety data in this subgroup.

Study KEYNOTE-355 enrolled patients with previously untreated metastatic TNBC or locally recurrent inoperable breast cancer who could not be treated with curative intent. A low proportion of only 3% of study participants (n=25) were recruited with locally recurrent inoperable breast cancer. The MAH did not provide efficacy data for this subgroup of patients. Considering the limitations of the small patient numbers with locally recurrent disease it is acknowledged that no reliable conclusions could be drawn from these analyses. In view of the MoA and the disease characteristics of TNBC, extrapolation of efficacy data from metastatic to locally recurrent disease is considered possible.

In the CPS≥10 subset, representing about 38% of the ITT population (220 vs 103 patients), baseline characteristics were overall similar to the ITT population. Although stratified by CPS with cut-off of 1 (and not 10), no pronounced unbalances in baseline characteristics are seen between the two arms clearly favouring the experimental arm. Few differences are however noted, such as age, number of patients receiving nab-paclitaxel or paclitaxel, patients with metastatic de novo/recurrence and DFI <12 months or history of brain metastases. Only 12% of enrolled subjects had mutational status assessed locally, of those 17% were positive, and most of the BRCA mutant patients have PD-L1 positive tumors. Due to the

[24] O'Shaughnessy J, et al. Phase III study of iniparib plus gemcitabine and carboplatin versus gemcitabine and carboplatin in patients with metastatic triple-negative breast cancer. J Clin Oncol. 2014 Dec 1;32(34):3840-7.
[25] Miles DW, et al. First-line bevacizumab in combination with chemotherapy for HER2-negative metastatic breast cancer: pooled and subgroup analyses of data from 2447 patients. Ann Oncol. 2013 Nov;24(11):2773-80.

limited data, no conclusion can be drawn at this stage, and the CHMP recommended that BRCA analyses could be provided as part of exploratory biomarker research in the future.

Baseline characteristics were generally representative of a patient population with advanced TNBC, the majority of patients were <65 years of age, postmenopausal, had recurrent disease and visceral metastasis. However, only 3.4% of patients had a history of brain metastasis. Only 4% of patients were enrolled with locally recurrent inoperable disease.

To **summarize IA2 results** (i.e. final analysis for PFS, interim for OS), PFS in the CPS≥10 population was the only endpoint reaching statistical significance. OS in CPS≥10, as well as PFS and OS in CPS≥1 did not cross the prespecified efficacy boundary at IA2. PFS and OS in the ITT population were not statistically tested at the IA2 per the prespecified multiplicity strategy. For the secondary endpoint ORR, ORR in all participants and in the CPS≥1 population were only tested at IA1 and the success criterion were not met. ORR was not formally tested at IA2 per the prespecified multiplicity strategy in all the three populations.

In the CPS≥10 population, with approximately 62% vs 77% of PFS events, a **PFS** advantage for pembrolizumab combo over chemotherapy was shown (HR=0.65, 95%CI 0.49, 0.86, p=0.0012), corresponding to gain in median PFS of about 4 months (9.7 vs 5.6 months). PFS curves were overlapping up to month 3, then diverged with a 15% improvement in PFS rate in favour of the pembrolizumab arm, which is maintained in the long term. A high number of censored events observed in the PFS curves in the two arms up to month 6 was similar in both arms and mainly due to subjects starting a new anticancer treatment before radiological disease progression. An updated PFS analysis performed at the time of the final analysis for OS, with nominal p-values only, was consistent with the primary PFS analysis.

With more than half of the population experiencing an **OS** event, a numerical OS advantage was observed at IA2 in the PD-L1 CPS≥10 population, with a gain in median survival of about 7 months: HR 0.69 (95%CI 0.51, 0.93), median OS 23 months (95%CI 18.8, 27.5) vs 16.1 (95%CI 12.6, 18.8). However, the observed p-value of p=0.0066 did not cross the prespecified efficacy boundary at IA2 (the multiplicity adjusted, one-sided nominal alpha level was 0.00472). The KM curves for OS separated since month 6 in favour of pembrolizumab + chemotherapy and remained separated over time; although curves tend to come closer toward the end, curves are no more interpretable after 18 months due to censoring. During the procedure, the MAH submitted the **final analysis (FA) for OS**. In the CPS≥10 population, OS result reached statistical significance. With 70.5% vs 81.6% of patients experiencing an OS event in the pembrolizumab + chemotherapy vs placebo + chemotherapy arm, the OS HR was 0.73 (95% CI: 0.55, 0.95), with the observed p-value of p=0.0093 successfully crossing the prespecified efficacy boundary at the FA (the multiplicity adjusted, one-sided nominal alpha level was 0.0113). Longer median OS in the pembrolizumab + chemotherapy group compared with the placebo + chemotherapy group was seen (23.0 vs 16.1 months), and OS rates by KM estimation at month 18 and 24 favoured the experimental arm. The KM OS separate starting at approximately 6 months in favor of pembrolizumab + chemotherapy in participants with PD-L1 positive tumors (CPS ≥10) and remained clearly separated over time (censoring observed after month 36). At the final analysis, OS did not reach statistical significance in the CPS≥1 population, and was not formally tested in the overall population.

In the CPS≥10 population, a numerical advantage in the secondary endpoint **ORR** was observed (53.2% vs 40%) for the experimental arm, including some more CRs (16.8% vs 12.6%). Durable (SD≥6 months) stable disease rate was similar in both arms, although more SD were recorded in the comparator arm (28% vs 44%).

As expected, median **DOR** for responders was longer for the pembrolizumab containing arm compared to placebo+chemotherapy. In the pembrolizumab combination arm, median DOR was longer in the CPS≥10 (19.3 months) than in the ITT population (10.1 months).

With regard to **PRO** assessment, the completion and compliance rate of PRO questionnaires in this double-blind study was high and similar in both arms. Overall, in the CPS≥10, no relevant differences were observed between treatment arms in the various PRO scores and parameters examined. These results do not provide supportive evidence for the clinical relevance of the combination therapy in the claimed indication. However, they also do not raise concerns about intolerable toxicities that would interfere with patients' quality of life.

PFS2 analysis by investigator showed a numerical advantage for the experimental treatment over the control arm, which was more pronounced in the CPS≥10 population and can be considered supportive of the benefit of pembrolizumab + chemotherapy over placebo + chemotherapy in higher PD-L1 expressors: HR 0.69 (95%CI 0.49, 0.87), median PFS2 16.9 months (95%CI 13.8, 19.9) vs 10.9 (95%CI 9.1, 13.2).

Various **PFS sensitivity analyses** were presented. Firstly, an analysis taking into account the few discrepancies between the stratification factors data entered in the IVRS and the actual data had almost the same results of the primary analyses, thus not raising concern. PFS assessed by investigator showed (unexpectedly) worse results compared to BICR assessment. Worse HR was noted in the most conservative sensitivity analysis 2 as a higher number of subjects in the experimental combination arm than in the chemotherapy arm started a new anticancer treatment before radiological progression (considered as events in this analysis). It is acknowledged that the PFS primary analysis censoring by BICR was prespecified in the protocol. The results of the provided sensitivity analyses overall, however, do not fully support the primary analysis, which is not very reassuring.

The mostly used **chemotherapy backbone** was carboplatin/gemcitabine (about 55% of patients), followed by nab-paclitaxel (about 30%) and paclitaxel (15%). It is of concern that patients randomized to carboplatin/gemcitabine, representing more than half of the population, obtained limited or no benefit at all in all efficacy endpoints (PFS, OS and ORR) from the addition of pembrolizumab to backbone chemotherapy, differently from what observed in patients receiving taxanes. In particular, it seems that patients who received carboplatin/gemcitabine in the control arm performed better than patients treated with taxanes. Some differences in baseline characteristics between chemotherapy backbones were notable, as well as some differences between the pembrolizumab + chemotherapy arm and the placebo + chemotherapy as to be expected. Cox regressions showed however that the difference between treatment effects of patients treated with Gemcitabine/Carboplatin and Taxane cannot be explained by baseline characteristics, even by adjusting for disease free interval. Based on an inter-trial comparison, the outcome in the placebo + carboplatin/gemcitabine or pemetrexed arms in KEYNOTE-355 was not necessarily very consistent with external data. However, due to the small number of patients in the placebo + chemotherapy arms (especially paclitaxel, n=11) and the limitations of indirect study comparisons, conclusions are hampered, and results are prone to random variations. The question whether gemcitabine/carboplatin would be less effective than pembrolizumab + taxanes when administered to patients with tumors that express PD-L1 (CPS ≥10) is clinically relevant. However, it is acknowledged that there are many uncertainties around this question and maybe available data are not sufficient to draw reliable conclusions. In conclusion, the criteria used to choose one of the chemotherapy regimens remain not fully clear. Differences in baseline and prognostic criteria are notable, though measured characteristics do not seem to have an impact on the results. The performance of the different chemotherapy backbones in the control arm is variable. Numbers are small in subgroups and differences cannot be explained. Given the experience with pembrolizumab as add-on to platinum compounds in other disease settings, it would not be biologically plausible to assume a lack of treatment effect with carboplatin/gemcitabine as backbone. When considering the relevance to add information in the SmPC about the different treatment effects per chemotherapy regimen, it was agreed that, based on the available evidence, such information might not be appropriate.

The benefit of the addition of pembrolizumab to paclitaxel vs paclitaxel alone seems more pronounced than for pembrolizumab + nab-paclitaxel vs nab-paclitaxel. This is in contrast with what observed in

studies IMpassion-130[26] [27]and IMpassion-131[28] [29] (atezolizumab + nab-paclitaxel or paclitaxel, respectively). While no concern is raised by KEYNOTE-355 results over the use of pembrolizumab combined with paclitaxel in this setting, limitations of subgroup analyses are acknowledged, especially for the limited number of patients receiving paclitaxel (33 vs 11 in the experimental and control arm, respectively, of the CPS≥10 population).

Patients with **early recurrences** (i.e. between 6 and 12 months following completion of definitive treatment for early disease) were enrolled in KEYNOTE-355 and represented about 20% of the total population, while not included instead in similar trials in the same setting (e.g. IMpassion-130 and -131). According to subgroup analyses, pembrolizumab on top of chemotherapy appears not to give survival or response advantage compared to chemotherapy alone in this subgroup. However, it is acknowledged the limited number of subjects who had early recurrence, especially in the CPS≥10 population and in the control arm (n=17), and the lack of support from other trials, limiting the possibility to draw conclusions in this population.

Regarding **age**, efficacy results were overall consistent in patients <65 and ≥65 years. No conclusions can be drawn regarding efficacy in patients ≥75 years (n=10).

Heterogeneous treatment effects were further observed taking **prior (neo)adjuvant chemotherapy treatments** into consideration. Patients with prior chemotherapy (n=193) had a smaller additional benefit by adding pembrolizumab compared with patients without prior (neo)adjuvant therapy (n=130): PFS HR 0.78 vs. 0.47, OS HR 0.90 vs. 0.46, and ORR difference 3.8% vs. 27.7% for patients with and without prior treatment, respectively. The same was observed in the analogous IMpower130 study. Assessment of baseline characteristics and prognostic factors for patients with and without prior (neo)adjuvant chemotherapy and sensitivity analyses to account for possible differences in baseline factors did not identify a single factor that could explain the observed differences in efficacy outcomes between both subgroups. Only "number of metastatic organ sites at baseline" changed the HR estimates in participants with prior (neo)adjuvant chemotherapy (PFS 0.78 to 0.66; OS 0.90 to 0.76), likely due to baseline imbalances, as a higher proportion of participants in the pembrolizumab arm had ≥3 metastatic organ sites as compared to the placebo arm in this subgroup.

In addition, no clear benefit was observed for the European population based on a post-hoc analysis (PFS HR 1.02; OS HR 1.41; ORR difference – 5.8% for the comparison of pembrolizumab + chemotherapy arm compared to the placebo + chemotherapy arm in the CPS ≥10 subgroup), within the limit of small number of EU patients (64 vs 28 in the CPS≥10 population). Compared to the ITT population, an outperformance of the control arm and more modest results in the experimental group were noted. Such negative trend was however not observed in the pre-specified subgroup Europe + North America + Australia (which includes EU patients). Some differences were observed in baseline characteristics between the two arms for participants enrolled in EU, as expected due to small number, but no single baseline factor seems to explain the observed results in the EU subgroup. Overall, within each region, intervention groups were generally well-balanced for all baseline characteristics and prognostic factors. Considering that the larger subgroup "Europe/ North America / Australia" with CPS ≥10 (n=212) derived a benefit, and that there is no biological plausible rationale that the European TNBC patients would derive an inferior benefit, the results in the European CPS ≥10 population could theoretically be a chance finding due to random variation.

[26] Schmid P, et al. Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer. N Engl J Med. 2018 Nov 29;379(22):2108-2121.
[27] EPAR Tecentriq Var II/X/17 EMA/CHMP/425313/2019
[28] Milles D. Primary results from IMpassion131, a double-blind placebo-controlled randomised phse 3 trial of first-line paclitaxel (PAC) +/- atezolizumab (atezo) for unresectable locally advanced/metastatic triple-negative breast cancer (mTNBC). In: ESMO 2020 Proffered paper - breast cancer, metastatic 1, 2020
[29] https://www.ema.europa.eu/en/news/ema-reminds-physicians-use-tecentriq-nab-paclitaxel-treating-breast-cancer

2.4.4. Conclusions on the clinical efficacy

The pivotal double-blind KEYNOTE-355 study, at the IA2 (final analysis for PFS), showed a statistically significant improvement in PFS for pembrolizumab+chemotherapy compared to placebo+chemotherapy as 1L treatment of locally recurrent unresectable/metastatic TNBC patients only in the subset whose tumor has high PD-L1 expression (CPS≥10) (HR=0.65, gain in median PFS of 4 months). This result is supported by a statistically significant OS advantage at the final analysis for OS. ORR, DOR and PFS2 were also in favour of the combination. The main concern derived from the late addition of the hypotheses in CPS≥10 population one year after conducting IA1, in an otherwise negative trial. The claim that the rational of the additional CPS≥10 cut off was based only on external results (KEYNOTE-119 and IMpassion-130) and no data from KEYNOTE-355 study itself was used is accepted. The biological rationale for an enriched pembrolizumab efficacy with higher PD-L1 expression is considered supported by the above external data, whose timing is also compatible with the amendment released, and by pembrolizumab data in various diseases. Additional data provided reassured that the MAH was blinded to data and that was comprehensible to set the cutoff at CPS 10. It is acknowledged that there are many uncertainties around the observed lower benefit of pembrolizumab in combination with carboplatin/gemcitabine and available data are not sufficient to draw reliable conclusions on this aspect.

2.5. Clinical safety

Introduction

The safety data of pembrolizumab (KEYTRUDA, MK-3475) in combination with chemotherapy (nab-paclitaxel, paclitaxel, or gemcitabine/carboplatin) in the context of its intended use for the treatment of patients with locally recurrent inoperable or metastatic TNBC, derive from the **pooled data** from Part 1 and Part 2 of study KEYNOTE-355.

Part 1 – safety run-in: unblinded, open-label, safety run-in that monitored participants (N=35) for unacceptable toxicities to study treatment (pembrolizumab + chemotherapy). Participants were assigned by forced randomization to ensure at least 10 participants were included in each treatment group (pembrolizumab + gemcitabine/carboplatin or pembrolizumab + taxane [paclitaxel or nab-paclitaxel]).

Part 2 – phase 3 study: double-blind, placebo-controlled study on a background of chemotherapy, with 847 eligible participants randomly assigned in a 2:1 ratio to receive pembrolizumab + chemotherapy or placebo + chemotherapy, respectively.

The following table provides an overview of safety datasets used in the current application:

Safety Datasets and Treatment Group Nomenclature

Dataset	Population	Study Treatment	Nomenclature in Tables	Nomenclature in Text
KEYNOTE-355 pembrolizumab + chemotherapy	N=596: Safety data from participants with locally recurrent inoperable or metastatic TNBC who received pembrolizumab in combination with chemotherapy in KEYNOTE-355. Includes safety data from Part 1 and Part 2 pooled together.	Pembrolizumab + chemotherapy (nab-paclitaxel, paclitaxel, or gemcitabine/carboplatin)	KN355 Data for Pembrolizumab + Chemotherapy[a]	Pembrolizumab + chemotherapy group

KEYNOTE-355 placebo + chemotherapy	N=281: Safety data from participants with locally recurrent inoperable or metastatic TNBC who received placebo in combination with chemotherapy in KEYNOTE-355.	Placebo + chemotherapy (nab-paclitaxel, paclitaxel, or gemcitabine/carboplatin)	KN355 Data for Placebo + Chemotherapy[b]	Placebo + chemotherapy group
TNBC pembrolizumab monotherapy	N=595: Pooled safety data from participants with metastatic TNBC treated with pembrolizumab monotherapy in Cohort A of KEYNOTE-012, KEYNOTE-086, and KEYNOTE-119.	Pembrolizumab Monotherapy	mTNBC Safety Dataset for Pembrolizumab Monotherapy[c]	metastatic TNBC monotherapy group
Pembrolizumab monotherapy reference safety	N=5884: Pooled safety data from participants treated with pembrolizumab monotherapy, including 2076 participants with advanced melanoma from KEYNOTE-001, KEYNOTE-002, KEYNOTE-006, and KEYNOTE-054; 2022 participants with NSCLC from KEYNOTE-001, KEYNOTE-010, KEYNOTE-024, and KEYNOTE-042; 909 participants with HNSCC from KEYNOTE 012, KEYNOTE-040, KEYNOTE-048, and KEYNOTE-055; 241 participants from HL in KEYNOTE-013 and KEYNOTE-087, and 636 participants from bladder cancer in KEYNOTE-045 and KEYNOTE-052.	Pembrolizumab Monotherapy	Reference Safety Dataset for Pembrolizumab Monotherapy[d]	Pembrolizumab monotherapy RSD

Abbreviations: HL=Hodgkin lymphoma; HNSCC=head and neck squamous cell carcinoma; ISS = Integrated Summary of Safety; mTNBC = metastatic triple negative breast cancer; N = number; NSCLC = non-small cell lung cancer; RSD = reference safety dataset; TNBC = triple negative breast cancer.

a. Includes all participants who received at least 1 dose of pembrolizumab or chemotherapy in KEYNOTE-355.
b. Includes all participants who received at least 1 dose of placebo or chemotherapy in KEYNOTE-355.
c. Includes all participants who received at least 1 dose of pembrolizumab in KEYNOTE-012 Cohort A, KEYNOTE-086, or KEYNOTE-119.
d. The studies that comprise the Pembrolizumab Monotherapy RSD are listed in the footnotes of the data tables in this document and in the ISS.

- Safety results of KEYNOTE-012 (data cutoff 26-APR-2016): pembrolizumab (10 mg/kg Q2W) in participants with PD-L1 positive advanced solid tumors. The study included 4 cohorts (Cohort A to D); Cohort A enrolled participants with metastatic TNBC (N=32).

- Safety results of KEYNOTE-086 (data cutoff 10-NOV-2017): pembrolizumab (200 mg Q3W) as 2L+ monotherapy in participants with metastatic TNBC independent of PD-L1 status (Cohort A; N=170) or as 1L monotherapy in participants with PD-L1 positive (defined as CPS ≥1) metastatic TNBC (Cohort B; N=84).

- Safety results of KEYNOTE-119 (data cutoff 11-APR-2019): pembrolizumab (200 mg Q3W; N=312) versus single-agent chemotherapy per physician's choice (ie, capecitabine, eribulin, gemcitabine, or vinorelbine; N=310) for participants receiving 2L or 3L treatment for metastatic TNBC.

Patient exposure

Summary of Drug Exposure (ASaT Population)

	KN355 Data for Pembrolizumab + Chemotherapy[††] (N=596)	KN355 Data for Placebo + Chemotherapy[¶¶] (N=281)	mTNBC Safety Dataset for Pembrolizumab Monotherapy[‡‡] (N=595)	Reference Safety Dataset for Pembrolizumab Monotherapy[§§] (N=5884)
Study Days On-Therapy (Months)				
Mean	8.6	7.4	4.0	7.1
Median	6.2	5.3	2.1	4.9
SD	7.15	6.57	5.27	6.55
Range	0.0 to 38.3	0.0 to 33.6	0.0 to 27.1	0.0 to 32.5

Each subject is counted once on each applicable duration category row.

Duration of Exposure is calculated as last dose date - first dose date + 1.

[††] Includes all subjects who received at least one dose of treatment in the pembrolizumab + chemotherapy arm of KN355.

[¶¶] Includes all subjects who received at least one dose of treatment in the placebo + chemotherapy arm of KN355.

[‡‡] Includes all subjects who received at least one dose of pembrolizumab in KN012-Cohort A, KN086 and KN119.

[§§] Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (Head and Neck Cancer), KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055 and KN087.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)

Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013-Cohort 3: 28SEP2018, KN087: 25SEP2016)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for TNBC (KN355: 11DEC2019, KN012: 26APR2016, KN086: 10NOV2017, KN119: 11APR2019)

	KN021 + KN048 + KN189 + KN407 Pembrolizumab Combo Data[¶¶] (N=1067)
Study Days On-Therapy (Months)	
Mean	9.7
Median	6.9
SD	8.37
Range	0.0 to 48.0

Each subject is counted once on each applicable duration category row.

Duration of Exposure is calculated as last dose date - first dose date + 1.

[††] Includes all subjects who received at least one dose of treatment in the pembrolizumab + chemotherapy arm of KN355.

[§§] Includes all subjects who received at least one dose of treatment in the placebo + chemotherapy arm of KN355.

[¶¶] Includes all subjects who received at least one dose of pembrolizumab combo therapy in KN021-A/C/G, KN048, KN189, and KN407.

MK-3475 Database Cutoff Date for Lung (KN021: 19AUG2019, KN189: 20MAY2019, KN407: 09MAY2019)

MK-3475 Database Cutoff Date for HNSCC (KN048: 25FEB2019)

MK-3475 Database Cutoff Date for mTNBC (KN355: 11DEC2019)

MedDRA version used is 23.0.

Drug exposure by duration (ASaT Population)

	KN355 Data for Pembrolizumab + Chemotherapy[††] (N=596)			KN355 Data for Placebo + Chemotherapy[¶¶] (N=281)			mTNBC Safety Dataset for Pembrolizumab Monotherapy[‡‡] (N=595)			Reference Safety Dataset for Pembrolizumab Monotherapy[§§] (N=5884)		
	n	(%)	Person-years	n	(%)	Person-years	n	(%)	Person-years	n	(%)	Person-years
Duration of exposure												
>0 m	596	(100)	(426.0)	281	(100.0)	(173.6)	595	(100.0)	(198.9)	5,884	(100.0)	(3,465.2)

>=1 m	568	(95.3)	(425.1)	266	(94.7)	(173.0)	459	(77.1)	(193.7)	5,033	(85.5)	(3,437.0)
>=3 m	469	(78.7)	(408.6)	214	(76.2)	(164.0)	222	(37.3)	(157.0)	3,620	(61.5)	(3,201.8)
>=6 m	302	(50.7)	(348.1)	125	(44.5)	(131.5)	105	(17.6)	(117.0)	2,610	(44.4)	(2,835.0)
>=12 m	151	(25.3)	(240.3)	47	(16.7)	(77.4)	48	(8.1)	(77.6)	1,196	(20.3)	(1,760.2)

Each subject is counted once on each applicable duration category row.

Duration of Exposure is calculated as last dose date - first dose date + 1.

[††] Includes all subjects who received at least one dose of treatment in the pembrolizumab + chemotherapy arm of KN355.

[¶¶] Includes all subjects who received at least one dose of treatment in the placebo + chemotherapy arm of KN355.

[‡‡] Includes all subjects who received at least one dose of pembrolizumab in KN012-Cohort A, KN086 and KN119.

[§§] Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (Head and Neck Cancer), KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055 and KN087.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)

Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013-Cohort 3: 28SEP2018, KN087: 25SEP2016)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for TNBC (KN355: 11DEC2019, KN012: 26APR2016, KN086: 10NOV2017, KN119: 11APR2019)

Subject characteristics (ASaT population)

	KN355 Data for Pembrolizumab + Chemotherapy[††]		KN355 Data for Placebo + Chemotherapy[¶¶]		mTNBC Safety Dataset for Pembrolizumab Monotherapy[‡‡]		Reference Safety Dataset for Pembrolizumab Monotherapy[§§]	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	596		281		595		5,884	
Gender								
Male	0	(0.0)	0	(0.0)	0	(0.0)	3,887	(66.1)
Female	596	(100.0)	281	(100.0)	595	(100.0)	1,997	(33.9)
Age (Years)								
<65	459	(77.0)	224	(79.7)	474	(79.7)	3,385	(57.5)
>=65	137	(23.0)	57	(20.3)	121	(20.3)	2,499	(42.5)
Mean	53.9		53.0		52.8		60.6	
SD	12.8		12.7		12.3		13.2	
Median	54.0		53.0		52.0		62.0	
Range	25 to 85		22 to 77		26 to 91		15 to 94	
Race								
American Indian Or Alaska Native	10	(1.7)	1	(0.4)	5	(0.8)	29	(0.5)
Asian	138	(23.2)	52	(18.5)	125	(21.0)	658	(11.2)
Black Or African American	21	(3.5)	17	(6.0)	45	(7.6)	108	(1.8)
Multiracial	11	(1.8)	8	(2.8)	15	(2.5)	66	(1.1)
Native Hawaiian Or Other Pacific Islander	0	(0.0)	0	(0.0)	0	(0.0)	4	(0.1)
White	399	(66.9)	195	(69.4)	390	(65.5)	4,444	(75.5)
Missing	17	(2.9)	8	(2.8)	15	(2.5)	575	(9.8)
Ethnicity								
Hispanic Or Latino	115	(19.3)	48	(17.1)	59	(9.9)	388	(6.6)
Not Hispanic Or Latino	453	(76.0)	218	(77.6)	500	(84.0)	4,697	(79.8)
Not Reported	18	(3.0)	10	(3.6)	14	(2.4)	174	(3.0)
Unknown	9	(1.5)	5	(1.8)	21	(3.5)	111	(1.9)
Missing	1	(0.2)	0	(0.0)	1	(0.2)	514	(8.7)
Age Class (Years)								
<65	459	(77.0)	224	(79.7)	474	(79.7)	3,385	(57.5)
65-74	103	(17.3)	48	(17.1)	91	(15.3)	1,737	(29.5)
75-84	33	(5.5)	9	(3.2)	27	(4.5)	663	(11.3)
>=85	1	(0.2)	0	(0.0)	3	(0.5)	99	(1.7)
ECOG Performance Scale								
[0] Normal Activity	357	(59.9)	173	(61.6)	160	(26.9)	2,761	(46.9)
[1] Symptoms, but ambulatory	238	(39.9)	108	(38.4)	293	(49.2)	2,931	(49.8)
Other/Missing	1	(0.2)	0	(0.0)	142	(23.9)	192	(3.3)
	KN355 Data for		KN355 Data for		mTNBC Safety		Reference	

	Pembrolizumab + Chemotherapy[†] [†]		Placebo + Chemotherapy[¶] [¶]		Dataset for Pembrolizumab Monotherapy[‡‡]		Safety Dataset for Pembrolizumab Monotherapy[§§]	
	n	(%)	n	(%)	n	(%)	n	(%)
Geographic Region								
EU	177	(29.7)	94	(33.5)	195	(32.8)	2,091	(35.5)
Ex-EU	419	(70.3)	187	(66.5)	400	(67.2)	3,793	(64.5)

[††] Includes all subjects who received at least one dose of treatment in the pembrolizumab + chemotherapy arm of KN355.

[¶¶] Includes all subjects who received at least one dose of treatment in the placebo + chemotherapy arm of KN355.

[‡‡] Includes all subjects who received at least one dose of pembrolizumab in KN012-Cohort A, KN086 and KN119.

[§§] Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (Head and Neck Cancer), KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055 and KN087.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)

Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013-Cohort 3: 28SEP2018, KN087: 25SEP2016)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for TNBC (KN355: 11DEC2019, KN012: 26APR2016, KN086: 10NOV2017, KN119: 11APR2019)

Adverse events

Overall AEs

Summary of Adverse Events (ASaT population)

	KN355 Data for Pembrolizumab + Chemotherapy[†] [†]		KN355 Data for Placebo + Chemotherapy[¶] [¶]		mTNBC Safety Dataset for Pembrolizumab Monotherapy[‡‡]		Reference Safety Dataset for Pembrolizumab Monotherapy[§§]	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	596		281		595		5,884	
with one or more adverse events	588	(98.7)	276	(98.2)	559	(93.9)	5,687	(96.7)
with no adverse event	8	(1.3)	5	(1.8)	36	(6.1)	197	(3.3)
with drug-related[†] adverse events	574	(96.3)	267	(95.0)	368	(61.8)	4,123	(70.1)
with toxicity grade 3-5 adverse events	465	(78.0)	207	(73.7)	218	(36.6)	2,813	(47.8)
with toxicity grade 3-5 drug-related adverse events	407	(68.3)	188	(66.9)	79	(13.3)	909	(15.4)
with serious adverse events	181	(30.4)	67	(23.8)	140	(23.5)	2,252	(38.3)
with serious drug-related adverse events	105	(17.6)	34	(12.1)	46	(7.7)	650	(11.0)
with any dose modification[‡] due to an adverse event	456	(76.5)	209	(74.4)	129	(21.7)	2,028	(34.5)
pembrolizumab dose modification	18	(3.0)	0	(0.0)	129	(21.7)	2,028	(34.5)
pembrolizumab/placebo dose modification	314	(52.7)	134	(47.7)	129	(21.7)	2,028	(34.5)
nab-paclitaxel dose	106	(17.8)	45	(16.0)	0	(0.0)	0	(0.0)

modification								
paclitaxel dose modification	60	(10.1)	21	(7.5)	0	(0.0)	0	(0.0)
gemcitabine dose modification	275	(46.1)	138	(49.1)	0	(0.0)	0	(0.0)
carboplatin dose modification	272	(45.6)	140	(49.8)	0	(0.0)	0	(0.0)
who died	15	(2.5)	5	(1.8)	11	(1.8)	311	(5.3)
who died due to a drug-related adverse event	2	(0.3)	0	(0.0)	2	(0.3)	39	(0.7)
discontinued any drug due to an adverse event	128	(21.5)	37	(13.2)	30	(5.0)	783	(13.3)
discontinued pembrolizumab	7	(1.2)	0	(0.0)	30	(5.0)	783	(13.3)
discontinued pembrolizumab/placebo	60	(10.1)	15	(5.3)	30	(5.0)	783	(13.3)
discontinued nab-paclitaxel	26	(4.4)	4	(1.4)	0	(0.0)	0	(0.0)
discontinued paclitaxel	19	(3.2)	6	(2.1)	0	(0.0)	0	(0.0)
discontinued gemcitabine	39	(6.5)	16	(5.7)	0	(0.0)	0	(0.0)
discontinued carboplatin	44	(7.4)	17	(6.0)	0	(0.0)	0	(0.0)
discontinued any drug due to a drug-related adverse event	111	(18.6)	31	(11.0)	20	(3.4)	405	(6.9)
discontinued pembrolizumab	3	(0.5)	0	(0.0)	20	(3.4)	405	(6.9)
discontinued pembrolizumab/placebo	51	(8.6)	10	(3.6)	20	(3.4)	405	(6.9)
discontinued nab-paclitaxel	22	(3.7)	3	(1.1)	0	(0.0)	0	(0.0)
discontinued paclitaxel	17	(2.9)	3	(1.1)	0	(0.0)	0	(0.0)
discontinued gemcitabine	34	(5.7)	15	(5.3)	0	(0.0)	0	(0.0)
discontinued carboplatin	38	(6.4)	16	(5.7)	0	(0.0)	0	(0.0)
discontinued any drug due to a serious adverse event	51	(8.6)	9	(3.2)	17	(2.9)	570	(9.7)
discontinued pembrolizumab	6	(1.0)	0	(0.0)	17	(2.9)	570	(9.7)
discontinued pembrolizumab/placebo	39	(6.5)	8	(2.8)	17	(2.9)	570	(9.7)
discontinued nab-paclitaxel	10	(1.7)	1	(0.4)	0	(0.0)	0	(0.0)

	KN355 Data for Pembrolizumab + Chemotherapy[†] [†]		KN355 Data for Placebo + Chemotherapy[¶] [¶]		mTNBC Safety Dataset for Pembrolizumab Monotherapy[‡‡]		Reference Safety Dataset for Pembrolizumab Monotherapy[§§]	
	n	(%)	n	(%)	n	(%)	n	(%)
discontinued paclitaxel	5	(0.8)	4	(1.4)	0	(0.0)	0	(0.0)
discontinued gemcitabine	10	(1.7)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued carboplatin	9	(1.5)	1	(0.4)	0	(0.0)	0	(0.0)
discontinued any drug due to a serious drug-related adverse event	40	(6.7)	4	(1.4)	10	(1.7)	244	(4.1)
discontinued pembrolizumab	3	(0.5)	0	(0.0)	10	(1.7)	244	(4.1)
discontinued pembrolizumab/placebo	32	(5.4)	3	(1.1)	10	(1.7)	244	(4.1)
discontinued nab-paclitaxel	6	(1.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued paclitaxel	4	(0.7)	1	(0.4)	0	(0.0)	0	(0.0)
discontinued gemcitabine	7	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued carboplatin	6	(1.0)	1	(0.4)	0	(0.0)	0	(0.0)

[†] Determined by the investigator to be related to the drug.

[‡] Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

[††] Includes all subjects who received at least one dose of treatment in the pembrolizumab + chemotherapy arm of KN355.

[¶¶] Includes all subjects who received at least one dose of treatment in the placebo + chemotherapy arm of KN355.

[‡‡] Includes all subjects who received at least one dose of pembrolizumab in KN012-Cohort A, KN086 and KN119.

§§ Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (Head and Neck Cancer), KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055 and KN087.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)

Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013-Cohort 3: 28SEP2018, KN087: 25SEP2016)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for TNBC (KN355: 11DEC2019, KN012: 26APR2016, KN086: 10NOV2017, KN119: 11APR2019)

Exposure-Adjusted Adverse Events summary

(Including multiple occurrences of events) ASaT population

Table 5.3.5.3.3-tnbc2: 2
Exposure-Adjusted Adverse Event Summary
(Including Multiple Occurrences of Events)
(ASaT Population)

	Event Count and Rate (Events/100 person-years)[†]			
	KN355 Data for Pembrolizumab + Chemotherapy[††]	KN355 Data for Placebo + Chemotherapy[¶¶]	mTNBC Safety Dataset for Pembrolizumab Monotherapy[‡‡]	Reference Safety Dataset for Pembrolizumab Monotherapy[§§]
Number of subjects exposed	596	281	595	5884
Total exposure[‡] in person-years	473.14	195.89	246.83	3894.24
Total events (rate)				
adverse events	13089 (2766.39)	5283 (2696.88)	4210 (1705.61)	60969 (1565.62)
drug-related[§] adverse events	8696 (1837.92)	3421 (1746.36)	1383 (560.30)	19170 (492.27)
toxicity grade 3-5 adverse events	2313 (488.86)	956 (488.02)	424 (171.78)	6130 (157.41)
toxicity grade 3-5 drug-related adverse events	1929 (407.70)	810 (413.49)	106 (42.94)	1371 (35.21)
serious adverse events	327 (69.11)	119 (60.75)	225 (91.16)	4072 (104.56)
serious drug-related adverse events	173 (36.56)	56 (28.59)	56 (22.69)	911 (23.39)
adverse events leading to death	15 (3.17)	5 (2.55)	11 (4.46)	318 (8.17)
drug-related adverse events leading to death	2 (0.42)	0 (0.00)	2 (0.81)	39 (1.00)
adverse events resulting in drug discontinuation	159 (33.61)	40 (20.42)	35 (14.18)	855 (21.96)
drug-related adverse events resulting in drug discontinuation	141 (29.80)	34 (17.36)	24 (9.72)	442 (11.35)
serious adverse events resulting in drug discontinuation	56 (11.84)	9 (4.59)	18 (7.29)	606 (15.56)
serious drug-related adverse events resulting in drug discontinuation	44 (9.30)	4 (2.04)	11 (4.46)	257 (6.60)

[†] Event rate per 100 person-years of exposure=event count *100/person-years of exposure.
[‡] Drug exposure is defined as the time between the first dose date + 1 day and the earlier of the last dose date + 30 or the database cutoff date.
[§] Determined by the investigator to be related to the drug.
For subjects who received second course treatment, adverse events which occurred in second course phase are excluded.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
[††] Includes all subjects who received at least one dose of treatment in the pembrolizumab + chemotherapy arm of KN355.
[¶¶] Includes all subjects who received at least one dose of treatment in the placebo + chemotherapy arm of KN355.
[‡‡] Includes all subjects who received at least one dose of pembrolizumab in KN012-Cohort A, KN086 and KN119.
[§§] Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (Head and Neck Cancer), KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055 and KN087.
Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)
Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)
Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)
Database cutoff date for cHL (KN013-Cohort 3: 28SEP2018, KN087: 25SEP2016)
Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)
Database cutoff date for TNBC (KN355: 11DEC2019, KN012: 26APR2016, KN086: 10NOV2017, KN119: 11APR2019)

Source: [ISS: adam-adsl; adae]

Subjects with Adverse events (Incidence ≥ 10% in One or More Treatment Groups) By Decreasing Frequency of Preferred Term (ASaT population)

	KN355 Data for Pembrolizumab + Chemotherapy[†] [†]		KN355 Data for Placebo + Chemotherapy[¶] [¶]		mTNBC Safety Dataset for Pembrolizumab Monotherapy[‡‡]		Reference Safety Dataset for Pembrolizumab Monotherapy[§§]	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	596		281		595		5,884	
with one or more adverse events	588	(98.7)	276	(98.2)	559	(93.9)	5,687	(96.7)
with no adverse events	8	(1.3)	5	(1.8)	36	(6.1)	197	(3.3)
Anaemia	318	(53.4)	143	(50.9)	62	(10.4)	834	(14.2)
Nausea	262	(44.0)	132	(47.0)	113	(19.0)	1,203	(20.4)
Neutropenia	243	(40.8)	109	(38.8)	6	(1.0)	49	(0.8)
Alopecia	201	(33.7)	97	(34.5)	8	(1.3)	85	(1.4)
Fatigue	182	(30.5)	97	(34.5)	152	(25.5)	1,878	(31.9)
Diarrhoea	168	(28.2)	66	(23.5)	75	(12.6)	1,193	(20.3)
Constipation	166	(27.9)	77	(27.4)	98	(16.5)	992	(16.9)
Vomiting	155	(26.0)	63	(22.4)	57	(9.6)	726	(12.3)
Alanine aminotransferase increased	146	(24.5)	55	(19.6)	39	(6.6)	388	(6.6)
Aspartate aminotransferase increased	137	(23.0)	47	(16.7)	60	(10.1)	380	(6.5)
Neutrophil count decreased	134	(22.5)	75	(26.7)	3	(0.5)	37	(0.6)
Decreased appetite	128	(21.5)	39	(13.9)	72	(12.1)	1,132	(19.2)
Cough	126	(21.1)	49	(17.4)	115	(19.3)	1,138	(19.3)
Thrombocytopenia	122	(20.5)	57	(20.3)	10	(1.7)	90	(1.5)
Asthenia	119	(20.0)	48	(17.1)	61	(10.3)	663	(11.3)
Headache	119	(20.0)	66	(23.5)	74	(12.4)	706	(12.0)
Rash	117	(19.6)	33	(11.7)	52	(8.7)	896	(15.2)
Leukopenia	116	(19.5)	50	(17.8)	6	(1.0)	45	(0.8)
White blood cell count decreased	111	(18.6)	54	(19.2)	6	(1.0)	56	(1.0)
Pyrexia	109	(18.3)	56	(19.9)	70	(11.8)	734	(12.5)
Arthralgia	99	(16.6)	39	(13.9)	82	(13.8)	846	(14.4)
Hypothyroidism	95	(15.9)	9	(3.2)	53	(8.9)	647	(11.0)
Pruritus	93	(15.6)	32	(11.4)	66	(11.1)	1,053	(17.9)
Platelet count decreased	90	(15.1)	44	(15.7)	7	(1.2)	73	(1.2)
Back pain	75	(12.6)	41	(14.6)	60	(10.1)	654	(11.1)
Dyspnoea	69	(11.6)	37	(13.2)	91	(15.3)	984	(16.7)
Upper respiratory tract infection	68	(11.4)	25	(8.9)	23	(3.9)	371	(6.3)
Neuropathy peripheral	67	(11.2)	35	(12.5)	14	(2.4)	114	(1.9)
Oedema peripheral	65	(10.9)	28	(10.0)	40	(6.7)	510	(8.7)
Myalgia	62	(10.4)	34	(12.1)	42	(7.1)	428	(7.3)

	KN355 Data for Pembrolizumab + Chemotherapy[†] [†]		KN355 Data for Placebo + Chemotherapy[¶] [¶]		mTNBC Safety Dataset for Pembrolizumab Monotherapy[‡‡]		Reference Safety Dataset for Pembrolizumab Monotherapy[§§]	
	n	(%)	n	(%)	n	(%)	n	(%)
Pain in extremity	59	(9.9)	41	(14.6)	42	(7.1)	389	(6.6)

Every subject is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

[††] Includes all subjects who received at least one dose of treatment in the pembrolizumab + chemotherapy arm of KN355.

[¶¶] Includes all subjects who received at least one dose of treatment in the placebo + chemotherapy arm of KN355.

[‡‡] Includes all subjects who received at least one dose of pembrolizumab in KN012-Cohort A, KN086 and KN119.

[§§] Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (Head and Neck Cancer), KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055 and KN087.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)

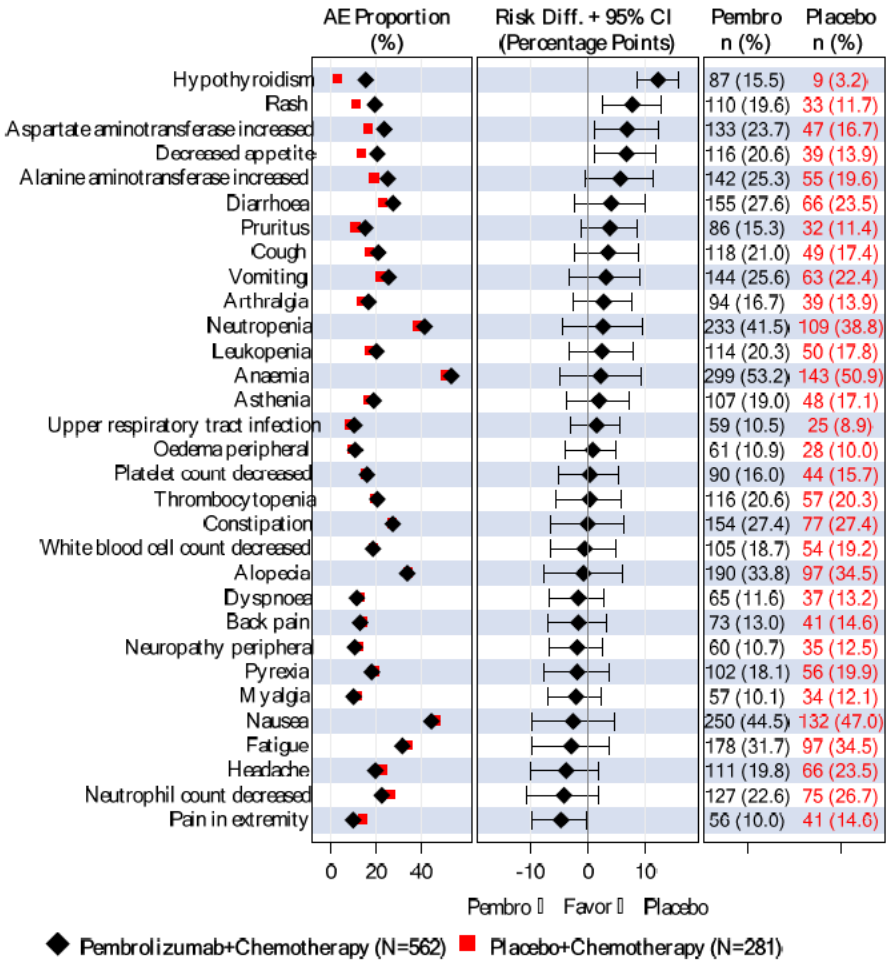
Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013-Cohort 3: 28SEP2018, KN087: 25SEP2016)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for TNBC (KN355: 11DEC2019, KN012: 26APR2016, KN086: 10NOV2017, KN119: 11APR2019)

Between-Treatment Comparisons in Adverse Events (Incidence ≥ 10% in One or More Treatment Groups)
Sorted by Risk Difference (Part 2 All Subjects) (ASaT Population)



Database Cutoff Date: 11DEC2019
Source: [P355V01MK3475: adam-adsl; adae]

Drug-related Adverse Events

Subjects With Drug-Related Adverse Events

(Incidence ≥ 5% in One or More Treatment Groups)
By Decreasing Frequency of Preferred Term (ASaT Population)

	KN355 Data for Pembrolizumab + Chemotherapy[†] [†]		KN355 Data for Placebo + Chemotherapy[¶] [¶]		mTNBC Safety Dataset for Pembrolizumab Monotherapy[‡‡]		Reference Safety Dataset for Pembrolizumab Monotherapy[§§]	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	596		281		595		5,884	
with one or more adverse events	574	(96.3)	267	(95.0)	368	(61.8)	4,123	(70.1)
with no adverse events	22	(3.7)	14	(5.0)	227	(38.2)	1,761	(29.9)
Anaemia	291	(48.8)	129	(45.9)	25	(4.2)	202	(3.4)
Neutropenia	241	(40.4)	107	(38.1)	3	(0.5)	30	(0.5)
Nausea	229	(38.4)	115	(40.9)	67	(11.3)	532	(9.0)
Alopecia	197	(33.1)	94	(33.5)	3	(0.5)	44	(0.7)
Fatigue	164	(27.5)	83	(29.5)	100	(16.8)	1,166	(19.8)
Neutrophil count decreased	132	(22.1)	74	(26.3)	2	(0.3)	26	(0.4)
Alanine aminotransferase increased	118	(19.8)	46	(16.4)	25	(4.2)	232	(3.9)
Diarrhoea	115	(19.3)	45	(16.0)	43	(7.2)	628	(10.7)
Thrombocytopenia	114	(19.1)	54	(19.2)	2	(0.3)	41	(0.7)
Leukopenia	113	(19.0)	49	(17.4)	3	(0.5)	29	(0.5)
Aspartate aminotransferase increased	111	(18.6)	42	(14.9)	32	(5.4)	217	(3.7)
Vomiting	111	(18.6)	42	(14.9)	20	(3.4)	196	(3.3)
White blood cell count decreased	108	(18.1)	54	(19.2)	3	(0.5)	28	(0.5)
Decreased appetite	97	(16.3)	25	(8.9)	33	(5.5)	461	(7.8)
Rash	92	(15.4)	26	(9.3)	29	(4.9)	669	(11.4)
Platelet count decreased	90	(15.1)	43	(15.3)	5	(0.8)	32	(0.5)
Asthenia	89	(14.9)	37	(13.2)	32	(5.4)	363	(6.2)
Constipation	80	(13.4)	37	(13.2)	19	(3.2)	156	(2.7)
Hypothyroidism	80	(13.4)	8	(2.8)	45	(7.6)	561	(9.5)
Pruritus	64	(10.7)	26	(9.3)	43	(7.2)	831	(14.1)
Neuropathy peripheral	61	(10.2)	32	(11.4)	5	(0.8)	40	(0.7)
Pyrexia	58	(9.7)	23	(8.2)	29	(4.9)	256	(4.4)
Peripheral sensory neuropathy	55	(9.2)	20	(7.1)	5	(0.8)	28	(0.5)
Arthralgia	48	(8.1)	23	(8.2)	36	(6.1)	434	(7.4)
Dysgeusia	47	(7.9)	12	(4.3)	8	(1.3)	60	(1.0)
Stomatitis	47	(7.9)	17	(6.0)	6	(1.0)	71	(1.2)
Myalgia	46	(7.7)	21	(7.5)	22	(3.7)	231	(3.9)
Headache	39	(6.5)	23	(8.2)	20	(3.4)	190	(3.2)
Blood alkaline phosphatase increased	35	(5.9)	12	(4.3)	12	(2.0)	84	(1.4)
Weight decreased	34	(5.7)	7	(2.5)	4	(0.7)	138	(2.3)
Lymphocyte count decreased	30	(5.0)	9	(3.2)	2	(0.3)	47	(0.8)

	KN355 Data for Pembrolizumab + Chemotherapy[†] [†]		KN355 Data for Placebo + Chemotherapy[¶] [¶]		mTNBC Safety Dataset for Pembrolizumab Monotherapy[‡‡]		Reference Safety Dataset for Pembrolizumab Monotherapy[§§]	
	n	(%)	n	(%)	n	(%)	n	(%)
Dizziness	14	(2.3)	15	(5.3)	11	(1.8)	83	(1.4)

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Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

[†] [†] Includes all subjects who received at least one dose of treatment in the pembrolizumab + chemotherapy arm of KN355.

[¶] [¶] Includes all subjects who received at least one dose of treatment in the placebo + chemotherapy arm of KN355.

[‡‡] Includes all subjects who received at least one dose of pembrolizumab in KN012-Cohort A, KN086 and KN119.

[§§] Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (Head and Neck Cancer), KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055 and KN087.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)

Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013-Cohort 3: 28SEP2018, KN087: 25SEP2016)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for TNBC (KN355: 11DEC2019, KN012: 26APR2016, KN086: 10NOV2017, KN119: 11APR2019)

All Grade 3 to 5 Adverse Events

Subjects With Grade 3-5 Adverse Events (Incidence ≥ 5% in One or More Treatment Groups) By Decreasing Frequency of Preferred Term (ASaT Population)

	KN355 Data for Pembrolizumab + Chemotherapy[†] [†]		KN355 Data for Placebo + Chemotherapy[¶] [¶]		mTNBC Safety Dataset for Pembrolizumab Monotherapy[‡‡]		Reference Safety Dataset for Pembrolizumab Monotherapy[§§]	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	596		281		595		5,884	
with one or more adverse events	465	(78.0)	207	(73.7)	218	(36.6)	2,813	(47.8)
with no adverse events	131	(22.0)	74	(26.3)	377	(63.4)	3,071	(52.2)
Neutropenia	176	(29.5)	85	(30.2)	2	(0.3)	15	(0.3)
Anaemia	107	(18.0)	46	(16.4)	18	(3.0)	234	(4.0)
Neutrophil count decreased	106	(17.8)	57	(20.3)	2	(0.3)	8	(0.1)
Thrombocytopenia	65	(10.9)	33	(11.7)	5	(0.8)	17	(0.3)
White blood cell count decreased	63	(10.6)	29	(10.3)	2	(0.3)	4	(0.1)
Leukopenia	59	(9.9)	31	(11.0)	0	(0.0)	7	(0.1)
Alanine aminotransferase increased	46	(7.7)	16	(5.7)	7	(1.2)	60	(1.0)
Platelet count decreased	36	(6.0)	20	(7.1)	0	(0.0)	8	(0.1)
Aspartate aminotransferase increased	32	(5.4)	10	(3.6)	19	(3.2)	65	(1.1)

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A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

[†] Includes all subjects who received at least one dose of treatment in the pembrolizumab + chemotherapy arm of KN355.

[¶] Includes all subjects who received at least one dose of treatment in the placebo + chemotherapy arm of KN355.

[‡] Includes all subjects who received at least one dose of pembrolizumab in KN012-Cohort A, KN086 and KN119.

[§] Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (Head and Neck Cancer), KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055 and KN087.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)

Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013-Cohort 3: 28SEP2018, KN087: 25SEP2016)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for TNBC (KN355: 11DEC2019, KN012: 26APR2016, KN086: 10NOV2017, KN119: 11APR2019)

Subjects With Grade 3-5 Drug-Related Adverse Events (Incidence ≥ 5% in One or More Treatment Groups) By Decreasing Frequency of Preferred Term (ASaT Population)

	KN355 Data for Pembrolizumab + Chemotherapy[†] [†]		KN355 Data for Placebo + Chemotherapy[¶] [¶]		mTNBC Safety Dataset for Pembrolizumab Monotherapy[‡‡]		Reference Safety Dataset for Pembrolizumab Monotherapy[§§]	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	596		281		595		5,884	

with one or more adverse events	407	(68.3)	188	(66.9)	79	(13.3)	909	(15.4)
with no adverse events	189	(31.7)	93	(33.1)	516	(86.7)	4,975	(84.6)
Neutropenia	174	(29.2)	84	(29.9)	1	(0.2)	9	(0.2)
Neutrophil count decreased	103	(17.3)	57	(20.3)	1	(0.2)	4	(0.1)
Anaemia	98	(16.4)	41	(14.6)	5	(0.8)	29	(0.5)
White blood cell count decreased	61	(10.2)	29	(10.3)	1	(0.2)	1	(0.0)
Thrombocytopenia	59	(9.9)	31	(11.0)	1	(0.2)	6	(0.1)
Leukopenia	58	(9.7)	30	(10.7)	0	(0.0)	3	(0.1)
Platelet count decreased	36	(6.0)	20	(7.1)	0	(0.0)	2	(0.0)
Alanine aminotransferase increased	34	(5.7)	13	(4.6)	4	(0.7)	34	(0.6)

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A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

[††] Includes all subjects who received at least one dose of treatment in the pembrolizumab + chemotherapy arm of KN355.

[¶¶] Includes all subjects who received at least one dose of treatment in the placebo + chemotherapy arm of KN355.

[‡‡] Includes all subjects who received at least one dose of pembrolizumab in KN012-Cohort A, KN086 and KN119.

[§§] Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (Head and Neck Cancer), KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055 and KN087.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)

Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013-Cohort 3: 28SEP2018, KN087: 25SEP2016)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for TNBC (KN355: 11DEC2019, KN012: 26APR2016, KN086: 10NOV2017, KN119: 11APR2019)

Serious adverse event/deaths/other significant events

Serious AEs

Subjects With Serious Adverse Events Up to 90 Days of Last Dose (Incidence ≥ 1% in One or More Treatment Groups) By Decreasing Frequency of Preferred Term (ASaT Population)

	KN355 Data for Pembrolizumab + Chemotherapy[†] [†]		KN355 Data for Placebo + Chemotherapy[¶] [¶]		mTNBC Safety Dataset for Pembrolizumab Monotherapy[‡‡]		Reference Safety Dataset for Pembrolizumab Monotherapy[§§]	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	596		281		595		5,884	
with one or more adverse events	181	(30.4)	67	(23.8)	140	(23.5)	2,252	(38.3)
with no adverse events	415	(69.6)	214	(76.2)	455	(76.5)	3,632	(61.7)
Anaemia	13	(2.2)	6	(2.1)	4	(0.7)	59	(1.0)
Pneumonia	12	(2.0)	7	(2.5)	11	(1.8)	243	(4.1)
Thrombocytopenia	12	(2.0)	4	(1.4)	0	(0.0)	7	(0.1)
Vomiting	10	(1.7)	6	(2.1)	0	(0.0)	28	(0.5)
Febrile neutropenia	9	(1.5)	3	(1.1)	2	(0.3)	4	(0.1)
Pneumonitis	7	(1.2)	0	(0.0)	4	(0.7)	116	(2.0)
Pulmonary embolism	7	(1.2)	3	(1.1)	5	(0.8)	71	(1.2)
Pyrexia	7	(1.2)	4	(1.4)	7	(1.2)	66	(1.1)
Sepsis	6	(1.0)	3	(1.1)	3	(0.5)	42	(0.7)
Neutropenia	5	(0.8)	4	(1.4)	1	(0.2)	3	(0.1)
Pleural effusion	5	(0.8)	3	(1.1)	19	(3.2)	83	(1.4)
Diarrhoea	4	(0.7)	0	(0.0)	2	(0.3)	58	(1.0)
Nausea	3	(0.5)	3	(1.1)	1	(0.2)	28	(0.5)

Dyspnoea	2	(0.3)	1	(0.4)	7	(1.2)	83	(1.4)
Urinary tract infection	2	(0.3)	1	(0.4)	2	(0.3)	59	(1.0)

	KN355 Data for Pembrolizumab + Chemotherapy[†] [†]		KN355 Data for Placebo + Chemotherapy[¶] [¶]		mTNBC Safety Dataset for Pembrolizumab Monotherapy[‡‡]		Reference Safety Dataset for Pembrolizumab Monotherapy[§§]	
	n	(%)	n	(%)	n	(%)	n	(%)
Colitis	1	(0.2)	0	(0.0)	2	(0.3)	59	(1.0)

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MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

[†] [†] Includes all subjects who received at least one dose of treatment in the pembrolizumab + chemotherapy arm of KN355.

[¶] [¶] Includes all subjects who received at least one dose of treatment in the placebo + chemotherapy arm of KN355.

[‡‡] Includes all subjects who received at least one dose of pembrolizumab in KN012-Cohort A, KN086 and KN119.

[§§] Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (Head and Neck Cancer), KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055 and KN087.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)

Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013-Cohort 3: 28SEP2018, KN087: 25SEP2016)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for TNBC (KN355: 11DEC2019, KN012: 26APR2016, KN086: 10NOV2017, KN119: 11APR2019)

Drug related SAEs

Subjects With Drug-related Serious Adverse Events Up to 90 Days of Last Dose (Incidence ≥ 1% in One or More Treatment Groups) By Decreasing Frequency of Preferred Term (ASaT Population)

	KN355 Data for Pembrolizumab + Chemotherapy[†] [†]		KN355 Data for Placebo + Chemotherapy[¶] [¶]		mTNBC Safety Dataset for Pembrolizumab Monotherapy[‡‡]		Reference Safety Dataset for Pembrolizumab Monotherapy[§§]	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	596		281		595		5,884	
with one or more adverse events	105	(17.6)	34	(12.1)	46	(7.7)	650	(11.0)
with no adverse events	491	(82.4)	247	(87.9)	549	(92.3)	5,234	(89.0)
Anaemia	13	(2.2)	4	(1.4)	2	(0.3)	5	(0.1)
Thrombocytopenia	10	(1.7)	3	(1.1)	0	(0.0)	3	(0.1)
Febrile neutropenia	8	(1.3)	3	(1.1)	0	(0.0)	0	(0.0)
Vomiting	8	(1.3)	3	(1.1)	0	(0.0)	9	(0.2)
Pneumonitis	7	(1.2)	0	(0.0)	4	(0.7)	110	(1.9)
Pyrexia	6	(1.0)	3	(1.1)	2	(0.3)	17	(0.3)
Neutropenia	5	(0.8)	4	(1.4)	0	(0.0)	1	(0.0)

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more of the columns meets the incidence criterion in the report title, after rounding.

[††] Includes all subjects who received at least one dose of treatment in the pembrolizumab + chemotherapy arm of KN355.

[¶¶] Includes all subjects who received at least one dose of treatment in the placebo + chemotherapy arm of KN355.

[‡‡] Includes all subjects who received at least one dose of pembrolizumab in KN012-Cohort A, KN086 and KN119.

[§§] Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (Head and Neck Cancer), KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055 and KN087.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)

Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013-Cohort 3: 28SEP2018, KN087: 25SEP2016)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for TNBC (KN355: 11DEC2019, KN012: 26APR2016, KN086: 10NOV2017, KN119: 11APR2019)

Subjects With Adverse Events Resulting in Death Up to 90 Days of Last Dose (Incidence > 0% in One or More Treatment Groups) By Decreasing Frequency of Preferred Term (ASaT Population)

	KN355 Data for Pembrolizumab + Chemotherapy[†][†]		KN355 Data for Placebo + Chemotherapy[¶¶]		mTNBC Safety Dataset for Pembrolizumab Monotherapy[‡‡]		Reference Safety Dataset for Pembrolizumab Monotherapy[§§]	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	596		281		595		5,884	
with one or more adverse events	15	(2.5)	5	(1.8)	11	(1.8)	311	(5.3)
with no adverse events	581	(97.5)	276	(98.2)	584	(98.2)	5,573	(94.7)
Cardio-respiratory arrest	2	(0.3)	0	(0.0)	2	(0.3)	4	(0.1)
Septic shock	2	(0.3)	0	(0.0)	0	(0.0)	10	(0.2)
Acute kidney injury	1	(0.2)	0	(0.0)	0	(0.0)	3	(0.1)
Acute myocardial infarction	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.0)
Arrhythmia	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Cardiac arrest	1	(0.2)	0	(0.0)	1	(0.2)	9	(0.2)
Cardiopulmonary failure	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.0)
Death	1	(0.2)	0	(0.0)	0	(0.0)	42	(0.7)
Hepatic encephalopathy	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Multiple organ dysfunction syndrome	1	(0.2)	0	(0.0)	0	(0.0)	5	(0.1)
Pneumonia	1	(0.2)	1	(0.4)	0	(0.0)	36	(0.6)
Pulmonary embolism	1	(0.2)	0	(0.0)	1	(0.2)	10	(0.2)
Shock haemorrhagic	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Accidental death	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Acute coronary syndrome	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Acute respiratory distress syndrome	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
Acute respiratory failure	0	(0.0)	0	(0.0)	0	(0.0)	5	(0.1)
Adenocarcinoma gastric	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Alcohol poisoning	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)

Anaemia	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Anaphylactic shock	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Arterial injury	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Aspiration	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.1)
Atypical pneumonia	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Autoinflammatory disease	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Brain oedema	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Cachexia	0	(0.0)	0	(0.0)	1	(0.2)	3	(0.1)
Cardiac complication associated with device	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Cardiac failure	0	(0.0)	1	(0.4)	0	(0.0)	2	(0.0)
Cardiac failure acute	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Cardiac failure congestive	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Cardiac tamponade	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Cellulitis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Cerebral haemorrhage	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Cerebrovascular accident	0	(0.0)	0	(0.0)	0	(0.0)	5	(0.1)

	KN355 Data for Pembrolizumab + Chemotherapy[†] [†]		KN355 Data for Placebo + Chemotherapy[¶] [¶]		mTNBC Safety Dataset for Pembrolizumab Monotherapy[‡‡]		Reference Safety Dataset for Pembrolizumab Monotherapy[§§]	
	n	(%)	n	(%)	n	(%)	n	(%)
Chronic kidney disease	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Chronic obstructive pulmonary disease	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Circulatory collapse	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
Clostridium difficile infection	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Coma	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Completed suicide	0	(0.0)	0	(0.0)	1	(0.2)	3	(0.1)
Diffuse alveolar damage	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Disseminated intravascular coagulation	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.0)
Diverticulitis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Drug reaction with eosinophilia and systemic symptoms	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Duodenal obstruction	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Dyspnoea	0	(0.0)	0	(0.0)	0	(0.0)	5	(0.1)
Embolism	0	(0.0)	0	(0.0)	0	(0.0)	5	(0.1)
Encephalopathy	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Fall	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Febrile neutropenia	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Gastric haemorrhage	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Gastric ulcer haemorrhage	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Gastrointestinal perforation	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
General physical health deterioration	0	(0.0)	0	(0.0)	0	(0.0)	8	(0.1)
Generalised oedema	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Graft versus host disease	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Haemoptysis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Haemorrhage intracranial	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Haemorrhagic infarction	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Haemorrhagic stroke	0	(0.0)	1	(0.4)	0	(0.0)	2	(0.0)
Haemothorax	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Hepatic failure	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.1)
Hyperglycaemia	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Hypoxia	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Ileus paralytic	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Infectious pleural effusion	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Interstitial lung disease	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Intestinal ischaemia	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Intestinal obstruction	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Intestinal perforation	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)

Ischaemic cardiomyopathy	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Ischaemic stroke	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Large intestine perforation	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)

	KN355 Data for Pembrolizumab + Chemotherapy[†] [†]		KN355 Data for Placebo + Chemotherapy[¶] [¶]		mTNBC Safety Dataset for Pembrolizumab Monotherapy[‡‡]		Reference Safety Dataset for Pembrolizumab Monotherapy[§§]	
	n	(%)	n	(%)	n	(%)	n	(%)
Lung neoplasm malignant	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Lymphangiosis carcinomatosa	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Malignant neoplasm progression	0	(0.0)	0	(0.0)	0	(0.0)	4	(0.1)
Mental status changes	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Metastatic malignant melanoma	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Myocardial infarction	0	(0.0)	0	(0.0)	0	(0.0)	6	(0.1)
Myositis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Neutropenic sepsis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Pelvic neoplasm	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
Peripheral artery occlusion	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Pleural effusion	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Pneumocystis jirovecii pneumonia	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Pneumonia aspiration	0	(0.0)	0	(0.0)	0	(0.0)	8	(0.1)
Pneumonia klebsiella	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Pneumonia staphylococcal	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Pneumonia streptococcal	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Pneumonitis	0	(0.0)	0	(0.0)	0	(0.0)	8	(0.1)
Pneumothorax	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Post procedural haemorrhage	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Pseudomonal sepsis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Pulmonary artery thrombosis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Pulmonary haemorrhage	0	(0.0)	0	(0.0)	0	(0.0)	5	(0.1)
Pulmonary oedema	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Pulmonary sepsis	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Renal failure	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Respiratory distress	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Respiratory failure	0	(0.0)	1	(0.4)	1	(0.2)	17	(0.3)
Sepsis	0	(0.0)	0	(0.0)	0	(0.0)	9	(0.2)
Soft tissue infection	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Spinal cord compression	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Stevens-Johnson syndrome	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Sudden death	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Superior vena cava syndrome	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Traumatic intracranial haemorrhage	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Tumour haemorrhage	0	(0.0)	0	(0.0)	0	(0.0)	5	(0.1)
Type 2 diabetes mellitus	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Upper gastrointestinal haemorrhage	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Urinary tract obstruction	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Urosepsis	0	(0.0)	0	(0.0)	0	(0.0)	5	(0.1)

	KN355 Data for Pembrolizumab + Chemotherapy[†] [†]		KN355 Data for Placebo + Chemotherapy[¶] [¶]		mTNBC Safety Dataset for Pembrolizumab Monotherapy[‡‡]		Reference Safety Dataset for Pembrolizumab Monotherapy[§§]	
	n	(%)	n	(%)	n	(%)	n	(%)
Vascular device infection	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)

Every subject is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

[††] Includes all subjects who received at least one dose of treatment in the pembrolizumab +

chemotherapy arm of KN355.

¶¶ Includes all subjects who received at least one dose of treatment in the placebo + chemotherapy arm of KN355.

‡‡ Includes all subjects who received at least one dose of pembrolizumab in KN012-Cohort A, KN086 and KN119.

§§ Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (Head and Neck Cancer), KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055 and KN087.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)

Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013-Cohort 3: 28SEP2018, KN087: 25SEP2016)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for TNBC (KN355: 11DEC2019, KN012: 26APR2016, KN086: 10NOV2017, KN119: 11APR2019)

Adverse events of Special Interest (AEOSIs)

Adverse Event Summary AEOSI (ASaT Population)

	KN355 Data for Pembrolizumab + Chemotherapy† †		KN355 Data for Placebo + Chemotherapy¶ ¶		mTNBC Safety Dataset for Pembrolizumab Monotherapy‡‡		Reference Safety Dataset for Pembrolizumab Monotherapy§§	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	596		281		595		5,884	
with one or more adverse events	168	(28.2)	30	(10.7)	99	(16.6)	1,464	(24.9)
with no adverse event	428	(71.8)	251	(89.3)	496	(83.4)	4,420	(75.1)
with drug-related† adverse events	152	(25.5)	25	(8.9)	86	(14.5)	1,272	(21.6)
with toxicity grade 3-5 adverse events	34	(5.7)	0	(0.0)	15	(2.5)	377	(6.4)
with toxicity grade 3-5 drug-related adverse events	32	(5.4)	0	(0.0)	12	(2.0)	329	(5.6)
with serious adverse events	20	(3.4)	0	(0.0)	16	(2.7)	378	(6.4)
with serious drug-related adverse events	18	(3.0)	0	(0.0)	16	(2.7)	335	(5.7)
with any dose modification‡ due to an adverse event	61	(10.2)	12	(4.3)	23	(3.9)	525	(8.9)
pembrolizumab dose modification	3	(0.5)	0	(0.0)	23	(3.9)	525	(8.9)
pembrolizumab/placebo dose modification	44	(7.4)	2	(0.7)	23	(3.9)	525	(8.9)
nab-paclitaxel dose modification	15	(2.5)	0	(0.0)	0	(0.0)	0	(0.0)
paclitaxel dose modification	10	(1.7)	1	(0.4)	0	(0.0)	0	(0.0)
gemcitabine dose modification	19	(3.2)	6	(2.1)	0	(0.0)	0	(0.0)
carboplatin dose modification	20	(3.4)	10	(3.6)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)	11	(0.2)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	11	(0.2)
discontinued any drug due to an adverse event	24	(4.0)	3	(1.1)	7	(1.2)	227	(3.9)
discontinued pembrolizumab	2	(0.3)	0	(0.0)	7	(1.2)	227	(3.9)
discontinued pembrolizumab/placebo	14	(2.3)	0	(0.0)	7	(1.2)	227	(3.9)

discontinued nab-paclitaxel	3	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued paclitaxel	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued gemcitabine	6	(1.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued carboplatin	6	(1.0)	3	(1.1)	0	(0.0)	0	(0.0)
discontinued any drug due to a drug-related adverse event	24	(4.0)	3	(1.1)	7	(1.2)	224	(3.8)
discontinued pembrolizumab	2	(0.3)	0	(0.0)	7	(1.2)	224	(3.8)
discontinued pembrolizumab/placebo	14	(2.3)	0	(0.0)	7	(1.2)	224	(3.8)
discontinued nab-paclitaxel	3	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued paclitaxel	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued gemcitabine	6	(1.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued carboplatin	6	(1.0)	3	(1.1)	0	(0.0)	0	(0.0)
discontinued any drug due to a serious adverse event	15	(2.5)	0	(0.0)	4	(0.7)	155	(2.6)
discontinued pembrolizumab	2	(0.3)	0	(0.0)	4	(0.7)	155	(2.6)
discontinued pembrolizumab/placebo	12	(2.0)	0	(0.0)	4	(0.7)	155	(2.6)

	KN355 Data for Pembrolizumab + Chemotherapy[†] [†]		KN355 Data for Placebo + Chemotherapy[¶] [¶]		mTNBC Safety Dataset for Pembrolizumab Monotherapy[‡‡]		Reference Safety Dataset for Pembrolizumab Monotherapy[§§]	
	n	(%)	n	(%)	n	(%)	n	(%)
discontinued nab-paclitaxel	2	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued paclitaxel	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued gemcitabine	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued carboplatin	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued any drug due to a serious drug-related adverse event	15	(2.5)	0	(0.0)	4	(0.7)	153	(2.6)
discontinued pembrolizumab	2	(0.3)	0	(0.0)	4	(0.7)	153	(2.6)
discontinued pembrolizumab/placebo	12	(2.0)	0	(0.0)	4	(0.7)	153	(2.6)
discontinued nab-paclitaxel	2	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued paclitaxel	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued gemcitabine	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued carboplatin	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)

[†] Determined by the investigator to be related to the drug.

[‡] Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

[††] Includes all subjects who received at least one dose of treatment in the pembrolizumab + chemotherapy arm of KN355.

[¶¶] Includes all subjects who received at least one dose of treatment in the placebo + chemotherapy arm of KN355.

[‡‡] Includes all subjects who received at least one dose of pembrolizumab in KN012-Cohort A, KN086 and KN119.

[§§] Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (Head and Neck Cancer), KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055 and KN087.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)

Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013-Cohort 3: 28SEP2018, KN087: 25SEP2016)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for TNBC (KN355: 11DEC2019, KN012: 26APR2016, KN086: 10NOV2017, KN119:

11APR2019)

Subjects With Adverse Events of Special Interest (Incidence > 0% in One or More Treatment Groups) By AEOSI Category and Preferred Term (ASaT Population)

	KN355 Data for Pembrolizumab + Chemotherapy[†] [†]		KN355 Data for Placebo + Chemotherapy[¶] [¶]		mTNBC Safety Dataset for Pembrolizumab Monotherapy[‡‡]		Reference Safety Dataset for Pembrolizumab Monotherapy[§§]	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	596		281		595		5,884	
with one or more adverse events	168	(28.2)	30	(10.7)	99	(16.6)	1,464	(24.9)
with no adverse events	428	(71.8)	251	(89.3)	496	(83.4)	4,420	(75.1)
Adrenal Insufficiency	**7**	**(1.2)**	**0**	**(0.0)**	**4**	**(0.7)**	**47**	**(0.8)**
Addison's disease	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Adrenal insufficiency	7	(1.2)	0	(0.0)	2	(0.3)	42	(0.7)
Adrenocortical insufficiency acute	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Secondary adrenocortical insufficiency	0	(0.0)	0	(0.0)	2	(0.3)	1	(0.0)
Colitis	**11**	**(1.8)**	**4**	**(1.4)**	**5**	**(0.8)**	**110**	**(1.9)**
Autoimmune colitis	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.1)
Colitis	10	(1.7)	3	(1.1)	4	(0.7)	95	(1.6)
Colitis microscopic	0	(0.0)	0	(0.0)	0	(0.0)	4	(0.1)
Enterocolitis	1	(0.2)	1	(0.4)	1	(0.2)	8	(0.1)
Immune-mediated enterocolitis	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.1)
Encephalitis	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(0.0)**
Encephalitis	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Guillain-Barre Syndrome	**1**	**(0.2)**	**0**	**(0.0)**	**0**	**(0.0)**	**4**	**(0.1)**
Axonal neuropathy	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Demyelinating polyneuropathy	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Guillain-Barre syndrome	1	(0.2)	0	(0.0)	0	(0.0)	2	(0.0)
Hepatitis	**5**	**(0.8)**	**2**	**(0.7)**	**1**	**(0.2)**	**55**	**(0.9)**
Autoimmune hepatitis	1	(0.2)	0	(0.0)	0	(0.0)	24	(0.4)
Drug-induced liver injury	0	(0.0)	0	(0.0)	0	(0.0)	6	(0.1)
Hepatitis	3	(0.5)	2	(0.7)	1	(0.2)	24	(0.4)
Hepatitis acute	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Immune-mediated hepatitis	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.0)
Hyperthyroidism	**31**	**(5.2)**	**3**	**(1.1)**	**24**	**(4.0)**	**245**	**(4.2)**
Hyperthyroidism	31	(5.2)	3	(1.1)	24	(4.0)	245	(4.2)
Hypophysitis	**1**	**(0.2)**	**0**	**(0.0)**	**0**	**(0.0)**	**36**	**(0.6)**
Hypophysitis	1	(0.2)	0	(0.0)	0	(0.0)	22	(0.4)
Hypopituitarism	0	(0.0)	0	(0.0)	0	(0.0)	14	(0.2)
Hypothyroidism	**95**	**(15.9)**	**9**	**(3.2)**	**53**	**(8.9)**	**648**	**(11.0)**

	KN355 Data for Pembrolizumab + Chemotherapy[†] [†]		KN355 Data for Placebo + Chemotherapy[¶] [¶]		mTNBC Safety Dataset for Pembrolizumab Monotherapy[‡‡]		Reference Safety Dataset for Pembrolizumab Monotherapy[§§]	
	n	(%)	n	(%)	n	(%)	n	(%)
Hypothyroidism	**95**	**(15.9)**	**9**	**(3.2)**	**53**	**(8.9)**	**648**	**(11.0)**
Hypothyroidism	95	(15.9)	9	(3.2)	53	(8.9)	647	(11.0)
Myxoedema	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)

Primary hypothyroidism	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Infusion Reactions	**22**	**(3.7)**	**14**	**(5.0)**	**5**	**(0.8)**	**135**	**(2.3)**
Anaphylactic reaction	1	(0.2)	0	(0.0)	0	(0.0)	10	(0.2)
Anaphylactoid reaction	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Cytokine release syndrome	0	(0.0)	0	(0.0)	0	(0.0)	8	(0.1)
Drug hypersensitivity	3	(0.5)	1	(0.4)	1	(0.2)	18	(0.3)
Hypersensitivity	10	(1.7)	8	(2.8)	1	(0.2)	45	(0.8)
Infusion related reaction	8	(1.3)	6	(2.1)	3	(0.5)	55	(0.9)
Myasthenic Syndrome	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.2)**	**3**	**(0.1)**
Myasthenia gravis	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.0)
Myasthenic syndrome	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Myelitis	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(0.0)**
Myelitis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Myelitis transverse	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Myocarditis	**1**	**(0.2)**	**0**	**(0.0)**	**1**	**(0.2)**	**5**	**(0.1)**
Myocarditis	1	(0.2)	0	(0.0)	1	(0.2)	5	(0.1)
Myositis	**3**	**(0.5)**	**0**	**(0.0)**	**2**	**(0.3)**	**19**	**(0.3)**
Dermatomyositis	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Myopathy	0	(0.0)	0	(0.0)	0	(0.0)	4	(0.1)
Myositis	2	(0.3)	0	(0.0)	2	(0.3)	14	(0.2)
Rhabdomyolysis	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.0)
Nephritis	**4**	**(0.7)**	**0**	**(0.0)**	**1**	**(0.2)**	**23**	**(0.4)**
Acute kidney injury	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Autoimmune nephritis	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.1)
Glomerulonephritis membranous	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Nephritis	4	(0.7)	0	(0.0)	0	(0.0)	3	(0.1)
Nephrotic syndrome	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Renal failure	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Tubulointerstitial nephritis	0	(0.0)	0	(0.0)	1	(0.2)	11	(0.2)
Pancreatitis	**1**	**(0.2)**	**0**	**(0.0)**	**0**	**(0.0)**	**18**	**(0.3)**

	KN355 Data for Pembrolizumab + Chemotherapy[†] [†]		KN355 Data for Placebo + Chemotherapy[¶] [¶]		mTNBC Safety Dataset for Pembrolizumab Monotherapy[‡‡]		Reference Safety Dataset for Pembrolizumab Monotherapy[§§]	
	n	(%)	n	(%)	n	(%)	n	(%)
Pancreatitis	**1**	**(0.2)**	**0**	**(0.0)**	**0**	**(0.0)**	**18**	**(0.3)**
Autoimmune pancreatitis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Pancreatitis	1	(0.2)	0	(0.0)	0	(0.0)	14	(0.2)
Pancreatitis acute	0	(0.0)	0	(0.0)	0	(0.0)	4	(0.1)
Pneumonitis	**15**	**(2.5)**	**0**	**(0.0)**	**16**	**(2.7)**	**259**	**(4.4)**
Interstitial lung disease	0	(0.0)	0	(0.0)	2	(0.3)	22	(0.4)
Organising pneumonia	1	(0.2)	0	(0.0)	1	(0.2)	2	(0.0)
Pneumonitis	14	(2.3)	0	(0.0)	13	(2.2)	238	(4.0)
Sarcoidosis	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**10**	**(0.2)**
Sarcoidosis	0	(0.0)	0	(0.0)	0	(0.0)	10	(0.2)
Severe Skin Reactions	**12**	**(2.0)**	**1**	**(0.4)**	**6**	**(1.0)**	**95**	**(1.6)**
Dermatitis bullous	0	(0.0)	0	(0.0)	1	(0.2)	8	(0.1)
Dermatitis exfoliative	0	(0.0)	0	(0.0)	0	(0.0)	5	(0.1)
Dermatitis exfoliative generalised	0	(0.0)	0	(0.0)	1	(0.2)	2	(0.0)
Erythema multiforme	0	(0.0)	1	(0.4)	1	(0.2)	5	(0.1)
Exfoliative rash	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Lichen planus	0	(0.0)	0	(0.0)	0	(0.0)	4	(0.1)
Oral lichen planus	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Pemphigoid	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.1)
Pemphigus	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)

Pruritus	1	(0.2)	0	(0.0)	1	(0.2)	11	(0.2)
Pruritus genital	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Rash	5	(0.8)	0	(0.0)	1	(0.2)	30	(0.5)
Rash erythematous	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Rash maculo-papular	7	(1.2)	0	(0.0)	1	(0.2)	16	(0.3)
Rash pruritic	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Rash pustular	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Skin necrosis	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Stevens-Johnson syndrome	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.1)
Toxic skin eruption	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Thyroiditis	**8**	**(1.3)**	**0**	**(0.0)**	**1**	**(0.2)**	**57**	**(1.0)**
Autoimmune thyroiditis	0	(0.0)	0	(0.0)	0	(0.0)	13	(0.2)
Thyroid disorder	0	(0.0)	0	(0.0)	0	(0.0)	5	(0.1)
Thyroiditis	7	(1.2)	0	(0.0)	1	(0.2)	41	(0.7)
Thyroiditis acute	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)

	KN355 Data for Pembrolizumab + Chemotherapy[†] [†]		KN355 Data for Placebo + Chemotherapy[¶] [¶]		mTNBC Safety Dataset for Pembrolizumab Monotherapy[‡‡]		Reference Safety Dataset for Pembrolizumab Monotherapy[§§]	
	n	(%)	n	(%)	n	(%)	n	(%)
Type 1 Diabetes Mellitus	**2**	**(0.3)**	**0**	**(0.0)**	**2**	**(0.3)**	**20**	**(0.3)**
Diabetic ketoacidosis	0	(0.0)	0	(0.0)	1	(0.2)	9	(0.2)
Type 1 diabetes mellitus	2	(0.3)	0	(0.0)	1	(0.2)	16	(0.3)
Uveitis	**1**	**(0.2)**	**0**	**(0.0)**	**0**	**(0.0)**	**20**	**(0.3)**
Iridocyclitis	0	(0.0)	0	(0.0)	0	(0.0)	4	(0.1)
Iritis	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.1)
Uveitis	1	(0.2)	0	(0.0)	0	(0.0)	13	(0.2)

Every subject is counted a single time for each applicable row and column.

A bolded term or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

[††] Includes all subjects who received at least one dose of treatment in the pembrolizumab + chemotherapy arm of KN355.

[¶¶] Includes all subjects who received at least one dose of treatment in the placebo + chemotherapy arm of KN355.

[‡‡] Includes all subjects who received at least one dose of pembrolizumab in KN012-Cohort A, KN086 and KN119.

[§§] Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (Head and Neck Cancer), KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055 and KN087.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)

Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013-Cohort 3: 28SEP2018, KN087: 25SEP2016)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for TNBC (KN355: 11DEC2019, KN012: 26APR2016, KN086: 10NOV2017, KN119: 11APR2019)

Time to Onset and Duration of AEOSI (ASaT Population)

	KN355 Data for Pembrolizumab + Chemotherapy[††] n (%)	KN355 Data for Placebo + Chemotherapy[¶¶] n (%)	mTNBC Safety Dataset for Pembrolizumab Monotherapy[‡‡] n (%)	Reference Safety Dataset for Pembrolizumab Monotherapy[§§] n (%)
Subjects in population	596	281	595	5884
Subjects with AEOSI	168 (28.2)	30 (10.7)	99 (16.6)	1464 (24.9)
Time to Onset of First AEOSI (days)†				
Mean (Std)	122.3 (122.5)	135.5 (148.1)	75.0 (82.4)	116.2 (118.7)
Median	84.0	77.5	60.0	78.0
Range	1 to 707	4 to 531	1 to 473	1 to 775
Total episodes of AEOSI	257	45	129	2077
Average Episodes per patient	1.53	1.50	1.30	1.42
Episode duration (days)‡				
Median	85.0	2.0	424.0	86.0
Range	1 to 1112+	1 to 745+	1 to 1044+	1 to 1640+

(%) = Number of subjects with AEOSI / Number of subjects in population.

† Time to onset statistics are based on number of subjects with AEOSI.

‡ From product-limit (Kaplan-Meier) method for censored data. If an adverse event is not resolved at the time of analysis or the subject died without adverse event resolved, the duration is censored at either data cutoff date or date of death, whichever occurred first.

+ indicates the AE episode is not recovered/resolved by the time of the cutoff date or date of death.

Std = Standard Deviation.

Grades are based on NCI CTCAE 4.0.

[††] Includes all subjects who received at least one dose of treatment in the pembrolizumab + chemotherapy arm of KN355.

[¶¶] Includes all subjects who received at least one dose of treatment in the placebo + chemotherapy arm of KN355.

[‡‡] Includes all subjects who received at least one dose of pembrolizumab in KN012-Cohort A, KN086 and KN119.

[§§] Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (Head and Neck Cancer), KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055 and KN087.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)

Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013-Cohort 3: 28SEP2018, KN087: 25SEP2016)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for TNBC (KN355: 11DEC2019, KN012: 26APR2016, KN086: 10NOV2017, KN119: 11APR2019)

Summary of Concomitant Corticosteroid Use for AEOSI (ASaT Population)

	KN355 Data for Pembrolizumab + Chemotherapy[††] (N=596)		KN355 Data for Placebo + Chemotherapy[¶¶] (N=281)		mTNBC Safety Dataset for Pembrolizumab Monotherapy[‡‡] (N=595)		Reference Safety Dataset for Pembrolizumab Monotherapy[§§] (N=5884)	
	n	%	n	%	n	%	n	%
Patients with one or more AEOSI	168		30		99		1464	
Treated with systemic corticosteroid	61	36.3	9	30.0	29	29.3	450	30.7
Not treated with systemic corticosteroid	107	63.7	21	70.0	70	70.7	1014	69.3

The number of Patients with one or more AEOSI is used as the denominator for the percentage calculation.

[††] Includes all subjects who received at least one dose of treatment in the pembrolizumab + chemotherapy arm of KN355.

[¶¶] Includes all subjects who received at least one dose of treatment in the placebo + chemotherapy arm of KN355.

[‡‡] Includes all subjects who received at least one dose of pembrolizumab in KN012-Cohort A, KN086 and KN119.

[§§] Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (Head and Neck Cancer), KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055 and KN087.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)

Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013-Cohort 3: 28SEP2018, KN087: 25SEP2016)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for TNBC (KN355: 11DEC2019, KN012: 26APR2016, KN086: 10NOV2017, KN119: 11APR2019)

Laboratory findings

Summary of Subjects with Increases from Baseline in Laboratory Test Toxicity Grade Based on Highest Post-baseline Toxicity Grade
(Overall Incidence > 0% in One or More Treatment Groups)
(Subjects with Baseline and Post-baseline Measurements)
(ASaT Population)

Laboratory Test	KN355 Data for Pembrolizumab + Chemotherapy[††] (N=596) n	(%)	KN355 Data for Placebo + Chemotherapy[¶¶] (N=281) n	(%)	mTNBC Safety Dataset for Pembrolizumab Monotherapy[‡‡] (N=595) n	(%)	Reference Safety Dataset for Pembrolizumab Monotherapy[§§] (N=5884) n	(%)
Activated Partial Thromboplastin Time Increased (Activated partial thromboplastin time prolonged)								
Subjects with Baseline and Post-baseline Measurements	182		85		171		1444	
Grade 1	21	(11.5)	9	(10.6)	23	(13.5)	143	(9.9)
Grade 2	9	(4.9)	2	(2.4)	9	(5.3)	27	(1.9)
Grade 3	6	(3.3)	1	(1.2)	5	(2.9)	25	(1.7)
Grade 4	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Grade 3-4	6	(3.3)	1	(1.2)	5	(2.9)	25	(1.7)
All Grades	36	(19.8)	12	(14.1)	37	(21.6)	195	(13.5)
Alanine Aminotransferase Increased (Alanine aminotransferase increased)								
Subjects with Baseline and Post-baseline Measurements	590		279		557		5133	
Grade 1	216	(36.6)	108	(38.7)	112	(20.1)	989	(19.3)
Grade 2	71	(12.0)	33	(11.8)	22	(3.9)	139	(2.7)
Grade 3	55	(9.3)	21	(7.5)	15	(2.7)	120	(2.3)
Grade 4	11	(1.9)	1	(0.4)	1	(0.2)	22	(0.4)
Grade 3-4	66	(11.2)	22	(7.9)	16	(2.9)	142	(2.8)
All Grades	353	(59.8)	163	(58.4)	150	(26.9)	1270	(24.7)
Albumin Decreased (Hypoalbuminemia)								
Subjects with Baseline and Post-baseline Measurements	587		278		548		5066	
Grade 1	142	(24.2)	64	(23.0)	125	(22.8)	1012	(20.0)
Grade 2	60	(10.2)	20	(7.2)	87	(15.9)	741	(14.6)
Grade 3	13	(2.2)	6	(2.2)	13	(2.4)	84	(1.7)
Grade 4	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Grade 3-4	13	(2.2)	6	(2.2)	13	(2.4)	84	(1.7)
All Grades	215	(36.6)	90	(32.4)	225	(41.1)	1837	(36.3)
Alkaline Phosphatase Increased (Alkaline phosphatase increased)								
Subjects with Baseline and Post-baseline Measurements	590		279		553		5112	
Grade 1	154	(26.1)	88	(31.5)	103	(18.6)	975	(19.1)
Grade 2	29	(4.9)	14	(5.0)	35	(6.3)	267	(5.2)
Grade 3	23	(3.9)	6	(2.2)	24	(4.3)	134	(2.6)
Grade 4	0	(0.0)	0	(0.0)	1	(0.2)	3	(0.1)

Laboratory Test	KN355 Data for Pembrolizumab + Chemotherapy†† (N=596) n	(%)	KN355 Data for Placebo + Chemotherapy¶¶ (N=281) n	(%)	mTNBC Safety Dataset for Pembrolizumab Monotherapy‡‡ (N=595) n	(%)	Reference Safety Dataset for Pembrolizumab Monotherapy§§ (N=5884) n	(%)
Alkaline Phosphatase Increased (Alkaline phosphatase increased)								
Grade 3-4	23	(3.9)	6	(2.2)	25	(4.5)	137	(2.7)
All Grades	206	(34.9)	108	(38.7)	163	(29.5)	1379	(27.0)
Aspartate Aminotransferase Increased (Aspartate aminotransferase increased)								
Subjects with Baseline and Post-baseline Measurements	587		277		556		5129	
Grade 1	227	(38.7)	113	(40.8)	132	(23.7)	1110	(21.6)
Grade 2	54	(9.2)	23	(8.3)	25	(4.5)	178	(3.5)
Grade 3	44	(7.5)	17	(6.1)	32	(5.8)	118	(2.3)
Grade 4	9	(1.5)	0	(0.0)	3	(0.5)	29	(0.6)
Grade 3-4	53	(9.0)	17	(6.1)	35	(6.3)	147	(2.9)
All Grades	334	(56.9)	153	(55.2)	192	(34.5)	1435	(28.0)
Bilirubin Increased (Blood bilirubin increased)								
Subjects with Baseline and Post-baseline Measurements	589		278		556		5133	
Grade 1	25	(4.2)	12	(4.3)	19	(3.4)	284	(5.5)
Grade 2	20	(3.4)	7	(2.5)	4	(0.7)	138	(2.7)
Grade 3	18	(3.1)	1	(0.4)	13	(2.3)	69	(1.3)
Grade 4	2	(0.3)	1	(0.4)	2	(0.4)	20	(0.4)
Grade 3-4	20	(3.4)	2	(0.7)	15	(2.7)	89	(1.7)
All Grades	65	(11.0)	21	(7.6)	38	(6.8)	511	(10.0)
Calcium Decreased (Hypocalcemia)								
Subjects with Baseline and Post-baseline Measurements	584		275		548		5449	
Grade 1	126	(21.6)	50	(18.2)	93	(17.0)	926	(17.0)
Grade 2	26	(4.5)	18	(6.5)	28	(5.1)	227	(4.2)
Grade 3	8	(1.4)	2	(0.7)	2	(0.4)	33	(0.6)
Grade 4	11	(1.9)	3	(1.1)	7	(1.3)	47	(0.9)
Grade 3-4	19	(3.3)	5	(1.8)	9	(1.6)	80	(1.5)
All Grades	171	(29.3)	73	(26.5)	130	(23.7)	1233	(22.6)

Laboratory Test	KN355 Data for Pembrolizumab + Chemotherapy†† (N=596) n	(%)	KN355 Data for Placebo + Chemotherapy¶¶ (N=281) n	(%)	mTNBC Safety Dataset for Pembrolizumab Monotherapy‡‡ (N=595) n	(%)	Reference Safety Dataset for Pembrolizumab Monotherapy§§ (N=5884) n	(%)
Calcium Increased (Hypercalcemia)								
Grade 1	70	(12.0)	26	(9.5)	18	(3.3)	448	(8.2)
Grade 2	2	(0.3)	0	(0.0)	4	(0.7)	67	(1.2)
Grade 3	0	(0.0)	0	(0.0)	0	(0.0)	41	(0.8)
Grade 4	4	(0.7)	3	(1.1)	0	(0.0)	63	(1.2)
Grade 3-4	4	(0.7)	3	(1.1)	0	(0.0)	104	(1.9)
All Grades	76	(13.0)	29	(10.5)	22	(4.0)	619	(11.4)
Cholesterol Increased (Cholesterol high)								
Subjects with Baseline and Post-baseline Measurements	0		0		0		2401	
Grade 1	0	(0.0)	0	(0.0)	0	(0.0)	427	(17.8)
Grade 2	0	(0.0)	0	(0.0)	0	(0.0)	75	(3.1)
Grade 3	0	(0.0)	0	(0.0)	0	(0.0)	12	(0.5)
Grade 4	0	(0.0)	0	(0.0)	0	(0.0)	12	(0.5)
Grade 3-4	0	(0.0)	0	(0.0)	0	(0.0)	24	(1.0)
All Grades	0	(0.0)	0	(0.0)	0	(0.0)	526	(21.9)
Creatinine Increased (Creatinine increased)								
Subjects with Baseline and Post-baseline Measurements	590		278		558		5156	
Grade 1	67	(11.4)	35	(12.6)	51	(9.1)	630	(12.2)
Grade 2	24	(4.1)	5	(1.8)	12	(2.2)	262	(5.1)
Grade 3	7	(1.2)	3	(1.1)	5	(0.9)	51	(1.0)
Grade 4	2	(0.3)	0	(0.0)	2	(0.4)	20	(0.4)
Grade 3-4	9	(1.5)	3	(1.1)	7	(1.3)	71	(1.4)
All Grades	100	(16.9)	43	(15.5)	70	(12.5)	963	(18.7)
Gamma Glutamyl Transferase Increased (GGT increased)								
Subjects with Baseline and Post-baseline Measurements	0		0		0		7	
Grade 1	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Grade 2	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Grade 3	0	(0.0)	0	(0.0)	0	(0.0)	1	(14.3)
Grade 4	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Grade 3-4	0	(0.0)	0	(0.0)	0	(0.0)	1	(14.3)
All Grades	0	(0.0)	0	(0.0)	0	(0.0)	1	(14.3)

Laboratory Test	KN355 Data for Pembrolizumab + Chemotherapy†† (N=596) n	(%)	KN355 Data for Placebo + Chemotherapy¶¶ (N=281) n	(%)	mTNBC Safety Dataset for Pembrolizumab Monotherapy‡‡ (N=595) n	(%)	Reference Safety Dataset for Pembrolizumab Monotherapy§§ (N=5884) n	(%)
Glucose Decreased (Hypoglycemia)								
Subjects with Baseline and Post-baseline Measurements	585		276		545		5025	
Grade 1	38	(6.5)	16	(5.8)	25	(4.6)	398	(7.9)
Grade 2	8	(1.4)	3	(1.1)	5	(0.9)	63	(1.3)
Grade 3	3	(0.5)	1	(0.4)	0	(0.0)	12	(0.2)
Grade 4	6	(1.0)	1	(0.4)	1	(0.2)	19	(0.4)
Grade 3-4	9	(1.5)	2	(0.7)	1	(0.2)	31	(0.6)
All Grades	55	(9.4)	21	(7.6)	31	(5.7)	492	(9.8)
Glucose Increased (Hyperglycemia)								
Subjects with Baseline and Post-baseline Measurements	585		276		545		5025	
Grade 1	207	(35.4)	104	(37.7)	176	(32.3)	1624	(32.3)
Grade 2	71	(12.1)	32	(11.6)	34	(6.2)	629	(12.5)
Grade 3	22	(3.8)	6	(2.2)	17	(3.1)	213	(4.2)
Grade 4	4	(0.7)	0	(0.0)	4	(0.7)	34	(0.7)
Grade 3-4	26	(4.4)	6	(2.2)	21	(3.9)	247	(4.9)
All Grades	304	(52.0)	142	(51.4)	231	(42.4)	2500	(49.8)
Hemoglobin Decreased (Anemia)								
Subjects with Baseline and Post-baseline Measurements	592		280		547		5152	
Grade 1	174	(29.4)	72	(25.7)	115	(21.0)	1096	(21.3)
Grade 2	236	(39.9)	113	(40.4)	75	(13.7)	831	(16.1)
Grade 3	120	(20.3)	52	(18.6)	35	(6.4)	321	(6.2)
Grade 4	0	(0.0)	0	(0.0)	0	(0.0)	9	(0.2)
Grade 3-4	120	(20.3)	52	(18.6)	35	(6.4)	330	(6.4)
All Grades	530	(89.5)	237	(84.6)	225	(41.1)	2257	(43.8)
Hemoglobin Increased (Hemoglobin increased)								
Subjects with Baseline and Post-baseline Measurements	592		280		547		5152	
Grade 1	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Grade 2	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Grade 3	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Grade 4	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

Laboratory Test	KN355 Data for Pembrolizumab + Chemotherapy†† (N=596) n	(%)	KN355 Data for Placebo + Chemotherapy¶¶ (N=281) n	(%)	mTNBC Safety Dataset for Pembrolizumab Monotherapy‡‡ (N=595) n	(%)	Reference Safety Dataset for Pembrolizumab Monotherapy§§ (N=5884) n	(%)
Hemoglobin Increased (Hemoglobin increased)								
Grade 3-4	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
All Grades	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.0)
Leukocytes Decreased (White blood cell decreased)								
Subjects with Baseline and Post-baseline Measurements	592		280		550		5151	
Grade 1	87	(14.7)	45	(16.1)	64	(11.6)	433	(8.4)
Grade 2	182	(30.7)	86	(30.7)	28	(5.1)	149	(2.9)
Grade 3	206	(34.8)	96	(34.3)	6	(1.1)	17	(0.3)
Grade 4	27	(4.6)	14	(5.0)	3	(0.5)	24	(0.5)
Grade 3-4	233	(39.4)	110	(39.3)	9	(1.6)	41	(0.8)
All Grades	502	(84.8)	241	(86.1)	101	(18.4)	623	(12.1)
Lymphocytes Decreased (Lymphocyte count decreased)								
Subjects with Baseline and Post-baseline Measurements	591		280		548		4787	
Grade 1	83	(14.0)	49	(17.5)	73	(13.3)	534	(11.2)
Grade 2	176	(29.8)	95	(33.9)	88	(16.1)	743	(15.5)
Grade 3	135	(22.8)	42	(15.0)	56	(10.2)	441	(9.2)
Grade 4	21	(3.6)	10	(3.6)	11	(2.0)	85	(1.8)
Grade 3-4	156	(26.4)	52	(18.6)	67	(12.2)	526	(11.0)
All Grades	415	(70.2)	196	(70.0)	228	(41.6)	1803	(37.7)
Magnesium Decreased (Hypomagnesemia)								
Subjects with Baseline and Post-baseline Measurements	0		0		83		3953	
Grade 1	0	(0.0)	0	(0.0)	11	(13.3)	492	(12.4)
Grade 2	0	(0.0)	0	(0.0)	2	(2.4)	107	(2.7)
Grade 3	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Grade 4	0	(0.0)	0	(0.0)	1	(1.2)	9	(0.2)
Grade 3-4	0	(0.0)	0	(0.0)	1	(1.2)	9	(0.2)
All Grades	0	(0.0)	0	(0.0)	14	(16.9)	608	(15.4)
Magnesium Increased (Hypermagnesemia)								
Subjects with Baseline and Post-baseline Measurements	0		0		83		3953	

Laboratory Test	KN355 Data for Pembrolizumab + Chemotherapy†† (N=596) n	(%)	KN355 Data for Placebo + Chemotherapy¶¶ (N=281) n	(%)	mTNBC Safety Dataset for Pembrolizumab Monotherapy‡‡ (N=595) n	(%)	Reference Safety Dataset for Pembrolizumab Monotherapy§§ (N=5884) n	(%)
Magnesium Increased (Hypermagnesemia)								
Grade 1	0	(0.0)	0	(0.0)	4	(4.8)	235	(5.9)
Grade 2	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Grade 3	0	(0.0)	0	(0.0)	1	(1.2)	17	(0.4)
Grade 4	0	(0.0)	0	(0.0)	0	(0.0)	12	(0.3)
Grade 3-4	0	(0.0)	0	(0.0)	1	(1.2)	29	(0.7)
All Grades	0	(0.0)	0	(0.0)	5	(6.0)	264	(6.7)
Neutrophils Decreased (Neutrophil count decreased)								
Subjects with Baseline and Post-baseline Measurements	592		280		549		4773	
Grade 1	46	(7.8)	21	(7.5)	28	(5.1)	162	(3.4)
Grade 2	112	(18.9)	48	(17.1)	17	(3.1)	104	(2.2)
Grade 3	161	(27.2)	82	(29.3)	3	(0.5)	34	(0.7)
Grade 4	129	(21.8)	64	(22.9)	8	(1.5)	56	(1.2)
Grade 3-4	290	(49.0)	146	(52.1)	11	(2.0)	90	(1.9)
All Grades	448	(75.7)	215	(76.8)	56	(10.2)	356	(7.5)
Phosphate Decreased (Hypophosphatemia)								
Subjects with Baseline and Post-baseline Measurements	566		269		529		4859	
Grade 1	15	(2.7)	6	(2.2)	7	(1.3)	112	(2.3)
Grade 2	66	(11.7)	30	(11.2)	43	(8.1)	675	(13.9)
Grade 3	36	(6.4)	12	(4.5)	12	(2.3)	247	(5.1)
Grade 4	3	(0.5)	1	(0.4)	1	(0.2)	10	(0.2)
Grade 3-4	39	(6.9)	13	(4.8)	13	(2.5)	257	(5.3)
All Grades	120	(21.2)	49	(18.2)	63	(11.9)	1044	(21.5)
Platelets Decreased (Platelet count decreased)								
Subjects with Baseline and Post-baseline Measurements	591		278		549		5144	
Grade 1	146	(24.7)	67	(24.1)	46	(8.4)	512	(10.0)
Grade 2	58	(9.8)	23	(8.3)	9	(1.6)	46	(0.9)
Grade 3	49	(8.3)	34	(12.2)	7	(1.3)	32	(0.6)
Grade 4	66	(11.2)	24	(8.6)	7	(1.3)	56	(1.1)
Grade 3-4	115	(19.5)	58	(20.9)	14	(2.6)	88	(1.7)
All Grades	319	(54.0)	148	(53.2)	69	(12.6)	646	(12.6)

Laboratory Test	KN355 Data for Pembrolizumab + Chemotherapy†† (N=596) n	(%)	KN355 Data for Placebo + Chemotherapy¶¶ (N=281) n	(%)	mTNBC Safety Dataset for Pembrolizumab Monotherapy‡‡ (N=595) n	(%)	Reference Safety Dataset for Pembrolizumab Monotherapy§§ (N=5884) n	(%)
Potassium Decreased (Hypokalemia)								
Subjects with Baseline and Post-baseline Measurements	590		278		551		5457	
Grade 1	94	(15.9)	39	(14.0)	59	(10.7)	562	(10.3)
Grade 2	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Grade 3	20	(3.4)	6	(2.2)	3	(0.5)	96	(1.8)
Grade 4	6	(1.0)	5	(1.8)	2	(0.4)	26	(0.5)
Grade 3-4	26	(4.4)	11	(4.0)	5	(0.9)	122	(2.2)
All Grades	120	(20.3)	50	(18.0)	64	(11.6)	684	(12.5)
Potassium Increased (Hyperkalemia)								
Subjects with Baseline and Post-baseline Measurements	590		278		551		5457	
Grade 1	45	(7.6)	31	(11.2)	33	(6.0)	657	(12.0)
Grade 2	32	(5.4)	5	(1.8)	12	(2.2)	215	(3.9)
Grade 3	9	(1.5)	3	(1.1)	2	(0.4)	62	(1.1)
Grade 4	5	(0.8)	0	(0.0)	5	(0.9)	36	(0.7)
Grade 3-4	14	(2.4)	3	(1.1)	7	(1.3)	98	(1.8)
All Grades	91	(15.4)	39	(14.0)	52	(9.4)	970	(17.8)
Prothrombin Intl. Normalized Ratio Increased (INR increased)								
Subjects with Baseline and Post-baseline Measurements	179		93		173		1417	
Grade 1	18	(10.1)	10	(10.8)	19	(11.0)	163	(11.5)
Grade 2	0	(0.0)	4	(4.3)	2	(1.2)	18	(1.3)
Grade 3	3	(1.7)	1	(1.1)	2	(1.2)	43	(3.0)
Grade 4	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Grade 3-4	3	(1.7)	1	(1.1)	2	(1.2)	43	(3.0)
All Grades	21	(11.7)	15	(16.1)	23	(13.3)	224	(15.8)
Sodium Decreased (Hyponatremia)								
Subjects with Baseline and Post-baseline Measurements	590		279		552		5471	
Grade 1	136	(23.1)	55	(19.7)	139	(25.2)	1485	(27.1)
Grade 2	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Grade 3	16	(2.7)	13	(4.7)	24	(4.3)	376	(6.9)
Grade 4	14	(2.4)	5	(1.8)	10	(1.8)	79	(1.4)

Laboratory Test	KN355 Data for Pembrolizumab + Chemotherapy[††] (N=596) n	(%)	KN355 Data for Placebo + Chemotherapy[¶¶] (N=281) n	(%)	mTNBC Safety Dataset for Pembrolizumab Monotherapy[‡‡] (N=595) n	(%)	Reference Safety Dataset for Pembrolizumab Monotherapy[§§] (N=5884) n	(%)
Sodium Decreased (Hyponatremia)								
Grade 3-4	30	(5.1)	18	(6.5)	34	(6.2)	455	(8.3)
All Grades	166	(28.1)	73	(26.2)	173	(31.3)	1940	(35.5)
Sodium Increased (Hypernatremia)								
Subjects with Baseline and Post-baseline Measurements	590		279		552		5471	
Grade 1	58	(9.8)	26	(9.3)	14	(2.5)	260	(4.8)
Grade 2	6	(1.0)	3	(1.1)	2	(0.4)	17	(0.3)
Grade 3	2	(0.3)	1	(0.4)	0	(0.0)	5	(0.1)
Grade 4	4	(0.7)	0	(0.0)	1	(0.2)	7	(0.1)
Grade 3-4	6	(1.0)	1	(0.4)	1	(0.2)	12	(0.2)
All Grades	70	(11.9)	30	(10.8)	17	(3.1)	289	(5.3)
Triglycerides Increased (Hypertriglyceridemia)								
Subjects with Baseline and Post-baseline Measurements	0		0		0		2309	
Grade 1	0	(0.0)	0	(0.0)	0	(0.0)	646	(28.0)
Grade 2	0	(0.0)	0	(0.0)	0	(0.0)	133	(5.8)
Grade 3	0	(0.0)	0	(0.0)	0	(0.0)	24	(1.0)
Grade 4	0	(0.0)	0	(0.0)	0	(0.0)	5	(0.2)
Grade 3-4	0	(0.0)	0	(0.0)	0	(0.0)	29	(1.3)

Laboratory Test	KN355 Data for Pembrolizumab + Chemotherapy[††] (N=596) n	(%)	KN355 Data for Placebo + Chemotherapy[¶¶] (N=281) n	(%)	mTNBC Safety Dataset for Pembrolizumab Monotherapy[‡‡] (N=595) n	(%)	Reference Safety Dataset for Pembrolizumab Monotherapy[§§] (N=5884) n	(%)
Triglycerides Increased (Hypertriglyceridemia)								
All Grades	0	(0.0)	0	(0.0)	0	(0.0)	808	(35.0)

If a subject had more than one toxicity grade for a laboratory test, only the highest grade is counted.

Number of subjects with at least one baseline and post-baseline laboratory measurement is used as the denominator in percentage calculation.

Grades are based on NCI CTCAE version 4.03.

[††] Includes all subjects who received at least one dose of treatment in the pembrolizumab + chemotherapy arm of KN355.

[¶¶] Includes all subjects who received at least one dose of treatment in the placebo + chemotherapy arm of KN355.

[‡‡] Includes all subjects who received at least one dose of pembrolizumab in KN012-Cohort A, KN086 and KN119.

[§§] Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (Head and Neck Cancer), KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055 and KN087.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)

Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013-Cohort 3: 28SEP2018, KN087: 25SEP2016)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for TNBC (KN355: 11DEC2019, KN012: 26APR2016, KN086: 10NOV2017, KN119: 11APR2019)

Safety in special populations

AGE

Adverse Event Summary by Age
(Part 2 All Subjects)
(ASaT Population)

	Pembrolizumab + Chemotherapy				Placebo + Chemotherapy			
	< 65		>= 65		< 65		>= 65	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	439		123		224		57	
with one or more adverse events	433	(98.6)	121	(98.4)	219	(97.8)	57	(100.0)
with no adverse event	6	(1.4)	2	(1.6)	5	(2.2)	0	(0.0)
with drug-related† adverse events	421	(95.9)	120	(97.6)	212	(94.6)	55	(96.5)
with toxicity grade 3-5 adverse events	341	(77.7)	97	(78.9)	161	(71.9)	46	(80.7)
with toxicity grade 3-5 drug-related adverse events	298	(67.9)	85	(69.1)	146	(65.2)	42	(73.7)
with serious adverse events	122	(27.8)	43	(35.0)	47	(21.0)	20	(35.1)
with serious drug-related adverse events	76	(17.3)	22	(17.9)	25	(11.2)	9	(15.8)
with any dose modification‡ due to an adverse event	325	(74.0)	104	(84.6)	163	(72.8)	46	(80.7)
pembrolizumab/placebo dose modification	232	(52.8)	82	(66.7)	105	(46.9)	29	(50.9)
nab-paclitaxel dose modification	70	(15.9)	29	(23.6)	32	(14.3)	13	(22.8)
paclitaxel dose modification	30	(6.8)	22	(17.9)	13	(5.8)	8	(14.0)
gemcitabine dose modification	214	(48.7)	50	(40.7)	114	(50.9)	24	(42.1)
carboplatin dose modification	211	(48.1)	50	(40.7)	116	(51.8)	24	(42.1)
who died	10	(2.3)	4	(3.3)	3	(1.3)	2	(3.5)
who died due to a drug-related adverse event	2	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued any drug due to an adverse event	82	(18.7)	33	(26.8)	27	(12.1)	10	(17.5)
discontinued pembrolizumab/placebo	45	(10.3)	15	(12.2)	10	(4.5)	5	(8.8)
discontinued nab-paclitaxel	11	(2.5)	11	(8.9)	3	(1.3)	1	(1.8)
discontinued paclitaxel	7	(1.6)	9	(7.3)	2	(0.9)	4	(7.0)
discontinued gemcitabine	32	(7.3)	5	(4.1)	12	(5.4)	4	(7.0)
discontinued carboplatin	36	(8.2)	6	(4.9)	15	(6.7)	2	(3.5)
discontinued any drug due to a drug-related adverse event	73	(16.6)	29	(23.6)	24	(10.7)	7	(12.3)
discontinued pembrolizumab/placebo	39	(8.9)	12	(9.8)	7	(3.1)	3	(5.3)
discontinued nab-paclitaxel	10	(2.3)	8	(6.5)	2	(0.9)	1	(1.8)
discontinued paclitaxel	7	(1.6)	9	(7.3)	1	(0.4)	2	(3.5)
discontinued gemcitabine	28	(6.4)	5	(4.1)	12	(5.4)	3	(5.3)
discontinued carboplatin	31	(7.1)	6	(4.9)	15	(6.7)	1	(1.8)
discontinued any drug due to a serious adverse event	31	(7.1)	13	(10.6)	5	(2.2)	4	(7.0)
discontinued pembrolizumab/placebo	28	(6.4)	11	(8.9)	5	(2.2)	3	(5.3)
discontinued nab-paclitaxel	4	(0.9)	5	(4.1)	1	(0.4)	0	(0.0)
discontinued paclitaxel	2	(0.5)	2	(1.6)	1	(0.4)	3	(5.3)
discontinued gemcitabine	9	(2.1)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued carboplatin	8	(1.8)	0	(0.0)	1	(0.4)	0	(0.0)
discontinued any drug due to a serious drug-related adverse event	27	(6.2)	9	(7.3)	2	(0.9)	2	(3.5)
discontinued pembrolizumab/placebo	24	(5.5)	8	(6.5)	2	(0.9)	1	(1.8)
discontinued nab-paclitaxel	3	(0.7)	2	(1.6)	0	(0.0)	0	(0.0)
discontinued paclitaxel	2	(0.5)	2	(1.6)	0	(0.0)	1	(1.8)
discontinued gemcitabine	7	(1.6)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued carboplatin	6	(1.4)	0	(0.0)	1	(0.4)	0	(0.0)

† Determined by the investigator to be related to the drug.
‡ Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.
Grades are based on NCI CTCAE version 4.0.
Non-serious adverse events up to 30 days after last dose and serious adverse events up to 90 days after last dose are included.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Database Cutoff Date: 11DEC2019

Adverse Event Summary by Age Category (<65, 65-74, 75-84, ≥85 Years) (ASaT Population)

	KN355 Data for Pembrolizumab + Chemotherapy††								Reference Safety Dataset for Pembrolizumab Monotherapy§§							
	<65		65-74		75-84		>=85		<65		65-74		75-84		>=85	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	459		103		33		1		3,385		1,737		663		99	
with one or more adverse events	453	(98.7)	101	(98.1)	33	(100.0)	1	(100.0)	3,266	(96.5)	1,677	(96.5)	646	(97.4)	98	(99.0)
with no adverse event	6	(1.3)	2	(1.9)	0	(0.0)	0	(0.0)	119	(3.5)	60	(3.5)	17	(2.6)	1	(1.0)
with drug-related† adverse events	441	(96.1)	100	(97.1)	32	(97.0)	1	(100.0)	2,358	(69.7)	1,223	(70.4)	467	(70.4)	75	(75.8)
with toxicity grade 3-5 adverse events	356	(77.6)	81	(78.6)	27	(81.8)	1	(100.0)	1,489	(44.0)	891	(51.3)	373	(56.3)	60	(60.6)
with toxicity grade 3-5 drug-related adverse events	312	(68.0)	73	(70.9)	21	(63.6)	1	(100.0)	452	(13.4)	311	(17.9)	128	(19.3)	18	(18.2)
with serious adverse events	132	(28.8)	36	(35.0)	13	(39.4)	0	(0.0)	1,168	(34.5)	719	(41.4)	315	(47.5)	50	(50.5)
with serious drug-related adverse events	81	(17.6)	17	(16.5)	7	(21.2)	0	(0.0)	339	(10.0)	214	(12.3)	85	(12.8)	12	(12.1)
with dose modification‡ due to an adverse event	339	(73.9)	84	(81.6)	32	(97.0)	1	(100.0)	1,060	(31.3)	649	(37.4)	284	(42.8)	35	(35.4)
who died	10	(2.2)	3	(2.9)	2	(6.1)	0	(0.0)	143	(4.2)	103	(5.9)	54	(8.1)	11	(11.1)
who died due to a drug-related adverse event	2	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)	21	(0.6)	12	(0.7)	5	(0.8)	1	(1.0)
discontinued drug due to an adverse event	89	(19.4)	28	(27.2)	11	(33.3)	0	(0.0)	392	(11.6)	246	(14.2)	131	(19.8)	14	(14.1)
discontinued drug due to a drug-related adverse event	78	(17.0)	25	(24.3)	8	(24.2)	0	(0.0)	202	(6.0)	135	(7.8)	62	(9.4)	6	(6.1)
discontinued drug due to a serious adverse event	36	(7.8)	10	(9.7)	5	(15.2)	0	(0.0)	285	(8.4)	174	(10.0)	100	(15.1)	11	(11.1)
discontinued drug due to a serious drug-related adverse event	30	(6.5)	7	(6.8)	3	(9.1)	0	(0.0)	122	(3.6)	81	(4.7)	38	(5.7)	3	(3.0)

† Determined by the investigator to be related to the drug.

‡ Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

†† Includes all subjects who received at least one dose of treatment in the pembrolizumab + chemotherapy arm of KN355.

§§ Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (Head and Neck Cancer), KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055 and KN087.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)

Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013-Cohort 3: 28SEP2018, KN087: 25SEP2016)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for TNBC (KN355: 11DEC2019, KN012: 26APR2016, KN086: 10NOV2017, KN119: 11APR2019)

Adverse Event Summary for Elderly Subjects by Age
(Part 2 All Subjects)
(ASaT Population)

	Age (Years)															
	Pembrolizumab + Chemotherapy								Placebo + Chemotherapy							
	< 65		≥ 65 to < 75		≥ 75 to < 85		≥ 85		< 65		≥ 65 to < 75		≥ 75 to < 85		≥ 85	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in Population	439		93		29		1		224		48		9		0	
with one or more adverse events	433	(98.6)	91	(97.8)	29	(100.0)	1	(100.0)	219	(97.8)	48	(100.0)	9	(100.0)	0	(0.0)
who died	10	(2.3)	3	(3.2)	1	(3.4)	0	(0.0)	3	(1.3)	1	(2.1)	1	(11.1)	0	(0.0)
with serious adverse events	122	(27.8)	33	(35.5)	10	(34.5)	0	(0.0)	47	(21.0)	16	(33.3)	4	(44.4)	0	(0.0)
discontinued drug due to an adverse event	82	(18.7)	25	(26.9)	8	(27.6)	0	(0.0)	27	(12.1)	7	(14.6)	3	(33.3)	0	(0.0)
CNS (confusion/extrapyramidal)	31	(7.1)	15	(16.1)	7	(24.1)	1	(100.0)	12	(5.4)	5	(10.4)	0	(0.0)	0	(0.0)
AE related to falling	34	(7.7)	9	(9.7)	7	(24.1)	0	(0.0)	15	(6.7)	5	(10.4)	0	(0.0)	0	(0.0)
Cardiovascular events	112	(25.5)	24	(25.8)	12	(41.4)	0	(0.0)	49	(21.9)	15	(31.3)	5	(55.6)	0	(0.0)
Cerebrovascular events	7	(1.6)	4	(4.3)	0	(0.0)	0	(0.0)	3	(1.3)	0	(0.0)	1	(11.1)	0	(0.0)
Infections	222	(50.6)	45	(48.4)	23	(79.3)	1	(100.0)	101	(45.1)	26	(54.2)	4	(44.4)	0	(0.0)

Non-serious adverse events up to 30 days after last dose and serious adverse events up to 90 days after last dose are included.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Database Cutoff Date: 11DEC2019.

Adverse Event Summary for Elderly Subjects by Age
(Subjects in ASaT Population Treated with Pembrolizumab)

	KN355 Data for Pembrolizumab + Chemotheraphy[§]								Reference Safety Dataset for Pembrolizumab Monotherapyy[††]							
	<65		65-74		75-84		>= 85		<65		65-74		75-84		>= 85	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	459	(100.0)	103	(100.0)	33	(100.0)	1	(100.0)	3385	(100.0)	1737	(100.0)	663	(100.0)	99	(100.0)
with one or more adverse events	453	(98.7)	101	(98.1)	33	(100.0)	1	(100.0)	3266	(96.5)	1677	(96.5)	646	(97.4)	98	(99.0)
who died	10	(2.2)	3	(2.9)	2	(6.1)	0	(0.0)	143	(4.2)	103	(5.9)	54	(8.1)	11	(11.1)
with serious adverse events	132	(28.8)	36	(35.0)	13	(39.4)	0	(0.0)	1168	(34.5)	719	(41.4)	315	(47.5)	50	(50.5)
discontinued‡ due to an adverse event	89	(19.4)	28	(27.2)	11	(33.3)	0	(0.0)	392	(11.6)	246	(14.2)	131	(19.8)	14	(14.1)
CNS (confusion/extrapyramidal)	31	(6.8)	15	(14.6)	6	(18.2)	1	(100.0)	247	(7.3)	157	(9.0)	46	(6.9)	16	(16.2)
AE related to falling	36	(7.8)	9	(8.7)	7	(21.2)	0	(0.0)	225	(6.6)	152	(8.8)	70	(10.6)	20	(20.2)
CV events	117	(25.5)	26	(25.2)	14	(42.4)	0	(0.0)	649	(19.2)	395	(22.7)	160	(24.1)	25	(25.3)
Cerebrovascular events	7	(1.5)	4	(3.9)	0	(0.0)	0	(0.0)	61	(1.8)	40	(2.3)	20	(3.0)	3	(3.0)
Infections	235	(51.2)	52	(50.5)	26	(78.8)	1	(100.0)	1434	(42.4)	773	(44.5)	308	(46.5)	44	(44.4)

MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
AEs were followed 30 days after last dose of study treatment; SAEs were followed 90 days after last dose of study treatment.
[§] Includes all subjects who received at least one dose of pembrolizumab or chemotheraphy in KN355.
[††] Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (Head and Neck Cancer), KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055 and KN087.
Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)
Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)
Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)
Database cutoff date for cHL (KN013-Cohort 3: 28SEP2018, KN087: 21MAR2019)
Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)
Database cutoff date for TNBC (KN355: 15JUN2020)

Upon request, the MAH provided a pooled analysis of safety data by age categories (<75 years and ≥ 75 years of age) comprising all pembrolizumab combination studies conducted across different indications. The sample size consisted of a total of 1871 patients aged <75 years and 162 patients aged ≥ 75 years who were exposed to the combination pembrolizumab+chemotherapy, compared to 1359 patients aged <75 years and 123 patients aged ≥ 75 years who were assigned to chemotherapy only. Data were pooled from individual studies conducted in lung, HNSCC, esophaegeal and TNBC tumours. The MAH also presented a pooled analysis related to pembrolizumab monotherapy across tumours.

Table
Summary of Drug Exposure
(ASaT Population)

	Pooled Pembrolizumab + Chemotherapy[††], Age < 75 Years (N=1871)	Pooled Pembrolizumab + Chemotherapy[††], Age >= 75 Years (N=162)	Pooled Comparator Chemotherapy[§§], Age < 75 Years (N=1359)	Pooled Comparator Chemotherapy[§§], Age >= 75 Years (N=123)
Study Days On-Therapy (Months)				
Mean	9.1	8.2	6.5	6.3
Median	6.3	5.7	4.9	4.7
SD	7.81	7.64	6.29	5.80
Range	0.0 to 48.0	0.0 to 28.7	0.0 to 49.2	0.0 to 26.2

Each subject is counted once on each applicable duration category row.

Duration of Exposure is calculated as last dose date - first dose date + 1.

[††] Includes all subjects who received at least one dose of pembrolizumab combo therapy in KN021-A/C/G, KN048, KN189, KN355, KN407 and KN590.

[§§] Includes all subjects who received at least one dose of comparator chemotherapy in KN021-A/C/G, KN048, KN189, KN355, KN407 and KN590.

MK-3475 Database Cutoff Date for Lung (KN021: 19AUG2019, KN189: 20MAY2019, KN407: 09MAY2019)

MK-3475 Database Cutoff Date for HNSCC (KN048: 25FEB2019)

MK-3475 Database Cutoff Date for Esophageal (KN590: 02JUL2020)

MK-3475 Database Cutoff Date for mTNBC (KN355: 11DEC2019)

MedDRA version used is 23.0.

Table 1
Summary of Drug Exposure
(ASaT Population)

	Pooled Pembrolizumab Monotherapy[††], Age < 75 Years (N=5384)	Pooled Pembrolizumab Monotherapy[††], Age >= 75 Years (N=801)
Study Days On-Therapy (Months)		
Mean	7.6	6.8
Median	5.0	4.2
SD	7.07	6.75
Range	0.0 to 32.5	0.0 to 30.6

Each subject is counted once on each applicable duration category row.

Duration of Exposure is calculated as last dose date - first dose date + 1.

[††] Includes all participants who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 (HNSCC), KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN177, and KN204.

Database Cutoff Date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)

Database Cutoff Date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)

Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013-Cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052:26SEP2018)

Database cutoff date for CRC MSI-H or dMMMR (KN177:19FEB2020)

MedDRA version used is 23.0.

Table 58
Adverse Event Summary
(ASaT Population)

	Pooled Pembrolizumab + Chemotherapy[††], Age < 75 Years		Pooled Pembrolizumab + Chemotherapy[††], Age >= 75 Years		Pooled Comparator Chemotherapy[§§], Age < 75 Years		Pooled Comparator Chemotherapy[§§], Age >= 75 Years	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	1,871		162		1,359		123	
with one or more adverse events	1,854	(99.1)	161	(99.4)	1,345	(99.0)	121	(98.4)
with no adverse event	17	(0.9)	1	(0.6)	14	(1.0)	2	(1.6)
with drug-related[†] adverse events	1,794	(95.9)	154	(95.1)	1,282	(94.3)	116	(94.3)
with toxicity grade 3-5 adverse events	1,446	(77.3)	137	(84.6)	1,017	(74.8)	101	(82.1)
with toxicity grade 3-5 drug-related adverse events	1,182	(63.2)	103	(63.6)	817	(60.1)	79	(64.2)
with serious adverse events	865	(46.2)	97	(59.9)	584	(43.0)	65	(52.8)
with serious drug-related adverse events	494	(26.4)	56	(34.6)	280	(20.6)	26	(21.1)
who died	107	(5.7)	32	(19.8)	91	(6.7)	15	(12.2)
who died due to a drug-related adverse event	32	(1.7)	11	(6.8)	17	(1.3)	5	(4.1)
discontinued drug due to an adverse event	482	(25.8)	67	(41.4)	241	(17.7)	31	(25.2)
discontinued drug due to a drug-related adverse event	387	(20.7)	45	(27.8)	161	(11.8)	21	(17.1)
discontinued drug due to a serious adverse event	275	(14.7)	51	(31.5)	132	(9.7)	23	(18.7)
discontinued drug due to a serious drug-related adverse event	188	(10.0)	30	(18.5)	59	(4.3)	12	(9.8)

[†] Determined by the investigator to be related to the drug.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

[††] Includes all subjects who received at least one dose of pembrolizumab combo therapy in KN021-A/C/G, KN048, KN189, KN355, KN407 and KN590.

[§§] Includes all subjects who received at least one dose of comparator chemotherapy in KN021-A/C/G, KN048, KN189, KN355, KN407 and KN590.

MK-3475 Database Cutoff Date for Lung (KN021: 19AUG2019, KN189: 20MAY2019, KN407: 09MAY2019)

MK-3475 Database Cutoff Date for HNSCC (KN048: 25FEB2019)

MK-3475 Database Cutoff Date for Esophageal (KN590: 02JUL2020)

MK-3475 Database Cutoff Date for mTNBC (KN355: 11DEC2019)

MedDRA version used is 23.0.

Table 2
Adverse Event Summary
(ASaT Population)

	Pooled Pembrolizumab Monotherapy[††], Age < 75 Years		Pooled Pembrolizumab Monotherapy[††], Age >= 75 Years	
	n	(%)	n	(%)
Subjects in population	5,384		801	
with one or more adverse events	5,202	(96.6)	782	(97.6)
with no adverse event	182	(3.4)	19	(2.4)
with drug-related[†] adverse events	3,791	(70.4)	573	(71.5)
with toxicity grade 3-5 adverse events	2,521	(46.8)	459	(57.3)
with toxicity grade 3-5 drug-related adverse events	816	(15.2)	159	(19.9)
with serious adverse events	1,987	(36.9)	385	(48.1)
with serious drug-related adverse events	598	(11.1)	107	(13.4)
who died	254	(4.7)	67	(8.4)
who died due to a drug-related adverse event	34	(0.6)	6	(0.7)
discontinued drug due to an adverse event	677	(12.6)	154	(19.2)
discontinued drug due to a drug-related adverse event	370	(6.9)	74	(9.2)
discontinued drug due to a serious adverse event	482	(9.0)	116	(14.5)
discontinued drug due to a serious drug-related adverse event	221	(4.1)	44	(5.5)

[†] Determined by the investigator to be related to the drug.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

[††] Includes all participants who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 (HNSCC), KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN177, and KN204.

Database Cutoff Date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)

Database Cutoff Date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)

Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013-Cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052:26SEP2018)

Database cutoff date for CRC MSI-H or dMMMR (KN177:19FEB2020)

MedDRA version used is 23.0.

Table 3
Adverse Event Summary
AEOSI
(ASaT Population)

	Pooled Pembrolizumab + Chemotherapy[††], Age < 75 Years		Pooled Pembrolizumab + Chemotherapy[††], Age >= 75 Years		Pooled Comparator Chemotherapy[§§], Age < 75 Years		Pooled Comparator Chemotherapy[§§], Age >= 75 Years	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	1,871		162		1,359		123	
with one or more adverse events	523	(28.0)	54	(33.3)	179	(13.2)	20	(16.3)
with no adverse event	1,348	(72.0)	108	(66.7)	1,180	(86.8)	103	(83.7)
with drug-related[†] adverse events	456	(24.4)	50	(30.9)	135	(9.9)	16	(13.0)
with toxicity grade 3-5 adverse events	147	(7.9)	20	(12.3)	45	(3.3)	11	(8.9)
with toxicity grade 3-5 drug-related adverse events	130	(6.9)	19	(11.7)	40	(2.9)	7	(5.7)
with serious adverse events	124	(6.6)	18	(11.1)	26	(1.9)	7	(5.7)
with serious drug-related adverse events	111	(5.9)	17	(10.5)	21	(1.5)	4	(3.3)
who died	3	(0.2)	3	(1.9)	1	(0.1)	1	(0.8)
who died due to a drug-related adverse event	3	(0.2)	3	(1.9)	1	(0.1)	0	(0.0)
discontinued drug due to an adverse event	98	(5.2)	17	(10.5)	29	(2.1)	4	(3.3)
discontinued drug due to a drug-related adverse event	95	(5.1)	17	(10.5)	29	(2.1)	3	(2.4)
discontinued drug due to a serious adverse event	70	(3.7)	14	(8.6)	15	(1.1)	3	(2.4)
discontinued drug due to a serious drug-related adverse event	67	(3.6)	14	(8.6)	15	(1.1)	2	(1.6)

[†] Determined by the investigator to be related to the drug.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
[††] Includes all subjects who received at least one dose of pembrolizumab combo therapy in KN021-A/C/G, KN048, KN189, KN355, KN407 and KN590.
[§§] Includes all subjects who received at least one dose of comparator chemotherapy in KN021-A/C/G, KN048, KN189, KN355, KN407 and KN590.
MK-3475 Database Cutoff Date for Lung (KN021: 19AUG2019, KN189: 20MAY2019, KN407: 09MAY2019)
MK-3475 Database Cutoff Date for HNSCC (KN048: 25FEB2019)
MK-3475 Database Cutoff Date for Esophageal (KN590: 02JUL2020)
MK-3475 Database Cutoff Date for mTNBC (KN355: 11DEC2019)
MedDRA version used is 23.0.

Table 4
Adverse Event Summary
AEOSI
(ASaT Population)

	Pooled Pembrolizumab Monotherapy[††], Age < 75 Years		Pooled Pembrolizumab Monotherapy[††], Age >= 75 Years	
	n	(%)	n	(%)
Subjects in population	5,384		801	
with one or more adverse events	1,372	(25.5)	202	(25.2)
with no adverse event	4,012	(74.5)	599	(74.8)
with drug-related[†] adverse events	1,187	(22.0)	179	(22.3)
with toxicity grade 3-5 adverse events	341	(6.3)	65	(8.1)
with toxicity grade 3-5 drug-related adverse events	290	(5.4)	62	(7.7)
with serious adverse events	352	(6.5)	58	(7.2)
with serious drug-related adverse events	308	(5.7)	55	(6.9)
who died	10	(0.2)	1	(0.1)
who died due to a drug-related adverse event	10	(0.2)	1	(0.1)
discontinued drug due to an adverse event	216	(4.0)	39	(4.9)
discontinued drug due to a drug-related adverse event	212	(3.9)	39	(4.9)
discontinued drug due to a serious adverse event	145	(2.7)	27	(3.4)
discontinued drug due to a serious drug-related adverse event	143	(2.7)	27	(3.4)

[†] Determined by the investigator to be related to the drug.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
[††] Includes all participants who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 (HNSCC), KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN177, and KN204.
Database Cutoff Date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)
Database Cutoff Date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)
Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)
Database cutoff date for cHL (KN013-Cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)
Database cutoff date for Bladder (KN045: 26OCT2017, KN052:26SEP2018)
Database cutoff date for CRC MSI-H or dMMMR (KN177:19FEB2020)
MedDRA version used is 23.0.

Table 5
Adverse Event Summary by Age
(ASaT Population)

	Pooled Pembrolizumab + Chemotherapy††				Pooled Comparator Chemotherapy§§			
	<75		>= 75		<75		>= 75	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	1871	(100.0)	162	(100.0)	1359	(100.0)	123	(100.0)
with one or more adverse events	1854	(99.1)	161	(99.4)	1345	(99.0)	121	(98.4)
who died	107	(5.7)	32	(19.8)	91	(6.7)	15	(12.2)
with serious adverse events	865	(46.2)	97	(59.9)	584	(43.0)	65	(52.8)
discontinued due to an adverse event	482	(25.8)	67	(41.4)	241	(17.7)	31	(25.2)
CNS (confusion/extrapyramidal)	185	(9.9)	27	(16.7)	117	(8.6)	13	(10.6)
AE related to falling	161	(8.6)	25	(15.4)	108	(7.9)	11	(8.9)
CV events	512	(27.4)	55	(34.0)	336	(24.7)	32	(26.0)
Cerebrovascular events	50	(2.7)	9	(5.6)	41	(3.0)	6	(4.9)
Infections	1003	(53.6)	89	(54.9)	647	(47.6)	69	(56.1)

MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
AEs were followed 30 days after last dose of study treatment; SAEs were followed 90 days after last dose of study treatment.
†† Includes all subjects who received at least one dose of pembrolizumab combo therapy in KN021-A/C/G, KN048, KN189, KN355, KN407 and KN590.
§§ Includes all subjects who received at least one dose of comparator chemotherapy in KN021-A/C/G, KN048, KN189, KN355, KN407 and KN590.
MK-3475 Database Cutoff Date for Lung (KN021: 19AUG2019, KN189: 20MAY2019, KN407: 09MAY2019)
MK-3475 Database Cutoff Date for HNSCC (KN048: 25FEB2019)
MK-3475 Database Cutoff Date for Esophageal (KN590: 02JUL2020)
MK-3475 Database Cutoff Date for mTNBC (KN355: 11DEC2019)
MedDRA version used is 23.0.

Table 6
Adverse Event Summary by Age
(ASaT Population)

	Pooled Pembrolizumab Monotherapy††			
	<75		>= 75	
	n	(%)	n	(%)
Subjects in population	5384	(100.0)	801	(100.0)
with one or more adverse events	5202	(96.6)	782	(97.6)
who died	254	(4.7)	67	(8.4)
with serious adverse events	1986	(36.9)	385	(48.1)
discontinued due to an adverse event	677	(12.6)	154	(19.2)
CNS (confusion/extrapyramidal)	495	(9.2)	88	(11.0)
AE related to falling	405	(7.5)	98	(12.2)
CV events	1091	(20.3)	199	(24.8)
Cerebrovascular events	104	(1.9)	24	(3.0)
Infections	2397	(44.5)	373	(46.6)

MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
AEs were followed 30 days after last dose of study treatment; SAEs were followed 90 days after last dose of study treatment.
†† Includes all participants who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 (HNSCC), KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN177, and KN204.
Database Cutoff Date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)
Database Cutoff Date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)
Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)
Database cutoff date for cHL (KN013-Cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)
Database cutoff date for Bladder (KN045: 26OCT2017, KN052:26SEP2018)
Database cutoff date for CRC MSI-H or dMMMR (KN177:19FEB2020)
MedDRA version used is 23.0.

Exposure in patients aged ≥ 75 years is generally lower than those with age <75 years, in both combination and monotherapy pooled datasets. This can be partly attributable to a higher rate of fatalities and drug discontinuation due to AEs, including SAEs, in older than younger participants.

In looking at the combined therapeutic scheme, it should be recognised that within the comparator arm (chemotherapy only) these events were generally more frequent in patients older than 75 years with respect to their younger counterpart, in line with the age-dependent frailty that clearly affects drug tolerability. However, the rate of fatalities and drug discontinuation increases with the combined therapy vs chemotherapy in both age categories. When considering AEOSI only, ageing in itself seems to increase the rate of these events in the control group (chemotherapy only); however, pembrolizumab in addition to

chemotherapy further amplifies the occurrence of events in both age categories, particularly in the oldest group.

The age-dependent increase in AEOSI that emerges in pembrolizumab+chemotherapy pooled dataset, is not observable in pembrolizumab monotherapy since an equal rate of events was reported in both age categories.

The analysis of specific AEs by age reveals that CNS, AE related to falling, CV and cerebrovascular events were all increased by pembrolizumab when added to chemotherapy in the group of patients ≥75 years, while a similar frequency of these events is recognisable between pembrolizymab+chemotherapy and chemotherapy alone in patients <75 years. Of note, within the comparator arm (chemotherapy only) there is no difference in the incidence of these events between age categories. In the monotherapy pooled dataset, patients ≥75 years experienced more numerous CNS, AE related to falling, CV and cerebrovascular events than their younger counterpart. However, as these are events commonly associated with ageing, disantangling the effect of age from drug is challenging. Taken together, these data suggest that pembrolizumab as add-on to chemotherapeutic agents is less tolerated in patients ≥75 years of age than their younger counterpart. This pooled analysis corroborates the consistent trend observed across individual studies showing increased toxicity of pembrolizumab as add-on to chemotherapy by age. Amendments to the SmPC to appropriately reflect these data has been requested (please refer to the PI)

CHEMOTHERAPY

Adverse Event Summary by Chemotherapy
(Part 2 All Subjects)
(ASaT Population)

	Pembrolizumab + Chemotherapy						Placebo + Chemotherapy					
	Nab-Paclitaxel		Paclitaxel		Gemcitabine/Carboplatin		Nab-Paclitaxel		Paclitaxel		Gemcitabine/Carboplatin	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	172		81		309		95		32		154	
with one or more adverse events	169	(98.3)	79	(97.5)	306	(99.0)	93	(97.9)	30	(93.8)	153	(99.4)
with no adverse event	3	(1.7)	2	(2.5)	3	(1.0)	2	(2.1)	2	(6.3)	1	(0.6)
with drug-related[†] adverse events	164	(95.3)	78	(96.3)	299	(96.8)	87	(91.6)	29	(90.6)	151	(98.1)
with toxicity grade 3-5 adverse events	108	(62.8)	51	(63.0)	279	(90.3)	47	(49.5)	19	(59.4)	141	(91.6)
with toxicity grade 3-5 drug-related adverse events	83	(48.3)	36	(44.4)	264	(85.4)	35	(36.8)	15	(46.9)	138	(89.6)
with serious adverse events	52	(30.2)	21	(25.9)	92	(29.8)	17	(17.9)	7	(21.9)	43	(27.9)
with serious drug-related adverse events	25	(14.5)	14	(17.3)	59	(19.1)	7	(7.4)	1	(3.1)	26	(16.9)
with any dose modification[‡] due to an adverse event	107	(62.2)	55	(67.9)	267	(86.4)	46	(48.4)	23	(71.9)	140	(90.9)
pembrolizumab/placebo dose modification	75	(43.6)	38	(46.9)	201	(65.0)	20	(21.1)	15	(46.9)	99	(64.3)
nab-paclitaxel dose modification	99	(57.6)	0	(0.0)	0	(0.0)	45	(47.4)	0	(0.0)	0	(0.0)
paclitaxel dose modification	0	(0.0)	52	(64.2)	0	(0.0)	0	(0.0)	21	(65.6)	0	(0.0)
gemcitabine dose modification	0	(0.0)	0	(0.0)	264	(85.4)	0	(0.0)	0	(0.0)	138	(89.6)
carboplatin dose modification	0	(0.0)	0	(0.0)	261	(84.5)	0	(0.0)	0	(0.0)	140	(90.9)
who died	7	(4.1)	1	(1.2)	6	(1.9)	1	(1.1)	2	(6.3)	2	(1.3)
who died due to a drug-related adverse event	1	(0.6)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)

	Pembrolizumab + Chemotherapy						Placebo + Chemotherapy					
	Nab-Paclitaxel		Paclitaxel		Gemcitabine/Carboplatin		Nab-Paclitaxel		Paclitaxel		Gemcitabine/Carboplatin	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
discontinued any drug due to an adverse event	28	(16.3)	26	(32.1)	61	(19.7)	5	(5.3)	7	(21.9)	25	(16.2)
discontinued pembrolizumab/placebo	16	(9.3)	15	(18.5)	29	(9.4)	2	(2.1)	4	(12.5)	9	(5.8)
discontinued nab-paclitaxel	22	(12.8)	0	(0.0)	0	(0.0)	4	(4.2)	0	(0.0)	0	(0.0)
discontinued paclitaxel	0	(0.0)	16	(19.8)	0	(0.0)	0	(0.0)	6	(18.8)	0	(0.0)
discontinued gemcitabine	0	(0.0)	0	(0.0)	37	(12.0)	0	(0.0)	0	(0.0)	16	(10.4)
discontinued carboplatin	0	(0.0)	0	(0.0)	42	(13.6)	0	(0.0)	0	(0.0)	17	(11.0)
discontinued any drug due to a drug-related adverse event	24	(14.0)	24	(29.6)	54	(17.5)	4	(4.2)	4	(12.5)	23	(14.9)
discontinued pembrolizumab/placebo	13	(7.6)	13	(16.0)	25	(8.1)	1	(1.1)	1	(3.1)	8	(5.2)
discontinued nab-paclitaxel	18	(10.5)	0	(0.0)	0	(0.0)	3	(3.2)	0	(0.0)	0	(0.0)
discontinued paclitaxel	0	(0.0)	16	(19.8)	0	(0.0)	0	(0.0)	3	(9.4)	0	(0.0)
discontinued gemcitabine	0	(0.0)	0	(0.0)	33	(10.7)	0	(0.0)	0	(0.0)	15	(9.7)
discontinued carboplatin	0	(0.0)	0	(0.0)	37	(12.0)	0	(0.0)	0	(0.0)	16	(10.4)
discontinued any drug due to a serious adverse event	14	(8.1)	8	(9.9)	22	(7.1)	2	(2.1)	4	(12.5)	3	(1.9)
discontinued pembrolizumab/placebo	12	(7.0)	7	(8.6)	20	(6.5)	2	(2.1)	3	(9.4)	3	(1.9)
discontinued nab-paclitaxel	9	(5.2)	0	(0.0)	0	(0.0)	1	(1.1)	0	(0.0)	0	(0.0)
discontinued paclitaxel	0	(0.0)	4	(4.9)	0	(0.0)	0	(0.0)	4	(12.5)	0	(0.0)

	Pembrolizumab + Chemotherapy						Placebo + Chemotherapy					
	Nab-Paclitaxel		Paclitaxel		Gemcitabine/Carboplatin		Nab-Paclitaxel		Paclitaxel		Gemcitabine/Carboplatin	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
discontinued gemcitabine	0	(0.0)	0	(0.0)	9	(2.9)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued carboplatin	0	(0.0)	0	(0.0)	8	(2.6)	0	(0.0)	0	(0.0)	1	(0.6)
discontinued any drug due to a serious drug-related adverse event	10	(5.8)	7	(8.6)	19	(6.1)	1	(1.1)	1	(3.1)	2	(1.3)
discontinued pembrolizumab/placebo	9	(5.2)	6	(7.4)	17	(5.5)	1	(1.1)	0	(0.0)	2	(1.3)
discontinued nab-paclitaxel	5	(2.9)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued paclitaxel	0	(0.0)	4	(4.9)	0	(0.0)	0	(0.0)	1	(3.1)	0	(0.0)
discontinued gemcitabine	0	(0.0)	0	(0.0)	7	(2.3)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued carboplatin	0	(0.0)	0	(0.0)	6	(1.9)	0	(0.0)	0	(0.0)	1	(0.6)

† Determined by the investigator to be related to the drug.
‡ Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.
Grades are based on NCI CTCAE version 4.0.
Non-serious adverse events up to 30 days after last dose and serious adverse events up to 90 days after last dose are included.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Database Cutoff Date: 11DEC2019

ECOG STATUS

Adverse Event Summary by ECOG Status
(Part 2 All Subjects)
(ASaT Population)

	Pembrolizumab + Chemotherapy						Placebo + Chemotherapy					
	0		1		2		0		1		2	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	331		230		1		173		108		0	
with one or more adverse events	327	(98.8)	226	(98.3)	1	(100.0)	170	(98.3)	106	(98.1)	0	(0.0)
with no adverse event	4	(1.2)	4	(1.7)	0	(0.0)	3	(1.7)	2	(1.9)	0	(0.0)
with drug-related† adverse events	320	(96.7)	220	(95.7)	1	(100.0)	164	(94.8)	103	(95.4)	0	(0.0)
with toxicity grade 3-5 adverse events	248	(74.9)	189	(82.2)	1	(100.0)	126	(72.8)	81	(75.0)	0	(0.0)
with toxicity grade 3-5 drug-related adverse events	222	(67.1)	161	(70.0)	0	(0.0)	113	(65.3)	75	(69.4)	0	(0.0)
with serious adverse events	83	(25.1)	81	(35.2)	1	(100.0)	36	(20.8)	31	(28.7)	0	(0.0)
with serious drug-related adverse events	47	(14.2)	51	(22.2)	0	(0.0)	16	(9.2)	18	(16.7)	0	(0.0)
with any dose modification‡ due to an adverse event	249	(75.2)	180	(78.3)	0	(0.0)	130	(75.1)	79	(73.1)	0	(0.0)
pembrolizumab/placebo dose modification	182	(55.0)	132	(57.4)	0	(0.0)	87	(50.3)	47	(43.5)	0	(0.0)
nab-paclitaxel dose modification	56	(16.9)	43	(18.7)	0	(0.0)	29	(16.8)	16	(14.8)	0	(0.0)
paclitaxel dose modification	27	(8.2)	25	(10.9)	0	(0.0)	14	(8.1)	7	(6.5)	0	(0.0)
gemcitabine dose modification	161	(48.6)	103	(44.8)	0	(0.0)	84	(48.6)	54	(50.0)	0	(0.0)
carboplatin dose modification	157	(47.4)	104	(45.2)	0	(0.0)	84	(48.6)	56	(51.9)	0	(0.0)
who died	6	(1.8)	8	(3.5)	0	(0.0)	4	(2.3)	1	(0.9)	0	(0.0)
who died due to a drug-related adverse event	1	(0.3)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued any drug due to an adverse event	69	(20.8)	46	(20.0)	0	(0.0)	25	(14.5)	12	(11.1)	0	(0.0)
discontinued pembrolizumab/placebo	31	(9.4)	29	(12.6)	0	(0.0)	12	(6.9)	3	(2.8)	0	(0.0)

	Pembrolizumab + Chemotherapy						Placebo + Chemotherapy					
	0		1		2		0		1		2	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
discontinued nab-paclitaxel	11	(3.3)	11	(4.8)	0	(0.0)	4	(2.3)	0	(0.0)	0	(0.0)
discontinued paclitaxel	8	(2.4)	8	(3.5)	0	(0.0)	4	(2.3)	2	(1.9)	0	(0.0)
discontinued gemcitabine	23	(6.9)	14	(6.1)	0	(0.0)	8	(4.6)	8	(7.4)	0	(0.0)
discontinued carboplatin	27	(8.2)	15	(6.5)	0	(0.0)	9	(5.2)	8	(7.4)	0	(0.0)
discontinued any drug due to a drug-related adverse event	61	(18.4)	41	(17.8)	0	(0.0)	21	(12.1)	10	(9.3)	0	(0.0)
discontinued pembrolizumab/placebo	26	(7.9)	25	(10.9)	0	(0.0)	8	(4.6)	2	(1.9)	0	(0.0)
discontinued nab-paclitaxel	9	(2.7)	9	(3.9)	0	(0.0)	3	(1.7)	0	(0.0)	0	(0.0)
discontinued paclitaxel	8	(2.4)	8	(3.5)	0	(0.0)	2	(1.2)	1	(0.9)	0	(0.0)
discontinued gemcitabine	21	(6.3)	12	(5.2)	0	(0.0)	8	(4.6)	7	(6.5)	0	(0.0)
discontinued carboplatin	24	(7.3)	13	(5.7)	0	(0.0)	9	(5.2)	7	(6.5)	0	(0.0)
discontinued any drug due to a serious adverse event	23	(6.9)	21	(9.1)	0	(0.0)	8	(4.6)	1	(0.9)	0	(0.0)
discontinued pembrolizumab/placebo	19	(5.7)	20	(8.7)	0	(0.0)	7	(4.0)	1	(0.9)	0	(0.0)
discontinued nab-paclitaxel	2	(0.6)	7	(3.0)	0	(0.0)	1	(0.6)	0	(0.0)	0	(0.0)
discontinued paclitaxel	2	(0.6)	2	(0.9)	0	(0.0)	3	(1.7)	1	(0.9)	0	(0.0)
discontinued gemcitabine	5	(1.5)	4	(1.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued carboplatin	4	(1.2)	4	(1.7)	0	(0.0)	1	(0.6)	0	(0.0)	0	(0.0)
discontinued any drug due to a serious drug-related adverse event	19	(5.7)	17	(7.4)	0	(0.0)	4	(2.3)	0	(0.0)	0	(0.0)

	Pembrolizumab + Chemotherapy						Placebo + Chemotherapy					
	0		1		2		0		1		2	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
discontinued pembrolizumab/placebo	16	(4.8)	16	(7.0)	0	(0.0)	3	(1.7)	0	(0.0)	0	(0.0)
discontinued nab-paclitaxel	0	(0.0)	5	(2.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued paclitaxel	2	(0.6)	2	(0.9)	0	(0.0)	1	(0.6)	0	(0.0)	0	(0.0)
discontinued gemcitabine	4	(1.2)	3	(1.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued carboplatin	3	(0.9)	3	(1.3)	0	(0.0)	1	(0.6)	0	(0.0)	0	(0.0)

† Determined by the investigator to be related to the drug.
‡ Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.
Grades are based on NCI CTCAE version 4.0.
Non-serious adverse events up to 30 days after last dose and serious adverse events up to 90 days after last dose are included.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Database Cutoff Date: 11DEC2019

RACE

Adverse Event Summary by Race
(Part 2 All Subjects)
(ASaT Population)

	Pembrolizumab + Chemotherapy				Placebo + Chemotherapy			
	WHITE		NON-WHITE		WHITE		NON-WHITE	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	381		164		195		78	
with one or more adverse events	374	(98.2)	163	(99.4)	190	(97.4)	78	(100.0)
with no adverse event	7	(1.8)	1	(0.6)	5	(2.6)	0	(0.0)
with drug-related† adverse events	365	(95.8)	159	(97.0)	183	(93.8)	76	(97.4)
with toxicity grade 3-5 adverse events	293	(76.9)	131	(79.9)	138	(70.8)	63	(80.8)
with toxicity grade 3-5 drug-related adverse events	250	(65.6)	121	(73.8)	123	(63.1)	59	(75.6)
with serious adverse events	117	(30.7)	43	(26.2)	42	(21.5)	22	(28.2)
with serious drug-related adverse events	70	(18.4)	25	(15.2)	20	(10.3)	12	(15.4)
with any dose modification‡ due to an adverse event	275	(72.2)	140	(85.4)	141	(72.3)	62	(79.5)
pembrolizumab/placebo dose modification	204	(53.5)	99	(60.4)	86	(44.1)	42	(53.8)
nab-paclitaxel dose modification	67	(17.6)	32	(19.5)	31	(15.9)	14	(17.9)
paclitaxel dose modification	38	(10.0)	8	(4.9)	16	(8.2)	3	(3.8)
gemcitabine dose modification	162	(42.5)	95	(57.9)	90	(46.2)	45	(57.7)
carboplatin dose modification	159	(41.7)	95	(57.9)	92	(47.2)	45	(57.7)
who died	10	(2.6)	4	(2.4)	5	(2.6)	0	(0.0)
who died due to a drug-related adverse event	2	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued any drug due to an adverse event	74	(19.4)	35	(21.3)	28	(14.4)	8	(10.3)
discontinued pembrolizumab/placebo	39	(10.2)	18	(11.0)	11	(5.6)	3	(3.8)
discontinued nab-paclitaxel	15	(3.9)	7	(4.3)	4	(2.1)	0	(0.0)

	Pembrolizumab + Chemotherapy				Placebo + Chemotherapy			
	WHITE		NON-WHITE		WHITE		NON-WHITE	
	n	(%)	n	(%)	n	(%)	n	(%)
discontinued paclitaxel	9	(2.4)	4	(2.4)	6	(3.1)	0	(0.0)
discontinued gemcitabine	27	(7.1)	9	(5.5)	12	(6.2)	4	(5.1)
discontinued carboplatin	27	(7.1)	14	(8.5)	11	(5.6)	6	(7.7)
discontinued any drug due to a drug-related adverse event	66	(17.3)	31	(18.9)	22	(11.3)	8	(10.3)
discontinued pembrolizumab/placebo	33	(8.7)	16	(9.8)	6	(3.1)	3	(3.8)
discontinued nab-paclitaxel	12	(3.1)	6	(3.7)	3	(1.5)	0	(0.0)
discontinued paclitaxel	9	(2.4)	4	(2.4)	3	(1.5)	0	(0.0)
discontinued gemcitabine	25	(6.6)	7	(4.3)	11	(5.6)	4	(5.1)
discontinued carboplatin	25	(6.6)	11	(6.7)	10	(5.1)	6	(7.7)
discontinued any drug due to a serious adverse event	29	(7.6)	14	(8.5)	7	(3.6)	1	(1.3)
discontinued pembrolizumab/placebo	27	(7.1)	11	(6.7)	6	(3.1)	1	(1.3)
discontinued nab-paclitaxel	7	(1.8)	2	(1.2)	1	(0.5)	0	(0.0)
discontinued paclitaxel	3	(0.8)	1	(0.6)	4	(2.1)	0	(0.0)
discontinued gemcitabine	6	(1.6)	3	(1.8)	0	(0.0)	0	(0.0)
discontinued carboplatin	6	(1.6)	2	(1.2)	0	(0.0)	1	(1.3)
discontinued any drug due to a serious drug-related adverse event	25	(6.6)	11	(6.7)	2	(1.0)	1	(1.3)
discontinued pembrolizumab/placebo	23	(6.0)	9	(5.5)	1	(0.5)	1	(1.3)
discontinued nab-paclitaxel	4	(1.0)	1	(0.6)	0	(0.0)	0	(0.0)

	Pembrolizumab + Chemotherapy				Placebo + Chemotherapy			
	WHITE		NON-WHITE		WHITE		NON-WHITE	
	n	(%)	n	(%)	n	(%)	n	(%)
discontinued paclitaxel	3	(0.8)	1	(0.6)	1	(0.5)	0	(0.0)
discontinued gemcitabine	6	(1.6)	1	(0.6)	0	(0.0)	0	(0.0)
discontinued carboplatin	6	(1.6)	0	(0.0)	0	(0.0)	1	(1.3)

† Determined by the investigator to be related to the drug.
‡ Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.
Grades are based on NCI CTCAE version 4.0.
Non-serious adverse events up to 30 days after last dose and serious adverse events up to 90 days after last dose are included.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Database Cutoff Date: 11DEC2019

Source: [P355V01MK3475: adam-adsl; adae]

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Table 14.3-47
Adverse Event Summary by Region (EU vs Non-EU)
(Part 2 All Subjects)
(ASaT Population)

	Pembrolizumab + Chemotherapy				Placebo + Chemotherapy			
	EU		Non-EU		EU		Non-EU	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	164		398		94		187	
with one or more adverse events	161	(98.2)	393	(98.7)	94	(100.0)	182	(97.3)
with no adverse event	3	(1.8)	5	(1.3)	0	(0.0)	5	(2.7)
with drug-related† adverse events	158	(96.3)	383	(96.2)	91	(96.8)	176	(94.1)
with toxicity grade 3-5 adverse events	117	(71.3)	321	(80.7)	72	(76.6)	135	(72.2)
with toxicity grade 3-5 drug-related adverse events	102	(62.2)	281	(70.6)	63	(67.0)	125	(66.8)
with serious adverse events	55	(33.5)	110	(27.6)	30	(31.9)	37	(19.8)
with serious drug-related adverse events	35	(21.3)	63	(15.8)	14	(14.9)	20	(10.7)
with any dose modification‡ due to an adverse event	117	(71.3)	312	(78.4)	70	(74.5)	139	(74.3)
pembrolizumab/placebo dose modification	84	(51.2)	230	(57.8)	48	(51.1)	86	(46.0)
nab-paclitaxel dose modification	37	(22.6)	62	(15.6)	19	(20.2)	26	(13.9)
paclitaxel dose modification	15	(9.1)	37	(9.3)	7	(7.4)	14	(7.5)
gemcitabine dose modification	63	(38.4)	201	(50.5)	42	(44.7)	96	(51.3)
carboplatin dose modification	61	(37.2)	200	(50.3)	42	(44.7)	98	(52.4)
who died	6	(3.7)	8	(2.0)	3	(3.2)	2	(1.1)
who died due to a drug-related adverse event	2	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued any drug due to an adverse event	38	(23.2)	77	(19.3)	13	(13.8)	24	(12.8)
discontinued pembrolizumab/placebo	22	(13.4)	38	(9.5)	6	(6.4)	9	(4.8)
discontinued nab-paclitaxel	9	(5.5)	13	(3.3)	3	(3.2)	1	(0.5)

	Pembrolizumab + Chemotherapy				Placebo + Chemotherapy			
	EU		Non-EU		EU		Non-EU	
	n	(%)	n	(%)	n	(%)	n	(%)
discontinued paclitaxel	5	(3.0)	11	(2.8)	2	(2.1)	4	(2.1)
discontinued gemcitabine	11	(6.7)	26	(6.5)	4	(4.3)	12	(6.4)
discontinued carboplatin	11	(6.7)	31	(7.8)	5	(5.3)	12	(6.4)
discontinued any drug due to a drug-related adverse event	33	(20.1)	69	(17.3)	11	(11.7)	20	(10.7)
discontinued pembrolizumab/placebo	17	(10.4)	34	(8.5)	4	(4.3)	6	(3.2)
discontinued nab-paclitaxel	6	(3.7)	12	(3.0)	2	(2.1)	1	(0.5)
discontinued paclitaxel	5	(3.0)	11	(2.8)	2	(2.1)	1	(0.5)
discontinued gemcitabine	11	(6.7)	22	(5.5)	4	(4.3)	11	(5.9)
discontinued carboplatin	11	(6.7)	26	(6.5)	5	(5.3)	11	(5.9)
discontinued any drug due to a serious adverse event	17	(10.4)	27	(6.8)	4	(4.3)	5	(2.7)
discontinued pembrolizumab/placebo	17	(10.4)	22	(5.5)	3	(3.2)	5	(2.7)
discontinued nab-paclitaxel	6	(3.7)	3	(0.8)	1	(1.1)	0	(0.0)
discontinued paclitaxel	0	(0.0)	4	(1.0)	1	(1.1)	3	(1.6)
discontinued gemcitabine	2	(1.2)	7	(1.8)	0	(0.0)	0	(0.0)
discontinued carboplatin	2	(1.2)	6	(1.5)	0	(0.0)	1	(0.5)
discontinued any drug due to a serious drug-related adverse event	12	(7.3)	24	(6.0)	2	(2.1)	2	(1.1)
discontinued pembrolizumab/placebo	12	(7.3)	20	(5.0)	1	(1.1)	2	(1.1)
discontinued nab-paclitaxel	3	(1.8)	2	(0.5)	0	(0.0)	0	(0.0)

	Pembrolizumab + Chemotherapy				Placebo + Chemotherapy			
	EU		Non-EU		EU		Non-EU	
	n	(%)	n	(%)	n	(%)	n	(%)
discontinued paclitaxel	0	(0.0)	4	(1.0)	1	(1.1)	0	(0.0)
discontinued gemcitabine	2	(1.2)	5	(1.3)	0	(0.0)	0	(0.0)
discontinued carboplatin	2	(1.2)	4	(1.0)	0	(0.0)	1	(0.5)

† Determined by the investigator to be related to the drug.
‡ Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.
Grades are based on NCI CTCAE version 4.0.
Non-serious adverse events up to 30 days after last dose and serious adverse events up to 90 days after last dose are included.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Database Cutoff Date: 11DEC2019

Table 7
Subjects With Adverse Events by Decreasing Incidence
(Incidence ≥ 10% in One or More Treatment Groups)
(Part 2 All Subjects-Chemotherapy with Gemcitabine/Carboplatin)
(ASaT Population)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy	
	n	(%)	n	(%)
Subjects in population	309		154	
with one or more adverse events	306	(99.0)	153	(99.4)
with no adverse events	3	(1.0)	1	(0.6)
Anaemia	207	(67.0)	107	(69.5)
Nausea	163	(52.8)	86	(55.8)
Neutropenia	161	(52.1)	79	(51.3)
Fatigue	111	(35.9)	54	(35.1)
Thrombocytopenia	107	(34.6)	56	(36.4)
Constipation	102	(33.0)	53	(34.4)
Neutrophil count decreased	100	(32.4)	54	(35.1)
Alanine aminotransferase increased	97	(31.4)	39	(25.3)
Vomiting	92	(29.8)	42	(27.3)
Aspartate aminotransferase increased	88	(28.5)	35	(22.7)
Platelet count decreased	88	(28.5)	44	(28.6)
Leukopenia	81	(26.2)	36	(23.4)
White blood cell count decreased	79	(25.6)	38	(24.7)
Headache	68	(22.0)	42	(27.3)
Cough	67	(21.7)	29	(18.8)
Pyrexia	62	(20.1)	37	(24.0)
Rash	62	(20.1)	15	(9.7)
Decreased appetite	61	(19.7)	26	(16.9)
Diarrhoea	60	(19.4)	38	(24.7)
Asthenia	50	(16.2)	29	(18.8)
Alopecia	49	(15.9)	23	(14.9)
Back pain	47	(15.2)	25	(16.2)
Arthralgia	43	(13.9)	20	(13.0)
Hypothyroidism	41	(13.3)	7	(4.5)
Pruritus	41	(13.3)	19	(12.3)
Dyspnoea	36	(11.7)	26	(16.9)
Dizziness	32	(10.4)	15	(9.7)
Stomatitis	32	(10.4)	9	(5.8)
Pain in extremity	26	(8.4)	20	(13.0)
Myalgia	24	(7.8)	17	(11.0)

Table 8
Subjects With Adverse Events by Decreasing Incidence
(Incidence ≥ 10% in One or More Treatment Groups)
(Part 2 All Subjects-Chemotherapy with Nab-Paclitaxel)
(ASaT Population)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy	
	n	(%)	n	(%)
Subjects in population	172		95	
with one or more adverse events	169	(98.3)	93	(97.9)
with no adverse events	3	(1.7)	2	(2.1)
Alopecia	90	(52.3)	54	(56.8)
Diarrhoea	62	(36.0)	23	(24.2)
Nausea	62	(36.0)	39	(41.1)
Anaemia	58	(33.7)	31	(32.6)
Neutropenia	50	(29.1)	24	(25.3)
Fatigue	46	(26.7)	32	(33.7)
Decreased appetite	40	(23.3)	9	(9.5)
Vomiting	40	(23.3)	18	(18.9)
Asthenia	39	(22.7)	17	(17.9)
Rash	37	(21.5)	14	(14.7)
Cough	35	(20.3)	18	(18.9)
Headache	33	(19.2)	21	(22.1)
Hypothyroidism	33	(19.2)	2	(2.1)
Pruritus	32	(18.6)	11	(11.6)
Constipation	30	(17.4)	21	(22.1)
Arthralgia	29	(16.9)	16	(16.8)
Neuropathy peripheral	27	(15.7)	23	(24.2)
Pyrexia	27	(15.7)	17	(17.9)
Alanine aminotransferase increased	26	(15.1)	11	(11.6)
Aspartate aminotransferase increased	25	(14.5)	9	(9.5)
Upper respiratory tract infection	25	(14.5)	13	(13.7)
Oedema peripheral	23	(13.4)	14	(14.7)
Myalgia	22	(12.8)	14	(14.7)
Pain in extremity	20	(11.6)	18	(18.9)
Neutrophil count decreased	19	(11.0)	13	(13.7)
Peripheral sensory neuropathy	19	(11.0)	8	(8.4)
Urinary tract infection	19	(11.0)	3	(3.2)
Back pain	18	(10.5)	13	(13.7)
Insomnia	14	(8.1)	14	(14.7)
Nasopharyngitis	12	(7.0)	10	(10.5)

Table 9
Subjects With Adverse Events by Decreasing Incidence
(Incidence ≥ 10% in One or More Treatment Groups)
(Part 2 All Subjects-Chemotherapy with Paclitaxel)
(ASaT Population)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy	
	n	(%)	n	(%)
Subjects in population	81		32	
with one or more adverse events	79	(97.5)	30	(93.8)
with no adverse events	2	(2.5)	2	(6.3)
Alopecia	51	(63.0)	20	(62.5)
Anaemia	34	(42.0)	5	(15.6)
Diarrhoea	33	(40.7)	5	(15.6)
Nausea	25	(30.9)	7	(21.9)
Arthralgia	22	(27.2)	3	(9.4)
Constipation	22	(27.2)	3	(9.4)
Neutropenia	22	(27.2)	6	(18.8)
Fatigue	21	(25.9)	11	(34.4)
Neuropathy peripheral	21	(25.9)	7	(21.9)
Aspartate aminotransferase increased	20	(24.7)	3	(9.4)
Alanine aminotransferase increased	19	(23.5)	5	(15.6)
Asthenia	18	(22.2)	2	(6.3)
Leukopenia	18	(22.2)	6	(18.8)
Peripheral sensory neuropathy	17	(21.0)	8	(25.0)
Cough	16	(19.8)	2	(6.3)
Decreased appetite	15	(18.5)	4	(12.5)
Oedema peripheral	14	(17.3)	5	(15.6)
Dysgeusia	13	(16.0)	1	(3.1)
Dyspnoea	13	(16.0)	3	(9.4)
Hypothyroidism	13	(16.0)	0	(0.0)
Pruritus	13	(16.0)	2	(6.3)
Pyrexia	13	(16.0)	2	(6.3)
White blood cell count decreased	13	(16.0)	7	(21.9)
Vomiting	12	(14.8)	3	(9.4)
Weight decreased	12	(14.8)	1	(3.1)
Blood alkaline phosphatase increased	11	(13.6)	3	(9.4)
Myalgia	11	(13.6)	3	(9.4)
Rash	11	(13.6)	4	(12.5)
Abdominal pain	10	(12.3)	2	(6.3)
Abdominal pain upper	10	(12.3)	0	(0.0)
Headache	10	(12.3)	3	(9.4)
Pain in extremity	10	(12.3)	3	(9.4)
Stomatitis	10	(12.3)	3	(9.4)
Nasopharyngitis	9	(11.1)	3	(9.4)
Neutrophil count decreased	8	(9.9)	8	(25.0)
Nail discolouration	3	(3.7)	4	(12.5)

Discontinuation due to adverse events

The overall incidence of drug-related AEs resulting in discontinuation of any study intervention was higher in the pembrolizumab + chemotherapy group (18.6%) compared with the placebo + chemotherapy group (11.0%). The higher incidence of drug-related AEs resulting in discontinuation of study intervention in the pembrolizumab + chemotherapy group were primarily driven by pneumonitis and events that occurred in <1% of participants. Pneumonitis is a known AEOSI for pembrolizumab and the observed incidence of pneumonitis leading to discontinuation of any study intervention was similar to the pembrolizumab monotherapy RSD (1.2% vs 1.5%, respectively). There were no trends observed suggesting a new safety concern for pembrolizumab + chemotherapy.

The overall incidence of drug-related AEs leading to the discontinuation of any study treatment was higher in the pembrolizumab + chemotherapy group (18.6%) compared with the pembrolizumab monotherapy RSD (6.9%). The higher incidence was primarily driven by the following: neutropenia (1.7% vs 0%), increased ALT (2.0% vs 0.3%), increased AST (1.5% vs 0.3%), decreased neutrophil count (1.2% vs 0%), neuropathy peripheral (1.3% vs 0%), and peripheral sensory neuropathy (1.0% vs 0%). These differences were consistent with the established safety profiles of the chemotherapies administered.

AE summary (Discontinuation due to AEs):

	KN355 Data for Pembrolizumab + Chemotherapy[†] [†]		KN355 Data for Placebo + Chemotherapy[¶] [¶]		mTNBC Safety Dataset for Pembrolizumab Monotherapy[‡‡]		Reference Safety Dataset for Pembrolizumab Monotherapy[§§]	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	596		281		595		5,884	
discontinued any drug due to an adverse event	128	(21.5)	37	(13.2)	30	(5.0)	783	(13.3)
discontinued pembrolizumab	7	(1.2)	0	(0.0)	30	(5.0)	783	(13.3)
discontinued pembrolizumab/placebo	60	(10.1)	15	(5.3)	30	(5.0)	783	(13.3)
discontinued nab-paclitaxel	26	(4.4)	4	(1.4)	0	(0.0)	0	(0.0)
discontinued paclitaxel	19	(3.2)	6	(2.1)	0	(0.0)	0	(0.0)
discontinued gemcitabine	39	(6.5)	16	(5.7)	0	(0.0)	0	(0.0)
discontinued carboplatin	44	(7.4)	17	(6.0)	0	(0.0)	0	(0.0)
discontinued any drug due to a drug-related adverse event	**111**	**(18.6)**	**31**	**(11.0)**	**20**	**(3.4)**	**405**	**(6.9)**
discontinued pembrolizumab	3	(0.5)	0	(0.0)	20	(3.4)	405	(6.9)
discontinued pembrolizumab/placebo	51	(8.6)	10	(3.6)	20	(3.4)	405	(6.9)
discontinued nab-paclitaxel	22	(3.7)	3	(1.1)	0	(0.0)	0	(0.0)
discontinued paclitaxel	17	(2.9)	3	(1.1)	0	(0.0)	0	(0.0)
discontinued gemcitabine	34	(5.7)	15	(5.3)	0	(0.0)	0	(0.0)
discontinued carboplatin	38	(6.4)	16	(5.7)	0	(0.0)	0	(0.0)
discontinued any drug due to a serious adverse event	51	(8.6)	9	(3.2)	17	(2.9)	570	(9.7)
discontinued pembrolizumab	6	(1.0)	0	(0.0)	17	(2.9)	570	(9.7)
discontinued pembrolizumab/placebo	39	(6.5)	8	(2.8)	17	(2.9)	570	(9.7)
discontinued nab-paclitaxel	10	(1.7)	1	(0.4)	0	(0.0)	0	(0.0)
discontinued paclitaxel	5	(0.8)	4	(1.4)	0	(0.0)	0	(0.0)
discontinued gemcitabine	10	(1.7)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued carboplatin	9	(1.5)	1	(0.4)	0	(0.0)	0	(0.0)
discontinued any drug due to a serious drug-related adverse event	40	(6.7)	4	(1.4)	10	(1.7)	244	(4.1)

discontinued pembrolizumab	3	(0.5)	0	(0.0)	10	(1.7)	244	(4.1)
discontinued pembrolizumab/placebo	32	(5.4)	3	(1.1)	10	(1.7)	244	(4.1)
discontinued nab-paclitaxel	6	(1.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued paclitaxel	4	(0.7)	1	(0.4)	0	(0.0)	0	(0.0)
discontinued gemcitabine	7	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued carboplatin	6	(1.0)	1	(0.4)	0	(0.0)	0	(0.0)

Table: Subjects With Drug-Related Adverse Events Resulting in Any Treatment Discontinuation (Incidence > 0% in One or More Treatment Groups) By Body System or Organ Class and Preferred Term (ASaT Population)

	KN355 Data for Pembrolizumab + Chemotherapy††		KN355 Data for Placebo + Chemotherapy¶¶		mTNBC Safety Dataset for Pembrolizumab Monotherapy‡‡		Reference Safety Dataset for Pembrolizumab Monotherapy§§	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	596		281		595		5,884	
with one or more adverse events	111	(18.6)	31	(11.0)	20	(3.4)	405	(6.9)
with no adverse events	485	(81.4)	250	(89.0)	575	(96.6)	5,479	(93.1)
Blood and lymphatic system disorders	**21**	**(3.5)**	**6**	**(2.1)**	**1**	**(0.2)**	**7**	**(0.1)**
Anaemia	4	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)
Autoimmune haemolytic anaemia	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Disseminated intravascular coagulation	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.0)
Haemolytic anaemia	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Immune thrombocytopenic purpura	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Leukopenia	2	(0.3)	1	(0.4)	0	(0.0)	0	(0.0)
Neutropenia	10	(1.7)	1	(0.4)	0	(0.0)	1	(0.0)
Thrombocytopenia	5	(0.8)	4	(1.4)	0	(0.0)	2	(0.0)
Thrombotic microangiopathy	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Cardiac disorders	**1**	**(0.2)**	**0**	**(0.0)**	**0**	**(0.0)**	**11**	**(0.2)**
Atrial fibrillation	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Atrioventricular block complete	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Autoimmune pericarditis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Cardiac disorder	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Cardio-respiratory arrest	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Myocarditis	1	(0.2)	0	(0.0)	0	(0.0)	4	(0.1)
Pericardial effusion	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Prosthetic cardiac valve thrombosis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Endocrine disorders	**2**	**(0.3)**	**0**	**(0.0)**	**1**	**(0.2)**	**17**	**(0.3)**
Addison's disease	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Adrenal insufficiency	1	(0.2)	0	(0.0)	0	(0.0)	4	(0.1)
Hyperthyroidism	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.1)
Hypophysitis	0	(0.0)	0	(0.0)	0	(0.0)	4	(0.1)
Hypopituitarism	0	(0.0)	0	(0.0)	0	(0.0)	4	(0.1)
Hypothyroidism	1	(0.2)	0	(0.0)	1	(0.2)	2	(0.0)
Eye disorders	**1**	**(0.2)**	**0**	**(0.0)**	**0**	**(0.0)**	**3**	**(0.1)**
Cystoid macular oedema	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Iridocyclitis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Uveitis	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Gastrointestinal disorders	**5**	**(0.8)**	**0**	**(0.0)**	**1**	**(0.2)**	**58**	**(1.0)**

	KN355 Data for Pembrolizumab + Chemotherapy††		KN355 Data for Placebo + Chemotherapy¶¶		mTNBC Safety Dataset for Pembrolizumab Monotherapy‡‡		Reference Safety Dataset for Pembrolizumab Monotherapy§§	
	n	(%)	n	(%)	n	(%)	n	(%)
Gastrointestinal disorders	**5**	**(0.8)**	**0**	**(0.0)**	**1**	**(0.2)**	**58**	**(1.0)**
Aptyalism	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Autoimmune pancreatitis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Cheilitis	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Colitis	1	(0.2)	0	(0.0)	0	(0.0)	27	(0.5)
Colitis microscopic	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Diarrhoea	1	(0.2)	0	(0.0)	1	(0.2)	11	(0.2)
Enteritis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Enterocolitis	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Gastritis	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Impaired gastric emptying	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Large intestine perforation	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Oesophageal fistula	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Oesophagitis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Oral lichen planus	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Pancreatitis	1	(0.2)	0	(0.0)	0	(0.0)	3	(0.1)
Salivary gland disorder	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Small intestinal perforation	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Stomatitis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Vomiting	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.0)
General disorders and administration site conditions	**5**	**(0.8)**	**2**	**(0.7)**	**1**	**(0.2)**	**27**	**(0.5)**
Asthenia	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)
Death	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.1)
Fatigue	2	(0.3)	1	(0.4)	0	(0.0)	11	(0.2)
General physical health deterioration	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
Generalised oedema	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.1)
Malaise	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Mucosal inflammation	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.0)
Oedema	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Oedema peripheral	1	(0.2)	1	(0.4)	0	(0.0)	0	(0.0)
Papillitis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Pyrexia	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Sudden death	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Swelling face	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Systemic inflammatory response syndrome	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)

	KN355 Data for Pembrolizumab + Chemotherapy††		KN355 Data for Placebo + Chemotherapy¶¶		mTNBC Safety Dataset for Pembrolizumab Monotherapy‡‡		Reference Safety Dataset for Pembrolizumab Monotherapy§§	
	n	(%)	n	(%)	n	(%)	n	(%)
Hepatobiliary disorders	**7**	**(1.2)**	**0**	**(0.0)**	**1**	**(0.2)**	**25**	**(0.4)**
Autoimmune hepatitis	1	(0.2)	0	(0.0)	0	(0.0)	11	(0.2)
Cholangitis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Drug-induced liver injury	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Hepatic function abnormal	3	(0.5)	0	(0.0)	0	(0.0)	1	(0.0)
Hepatitis	2	(0.3)	0	(0.0)	0	(0.0)	7	(0.1)
Hepatitis toxic	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Hyperbilirubinaemia	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Immune-mediated hepatitis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Liver disorder	1	(0.2)	0	(0.0)	1	(0.2)	0	(0.0)
Liver injury	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Immune system disorders	**4**	**(0.7)**	**2**	**(0.7)**	**0**	**(0.0)**	**9**	**(0.2)**
Anaphylactoid reaction	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Autoimmune disorder	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Autoinflammatory disease	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Cytokine release syndrome	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Drug hypersensitivity	2	(0.3)	0	(0.0)	0	(0.0)	1	(0.0)
Hypersensitivity	2	(0.3)	2	(0.7)	0	(0.0)	0	(0.0)
Sarcoidosis	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.1)
Serum sickness	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Infections and infestations	**3**	**(0.5)**	**0**	**(0.0)**	**0**	**(0.0)**	**6**	**(0.1)**
Bronchitis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Device related sepsis	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Encephalitis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Myelitis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Paronychia	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Pneumonia	1	(0.2)	0	(0.0)	0	(0.0)	2	(0.0)
Pneumonia klebsiella	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Injury, poisoning and procedural complications	**3**	**(0.5)**	**2**	**(0.7)**	**0**	**(0.0)**	**3**	**(0.1)**
Alcohol poisoning	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Infusion related reaction	2	(0.3)	1	(0.4)	0	(0.0)	2	(0.0)
Pneumonitis chemical	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Recall phenomenon	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)
Investigations	**27**	**(4.5)**	**11**	**(3.9)**	**5**	**(0.8)**	**41**	**(0.7)**

	KN355 Data for Pembrolizumab + Chemotherapy††		KN355 Data for Placebo + Chemotherapy¶¶		mTNBC Safety Dataset for Pembrolizumab Monotherapy‡‡		Reference Safety Dataset for Pembrolizumab Monotherapy§§	
	n	(%)	n	(%)	n	(%)	n	(%)
Investigations	**27**	**(4.5)**	**11**	**(3.9)**	**5**	**(0.8)**	**41**	**(0.7)**
Alanine aminotransferase increased	12	(2.0)	4	(1.4)	4	(0.7)	18	(0.3)
Aspartate aminotransferase increased	9	(1.5)	2	(0.7)	4	(0.7)	16	(0.3)
Bilirubin conjugated increased	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Blood alkaline phosphatase increased	1	(0.2)	0	(0.0)	0	(0.0)	2	(0.0)
Blood bilirubin increased	1	(0.2)	0	(0.0)	0	(0.0)	3	(0.1)
Blood creatine increased	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Blood creatine phosphokinase increased	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Blood creatinine increased	1	(0.2)	2	(0.7)	0	(0.0)	1	(0.0)
Blood lactate dehydrogenase increased	1	(0.2)	0	(0.0)	1	(0.2)	0	(0.0)
Blood uric acid increased	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Gamma-glutamyltransferase increased	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.1)
Intraocular pressure decreased	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Lipase increased	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Liver function test abnormal	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Liver function test increased	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Neutrophil count decreased	7	(1.2)	3	(1.1)	0	(0.0)	1	(0.0)
Platelet count decreased	5	(0.8)	1	(0.4)	0	(0.0)	0	(0.0)
Transaminases increased	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Weight decreased	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Metabolism and nutrition disorders	**1**	**(0.2)**	**0**	**(0.0)**	**0**	**(0.0)**	**12**	**(0.2)**
Decreased appetite	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Diabetes mellitus	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Diabetic ketoacidosis	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Hyponatraemia	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Insulin resistant diabetes	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Type 1 diabetes mellitus	1	(0.2)	0	(0.0)	0	(0.0)	4	(0.1)
Musculoskeletal and connective tissue disorders	**4**	**(0.7)**	**1**	**(0.4)**	**3**	**(0.5)**	**25**	**(0.4)**
Arthralgia	1	(0.2)	0	(0.0)	2	(0.3)	6	(0.1)
Arthritis	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Joint stiffness	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Muscle necrosis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Musculoskeletal pain	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Myalgia	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.0)
Myopathy	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)

	KN355 Data for Pembrolizumab + Chemotherapy††		KN355 Data for Placebo + Chemotherapy¶¶		mTNBC Safety Dataset for Pembrolizumab Monotherapy‡‡		Reference Safety Dataset for Pembrolizumab Monotherapy§§	
	n	(%)	n	(%)	n	(%)	n	(%)
Musculoskeletal and connective tissue disorders	**4**	**(0.7)**	**1**	**(0.4)**	**3**	**(0.5)**	**25**	**(0.4)**
Myositis	0	(0.0)	0	(0.0)	0	(0.0)	6	(0.1)
Polyarthritis	1	(0.2)	0	(0.0)	0	(0.0)	2	(0.0)
Polymyalgia rheumatica	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Rhabdomyolysis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Rheumatoid arthritis	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.0)
Scleroderma	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)
Sjogren's syndrome	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Soft tissue haemorrhage	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Tenosynovitis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**(0.0)**	**1**	**(0.4)**	**0**	**(0.0)**	**6**	**(0.1)**
Haemangioma	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)
Infected neoplasm	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Malignant neoplasm progression	0	(0.0)	0	(0.0)	0	(0.0)	5	(0.1)
Nervous system disorders	**22**	**(3.7)**	**7**	**(2.5)**	**0**	**(0.0)**	**19**	**(0.3)**
Ataxia	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Autoimmune neuropathy	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Cerebrovascular accident	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Chronic inflammatory demyelinating polyradiculoneuropathy	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)
Cognitive disorder	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Demyelinating polyneuropathy	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Encephalopathy	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Epilepsy	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Guillain-Barre syndrome	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.0)
Lethargy	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Myasthenia gravis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Myelitis transverse	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Neuralgia	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Neuropathy peripheral	8	(1.3)	3	(1.1)	0	(0.0)	0	(0.0)
Neurotoxicity	2	(0.3)	1	(0.4)	0	(0.0)	0	(0.0)
Optic neuritis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Paraesthesia	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Partial seizures	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Peripheral motor neuropathy	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)

	KN355 Data for Pembrolizumab + Chemotherapy††		KN355 Data for Placebo + Chemotherapy¶¶		mTNBC Safety Dataset for Pembrolizumab Monotherapy‡‡		Reference Safety Dataset for Pembrolizumab Monotherapy§§	
	n	(%)	n	(%)	n	(%)	n	(%)
Nervous system disorders	**22**	**(3.7)**	**7**	**(2.5)**	**0**	**(0.0)**	**19**	**(0.3)**
Peripheral sensory neuropathy	6	(1.0)	2	(0.7)	0	(0.0)	2	(0.0)
Polyneuropathy	2	(0.3)	0	(0.0)	0	(0.0)	1	(0.0)
Seizure	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Toxic leukoencephalopathy	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Psychiatric disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.0)**
Disorientation	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Renal and urinary disorders	**2**	**(0.3)**	**0**	**(0.0)**	**0**	**(0.0)**	**16**	**(0.3)**
Acute kidney injury	0	(0.0)	0	(0.0)	0	(0.0)	5	(0.1)
Autoimmune nephritis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Glomerulonephritis membranous	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Nephritis	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.0)
Nephrotic syndrome	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Renal failure	1	(0.2)	0	(0.0)	0	(0.0)	2	(0.0)
Tubulointerstitial nephritis	0	(0.0)	0	(0.0)	0	(0.0)	4	(0.1)
Urinary tract obstruction	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Reproductive system and breast disorders	**1**	**(0.2)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Pelvic pain	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	**9**	**(1.5)**	**0**	**(0.0)**	**6**	**(1.0)**	**106**	**(1.8)**
Cough	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Dyspnoea	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.0)
Hypoxia	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Interstitial lung disease	0	(0.0)	0	(0.0)	1	(0.2)	8	(0.1)
Organising pneumonia	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
Pleural effusion	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Pneumonitis	7	(1.2)	0	(0.0)	4	(0.7)	91	(1.5)
Pulmonary embolism	1	(0.2)	0	(0.0)	0	(0.0)	3	(0.1)
Respiratory failure	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Skin and subcutaneous tissue disorders	**3**	**(0.5)**	**0**	**(0.0)**	**1**	**(0.2)**	**25**	**(0.4)**
Dermatitis allergic	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.0)
Erythema multiforme	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)

	KN355 Data for Pembrolizumab + Chemotherapy††		KN355 Data for Placebo + Chemotherapy¶¶		mTNBC Safety Dataset for Pembrolizumab Monotherapy‡‡		Reference Safety Dataset for Pembrolizumab Monotherapy§§	
	n	(%)	n	(%)	n	(%)	n	(%)
Skin and subcutaneous tissue disorders	**3**	**(0.5)**	**0**	**(0.0)**	**1**	**(0.2)**	**25**	**(0.4)**
Hyperkeratosis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Lichen planus	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Palmar-plantar erythrodysaesthesia syndrome	1	(0.2)	0	(0.0)	1	(0.2)	1	(0.0)
Pemphigus	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Pruritus	0	(0.0)	0	(0.0)	0	(0.0)	5	(0.1)
Psoriasis	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Rash	0	(0.0)	0	(0.0)	0	(0.0)	6	(0.1)
Rash maculo-papular	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.0)
Seborrhoeic dermatitis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Skin ulcer	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Stevens-Johnson syndrome	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.1)
Vitiligo	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Vascular disorders	**3**	**(0.5)**	**0**	**(0.0)**	**0**	**(0.0)**	**3**	**(0.1)**
Arterial thrombosis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Hypertension	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Hypertensive emergency	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Peripheral ischaemia	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Superior vena cava syndrome	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)

	KN355 Data for Pembrolizumab + Chemotherapy††		KN355 Data for Placebo + Chemotherapy¶¶		mTNBC Safety Dataset for Pembrolizumab Monotherapy‡‡		Reference Safety Dataset for Pembrolizumab Monotherapy§§	
	n	(%)	n	(%)	n	(%)	n	(%)
Vascular disorders	**3**	**(0.5)**	**0**	**(0.0)**	**0**	**(0.0)**	**3**	**(0.1)**
Venous thrombosis limb	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)

UPDATED SAFETY RESULTS - FINAL ANALYSIS

During the procedure, the MAH submitted the results of the final analysis (FA) for OS with data cut-off date 15 Jun 2021.

The safety profile of pembrolizumab in combination chemotherapy observed at the FA is generally consistent with the known safety profiles of pembrolizumab monotherapy and the chemotherapies administered and is consistent with safety at IA2. No new safety concerns were identified at the FA for pembrolizumab.

A summary of the updated safety data is presented in the tables below:

Summary of Drug Exposure
(Part 2 All Subjects)
(ASaT Population)

	Pembrolizumab + Chemotherapy	Placebo + Chemotherapy
Subjects in population	562	281
All Drugs		
Number of Weeks on Therapy (weeks)		
n	562	281
Mean	39.1	33.9
SD	36.6	35.0
Median	26.4	23.1
Range	0.1 to 212.1	0.1 to 224.1
Pembrolizumab/Placebo		
Number of Weeks on Therapy (weeks)		
n	562	281
Mean	35.9	31.3
SD	32.0	28.0
Median	24.2	22.1
Range	0.1 to 140.1	0.1 to 119.6
Number of Administrations		
n	562	281
Mean	12.0	10.6
SD	9.9	8.7
Median	8.0	8.0
Range	1.0 to 35.0	1.0 to 35.0

Nab-Paclitaxel		
Number of Weeks on Therapy (weeks)		
n	174	95
Mean	35.4	30.3
SD	37.2	34.5
Median	23.1	18.1
Range	0.1 to 212.1	0.1 to 208.1
Number of Administrations		
n	174	95
Mean	25.5	22.6
SD	25.7	24.2
Median	18.0	14.0
Range	1.0 to 159.0	1.0 to 143.0
Paclitaxel		
Number of Weeks on Therapy (weeks)		
n	81	32
Mean	29.3	26.5
SD	23.9	38.2
Median	21.6	17.4
Range	1.1 to 108.9	0.1 to 224.1
Number of Administrations		
n	81	32
Mean	20.9	19.8
SD	15.5	28.2
Median	16.0	13.5
Range	2.0 to 79.0	1.0 to 167.0
Gemcitabine		
Number of Weeks on Therapy (weeks)		
n	309	154
Mean	32.6	30.8
SD	32.3	30.2
Median	22.1	23.1
Range	0.1 to 199.1	0.1 to 215.7
Number of Administrations		
n	309	154
Mean	16.4	16.6
SD	13.9	16.1
Median	12.0	13.0
Range	1.0 to 98.0	1.0 to 137.0
Carboplatin		
Number of Weeks on Therapy (weeks)		

n	309	154
Mean	31.4	30.6
SD	30.6	30.1
Median	22.1	22.9
Range	0.1 to 199.1	0.1 to 215.7
Number of Administrations		
n	309	154
Mean	15.8	16.5
SD	13.0	16.0
Median	12.0	13.0
Range	1.0 to 98.0	1.0 to 137.0
Database Cutoff Date: 15JUN2021		

Adverse Event Summary
(Part 2 All Subjects)
(ASaT Population)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy	
	n	(%)	n	(%)
Subjects in population	562		281	
with one or more adverse events	554	(98.6)	276	(98.2)
with no adverse event	8	(1.4)	5	(1.8)
with drug-related[†] adverse events	541	(96.3)	267	(95.0)
with toxicity grade 3-5 adverse events	438	(77.9)	207	(73.7)
with toxicity grade 3-5 drug-related adverse events	383	(68.1)	188	(66.9)
with serious adverse events	169	(30.1)	67	(23.8)
with serious drug-related adverse events	100	(17.8)	34	(12.1)
with any dose modification[‡] due to an adverse event	429	(76.3)	209	(74.4)
pembrolizumab/placebo dose modification	313	(55.7)	133	(47.3)
nab-paclitaxel dose modification	101	(18.0)	45	(16.0)
paclitaxel dose modification	52	(9.3)	21	(7.5)
gemcitabine dose modification	264	(47.0)	138	(49.1)
carboplatin dose modification	261	(46.4)	140	(49.8)
who died	17	(3.0)	5	(1.8)
who died due to a drug-related adverse event	2	(0.4)	0	(0.0)
discontinued any drug due to an adverse event	115	(20.5)	38	(13.5)
discontinued pembrolizumab/placebo	60	(10.7)	15	(5.3)
discontinued nab-paclitaxel	22	(3.9)	5	(1.8)
discontinued paclitaxel	16	(2.8)	6	(2.1)
discontinued gemcitabine	37	(6.6)	16	(5.7)
discontinued carboplatin	42	(7.5)	17	(6.0)
discontinued any drug due to a drug-related adverse event	103	(18.3)	31	(11.0)
discontinued pembrolizumab/placebo	51	(9.1)	9	(3.2)
discontinued nab-paclitaxel	18	(3.2)	4	(1.4)
discontinued paclitaxel	16	(2.8)	3	(1.1)
discontinued gemcitabine	33	(5.9)	15	(5.3)
discontinued carboplatin	37	(6.6)	15	(5.3)
discontinued any drug due to a serious adverse event	44	(7.8)	9	(3.2)
discontinued pembrolizumab/placebo	40	(7.1)	8	(2.8)
discontinued nab-paclitaxel	9	(1.6)	1	(0.4)
discontinued paclitaxel	4	(0.7)	4	(1.4)
discontinued gemcitabine	9	(1.6)	0	(0.0)
discontinued carboplatin	8	(1.4)	1	(0.4)
discontinued any drug due to a serious drug-related adverse event	36	(6.4)	3	(1.1)
discontinued pembrolizumab/placebo	32	(5.7)	2	(0.7)

discontinued nab-paclitaxel	5	(0.9)	0	(0.0)
discontinued paclitaxel	4	(0.7)	1	(0.4)
discontinued gemcitabine	7	(1.2)	0	(0.0)
discontinued carboplatin	6	(1.1)	0	(0.0)

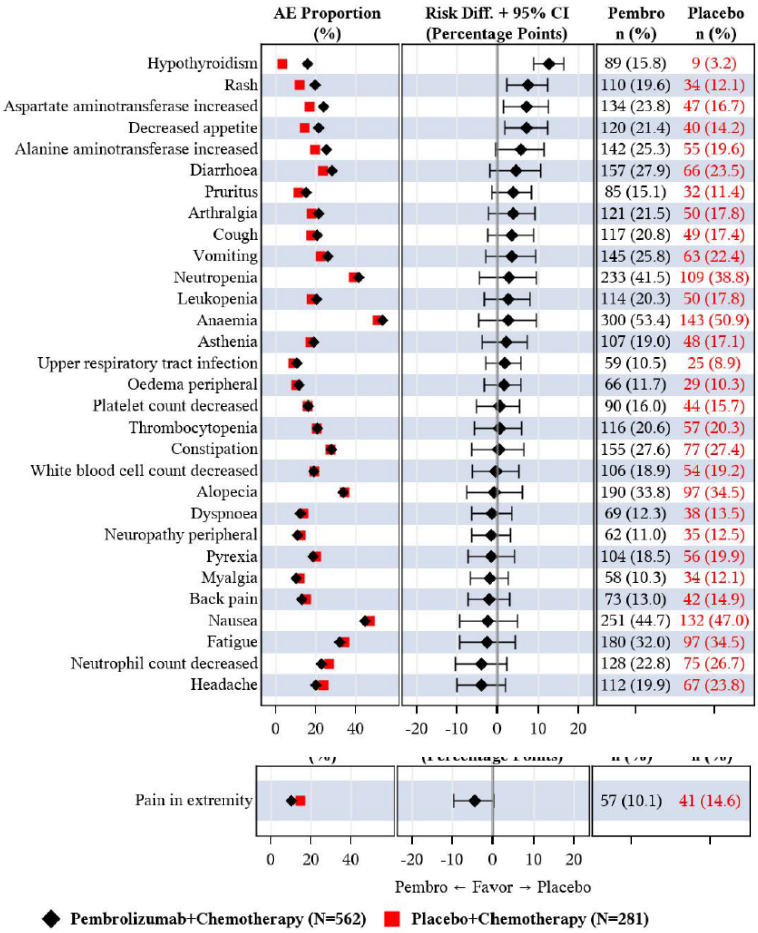
† Determined by the investigator to be related to the drug.
‡ Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.
Grades are based on NCI CTCAE version 4.03.
Non-serious adverse events up to 30 days after last dose and serious adverse events up to 90 days after last dose are included.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Database Cutoff Date: 15JUN2021

Subjects With Adverse Events by Decreasing Incidence
(Incidence ≥ 10% in One or More Treatment Groups)
(Part 2 All Subjects)
(ASaT Population)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy	
	n	(%)	n	(%)
Subjects in population	562		281	
with one or more adverse events	554	(98.6)	276	(98.2)
with no adverse events	8	(1.4)	5	(1.8)
Anaemia	300	(53.4)	143	(50.9)
Nausea	251	(44.7)	132	(47.0)
Neutropenia	233	(41.5)	109	(38.8)
Alopecia	190	(33.8)	97	(34.5)
Fatigue	180	(32.0)	97	(34.5)
Diarrhoea	157	(27.9)	66	(23.5)
Constipation	155	(27.6)	77	(27.4)
Vomiting	145	(25.8)	63	(22.4)
Alanine aminotransferase increased	142	(25.3)	55	(19.6)
Aspartate aminotransferase increased	134	(23.8)	47	(16.7)
Neutrophil count decreased	128	(22.8)	75	(26.7)
Arthralgia	121	(21.5)	50	(17.8)
Decreased appetite	120	(21.4)	40	(14.2)
Cough	117	(20.8)	49	(17.4)
Thrombocytopenia	116	(20.6)	57	(20.3)
Leukopenia	114	(20.3)	50	(17.8)
Headache	112	(19.9)	67	(23.8)
Rash	110	(19.6)	34	(12.1)
Asthenia	107	(19.0)	48	(17.1)
White blood cell count decreased	106	(18.9)	54	(19.2)
Pyrexia	104	(18.5)	56	(19.9)
Platelet count decreased	90	(16.0)	44	(15.7)
Hypothyroidism	89	(15.8)	9	(3.2)
Pruritus	85	(15.1)	32	(11.4)
Back pain	73	(13.0)	42	(14.9)
Dyspnoea	69	(12.3)	38	(13.5)
Oedema peripheral	66	(11.7)	29	(10.3)
Neuropathy peripheral	62	(11.0)	35	(12.5)
Upper respiratory tract infection	59	(10.5)	25	(8.9)
Myalgia	58	(10.3)	34	(12.1)
Pain in extremity	57	(10.1)	41	(14.6)

Every subject is counted a single time for each applicable row and column.
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Non-serious adverse events up to 30 days after last dose and serious adverse events up to 90 days after last dose are included.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Database Cutoff Date: 15JUN2021

Between-Treatment Comparisons in Adverse Events (Incidence ≥ 10% in One or More Treatment Groups)
Sorted by Risk Difference (Part 2 All Subjects) (ASaT Population)



Subjects With Drug-Related Adverse Events by Decreasing Incidence
(Incidence ≥ 5% in One or More Treatment Groups)
(Part 2 All Subjects)
(ASaT Population)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy	
	n	(%)	n	(%)
Subjects in population	562		281	
with one or more adverse events	541	(96.3)	267	(95.0)
with no adverse events	21	(3.7)	14	(5.0)
Anaemia	276	(49.1)	129	(45.9)
Neutropenia	231	(41.1)	107	(38.1)
Nausea	221	(39.3)	116	(41.3)
Alopecia	186	(33.1)	94	(33.5)
Fatigue	161	(28.6)	84	(29.9)
Neutrophil count decreased	126	(22.4)	74	(26.3)
Alanine aminotransferase increased	115	(20.5)	46	(16.4)
Diarrhoea	111	(19.8)	46	(16.4)
Leukopenia	111	(19.8)	49	(17.4)
Thrombocytopenia	109	(19.4)	54	(19.2)
Aspartate aminotransferase increased	108	(19.2)	42	(14.9)
Vomiting	107	(19.0)	42	(14.9)
White blood cell count decreased	103	(18.3)	54	(19.2)
Decreased appetite	95	(16.9)	26	(9.3)
Platelet count decreased	90	(16.0)	43	(15.3)
Rash	87	(15.5)	26	(9.3)
Asthenia	78	(13.9)	37	(13.2)
Constipation	78	(13.9)	37	(13.2)
Hypothyroidism	75	(13.3)	8	(2.8)
Pruritus	57	(10.1)	26	(9.3)
Neuropathy peripheral	56	(10.0)	32	(11.4)
Pyrexia	56	(10.0)	23	(8.2)
Peripheral sensory neuropathy	49	(8.7)	20	(7.1)
Dysgeusia	47	(8.4)	12	(4.3)
Arthralgia	46	(8.2)	24	(8.5)
Stomatitis	46	(8.2)	17	(6.0)
Myalgia	41	(7.3)	21	(7.5)
Headache	38	(6.8)	24	(8.5)
Blood alkaline phosphatase increased	34	(6.0)	13	(4.6)
Weight decreased	31	(5.5)	7	(2.5)
Oedema peripheral	29	(5.2)	13	(4.6)
Lymphopenia	28	(5.0)	4	(1.4)
Dizziness	14	(2.5)	15	(5.3)

Every subject is counted a single time for each applicable row and column.
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Non-serious adverse events up to 30 days after last dose and serious adverse events up to 90 days after last dose are included.
Database Cutoff Date: 15JUN2021

Subjects With Grade 3-5 Adverse Events by Decreasing Incidence
(Incidence ≥ 5% in One or More Treatment Groups)
(Part 2 All Subjects)
(ASaT Population)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy	
	n	(%)	n	(%)
Subjects in population	562		281	
with one or more adverse events	438	(77.9)	207	(73.7)
with no adverse events	124	(22.1)	74	(26.3)
Neutropenia	169	(30.1)	85	(30.2)
Anaemia	101	(18.0)	46	(16.4)
Neutrophil count decreased	101	(18.0)	57	(20.3)
Thrombocytopenia	63	(11.2)	33	(11.7)
White blood cell count decreased	59	(10.5)	29	(10.3)
Leukopenia	57	(10.1)	31	(11.0)
Alanine aminotransferase increased	44	(7.8)	16	(5.7)
Platelet count decreased	36	(6.4)	20	(7.1)
Aspartate aminotransferase increased	32	(5.7)	11	(3.9)

Every subject is counted a single time for each applicable row and column.
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Non-serious adverse events up to 30 days after last dose and serious adverse events up to 90 days after last dose are included.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Grades are based on NCI CTCAE version 4.03.
Database Cutoff Date: 15JUN2021

Subjects With Drug-Related Grade 3-5 Adverse Events by Decreasing Incidence
(Incidence ≥ 5% in One or More Treatment Groups)
(Part 2 All Subjects)
(ASaT Population)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy	
	n	(%)	n	(%)
Subjects in population	562		281	
with one or more adverse events	383	(68.1)	188	(66.9)
with no adverse events	179	(31.9)	93	(33.1)
Neutropenia	167	(29.7)	84	(29.9)
Neutrophil count decreased	98	(17.4)	57	(20.3)
Anaemia	93	(16.5)	41	(14.6)
Thrombocytopenia	57	(10.1)	31	(11.0)
White blood cell count decreased	57	(10.1)	29	(10.3)
Leukopenia	56	(10.0)	30	(10.7)
Platelet count decreased	36	(6.4)	20	(7.1)
Alanine aminotransferase increased	34	(6.0)	13	(4.6)

Every subject is counted a single time for each applicable row and column.
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Non-serious adverse events up to 30 days after last dose and serious adverse events up to 90 days after last dose are included.
Grades are based on NCI CTCAE version 4.03.
Database Cutoff Date: 15JUN2021

Subjects With Adverse Events Resulting in Death by Decreasing Incidence
(Incidence > 0% in One or More Treatment Groups)
(Part 2 All Subjects)
(ASaT Population)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy	
	n	(%)	n	(%)
Subjects in population	562		281	
with one or more adverse events	17	(3.0)	5	(1.8)
with no adverse events	545	(97.0)	276	(98.2)
Cardio-respiratory arrest	2	(0.4)	0	(0.0)
Pneumonia	2	(0.4)	1	(0.4)
Septic shock	2	(0.4)	0	(0.0)
Acute kidney injury	1	(0.2)	0	(0.0)
Acute myocardial infarction	1	(0.2)	0	(0.0)
Assisted suicide	1	(0.2)	0	(0.0)
Cardiac arrest	1	(0.2)	0	(0.0)
Cardiopulmonary failure	1	(0.2)	0	(0.0)
Death	1	(0.2)	0	(0.0)
Hepatic encephalopathy	1	(0.2)	0	(0.0)
Multiple organ dysfunction syndrome	1	(0.2)	0	(0.0)
Pulmonary embolism	1	(0.2)	0	(0.0)
Sepsis	1	(0.2)	0	(0.0)
Shock haemorrhagic	1	(0.2)	0	(0.0)
Cardiac failure	0	(0.0)	1	(0.4)
Haemorrhagic stroke	0	(0.0)	1	(0.4)
Respiratory failure	0	(0.0)	1	(0.4)
Vascular device infection	0	(0.0)	1	(0.4)

Every subject is counted a single time for each applicable row and column.
Non-serious adverse events up to 30 days after last dose and serious adverse events up to 90 days after last dose are included.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Database Cutoff Date: 15JUN2021

Subjects With Serious Adverse Events up to 90 Days After Last Dose by Decreasing Incidence
(Incidence ≥ 1% in One or More Treatment Groups)
(Part 2 All Subjects)
(ASaT Population)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy	
	n	(%)	n	(%)
Subjects in population	562		281	
with one or more adverse events	169	(30.1)	67	(23.8)
with no adverse events	393	(69.9)	214	(76.2)
Anaemia	11	(2.0)	6	(2.1)
Pneumonia	11	(2.0)	7	(2.5)
Thrombocytopenia	11	(2.0)	4	(1.4)
Vomiting	10	(1.8)	6	(2.1)
Febrile neutropenia	7	(1.2)	3	(1.1)
Pulmonary embolism	7	(1.2)	3	(1.1)
Pyrexia	7	(1.2)	4	(1.4)
Pneumonitis	6	(1.1)	0	(0.0)
Sepsis	6	(1.1)	3	(1.1)
Neutropenia	5	(0.9)	4	(1.4)
Pleural effusion	5	(0.9)	3	(1.1)
Nausea	3	(0.5)	3	(1.1)

Every subject is counted a single time for each applicable row and column.
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Serious adverse events up to 90 days after last dose are included.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Database Cutoff Date: 15JUN2021

Subjects With Drug-Related Serious Adverse Events up to 90 Days After Last Dose by Decreasing Incidence
(Incidence > 0% in One or More Treatment Groups)
(Part 2 All Subjects)
(ASaT Population)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy	
	n	(%)	n	(%)
Subjects in population	562		281	
with one or more adverse events	100	(17.8)	34	(12.1)
with no adverse events	462	(82.2)	247	(87.9)
Anaemia	11	(2.0)	4	(1.4)
Thrombocytopenia	9	(1.6)	3	(1.1)
Vomiting	8	(1.4)	3	(1.1)
Febrile neutropenia	6	(1.1)	3	(1.1)
Pneumonitis	6	(1.1)	0	(0.0)
Pyrexia	6	(1.1)	3	(1.1)
Neutropenia	5	(0.9)	4	(1.4)
Platelet count decreased	5	(0.9)	2	(0.7)
Alanine aminotransferase increased	4	(0.7)	1	(0.4)
Aspartate aminotransferase increased	4	(0.7)	1	(0.4)
Leukopenia	4	(0.7)	0	(0.0)
Adrenal insufficiency	3	(0.5)	0	(0.0)
Hepatitis	3	(0.5)	0	(0.0)
Nausea	3	(0.5)	2	(0.7)
Acute kidney injury	2	(0.4)	1	(0.4)
Decreased appetite	2	(0.4)	1	(0.4)
Diarrhoea	2	(0.4)	0	(0.0)
Hepatic function abnormal	2	(0.4)	1	(0.4)
Pneumonia	2	(0.4)	1	(0.4)
Pulmonary embolism	2	(0.4)	0	(0.0)
Renal failure	2	(0.4)	0	(0.0)
Sepsis	2	(0.4)	2	(0.7)
Autoimmune hepatitis	1	(0.2)	0	(0.0)
Bone pain	1	(0.2)	0	(0.0)
Breast pain	1	(0.2)	0	(0.0)
Cardiac failure	1	(0.2)	0	(0.0)
Cheilitis	1	(0.2)	0	(0.0)
Colitis	1	(0.2)	0	(0.0)
Device related sepsis	1	(0.2)	0	(0.0)
Dysphagia	1	(0.2)	0	(0.0)
Electrolyte imbalance	1	(0.2)	0	(0.0)
Gastric ulcer haemorrhage	1	(0.2)	0	(0.0)
Gastroenteritis	1	(0.2)	0	(0.0)

Guillain-Barre syndrome	1	(0.2)	0	(0.0)
Hypertension	1	(0.2)	0	(0.0)
Hypertensive emergency	1	(0.2)	0	(0.0)
Hyponatraemia	1	(0.2)	1	(0.4)
Inappropriate antidiuretic hormone secretion	1	(0.2)	0	(0.0)
Limb injury	1	(0.2)	0	(0.0)
Liver disorder	1	(0.2)	0	(0.0)
Liver function test abnormal	1	(0.2)	0	(0.0)
Lower gastrointestinal haemorrhage	1	(0.2)	0	(0.0)
Lymphopenia	1	(0.2)	0	(0.0)
Malaise	1	(0.2)	0	(0.0)
Meningitis aseptic	1	(0.2)	0	(0.0)
Myelopathy	1	(0.2)	0	(0.0)
Myelosuppression	1	(0.2)	0	(0.0)
Myocarditis	1	(0.2)	0	(0.0)
Myositis	1	(0.2)	0	(0.0)
Neutropenic sepsis	1	(0.2)	0	(0.0)
Neutrophil count decreased	1	(0.2)	0	(0.0)
Palmar-plantar erythrodysaesthesia syndrome	1	(0.2)	0	(0.0)
Pancreatic enzymes increased	1	(0.2)	0	(0.0)
Pancreatitis	1	(0.2)	0	(0.0)
Pancytopenia	1	(0.2)	1	(0.4)
Peripheral motor neuropathy	1	(0.2)	1	(0.4)
Peripheral sensory neuropathy	1	(0.2)	2	(0.7)
Pleural effusion	1	(0.2)	0	(0.0)
Pneumonia bacterial	1	(0.2)	0	(0.0)
Pneumonia streptococcal	1	(0.2)	0	(0.0)
Polyarthritis	1	(0.2)	0	(0.0)
Pulmonary hypertension	1	(0.2)	0	(0.0)
Rash maculo-papular	1	(0.2)	0	(0.0)
Respiratory tract infection	1	(0.2)	0	(0.0)
Sinus bradycardia	1	(0.2)	0	(0.0)
Soft tissue infection	1	(0.2)	0	(0.0)
Steatohepatitis	1	(0.2)	0	(0.0)
Thrombotic microangiopathy	1	(0.2)	0	(0.0)
Transaminases increased	1	(0.2)	0	(0.0)
Upper respiratory tract infection	1	(0.2)	0	(0.0)
Venous thrombosis limb	1	(0.2)	0	(0.0)
Chronic inflammatory demyelinating polyradiculoneuropathy	0	(0.0)	1	(0.4)
Deep vein thrombosis	0	(0.0)	1	(0.4)
Dyspnoea	0	(0.0)	1	(0.4)
Fatigue	0	(0.0)	1	(0.4)
Haematemesis	0	(0.0)	1	(0.4)
Hepatotoxicity	0	(0.0)	1	(0.4)
Hypocalcaemia	0	(0.0)	1	(0.4)
Pulmonary fibrosis	0	(0.0)	1	(0.4)
Scleroderma	0	(0.0)	1	(0.4)
Urinary retention	0	(0.0)	1	(0.4)
Uterine haemorrhage	0	(0.0)	1	(0.4)

Every subject is counted a single time for each applicable row and column.
Serious adverse events up to 90 days after last dose are included.
Database Cutoff Date: 15JUN2021

Adverse Event Summary
Adverse Event of Special Interest (AEOSI)
(Part 2 All Subjects)
(ASaT Population)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy	
	n	(%)	n	(%)
Subjects in population	562		281	
with one or more adverse events	157	(27.9)	31	(11.0)
with no adverse event	405	(72.1)	250	(89.0)
with drug-related[†] adverse events	143	(25.4)	26	(9.3)
with toxicity grade 3-5 adverse events	32	(5.7)	0	(0.0)
with toxicity grade 3-5 drug-related adverse events	31	(5.5)	0	(0.0)
with serious adverse events	19	(3.4)	0	(0.0)
with serious drug-related adverse events	17	(3.0)	0	(0.0)
with any dose modification[‡] due to an adverse event	59	(10.5)	12	(4.3)
pembrolizumab/placebo dose modification	44	(7.8)	2	(0.7)
nab-paclitaxel dose modification	15	(2.7)	0	(0.0)
paclitaxel dose modification	7	(1.2)	1	(0.4)
gemcitabine dose modification	21	(3.7)	6	(2.1)
carboplatin dose modification	22	(3.9)	10	(3.6)
who died	0	(0.0)	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)
discontinued any drug due to an adverse event	23	(4.1)	3	(1.1)
discontinued pembrolizumab/placebo	14	(2.5)	0	(0.0)
discontinued nab-paclitaxel	3	(0.5)	0	(0.0)
discontinued paclitaxel	1	(0.2)	0	(0.0)
discontinued gemcitabine	6	(1.1)	0	(0.0)
discontinued carboplatin	6	(1.1)	3	(1.1)
discontinued any drug due to a drug-related adverse event	23	(4.1)	3	(1.1)
discontinued pembrolizumab/placebo	14	(2.5)	0	(0.0)
discontinued nab-paclitaxel	3	(0.5)	0	(0.0)
discontinued paclitaxel	1	(0.2)	0	(0.0)
discontinued gemcitabine	6	(1.1)	0	(0.0)
discontinued carboplatin	6	(1.1)	3	(1.1)
discontinued any drug due to a serious adverse event	13	(2.3)	0	(0.0)
discontinued pembrolizumab/placebo	12	(2.1)	0	(0.0)
discontinued nab-paclitaxel	2	(0.4)	0	(0.0)
discontinued paclitaxel	1	(0.2)	0	(0.0)
discontinued gemcitabine	1	(0.2)	0	(0.0)
discontinued carboplatin	1	(0.2)	0	(0.0)
discontinued any drug due to a serious drug-related adverse event	13	(2.3)	0	(0.0)
discontinued pembrolizumab/placebo	12	(2.1)	0	(0.0)
discontinued nab-paclitaxel	2	(0.4)	0	(0.0)
discontinued paclitaxel	1	(0.2)	0	(0.0)
discontinued gemcitabine	1	(0.2)	0	(0.0)
discontinued carboplatin	1	(0.2)	0	(0.0)

[†] Determined by the investigator to be related to the drug.
[‡] Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.
Grades are based on NCI CTCAE version 4.03.
Non-serious adverse events up to 30 days after last dose and serious adverse events up to 90 days after last dose are included.
Database Cutoff Date: 15JUN2021

Subjects With Adverse Events of Special Interest (AEOSI) by AEOSI Category and Preferred Term
(Incidence > 0% in One or More Treatment Groups)
(Part 2 All Subjects)
(ASaT Population)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy	
	n	(%)	n	(%)
Subjects in population	562		281	
with one or more adverse events	157	(27.9)	31	(11.0)
with no adverse events	405	(72.1)	250	(89.0)
Adrenal Insufficiency	**8**	**(1.4)**	**0**	**(0.0)**
Adrenal insufficiency	8	(1.4)	0	(0.0)
Colitis	**10**	**(1.8)**	**4**	**(1.4)**
Colitis	9	(1.6)	3	(1.1)
Enterocolitis	1	(0.2)	1	(0.4)
Guillain-Barre Syndrome	**1**	**(0.2)**	**0**	**(0.0)**
Guillain-Barre syndrome	1	(0.2)	0	(0.0)
Hepatitis	**5**	**(0.9)**	**2**	**(0.7)**
Autoimmune hepatitis	1	(0.2)	0	(0.0)
Hepatitis	3	(0.5)	2	(0.7)
Immune-mediated hepatitis	1	(0.2)	0	(0.0)
Hyperthyroidism	**24**	**(4.3)**	**3**	**(1.1)**
Hyperthyroidism	24	(4.3)	3	(1.1)
Hypothyroidism	**89**	**(15.8)**	**9**	**(3.2)**
Hypothyroidism	89	(15.8)	9	(3.2)
Infusion Reactions	**21**	**(3.7)**	**14**	**(5.0)**
Anaphylactic reaction	1	(0.2)	0	(0.0)
Drug hypersensitivity	3	(0.5)	1	(0.4)
Hypersensitivity	8	(1.4)	8	(2.8)
Infusion related reaction	9	(1.6)	6	(2.1)
Myocarditis	**1**	**(0.2)**	**0**	**(0.0)**
Myocarditis	1	(0.2)	0	(0.0)
Myositis	**3**	**(0.5)**	**0**	**(0.0)**
Dermatomyositis	1	(0.2)	0	(0.0)
Myositis	2	(0.4)	0	(0.0)
Nephritis	**3**	**(0.5)**	**0**	**(0.0)**
Nephritis	3	(0.5)	0	(0.0)
Pancreatitis	**1**	**(0.2)**	**0**	**(0.0)**
Pancreatitis	1	(0.2)	0	(0.0)
Pneumonitis	**14**	**(2.5)**	**0**	**(0.0)**
Organising pneumonia	1	(0.2)	0	(0.0)
Pneumonitis	13	(2.3)	0	(0.0)
Severe Skin Reactions	**10**	**(1.8)**	**1**	**(0.4)**
Erythema multiforme	0	(0.0)	1	(0.4)
Pruritus	1	(0.2)	0	(0.0)
Rash	4	(0.7)	0	(0.0)
Rash maculo-papular	6	(1.1)	0	(0.0)
Thyroiditis	**7**	**(1.2)**	**0**	**(0.0)**
Thyroiditis	6	(1.1)	0	(0.0)
Thyroiditis acute	1	(0.2)	0	(0.0)
Type 1 Diabetes Mellitus	**1**	**(0.2)**	**0**	**(0.0)**
Type 1 diabetes mellitus	1	(0.2)	0	(0.0)
Uveitis	**2**	**(0.4)**	**0**	**(0.0)**
Uveitis	2	(0.4)	0	(0.0)
Vasculitis	**2**	**(0.4)**	**1**	**(0.4)**
Vasculitis	2	(0.4)	1	(0.4)

Every subject is counted a single time for each applicable row and column.
Non-serious adverse events up to 30 days after last dose and serious adverse events up to 90 days after last dose are included.
Database Cutoff Date: 15JUN2021

Post marketing experience

The safety profile of pembrolizumab was summarized in the Periodic Safety Update Report covering the period 04-SEP-2019 through 03-SEP-2020. There are no records of any pembrolizumab registration being revoked or withdrawn for safety reasons in any country.

2.5.1. Discussion on clinical safety

The safety data in support of the new indication of pembrolizumab (KEYTRUDA®, MK-3475) in combination with chemotherapy (nab-paclitaxel, paclitaxel, or gemcitabine/carboplatin) for the treatment of patients with locally recurrent inoperable or metastatic TNBC, derive from the **pooled data** from Part 1 and Part 2 of **study KEYNOTE-355.** With a cutoff date of 11 DEC 2019, the safety database includes a total of **596** participants who were exposed to the drug combination for a median length of 6.2 months (50.7% had > 6-month exposure), compared to a total of 281 subjects recruited in the placebo arm for which exposure slightly shorter, i.e. 5.3 months in median (44.5% had >6-month exposure).

As an indirect comparative analysis, the MAH also presented data on pembrolizumab monotherapy in participants with metastatic TNBC as derived from studies KEYNOTE-012, KEYNOTE-086, and KEYNOTE-119, for a total of 595 subjects who, however, received treatment for a considerably short time course of only 2.1 months in median (only 17.6% of total subjects has exposure >6 months). Therefore, the information provided by this safety dataset is limited to a short-term estimation of the safety profile of pembrolizumab as add-on to chemotherapy vs pembrolizumab alone in the target population. More informative, for the long-term evaluation, is the reference safety dataset (RSD, N=5884) including all currently approved indications for pembrolizumab monotherapy, that provides data for an exposure median length of 4.9 months. However, given the underlying disease, study KEYNOTE-355 offers a safety analysis specifically restricted to female subjects who generally constituted a minority of previous safety database (33.9% of RSD), and younger patients than previously treated (median age of 54 and 53 years in the pembrolizumab and placebo arm, respectively, vs 62 years in RSD).

In the pivotal trial, the main **demographic characteristics** appeared generally well-balanced between pembrolizumab+ chemotherapy and placebo+chemotherapy groups. Overall features were: 100% females, 78% <65 years, 68% White race, 60% ECOG PS 1. When compared to the pooled pembrolizumab monotherapy RSD, TNBC patients were younger.

The majority of patients (55%) received pembrolizumab in combination with carboplatin/gemcitabine, 32% of the patients were treated with the combination of pembrolizumab and nab-paclitaxel and only 13% of the patients were treated with pembrolizumab and paclitaxel.

The analysis of **summary of adverse events** revealed an unfavourable toxicity profile for the experimental therapy, based on significant between-treatment arm differences in terms of SAEs (30.4% vs 23.8%), drug-related SAEs (17.6% vs 12.1%), pembrolizumab/placebo dose modifications (52.7% vs 47.7%) and paclitaxel dose modification (10.1% vs 7.5%), any drug discontinuation due to adverse events (21.5% vs 13.2%) with particular reference to pembrolizumab/placebo (10.1% vs 5.3%) and, to a less extent, nab-paclitaxel (4.4% vs 1.4%), paclitaxel (3.2% vs 2.1%), gemcitabine (6.5% vs 5.7%) and carboplatin (7.4% vs 6.0%) discontinuations; a similar trend was observable for drug discontinuations due to drug-related adverse events (18.6% vs 11%), including serious drug-related adverse events (8.6% vs 3.2%). Of note, fatalities (2.5% vs 1.8%) were also more frequent in the experimental vs control arm.

In the comparison with pembrolizumab monotherapy as based on the RSD, all the above mentioned AE categories occurred at higher rate in the pembrolizumab+chemotherapy arm of KEYNOTE-355, with the exception of SAEs (38.3% in RSD) and deaths (5.3% in RSD), likely due to the older age of patients and

the different tumour-related symptoms and severity of disease of the RSD database. These finding were confirmed in the exposure-adjusted analysis.

The most common AEs (incidence ≥40%) that occurred at a similar rate in both arms were anaemia, nausea and neutropenia, likely associated to chemotherapy side effects. Alopecia, fatigue, diarrhoea, constipation and vomiting were also very common (incidence ≥20%) and comparable between treatment groups. Significantly more frequent in the pembrolizumab+chemotherapy arm were alanine (24.5% vs 19.6%) and aspartase (23% vs 16.7%) aminotransferase increase, decreased appetite (21.5% vs 13.9%), cough (21.1% vs 17.4%), rash (19.6% vs 11.7%), pruritus (15.6% vs 11.4%), hypothyroidism (15.9% vs 3.2%) and upper respiratory tract infections (11.4% vs 8.9%). Data suggest a potentiating effect of pembrolizumab on chemotherapy-associated toxicities, as previously observed in other indications.

The **drug-related AEs** observed for participants treated with pembrolizumab + chemotherapy (96.3% vs 95%) were consistent with the known safety profiles of chemotherapy, being blood disorders (anemia, neutropenia, thrombocytopenia), nausea, alopecia and liver toxicity (ALT and AST increase) the prevailing reported events in both arms; rash (15.4% vs 9.3%) and hypothyroidism (13.4% vs 2.8%), that are known side effects of pembrolizumab, also presented with common frequency (>10% in rate) in the experimental but not the placebo arm; and with higher frequency than the RSD (11.4% and 9.5% for rash and hypothyroidism, respectively).

In terms of severity, the majority of patients experienced **Grade 3-5 AEs** (78% vs 73.7% in pembrolizumab+chemotherapy and placebo+chemotherapy, respectively). Blood disorders and liver toxicity were the most frequently reported AEs with a comparable rate (>5% incidence rate) in both arms. Most of these were **drug-related Grade 3-5 AEs** (68.3% vs 66.9%). Their incidence was substantially higher than what observed in the RSD (47.8% and 15.4% for grade 3-5 AEs and drug-related grade 3-5 AEs, respectively).

As regards **SAEs** (30.4% vs 23.8%)**,** events demonstrated a pattern that is consistent with chemotherapy-associated toxicities (anaemia, neutropenia, thrombocytopenia, vomiting, sepsis, pneumonia were among the most prevalent cases); colitis, which is a known AEOSI for pembrolizumab, occurred with an incidence of 0.2%, below the previously reported rate of 1% in the RSD. **Drug-related SAEs** occurred more frequently in the pembrolizumab+chemotherapy arm than chemotherapy alone; they were mostly related to the blood disorder (5.7% vs 4.6%), gastrointestinal (2.9% vs 2.1%), laboratory investigation (2.5% vs 1.4%) and liver (1.3% vs 0.7%) categories; however, also, renal (0.8% vs 0.7%) and endocrine (0.5% vs 0%) toxicities were registered with higher rate in the experimental arm than either control of KN-355 or RSD, except for endocrine disorders that were more frequent in RSD (1%).

The overall incidence of **AEs resulting in death** was worse in the combination pembrolizumab + chemotherapy compared to chemotherapy alone (15 vs 5 patients, 2.5% vs 1.8%). The majority of fatal AEs were related to cardiovascular events, but also septic shock and acute kidney injury occurred, both of them in the experimental arm and none in the placebo group. Two deaths in the pembrolizumab plus chemotherapy group were considered drug-related by the investigator. One event (pneumonia) was considered related to pembrolizumab and nab-paclitaxel and one event (acute kidney injury) was considered related to pembrolizumab.

The incidence of **AEOSI** in the pembrolizumab plus chemotherapy group was 28.2% (vs 10.7% in the control arm), which is similar to the previous experience with pembrolizumab monotherapy (24.9%). In study KEYNOTE-355, less SAEs (3.4% vs 6.4%) and drug-related SAEs (3% vs 5.7%) were reported in the experimental arm compared to the RSD. There were no deaths related to AEOSIs. The rate of any study drug dose modification (10.2% vs 8.9%) or discontinuation (4% vs 3.9%) was similar between pembrolizumab+chemotherapy and pembrolizumab monotherapy as reported in the RSD. The addition of

chemotherapy apparently did not increase the risk and severity of AEOSI related to pembrolizumab compared to pembrolizumab monotherapy. The pattern of events is typical of pembrolizumab monotherapy; this consideration also applies to time of onset and event duration of events. There is, however, a higher incidence of hypothyroidism (15.9% vs 11%), with more events requiring corticosteroids (5.3% vs 1.5%) in KEYNOTE-355 relative to RSD. The exposure and sex-adjusted analysis confirmed no differences in the rate of AEOSI between KEYNOTE-355 and RSD. In terms of **laboratory** finding, blood cell count decrease and transaminase increase were the prevailing events, that were more marked in the pembrolizumab-chemotherapy group than in control; the pattern is typical of chemotherapy-induced toxicities, so they occurred significantly more frequently than what observed in the RSD with pembrolizumab monotherapy.

Discontinuation of any study intervention due to drug-related AEs was higher in the pembrolizumab + chemotherapy group (18.6%) compared with the placebo + chemotherapy group (11.0%); the comparison with pembrolizumab monotherapy also demonstrated a worse profile in the experimental arm than previously reported in the RSD (6.9%). Neutropenia (1.7% vs 0%), increased ALT (2.0% vs 0.3%), increased AST (1.5% vs 0.3%), decreased neutrophil count (1.2% vs 0%), neuropathy peripheral (1.3% vs 0%), and peripheral sensory neuropathy (1.0% vs 0%) were the most common reasons for drug discontinuation, which is consistent with the safety profile of chemotherapeutics co-administrated. However, the tolerability of pembrolizumab +paclitaxel compared to pembrolizumab+ nab-paclitaxel and also to pembrolizumab +platinum-based chemotherapy is worrisome. 29.6% of the subjects discontinued any drug in the pembrolizumab + paclitaxel group (compared to 12.5% in the placebo + paclitaxel group). 16% discontinued pembrolizumab which is twice as high as the proportion of pembrolizumab discontinuations in the pembrolizumab + nab-paclitaxel group (7.6%) and the pembrolizumab + carboplatin/gemcitabine group (8.1%). The incidences of AEs and drug-related AEs leading to discontinuation of pembrolizumab were higher in the pembrolizumab + paclitaxel group compared to the pembrolizumab + nab-paclitaxel group. This was primarily driven by AEs of ALT increased (3.7% vs 1.7%) and AST increased (6.2% vs 1.7%), which all occurred in ≤5 participants. Overall, the addition of pembrolizumab to paclitaxel is less tolerable than the addition of pembrolizumab to nab-paclitaxel. However, as the numbers are limited this should be interpreted with caution.

Safety profile by subgroups

Age: In study KN-355, a similar age-dependent increase in toxicity can be observed in both treatment arms when safety is analysed by using a cut-off of 65 years. The analysis by age groups <65, 65-74, 75-84, 85+ revealed that pembrolizumab augmented the rate of CNS disorders, AEs related to falling and infections across all patient categories; particularly marked is the increase in CNS (24.1% vs 0%), AEs related falling (24.1% vs 0%) and infections (79.3% vs 44.4%) that is observable in the oldest patient group receiving the combined therapy compared to the corrispective in the chemotherapy arm. The comparison between pembrolizumab + chemotherapy and pembrolizumab monotherapy revealed an increase in events across all AEs categories, which is particularly evident marked for the group of >75-year old. As previously observed in other indications for which combined regimens have been approved or are currently under review, the tolerability of pembrolizumab + chemotherapy is a concern for patients aged ≥75 years. Given the limited number of subjects in this category within individual trials, a pooled analyses of pembrolizumab + chemotherapy across indications was requested. Data suggested that pembrolizumab as add-on to chemotherapeutic agents is less tolerated in patients ≥75 years of age than their younger counterpart. The pooled analysis corroborates the consistent trend observed across individual studies showing increased toxicity of pembrolizumab as add-on to chemotherapy by age. On this basis, a revision of section 4.4 and 5.1 of the SmPC was deemed necessary.

Chemotherapy: Pembrolizumab generally increased the toxicity of all chemotherapeutic agents tested in the trial. The different drug combinations were overall comparable in terms of incidence of AEs. However, given the better tolerability of nab-paclitaxel compared to the other agents when used alone, the most

relevant impact of pembrolizumab on safety appears within the nab-paclitaxel groups, with a worsening in toxicity grade 3-5 events (62.8% vs 49.5%), drug-related grade 3-5 events (48.3% vs 36.8%), SAEs events (30.2% vs 17.9%) and drug-related SAEs (14.5% vs 7.4%), discontinuation due to adverse (16.3% vs 5.3%) or drug-related events (14% vs 4.2%) in patients treated with pembrolizumab+nab-paclitaxel versus nab-paclitaxel alone. The frequency of these events, however, was similar compared to the other combinations.

ECOG score: As expected, participants with a higher (1 vs 0) **ECOG** PS at baseline reported higher frequencies AEs across all categories and in both treatment arms; pembrolizumab slightly augmented the toxicity of therapy in both ECOG score categories.

Race: Race does not seem to influence the toxicity profile of either regimens since similar rate of events is observable in white and non-white across all AEs categories; pembrolizumab worsened the toxicity of chemotherapy regardless of race.

Region: the pattern of AEs as stratified by EU vs non-EU is similar.

Updated safety data

During the procedure, the MAH submitted the results of the final analysis for OS (data cut-off date 15 Jun 2021). Overall, the updated safety results at the FA were generally consistent with those observed at IA2, with no new safety concerns identified.

2.5.2. Conclusions on clinical safety

Pembrolizumab as adds-on to chemotherapy presents an unfavourable profile compared to chemotherapy alone or pembrolizumab in monotherapy. The pattern of observed AEs is consistent with chemotherapy-related toxicities; AEOSIs associated to the known safety profile of pembrolizumab were also observed and generally occurred at a similar rate than previously reported. The tolerability of the combined regimen appears worse in the oldest group of patients.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted/was requested to submit an updated RMP version with this application.

The PRAC considered that the risk management plan version 32 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 32 with the following content:

Safety concerns

Table: List of safety concerns

List of safety concerns	
Important identified risks	Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis, and endocrinopathies)
Important potential risks	For hematologic malignancies: increased risk of severe complications of allogeneic stem cell transplantation (SCT) in patients who have previously received pembrolizumab Graft versus host disease (GVHD) after pembrolizumab administration in patients with a history of allogeneic stem cell transplant (SCT)
Missing information	None

Pharmacovigilance plan

There are no ongoing or planned additional pharmacovigilance studies that are required for pembrolizumab

Risk minimisation measures

Table : Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	**Risk minimisation Measures**	**Pharmacovigilance Activities**
Important Identified Risks: Immune-Related Adverse Reactions		
Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and endocrinopathies)	Routine risk minimisation measures: ▪ The risk of the immune-related adverse reactions (including immune-related pneumonitis colitis, hepatitis, nephritis, and endocrinopathies) associated with the use of pembrolizumab is described in the SmPC, Section 4.2, 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk.	Routine pharmacovigilance activities Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted questionnaire for spontaneous postmarketing reports of all adverse events
	Additional risk minimisation measures: Patient educational materials	Additional pharmacovigilance including: • Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types

Table : **Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern**

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
Important Potential Risks		
For hematologic malignancies: increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab	Routine risk minimisation measures: ▪ For Hematologic malignancies: the increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab is described in the SmPC, Section 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk. No additional risk minimisation measures warranted	Routine pharmacovigilance activities Additional pharmacovigilance including: ▪ Safety monitoring in the ongoing HL trials (KN087, KN204).
GVHD after pembrolizumab administration in patients with a history of allogeneic SCT	Routine risk minimisation measures: ▪ GVHD after pembrolizumab administration in patients with a history of allogeneic SCT is described in the SmPC, Section 4.4 and appropriate advice is provided to the prescriber to minimize the risk. No additional risk minimisation measures warranted	Routine pharmacovigilance activities Additional pharmacovigilance including: • Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

- no significant changes are made to the package leaflet; in particular, the key messages for the safe use of the medicinal product are not impacted.

- the design, layout and format of the package leaflet will not be affected.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The sought indication is for Keytruda, in combination with chemotherapy, for the treatment of locally recurrent unresectable or metastatic triple negative breast cancer in adults whose tumours express PD-L1 with a CPS ≥ 10 and who have not received prior chemotherapy for metastatic disease.

3.1.2. Available therapies and unmet medical need

Due to the ER, PgR and HER-2 negativity, treatment of TNBC is challenging due to the lack of therapeutic target. In the sought locally advanced unresectable/metastatic first line setting, chemotherapy remains the only available non-investigational systemic treatment option for non-BRCA-mutated patients, with no specific recommendations regarding types of agents, with the possible exception of platinum compounds for BRCA-mutated patients. Anthracyclines and taxanes are preferred (depending on prior use), single agent capecitabine, vinorelbine or eribulin are also possible choices. In 2019, Tecentriq in combination with nab-paclitaxel was approved in the 1L TNBC setting for tumours having PD-L1 expression ≥1%, based on PFS advantage and positive OS trend shown in the pivotal IMpassion130 study[30].

3.1.3. Main clinical studies

KEYNOTE-355: A Randomized, Double-Blind, Phase III Study of Pembrolizumab (MK-3475) plus Chemotherapy vs Placebo plus Chemotherapy for Previously Untreated Locally Recurrent Inoperable or Metastatic Triple Negative Breast Cancer. Results of Interim Analysis 2 (IA2, i.e. final for PFS, interim for OS) with data cut-off date 11 Dec 2019, median follow up of 19.2 months (range 0.3, 35) in the CPS≥10 population, have been submitted. During the procedure, the final analysis (FA) for OS was also submitted (data cut-off date 15 Jun 2021), with median follow up of 20.2 months (range 0.3, 53.1) in the CPS≥10 population.

3.2. Favourable effects

In participants whose tumors express **PD-L1 CPS≥10**, pembrolizumab plus chemotherapy provided:

- Statistically significant PFS by BICR per RECIST 1.1 benefit of pembrolizumab+chemotherapy vs placebo+chemotherapy: HR=0.65, 95%CI 0.49, 0.86, p=0.0012, corresponding to gain in median PFS of about 4 months (9.7 vs 5.6 months) at the IA2 (final for PFS), confirmed in an updated PFS analysis.
- Statistically significant OS results at the FA, with a gain in median survival of about 7 months: OS HR of 0.73 (95% CI: 0.55, 0.95), median OS 23 months (95%CI 19, 26.3) vs 16.1 (95%CI 12.6, 18.8). KM curves separate at month 6 and remain separated over time.
- Numerical advantage in ORR based on BICR assessment (52.7% vs 40.8%), including higher CRs (16.8% vs 12.6%).

[30] Tecentriq-H-C-004143-X-0017 EPAR (EMA/CHMP/425313/2019)

- Median DOR longer in the CPS≥10 (12.1 months) than in the ITT population (7.3 months).
- Supportive PFS2 trend: HR 0.69 (95%CI 0.49, 0.87), median PFS2 16.9 vs 10.9 months.
- No relevant differences were observed between treatment arms in the various PRO scores and parameters examined, neither supporting a benefit nor indicating a detrimental effect of additional toxicity by the addition of pembrolizumab

3.3. Uncertainties and limitations about favourable effects

- There are many uncertainties around the observation in KEYNOTE-355 that gemcitabine/carboplatin would be less effective than pembrolizumab + taxanes and maybe available data are finally not sufficient to draw reliable conclusions.
- A post-hoc analysis on EU patients showed PFS and OS HR >1 and negative ORR difference. The small number of patients however (64 vs 28 in the CPS≥10 population) preclude further investigation, and it could be agreed that differences noted are likely due to random variation.
- The treatment benefit is uncertain for patients with disease free interval <12 months [n=66]: PFS HR 1.0, OS HR 1.19, ORR diff. minus 14.2%. Numbers are limited (especially in the control arm n=17), and there is no support from external studies, therefore no conclusions can be drawn in this population.
- A smaller treatment effect was also observed for patients with prior (neo)adjuvant treatment (n=193): PFS HR 0.78, OS HR 0.90, ORR difference 3.8%, similarly observed in the IMpower130 study in the same setting.

3.4. Unfavourable effects

- Overall AEs were more frequent with the addition of pembrolizumab to chemotherapy compared to chemotherapy alone, based on significant between-treatment arm differences in terms of SAEs (30.4% vs 23.8%), drug-related SAEs (17.6% vs 12.1%), pembrolizumab/placebo dose modifications (52.7% vs 47.7%) and paclitaxel dose modification (10.1% vs 7.5%), any drug discontinuation due to adverse events (21.5% vs 13.2%) with particular reference to pembrolizumab/placebo (10.1% vs 5.3%) and, to a less extent, nab-paclitaxel (4.4% vs 1.4%), paclitaxel (3.2% vs 2.1%), gemcitabine (6.5% vs 5.7%) and carboplatin (7.4% vs 6.0%) discontinuations; a similar trend was observed for drug discontinuations due to drug-related adverse events (18.6% vs 11%), including serious drug-related adverse events (8.6% vs 3.2%). Of note, fatalities (2.5% vs 1.8%) were also more frequent in the experimental vs control arm.
- The most common AEs (incidence ≥40%) that occurred at a similar rate in both arms were anaemia, nausea and neutropenia, likely associated to chemotherapy side effects. Alopecia, fatigue, diarreha, constipation and vomiting were also very common (incidence ≥20%) and comparable between treatment groups.
- Significantly more frequent in the pembrolizumab+chemotherapy arm were alanine (24.5% vs 19.6%) and aspartase (23% vs 16.7%) aminotransferase increase, decreased appetite (21.5% vs 13.9%), cough (21.1% vs 17.4%), rash (19.6% vs 11.7%), pruritus (15.6% vs 11.4%), hypothyroidism (15.9% vs 3.1%) and upper respiratory tract infections (11.4% vs 8.9%).
- The drug-related AEs observed for participants treated with pembrolizumab + chemotherapy (96.3% vs 95%) were consistent with the known safety profiles of chemotherapy, being blood disorders

(anemia, neutropenia, thrombocytopenia), nausea, alopecia and liver toxicity (ALT and AST increase) the prevailing reported events in both arms; rash (15.4% vs 9.3%) and hypothyroidism (13.4% vs 2.8%), that are known side effects of pembrolizumab, also presented with common frequency (>10% in rate) in the experimental but not the placebo arm;

- Drug-related SAEs occurred more frequently in the pembrolizumab+chemotherapy arm than chemotherapy alone; they were mostly related to the blood disorder (5.7% vs 4.6%), gastrointestinal (2.9% vs 2.1%), laboratory investigation (2.5% vs 1.4%) and liver (1.3% vs 0.7%) categories. The overall incidence of AEs resulting in death was worse in the combination pembrolizumab + chemotherapy compared to chemotherapy alone (15 vs 5 patients, 2.5% vs 1.8%). The majority of fatal AEs were related to cardiovascular events, but also septic shock and acute kidney injury occurred, both of them in the experimental arm and none in the placebo group.
- The incidence of AEOSI in the pembrolizumab plus chemotherapy group was 28.2% (vs 10.7% in the control arm), which is similar to the previous experience with pembrolizumab monotherapy (24.9%). In study KEYNOTE-355, less SAEs (3.4% vs 6.4%) and drug-related SAEs (3% vs 5.7%) were reported in the experimental arm compared to the RSD. There were no deaths related to AEOSIs.

3.5. Uncertainties and limitations about unfavourable effects

- Data demonstrate a potentiating effect of pembrolizumab on chemotherapy-associated toxicities, as previously observed on other indications for which combined regimens have been approved. The tolerability of pembrolizumab + chemotherapy is a concern for patients aged ≥75 years. Relevant wording in the SmPC has been included on this aspect.

3.6. Effects Table

Table 2. Effects Table for Keytruda in combination with chemotherapy for 1L locally advanced unresectable/metastatic TNBC with PD-L1 CPS⩾10 - KEYNOTE-355 IA2, 11 Dec 2019; FA 15 Jun 2021

Effect	Short description	Unit	Treatment Pembro +chemo (n=220)	Control Placebo +chemo (n=103)	Uncertainties / Strength of evidence	References
Favourable Effects in the CPS≥10 subgroup						
PFS (by CIV per RECIST 1.1)	Time from randomization to first documented disease progression per RECIST 1.1 based on blinded CIV or death due to any cause, whichever occurs first	months (95% CI)	9.7 (7.6, 11.3)	5.6 (5.3, 7.5)	At the IA2 (i.e. final analysis for PFS), statistically significant advantage in PFS in CPS≥10, supported by other endpoints. Treatment effect not consistent across all subgroups. Limited data in ≥75 years	CSR KN-355
		n/a	HR 0.65 (95%CI (0.49, 0.86) p-value 0.0012			
OS	Time from randomization to death due to any cause	months (95% CI)	23 (19, 26.3)	16.1 (12.6, 18.8)	At the FA for OS, statistically significant OS benefit in CPS⩾10	
		n/a	HR 0.73 (95%CI 0.55, 0.95) p-value 0.0093			
ORR	Confirmed CR or PR (by BICR per RECIST 1.1)	% (95% CI)	53.2% (46.4, 59.9)	39.8 % (30.3, 49.9)	Trend towards higher ORR and CR/ less SD and more PD	
DOR	Time from first response to PD or death due to any cause, whichever occurs first, in subjects who achieve PR or CR	months (range)	19.3 (1.6+ – 29.8)	7.3 (1.5 – 32.5+)	Durable responses	
Unfavourable Effects						

Effect	Short description	Unit	Treatment Pembro +chemo (n=220)	Control Placebo +chemo (n=103)	Uncertainties / Strength of evidence	References
AE summary	drug related G3-5 AE	%	68.3	66.9	Safety of the combination consistent with the established safety profile of the chemotherapy and pembrolizumab. No new safety concern identified. Concern over toxicity in elderly (⩾75 years).	CSR KN-355
	drug related SAE	%	17.6	12.1		
	death due to drug related AE	%	0.3	0		
	discontinuation of any drug due to drug related AE	%	18.6	11		
	discontinuation of any drug due to drug related SAE	%	6.7	1.4		
AEOSI	Hypothyroidism	%	15.9	3.2		
	Pneumonitis	%	2.5	0		
	hyperthyroidism	%	5.2	1.1		

Abbreviations: PFS: progression free survival; OS: overall survival; ORR: objective response rate; DOR: duration of response; CIV: central imaging vendor; NR: not reached; CI: confidence interval; AE: adverse event; SAE: serious adverse event; AEOSI: Adverse Events of Special Interest; CRS: clinical study report

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Pembrolizumab in combination with chemotherapy showed PFS and OS advantage compared to chemotherapy in the subgroup with PD-L1 expression CPS≥10 as first line treatment of locally advanced unresectable/metastatic TNBC in the pivotal KEYNOTE-355 study. The statistically significant PFS benefit seen at the IA2 was later supported by a statistically significant OS at the FA, and supportive ORR, DOR and PFS2 results. The PFS and OS hypotheses in the CPS≥10 subgroup, defining about 38% of the ITT population, were however added with a protocol amendment one year after the IA1 conduction. The MAH claims that the choice of the additional CPS≥10 cut off was based only on external results (KEYNOTE-119 and IMpassion130) and that no data from KEYNOTE-355 study itself was used. The biological rationale for an enriched pembrolizumab efficacy with higher PD-L1 expression is indeed considered supported by the above mentioned external data, whose timing is also compatible with Amendment 5 release, and by pembrolizumab study results in various diseases. At the same time, pembrolizumab monotherapy in pretreated TNBC in KEYNOTE-119 did not show outstanding results in this disease.

As expected, pembrolizumab as add-on to chemotherapy presents an unfavourable profile compared to chemotherapy alone or pembrolizumab in monotherapy. The pattern of observed AEs is consistent with chemotherapy-related toxicities; AEOSIs associated to the known safety profile of pembrolizumab were also observed and generally occurred at a similar rate as previously reported. The tolerability of the combined regimen appears worse in the oldest group of patients.

3.7.2. Balance of benefits and risks

Pembrolizumab in combination with chemotherapy showed significant OS and PFS advantage compared to chemotherapy as 1L treatment in TNBC with PD-L1 CPS≥10 based on KEYNOTE-355 study. This outweighs the unfavourable profile compared to chemotherapy alone or pembrolizumab in monotherapy, and it can be concluded that the benefit/risk balance is positive.

3.7.3. Additional considerations on the benefit-risk balance

The relevance of the generic wording "pembrolizumab **in combination with chemotherapy**" proposed in the indication was considered in view that the pivotal study KEYNOTE-355 was performed with

pembrolizumab in combination with specific chemotherapy drugs. According to EMA guideline on the Wording of therapeutic indication (EMA/CHMP/483022/2019), "*From a regulatory point of view, the therapeutic indication should be clearly stated in section 4.1 of the SmPC to reflect in which disease/condition and target population* ***the benefit/risk balance is established to be positive***." Furthermore, "*If there is a need to specify use in combination therapy in SmPC section 4.1: Is there a need to specify particular combinations (e.g.* ***the studied combinations if it is expected that the benefit risk balance may differ with other combinations****) or could a general statement ("in combination with other products") be used (with information on combinations studied reflected in other parts of the SmPC)? If so,* ***since the description of performed studies in section 5.1 cannot be seen as restricting or broadening the indication, restriction or extrapolation in section 4.1 in terms of combination therapy should be justified in the assessment report****.*" The possibility to extrapolate the use of pembrolizumab in combination with **any** chemotherapy currently used in TNBC was supported by efficacy shown in available clinical trials in TNBC, although in different setting, such as KEYNOTE-522 (phase III, carboplatin-paclitaxel, doxorubicin or epirubicin-ciclophosphamide in the neoadjuvant setting) and ENHANCE-1 (phase Ib/II single arm, pembrolizumab+eribulin). It was agreed that there are no data to suggest that the benefit of adding pembrolizumab to any of recommended treatment regimens for patients with locally recurrent unresectable or metastatic TNBC would be altered depending on the chemotherapy backbone chosen.

According to current guidelines (ESMO ABC 5th) for most patients, "chemotherapy remains the only available non-investigational systemic treatment option for non-BRCA-mutated triple-negative ABC, with no specific recommendations regarding types of agents, with the possible exception of platinum compounds for patients with BRCA-mutated triple-negative ABC." Chemotherapy regimens that can be used include anthracyclines, taxanes, antimetabolite (capecitabine, gemcitabine), eribulin, platinum, and combination chemotherapies in patients with rapid clinical progression, life-threatening visceral metastases, or need for rapid symptom and/or disease control.

On the one hand, there are previous experiences in other trials (atezolizumab + nab-paclitaxel and atezolizumab + paclitaxel in IMpassion130 and IMpassion 131 studies) showing a different outcome according to backbone chemotherapy in the same setting, that could suggest caution in extrapolation. On the other hand, the pembrolizumab study KEYNOTE-355 study showed no concern over the use of paclitaxel in combination with pembrolizumab (contrary to atezolizumab), though based on subgroup data.

With regard to pembrolizumab in combination with carboplatin-gemcitabine, where a lower treatment effect was seen, it is considered that it is unlikely from a biological perspective to assume a lack of treatment effect with carboplatin/gemcitabine as backbone, given prior experience with this combination. The same reasoning could potentially apply to other chemotherapies. Although not all drugs have been combined with pembrolizumab, and there are not necessarily safety data available for each combination, it is not expected that the benefit/risk balance will differ with other combinations, therefore, in line with EMA guidelines, the use of "chemotherapy" in SmPC 4.1 can be considered acceptable. A reference to SmPC 5.1 was added at the end of the wording of the indication to raise awareness of the chemotherapy drugs used in the pivotal KEYNOTE-355 study (see SmPC section 4.1). It can be expected that physicians will use the combinations for whom there is clinical trial experience, although as noted in the EMA guidelines, 5.1 section does not restrict the indication.

3.8. Conclusions

The overall B/R of Keytruda in combination with chemotherapy for the 1L treatment of locally recurrent unresectable or metastatic TNBC in subjects with PD-L1 positive tumours (CPS $\geqslant$10) is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication for Keytruda to include in combination with chemotherapy, treatment of locally recurrent unresectable or metastatic triple negative breast cancer in adults whose tumours express PD L1 with a CPS ≥ 10 and who have not received prior chemotherapy for metastatic disease; as a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 32 of the RMP has also been submitted.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.