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

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1. We note that the current submission still contains some textual overlap with other previously published works, in particular:


This overlap mainly exists in the Methods sections, particularly in the ‘Screening’ and ‘Study visits’ subsections.

Our response: The study protocol of the “Relapse study” and the “HD 6 study” were developed by the same study group. Therefore some contextual overlap regarding the diagnostic investigations have to be expected. Although we believe the changes regarding the phrasing in the last revision differs significantly enough to distinguish the two texts. In the “Study Visits” section we cannot find an overlap regarding the context or phrasing of the “HD 6 study” protocol paper and the “Relapse study” publication. Please find attached to this letter our comparison regarding the ‘Screening’ and ‘Study visits’ subsections.

With Kind regards

Hans Salwender
Screening

Paper HD 6 study last revision 06.03.2019

Screening

All patients have to undergo physical examination including assessment of WHO performance score, body weight, body height and concomitant diseases.

Before the inclusion into the trial for a patient is possible, the following laboratory investigations are necessary: C reactive protein, lactate dehydrogenase, β-2 microglobulin, albumin, total protein, pregnancy test (only for woman in childbearing age), immunoglobulins, monoclonal protein and free light chains in serum, monoclonal protein in urine, immunofixation in serum, immunofixation in urine, complete blood count including Absolute Neutrophil Count (ANC), electrolytes, renal parameters, hepatic parameters, thyroid stimulating hormone. A bone marrow puncture has to be performed for bone marrow aspiration (cytology, iFISH) and bone marrow histology.

For the documentation of the skeletal status medical imaging with low dose, whole body computed tomography or conventional X-ray imaging is required.

An ECG and an echocardiogram have to be performed prior to study inclusion to document the cardiac condition of the patient.

Paper HD 6 study submission 19.02.2019

Screening

The following diagnostic investigations have to be performed at screening to determine patient eligibility for study participation and to assess disease status before study treatment: patient history and physical examination (including body weight, height, WHO performance score (PS), and concomitant diseases), laboratory investigations (complete blood count including absolute neutrophil count (ANC), electrolytes, renal parameters, hepatic parameters, thyroid stimulating hormone, C reactive protein, lactate dehydrogenase, albumin, total protein, pregnancy test if applicable, β-2 microglobulin, immunoglobulins, monoclonal protein and free light chains in serum, monoclonal protein in urine, immunofixation in serum and urine), bone marrow aspiration (cytology, iFISH), bone marrow histology, radiographic imaging of the skeleton (low dose, whole body computed tomography (CT) or conventional X-ray imaging), electrocardiogram (ECG) and echocardiogram.
Relapse study protocol publication in BMC Cancer

Screening

The following diagnostic investigations are performed at screening to determine patient eligibility for study participation and to assess disease status before study treatment: patient history and physical examination (including body weight, height, WHO performance score (PS), and concomitant diseases), laboratory investigations (complete blood count including absolute neutrophil count (ANC), electrolytes, renal parameters, hepatic parameters, thyroid stimulating hormone, C reactive protein, lactate dehydrogenase, albumin, total protein, pregnancy test if applicable, β-2 microglobulin, immuno- globulins, monoclonal protein and free light chains in serum, monoclonal protein in urine, immunofixation in serum and urine), bone marrow aspiration (cytology, interphase fluorescence in situ hybridization (iFISH) in CD138-purified plasma cells as described previously [50]) radiographic imaging of the skeleton (low dose, whole body computed tomography (CT) or conventional X-ray imaging; appropriate imaging for disease quantification in case of non-secretory myeloma), electrocardiogram (ECG) and echocardiogram (exercise ECG if clinically indicated).

Study visits

Paper HD 6 last revision 06.03.2019

Study visits

Monitoring will be done by personal visits from a clinical monitor according to SOPs of the coordination centers for clinical trials (KKS).

The monitor will review the entries into the CRFs on the basis of source documents (source data verification). The investigator must allow the monitor to verify all essential documents and must provide support at all times to the monitor.

By frequent communications (letters, telephone, fax), the site monitor will ensure that the trial is conducted according to the protocol and regulatory requirements.

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Relapse study protocol publication in BMC Cancer

Study visits

Study visits are scheduled at the respective study site after the initial 3 Rd cycles, after Rd cycle 5 (arm A) or 2 months after HDCT/ASCT (arm B), every three months thereafter and at the end of study participation. Diagnostic investigations performed at these visits for assessment of efficacy and safety, as well as patient eligibility to continue study treatment include: patient history and physical examination (including AEs, WHO PS, signs of thrombosis, assessment of soft tissue plasmacytomas), laboratory investigations (listed in Screening), bone marrow aspiration (only if CR or PD are suspected), radiographic imaging of the skeleton (if clinically indicated or at least once a year; more frequently for response assessment in non-secretory MM), and ECG and echocardiography (after the initial 3 Rd cycles, before HDCT and if clinically indicated). Additionally, complete blood counts including ANC are determined weekly during Rd cycles 1 and 2 and every 2 to 4 weeks thereafter for safety reasons. During HDCT/ASCT safety investigations are performed according to study site standards.