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Executive Director

Letter of support for Measurable Residual Disease (MRD) as a Surrogate Efficacy Endpoint in Clinical Studies with Acute Myeloid Leukemia

On 21 October 2022, the Applicant, Novartis Europharm Limited, acting on behalf of the MPAACT (Measurable Residual Disease Partnership and Alliance in acute myeloid leukaemia Clinical Treatments) consortium, requested a follow-up qualification advice for the biomarker Measurable Residual Disease (MRD) as a surrogate efficacy endpoint in Acute Myeloid Leukaemia (AML), pursuant to Article 57(1)(n) of Regulation (EC) 726/2004 of the European Parliament and of the Council.

The alliance named Measurable Residual Disease (MRD) Partnership and Alliance in acute myeloid leukemia (AML) Clinical Treatments (MPAACT) was established in 2018 by Janssen, Celgene Corporation, a wholly owned subsidiary of Bristol Myers Squibb, Genentech Roche, and Novartis. In 2021, MPAACT became a consortium and expanded with additional members Amgen, AbbVie, Servier and Kura Oncology. The overall goal of MPAACT is to investigate the potential utility of MRD as a surrogate endpoint for overall survival (OS) in patients with AML. To achieve this goal, MPAACT is partnering with experts in the field to share knowledge and to create a sizeable data pool for evaluation.

A discussion meeting with the Applicant took place on 13 March 2023. On 16 March 2023 the SAWP agreed on the advice to be given to the Applicant. On 30 March 2023, the CHMP adopted the advice to be given to the Applicant.

Background and proposed approach to establish MRD as surrogate endpoint

Recent studies have suggested that results from the quantitation of MRD can be used to predict OS across multiple AML subtypes and lines of therapy (Ivey et al. 2016; Short et al. 2020; Walter et al. 2021). Therefore, the goal of this effort is to establish MRD as a primary endpoint by conducting a retrospective meta-analysis, towards supporting future initial Marketing Authorization Applications (MAA) once MRD is accepted as a validated surrogate endpoint. The Mayo Clinic Statistics and Data Management Center, an independent statistical partner, will perform the meta-analysis to assess association of MRD with OS. Since the complexity of AML has led to various technological and methodological developments for MRD, an additional goal is to harmonize assessment of MRD in AML (Walter et al. 2021) to ensure more standardized and robust data collection and analysis for future clinical trials.

In the follow-up qualification advice, the Applicant presented the overall approach, general methodology and analysis population for the meta-analysis. In addition, datasets to be included in the meta-analysis, planned subgroup and sensitivity analyses as well as methods to assess MRD were also discussed.

The Applicant plans to follow a two-stage process to establish MRD as a surrogate endpoint in front line AML. The first stage aims at providing some initial evidence of the prognostic value of MRD, on the basis of single-arm trials. Assuming the prognostic value of MRD is reasonably established during stage 1, the main objective of the second stage would then be to assess the predictive nature of MRD for OS, i.e. whether a treatment effect on MRD can predict a treatment effect on OS (also referred to as trial-level surrogacy). For this purpose, a meta-analysis would be performed using individual patient data from randomized controlled trials. The prognostic nature of MRD for OS is also meant to be confirmed during the second stage.

Two primary surrogacy analysis populations are planned by the Applicant. The first analysis population is expected to include adult patients with newly diagnosed AML treated with intensive and non-intensive regimens, who are randomised (regardless of treatment being received or not) and from trials where survival was collected as a study endpoint. The second primary analysis population is the paediatric population, for which analyses are to be performed in parallel.

Separate analysis populations are defined on the basis of intensity of treatment received and for fit and unfit adult newly diagnosed patients with AML for secondary analysis populations. Another secondary surrogacy population is planned to include fit adult and paediatric newly diagnosed patients with AML.

Trial-level surrogacy (assessed in stage 2) will be the primary measure of surrogacy of MRD for decision making. The evaluation of individual-level surrogacy will be considered as supportive to the trial-level analysis.

Preliminary consideration of the Qualification time assessment

The Agency agreed to the two-stage approach and the principle to define the MRD based on data different from the data used to perform the surrogacy analysis is supported, as this avoids data dredging in the search for the best surrogate endpoint definition.

However, a concern was raised that the stage 1 analysis will be performed in the first line AML treatment setting excluding studies with patients who received haematopoietic stem cell transplant (HSCT) as part of the treatment, while the primary stage 2 meta-analysis is planned to be performed in newly diagnosed AML paediatric and adult patients, separately, for whom HSCT was allowed. A distinction between transplanted and non-transplanted patients should be made.

Another concern raised was the heterogeneity of the patient populations to be included in the meta-analyses: the mode of action of the study treatments, the patient population (in particular, fit or unfit for intensive chemotherapy), the timing of MRD and its assay methodology may all have an important impact on MRD surrogacy. Therefore, it may be more appropriate to analyse surrogacy in a more homogeneous group of patients first before considering wider AML populations, e.g. in non-transplant adult patients for a distribution of rather early events or in the paediatric population for later events.

During the discussion meeting and as suggested by CHMP, the Applicant agreed to modify the study design and the SAP in order to use intensity of treatment (rather than fitness of patients) as first analysis population. An exploratory sensitivity analysis will be performed to evaluate the potential of MRD for surrogacy in both fit versus unfit and intensive versus non intensive regimens. Therefore, the first analysis population is expected to include adult patients with newly diagnosed AML treated with

intensive and non-intensive regimens, who are randomised (regardless of treatment being received or not) with non-missing data on the primary clinical endpoint of OS. The initial focus on newly diagnosed AML adult patients is supported and in line with previous advice. The use of intensity of treatment as parameter is also endorsed as, in contrast to fitness, the choice for (less) intensive treatment is dependent on multiple factors, which include fitness of patients, but also disease characteristics, such as cytogenetic risk.

The Applicant was encouraged to conduct separate analyses on the basis of intensity of treatment, as well as for fit and unfit patients, adults and paediatric patients, and any other identified heterogeneous subgroups potentially requiring independent analyses due to the small number of trials in scope for the meta-analysis. These separate analyses should be pre-specified and performed before considering a pooled patient population of AML patients (to ensure sufficient homogeneity across subgroups).

The Applicant was reminded that the validation of stage 2 trial-level meta-analysis results will be a requirement to formally confirm surrogacy. It is strongly advised that such validation is prospectively planned, besides the current two stages, as an additional development step. Considering the heterogeneity of the AML population, a validation plan using an external database is strongly advised, preferably using future planned clinical trials.

Several recommendations were made regarding surrogacy evaluation methodology. The Applicant was notably advised that qualification criteria should capture measures of predictive performance (e.g. accuracy and discrimination) and should be pre-planned with adequate justification. The performance of a feasibility assessment was recommended for the primary and secondary analyses. The Applicant was generally encouraged to pre-specify all included datasets and statistical models to the maximum extent possible.

It was agreed to group MRD methods for the purpose of meta-analyses, while also performing subgroup analyses for NGS versus PCR versus MFC/NFC. In addition, different MRD sensitivity levels should be explored; it was recommended to test MRD negativity at the 10^{-3}, 10^{-4}, 10^{-5}, and 10^{-6} cut-off.

The Applicant's challenges in developing an NGS-MRD approach that can meet acceptable sensitivity / specificity profiles across both known and de novo variants are acknowledged. The rationale for the proposed tiering approach with de novo mutations called at a higher VAF cut-off than known mutations is understood, and its general principle can be supported. Evaluation of multiple options to address the required sensitivity/specificity parameters is endorsed. An optimal target cut-off of 0.1% VAF can be agreed, but it is emphasised that the optimal NGS-MRD threshold level that best discriminates subsequent relapse risk has not yet been defined for individual mutations, combinations of mutations, or treatment time points. In addition, it is difficult to comment on the adequacy of the selected thresholds for de novo variant calling, particularly as this may differ per mutation. In the end, the chosen cut-off should be justified based on analytical performance of the NGS for that marker. Further validation work will be needed to demonstrate its optimality. Moreover, an MRD definition associated with a given threshold may be prognostic of later outcomes without necessarily providing the optimal cut-off for establishing surrogacy.

It is agreed with the Applicant that bone marrow is the preferred substrate for MRD analysis at this stage. However, the Applicant is encouraged to study paired samples if feasible, of bone marrow and peripheral blood, at the time points decided, for MRD analysis. Bone marrow analysis is the golden standard in any AML setting for response assessment. It would be a major benefit as non-invasive, more practical in any aspect and a patient preference, if blood samples could substitute bone marrow

aspiration as the substrate for MRD analysis in AML. This may depend on the disease driver and methodology for MRD.

The EMA has issued this letter of support, based on the qualification advice provided to MPAACT, to encourage further steps to demonstrate surrogacy of MRD including extending collaboration with other partners to increase the sample size for the analyses.

Yours sincerely,

Emer Cooke

Executive Director

References

- Ivey A, Hills RK, Simpson MA, et al. UK National Cancer Research Institute AML Working Group. Assessment of minimal residual disease in standardrisk AML. N Engl J Med. 2016.374(5):422433.
- Short NJ, Zhou S, Fu C, et al. Association of measurable residual disease with survival outcomes in patients with acute myeloid leukemia a systematic review and metaanalysis. JAMA Oncol. 2020;6(12):18901899.
- Walter RM, Ofran Y Wierbowska A, et al. Measurable residual disease as a biomarker in acute myeloid leukemia theoretical and practical considerations. Leukemia. 2021;35(6):15291538.