

Points to consider for trials allowing inclusion of patients previously treated with an Advanced Therapy Medicinal Product (CAR-T cells, gene therapy, tumour vaccines)

Previous use of an Advanced Therapy Medicinal Product (ATMP) was a standard exclusion criterion for participation in a clinical trial.

However, despite previous ATMP administration some patients present with disease progression or relapse. With limited therapeutic options enrolment in a trial and therefore administration of a new Investigational Medicinal Product (IMP) could be justifiable.

This guidance provides points to consider when submitting a Clinical Trial Authorisation (CTA) application for a trial of an IMP administered after previous ATMP use.

1. Trial rationale

Patients who experienced relapse and/or disease progression and recovered from acute toxicity associated with previous ATMP administration may be amenable to new therapy. Standard of care treatment options should be identified and there should be a clear rationale why the IMP should be administered to the trial participants rather than any other available options. The absence of any therapeutic alternatives cannot be considered a sufficient rationale.

2. Trial population

The trial population should be carefully defined. The protocol should include exclusion criteria, which are specific to any previously administered ATMP. In the absence of information about the persistence and long-term safety of previous ATMPs the eligibility criteria should initially be conservative and modified subsequently only if accumulated data support a broadening of the trial population.

The trial protocol should clarify whether the diagnosis of disease progression or relapse will be based both on clinical presentation and exclusion of residual biological/immunological activity of the previous ATMP. In the absence of a test for residual biological activity the Sponsor should identify which measures will be utilised to mitigate any associated potential risks.

If the Sponsors propose inclusion of patients during the period of maximal pharmacodynamic activity of an ATMP a scientifically plausible rationale should be provided to support early treatment.

3. New IMP characteristics

The new IMP should be adequately characterised. A first in human trial of the new IMP should take into consideration the Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products (EMA/CHMP/SWP/28367/07 Rev. 1). If the new IMP is an ATMP, autologous cells can only be used for the manufacture of the new ATMP if they have not previously been genetically modified. The Sponsor should be able to assess the potency of the new IMP and monitor its biological activity. Any surrogate biomarker used for this purpose should be adequately validated.

4. Risk mitigation strategies

The Sponsor should discuss the potential drug interactions between the new IMP and any of the previously administered ATMPs in a particular trial and whether they are expected to be detrimental or beneficial. The overall impact on the immune system of the combinations of

the new IMP and the ATMPs should also be elucidated. Within the limits of the current information on long-term safety and efficacy, the potential risks/hazards of all ATMPs should be clearly identified as well as possible mitigation strategies such as assays for measuring residual biological activity, level of residual circulating CAR-T cells, careful dose selection and dose titration of the new IMP for example. Increased trial-specific monitoring is strongly recommended. Safety monitoring should always include not only assessments needed to minimise the risks associated with the new IMP, but also those necessary to monitor the safety profile of the previous ATMPs.

5. Careful benefit-risk assessment

The benefit-risk balance should be positive at a trial level and an individual level. As trial participants could have received different types of ATMP the Sponsor should clarify which sort of data e.g. data in the public domain, data from ATMP manufacturers will be used when assessing the individual benefit-risk and whether an independent committee will review those data.

6. Scientific validity of the trial

The Sponsor should discuss the scientific validity of the trial and how efficacy/safety parameters will be attributed to one product rather than to the other. The impact of the previous ATMP treatment on the trial endpoints should be acknowledged and discussed, taking into consideration whether the proposed trial design incorporates randomisation.

Enrolment of patients who represent small subpopulations within a specific disease (patients with high activity/risk disease who relapsed after previous ATMPs) and are highly heterogeneous in terms of previous treatment can negatively impact the validity of the trial and its ability to produce meaningful results.

Whenever possible all relevant data should be integrated and used to inform trial decisions. Consideration should be given to model-based designs and to methodology applicable to trials in small populations/rare diseases. The trial design should be chosen in order to maximise any information from a single patient.

7. Blood sample collection

Sponsors should collect blood samples before administering the new IMP and store them for future use such as for exploratory research, ex vivo T cell monitoring, potential biomarkers and other additional tests in case of safety issues.

8. Ethical issues

Registries should be set up in order to collect adequate data concerning trials investigating a new IMP after previous ATMP use. Pseudo-anonymised data is crucial for the successful creation and use of registries. Patient informed consent forms should include specific consent to use of trackable data for registry purposes. In paediatric trials patients should be re-consented when acquiring capacity.

Useful Resources

For ATMP definition: Regulation (EC) No 726/2004, Article 2 (1).

Example of administration of a new IMP after previous ATMP: Inotuzumab ozogamicin in pediatric patients with relapsed/refractory acute lymphoblastic leukemia (R/R ALL). Deepa Bhojwani, Richard Sposto, Nirali Shah, Vilmarie Rodriguez, Maureen Megan O'Brien, Jennifer Lynn McNeer, Mignon L. Loh, and Susan R. Rheingold. *Journal of Clinical Oncology* 2017 35:15_suppl, 10512-10512