MultipleMyelomaHub

ASH 2018

Practice changing abstracts

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Newly Diagnosed

#301: Maintenance Therapy with the Oral Proteasome Inhibitor (PI) Ixazomib Significantly Prolongs Progression-Free Survival (PFS) Following Autologous Stem Cell Transplantation (ASCT) in Patients with Newly Diagnosed Multiple Myeloma (NDMM): Phase 3 **Tourmaline-MM3 Trial**

Comments from Philippe Moreau

- This study is the first evaluating ixazomib maintenance after ASCT. The primary endpoint was PFS. Ixazomib, the only oral PI available, was administered on Day 1, 8, and 15 in 28-day cycles during 2 years, *versus* placebo.
- All patients received frontline single ASCT and disease response was at least partial response at the time of 3:2 randomization. 656 patients were randomized; 395 in the ixazomib arm and 261 in the placebo arm.
- The study met its primary endpoint, with a median PFS from randomization of 26.5 months with ixazomib *versus* 21.3 months in the placebo arm (HR 0.72, CI: 0.58–0.89).
- Almost all subgroups of patients benefited from ixazomib maintenance, including patients with high-risk cytogenetics.
- Ixazomib maintenance was associated with low toxicity. Survival data are not mature.
- Overall, this study is important showing that ixazomib maintenance is feasible and improves PFS.
- We were expecting a stronger benefit.

Link: http://www.multiplemyelomahub.com/medical-information/ash-2018-ixazomib-maintenance-for-patients-with-newly-diagnosed-multiple-myeloma-results-from-the-tourmaline-mm3-trial

Newly Diagnosed

#126: VTD (Bortezomib/Thalidomide/Dexamethasone) As Pretransplant Induction Therapy for Multiple Myeloma: Definitive Results of a Randomized Phase 3 **Pethema/GEM Study**

Comments from Maria Victoria Mateos

This abstract shows how the introduction of induction with three drug-based combinations including proteasome inhibitors, immunomodulatory drugs and dexamethasone, like VTD, maintaining the autologous stem cell transplantation and following with maintenance with either interferon, VT or T make it possible that one out of four newly diagnosed multiple myeloma (NDMM) patients remain alive and free of progression at 10 years and more than 50% of patients remain alive at 10 years.

This is a general and key message for young NDMM patients but, in addition, the evaluation of undetectable minimal residual disease (MRD) allows us also to give two key messages:

1) Undetectable MRD is a surrogate marker predicting progression-free survival and overall survival
2) In patients with high-risk cytogenetic abnormalities, the achievement of undetectable MRD can overcome the poor prognosis associated with their presence

Link: http://www.multiplemyelomahub.com/medical-information/long-term-follow-up-of-the-gem05menos65-clinical-trial-for-newly-diagnosed-multiple-myeloma

Transplant Ineligible

#156: One-Year Update of a Phase 3 Randomized Study of Daratumumab Plus Bortezomib, Melphalan, and Prednisone (D-VMP) *Versus* Bortezomib, Melphalan, and Prednisone (VMP) in Patients with Transplant-Ineligible Newly Diagnosed Multiple Myeloma (NDMM): **Alcyone**

Comments from Shaji Kumar

Given the significant clinical activity seen with the anti-CD38 monoclonal antibody daratumumab in the setting of relapsed disease in various combinations, it is logical to explore the activity and tolerability of this agent in combination with standard regimens used for initial therapy of MM. The Alcyone study showed a significant improvement in progression free survival (PFS) with the addition of daratumumab to the standard combination of VMP in patients who are not transplant eligible. The updated results of the phase 3 clinical trial once again confirms the benefit of adding the monoclonal antibody to the standard VMP regimen. It shows continued improvement in PFS among patients receiving the monoclonal antibody. Most importantly it demonstrates an improved PFS2 (time from randomization to progression on the next line of subsequent treatment or death) for these patients suggesting that this will likely translate to an improved overall survival with longer follow-up. Importantly, there are no long-term safety signals with the continued administration of the monoclonal antibody and no collective hematological toxicity has been observed. The benefit of the four drug combination is seen in all patient groups irrespective of age, performance status, renal function or ISS staging. However, as seen with other trials, patients with high-risk disease do not appear to derive significant benefit. With longer follow-up, improvements in depth of response continue to be observed as indicated by the minimal residual disease negativity status. The results do make a strong argument for routine incorporation of a monoclonal antibody as part of the operant strategy in patients with MM who are not eligible to undergo high-dose therapy.

Link: https://ash.confex.com/ash/2018/webprogram/Paper113183.html

Transplant Ineligible

#LBA-2: Phase 3 Randomized Study of Daratumumab Plus Lenalidomide and Dexamethasone (D-Rd) Versus Lenalidomide and Dexamethasone (Rd) in Patients with Newly Diagnosed Multiple Myeloma (NDMM) Ineligible for Transplant (**MAIA**)

Comments from Shaji Kumar

The current standard of care for patients with newly diagnosed myeloma remains the combination of a proteasome inhibitor (PI) and immunomodulatory drug. However, given the significant activity seen with monoclonal antibodies the important question is, what role can this drug play for initial therapy of MM? Incorporation of another class of drug into the upfront setting can be done in one of two ways: either adding it to one of the three drug regimens currently used or replacing one of the drugs from the current three-drug combinations. The MAIA trial explores the latter concept while the former is currently being evaluated in other phase 3 trials.

This trial examined the efficacy of daratumumab added to lenalidomide and dexamethasone, comparing it to a current standard of lenalidomide-dexamethasone in patients who are not eligible to undergo autologous stem cell transplantation. The trial clearly demonstrated a significant improvement in the progression free survival (PFS) with a hazard ratio of 0.39 in favor of the three-drug combination. While it appears to be obvious that a three-drug combination would do better than the two-drug combination in terms of PFS, the magnitude of improvement such as this will likely translate into overall survival improvement with longer follow-up. A deep response was seen with daratumumab combination as indicated by the higher rate of minimal residual disease negativity in the three-drug group. In the longer term, this again is likely to contribute to improved survival outcomes. Disappointingly, the high-risk group did not seem to derive as much benefit from this combination as we have seen in the context of a PI-containing combination. However the data clearly supports incorporation of this combination into the upfront therapy of standard risk, transplant ineligible patients once it is approved by the regulatory authorities.

Link: http://www.multiplemyelomahub.com/medical-information/daratumumab-triplet-regimen-as-a-frontline-treatment-for-multiple-myeloma-patients-non-eligible-for-asct-interim-results-of-the-maia-trial

Relapsed/Refractory

#598: Results of the Pivotal **STORM Study (Part 2)** in Penta-Refractory Multiple Myeloma (MM): Deep and Durable Responses with Oral Selinexor Plus Low Dose Dexamethasone in Patients with Penta Exposed and Triple Class-Refractory MM

Comments from Paul Richardson:

- XPO1 transports over 200 proteins from the nucleus to the cytoplasm and its overexpression in MM is associated with shorter survival and increased bone disease.
- Selinexor is a first-in-class oral agent which inhibits XPO1 through reversible covalent modification resulting in the retention/activation of tumor suppressor proteins as well as glucocorticoid receptors, and a reduction of oncoproteins through nuclear retention of their mRNAs.
- This therefore constitutes a unique mechanism of action in this setting and in a very heavily pre-treated, triple class and penta-refractory patient population evaluated in the context of a large multi-center phase 2 study.
- Therapy with selinexor plus dexamethasone achieved an overall response rate of 26.2%, including 2 patients with stringent complete responses who were both minimal residual disease (MRD) negative as well as 2 patients with progression after chimeric antigen receptor T-cell therapy (CAR-T) who achieved a partial response.
- Median duration of response was 4.4 months with a ≥ minimal response (MR) rate of 39.3% and ≥ stable disease in 78.7%. Median overall survival was 8.6 months, with 15.6 month median survival seen in patients who achieved ≥MR *versus* 1.7 months in patients with progressive disease.
- Toxicity was important and predominantly included gastrointestinal toxicity and fatigue as well as thrombocytopenia but proved manageable with dose modification, weekly administration and supportive care.
- Encouragingly, combination studies with selinexor are also showing promise and better tolerability.

Link: https://ash.confex.com/ash/2018/webprogram/Paper116663.html

Relapsed/Refractory

#600 OP-106: Horizon - Melflufen Therapy for RRMM Patients Refractory to Daratumumab and/or Pomalidomide; Updated Results and First Report on PFS

Comments from Enrique Ocio:

- Melflufen is a novel alkylator composed by melfalan with a lipophilic radical that makes it inactive and favors its entrance inside the cells. Once inside, aminopeptidases (enzymes overexpressed on tumor cells), cleave the lipophilic radical, releasing the active and hydrophilic melphalan, that is therefore kept at high concentrations inside the tumor cells.
- In this particular trial, relapsed/refractory multiple myeloma (RRMM) patients, having received two or more prior lines of therapy including an immunomodulatory drug (IMiD) and proteasome inhibitor (PI) and refractory to pomalidomide and/or daratumumab, were treated with melflufen in combination with dexamethasone.
- Thirty-eight patients were treated with a median of 6 (3–1) prior lines; 57% of them were previously alkylator refractory and 96% and 62% were refractory to pomalidomide and daratumumab + pomalidomide, respectively.
- 27% of patients achieved a response (2 very good partial response [VGPR] and 6 PR), which is quite compelling in this refractory population. Responses were quite durable, such as that of a very heavily pretreated patients with bad performance status after 11 prior lines of therapy including an allogeneic transplantation that achieved a VGPR that lasted for several months with an amazing clinical response.
- Regarding toxicity, overall it is well tolerated with the main toxicity being hematological: Grade 3/4 treatment-related adverse events: thrombocytopenia 45%, neutropenia: 39% and anemia 21%.

Link: https://ash.confex.com/ash/2018/webprogram/Paper113095.html