From: JDELGADO@clinic.cat
Sent: 28 September 2018 10:59
To: SANTE PHARMACEUTICALS B5
Subject: RE: Guidelines on Good Clinical Practice for ATMP

Dear Sir/Madam,

First of all, thank you very much for giving us the opportunity to comment on these new and very important guidelines. Let me just begin by saying that at Hospital Clinic, Barcelona, we have been working on the development of our own chimeric antigen receptor (CAR) targeting CD19 since 2013 and, since 2017, we have been treating patients with CD19+ malignancies in the context of our first pilot clinical trial.

All in all, I believe that these guidelines are a very important and timely document, and I only have very minor comments:

1. Lines 184-186: These guidelines would allow for a ATMP release before the results of sterility tests are available. I guess the writers are thinking about ATMPs that are kept fresh and therefore any delay in their administration may result in a reduced efficacy. Some other products, such as CART cells, are cryopreserved and therefore a product release can wait until all results are available in most, if not all, cases. I think if would be reasonable to clarify that ATMP that are cryopreserved should be generally administered after all sterility tests are available. We are talking here about 7-14 days maximum, it is rarely the case that the patient requires the cell infusion with such immediacy.
2. Lines 215-229: I applaud the writers clarification on the role of pre-clinical (in vitro or in vivo) models in ATMP. It is very true that, for instance, murine xenograph models provide very little information regarding the toxic effect of CART cells in humans for obvious reasons. However, these very same murine models provide important information on efficacy and, on the other hand, several research groups have recently developed very advanced murine models that would be suitable for evaluating the cytokine release syndrome or even neurotoxicity. In summary, whilst difficult and not terribly informative, in vitro and in vivo models should not be completely omitted by investigators wishing to develop a new ATMP.
3. Lines 339-340: Retention of samples is important for many reasons. I would urge investigators to make every possible effort to keep samples of every ATMP produced and administered. Many ATMP are already cryopreserved so I don't see why this should be a problem.
4. Lines 379-383: Remote follow-up is not ideal, not for a more "conventional" drug, and less so for an ATMP. I believe that long-term follow-up visits (every six months, every year) are not that difficult, even across different countries. It is OK to allow for that possibility, but we should not encourage centers and patients to pursue it.
5. Lines 415-419: I agree that it would be "interesting" to know exactly which side effects are attributable to the ATMP and which side effects are attributable to other therapy elements (e.g. conditioning chemotherapy in the case of CART cells). However, this is actually quite difficult (e.g. a patient developing an infection after CART19 therapy. Both the conditioning chemotherapy and the ATMP increase the risk of infections). On the other hand, this does not make any difference to the physician or the patient, all side effects need to be taken care of regardless of their cause, and conditioning chemotherapy

is an important part of the treatment. It is not like it is “optional”. In summary, in my opinion all side effects are equally relevant and I don’t see why “SAE forms should be adapted to reflect a differential causality assessment for each of the ATMP components”.

And that’s it. Thanks again for allowing us to comment on this very important document.

Best wishes,

Julio

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