classified as having sustained undetectable MRD (n = 88; MRD– to MRD–), conversion from MRD+ to MRD– (n = 41) or from MRD– to MRD+ (n = 88), or persistent MRD (n = 365; MRD+ to MRD+). Median PFS was not reached in patients converting from MRD+ to MRD– and in patients with sustained undetectable MRD (Figure), supporting undetectable MRD as a treatment endpoint in this setting. PFS was prolonged with ixazomib vs placebo in patients converting from MRD+ to MRD– (HR 0.104; p = 0.01). PFS was dismal and similar in patients converting from MRD– to MRD+ and in those with persistent MRD throughout maintenance (median PFS of 22.3 and 20.2 months, respectively, Figure), although PFS was prolonged with ixazomib vs placebo in the latter group (HR 0.745, p = 0.02). These results suggest the need for additional/alternative treatment strategies in patients with post-transplant persistent MRD, and for periodic monitoring of MRD status during maintenance to uncover possible MRD reappearance before clinical relapse. Accordingly, failure to achieve or maintain MRD– status resulted in a > 8-fold increased risk of progression and/or death (HR 8.44; 95% CI, 5.3–13.4; p < 0.001). Patient- and treatment-related factors associated with evolving MRD kinetics during maintenance are also being analyzed and will be reported.

Summary/Conclusion: This is one of the largest studies with longitudinal MRD assessment in the maintenance setting. Our analyses of data from the randomized phase 3 TOURMALINE-MM3 study confirm the dismal PFS of patients with reappearing or persistent MRD while demonstrating the clinical benefit of ixazomib maintenance in this setting. Overall, this study supports undetectable MRD as an endpoint of maintenance therapy, and underpins the importance of periodic MRD assessment for guiding the intensity and duration of treatment.

EP933 A NEW RISK STRATIFICATION STRATEGY IN NEWLY DIAGNOSED MULTIPLE MYELOMA: AN ANALYSIS ON MATURE DATA FROM EUROPEAN CLINICAL TRIALS WITHIN THE HARMONY BIG DATA PLATFORM

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Background: The Revised-ISS (R-ISS) is a risk stratification model for newly diagnosed (ND) multiple myeloma (MM) integrating International Staging System (ISS), high risk chromosomal abnormalities [del(17), t(4;14) or t(14;16)] and LDH. Yet, 60% of patients (pts) are considered as intermediate-risk (R-ISS2), possibly including pts with different risk of progression/death. We previously showed that t(14;16) was not an independent predictor of survival within the R-ISS and we identified other features currently not included in the R-ISS [amp(1q), IgA isotype, impaired renal function, poor performance status] predicting a worse OS (D'Agostino et al. ASH 2019).

Aims: Our aim was to develop an improved prognostic scoring system for NDMM.

Methods: Data from 14 European clinical trials enrolling NDMM pts were collected through the European Myeloma Network and registered in HARMONY platform, a European public-private partnership focusing on hematologic malignancies with unmet medical needs. OMOP Common Data Model was used to harmonize data. All pts received an immunomodulatory agent (IMiD) and/or a proteasome inhibitor (PI) upfront. In a multivariate Cox regression analysis adjusted for age, sex and therapy, the impact of each risk feature on pts' survival was evaluated. The hazard ratio for death of each variable was used to create an additive risk score.

Results: 1258 pts had complete data on the analyzed risk features and were included in the analysis. Median follow-up was 72 months; median age was 62 years. The majority of pts were transplant-eligible (71%). 40% received IMiDs only, 19% PIs only, 41% both drug classes.

In a multivariate Cox model, ISS2 (HR 1.72, p < 0.001), ISS3 (HR 2.14, p < 0.001), del(17p) (HR 1.77, p < 0.001), t(4;14) (HR 1.52, p < 0.001), amp(1q) (HR 1.48, p < 0.001), high LDH (HR 1.52, p < 0.001) and poor performance status (ECOG > 1 or Karnofsky < 80, HR 1.63, p < 0.001) confirmed to be independent OS predictors, while IgA isotype (HR 1.03, p = 0.77) and impaired renal function (creatinine clearance ≤45 ml/min, HR 1.21, p = 0.11) did not.

Among these, we selected only disease-related factors and exploited their impact on OS to create a scoring system (Table 1).

Pts were stratified into 4 groups with significantly different OS (Figure 1A) and PFS (Figure 1B): Low [(n = 232 (18.4%), score 0)], Low-Intermediate [(n = 384 (30.5%), score 0.5-1], Intermediate-High [(n = 525 (41.7%), score 1.5-2.5] and High [(n = 117 (9.3%), score 3-5].

Median OS was not reached vs 91.7 vs 63.8 vs 32.2 months and median PFS was 62.5 vs 38.7 vs 27 vs 18.2 months in the above 4 risk groups, respectively. R-ISS2 pts (n = 770) were reclassified into Low-intermediate (n = 289), Intermediate-High (n = 456) and High risk (n = 25) groups, thus confirming that this wide group included pts with a different risk of progression and/or death.

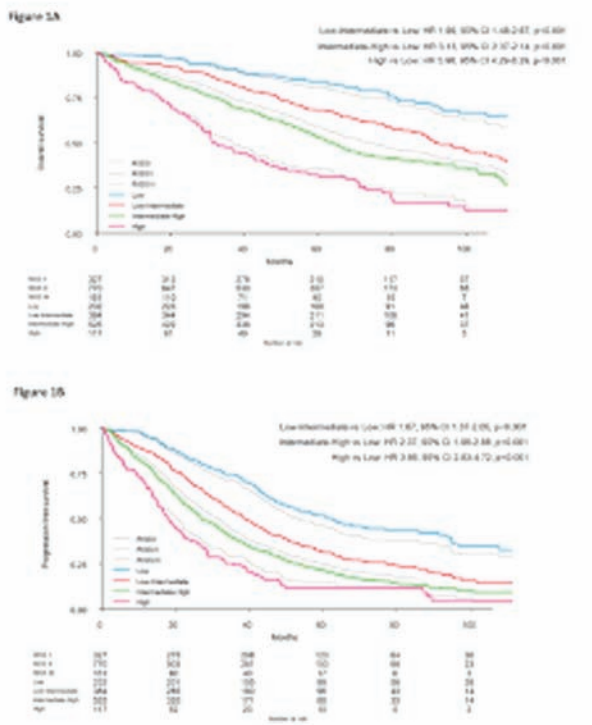
Table 1. Score calculation and stratification into 4 risk groups according to the total additive score.

Risk feature	OS Hazard ratio*	PFS Hazard ratio*	Score value**
ISS2	1.72 (1.40-2.11)	1.54 (1.32-1.80)	1
ISS3	2.14 (1.68-2.74)	1.64 (1.35-1.99)	1.5
Del(17p)	1.77 (1.42-2.21)	1.44 (1.19-1.74)	1
t(4;14)	1.52 (1.21-1.91)	1.53 (1.27-1.86)	1
Amp(1q)	1.48 (1.25-1.75)	1.39 (1.22-1.60)	0.5
High LDH	1.52 (1.23-1.86)	1.32 (1.11-1.56)	1

Group	Number of patients (%)	Total additive score
Low	232 (18.4%)	0
Low-Intermediate	384 (30.5%)	0.5-1
Intermediate-High	525 (41.7%)	1.5-2.5
High	117 (9.3%)	3-5

*Cox Model adjusted for Age, Sex, Creatinine Clearance, Isotype, Performance status and therapy.
**calculated on OS, value rounded at the nearest 0.5

Figure 1. OS (A) and PFS (B) according to the newly defined risk groups. In Grey the outcome of the same cohort of pts stratified by R-ISS is shown.



The new risk stratification maintained its prognostic value in transplant-eligible, transplant-ineligible, IMiD-treated and PI-treated pts.

The survival disadvantage of Low-Intermediate vs Low risk pts was overcome in pts treated with a first-line therapy including a PI and an IMiD (HR 1.21, p = 0.513), while High-intermediate and High risk group still showed a dismal survival.

Summary/Conclusion: Our new scoring system improves risk stratification in NDMM, representing a possible first step towards a risk-adapted approach. Such additive risk score easily allows the inclusion of new

prognostic variables in the future. Validation in an independent cohort is ongoing.

EP934 A PHASE 2 STUDY OF BELANTAMAB MAFODOTIN (GSK2857916) IN COMBINATION WITH POMALIDOMIDE AND DEXAMETHASONE IN RELAPSED/REFRACTORY MULTIPLE MYELOMA (RRMM): RESULTS FOR PART 1 DOSE FINDING

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Background: Belantamab mafodotin (belamaf), a first-in-class immunoconjugate targeting B-cell maturation antigen, showed clinically meaningful activity with a manageable safety profile in patients (pts) with RRMM. Pomalidomide (POM) is an immunomodulatory drug (IMiD), that can enhance T cell and natural killer cell-mediated immunity. The ability of IMiDS to enhance immune responses including ADCC forms the basis for combining belamaf with POM and dexamethasone (DEX).
Aims: A phase 1, 2 part multicenter, dose-escalation study is evaluating the MTD, recommended phase 2 dose (RP2D), safety, tolerability and efficacy of belamaf in combination with POM and DEX in pts with RRMM.
Methods: Eligible pts have received > 2 prior lines of treatment and failed treatment with lenalidomide (LEN) and/or a proteasome inhibitor (PI) and progressed on or within 60 days of last MM therapy. POM is administered at 4 mg days 1-21, DEX 40 mg (20 mg age > 75 years) weekly in conjunction with belamaf, 1.92 or 2.5 mg/kg IV, day 1, belamaf 2.5 mg/kg loading dosed on cycle 1 day 1 followed by 1.92 mg/kg day 1 of subsequent cycles or belamaf, 1.25 or 1.7 mg/kg IV on days 1 and 8, of Q4W dosing schedule. Dose escalation was accomplished using standard 3+3 dose escalation design. To acquire additional safety and tolerability data and to better inform the RP2D for the Part 2 expansion cohort, up to 12 pts could be enrolled at dose levels not exceeding the MTD.
Results: As of Feb 1, 2020, 24 pts have enrolled and completed the 28-day DLT observation period. Pts were enrolled at the following dose levels/schedules: 1.92 mg/kg Q4W (n = 11), 2.5 mg/kg Q4W (n = 7), 1.25 mg/kg D1/D8 Q4W (n = 3), 1.7 mg/kg D1/D8 Q4W (n = 3). Median age was 62.5 years (range 36-78), median number of prior regimens was 3.0 (range 2-5). Prior therapies included stem cell transplant (58.3%), PI (100%, 83.3% refractory), LEN (100%, 87.5% refractory), daratumumab (DARA) (37.5%, 37.5% refractory). 75% of pts were refractory to LEN and a PI and 33% were refractory to LEN, PI and DARA. Of 12 pts with available cytogenetics, 5 (41.7%) were high risk, defined as del17p13, t(4;14) or t(14;16). Overall, 22 pts (91.7%) experienced adverse events (AEs). The most frequent treatment emergent AEs (TEAEs) (> 25%) were keratopathy (62.5%) leading to decreased visual acuity (45.8%) and blurred vision (29.2%). Other commonly reported AEs were thrombocytopenia (50%), neutropenia (50%), fatigue (41.7), fever (33.3%), glaucoma (29.2%), diarrhea (29.2%), constipation (25%), dyspnea (25%) and rash (25%). Gr 3/4 TEAEs reported in > 10% of pts were keratopathy (37.5%), neutropenia (33%) and thrombocytopenia (29.2%). Serious AEs were reported in 9 (37.5%) pts. Two DLTs of Grade 3 corneal events were reported, 1 each in the 2.5 mg/kg Q4W and 1.7 mg/kg D1/D8 Q4W dosing cohorts. The RP2D selection is pending completion of the current cohorts and updated details will be presented.
Of 14 pts evaluable for confirmed response, there were 2 PR, 9 VGPR, and 1 sCR; resulting in a ORR of 85.7%. To date, 2 pts discontinued treatment due to disease progression (n = 1) and patient decision (n = 1); 22 pts are ongoing. In the cohort with the longest follow-up (2.5 mg/kg Q4W; n = 7), 6 have a achieved a VGPR and 1 a sCR. The median number of cycles administered for this group is 12 (range 10-14); all are ongoing.
Summary/Conclusion: The results show that AEs were manageable and consistent with the known safety profiles for Belamaf and POM. Promising preliminary efficacy was observed. Complete safety and clinical activity data from all dose cohorts evaluated in Part 1 will be presented.

EP935 COMBINED INFUSION OF ANTI-CD19 AND ANTI-BCMA CAR-T CELLS AFTER ASCT IN THE FRONT LINE WAS SUPERIOR TO SINGLE ASCT FOR HIGH RISK MM

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Background: Multiple myeloma (MM) is an incurable plasma cell malignancies despite the advent of numerously new drugs especially for high risk patients. Our previous study showed good response for the de novo high risk patients who received CD19 and BCMA-specific CAR-T cell therapy after ASCT in the front line with mild CRS and other side effects (reported on the 2018 ASH meeting).
Aims: To compare the benefits of ASCT followed with CAR-T therapy versus single ASCT for high risk MM patients in China, we retrospectively analyzed the patients' outcome. (NCT 03455972).
Methods: The high risk MM patients defined in this study were in R-ISS stage III, IgD/IgE type, or with measurable EMD,or who only achieved PR or less after 4 cycles of triplet induction. Study intervention in this clinical trial consisted of 4 cycles of bortezomib-based induction treatment followed stem cell mobilization by cyclophosphamide 3 g/m^2. BuCy was used as conditioning, followed by infusion of autologous stem cells. For some patients, lymphocytes were collected from PBSCs and cultured with an anti-CD3 monoclonal antibody to activate T-cell proliferation after stem cell collection. The cells were transduced with recombinant lentiviral verctors which respectively contained the anti-BCMA or anti-CD19 single chain variable fragment (scFv), the cytoplasmic portion of the OX40 and CD28 costimulatory moiety, and the CD3z T-cell activation domain. This is the new third generation CAR technique applied in clinic. CART-19 (1×10^7/kg on d0) and CART-BCMA cells as split-dose (40% on d1 and 60% on d2) were infused directly on d14 to d20 after transplantation. IMiDs alone were given as maintenance therapy. Responses were assessed by IMWG criteria. 10-color flow cytometry was used to monitor MRD regularly after CART treatment. The median of follow-up was 15 (5~24) months.
Results: From March 2018 to March 2019, 15 high risk patients received ASCT followed with CAR-T therapy, while 11 patients for single ASCT without CAR-T infusion for unwillness or seropositive HBS-Ag during the same period. The overall response rate (ORR) was 100% for ASCT combined CAR-T (15/15), with best response of 86.7% (13/15) stringent complete remission (sCR), 6.7% (1/15) complete remission (CR) and 6.7% (1/15) very good partial response (VGPR). The acute and chronic toxicities were mild and reversable. MRD negative conversion rate of single ASCT group was significant lower than patients received ASCT combined CAR-T therapy (22.2% vs. 87.5%, P < 0.05). With median 15 (5~24) months of follow-up, for single ASCT group, 5/11 patients progressed and 4/5 patients died, while 2/15 patients progressed without death for ASCT combined CAR-T therapy group. The median PFS and OS of the patients in two groups were all not reached but 21-months PFS was 73% and 55% for two groups respectively (p < 0.05); 21-months OS was 100% and 61% for each group (p < 0.05) (Figure 1).

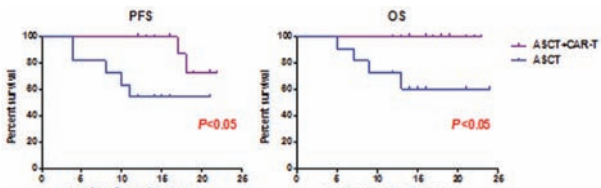

Figure 1. Survival of high risk MM patients after different therapy

Summary/Conclusion: Combined infusion of anti-CD19 and anti-BCMA CART cells after ASCT for high risk MM was safe and effective, and can significantly prolong the PFS and OS compared to single ASCT.