Title

P-053: A systematic review of measurable residual disease (MRD) assessment characteristics in myeloma trials from 2015-2020

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Introduction: There are promising yet scarce data on the value of MRD assessment during continuous or fixed-duration maintenance. By contrast, there are minimal data on MRD status during observation. Paradoxically, maintenance and observation are the settings where MRD status is anticipated to help tailor treatment duration. We investigated the prognostic value of MRD dynamics over time in patients (pts) with NDMM receiving ixazomib or placebo maintenance. **Methods:** Pts were randomized 3:2 to receive maintenance with ixazomib vs placebo for up to 2 years (26 cycles). Bone marrow aspirates were collected from all pts in complete response (CR; and/or very good partial response in TOURMALINE-MM3 only) at randomization, cycle 13, and end of treatment. MRD status, assessed by 8-color flow cytometry with a median limit of detection of 7.4x10-6, was available at randomization in 1280 pts. Pts with < CR who were missing MRD data were imputed as MRD+. Progression-free survival (PFS) was analyzed based on MRD dynamics over time, landmarked at 14 and 28 months. **Results:** MRD status at randomization was an independent prognostic factor for PFS, with a median of 38.6 vs 15.6 months in MRD– vs MRD+ pts (hazard ratio [HR] 0.47). The prolonged PFS observed with MRD– vs MRD+ status was consistent in nearly all pt subgroups. Paired assessments of MRD status at randomization and during maintenance were evaluable in 1166 pts. The 14-month landmark analysis demonstrated prolonged PFS in pts converting from MRD+ to MRD– status (n=58) vs those with persistent MRD+ status (n=365), with 2-year PFS rates of 76.8% vs 27.6%. PFS was also prolonged in pts with sustained MRD– status (n=114) vs those converting from MRD– to MRD+ status (n=50), with 2-year PFS rates of 75.0% vs 34.2%. There was an increased risk of progression and/or death in pts who had converted from MRD– to MRD+ status vs those with sustained undetectable MRD (HR 3.31; p< 0.001), and in pts with persistent MRD+ vs those who had converted from MRD+ to MRD– status (HR 3.72; p< 0.001). Similar results were noted in the 28-month landmark analysis. Ixazomib maintenance improved PFS vs placebo in pts who were MRD+ at randomization (median 18.8 vs 11.6 months; HR 0.65; p< 0.001) and at the 14-month landmark (median 16.8 vs 10.6 months; HR 0.65; p=0.003); no difference was observed in pts who were MRD–. **Conclusions:** This is the largest multiple myeloma dataset ever reported evaluating yearly MRD status during maintenance. Four main conclusions emerged from this study: 1) MRD status is dynamic, and its prognostic value increased considerably with periodic vs single assessment; 2) the favorable prognosis of undetectable MRD was similar if achieved before or during maintenance, and thus it can become a relevant endpoint in this setting; 3) loss of MRD– status vs sustained MRD– status markedly increases the risk of progression; and 4) treatment with ixazomib vs placebo improves the PFS in pts who were MRD+ at randomization or at the 14-month landmark in these studies.

P-053

A systematic review of measurable residual disease (MRD) assessment characteristics in myeloma trials from 2015-2020

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Introduction: Implementation of effective treatment combinations in multiple myeloma (MM) has led to increased response rates and improved survival over the last years. As survival of patients with newly diagnosed MM (NDMM) has improved, there is a need for prolonged follow-up to evaluate for progression free or overall survival benefit. Achievement of measurable residual disease (MRD) negativity is prognostic for progression free survival and has been suggested as a surrogate endpoint for drug approval. However, the landscape of MRD assessment in MM clinical trials has not been comprehensively assessed to date. **Methods:** Here, we examined the use of MRD in 607 interventional MM trials from 2015 through 2020, utilizing data from clinicaltrials.gov. For studies that included MRD assessment in the database, an additional manual online search strategy was employed to identify published trials and publicly available trial protocols at time of writing. **Results:** Of the 147 trials that contained MRD assessment (24.2% of all trials), 15 included MRD as part of the inclusion criteria, 36 (24.4%) as a primary endpoint, and 92 (62.6%) as a secondary endpoint. Nine

trials (6.1%) employed MRD as a stratification tool to determine treatment. A total of 77 trials (52.4%) specified methodology of MRD assessment (i.e., flow cytometry versus sequencing). Among the 77 studies that did report method of MRD assessment, 29/77 (19.7%) used flow cytometry, and 37/77 (25.2%) NGS. A total of 36 trials (24.5%) specified sensitivity of MRD testing, which ranged from 1/104 to 1/106 cells. Of the 147 trials, 80 (54.4%) had reported results at the time of writing (54 abstracts and 26 peer-reviewed articles), of which 60 (75%) mentioned MRD assessment. For the studies that did not specify method/sensitivity on clinicaltrials.gov, published data provided clarification on the method (19/35, 54.2%) or sensitivity (23/54, 42.6%). Studies with MRD assessment were more likely to be Phase 2 (Ph2) (49.7% vs 31.1%, p< 0.001) or Ph3 (22.4% vs 7.0%, p< 001) and less likely to be Ph1 (12.9% vs 36.5%, p< 0.001). Studies that assessed MRD were more likely aimed at NDMM (32.7% vs 14.8%, p< 0.001) or to involve maintenance therapy (10.9% vs 5.2%, p=0.02) and were more likely randomized (37.4% vs 22.4%, p< 0.001). There was an upward trend in the proportion of trials utilizing MRD assessment from 13.0% in 2015 to 29.3% in 2020. **Conclusions:** In conclusion, use of MRD as an endpoint of clinical trials in MM has increased between 2015 and 2020 and was present in 24.2% of studies overall. Recent trials have begun to incorporate MRD in decision making, with the prospect of treatment individualization. However, there was significant heterogeneity in MRD assessment, including methodology, assay sensitivity, and reporting of results. Although efforts have been made to standardize this, the current landscape of trials limits the use of MRD in clinic beyond prognostic assessment.

P-054

Neoplastic plasma cells in stem cell collection have no effect on the survival of multiple myeloma patients receiving autologous stem cell transplantation

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Introduction: Autologous stem-cell transplantation (ASCT) is considered as the standard of care for transplant-eligible multiple myeloma patients (TEMM), but no randomized trials have assessed the optimal number of induction cycles or the ideal depth of response required before ASCT. Whether it can lead to the presence of tumor cells in stem cell collection (SCC) without complete response (CR) before ASCT and impose negative impact on survival is being debated. Here we evaluated the effect of the minimal residual disease (MRD) of SCC on TEMM. **Methods:** We analyzed clinical data of 90 MM patients undergoing ASCT between January 1, 2013 to June 1, 2021 in our hospital. MRD evaluation of both BM and SCC were carried out at the same time before ASCT. Response assessment was defined according to International Myeloma Working Group criteria. MRD was evaluated by multiparameter flow cytometry (MFC) with 10-5 sensitivity. Time from ASCT to disease progression was defined as modified progression-free survival (mPFS) and time from ASCT to death as modified overall survival (mOS). **Results:** Ninety patients met the inclusion criteria. The median age was 54 and 62.2% were males. 25 had high-risk cytogenetic abnormalities determined by FISH with the presence of at least one of t (4;14), t (14;16) or del (17p). Before ASCT, the percentages of MRD negativity in BM and SCC were 31.1% and 76.7%. By comparing the MRD-positivity status with different sensitivity and numeric levels of tumor cells, we found the percentage of patients with MRD-positivity in SCC was much less than that in BM, regardless of sensitivity (P < 0.001). The median follow-up was 26.8 months. The achievement of negative MRD in BM before ASCT was associated with longer mPFS (P=0.0094, 55.88m vs 34.17m) but not mOS (P=0.11, NR vs. 58.86m). Patients with different MRD status in SCC experienced the similar mPFS (P=0.937, 40.54m vs. 76.45m for negativity vs. positivity) and mOS (P=0.884, NR vs. 58.86m for negativity vs. positivity). Patients were divided into 3 groups according to MRD status, namely MRD negativity in BM and SCC (Group A, 32.3%), MRD positivity in BM and SCC (Group B, 23.3%) and MRD positivity in BM but negativity in SCC (Group C, 44.4%). Patients in Group A had better mPFS (P=0.047, median mPFS, 55.88m vs. 34.17m vs. 27.11m, for Group A, B, C), but mOS (P=0.53, median mOS, NR vs. 58.88m vs. 58.61m for Group A, B, C) showed no statistical difference. In patients achieving CR for best response, the presence of MRD negativity predicted longer survival compared with MRD positive CR and VGPR or less in mPFS (P < 0.0001, median mPFS, 55.88m vs. 24.74m vs. 27.10m) and mOS (P=0.0064, median mOS, NR vs. NR vs. 41.65m). **Conclusions:** We discovered little association between MRD status in SCC before ASCT and survival prognosis in MM patients. It is reasonable to carry out ASCT when TEMM patients achieve PR. MRD negativity after ASCT can be a more valuable predictor of outcome compared with other prognostic factors for MM.

P-055

Monitoring the emergence of multiple myeloma high-risk subclones with whole-genome sequencing of circulating tumor cells

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