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EMA/CHMP/637356/2016
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

## Keytruda

pembrolizumab

Procedure no: EMEA/H/C/003820/P46/009

## Note

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

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# 1. Introduction

On 10 May 2016, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, the MAH submitted the final study report of study PN002 (*"Randomized, Phase II Study of MK-3475 versus Chemotherapy in Patients with Advanced Melanoma "*) in which one patient at the start of treatment with KEYTRUDA was included.

A short critical expert overview has also been provided.

# 2. Scientific discussion

## *2.1. Information on the development program*

The MAH stated that study P002 *"Randomized, Phase II Study of MK-3475 versus Chemotherapy in Patients with Advanced Melanoma "* is stand-alone study.

A positive PDCO Opinion was granted for the pembrolizumab pediatric investigation plan (PIP) on 14 Feb 2014 and the EMA decision was received on 7 Mar 2014. The condition for this PIP is treatment of all conditions included in the category of malignant neoplasms (except nervous system, haematopoietic and lymphoid tissue), with the two following indications:

- Treatment of advanced, untreatable or previously treated malignant melanoma in children from 12 year old to <18 years of age
- Treatment as monotherapy of a PD-L1 positive paediatric malignant solid tumor in children from 6 months to less than 18 years of age

The pembrolizumab development in paediatric solid tumors is currently ongoing in the Phase 1/2 study P051. Because melanoma is rare in children, as many children with melanoma as feasible will be enrolled in this study, and efficacy results will be compared to data with pembrolizumab in the adult melanoma studies. The PIP also seeks to identify additional paediatric tumors that could be amenable to anti-PD-1 therapy. Thus, study P051 will also enroll any advanced, relapsed or refractory PDL1-positive solid tumor or lymphoma to look for signals of efficacy within a given tumor indication. A safe and tolerated dose in children will be selected that assures a similar exposure to adults at the recommended phase 2 dose, and that the pharmacodynamic (IL-2 release assay) target is also met.

At the conclusion of Study P051 (Part 2), responses in each enrolled tumor type will be evaluated in order to select a solid tumor for further efficacy and safety investigation.

## *2.2. Information on the pharmaceutical formulation used in the study*

Pembrolizumab was provided as 50 mg lyophilized drug in vials to be reconstituted in sterile water and then diluted further in normal saline for IV administration.

A specific formulation will not be developed, as the available IV is considered appropriate for the paediatric population.

## *2.3. Clinical aspects*

### 2.3.1. Introduction

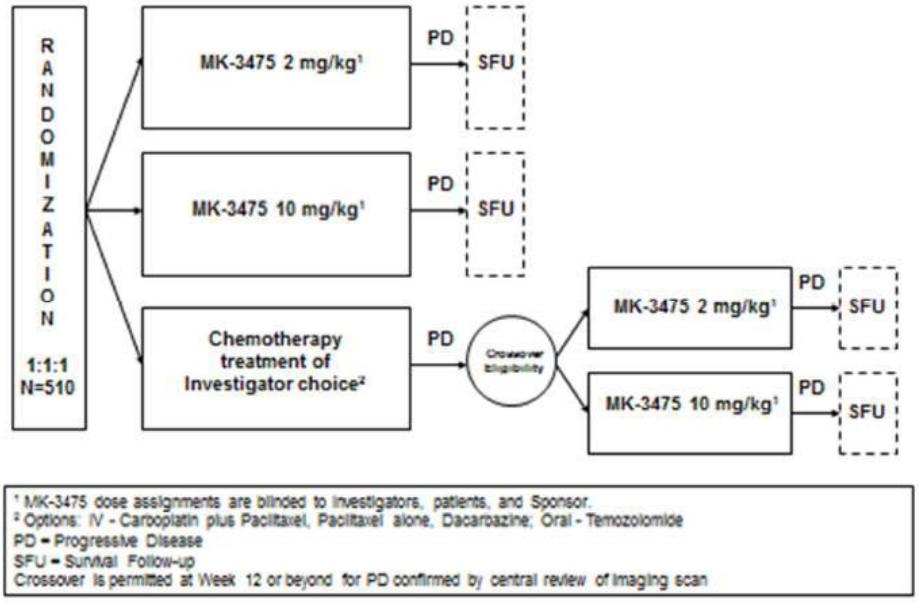
The final results of study P002 have been submitted as a Clinical Study Report (CSR), in accordance with Article 46 of the EU Paediatric Regulation (EC No 1901/2006) which requires that any MAH-sponsored study which involves the use in the paediatric population of a medicinal product covered by a marketing authorization, whether or not they are conducted in compliance with an agreed paediatric investigation plan, is to be submitted to the competent authority within 6 months of study completion (last subject last visit for P002 was 16-Nov-2015).

### 2.3.2. Clinical study

Study P002: Randomized, Phase II Study of MK-3475 versus Chemotherapy in Patients with Advanced Melanoma

### Description

P002 is a randomized, Phase 2 study of pembrolizumab vs. chemotherapy in subjects with advanced melanoma refractory to ipilimumab (IPI). Subjects were randomized in a 1:1:1 ratio to receive blinded pembrolizumab 2 mg/kg, pembrolizumab 10 mg/kg, or chemotherapy (Investigator choices).



## Methods

### *Objective(s)*

The study objective was to evaluate the overall benefit of pembrolizumab compared to control.

### *Study population /Sample size*

The study included male and female subjects ≥18 years old, with a histological or cytological diagnosis of melanoma and progressive locally advanced or metastatic disease that was not amenable to definitive local therapy with curative intent.

Patients were eligible only if ipilimumab-refractory (progression documented in two separate assessment and following at least 2 doses of IPI at a minimum dose of 3 mg/kg and within 6 months of the last dose of IPI). In addition, patients with BRAF V600 mutant melanoma must have had a prior treatment regimen that included vemurafenib, dabrafenib, or other approved BRAF and/or MEK inhibitors.

The age eligibility in the original protocol of ≥16 years old was amended (version 01) to ≥18 years due to difficulty enrolling younger subjects as well as requests from country agencies and IRBs/IRCs.

At the time that study eligibility required that subjects be≥18 years old, an exception was granted for oneyea younger subject with advanced, IPI-refractory melanoma. This protocol deviation was requested based on there being no available alternative therapies. The subject was allowed to be randomized in the trial by the IRB/IEC and this was authorized by the Sponsor based on the medical need.

The sample size calculation (510 patients randomized 1:1:1, with 170 subjects per arm) was based on the assumption of an HR of 0.65 between each of the MK-3475 arms and chemotherapy arm.

### *Treatments*

Patients were randomized to one of the following 3 treatment arms:

a) Pembrolizumab 2 mg/kg every three weeks

b) Pembrolizumab 10 mg/kg every three weeks

c) Investigator-choice standard of care (SOC) chemotherapy (supplied locally). The chemotherapy options were initially carboplatin in combination with paclitaxel, carboplatin monotherapy, paclitaxel monotherapy, dacarbazine, temozolomide IV, or oral temozolomide. Protocol amendment 01 removed carboplatin monotherapy and temozolomide IV in response to regulatory agency feedback.

An integrated radiology and oncology (IRO) assessment was used as the primary method of analysis. This assessment included the review of images by independent radiologists and the review of objective clinical data by an independent oncologist (e.g. qualitative skin photographs, biopsy reports from suspicious lesions if performed) when such data were available.

Radiological assessment per RECIST 1.1 of tumor response status was performed starting at Week 12 following the initial dose of study medication, and then every 6 weeks until Week 48 and every 12 weeks thereafter. Crossover to pembrolizumab was permitted starting at Week 12 for subjects in the chemotherapy control arm who had PD confirmed by central imaging review.

***Outcomes / endpoints***

There were two primary endpoints in this study, progression-free survival (PFS) and overall survival (OS). The overall type I error rate for this study was strictly controlled at 2.5% (one-sided) that allowed the trial to declare positive in either or both of the two primary endpoints (PFS and OS) at either of the two pembrolizumab dose levels.

*Progression-Free-Survival*: PFS was defined as the time from randomization to the first documented PD (based on assessment from a central imaging vendor using the RECIST 1.1 criteria) or death due to any cause, whichever occurs first. For the primary PFS analysis, subjects without PD, death, or new anti-cancer treatment were censored at the last disease assessment; for subjects who started new anti-cancer treatment, subjects were censored at the last disease assessment before starting new anti-cancer treatment; for subjects with missing disease assessments, events were considered on the date PD or death was documented.

Analysis of PFS based on Investigator assessment using RECIST 1.1 was performed as a supportive analysis. For subjects whose subsequent assessments right after RECIST-defined PD showed stable disease or better and who remained on study treatment, a sensitivity analysis was conducted that did not count the initial RECIST-defined PD assessment as an event.

*Overall Survival*: OS was defined as the time from randomization to death due to any cause. Subjects without documented death at the time of the analysis were censored at the date of the last follow-up.

The secondary endpoints were *Overall response rate* (ORR) based on confirmed assessments from a central imaging vendor review using the RECIST 1.1 criteria and *Response Duration*.

Additional exploratory endpoints included:

- Response rate, response duration, PFS and OS following crossover to pembrolizumab.
- Response rate by Week 12, PFS and OS in the biomarker (PD-L1 high expression) subgroup.
- European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC-QLQ C30), European Quality of Life five dimensions questionnaire (EuroQoL EQ-5D), and tumor volumetric changes at Week 12.

For the evaluation of OS, PFS and ORR in the PD-L1 positive subgroup, the PD-L1 cutoff point was defined and validated using data from the melanoma subjects in P001. PD-L1 positive was defined as Allred proportion score (APS) of 2 or higher and PD-L1 negative is defined as APS of 0 or 1.

***Statistical Methods***

An outline of the efficacy analysis strategy is shown in the following Table:

**Table: Analysis Strategy for Key Efficacy Endpoints**

| Endpoint (Description, Time Point) | Approach† | Statistical Method‡ | Analysis Population | Missing Data Approach |
|---|---|---|---|---|
| **Primary** | | | | |
| PFS | P | Stratified Log-rank test<br>Stratified Cox model with Efron's tie handling method for estimation<br>Kaplan-Meier method for PFS curve estimation in each treatment group | ITT | Model based |
| OS | P | Stratified Log-rank test<br>Stratified Cox model with Efron's tie handling method for estimation<br>Kaplan-Meier method for OS curve estimation in each treatment group | ITT | Model based |
| **Secondary** | | | | |
| ORR | P | Stratified M&N method ‡ | FAS and ITT | Patients with missing data are considered non-responders |
| Response Duration | P | Summary statistics using Kaplan-Meier method | All responders | Non-responders are excluded in analysis |

† P=Primary approach

‡ Miettinen and Nurminen method.

There were two planned interim analyses for which strategy and timing are reported below:

**Table: Summary of Interim Analysis Strategy**

| Interim Analysis Number | Key Endpoints for Interim Analysis | Anticipated Approximate Timing of Interim Analysis (from study start) | Sample size included for analysis (Three arms) | Number of events included for analysis (Three arms) | Purpose of Analysis |
|---|---|---|---|---|---|
| Interim Analysis 1 | ORR | 10 months | 120 | NA | Discontinue one inferior MK-3475 arm |
| Interim Analysis 2 | PFS/OS | 15 months | 510 | 270 PFS events | • Demonstrate superiority of MK-3475 in PFS<br>• Stop for futility based on OS |
| Final analysis | OS | 24 months | 510 | 370 OS events | Demonstrate superiority of MK-3475 in OS |

## Results

***Recruitment / Number analysed***

***Baseline data***

The only paediatric patient enrolled in the trial was a male subject with BRAF wild-type mucosal melanoma metastatic at baseline. For advanced melanoma, the subject had ipilimumab induction and maintenance treatment.

***Efficacy results***

The patient was randomized in the pembrolizumab 2 mg/kg Q3W arm. He received 8 doses of pembrolizumab (last dose on Day 148) and had a best response of stable disease based on independent central review of imaging. Treatment was discontinued due to progressive disease on Day 175 and eventually the patient died on Day 272 due to progression of advanced melanoma.

***Safety results***

The AEs are all Grade 1 in severity, and none were considered to be related to study treatment by the investigator. No action was taken with respect to study medication for any of the AEs recorded for this subject.

It is notable that the subject developed hypothyroidism on day 42 of study treatment, managed with levothyroxine. Although this AE was reported as unrelated to study treatment by the investigator, hypothyroidism is an identified risk for pembrolizumab.

## 2.3.3. Discussion on clinical aspects

This application, submitted in accordance with article 46 of regulation (EC) No 1901/2006, does not provide any additional and relevant information on the use of pembrolizumab in the paediatric population. According to the agreed PIP for Keytruda (EMEA- 001474-PIP01-13), study KEYNOTE- 051 (*A Phase I/II study of Pembrolizumab in children with advanced melanoma or a PD-L1 positive advanced, relapsed or refractory solid tumor or lymphoma*) is at present ongoing and it is expected to be completed by January 2019.

Indeed, the submitted study P002, a phase 2 trial comparing pembrolizumab and chemotherapy in advanced IPI-refractory melanoma patients, was not designed to evaluate the pembrolizumab efficacy and safety in the paediatric population, and the only subject enrolled was considered as a protocol deviation. Due to this single case report, any comparison of available data in the young patient with those in the adult population is of very limited value. Overall, a consistent pembrolizumab safety profile, that does not seem to be influenced by the young age of the patient, was registered. However, even if considered by the investigator not-treatment related, a newly occurred event (*Testicular atrophy*), never observed in the adult population, was reported.

In the pembrolizumab non-clinical development, no studies were specifically conducted in juvenile animals. However, in a repeat-dose toxicity study (SN 08396: *One-month IV bolus toxicity and toxicokinetic study in cynomolgus monkeys with a four-month recovery period*) conducted in juvenile to young adult cynomolgus monkeys**,** *Testicular atrophy* was observed in one animal (N. 3003) that was treated with pembrolizumab 200 mg/kg.

More details on the *Testicular atrophy* event reported in the young patient in study P002 have been submitted by the MAH. Due to the lack of baseline information, regarding the size measurements of the testes and the levels of testosterone, LH, and FSH, the pembrolizumab contribution to the reported testicular atrophy cannot be characterized. In addition, no additional testicular atrophy events are reported in the overall 22 male children enrolled in study P051 up to 27 July 2016 . Any further occurrence of Testicular atrophy should be carefully monitored.

The final results from study P002, that were requested as post-marketing measure at the time of the initial MA, will be evaluated within a specific variation for the fulfilment of the Annex II condition by 1Q 2017.

# 3. Rapporteur's overall conclusion and recommendation

No meaningful information on the use of pembrolizumab in paediatric patients can be obtained from the single melanoma patient included as protocol violation in study P002. It is therefore agreed that no change of the SmPC is requested at present

☒ **Fulfilled:**

No regulatory action required.

☐ **Not fulfilled:**

# 4. Additional clarification requested

Based on the data submitted, the MAH should address the following questions as part of this procedure:

- The MAH should provide more details on the Testicular Atrophy event, including the narrative, and explain on which basis the investigator classified the event as not related to pembrolizumab.
- The MAH should clarify whether additional *Testicular atrophy* events have been registered in the ongoing paediatric study P051.

The timetable is a 30 day response timetable without clock stop.

## MAH responses to Request for supplementary information

**Question 1**

The MAH should provide more details on the Testicular Atrophy event, including the narrative, and explain on which basis the investigator classified the event as not related to pembrolizumab.

**MAH's response**

The subject who entered the trial had BRAF wild type melanoma of the mucosa with metastases .. He was noted to have Grade 1 testicular atrophy approximately 3 and a half months after having received the first dose, which was considered not related to pembrolizumab.). The patient continued to receive study treatment without interruption.

Since the adverse event was Grade 1 and not related to pembrolizumab, data supporting a narrative was not required to be submitted to the Inform database by the investigator. We have since contacted the investigator for additional information and rationale for assessing the event as not drug-related.

No prior size measurements of the testes nor previous levels of testosterone, LH, and FSH were obtained before entry onto P002, so it is not possible to determine whether the findings of small testes predated the patient's participation in P002.

The MAH agrees with the assessment of the investigator that the adverse event of testicular atrophy was not drug related. There are no prior physical examination findings or laboratory evaluations to show that the patient had normal testicular size and/or gonadal function at baseline, and to show that the testicular atrophy did not predate the initiation of therapy on pembrolizumab.

**Assessment of MAH's response**

The lack of baseline information, regarding the size measurements of the testes and the levels of testosterone, LH, and FSH, do not allow to characterize the pembrolizumab contribution to the reported testicular atrophy.

*Issue solved*

**Question 2**

The MAH should clarify whether additional Testicular atrophy events have been registered in the ongoing paediatric study P051.

**MAH's response**

There are currently 43 pediatric patients enrolled in study P051, 22 of those patients are male. The adverse event listings were reviewed on 27-Jul-2016, and there were no reports of testicular atrophy within the clinical database.

**Assessment of MAH's response**

At present, no additional testicular atrophy events were reported in study P051.

*Issue solved*