Author’s response to reviews

Title: Rationale and design of the German-Speaking Myeloma Multicenter Group (GMMG) trial HD6: A randomized phase III trial on the effect of elotuzumab in VRD induction/consolidation and lenalidomide maintenance in patients with newly diagnosed myeloma

Authors:

Hans Salwender (h.salwender@asklepios.com)
Uta Bertsch (Uta.Bertsch@med.uni-heidelberg.de)
Katja Weisel (katja.weisel@med.uni-tuebingen.de)
Jan Duerig (Jan.Duerig@uk-essen.de)
Christina Kunz (christina.kunz@dkfz-heidelberg.de)
Axel Benner (benner@dkfz.de)
Igor Blau (igor.blau@charite.de)
Marc Raab (marc.raab@med.uni-heidelberg.de)
Jens Hillengaß (jens.hillengass@med.uni-heidelberg.de)
Dirk Hose (dirk.hose@med.uni-heidelberg.de)
Stefanie Huhn (stefanie.huhn@med.uni-heidelberg.de)
Michael Hundemer (michael.hundemer@med.uni-heidelberg.de)
Mindaugas Andrulis (pathologie@klilu.de)
Anna Jauch (anna.jauch@med.uni-heidelberg.de)
Andrea Seidel-Glaetzer (Andrea.Seidel-Glaetzer@med.uni-heidelberg.de)
Hans Lindemann (w.lindemann@kkh-hagen.de)
Manfred Hensel (hensel@onkologische-praxis-mannheim.de)
Stefan Fronhoffs (sfronhoffs@zaho-rheinland.de)
Uwe Martens (uwe.martens@slk-kliniken.de)
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Author’s response to reviews:

Dear Dr. Gummlich,

First of all, I would like to thank the reviewers Dr. Holstein and Dr. Gonsalves for their kind and insightful review of our manuscript, and of course you for the opportunity to submit a revised version of our article “Rationale and design of the German-Speaking Myeloma Multicenter Group (GMMG) trial HD6: A randomized phase III trial on the effect of elotuzumab in VRD induction/consolidation and lenalidomide maintenance in patients with newly diagnosed myeloma”.

Listed below please find our responses to the reviewer’s comments detailed below:

1. Given the increasing interest in the potential role of MRD negativity as a surrogate endpoint, the authors should specify at what time points MRD analysis will be performed.

We thank Dr. Holstein for this comment. On page 8, Section Response Assessment, Line 4, we added:

“According to the trial protocol, in case of a suspected CR based on routine testing at any time during therapy, a bone marrow puncture is performed to confirm the response. At the same time, MRD-analysis is performed. If CR is confirmed MRD assessment is repeated once after 6 months.”
2. A personal communication from an investigator from 5 years ago is not sufficient to support a statement that no major serious toxicity has been observed in the SWOG study (ref 19) which has also evaluated Elo-VRD. Either delete this reference and statement or provide more recent data.

We completely agree with the reviewer and exchanged the respective quotation, see also comment #3.

3. The authors fail to reference the presentation by Laubach et al from ASCO 2017 in which the initial results of a phase IIa study evaluating Elo-VRD were reported. In particular, there were two deaths in this study.

We apologize for this mistake and included the mentioned abstract, see page 3, Section Background, Line 44

“The combination of VRD plus elotuzumab is investigated by the Southwest Oncology Group in the US in a phase I/II trial for newly diagnosed high risk myeloma patients.[18] Another phase IIa study investigating the VRD plus elotuzumab combination in patients eligible for HDT and ASCT showed a low incidence of high grade toxicities, although there were two deaths in the study group.[19]”

4. Many of the references are outdated—the authors cite abstracts from meetings which are now published (e.g., refs 13, 20, 34, 35)

Pls. see, page 12-13

We thank for this comment and updated references 1, 13, 20, 34, and 35.

5. Are patients undergoing 1 or 2 transplants?

We thank the reviewer for this comment and clarified on Page 7, Section Trial Treatment, Line 11:

“GMMG standard is a single HDT and ASCT for patients who reach at least a nCR and tandem HDT and ASCT for patients who do not reach nCR. Although the details of stem cell collection, HDT and ASCT are not specified in the study protocol.”
6. The authors should address the rationale for 2 years of maintenance therapy as opposed to treatment until progression.

Page 7, Section Trial Treatment, Line 27

“A two years maintenance therapy timeframe was chosen to define a clear endpoint for the trial as required by the German authorities. Benefits of prolonged maintenance therapy beyond 2 years had not been shown in trials at the time of submission of this study protocol. Nonetheless, after the end of the study, all patients not encountering disease progression or unacceptable toxicity are suggested continuing lenalidomide maintenance treatment.”

7. The authors should address other ongoing studies in this space incorporating anti CD38 antibody therapy.

Page 10, Section Discussion, Line 12

“In addition to testing the anti-SLAMF7 antibody Elotuzumab in upfront induction and maintenance treatment of transplant-eligible patients, the CD38 targeting antibodies Daratumumab and Isatuximab are currently tested in ongoing trials, e.g. by the Intergroupe Francophone du Myélome (IFM) (Cassiopeia, NCT02541383).”

With many thanks and kind regards

Hans Salwender