Multiple myeloma - Translational and clinical studies 2

P764

PHASE (PH) I/II STUDY OF ELOTUZUMAB PLUS LENALIDOMIDE/DEXAMETHASONE (LEN/DEX) IN RELAPSED/REFRACTORY MULTIPLE MYELOMA (RR MM): UPDATED PH II RESULTS AND PH I/II LONG TERM SAFETY

T Facon[1,*], P Richardson[2,3], S Jagannath[2,4], P Moreau[5], A Jakubowiak[2,6], M Raab[7], R Vij[2,8], D White[9], D Reece[10], L Benboubker[11], J Zonder[2,12], W Deng[13], E Bleickardt[14], A Singhal[13], S Lonial[2,15]
[1]Hopital Claude Huriez, Service des Maladies du Sang, Lille, France, [2]Multiple Myeloma Research Consortium, Norwalk, [3]Dana-Farber Cancer Institute, Boston, [4]Mount Sinai Medical Center, New York, United States, [5]Hematology Department, University Hospital, Nantes, France, [6]University of Chicago Medical Center, Chicago, United States, [7]Universitaetsklinikum Heidelberg, Heidelberg, Germany, [8]Washington University School of Medicine, St. Louis, United States, [9]Queen Elizabeth II Health Sciences Centre, Halifax, [10]Princess Margaret Hospital, Toronto, Canada, [11]CHU Tours-Hopital Bretonneau, Tours, France, [12]Karmanos Cancer Institute, Detroit, [13]AbbVie Biotherapeutics Incorporated, Redwood City, [14]Britol-Myers Squibb, Wallingford, [15]Winship Cancer Institute, Atlanta, United States

Background: Elotuzumab (Elo) is a humanized anti-CS1monoclonal antibody that enhances natural killer cell mediated antibody dependent cellular cytotoxicity of CS1 expressing myeloma cells. This study included a dose finding Ph I cohort (N=28) and a Ph II cohort (N=73).
Aims: To update the Ph II safety/efficacy data and provide long term safety data from both cohorts.
Methods: Patients (pts) treated with ≥1 (Ph I) or 1–3 (Ph II) prior therapies received Elo+Len/dex as described previously (Lonial JCO 2012; Richardson ASH 2012) until disease progression, unacceptable toxicity, or death. All pts received a premedication regimen including methylprednisolone, diphenhydramine or equivalent, ranitidine or equivalent, and acetaminophen to mitigate infusion reactions. Adverse events (AEs) in Ph I/II pts occurring ≤18 months (mo) (N=98) were compared to AEs with a >18 mo onset in a subgroup of pts treated >18 mo (n=49). This safety analysis excluded 3 Ph I pts treated with Elo 5 mg/kg, since Ph III studies are evaluating a 10 mg/kg dose.
Results: In the Ph II cohort (median 63 yr), objective response rate (ORR) was 84%; 92% with 10 mg/kg (n=36) and 76% with 20 mg/kg (n=37). At a median follow-up of 20.8 mo, median progression free survival (PFS) was not reached (10 mg/kg) and 18.6 mo (20 mg/kg). The most common treatment emergent grade ≥3 AEs were lymphopenia (19%), neutropenia (18%), thrombocytopenia (16%) and anemia (14%). The most common grade 3/4 AEs emerging ≤18 *vs* >18 mo in Ph I/II cohorts are shown (Table 1). 15 pts discontinued due to AEs; none after 18 mo of treatment. There were 4 second primary malignancies; none were reported after 18 mo.

Table 1.

	Onset	
Grade 3/4 AEs*	≤18 mo N=98	>18 mo n=49
Neutropenia	21%	2%
Thrombocytopenia	18%	2%
Lymphopenia	15%	2%
Anemia	12%	2%
Hyperglycemia	9%	0%
Fatigue	8%	0%
Diarrhea	7%	2%
Leukopenia	7%	2%
Hypokalemia	6%	4%
Pneumonia	6%	2%

*In >5% of pts.

Summary and Conclusions: Elo 10 mg/kg+Len/dex was generally well tolerated and resulted in a high ORR and encouraging PFS in pts with RR MM. AEs emergent after 18 mo of therapy were consistent with AEs emergent during the initial 18 mo. Updated Ph II safety/efficacy data and long term safety data from Ph I/II cohorts will be presented.

P765

NEW DRUG PARTNER FOR COMBINATION THERAPY IN MULTIPLE MYELOMA (MM): DEVELOPMENT OF ACY-1215, A SELECTIVE HISTONE DEACETYLASE 6 INHIBITOR ALONE AND IN COMBINATION WITH BORTEZOMIB OR LENALIDOMIDE

N Raje[1,*], A Mahindra[1], D Vogl[2], P Voorhees[3], W Bensinger[4], P Hari[5], J Berdeja[6], S Jagannath[7], S Jones[8], C Wheeler[8], J Supko[1], R Orlowski[9], S Lonial[10]
[1]Massachusetts General Hospital, Boston, [2]University of Pennsylvania, Philadelphia, [3]University of North Carolina at Chapel Hill, Chapel Hill, [4]Fred Hutchinson Cancer Research Center, Seattle, [5]Medical College of Wisconsin, Milwaukee, [6]Sarah Cannon Research Institute, Nashville, [7]Mount Sinai Hospital, New York City, [8]Acetylon Pharmaceuticals, Boston, [9]MD Anderson Cancer Institute, Houston, [10]Winship Cancer Institute, Emory University School of Medicine, Atlanta, United States

Background: First generation HDAC inhibitors (HDACi) active in combination with standard agents in MM are limited by fatigue, vomiting, diarrhea, and myleosuppression. ACY-1215, the first oral next generation selective HDACi in the clinic is 11 fold selective for HDAC6 over class 1 HDACs, is well tolerated preclinically and synergizes with bortezomib (Bort) in MM cell lines and animal models (Blood, V20(210):4061) and synergizes with lenalidomide (Len) *in vitro* with or without dexamethasone (D). Two clinical trials are ongoing: ACY-100 with ACY-1215 monotherapy and in combination with Bort and D, and ACE-MM-101 with ACY-1215 in combination with Len and D.
Aims: The aims of the development program are to characterize safety, pharmacokinetics (PK) and pharmacodynamics (PD) of ACY-1215 alone and in combination with D and Bort or Len and to identify phase 2 combination regimens.
Methods: ACY-100 is a single arm open label study with dose escalation in a 3+3 design. Relapsed/refractory (R/R) patients (pts) who received at least two lines of therapy (tx) including a proteasome inhibitor and an immunomodulatory agents, refused or were ineligible for autologous stem cell transplant (ASCT), had adequate marrow reserve and hepatic function, and creatinine clearance (CrCl) >30, were eligible for the phase 1a and 1b portions after informed consent. Pts received 40 mg to 360 mg of ACY-1215 orally on days 1-5 and 8-12 of a 21 day cycle in part 1a, and in 1b with Bort 1.0-1.3 mg/m^2 on days1,4, 8 and 11 and D 40 mg/week. Peripheral blood samples were obtained for PK and PD assessment of acetylated tubulin and histones in peripheral blood mononuclear cells (PBMC). ACE-MM-101 R/R pts received at least one prior rx and have CrCl>60. Len, 25 mg after an initial 15 mg safety cohort, is given orally daily on 21 days of a 28 day schedule with 40 mg D/week, and if well tolerated a third week of ACY-1215 days 15-19 will be added. ACY-1215 doses of 40 to 240 mg will be explored. PK and PD assessment is similar to ACY-100.
Results: ACY-100: In 15 pts on ACY-1215 monotherapy, no dose limiting toxicity (DLT) was observed, and creatinine elevations, anemia, fatigue, hypercalcemia and respiratory infection, the most common toxicities, were most low grade and not attributed to ACY-1215. Possibly related grade 3 toxicities were anemia and low white blood cell counts (n=1 each). Stable disease was observed in 6 pts, up to 10 cycles of therapy. Doses of ≥160 mg gave similar PK with μM concentrations at C_{max} in all pts with $t_{1/2}$ of 3 hr and no accumulation. At least doubling of acetylated tubulin was seen in PBMCs at ≥160 mg, while increases in acetylated histones were observed only at 240 mg. Two cohorts with Bort (1.0 and 1.3 mg/m^2) are enrolled and one cohort was expanded due to a DLT, asymptomatic elevation in amylase that appeared temporally associated with rx. No further DLTs occurred. One partial response (PR) ongoing at 9 cycles and enrollment is ongoing at 80 mg. ACE-MM-101: The first 3 cohorts, up to 80 mg ACY-1215 and 25 mg Len and 40 mg D enrolled 9 pts, five of whom had previously received an immunomodulatory agent. No DLTs were observed. Four episodes of neutropenia and one ALT elevation were probably attributed to Len. Three pts have withdrawn, two due to progressive disease and one to persistent neutropenia leading to missed L doses. There are four PRs, one VGPR, and one minimal response in the first 6 pts.
Summary and Conclusions: ACY-1215 is well tolerated as monotherapy at doses leading to PD activity and can safely be combined with full doses of B or L with D at ACY-1215 doses explored in combination. Responses have been seen in both studies and dose escalation continues.

P766

HIGH RATES OF PROLONGED MOLECULAR REMISSIONS AFTER TANDEM AUTOLOGOUS-NONMYELOABLATIVE ALLOGRAFTING IN NEWLY DIAGNOSED MYELOMA

M Ladetto[1,*], S Ferrero[1], D Drandi[1], P Omedè[2], M Festuccia[1], F Patriarca[3], N Mordini[4], S Cena[1], L Monitillo[1], L Giaccone[1], Daniela Barbero[1], Alberto Rocci[1], Sara Barbiero[1], Andrea Gallamini[4], Renato Fanin[3], Roberto Passera[5], A Palumbo[1], M Boccadoro[1], B Bruno[1]
[1]Department of Molecular Biotechnology and Health Science, [2]Division of Hematology, A.O. San Giovanni Battista, Torino Italy, University of Torino, Torino, [3]A.O.U. Haematological Clinic, University of Udine, Udine, [4]Hematology, A.O. S. Croce Carle, Cuneo, [5]Division of Nuclear Medicine, Statistical Consultant, University of Torino, Torino, Italy

Background: Myeloablative allografting induces high rates of persistent molecular remissions (MR) in multiple myeloma (MM) (Corradini, J Clin Oncol 1999) and greatly reduces the risk of relapse. Similar results have also been reported after reduced-intensity conditioning (Kröger, Biol Bone Marrow Transpl 2012). Long term data on minimal residual disease (MRD) kinetics after combined autologous and nonmyeloablative allografting (auto-allo) are lacking. We here present the results of MRD analyses by nested qualitative PCR (Nested-PCR) and real time quantitative (RQ)–PCR.
Aims: To performe MRD analysis by Nested-PCR and RQ-PCR on newly diagnosed MM patients treated with auto-allo on a prospective clinical trial [ClinicalTrial.gov, NCT-00702247].
Methods: 26 patients (pts) with stage II-III MM and a diagnostic bone marrow (BM) specimen suitable for immunoglobulin heavy-chain gene rearrangement (IGH) sequencing, were evaluated for MRD by PCR methods. Auto-allo consisted of an autograft followed by 200 cGy TBI and an allograft. BM samples were collected at diagnosis, after the autograft, at month1,3, 6 after the allograft and then every 6 months. Nested-PCR and RQ-PCR analyses were carried out using patient-specific primers as previously described (Voena, Leukemia 1997; Ladetto, Biol Bone Marrow Transpl 2000). For outcome analysis pts were grouped according to reported criteria (Ladetto, ASH 2011): FullMR and StandardMR indicated MRD negativity on two consecutive samples by nested-PCR or RQ-PCR respectively, the latter standardized according to European Study Group on MRD detection guidelines (van der Vendel, Leukemia 2007).
Results: 19/26 pts had a molecular marker. At a median follow-up of 10 years (4.4-12) from diagnosis and 8.9 years (3.5-11) from the allograft, overall survival (OS) was 61% and median time-to-progression (TTP) 5.6 years. Transplant-related mortality occurred in 3/19 pts (16%), while 4/19 pts (21%) died of disease progression. MRD analysis showed that after the autograft 3/19 pts (16%) were negative by nested-PCR. After the autograft 3/19 pts (16%) were PCR-negative. After allograft, the rate of PCR negativity remained low at month 1 (5/19, 26%) and 3 (3/19, 16%). Starting from month 6 PCR-negativity occurred up to 44% (8/18) at 6 months and 47% (7/15) at one year post-transplant. Overall, 8 pts achieved FullMR at a median time from allograft of 6 months (1-12) and for a median duration of 33 months (6-102). Overall, 8 relapses occurred, 6 among 11 pts who never achieved FullMR and 2 in 8 pts who reached FullMR. Of these one has incomplete follow up and in the other one clinical relapsed was heralded by a molecular relapse. Pts in FullMR had better median TTP (not reached *vs* 1.6 years, P=0.043) and OS (not reached *vs* 3.3 years, P=0.008) than pts who did not achieve FullMR (Figure 1). StandardMR occurred in 12/19 pts (63%) during the first 24 months post-transplant, at a median time of 2 months (1-18) and for a median duration of 27 months (3-102). Pts in StandardMR showed better median TTP (not reached *vs* 1 year, P=0.005) and OS (not reached *vs* 3.3 years, P=0.031) as compared to pts with positive PCR (Figure 2). There was no correlation between MR and chronic graft-*vs*-host disease, suggesting specific graft-*vs*-myeloma.

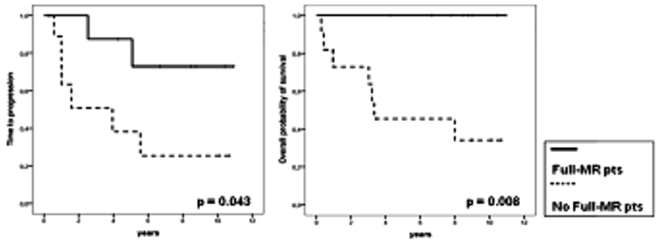

Figure 1. TIP (A) and OS (B) by FullMR status.

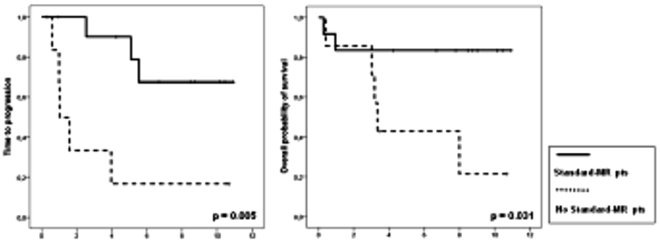

Figure 2. TIP (A) and OS (B) by StandardMR status.

Summary and Conclusions: Auto-allo induces high molecular remission rates, significantly associated with better TTP and OS, clearly documenting the existence of an effective and persistent graft-*vs*-myeloma effect, potentially curative in a subset of patients.

P767

INTEGRATED ANALYSIS OF DATA FROM PHASE 3 RANDOMIZED, CONTROLLED TRIALS OF BORTEZOMIB-BASED VS NON-BORTEZOMIB-BASED INDUCTION PRIOR TO ASCT IN PATIENTS WITH PREVIOUSLY UNTREATED MULTIPLE MYELOMA (MM)

P Sonneveld[1,*], H Goldschmidt[2], L Rosiñol[3], J Bladé[3], J Lahuerta[4], M Cavo[5], P Tacchetti[5], E Zamagni[5], M Attal[6], H Lokhorst[7], A Desai[8], A Cakana[9], K Liu[10], H van de Velde[11], D Esseltine[12], P Moreau[13]
[1]Hematology, Erasmus Medical Center, Rotterdam, Netherlands, [2]University Hospital of Heidelberg, Heidelberg, Germany, [3]Hematology Department, Hospital Clínic de Barcelona, IDIBAPS, Barcelona, [4]Servicio de Hematología, Hospital Universitario 12 de Octubre, Madrid, Spain, [5]Istituto di Ematologia Seràgnoli, Università degli Studi di Bologna, Bologna, Italy, [6]Department of Hematology, Hopital Purpan, Toulouse, France, [7]Utrecht Medical Center, Utrecht, Netherlands, [8]Janssen Global Services, Raritan, NJ, United States, [9]Janssen Research & Development, High Wycombe, United Kingdom, [10]Janssen Research & Development, Raritan, NJ, United States, [11]Janssen Research & Development, Beerse, Belgium, [12]Millennium: The Takeda Oncology Company, Cambridge, MA, United States, [13]University Hospital, Nantes, France

Background: A total of four large, multicenter, cooperative group studies have investigated bortezomib-based regimens compared with non-bortezomib-based previous standards of care as induction prior to autologous stem cell transplant (ASCT) in previously untreated MM: IFM 2005-01, bortezomib-dexamethasone *vs* vincristine-doxorubicin-dexamethasone (VAD); HOVON-65/GMMG-HD4, bortezomib-doxorubicin-dexamethasone *vs* VAD; PETHEMA GEM2005 MENOS65, bortezomib-thalidomide-dexamethasone (VTD) *vs* thalidomide-dexamethasone (TD) *vs* combination chemotherapy followed by bortezomib; and GIMEMA MM-BO2005, VTD *vs* TD.
Aims: This integrated analysis aimed to characterize the overall impact of bortezomib-based *vs* non-bortezomib-based induction therapy on efficacy, outcomes, and safety using data from these phase 3 studies in patients with previously untreated MM. The two key efficacy endpoints were post-transplant complete plus near-complete response (CR+nCR) rate and progression-free survival (PFS).
Methods: Patient-level data were pooled in a thorough integrated analysis of efficacy and safety from the IFM 2005-01, HOVON-65/GMMG-HD4, and PETHEMA GEM2005MENOS65 studies. Patient-level data were not available from GIMEMA MM-BO2005 due to local legal restrictions, but study-level data were used to supplement the integrated analysis.
Results: The integrated analysis incorporated data from 787 and 785 patients treated with bortezomib-based and non-bortezomib-based induction, respectively; demographics and disease characteristics were well balanced between the groups. Post-transplant CR+nCR rate and all other response rates post-induction and post-transplant were significantly higher in the bortezomib-based *vs* non-bortezomib-based group (Table 1). With inclusion of study-level data from GIMEMA MM-BO2005, the pooled odds ratio for post-transplant CR+nCR rate remained similar, at 1.96. The significant improvement in post-transplant CR+nCR rate was seen across patient subgroups, including patients with high-risk features. The median PFS was 35.9 *vs* 28.6 months in the bortezomib-based *vs* non-bortezomib-based groups (hazard ratio [HR] 0.75, P<0.0001); 3-year PFS rates were 50.0% and 41.1%, respectively. HRs for PFS were consistent across studies. After a median follow-up of ~37 months, 3-year overall survival (OS) rates were 79.7% and 74.7%, respectively (HR 0.81, P=0.0402). Median duration of induction therapy was 11 weeks in both groups. During bortezomib-based and non-bortezomib-based induction, respectively, 63% and 59% of patients had grade ≥3 adverse events (AEs), 41% and 37% had serious AEs, 6% and 5% had AEs resulting in discontinuation, and 3% and 4% of patients died. Overall rates of peripheral neuropathy (PN) during induction were 34% *vs* 17%, respectively, including 6% *vs* 1% grade ≥3 PN.

Table 1.

Response rate, n (%)	Btz-based (n=775)	Non-btz-based (n=772)	Odds ratio
Post-induction			
CR	105 (14)	32 (4)	3.92
CR+nCR	175 (23)	63 (8)	3.45
≥VGPR	362 (47)	139 (18)	4.03
ORR	646 (83)	480 (62)	3.05
Post-ASCT			
CR	199 (26)	106 (14)	2.21
CR+nCR	298 (38)	182 (24)	2.05
≥VGPR	463 (60)	315 (41)	2.16
ORR	615 (79)	526 (68)	1.81

For all comparisons, p<0.0001 by Cochran-Mantel-Haenszel chi-squared test.
Btz, bortezomib; CR, complete response; nCR, near-CR; ORR, overall response rate; VGPR, very good partial response

Summary and Conclusions: The findings of the integrated analysis demonstrate that bortezomib-based induction results in a consistent and robust benefit in terms of response rates, PFS, and OS compared to non-bortezomib-based induction. Bortezomib-based induction was generally well tolerated, with a higher rate of PN but no increase in the risk of death during induction *vs* non-bortezomib-based induction.

P768

SAFETY AND EFFICACY OF POMALIDOMIDE WITH OR WITHOUT LOW-DOSE DEXAMETHASONE IN RELAPSED AND REFRACTORY MULTIPLE MYELOMA: LONG-TERM FOLLOW-UP OF PATIENTS ENROLLED IN THE MM-002 PHASE 2 TRIAL

P Richardson[1,*], D Siegel[2], R Vij[3], C Hofmeister[4], R Baz [5], S Jagannath[6], C Chen [7], S Lonial[8], A Jakubowiak [9], N Bahlis[10], K Song[11], A Belch[12], N Raje[13], C Shustik[14], S Lentzsch[15], M Chen[16], M Zaki[16], K Anderson[1]
[1]Dana-Farber Cancer Institute, Boston, MA, [2]John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ, [3] Washington University School of Medicine, St. Louis, MO, [4]Ohio State University Medical Center, Columbus, OH, [5]H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, [6]Mount Sinai Medical Center, New York, United States, [7]Princess Margaret Hospital, Toronto, ON, Canada, [8]Emory University School of Medicine, Atlanta, GA, [9]University of Chicago Medical Center, Chicago, IL, United States, [10]University of Calgary, Calgary, AB, [11]Vancouver General Hospital, Vancouver, BC, [12]University of Alberta, Edmonton, AL, Canada, [13]Massachusetts General Hospital, Boston, MA, United States, [14]Royal Victoria Hospital McGill University Heath Centre, Montreal, QC, Canada, [15]College of Physicians and Surgeons of Columbia University, New York, [16]Celgene Corporation, Summit, NJ, United States

Background: MM-002 is a randomized, open-label, multicenter, phase 2 trial evaluating the safety and efficacy of pomalidomide (POM) with or without low-dose dexamethasone (LoDEX) in advanced relapsed and refractory multiple myeloma (RRMM) patients (pts) who have received prior treatment with lenalidomide (LEN) and bortezomib (BORT).
Aims: The objective of this analysis of MM-002 trial data was to assess the safety and efficacy of POM with or without LoDEX with extended follow-up.
Methods: Pts who had received ≥2 prior therapies, including LEN and BORT, and were refractory to their last treatment were randomized to POM+LoDEX (POM 4 mg/day, days 1–21 of a 28-day cycle; LoDEX 40 mg/week) or POM alone. Refractory disease was defined as documented progression during treatment or within 60 days of the last dose of treatment. At progression, pts receiving POM alone could receive POM+LoDEX at investigator's discretion. Pts aged >75 yrs received LoDEX, 20 mg/week. All pts received mandatory thromboprophylaxis (daily low-dose aspirin). End-points included progression-free survival (PFS), response rate (according to EBMT criteria and investigator assessment), response duration, overall survival (OS), and safety. The efficacy outcomes are based on the intent-to-treat population (POM+LoDEX, n=113; POM, n=108). Data with a median follow-up of 14.2 mos is presented here.
Results: The median number of prior therapies in each group was 5 (range 1–13). All pts (100%) had prior exposure to LEN, BORT, and steroids; 62% of pts were LEN and BORT dual-refractory. In the POM+LoDEX arm, 30 (27%) pts had high-risk cytogenetics, including del(17p13) and/or t(4p16/14q32). The overall response rate (ORR; defined as at least partial response) was 34% and 15% with POM+LoDEX and POM, respectively, with a median duration of 8.3 mos (95% confidence interval [CI]: 5.8–10.1) and 8.8 mos (95% CI: 5.5–11.4), and at least a minimal response was observed in 45% and 31% of pts, respectively. Median PFS was 4.6 mos (95% CI: 3.6–5.5) and 2.6 mos (95% CI: 1.9–2.8); with a median follow-up of 16.0 and 12.2 mos, median OS was 16.5 mos (95% CI: 12.4–18.5) and 13.6 mos (95% CI: 9.6–18.1), with POM+LoDEX and POM, respectively. Among pts with LEN and BORT refractory disease, ORRs were 33% with combination therapy and 17% with POM alone, with median response duration of 6.5 mos (95% CI: 3.7–8.3) and 8.3 mos (95% CI: 2.8–13.1); 46% and 33% of pts achieved at least minimal response, respectively. Median PFS was 3.8 mos (95% CI: 2.8–5.8) and 2.0 mos (95% CI: 1.8–2.9); median OS was 13.4 mos (95% CI: 11.0–17.6) and 12.4 mos (95% CI: 8.2–18.0), with POM+LoDEX and POM, respectively. The most common treatment emergent grade 3/4 adverse events (AEs) reported in the safety population (n=219) were neutropenia (44%), anemia (23%), thrombocytopenia (21%), and pneumonia (18%); there were no reports of grade 3/4 peripheral neuropathy. The incidence of deeP-vein thrombosis was low (2%). In this overall safety population, AEs were managed through dose reductions or interruptions (30% and 64% of pts with at least one, respectively), and supportive care with granulocyte colony-stimulating factor (53%), and red blood cell (48%) and platelet transfusions (18%). Discontinuations of POM due to AEs were 10%.
Summary and Conclusions: POM with or without LoDEX represents a new clinical option for pts with advanced RRMM, including pts with LEN and BORT refractory disease. AEs were predictable and manageable. Updated data with extended follow-up will be presented at the meeting.

P769

CONSOLIDATION WITH HD- MELPHALAN AND AUTOTRANSPLANT (ASCT) AFTER SECOND-LINE TREATMENT INCREASES RESPONSE RATE AND PROGRESSION-FREE SURVIVAL IN MYELOMA PATIENTS RELAPSED AFTER FIRST-LINE ASCT

C Claudia[1,*], F Cavallo[2], S Ferrari[1], E Cerqui[1], F Antoniazzi[1], C Palladino[2], F Schieppati[1], C Pagani[1], A Palumbo[2], G Rossi[1]
[1]Division of hematology, Spedali Civili Brescia, Brescia, [2]Myeloma Unit, Division of hematology, University of Torino, Torino, Italy

Background: Therapeutic options for patients relapsing after first-line HD-Mel and ASCT are not standardized. Few studies have addressed the potential role of ASCT consolidation after II-line treatment in patients relapsed after first-line ASCT.
Aims: To compare the outcome of MM patients relapsed after first-line ASCT who received second-line therapy with or without consolidation with ASCT
Methods: In 159 MM patients treated at two Italian Institution between 1997 and 2010 and relapsed after first-line HD-Mel and ASCT, second-line therapy was given to 98 pts (61%) with bortezomib-or Imids-or thalidomide-based regimens only (ND group) and to 61 pts (38%) with ASCT consolidation after ND-based regimens (45 pts) or chemotherapy (16 pts) (ASCT group). ND and ASCT groups did not differ in baseline characteristics, including age (median 59), type of first-line therapy, median follow-up from diagnosis.CR/VGPR rates and ORR obtained after first-line treatment (ND 52% and 89%; ASCT 62% and 90%, respectively) were also similar. Median duration of first response and time to second treatment were 14 and 24 months in both group respectively. Proportion of patients receiving a double ASCT at first line therapy was 21% in ND and 33% in ASCT group (P=0.079).
Results: After second line therapy ORR(CR+VGPR+PR) was 77% in ASCT group, significantly better than ND group (48%)(P=0.0001).The second CR/VGPR rate was significantly higher after ASCT (41%) than after ND (21%)(P=0.012), independently from the type of second line treatment received before consolidation ASCT (ORR:ND 91% *vs* CT 75%; P=0.21).After a median follow-up from second-line treatment of 28 months (range 1-128 mo), 2-year PFS was 17% after ND (median 12 mo) and 26% after ASCT (median 19mo)(P=0.013).Two-year OS was 62% (median 33mo) and 80% (median 44mo) after ND and ASCT group, respectively (P=0.3). PFS after salvage did not differ between pts receiving single or double first-line ASCT (P=0.066).
Summary and Conclusions: The use of ASCT as consolidation after second-line treatment increased both ORR and CR/VGPR rates, independently from the type of debulking treatment used (chemotherapy *versus* novel drugs) and significantly impacted on PFS when compared with second-line ND-based regimens without ASCT.

P770

TOTAL THERAPY 3 (TT3)-BASED TREATMENT FOR MULTIPLE MYELOMA–AN EXTENDED SINGLE CENTER EXPERIENCE

E Muchtar[1,*], R Ram[1], P Raanani[1], M Yeshurun[1], N Oniashvili [2], O Shpliberg[1], H Magen-Nativ[1]
[1]Institute of hematology, [2]The Raphael Recanati Genetic Institute, Rabin Medical Center, Petah tikva, Israel

Background: Total therapy 3 (TT3) is an intensified treatment for multiple myeloma (MM) introduced by the Arkansas group, designed for newly diagnosed patients. Originally, this regimen incorporates a component of the novel agents bortezomib and thalidomide plus dexamethasone (=VDT) to PACE (cisplatinum, doxorubicin, cyclophosphamide, and etoposide) chemotherapy for 2 cycles, followed by consolidation with high dose melphalan tandem autotransplantation. Thereafter, additional 2 cycles of VDT-PACE are given followed by VDT maintenance. This protocol has not been adopted by many centers and its results have rarely been reported. In 2010 we described a short-term follow up of 23 patients treated TT3-based protocol (Ann Hematol 89:53-9, 2010).
Aims: to review an extended group of MM patients treated with TT3-based protocol, administrated mainly to patients with aggressive clinical course and/or high risk cytogenetic abnormalities at different treatment settings (induction; induction failure; relapse; relapsed-and-refractory MM (RR-MM)].
Methods: We retrospectively analyzed all sequential patients (n=80) from 2004 to 2012 that were given at least one cycle of (V)DT-PACE. For efficacy evaluation, we used the IMWG response criteria.
Results: median age was 58 years (range 35-75). ISS score at diagnosis was I, II and III in 22%, 44% and 29% of patients, respectively (5% undetermined). 53% of patients (32/60) had poor cytogenetic abnormalities. (V)DT-PACE was given in 44 patients for induction, in 11 patients for induction failure, in 13 patients for relapse and in 12 patients for RR-MM. Median cycles per patient was 2 (range 1-4). Bortezomib was given in 66% of cycles. 75% of patients (60/80) were subsequently given high dose melphalan with autograft, of which 8 patients had tandem transplantation (2 of them had auto-allo). 83% of patients were given maintenance. Overall response rate (ORR) following (V)DT-PACE induction treatment was 92% (CR=4%, VGPR=57.3%, PR=30.7%). Patients

receiving (V)DT-PACE for induction and relapse achieved higher rates of VGPR and above (76.7% and 54.5%, respectively) than those treated for induction failure or RR-MM (36.4% and 30%, respectively) (P=.009). Following autologous transplantation, ORR increased to 98%, with substantial improvement in CR/sCR rates (sCR=25.4%, CR=11.9%, VGPR=49.1%, PR=11.9%). With a median follow-up of 21 months, progression free survival at 1 and 2 years was 85% and 67% for induction, 76% and 57% for induction failure, 28% and 0% for relapse and 12% and 0% for RR-MM, respectively. Overall survival at 2 years was 85%, 100%, 39% and 19%, respectively. Considering all treatment cycles (n=152), grade 3/4 hematological toxicity rate was 79% and 46% for neutropenia and thrombocytopenia, respectively. The rate of neutropenic fever was 25.7%, with 19/39 of episodes associated with clinically or microbiologically documented infections. Venous thrombosis was infrequent (3.3%). Death attributed to treatment was relatively low (5/80, 6.25%), occurred mainly in the non-induction settings (4/36, 11.1%). Causes of death were arrhythmia (n=3, of which 2 with known systemic amyloidosis), severe infection (n=1) and multi-organ failure (n=1) (Figure 1).

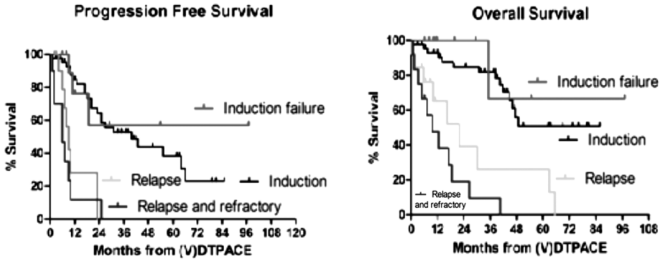

Figure 1.

Summary and Conclusions: TT3-based approach achieved high response rate among MM patients with high-risk disease, with considerable but manageable toxicities. However efficacy was mainly translated into long-term remission in the induction and induction failure settings, while results in relapse and RR-MM are unsatisfactory.

P771

PHASE I STUDY OF THE COMBINATION OF CARFILZOMIB AND PANOBINOSTAT FOR PATIENTS WITH RELAPSED AND REFRACTORY MYELOMA: A MULTICENTER MMRC CLINICAL TRIAL

J Kaufman, MD[1,*], T Zimmerman, MD[2], A Jakubowiak[2], C Rosenbaum[2], C Lewis, D Harvey[1], A Nooka, L Heffner[1], Sagar Lonial,[1]
[1]Hematology and Medical Oncology, Winship Cancer Institute of Emory University, Atlanta, [2]University of Chicago, Chicago, United States

Background: Patients with myeloma ultimately become refractory to current therapies, requiring new approaches to treatment. Carfilzomib is a selective proteasome inhibitor that has demonstrated significant activity in patients with relapsed and refractory myeloma. Panobinostat is a pan-deacetylase inhibitor that can overcome resistance in combination with bortezomib in refractory multiple myeloma patients. Based on preclinical data showing synergistic cytotoxicity of histone deacetylase and proteasome inhibitors, we hypothesized that carfilzomib and panobinostat would be safe and effective for the treatment of relapsed/refractory multiple myeloma. Herein we report the initial findings of the MMRC multicenter phase I study investigtating the combination of panobinostat and carfilzomib in patients with relapsed and refractory multiple myeloma.
Aims: The primary objective is to determine the maximum tolerated dose (MTD) of the combination of panobinostat and carfilzomib using a standard 3+3 design with 5 planned cohorts. An additional 12 patients will be treated at the MTD in an expansion phase to gain further data on safety and efficacy. Secondary objectives are to evaluate response and survival endpoints of enrolled patients.
Methods: Panobinostat is administered orally three times weekly for three of four weeks (range, 15-25 mg).Carfilzomib is administered IV days1,2,8,9,15, and16, ranging from 20/27 mg/m^2 to 20/56 mg/m^2. Doses above 20/27 are administered over 30 minutes. Cycles are repeated every 4 weeks. Dose limiting toxicities (DLT) are determined in the first cycle, and all adverse events are assessed according to CTCAE Version 4. Responses are assessed using IMWG criteria (plus MRs as per the EBMT criteria).
Results: To date, 10 patients in three cohorts have been enrolled, and 9 have completed the first cycle. Median age is 60.6 years (range, 48-73). All patients had refractory and progressive disease. No DLTs were observed in the first 2 cohorts, with 1 patient in cohort 1 being inevaluable due to disease progression. There are currently 2 patients in cohort 3 (panobinostat 20 mg and carfilzomib 20/36 mg/m^2), one of whom had a DLT of grade 4 thrombocytopenia and grade 3 elevated creatinine. Both toxicities resolved after discontinuation of study therapy. Four serious adverse events have occurred, with two (one patient with a grade 5 cardiac arrest and a different patient with elevated creatinine) considered related to study therapy. Patients have completed a median of 3 cycles (range, <1 to 13). Grade 3 thrombocytopenia occurred in 40% and grade 3 neutropenia in 30% of all subjects. The most common non-hematologic toxicities were nausea, diarrhea, vomiting, hypokalemia and cough, all effectively managed with standard interventions. Preliminary assessment of response revealed an ORR of 30% with 1 sCR and two PRs.
Summary and Conclusions: The combination of carfilzomib and panobinostat is well tolerated with no unexpected toxicities. Preliminary assessment of response data is encouraging, and the study is ongoing with planned dose escalation of carfilzomib to 56mg/m^2 and panobinostat to 20 mg.

P772

MM-008: A PHASE 1 TRIAL EVALUATING PHARMACOKINETICS AND TOLERABILITY OF POMALIDOMIDE+LOW-DOSE DEXAMETHASONE IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA (RRMM) WITH RENAL IMPAIRMENT

J Matous[1,*], D Siegel[2], H Duong[3], C Kasserra[4], L Sternas[4], C Jacques[4], K Klesczewski[4], M Zaki[4], J Shah[5]
[1]Colorado Blood Cancer Institute, Denver, CO, [2]John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ, [3]Hematologic Oncology and Blood Disorders, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, [4]Celgene Corporation, Summit, NJ, [5]Lymphoma/Myeloma, University of Texas MD Anderson Cancer Center, Houston, TX, United States

Background: Pomalidomide (POM) recently received US Food and Drug Administration approval for the treatment of patients with RRMM who have received ≥2 prior treatments including lenalidomide and bortezomib. In phase 2 trials, POM+low-dose dexamethasone (LoDEX) has shown significant clinical activity in this patient population (Leleu X, *et al. Blood*. 2013; Richardson *et al. Blood.* 2012). Renal impairment is a common comorbidity for myeloma patients, occurring in over 40% of patients (Eleutherakis-Papaikovou V, *et al. Leuk Lymphoma.* 2007). POM is extensively metabolized, with 2% eliminated renally as the parent drug (Hoffmann M, *et al. Cancer Chemother Pharmacol.* 2013*)*. Thus, renal function may not substantively affect exposure of the parent drug. POM+LoDEX has shown efficacy in RRMM patients with moderate renal impairment (Siegel DS, *et al.* ASH. 2012). However, patients with severe renal impairment have been excluded from previous POM trials. To date, the safety, efficacy, and pharmacokinetics (PK) of POM in patients with renal impairment have not been prospectively evaluated.
Aims: MM-008 is a multicenter, open-label, phase 1 study designed to prospectively assess the PK and safety of POM+LoDEX in patients with RRMM and normal or impaired renal function.
Methods: Patients with RRMM and ≥1 prior therapy were eligible to enroll in this study. Patients with normal renal function (creatinine clearance [CrCl] ≥60 mL/min [cohort A]) or severe renal impairment (CrCl <30 mL/min [cohort B]), but not requiring dialysis, were included. Patients in cohort A received POM 4 mg and patients in cohort B received POM 2 mg or 4 mg on days 1-21 of a 28-day cycle, following a standard 3+3 dose-escalation design. Both cohorts received DEX 40 mg (20 mg for patients aged >75 years) on days1,8,15, and 22. Cohort C will assess patients with severe renal impairment (CrCl <30 mL/min) and requiring dialysis (up to approximately 14 patients planned). Patients were not permitted to enroll in more than 1 cohort. Granulocyte colony-stimulating factor for management of neutropenia was not permitted in cycle1, but could be started on day 1 of the next cycle at the physician's discretion. Treatment was continued until progressive disease or unacceptable toxicity. Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for AEs (V 4.0).
Results: As of February5, 2013, eleven patients have been treated (8 in cohort A; 3 in cohort B). Patients were ages 46-71 years (cohort A) and 57-64 years (cohort B). Five patients are >65 years of age in cohort A (66, 69 [n=3], and 71 years). Seven patients in cohort A have received more than 1 cycle of treatment; 5 have received 3 or more cycles. One patient in cohort B has received more than 3 cycles. All 3 patients in cohort B have completed 1 full cycle of treatment with no dose-limiting toxicities reported. Dose escalation is planned and all patients remain on study. Updated pharmacokinetic and AE data will be presented at the meeting.
Summary and Conclusions: MM-008 is an ongoing trial prospectively evaluating the pharmacokinetics and safety of POM+LoDEX in patients with severe renal impairment. Early tolerability data are encouraging, with dose escalation planned.

P773

CAUSES OF DEATH 30 AND 180 DAYS AFTER DIAGNOSIS IN NON-HDT TREATED DANISH MULTIPLE MYELOMA PATIENTS: A STUDY FROM THE DANISH MYELOMA STUDY GROUP

M Orebo Holmström[1,*], P Gimsing[2], N Abildgaard[3], N Andersen[4], N Clausen[5], M Frederiksen[6], H Gregersen[7], D Kristensen[8], H Larsen[9], P Trøllund Pedersen[10], T Plesner[11], S Pulczynski[12], A Vangsted[1]
[1]Department of Hematology, Roskilde Sygehus, University Hospital Copenhagen at Roskilde, Roskilde, [2]Rigshospitalet, Copenhagen, [3]Department of Hematology, Odense University Hospital, Odense, [4]Department of Hematology,

Aarhus University Hospital, Aarhus, [5]Department of Hematology, University Hospital of Copenhagen at Herlev, Herlev, [6]Department of Hematology, Haderslev Hospital, Haderslev, [7]Department of Hematology, University Hospital of Aalborg, Aalborg, [8]Department of Hematology, Næstved Hospital, Næstved, [9]Department of Hematology, Viborg Hospital, Viborg, [10]Department of Hematology, Esbjerg Hospital, Esbjerg, [11]Department of Hematology, Vejle Hospital, Vejle, [12]Department of Hematology, Holstebro Hospital, Holstebro, Denmark

Background: Many elderly patients with multiple myeloma (MM), not eligible for high-dose melphalan with hematopoietic stem cell support (HDT), die shortly after diagnosis.
Aims: To determine the cause of death in non-HDT MM-patients dying within 30 and 180 days of diagnosis in a population based setting.
Methods: The cause of death in non-HDT-treated patients who died within 180 days of diagnosis was identified in the population based nationwide Danish myeloma database (DMMD) established by the Danish Myeloma Study Group. DMMD includes all patients diagnosed with MM since 2005. The cause of death was divided into 1) pneumonia defined by the presence of fever, cough and positive x-rays, 2) septicemia defined by fever and positive blood cultures, 3) other infection defined in case of fever, elevated CRP and infection not identified as pneumonia nor septicemia 4) respiratory failure defined as respiratory distress with no fever. 5) Cardiovascular disease defined as cardiovascular infarction including pulmonary embolism or by the presence of congestive heart disease, 6) intracranial infarction or hemorrhage diagnosed by CTC, MRI or bedside neurological examination defined as stroke and 7) patients on dialysis were classified as having renal failure. All other causes of death were classified as other cause of death.
Results: We found 2071 patients included in DMMD of whom 1497 (72.3%) did not receive HDT. Of these 330 (22.0%) died within 180 days of diagnosis. Medical history was not available in 25 (7.6%) patients. No specific cause of death was found in 17 (5.2%) of the patients. Seventy-six (23.0%) patients died at home, or at a nursing home. Among 212 (64.2%) eligible patients 72 (40.0%) died within 30 days and 140 (60.0%) died within 31-180 days. The following causes of death were found: Infection was the leading cause of death with 96 (45.3%) of the patients dying from infection in total. Thirty-three (45.8%) and 63 (45.0%) patients died from infection within 30 and 31-180 days, respectively. Septicemia was the cause of death in 40 (18.9%) of the patients in total; 17 (23.6%) and 23 (16.4%) patients dying within 30 and 31-180 days. Pneumonia was the cause of death within 30 and 31-180 days in 12 (16.7%) and 25 (17.9%) patients, 37 (17.5%) in total. Nineteen patients (9.0%) died from other infections. Renal failure was the cause of death in 35 (16.5%) patients, cardiovascular causes in 21 (9.9%) patients, respiratory failure in 13 (6.1%) patients and stroke in 9 (4.2%) of the patients. Thirty-eight (18.0%) patients died from other causes. There was no significant difference (Fisher's exact test) in the causes of death within 30 and 31-180 days after diagnosis (P=0.727) (Table 1).

Table 1.

Cause of death	Patients dead 0-30 days after diagnosis (% of patients in group)	Patients dead 31-180 days after diagnosis (% of patients in group)	All patients (% of patients in group)
Pneumonia	12 (16.7)	25 (17.9)	37 (17.5)
Septicemia	17 (23.6)	23 (16.4)	40 (18.9)
Other infections	4 (5.6)	15 (10.7)	19 (9.0)
Renal failure	14 (19.4)	21 (15.0)	35 (16.5)
Cardiovascular	8 (11.1)	13 (9.3)	21 (9.9)
Respiratory failure	5 (6.9)	8 (5.7)	13 (6.1)
Stroke	3 (4.2)	6 (4.3)	9 (4.2)
Other cause of death	9 (12.5)	29 (20.8)	38 (18.0)

Summary and Conclusions: The main causes of death within 180 days of diagnosis in non-HDT-treated MM-patients were infections; with pneumonia and septicemia as the most common specific causes. Renal failure was the second most common cause of death. The failure to produce normal polyclonal IgG, treatment with corticosteroid and myelosuppressive chemotherapy, T cell defects and renal failure are major causes of infections in patients with MM. Early use of prophylactic intravenous IgG and/or prophylactic antibiotic treatment in non-HDT treated patients could possibly prevent some or most of these early deaths.

P774

PRELIMINARY RESULTS OF A PHASE I/II STUDY OF CARFILZOMIB, LENALIDOMIDE, VORINOSTAT AND DEXAMETHASONE (QUAD) IN RELAPSED AND/OR REFRACTORY MULTIPLE MYELOMA (MM)

El Bilotti[1,*], D Vesole[1], J Richter[1], A McNeill[1], P Anand[1], U Bednarz[1], K Ivanovski[1], L McBride[1], L Raucci[1], V Batra[1], D Siegel[1]
[1]John Theurer Cancer Center at Hackensack University Medical Center, Hackensack, United States

Background: The results from Phase I/II studies suggest that carfilzomib as a single agent has clinical activity in relapsed and relapsed/refractory multiple myeloma (MM). Phase I/II data indicate that combining a proteasome inhibitor and corticosteroids with an immunomodulatory agent or a histone-deacetylase (HDAC) inhibitor are synergistic.
Aims: We investigated the tolerability and synergy of the quadruplet using carfilzomib as the proteasome inhibitor in combination with lenalidomide, vorinostat and dexamethasone.
Methods: The primary objectives were to determine the maximum tolerated dose (MTD) and the safety/tolerability of the QUAD combination. Secondary objectives included overall response rate, duration of response, time to progression and time to next therapy. All patients were required to have relapsed or relapsed/refractory disease following at least one line of therapy. Treatment consisted of 28-day cycles of oral lenalidomide days 1-21, oral vorinostat days 1-7 and 15-21, intravenous (IV) carfilzomib days1,2,8,9,15 and 16 and IV or oral dexamethasone 40mg days1,8,15 and 22. A standard 3+3 dose escalation schema was followed based on dose-limiting toxicities (DLTs) occurring in Cycle 1. (See Table 1) Adverse events (AEs) were graded using the NCI-CTCAE v3. Response was assessed by the modified International Myeloma Working Group criteria.
Results: As of February 28, 2013, fifteen patients have been enrolled, with one patient replaced due to inability to complete Cycle 1 due to AE. Four patients failed screening, 3 due to cytopenias and 1 due to QTC interval. The median age was 58 years (range 47-65), 55% were male. The median number of prior regimens was 3 (range 1-9), with a median time from diagnosis of 4 years. All patients had prior stem cell transplant, 10 had prior bortezomib, 10 had prior lenalidomide and 2 had prior vorinostat. Of the 7 patients who received prior VRD, 4 were refractory. Drug-related AEs were experienced by 100% of patients. The most common of these drug-related AEs included anemia (10pts), fatigue (8), thrombocytopenia (8), neutropenia (6), muscle cramping (6) and diarrhea (6). No febrile neutropenia occurred. Nine patients experienced ≥grade 3 AEs including neutropenia (5pts), anemia (3), thrombocytopenia (2), infection (2), electrolyte imbalances (2), hyperglycemia (1), fatigue (1) and constipation (1) and no grade 5 events. Eight SAEs occurred on study, most of which were infection and one was possibly study drug(s) related. Currently in cohort4, the MTD has not yet been determined with no DLTs to date. All 11 patients were evaluable for response with an ORR of 40%. Four patients had a partial response (PR), 2 stable disease (SD), 4 with progressive disease (PD) as best response and one has restaging pending. Of the seven patients treated in cohorts 2 and above, four have had a PR. Five patients have come off study due to PD and one due to patient choice. No patients have discontinued due to toxicity. Two patients have completed 18 cycles of therapy.

Table 1.

Cohort	Carfilzomib (mg/m²)	Lenalidomide (mg)	Vorinostat (mg)	Dexamethasone (mg)
1	15	15	300	40
2	20	15	300	40
3	20	25	300	40
4	20/27*	25	300	40
5	20/27*	25	400	40

* Step-up dosing of carfilzomib 20 mg/m² on Days 1 and 2 of Cycle 1, followed by 27 mg/m² for the remainder of treatment.

Summary and Conclusions: The combination of QUAD is well tolerated in both relapsed and relapsed/refractory MM patients, with no DLTs identified. The overall safety profile is manageable and the response rate of 40% noted in cohort 2 and above is encouraging in this patient population. Accrual is ongoing and additional data will be available at the time of presentation.

P775

CLINICAL RESPONSE BY BASELINE CHARACTERISTICS IN PATIENTS WITH RELAPSED AND BORTEZOMIB-REFRACTORY MULTIPLE MYELOMA TREATED WITH PANOBINOSTAT, BORTEZOMIB, AND DEXAMETHASONE (PANORAMA 2)

P Richardson[1,*], R Schlossman[1], M Alsina[2], S Coutre[3], C Gasparetto[4], S Mukhopadhyay[5], M Ondovik[5], M Khan[5], C Paley[5], S Lonial[6]
[1]Dana-Farber Cancer Institute, Boston, [2]H. Lee Moffitt Cancer Center & Research Institute, Tampa, [3]Stanford University, Stanford, [4]Duke University Medical Center, Durham, [5]Novartis Pharmaceuticals Corporation, East Hanover, [6]Emory University School of Medicine, Atlanta, United States

Background: In PANORAMA2, panobinostat combined with bortezomib and dexamethasone recaptured responses in heavily pretreated patients with bortezomib-refractory multiple myeloma; overall response rate, clinical benefit rate,

and progression-free survival were 34.5%, 52.7%, and 5.4 months, respectively, with manageable toxicity (Richardson *et al.* ASH 2012 [abstract 1852]).
Aims: Here, we evaluate clinical response by prior use of bortezomib and dexamethasone, progression on or within 60 days of of a patient's last bortezomib-containing regimen, or high-risk cytogenetics at baseline. Additionally, we evaluate quality of life parameters.
Methods: In the single-arm, phase 2 PANORAMA 2 study, patients with relapsed and bortezomib-refractory multiple myeloma received panobinostat (20 mg, oral)+bortezomib (1.3 mg/m^2, intravenous)+dexamethasone (20 mg, oral). Treatment phase 1 (TP1) consisted of eight 3-week cycles of panobinostat (thrice weekly) and bortezomib (twice weekly) during weeks 1 and2, with oral dexamethasone administered on the days of and after bortezomib dosing. Patients demonstrating clinical benefit entered treatment phase2, which consisted of four 6-week cycles of panobinostat (thrice weekly) and bortezomib (once weekly) during weeks1,2,4, and5, with dexamethasone on the days of and after bortezomib. The primary endpoint was overall response (≥partial response) in TP1. Response was based on European Group of Blood and Marrow Transplantation 1998 criteria. High-risk cytogenetics was defined as del(17p), t(4;14), or t(14;16). Quality of life was measured with the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group Neurotoxicity (FACT/GOG-Ntx) v4.0 scales. All patients provided written informed consent prior to study entry.
Results: Response rate trended higher in patients whose prior bortezomib therapy was not their last line of therapy (Table 1). Although no trend in response rate was noted, progression-free survival appeared longer in patients progressing within 60 days of their last bortezomib-containing regimen than in those progressing on their last bortezomib-containing regimen. In the 14 patients with high-risk cytogenetics, overall response rate (complete response, near complete response, or partial response) was 42.9% and clinical benefit rate (complete response, near complete response, partial response, or minimal response) was 71.4%. The mean FACT/GOG-Ntx subscale did not exhibit a clinically meaningful change from baseline (mean±standard deviation, 114.2±21.1; n=41) to cycle 9 day 1 (day 169; 104.2±15.4; n=16) as determined by 50% standard deviation threshold for minimally important difference. Other quality of life parameters were similarly unchanged.

Table 1.

	N	ORR, % (95% CI)	CBR, % (95% CI)	PFS, months (95% CI)
Disease progression				
On BTZ	40	37.5 (22.7-54.2)	55.0 (38.5-70.7)	4.2 (2.6-5.8)
≤ 60 days of BTZ	15	26.7 (7.8-55.1)	46.7 (21.3-73.4)	7.6 (6.7-9.0)
BTZ in last prior line of therapy				
Yes	27	25.9 (11.1-46.3)	48.1 (28.7-68.1)	4.9 (2.1-7.6)
No	28	42.9 (24.5-62.8)	57.1 (37.2-75.5)	6.0 (3.9-7.6)
Dexamethasone in last BTZ-containing regimen				
Yes	45	26.7 (14.6-41.9)	46.7 (31.7-62.1)	4.9 (2.6-6.7)
No	10	70.0 (34.8-93.3)	80.0 (44.4-97.5)	6.2 (2.6-8.3)
Dexamethasone in last prior line of therapy				
Yes	37	32.4 (18.0-49.8)	54.1 (36.9-70.5)	4.2 (2.6-6.7)
No	18	38.9 (17.3-64.3)	50.0 (26.0-74.0)	6.5 (2.6-9.7)

BTZ, bortezomib; CBR, clinical benefit rate; ORR, overall response rate; PFS, progression-free survival.

Summary and Conclusions: Panobinostat combined with bortezomib and dexamethasone demonstrated activity regardless of baseline demographics in heavily pretreated patients with bortezomib-refractory multiple myeloma.

P776

PHASE 2A, OPEN-LABEL, MULTI-DOSE STUDY OF ANTI-KAPPA MONOCLONAL ANTIBODY, MDX-1097, IN RELAPSED KAPPA-CHAIN RESTRICTED MULTIPLE MYELOMA WITH STABLE MEASURABLE DISEASE

R Dunn[1], A Spencer[2,*], B Augustson[3], P Mollee[4], M Copeman[5], P Asvadi[1]
[1]Immune System Therapeutics, Sydney, [2]Malignant Haematology & Stem cell Transplantation Service, Alfred Hospital, Melbourne, [3]Haematology, Sir Charles Gairdner Hospital, Perth, [4]Haematology, Princess Alexandra Hospital, Brisbane, [5]Northern Beaches Cancer Service, Sydney, Australia

Background: MDX-1097 is a monoclonal antibody that binds to a kappa light chain surface antigen (called KMA), on malignant B cells but not normal leucocytes or other cells. A Phase 1 study of single doses of MDX-1097 has been completed in kappa-light-chain restricted multiple myeloma patients. Based on positive safety, pharmacokinetic and efficacy data at a 10mg/kg dose, we now conducted a phase 2a study of repeated dosing of MDX-1097.
Aims: This study aimed to test efficacy and safety of MDX-1097 at 10mg/kg weekly ×8 in relapsed kappa myeloma patients with stable measurable disease.
Methods: We initially enrolled 13 relapsed kappa myeloma patients with stable disease, including patients on maintenance lenalidomide or thalidomide and low-dose steroids. The study followed a Simon 2-stage minimax design, with ≥1 response needed in the first 13 patients to expand the study. Responses were evaluated by IMWG guidelines (Durie *et al*, 2006). MDX-1097 10mg/kg was given by 90 minute intravenous infusion weekly for 8 weeks. Efficacy and safety data included vital signs, physical examination, ECG, hematology assessments, clinical chemistry, C-reactive protein, β2 microglobulin, immunoglobulin quantification, urinalysis, and creatinine clearance. This study was performed according to ICH-GCP guidelines.
Results: A total of 19 patients completed the study. Repeated MDX-1097 dosing was well tolerated: 4 patients had Grade 1-2 drug-related infusion reactions; 4 patients had Grade 3 AE's (complete heart block, pneumonia, anaemia and pancreatitis), considered unlikely to relate to MDX-1097. There was no evidence of serum sickness, no alteration of renal function, no evidence of increased immunosuppression and no ECG changes. One patient had a VGPR maintained for 12 months post MDX-1097 therapy. A second patient had PR. A third patient with light-chain-only myeloma had PR. On study, 26% of patients continued IMiD(R) maintenance therapy; with no signs that MDX-1097 affected their safety profile.
Summary and Conclusions: Multiple weekly doses of MDX-1097 at 10 mg/kg were safe and well tolerated in patients with relapsed kappa myeloma. Responses to therapy were seen in 3/19 (16%) of patients.

P777

THE UK LENALIDOMIDE TREATMENT CONTINUATION SCHEME™: TRENDS OF LONG-TERM TREATMENT IN A CLINICAL SETTING

Cathy D. Williams[1,*], Mathew Simcock[2], Imran Lodhi[3], Suzanne K. Robinson [2], Faith E. Davies[4]
[1]Centre for Clinical Haematology, Nottingham University Hospital, Nottingham, United Kingdom, [2]Celgene International, Boudry, Switzerland, [3]Celgene Limited, Uxbridge, [4]Institute of Cancer Research, Royal Marsden Hospital, London, United Kingdom

Background: Patients (pts) with relapsed/refractory multiple myeloma (RRMM) who respond to therapy experience improved survival if treatment with lenalidomide (LEN) plus dexamethasone (DEX) is continued until disease progression. In the United Kingdom, LEN+DEX is reimbursed for the treatment of RRMM pts after ≥2 therapies (current license after ≥1 prior therapy) in accordance with the National Institute for Health and Clinical Excellence (NICE) guidelines. The Treatment Continuation Scheme (TCS) database was part of the NICE-agreed reimbursement scheme. It was designed to track the duration of LEN+DEX treatment in RRMM pts, but not the reasons for dose adjustments or treatment discontinuation.
Aims: To investigate how LEN starting dose and dose modifications during therapy impact treatment duration.
Methods: This anonymised prospective cohort analysis focused on pts with RRMM enrolled in the TCS program between 1 July, 2009 and 30 September, 2010. The cutoff date was 31 October, 2012 allowing at least 2 yrs follow up. Associations between ordered categorical variables (first dose administered, age group, treatment scheme, and number of cycles administered per pt) were measured by Spearman's rank correlation and associations between continuous variables (number of cycles, age, and number of dose changes) were measured by Pearson's correlation. Baseline covariates (age and starting dose) were modeled using multivariable logistic regression with possible interactions considered; $P<0.05$ was considered statistically significant.
Results: A total of1,779 pts from 193 treatment centers were evaluable. The median age was 69 yrs (range 23–91); 35% (624) were aged <65, 40% (702) were 65–74, and 25% (453) of the patients were >75 yrs. The majority of pts (65%; n=1,149) initiated LEN treatment according to the recommended starting dose of 25 mg/day, 15% of pts each started at 15 and 10 mg/day, and 5% at 5 mg/day. Dose modifications were reported in 48% of pts. The median number of dose modifications per pt was 1 (range 0–15). Of pts who started on 25 mg/day and received >1 cycle, almost half (48%) required no dose adjustments. Pts who had at least 1 form of dose adjustment had longer treatment duration compared with pts without a dose adjustment (15.0 *vs* 7.3 cycles, respectively; $P<0.0001$). The median number of cycles administered was 7 (range 1–48); 33.4% pts remained on therapy for ≥12 cycles, 17.6% of pts for ≥24 cycles, and 14.5% pts for ≥26 cycles. Of pts who continued therapy ≥24 cycles, 11.8% required dose modifications directly after cycle1, but the percentage of dose modifications steadily decreased from cycle 6 onwards. There was a positive association between a higher starting dose and longer treatment duration ($P<0.0001$). A significant negative correlation between age and the number of cycles administered was observed: pts aged <75 yrs were 1.51 times more likely to receive ≥24 cycles compared with pts aged ≥75 yrs ($P=0.0093$). In multivariate analyses, age and LEN starting dose were both statistically significant predictors for a treatment duration lasting ≥24 mos (Table 1).
Summary and Conclusions: This large dataset (N=1,779) from a clinical practice setting of pts with RRMM in the United Kingdom shows a positive correlation between the recommended LEN 25 mg/day starting dose and longer treatment duration. Age (<75 yrs) and individual dose adjustments of LEN during therapy were also associated with longer treatment duration.

Table 1. Predictors of treatment duration lasting ≥24 mos.

Factor	Odds ratio (95% CI) [*P* value]	
	Univariate model	Multivariate model
Age	0.983 (0.972–0.995) [0.0068]	0.986 (0.974–0.998) [0.0233]
LEN starting dose		
5 mg vs 25 mg	0.738 (0.402–1.354) [0.3262]	0.746 (0.406–1.371) [0.3451]
10 mg vs 25 mg	0.595 (0.404–0.877) [0.0087]	0.635 (0.429–0.941) [0.0235]
15 mg vs 25 mg	0.844 (0.593–1.20) [0.8962]	0.982 (0.625–1.273) [0.5278]

CI, confidence interval.

P778

THE EFFICACY AND SAFETY OF POMALIDOMIDE WITH OR WITHOUT LOW-DOSE DEXAMETHASONE IS NOT IMPACTED BY AGE IN PATIENTS WITH ADVANCED RELAPSED AND REFRACTORY MULTIPLE MYELOMA: MM-002 SUBGROUP ANALYSIS

S Jagannath[1,*], C Hofmeister[2], R Baz[3], David S. Siegel[4], R Vij[5], C Chen[6], S Lonial[7], K Anderson[8], M Chen[9], M Zaki[9], P Richardson[8]
[1]Mount Sinai Medical Center, New York, [2]Ohio State University Medical Center, Columbus, OH, [3]H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, [4]John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ, [5]Washington University School of Medicine, St. Louis, MO, United States, [6]Princess Margaret Hospital, Toronto, ON, Canada, [7]Emory University School of Medicine, Atlanta, GA, [8]Dana-Farber Cancer Institute, Boston, MA, [9]Celgene Corporation, Summit, NJ, United States

Background: Pomalidomide (POM) demonstrated clinical efficacy and acceptable tolerability in relapsed and refractory multiple myeloma (RRMM) patients previously treated with lenalidomide (LEN) and bortezomib (BORT), in the randomized, multicenter, open label MM-002 phase 2 trial.
Aims: The impact of age (≤65 *vs* >65 yrs) on efficacy and safety outcomes was assessed in a post-hoc analysis.
Methods: Patients with RRMM who had received ≥2 prior therapies, including LEN and BORT, and were refractory to their last regimen were randomized to either POM+low-dose dexamethasone (POM 4 mg/day, days 1–21 of a 28-day cycle; LoDEX 40 mg/week) or POM alone. At progression, patients receiving POM alone could receive POM+LoDEX at the investigator's discretion. Patients >over 75 yrs received LoDEX, 20 mg/week. All patients received mandatory thromboprophylaxis (daily low-dose aspirin). End points included progression-free survival (PFS), response rate (based on EBMT criteria), response duration, and safety.
Results: A total of 221 patients with a median age of 63 yrs (range 34–88) were randomized to POM+LoDEX (n=113) or POM alone (n=108). Overall, 77 (35%) of patients had LEN as their last prior therapy. The efficacy outcomes and the most common treatment emergent grade 3/4 adverse events (AEs) for the age subgroups according to treatment arm are presented in the Table 1. Median response was durable (7.7–10.6 mos) across the age groups with POM regardless of the addition of LoDEX, and was not impacted by age. Of patients aged ≤65 yrs, 28% (POM+LoDEX) and 32% (POM) required at least one dose reduction; for patients aged >65 yrs these proportions were 29% and 44%, respectively. Median relative dose intensity was 90% in both POM+LoDEX and POM arms in patients aged ≤65 yrs; in older patients it was 90% and 100%, respectively.

Table 1. Efficacy and safety outcomes.

	≤ 65 yrs		> 65 yrs	
	POM + LoDEX (n = 62)	POM (n = 69)	POM + LoDEX (n = 51)	POM (n = 39)
Median age, yrs (range)	59 (34–65)	58 (37–65)	72 (66–88)	74 (66–88)
Efficacy, %				
At least partial response	31	13	37	18
At least minimal response	47	23	43	44
Median duration of response,[a] mos	10.1	8.3	7.7	10.6
Median PFS, mos (range)	4.7 (3.7–6.7)	1.9 (1.8–2.7)	3.7 (2.1–5.5)	3.3 (2.8–5.5)
Safety	**POM + LoDEX (n = 61)**	**POM (n = 68)**	**POM + LoDEX (n = 51)**	**POM (n = 39)**
Grade 3/4 hematologic AEs, %				
Neutropenia	46	40	35	59
Anemia	26	24	18	26
Thrombocytopenia	18	24	20	21
Grade 3/4 non-hematologic AEs, %				
Pneumonia	16	10	29	21
Urinary tract infection	10	3	8	0

[a]For patients who achieved at least partial response.

Summary and Conclusions: POM with or without LoDEX was effective and generally well tolerated in heavily pretreated RRMM patients who had already received LEN and BORT, including patients who had progressed on prior LEN. In general, age had no impact on overall response rate, duration of response, or safety. Updated data will be presented at the meeting.

P779

PROMISING ROLES OF AMIFOSTINE AS PROPHYLACTIC AGENTS AGAINST BORTEZOMIB-INDUCED PERIPHERAL NEUROPATHY

M Fang[1,*], Y Gun[1]
[1]Department of Hematology, the First Affiliated Hospital of Dalian Medical University, Dalian, China

Background: Up to now, as the first proteasome inhibitor to be approved for the treatment of both relapsed/refractory and newly diagnosed multiple myeloma (MM) patients, the bortezomib has emerged as an important therapeutic strategy in the treatment of MM. On account of the BiPN as an adverse effect, the dose and duration of bortezomib treatment were often limited. The incidence of BiPN reached as high as 37%. In addition, there was a lack of the effective evidence concerned with the treatments and prevention measures for BiPN. As an organic thiophosphate, amifostine, was used as a "detoxifying agent" during a cytotoxic treatment procedure. Besides, it was also thought to act as a ROS scavenger, which is an important component for cancer therapy. What's more, it was demonstrated that amifostine could play a potential neuroprotective role on preventing the cisplatin- and paclitaxel-induced neurotoxicityin.
Aims: To examine whether amifostine could protect patients with multiple myeloma (MM) from bortezomib-induced peripheral neuropathy while maintaining the therapeutic efficacy.
Methods: 47previously untreated patients with MM were enrolled and randomly assigned to treatment.All patients receivedbortezomib (1.0 mg/m^2 on days1,4,8, 11),dexamethasone (20-40mg/don days1-4, 8-11) andthalidomide(100mg/d)for four 21-day cycles. Patientswere randomly assigned to receive 400 mg of amifostinebefore bortezomib,then assessed incidence and severity of BiPN after every cycle. *In vitro*, schwann cells(SCs)and myeloma cells(MCs)were pretreated with amifostineat 0,1,2, 4mM for 30min prior to bortezomib exposurefor 5 h at 400nM and 100nM, respectively. After Cell viability and reactive oxygen species (ROS) were examined, aggresome formation and activation of chaperone-mediated autophagy (CMA) in SCswere observed through immunofluorescent analyses and TEM.
Results: Complete response rates did not differ in thepresence or absence of amfostine therapy(34.78% v 37.5%, P>0.05). Incidence of BiPN was lower in patients whoreceived amfostine compared with those who received no amifostine (62.5%v 78.26%, P>0.05), though the difference was not significant. Among the patients with BiPN,NCI grade 3-4 incidence wassignificantly lower in patients who received amifostinethan those who received no amifostine (8.33% v 39.13%, P<0.05).*In vitro*, amifostine pretreatment increased thecell viability while decreased the level of ROS in SCs.In addition, amifostine pretreatment decreased the percentage of SCs forming peripheral myelin protein22 (PMP22) aggregatesandinduced high expression of cytoplasmic chaperoneand receptor of CMA at lysosomal membrane. TEM observedautophagosomes of different stages in SCsinduced by amifostine. Amiforstine did not increased the cell viability and decreased the level of ROS in MCs.
Summary and Conclusions: These results indicate promising roles of amifostine as prophylactic agents against BiPN by reducing ROS generation and aggresome formation through activation of CMA.

P780

MP VS MPT IN FIRST TO FOURTH LINE OF TREATMENT IN MULTIPLE MYELOMA PATIENTS

J Lund[1,*], K Uttervall[1], J Liwing[1], J Aschan[2], E Alici[1], E Holmberg[3], H Nahi[1]
[1]Divison of Hematology, Department of Medicine, Huddinge, Karolinska Institute, Stockholm, [2]Jansen-Cilag AB, Sollentuna, [3]Department of Oncology, Institute of Clinical Sciences, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden

Background: Combination of melphalan and prednisolone (MP) was standard treatment of multiple myeloma (MM) for decades. Since the introduction of novel agents the clinical outcome in MM has improved. Several prospective studies with thalidomide, the first novel agent, combined with MP, (MPT) compared to MP have been performed, most of them showing MPT gives a better response rate and median overall survival than MP. A metaanalysis of 6 prospective studies show a rise of median OS and EFS when treating with MPT of 6 months when comparing to MP.
Aims: The aim of the study was to look upon a real life population and see if addition of thalidomide to MP gained real life patients.
Methods: From a material of 1642 patients with symptomatic MM collected from 15 Swedish sites from earliest January 2000, until latest June 2012 we collected all patients treated in first, second, third and fourth line of therapy with MP (n=600, 213, 54 and 21) and MPT (n=170, 66, 23 and 15). MM patients were iden-

tified from the Swedish National Cancer Register and medical data were obtained from medical records. Patients were evaluated for response rate, OS and EFS. Multivariate Cox model analysis was made to adjust for Ig-class, age, hypercalcemia haemoglobin and albumin levels at time for MM-diagnose.
Results: The distribution of response rate of nCR/VGPR/PR and NR in the MP population was5,3, 31 and 61% and4,4, 27 and 65% in 1st and 2nd line of therapy respectively. In the MPT population the response rate were significantly better;12,12,46 and 30% in 1st line and9,9, 47 and 34% in 2nd line. Median OS in the MP group after 1st line of therapy was 27 months and in the MPT group 50 months, 95% CI [24;30] and [44;84] respectively (P<0.0001). The relative risk for death in the MPT group *vs.* the MP group was 0.61, 95% CI [0.45;0.84] after adjusting for other prognostic markers. Two years from start of treatment 55% of the patients treated with MP were still alive and hadn't started new treatment *vs.* 70% after MPT. After 2nd line of therapy OS in the MP group was 22 months and in the MPT group 35 months, 95% CI [18;25] and [29;-]. Relative risk for death after MPT *vs* MP was 0.55, 95% CI[0.38;0.83], P<0.01. After 3rd and 4th lines of therapy median OS for MP were 17 and 14 months, 95%CI [13;30] and [4;23] respectively and for MPT 19 and 23, 95% CI[8;32] and [8;-]. The difference after 4th line of treatment was not significant, probably due to the small amount of patients. EFS for patients receiving MP in 1st, 2nd and 3rd lines of treatment was 12.6, 8 and 8 months respectively compared to patients who received MPT where EFS was 22, 18 and 3.2 months respectively, (P<0.001, <0,001 and=0.374 respectively). The reason for the short EFS after 3rd line of treatment in the MPT group is unclear and does not correspond to OS for the same group (Figure 1).

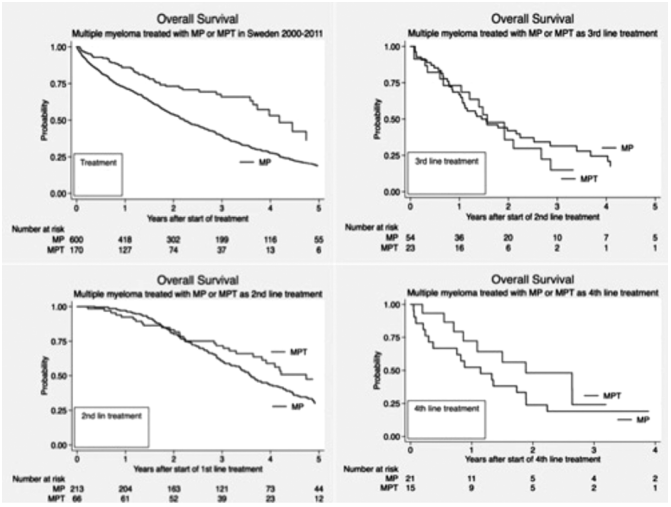

Figure 1.

Summary and Conclusions: Response rates with MPT were significantly better than with MP both in 1st and 2nd line of treatment. Treatment with MPT significantly increased OS and EFS in treatment lines 1 through 3. MPT benefits in our retrospective study of patients in a standard clinical setting were even bigger than in the prospective trials performed.

P781

CAN NOVEL AGENTS OVERCOME THE NEGATIVE PROGNOSTIC IMPACT OF RENAL IMPAIRMENT IN MULTIPLE MYELOMA? - A POPULATION BASED STUDY INCLUDING 1538 PATIENTS

K Uttervall[1,*], J Lund[1], J Liwing[1], E Holmberg[2], E Alici[1], J Aschan[3], H Nahi[1]
[1]Department of Medicine, Karolinska Institutet, Stockholm, [2]Department of Oncology, Institute of Clinical Sciences, Sahlgrenska Academy at University of Gothenburg, Gothenburg, [3]Janssen-Cilag AB, Sollentuna, Sweden

Background: Renal impairment (RI) is a relatively common feature of multiple myeloma (MM) and it has been shown in several studies that RI at the time of diagnosis correlates to inferior survival.
Aims: To understand the impact of RI on survival in the era of novel agents. The primary endpoint of this retrospective study was overall survival (OS). Time to next treatment (TTNT) was the secondary endpoint.
Methods: The study population included all patients diagnosed with MM since earliest January 2000 until latest June 2011 at 14 Swedish sites. The estimated glomerular filtration rate (eGFR) was calculated using the MDRD-formula and RI was defined as eGFR <60 mL/min/1.73 m^2. Multivariate Cox model analysis was made to adjust for age, calcium, haemoglobin and albumin levels at time for MM-diagnose.
Results: The study population consisted of 1538 patients. Patients with RI at diagnosis (n=680) had a significantly worse median OS of 33 months 95% CI[28;36] compared to those without RI (n=858), with a median OS of 52 months 95% CI[48;56], (P<0.001). High dose treatment (HDT) in 1st line improved median OS in patients with RI (76 *vs* 26 months, P<0.001). Novel treatment in 1st line significantly improved OS for non-HDT patients with RI (60 *vs* 21 months, P<0.001). This difference was still significant in the multivariate analysis. There was no difference in median OS between non-HDT patients with and without RI that had been treated with novel drugs (60 *vs* 50 months, P=0.86). RI implied a shorter median TTNT after 1st line (13 *vs* 20 months, P<0.001). HDT prolonged TTNT (30 *vs* 11 months, P<0.001). For non-HDT patients with RI novel treament in 1st line also prolonged TTNT from 9 to 19 months, P<0.001 (Figure 1).

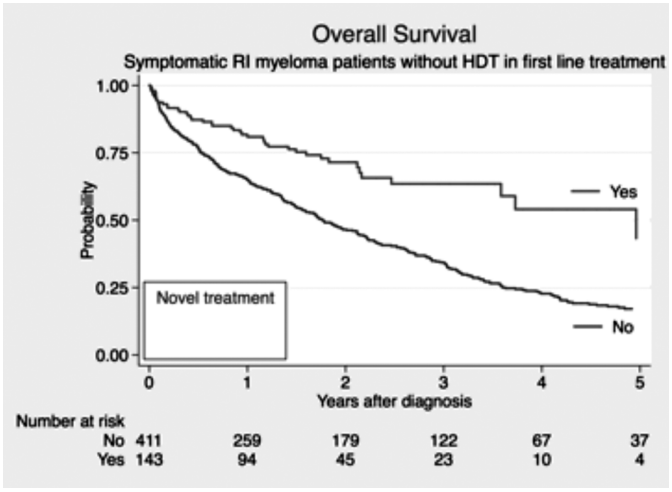

Figure 1.

Summary and Conclusions: RI is still an important prognostic marker in MM. HDT and novel treament regimens can partly overcome the negative impact of RI with improved median OS and prolonged TTNT.

P782

SIGNIFICANCE OF THE ISS AND IMWG RESPONSE CRITERIA IN PATIENTS WITH MULTIPLE MYELOMA WHO RECEIVED ASCT IN THE NOVEL AGENT ERA: A RETROSPECTIVE ANALYSIS OF 1701 JAPANESE PATIENTS

H Takamatsu[1,*], T Miyamoto[2], S Hagiwara[3], K Yokoyama[4], T Ito[5], M Matsumoto[6], K Nishiwaki[7], H Sakamaki[8], R Suzuki[9], K Sunami[10]
[1]Cellular Transplantation Biology (Hematology/Respirology), Kanazawa University Graduate School of Medical Science, Kanazawa, [2]Department of Hematology/Oncology, Kyushu University, Fukuoka, [3]Division of Hematology, Internal Medicine, National Center for Global Health and Medicine, [4]Division of Hematology, Department of Medicine, Keio University School of Medicine, Tokyo, [5]Division of Hematology, Second Department of Internal Medicine, Shinshu University School of Medicine, Matsumoto, [6]Department of Hematology, National Hospital Organization Nishigunma National Hospital, Shibukawa, [7]Division of Oncology and Hematology, Department of Internal Medicine, Jikei University School of Medicine, Kashiwa Hospital, [8]Division of Hematology, Tokyo Metropolitan Cancer and Infectious diseases Center Komagome Hospital, Tokyo, [9]Department of HSCT Data Management and Biostatistics, Nagoya University Graduate School of Medicine, Nagoya, [10]Department of Hematology, National Hospital Organization Okayama Medical Center, Okayama, Japan

Background: Although the International Staging System (ISS) and International Myeloma Working Group (IMWG) response criteria for multiple myeloma (MM) are used worldwide, there have been few reports on prognostic assessment of Asian patients using these criteria in the novel agent era.
Aims: The objective of our study was to evaluate the clinical significance of ISS and IMWG response criteria in Japanese patients with MM who were treated with autologous stem cell transplantation (ASCT).
Methods: Study participants included 1701 Japanese patients (967 men and 734 women) with a median age of 57 years (range: 19-73 years) who underwent a single ASCT after high-dose melphalan (200 mg/sqm) (Mel 200) treatment for MM in Japan between October 1995 and December 2011. Data were collected and analyzed retrospectively using the Transplant Registry Unified Management Program (TRUMP) of the Japan Society for Hematopoietic Cell Transplantation. Given that bortezomib, thalidomide and lenalidomide were approved in Japan in December 2006, October 2008 and June 2010, respectively, we categorized patients into two treatment cohorts: pre-novel agent era (1995-2006) and novel agent era (2008-2010).
Results: During the pre-novel agent era (1995-2006) in Japan, 695 patients (386 men and 309 women) with a median age of 56 years (range: 22-70 years) received a single ASCT after Mel 200 treatment between October 1995 and December 2006. The median follow-up time was 4.3 years with a 4-year overall

survival (OS) rate of 66%. Median survival rates for ISS I (n=176), II (n=204) and III (n=113) groups were 7.3, 6.4 and 5.3 years, respectively. We could not obtain ISS data for 202 patients. In the ISS I group, OS was significantly prolonged compared to ISS II (P=0.046) and III (P=0.002) groups; however, no significant difference was found between ISS II and III groups (P=0.155). Responses before ASCT were as follows: 64 CR (9.2%), 139 VGPR (20.0%), 374 PR (53.8%), 83 SD (11.9%), 21 PD (3.0%) and 14 non-data (2.1%). Median survival rates for CR, VGPR, PR, SD, and PD groups were 11.3, 5.9, 6.2, 5.4 and 3.3 years, respectively. There were no significant differences in OS between the CR group and other response groups, except for CR *versus* PD (P=0.014) groups. During the novel agent era (2008-2010) in Japan, 1006 patients (581 men and 425 women) with MM received a single ASCT after Mel 200 treatment between January 2008 and December 2010. The median follow-up time was 1.5 years with a 2-year OS rate of 87%. Two-year OS rates for ISS I (n=392), II (n=410) and III (n=204) groups were 90%, 87%, and 82%, respectively. In the ISS I group, OS was significantly prolonged compared to the ISS III group (P=0.03), but no significant differences were found between ISS I and II groups (P=0.59) and between ISS II and III groups (P=0.07) (Figure 1). Responses before ASCT were as follows: 107 CR (10.6%), 316 VGPR (31.4%), 473 PR (47.0%), 80 SD (8.0%), 21 PD (2.1%) and 9 non-data (0.9%). Two-year OS rates for CR, VGPR, PR, SD and PD groups were 90%, 89%, 86%, 83% and 61%, respectively. There were no significant differences in OS between the CR group and other response groups, except for CR *versus* PD groups (P<0.001) (Figure 2). The percentage of CR+VGPR cases (423 of 1006 [42.0%]) before ASCT in the novel agent era increased significantly compared to the pre-novel agent era (203 of 695 [29.2%]) (P<0.0001).

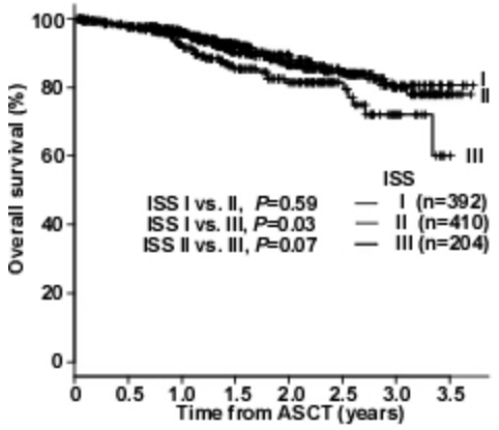

Figure 1.

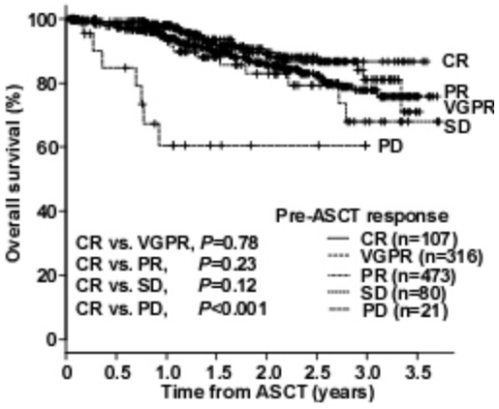

Figure 2.

Summary and Conclusions: In the novel agent era, CR+VGPR cases before ASCT increased. Although the ISS did not clearly stratify the prognosis of Japanese patients with MM who received a single ASCT, this finding should be confirmed in prospective studies.

P783

PREVALENCE AND CLINICAL SIGNIFICANCE OF BRAF V600E MUTATION IN MULTIPLE MYELOMA

E Rustad[1,*], H Dai[2], K Wader[3], K Misund[1], H Hov[2], A Sundan[1], H Aarset[2], A Waage[1,4]

[1]Department of Cancer Research and Molecular Medicine, Norwegian University of Science and Technology, [2]Department of Pathology, [3]Department of Oncology, [4]Department of Haematology, St. Olavs Hospital, Trondheim, Norway

Background: Activating mutations in the BRAF are found in 100% of patients with hairy cell leukemia, 60% with malignant melanoma and 4% with multiple myeloma. Mutation V600E is the most common of approximately 30 BRAF mutations. Clinical characteristics of myeloma patients with BRAF mutations have been published, but the number is still too low to decide whether they have a common phenotype. Here we present 10 cases with BRAF mutation V600E.
Aims: Our objective is to further examine the prevalence and clinical significance of BRAF mutations in multiple myeloma.
Methods: The patient material consists of 153 bone marrow biopsies collected as a part of routine diagnostics at St. Olavs Hospital in Trondheim, Norway in the period 2006-2012. All patients fullfilled criteria for multiple meyloma (>10% plasma cells in BM and/or >30 g/l of M protein). All patients who were still alive at the time of inclusion gave passive consent to analyze the clinical information and biological material. Ethics committee approved the study. Patient samples were examined by real time PCR for the two most common BRAF mutations, V600E and K601N. Clinical disease characteristics from each patient were obtained from clinical records.
Results: In 153 patients we found 10 patients (6,5%) with V600E mutation and no patients with K601N mutation. Median age was 69 (range 52-82) years, 6 male and 4 female, IgG5, IgA 2 (3 missing), kappa8, lambda2, creatinine median 146 (59-900) µmol/l, corrected Ca median2,80 (2,40-3,60), ISS stage II: 3 pts, ISS stage III: 4 pts (3 missing), 8 pts had skeletal disease. Median overall survival was 52 months in BRAF- patients and 26 months in BRAF+ patients. None of the differences were statistically significant.
Summary and Conclusions: The prevalence of BRAF mutation V600E was6,5%. 10 patients with BRAF mutation V600E were more affected by the disease and had shorter survival compared with 143 patients without the mutation indicating that BRAF+ patients may have a more agressive disease.

P784

SESTAMIBI TECHNETIUM-99M BONE MARROW SCAN IS ABLE TO PREDICT OVERALL DISEASE OUTCOME AND MORTALITY COMPARED TO WHOLE BODY MAGNETIC RESONANCE IMAGING IN MULTIPLE MYELOMA

A Khalafallah[1,2,*], A Snarski[3], R Heng[4]

[1]Haematology, LAUNCESTON GENERAL HOSPITAL, [2]School of Human Life Sciences, University of Tasmania, [3]Nuclear Medicine, Northern Nuclear Medicine Tasmania, [4]Radiology Department, LAUNCESTON GENERAL HOSPITAL, Launceston, Australia

Background: Bone disease occurs in about 90% of multiple myeloma (MM) patients. There are no data comparing the new diagnostic modalities with whole body Magnetic Resonance Imaging (WB-MRI) and Sestamibi Technetium-99m-MIBI Bone Marrow Scan (MIBI) in MM.
Aims: This study aims to determine whether WB-MRI and MIBI scans in the same myeloma patients produce the same estimate of disease load and location and to study possible association between the bone disease detected by these scans and the effect on disease outcome and survival.
Methods: A prospective comparative study was conducted between WB-MRI and MIBI scans in assessing bone disease and outcome of MM. Sixty two consecutive patients with confirmed MM underwent simultaneous WB-MRI and MIBI scans at the Launceston General Hospital from January 2010 to January 2011, and their survival status was determined in January 2012. The median age was 62 years (range 37-88) with a male to female ratio of 33:29. For the examination of the spines, MRI-T1 weighted turbo spin-echo and turbo spin echo MRI-STIR (Short Tau Inversion Recovery) were performed in the sagittal plane. Within 48 hours all patients underwent MIBI scan. Imaging started at five minutes post injection of MIBI–30mCi (1110MBq) with a wide field of view gamma camera equipped with a low energy high resolution collimator. The whole body scan proceeded at 30cm/minute. When completed, lateral femora images were taken with each view, which took approximately two minutes and, if required, a single positron emission computed tomography (SPECT) was performed. This study is approved by the Tasmanian Human Ethics Committee, Australia. The study was registered prospectively in the Australian and New Zealand Clinical Trials Registry at http://www.ANZCTR.org.au under No: ACTRN12609000761268.
Results: Overall in all bones, the mean MIBI scan result provides a better and earlier prediction of disease progression and mortality than the mean result from the MRI scan versions taken together (MRI_T1 HR for trend 0.51; 95%CI 0.33 to 0.81; P=0.012: and MRI-STIR HR for trend 0.58; 95%CI 0.35 to 0.97; P=0.038) when patients receive standard therapy for myeloma. In vertebrae and long bones, MRI scan detected more disease compared to MIBI scan (P<0.001) but there was less difference in the skull (P=0.09). In the rib-cage, the MIBI scan detected more lytic lesions of the ribs compared to MRI scan (P<0.001). Thirteen of the 62 patients died during the 24 months follow-up. Increased disease detected in all bones by both scans was associated with increased mortality risk (MIBI P=0.001; MRI-STIR P=0.044; but not MRI-T1 P=0.44). In all combined bone groups, the mean MIBI scan results provided a better prediction of mortality than MRI scan over the follow-up period (MRI-T1 *vs* MIBI P=0.019; MRI-STIR *vs* MIBI P=0.047).

Summary and Conclusions: Our study confirms that WB-MRI is more accurate and with a higher sensitivity in detecting myeloma bone lesions.A novel finding shows that MIBI scan obtains an image of all important bone compartments in the body in one single examination, and is less time consuming and more comfortable for the patient than MRI. Furthermore, MIBI scan was able to predict overall disease outcome and mortality better than MRI scan. Further studies to define optimum use of these imaging techniques are warranted.

P785

HETEROGENEITY OF IMWG DEFINED CR AND VGPR ASSESSED BY FREE LIGHT CHAIN ASSAY AND MULTIPARAMETER FLOWCYTOMETRY

H Sugihara[1,*], T Ugai[1], Y Nishida[1], K Tsuda[1], M Yamakura[1], M Takeuchi[1], K Matsue[1]
[1]Hematology, Kameda Medical Center, Kamogawa, Japan

Background: With the development of novel therapeutic agents, complete response (CR) and very good partial-response (VGPR) have become treatment goals in patients with multiple myeloma (MM). Although, the current definition of CR is not fully satisfactory, and other techniques such as serum free light chain (sFLC) assay, immunophenotyping and molecular methods are being investigated. The incorporation of FLC assay in addition to IMWG defined CR criteria defines a more stringent degree of CR (sCR), whereas multiparameter flowcytometry (MFC) may allow the more deeper level of response compared to conventional immunofixation negative response or sCR.
Aims: We retrospectively analyzed the relationship of different level of responses and its clinical relevance on the prognosis after treatment of MM.
Methods: A total of 131 consecutive patients with MM treated from April 2005 to December 2012 at our institute were subjected to this study. sFLC was serially measured at least once a week during admission and once a month during the period of outpatient care, and bone marrow examination was performed before and after treatments as clinically indicated. Treatment response was assessed using the IMWG criteria, and the best response to treatment during the course of disease was evaluated by simultaneous serum immunofixation test, sFLC measurements and MFC analysis of bone marrow plasma cells.
Results: Among 131 patients, 32% of patients achieved CR, 27.5% achieved sCR, and 20% achieved immunophenotypic CR. VGPR was obtained 25% of patients and the rest of 42% of patients remained PR or less responses. Survival of patients was correlated with the depth of response in IMWG criteria. Normalization of FLC ratio among patients with CR, VGPR, and PR or less was 86%, 60%, and 9%, respectively. Among 36 CR patients with normal sFLCκ/λ, 26 (72%) were MFC-negative and 10 (28%) were MFC-positive; 4 of 6 CR patients without normal sFLCκ/λ (29%) were MFC-positive. 20 VGPR patients (61%) obtained normal sFLCκ/λ, while only one became MFC-negative. Among 56 patients with less than PR, only 3 obtained normal sFLCκ/λ and none achieved MFC negativity. Among the patients with CR and VGPR, patients achieved sFLC normalization showed significantly better survival compared to those who did not. Patients achieved MFC negativity showed significantly better survival compared to those who did not. Among patients with CR, patients achieved MFC negativity showed better PFS, but other conventional prognostic markers did not give negative impact on PFS, probably due to short follow up and excellent outcome in this group of patients. On multivariate Cox regression analysis for PFS, only MFC negativity was an independent prognostic factor (Hazard-ratio 0.028; 95% CI, 0.004 to 0.21; *P*=0.0005).
Summary and Conclusions: This study confirmed that magnitude of CR and VGPR response defined by IMWG criteria was heterogeneous in terms of sFLCκ/λ normalization and MFC negativity. Although MFC and sFLC analysis frequently gave discrepant results among patients with CR and VGPR, both analyses appeared to give complementary important complementary information for assessing the depth of CR and VGPR category. Achieving immunophenotypic CR translates into superior PFS compared with conventional CR or sCR.

P786

ALPHA 1-ACID GLYCOPROTEIN (AAG) IS A POTENTIAL PATIENT SELECTION BIOMARKER FOR IMPROVED CLINICAL ACTIVITY OF ARRY-520 IN RELAPSED AND REFRACTORY MULTIPLE MYELOMA (MM)

B Tunquist[1,*], K Brown[1], G Hingorani[1], R Aitchison[1], J Regensburger[1], S Lonial[2], J Kaufman[2], J Zonder[3], A Cohen[4], W Bensinger[5], R Orlowski[6], J Shah[6], B Hilder[1], M Ptaszynski[1], K Litwiler[1], D Walker[1]
[1]Array BioPharma, Boulder, [2]Emory Winship Cancer Institute, Atlanta, [3]Karmanos Cancer Institute, Detroit, [4]Fox Chase Cancer Institute, Philadelphia, [5]Fred Hutchinson Cancer Research Center, Seattle, [6]MD Anderson Cancer Center, Houston, United States

Background: ARRY-520 is a selective inhibitor of kinesin spindle protein (KSP) that has preferential activity in Mcl-1-dependent tumors and is being developed for patients with relapsed and refractory multiple myeloma (MM). The acute-phase plasma protein alpha 1-acid glycoprotein (AAG) can bind certain drugs, potentially affecting pharmacokinetics (PK), and thus efficacy. AAG levels vary considerably among patients with cancer, including MM.
Aims: To investigate the interaction of ARRY-520 and AAG as it relates to patient outcome following ARRY-520 administration.
Methods: Protein binding, and the effect of [AAG] and [compound] on MM cell line viability were measured *in vitro*. Patient data were obtained from 3 clinical studies of ARRY-520: Ph1 solid tumor study, Ph1/2 AML study, and Ph1/2 study in MM. The MM Phase 2 study consists of two separate cohorts: single agent ARRY-520 and ARRY-520 plus low-dose dexamethasone (dex). [AAG] and the degree of ARRY-520 total protein binding were measured in pre- and post-dose blood samples.
Results: ARRY-520 shows preferential affinity for AAG relative to other common serum proteins, such as HSA. In *in vitro* assays, increasing [AAG] across a clinically relevant range (0.6–3.0 g/L) decreased the unbound concentration of ARRY-520 five-fold and this correlated with increased IC_{50} values for ARRY-520 in MM cell line viability assays. A similar effect on MM cell viability was not seen for several other standard of care MM agents, which do not bind to AAG. Thus, we hypothesize that elevated AAG decreases free concentration of ARRY-520 and leads to a loss of potency. In pre-dose blood samples (n=140), [AAG] ranged from 0.2 to 4.1 g/L. Both [AAG] and measured unbound ARRY-520 correlated with changes in PK: CL and V_d decreased with increasing AAG, consistent with a lower unbound fraction in patients with higher [AAG]. Post-dose blood samples from the MM study indicated that AAG levels did not significantly change with time. Of 72 MM patients evaluated for AAG to date, 26% exhibited pre-dose [AAG] ≥1.1 g/L, and this correlated with a decreased median event-free survival (EFS) (2.3 *vs* 7.8 months; P=0.0024) and no clinical responses (0/19 *vs* 12/53; P=0.028) compared to patients below this cutoff. In the ARRY-520+dex cohort, a 22% ORR (≥PR) in the 1st-stage of this study was observed. The ORR for the subgroup of patients with AAG ≥1.1g/L was 0% (0/6). By contrast, in patients with AAG <1.1g/L ORR was 33% (4/12). High [AAG] also associated with a shorter median overall survival (OS) of 4.5 months *vs.* 20.2 months in patients with AAG ≥1.1g/L. The reported relationship between [AAG] and MM patient prognosis is unclear. In our study, we observed no relationship between pre-study [AAG] and various prognostic markers (*e.g.* b2-microglobulin, HSA, LDH, and ISS score). These results are consistent with AAG not having prognostic value in this disease.
Summary and Conclusions: Preclinical and interim clinical data suggest AAG levels affect the PK and activity of ARRY-520. In preclinical analyses, this effect is specific to ARRY-520 relative to other MM drugs. Patients with [AAG] above a cutoff are predicted to achieve insufficient exposure to gain therapeutic benefit, with a 0% ORR and significantly shorter EFS and OS compared to patients below this cutoff. We hypothesize that selecting patients based on low AAG levels may allow for identification of those patients most likely to benefit from ARRY-520. Additional work is ongoing and will be reported at a later time.

P787

COMPARISON OF FREELITE AND N LATEX SERUM FREE LIGHT CHAIN ASSAYS AND PREDICTING SURVIVAL

S Mahmood[1,*], N Wassef[2], S Sachchithanantham[1], L Rannigan[1], W Taylor[1], T Lane[1], D Foard[1], A Tekle[3], K Patel[1], J Pinney[1], C Whelan[1], H Lachmann[1], J Gillmore[1], P Hawkins[1], A Wechalekar[1]
[1]Inflammation, National Amyloidosis Centre, University College London Medical School, Royal Free Campus, [2]Head of Proteins, Enzymes, Clinical Biochemistry, [3]Clinical Biochemistry, Royal Free London Foundation Trust, London, United Kingdom

Background: Availability of serum immunoglobulin-free light chain (FLC) assays Freelite (Binding Site UK) and N Latex (Siemens, Germany) allows for measurement free kappa and lambda immunoglobulin light chains. FLC measurements are an important tool in diagnosing and monitoring patients with multiple myeloma and AL amyloidosis. We report a comparison of the Freelite (a polyclonal assay) and N Latex (a new monoclonal assay) immunoassays in diagnosis and monitoring of patients with systemic AL amyloidosis.
Aims: We assessed the concordance of the assays in detecting the abnormal light chain component, time to first dFLC response, dFLC response at2,4,6 months and outcomes by degree of clonal response.
Methods: Our primary cohort consisted of 94 consecutive AL amyloidosis patients assessed at the UK national amyloidosis centre between January 2011 and April 2012, treated with chemotherapy and available for serial follow up for six months. All patients had serum FLC monitoring at baseline and two monthly thereafter to assess treatment response. The FLC measurements were repeated in duplicate for both the Freelite and N Latex assays at 0,2, 4 and 6 months.
Results: The median age was 64 yrs (range 55-72 yrs) with cardiac involvement in 43% (23% Mayo stage 3) and renal involvement in 76%. Patients had a kappa and lambda clonal light chain in 21% and 79% respectively. 46% had a measurable monoclonal protein (≥1g/L). The follow up was 8.6 months and median overall survival was 24.1 months. The median kappa was 17.3mg/L and 16mg/L, median lambda 48.8mg/L and 52.6mg/L and median dFLC was 107mg/L and 199mg/L by Freelite and by N Latex respectively. There was an abnormal kappa in 41% and lambda in 63% by Freelite assay, and abnormal kappa in 32% and 67% by N Latex assay. An abnormal kappa or lambda was correctly identified in 85%/78% and 82%/83% by Freelite and N latex assays. There were discordant kappa/lambda ratios at presentation with 11/90 abnormal by N Latex and normal by Freelite, and 10/90 abnormal by Freelite but normal by N Latex. The correlation coefficient for kappa was R^2=0.91, lambda

was R^2=0.52 and kappa to lambda ratio was R^2=0.87. At 2 months, a complete response (CR) was achieved in 20% and 21%, partial response (PR) 0% and 14% by Freelite and N Latex assays respectively. At 4 months a PR was present in 7% and 16% by the Freelite and N Latex assays (Table 1). Achieving a PR or greater at 4 months post treatment predicted a statistical significant survival advantage by both assays: Freelite (P=0.011) and N Latex (P=0.049).

Table 1.

		Freelite	N Latex
2 months	CR	8	9
	vGPR	4	6
	PR	0	6
	NR	28	22
4 months	CR	13	11
	vGPR	6	6
	PR	3	6
	NR	23	18
6 months	CR	13	13
	vGPR	5	4
	PR	3	5
	NR	10	9

Summary and Conclusions: Both FreeLite and N latex assay can detect abnormal free light chains in patients with systemic AL amyloidosis. In general, there was a good correlation between the assays for detecting the abnormal light chain subtype. However, both assays showed discrepancies in the absolute values of FLC and each assay missed different patients. N Latex assay appears to detect PR earlier than Freelite assay but the clinical significance remains unclear as the p values for improved survival were different for both assays. Although both assays are useful for detection of abnormal FLC measurements in amyloidosis, the values are not interchangeable. Further studies are needed to validate the biological significance of abnormal FLC by the N Latex assay. Joint first authors (S Mahmood and NL Wassef)

P788

ADVERSE EVENTS AND MANAGEMENT IN MM-003, A PHASE 3 STUDY OF POMALIDOMIDE+LOW-DOSE DEXAMETHASONE (POM+LODEX) VS. HIGH-DOSE DEXAMETHASONE (HIDEX) IN RELAPSED/REFRACTORY MULTIPLE MYELOMA (RRMM)

M Delforge[1,*], M Dimopoulos[2], K Weisel[3], P Moreau[4], M Lacy[5], K Song[6], L Karlin[7], H Goldschmidt[8], A Banos[9], A Oriol[10], A Alegre[11], C Chen[12], M Cavo[13], L Garderet[14], V Ivanova[15], J Martinez-Lopez[16], X Yu[17], L Sternas[17], C Jacques[17], M Zaki[17], J Miguel[18]

[1]Hematology, University Hospital Leuven, Leuven, Belgium, [2]Alexandra Hospital, Athens, Greece, [3]Hematology & Oncology, Medicine, University Hospital Tuebingen, Tuebingen, Germany, [4]Hematology, University Hospital Hôtel-Dieu, Nantes, France, [5]Hematology, Mayo Clinic, Rochester, MN, United States, [6]Vancouver General Hospital, Vancouver, BC, Canada, [7]Centre Hospitalier Lyon Sud/Hospices Civils de Lyon, Pierre-Bénite, France, [8]Universitätsklinikum Heidelberg, Heidelberg, Germany, [9]Hematology, Centre Hospitalier de la Côte Basque, Bayonne, France, [10]Institut Catala d'Oncologia, HGTiP, Barcelona, [11]Hospital Universitario La Princesa, Madrid, Spain, [12]Princess Margaret Hospital, Toronto, ON, Canada, [13]Bologna University School of Medicine, Institute of Hematology and Medical Oncology, Bologna, Italy, [14]Hôpital Saint Antoine, Paris, France, [15]GUZ Moscow City Clinical Hospital S.P.Botkin, Moscow, Russian Federation, [16]Hospital Universatario 12 de Octubre, Madrid, Spain, [17]Celgene Corporation, Summit, NJ, United States, [18]Hematology, Hospital Universitario de Salamanca, Salamanca, Spain

Background: Optimization of adverse event (AE) management in RRMM patients (pts) is important in order to permit full-dose treatment (Tx) and maximize therapeutic benefit. RRMM pts with advanced disease exposed to multiple prior Tx present with comorbidities and may be predisposed to more frequent AEs. POM was recently approved by the US FDA for use in RRMM following at least 2 prior Tx, including bortezomib (BORT) and lenalidomide (LEN). POM+LoDEX has previously been shown to be effective and well tolerated in this pt population. MM-003 is an open-label, multicenter, phase 3 trial comparing POM+LoDEX *vs.* HiDEX in pts who failed prior LEN and BORT.
Aims: This subanalysis examined the MM-003 safety profile and AE management.
Methods: Pts must have been refractory to their last prior therapy (progressive disease [PD] during or within 60 days) and failed LEN and BORT after ≥2 consecutive cycles of each (alone or in combination). Pts were randomized 2:1 to receive 28-day cycles of POM 4 mg on days 1-21+LoDEX 40 mg (20 mg for those >75 years of age) weekly; or HiDEX 40 mg (20 mg for those >75 years of age) on days 1-4, 9-12, and 17-20. Tx continued until PD or unacceptable toxicity. Thromboprophylaxis with low-dose aspirin, low-molecular weight heparin, or equivalent was required for all pts receiving POM and those at high risk of thromboembolic events. AEs were graded according to the National Cancer Institute Common Terminology Criteria for AEs (v 4.0). Tx was withheld and started at a lower dose in subsequent cycles for any grade 4 hematologic or ≥grade 3 non-hematologic AE. Dose reduction schemes were predefined. Supportive care in the form of bisphosphonates, antibiotics, hematopoietic growth factors, erythropoietin, and platelet or red blood cell transfusions was allowed. The primary endpoint was progression-free survival (PFS), and safety was a secondary endpoint.
Results: A total of 455 pts were enrolled; 449 pts were included in the safety study population: POM+LoDEX (n=300); HiDEX (n=149). POM+LoDEX significantly improved PFS and overall survival (OS) *vs.* HiDEX. Median follow-up was 4 months. The most common grade 3-4 AEs (POM+LoDEX *vs.* HiDEX) were neutropenia (42% *vs.* 15%), anemia (27% *vs.* 29%), infections (24% *vs.* 23%), and thrombocytopenia (21% *vs.* 24%). With thromboprophylaxis, the incidence of any-grade venous thromboembolism was low (3% *vs.* 2%). Grade 3-4 febrile neutropenia occurred in 7% and 0% of pts, respectively. Any-grade peripheral neuropathy (PN) occurred in 12% and 11%, respectively (new onset: 7% and 7%). Grade 3-4 PN occurred in 1% of pts in each arm. AEs were primarily managed by dose modification and/or supportive care (Table 1). AEs of interest necessitating POM or HiDEX dose reduction included neutropenia (8%; 0%), thrombocytopenia (6%; 0%), anemia (0% for both), infection (1%; 4%), and febrile neutropenia (1%; 0%). Discontinuation due to AEs was infrequent: 7% *vs.* 6% (POM+LoDEX *vs.* HiDEX, respectively). Tx-emergent AEs that led to discontinuation of POM included infections (2%), renal failure (1%), and thrombocytopenia (0.7%). AEs causing discontinuation of DEX in either arm included infection (2%), renal failure (0.9%), and thrombocytopenia (0.4%). Updated data will be presented at the meeting.

Table 1.

	POM + LoDEX (n = 300)	HiDEX (n = 149)
Dose management		
Median average dose, mg (range)	POM: 4.0 (2.6-4.0) LoDEX: 40 (8-40)	40 (20-40)
≥ 1 dose reduction (%)	POM: 24 LoDEX: 17	26
Dose reduction for neutropenia (%)	POM: 8 LoDEX: 0	0
Dose reduction for febrile neutropenia (%)	POM: 1 LoDEX: 0.3	0
Median time to first dose reduction, mo (range)	POM: 1.0 (0.3-7.6) LoDEX: 1.9 (0.3-10.3)	1.1 (0.9-10.2)
Supportive care (%)		
Granulocyte colony-stimulating factor	38	9
Red blood cell transfusion	43	48
Platelet transfusion	17	19
Antibiotics	72	67

Summary and Conclusions: In this study, POM+LoDEX improved PFS and OS with manageable and acceptable tolerability in advanced RRMM. The majority of pts did not have a dose reduction and there were few discontinuations due to AE. POM+LoDEX should be considered a new Tx option for these pts.