Managing Myeloma

Table 3. Ixazomib, Panobinostat, Elotuzumab, and Daratumumab and SAR650984: Regimens and Outcomes.

Study Regimen	Dose Schedule	Response Rates	Progression-free Survival (PFS)	Side Effects
Ixazomib Citrate Phase 1 Trial in Relapsed Refractory MM [Richardson, 2014a] Monotherapy 2x weekly	Received single-agent ixazomib 0.24 to 2.23 mg/m^2 (days 1, 4, 8, 11; 21-day cycles) Note: twice-weekly schedule. The terminal half-life of ixazomib was 3.3 to 7.4 days; plasma exposure increased proportionally with dose (0.48-2.23 mg/m^2	**ORR: 15%** (N=55) CBR:76%	Not evaluated	Two dose-limiting toxicities (grade 3 rash; grade 4 thrombocytopenia) occurred at 2.23 mg/m^2. The maximum tolerated dose was 2.0 mg/m^2, which 40 patients received in 4 expansion cohorts. Eighty-eight percent had drug-related adverse events, including nausea (42%), thrombocytopenia (42%), fatigue (40%), and rash (40%); drug-related grade ≥3 events included thrombocytopenia (37%) and neutropenia (17%). Grade 1/2 drug-related peripheral neuropathy occurred in 12% (no grade ≥3). Two patients died on the study (both considered unrelated to treatment). Estimated dosing compliance was 94% (mean of 27.7 doses received in a mean of 7.4 cycles [29.6 planned doses]. 60 pts with elapsed/refractory multiple myeloma (median of 4 prior lines of therapy; bortezomib, lenalidomide, thalidomide, and carfilzomib/marizomib in 88%, 88%, 62%, and 5%, respectively)
Ixazomib Citrate Phase 1 Trial in Relapsed Refractory MM **[Kumar, 2014]** Safety, tolerability and MTD Monotherapy 1x weekly	Ixazomib PO (days 1, 8, 16; 28-day cycle) 1x weekly for 3 weeks of a 4-week cycle The MTD was determined to be 2.97 mg/m^2	**ORR: 18%** (n=50)	Not evaluated	Dose-limiting toxicities were grade 3 nausea, vomiting, and diarrhea in 2 patients, and grade 3 skin rash in 1 patient. Common drug-related adverse events were thrombocytopenia (43%), diarrhea (38%), nausea (38%), fatigue (37%), and vomiting (35%). Observed rate of peripheral neuropathy was 20%, with only 1 grade 3 event reported.
IRD *Ixazomib citrate, lenalidomide, dexamethasone* Phase 1/2 trial Once-weekly ixazomib citrate in combination with lenalidomide and dexamethasone in pts with previously untreated MM [Kumar, 2012]	Ixazomib PO (days 1, 8, and 15) plus lenalidomide 25 mg (days 1–21) and dexamethasone 40 mg (days 1, 8, 15, 22) for up to twelve 28-day cycles Patients could undergo stem cell collection after 3 cycles and discontinue for autologous stem cell transplant (ASCT) after 6 cycles. In Ph 1, dose escalation (1.68–3.95 mg/m^2) proceeded	ORR: 88% (ORR: 100% in Ph 1; 84% in Ph 2) 40% ≥VGPR (53% in Ph 1 and 36% in Ph 2) 18% CR (33% in Ph 1 and 14% in Ph 2). Note: Median cycle number was limited, but n=50 received ≥4 cycles: ORR: 96%,	Not Evaluated At data cut-off, 50 of 52 responders remained in response, with responses durable for up to 13.2+ months.	All-grade AEs related to any regimen drug and seen in ≥25% of patients were fatigue (32%), nausea (31%), and vomiting (25%). Grade 3 any-drug-related AEs were reported in 26 (40%) patients, including erythematous rash, nausea and vomiting (5% each). Grade 4 any-drug-related AEs were end-stage renal disease (related to progressing MM) and deep vein thrombosis in 1 patient each. One patient experienced grade 3 PN at the RP2D. 3 patients discontinued due to drug-related AEs – 1 in Ph 2 who stopped due to grade 1 resting tremor, grade 2 occasional memory loss (neurologic work-up was negative), and grade 2 peripheral sensory neuropathy, 1 patient in Ph 2 due to drug-related RSV pneumonia who subsequently died on study due to this AE, and 1 patient in Ph 1 with syncope (a DLT)

	using a standard 3+3 design, based on cycle 1 dose-limiting toxicities (DLTs). Ixazomib MTD was established as 2.97 mg/m^2 and RP2D was selected as 2.23 mg/m^2; RP2D converts to a 4.0 mg fixed dose based on population PK results.	44% ≥VGPR 26% CR. Median time to first response was 0.92 months (range 0.89–6.44).		At time of report, pts received a median of 5 cycles (range 1–15) – 6 cycles (range 1–15) in Ph 1 and 5 cycles (range 1–8) in Ph 2. 42 (65%) patients remained on treatment, 4 (27%) in Ph 1 and 38 (76%) in Ph 2. 22 pts discontinued: 16 to receive ASCT, 4 due to AEs (3 drug-related, 1 not drug-related GI bleed), 2 for other reasons (1 disease progression, 1 due to investigator decision). Among all 65 pts, median follow-up was 3.88 months (Ph 1: 9.03 months, Ph 2: 3.68 months).
IRD *Ixazomib citrate, lenalidomide, dexamethasone* Phase 1/2 trial twice-weekly ixazomib citrate in combination with lenalidomide and dexamethasone in pts with previously untreated MM [Richardson, 2013a]	Ixazomib citrate 3.0 or 3.7 mg PO (d 1, 4, 8, 11), len 25 mg PO (d 1–14), and dex 20/10 mg PO (cycles 1–8/9–16; d 1, 2, 4, 5, 8, 9, 11, 12) for up to 16 21-day cycles, followed by Ixazomib citrate maintenance (same schedule) until progression or unacceptable toxicity. Transplant-eligible pts could undergo stem cell collection after ≥4 cycles and discontinue for ASCT after ≥8 cycles.	OR:93% (n=58) 67% ≥VGPR 24% CR, 14% sCR 54% of pts had 100% decreases in M-protein or serum free light chain from baseline. Analysis of minimal residual disease was performed Depth of response increased over the course of treatment; median time to first response (≥PR) was 0.69 mos and to best response to date was 2.07 mos. Median DOR to date was 5.9+ mos, ranging up to 18+ mos.	Not Evaluated	Most common AEs were rash (61%; pooled high-level terms), fatigue, peripheral edema (each 50%), diarrhea (41%), and neuropathy peripheral (36%). Drug-related (to any drug in the regimen) grade 3 AEs were seen in 56% of pts, including rash (16%), hyperglycemia (8%), pneumonia (6%), and PN (5%; high-level term). No drug-related grade 4 AEs were seen; 58% of pts required dose reductions of at least one drug due to AEs including rash (16%), anxiety (11%), and PN (8%). AEs resulting in discontinuation were seen in 11%, with the majority reported as not related to therapy. There was 1 on-study death due to cardio-respiratory arrest, likely a pulmonary embolism, considered by the investigator to be unrelated to ixazomib or dex, but probably len. 64 pts enrolled; median age 64 yrs (range 34–82), 63% male, and 31%/16% had ISS stage II/III MM. In phase 1, 14 pts received ixazomib citrate 3.0 mg (n=7) and 3.7 mg (n=7). No DLTs were seen in cycle 1; based on overall tolerability and incidence of rash at 3.7 mg, the RP2D was chosen as 3.0 mg. 50 pts were enrolled at this dose in phase 2. At data cut-off (July 1, 2013), the median follow-up was 6.9 months and median number of cycles received was 8 (range 1–26); 73% had received ≥8 cycles and 9% had received ≥16 cycles. At data cut-off, 22% of pts had discontinued to undergo ASCT (median CD34+ stem cell yield 14.9 x 10^6/kg [range 7–52 x 10^6]), a further 14%, 5%, and 19% had discontinued due to AEs, progressive disease, and other reasons, respectively, and the other 41% remained on treatment. Based on phase 1 preliminary PK data, ixazomib was absorbed quickly with a T_{max} of 0.5–4 hours. Terminal half-life was 2–8 days. PK data were similar to single-agent twice-

				weekly dosing studies, suggesting no ixazomib PK interaction with len or dex. Rates of rash, PN, and dose reductions appear higher than in the parallel study using weekly ixazomib citrate, with similar response rates and better convenience, supporting use of weekly dosing in ongoing phase 3 trials.
Pan-VD *Panobinostat, bortezomib, dexamethasone* PANORAMA-2 [Richardson, 2013b]	Phase 1 : 8 three-week cycles of panobinostat PO (20 mg) 3x per week on weeks 1 and 2, bortezomib IV (1.3 mg/m^2) 2x per week on weeks 1 and 2, and dexamethasone PO (20 mg) 4x per week on weeks 1 and 2 on days of and after bortezomib use. Patients who showed evidence of clinical benefit in phase 1 treatment continued study therapy in phase 2 treatment. Phase 2: 6-week cycles of panobinostat 3x per week on weeks 1, 2, 4, and 5; bortezomib 1x per week on weeks 1, 2, 4, and 5; and dexamethasone on the days of and after bortezomib until disease progression, death, toxicity, or withdrawal of consent.	OR: 34.5% nCR:1.8% (n=1) PR:32.7% (n=18) 18% MR: 18.2% (n=10) CBR: 52.7% VGPR: 5.5% (n=3) SD: 36.4% (n=20) PD: 5.5% (n=3) No assessment for 5.5% (n=3) ≥PR (n=19) Median TTR=1.4 months median DoR= 6.0 months.	Median PFS: 5.4 mo With median f/u 8.3 months, median OS had not been reached	Seventeen of the 55 patients completed treatment phase 1 and entered treatment phase 2. At the time of data cutoff, 7 of these 17 patients remained on treatment. The primary reasons for discontinuing treatment (n = 48) were disease progression (n = 31; 56.4%), AE (n = 10; 18.2%), withdrawal of consent (n = 5; 9.1%), death (n = 1; 1.8%), and start of a new cancer therapy (n = 1; 1.8%). The most common AEs leading to study treatment discontinuation were fatigue (n = 4), diarrhea (n = 2), asthenia (n = 2), and pneumonia (n = 2). One patient died during study treatment and 3 others died within 28 days of study treatment (3 deaths from disease progression/MM and 1 from influenza). None of the deaths were assessed as being study treatment related. Median exposure was 4.6 months (range, 0.1-14.8). Two patients completed ≥12 cycles (48 weeks) of treatment. Dose reductions of panobinostat, bortezomib, and dexamethasone occurred in 35 (63.6%), 36 (65.5%), and 15 (27.3%) patients, respectively. Dose interruptions of panobinostat, bortezomib, and dexamethasone occurred in 32 (58.2%), 27 (49.1%), and 40 (72.7%) patients, respectively. Median relative dose intensity was 72.9% for panobinostat. The median relative dose intensities for bortezomib and dexamethasone were 79.8% and 87.5%, respectively. The most common AEs requiring dose adjustment or study treatment interruption, regardless of study drug relationship, were thrombocytopenia, fatigue, diarrhea, and vomiting.
Pan-VD *Panobinostat, bortezomib, dexamethasone* PANORAMA-1 [Richardson, 2014b; Inman, 2014]	Patients received oral PAN (20 mg) or placebo (pbo) 3×/wk + IV BTZ (1.3 mg/m^2; D 1, 4, 8, 11) during wks 1-2 with oral Dex (20 mg) on the days of and after BTZ in treatment phase (TP) 1, eight 3-wk cycles. Patients demonstrating benefit could proceed to TP2, with PAN dosing maintained and	ORR: 60.7% vs 54.6% (*P* = .087) nCR/CR: 27.6% versus 15.7% (*P* = .00006) Median DoR: 13.1 vs 10.9 mo TTR: 1.5 vs 2 mo TTP: 12.7 vs 8.5	Median PFS: 12 mo vs 8.1 mo (*P* < .0001; HR 0.63, 95% CI [0.52, 0.76]) PAN vs pbo arm. FDA Review: median PFS was 9.9 months with panobinostat versus 7.7 months with placebo. Median OS: 38.2 vs 35.4 PAN vs Placebo	Most frequently reported (>10%) grade 3/4 adverse events in the panobinostat versus the placebo arm: thrombocytopenia (56.7% vs 24.7%), diarrhea (25.4% vs 7.8%), fatigue (24.6% vs 12.6%), neutropenia (23.8% vs 8.1%), and hypokalemia (19.2% vs 6.5%), according to FDA review. Grade 3/4 events occurred in 96% of patients treated with panobinostat versus 82% with placebo. Non-fatal serious adverse events occurred in 60% of patients with panobinostat versus 42% with placebo. The most common serious adverse events were pneumonia, diarrhea, thrombocytopenia, and sepsis. ECG changes following treatment occurred in 64% of patients treated with panobinostat versus 42%

	BTZ/Dex less frequent.		(HR = 0.87; 95% CI, 0.70-1.07; P = .1783). *Analysis followed 86.5% of the required events.*	with placebo. New T-wave changes were 40% and 18% and ST-segment depressions were 22% and 4%, for panobinostat and placebo, respectively. QT prolongation was similar in both arms.
Elotuzumab Phase 1 MTD study (mono-therapy) [Zonder, 2012]	6 dose levels were evaluated (0.5, 1.0, 2.5, 5.0, 10, or 20 mg/kg) in patients with advanced MM. Patients received elotuzumab (IV) once every 14 days for 8 weeks. Patients who did not show evidence of progressive disease (PD) or relapse at week 8 had the option of receiving a second 8-week treatment course at the same dose level and schedule.	ORR: 0 SD:26.5% (9) PD: 73.5% (34)	Not Evaluated	Overall, 30 patients (88.2%) reported treatment-emergent AEs. The most frequent treatment-emergent AEs, regardless of attribution to study medication, included chills, fatigue, pyrexia, cough, headache, anemia, nausea, and back pain. Most events were grade 1 or 2 in severity. Eighteen patients (52.9%) experienced AEs attributed to elotuzumab. Common AEs: Chills 32,4%(11), pyrexia 17.6% (6), flushing 11.8% (4), chest discomfort 8.8% (3), fatigue 8.8% (3), headache 8.8% (3), sinus tachycardia 8.8% (3), vomiting8.8% (3), anorexia 5.9% (2), dyspnea 8.8% (3), serum creatinine increase 8.8% (3). Thirty-one serious AEs were reported in 15 patients (44.1%). Six serious AEs occurring in 4 patients were assessed as related to treatment with elotuzumab: bradycardia (grade 2), chest discomfort (grade 2), chills (grade 2), hypersensitivity (grade 3), pyrexia (grade 2), and acute renal failure (grade 4), which was treated with medications, resolved to grade 3 at 5 days later, and required dialysis after the patient's discharge from the hospital. Overall, there were 10 (29.4%) patients who developed an infection during the course of therapy, including 7 patients who had grade 3 or 4 infections assessed as unrelated to elotuzumab. There were no opportunistic viral or fungal infections. The analysis of infection AEs and serious AEs did not reveal a dose-dependent relationship to elotuzumab. Four patients died during the course of the study. The events leading to death were assessed as not related to study drug. Before the implementation of the revised infusion management guidelines, 13 of 25 treated patients experienced infusion reactions, which with one exception (grade 3 hypersensitivity reaction) were grade 1 or 2 in severity. In total, 5 patients had at least one infusion interrupted, discontinued, or rate of infusion reduced in response to an infusion reaction. Most frequent infusion reactions presented as chills, pyrexia, headache, and flushing. Twenty (58.8%) patients reported an infusion reaction during the first elotuzumab infusion. However, 10 patients had reactions at subsequent infusions. Following a protocol amendment to require infusion reaction premedication immediately before a first dose of elotuzumab, no further serious or grade 3 and 4 infusion reactions were observed. Grade 1 and 2 infusion reactions either resolved spontaneously, typically within 24 hours, or were managed as clinically indicated.

Elo-LD *Elotuzumab, lenalidomide, dexamethasone* Phase I study evaluated elotuzumab, lenalidomide, and dexamethasone in patients with relapsed or refractory multiple myeloma (MM). [Lonial, 2012]	Three cohorts were enrolled and treated with elotuzumab (5, 10, or 20 mg/kg intravenously) on days 1, 8, 15, and 22 of a 28-day cycle in the first two cycles, and days 1 and 15 of each subsequent cycle; lenalidomide 25 mg orally [PO] on days 1 to 21; and dexamethasone 40 mg PO weekly. Patients received a median of 10.5 treatment cycles (range, 1.0 to 21.0 cycles) as of August 20, 2010. At doses of 10 mg/kg and 20 mg/kg, the observed minimum elotuzumab serum concentrations (Cmin) at steady-state were consistently maintained above 70 µg/mL, the antibody trough level required for optimal antitumor activity based on the preclinical xenograft mouse model.	OR: 82% (23/28) ≥VGPR 32% (9) SD: 10.7% (3) PD: 7% (2) [both received prior lenalidomide therapy]. Median TTR: 50 days (range, 22 to 167 days). Median duration of exposure: 289 days (range, 22 to 561 days) for elotuzumab	Not Evaluated	The most frequent grade 3 to 4 toxicities were neutropenia (36%) and thrombocytopenia (21%). Two patients experienced a serious infusion reaction (one grade 4 anaphylactic reaction and one grade 3 stridor) during the first treatment cycle. Twenty-five (89%) of 28 patients experienced at least one infusion reaction that fit the predefined criteria. The most common of these were nausea (six patients; 21%), headache (six patients; 21%), dyspnea (five patients; 18%), chills (four patients; 14%), dizziness (three patients; 11%), hyperhidrosis (three patients; 11%), cough (three patients; 11%), and rash (three patients; 11%). Other infusion reactions were seen in less than 10% of patients (less than three). Most of these infusion reactions resolved within 24 hours either spontaneously or following treatment as indicated. 21% (6) experienced at least one elotuzumab dose interruption or discontinuation.
ELo-LD *Elotuzumab, lenalidomide, dexamethasone* Phase II study evaluated elotuzumab, lenalidomide, and dexamethasone in patients with relapsed or refractory multiple myeloma (MM). [Richardson, 2012] Note: This study established 10 mg/kg IV as the preferred dose.	Pts with R/R MM previously treated with 1–3 prior therapies were randomized to Elo 10 or 20 mg/kg IV (days 1, 8, 15, 22 every 28 days in cycles 1–2 and days 1, 15 in cycles ≥3) plus lenalidomide 25 mg (PO) (days 1–21) and dexamethasone 40 mg PO weekly or 28 mg PO plus 8 mg IV on Elo dosing days. All pts received a premedication regimen of methylprednisolone or dexamethasone, diphenhydramine, ranitidine, and acetaminophen prior to elo dosing to minimize infusion	Overall ORR: 84% (61) 10 mg/kg ORR: 92% (33) 20 mg/kg OR: 76% (28) Overall median time to objective response was 1 month (range, 0.7-19.2). Subgroup analyses combining 10 and 20 mg/kg cohorts ORRs for pts with 1 (n=33) or ≥2 prior therapies (n=40) were 91% and 78%, respectively.	Med PFS: 25 mo 10 mg/kg Med PFS: 26.9 mo (95% confidence interval [CI]: 14.9–NR); 20 mg/kg Med PFS: 18.6 mo (95% CI: 12.9–NR). Subgroup analysis combining 10 and 20 mg/kg cohorts median PFS for pts with 1 (n=33) or ≥2 prior therapies (n=40) were 25.0 (95% CI: 15.7–NR) and 21.3 mos (95% CI: 14.0–NR), respectively.	Fifty-six (78%) pts experienced ≥1 treatment emergent grade ≥3 event. Most common were lymphopenia (19%), neutropenia (18%), thrombocytopenia (16%), anemia (12%), leukopenia (10%), hyperglycemia (10%), pneumonia (7%), diarrhea (7%), fatigue (7%), and hypokalemia (6%). Two deaths occurred on study (multiple adverse events [n=1; pneumonia, multiple organ failure and sepsis]; disease progression [n=1]). Investigator-designated (any grade) infusion reactions were reported in 12% of pts; 1 pt had a grade 3 event (rash). There were 4 cases of second primary malignancies (prostate; bladder; myelodysplastic syndrome; nasal squamous cell); all were deemed unrelated to elotuzumab.

	reactions. Treatment continued until disease progression, unacceptable toxicity, or death 73 pts were treated (10 mg/kg, n=36; 20 mg/kg, n=37). Median age was 63 (range, 39-82) years, 55% received ≥2 prior therapies, 60% prior bortezomib, and 62% prior thalidomide. Median (range) duration of treatment was 20.5 (3.0-31.0) and 16.0 (1.0-32.0) cycles with 10 and 20 mg/kg, respectively.	Pts with prior thalidomide (n=45) had an ORR of 82% At the data cutoff (July 10 2012), 27 pts (10 mg/kg, n=15; 20 mg/kg, n=12) were ongoing and 46 pts discontinued (disease progression, n=26	Pts with prior thalidomide (n=45) had a median PFS of 26.9 mos (95% CI: 14.9–NR).	
Daratumumab [anti-CD38] Dose-dependent efficacy of daratumumab (DARA) as monotherapy in patients with relapsed or refractory multiple myeloma (RR MM). [Lokhorst, 2014]	A: 8 mg/kg +/- pre-dose daratumumab IV (10mg) wkly for the first 8 infusions. B: 16 mg/kg daratumumab without pre-dose with a 3-wk washout period between the first 2 doses followed by 7 wkly doses. Then all pts were dosed every 2nd wk for 16 wks followed by dosing every 4th wk until disease progression, toxicity or for max 24 mos. 30 pts in the 8mg/kg cohort and 15 pts in the 16 mg/kg cohort recruited into the GEN501 expansion part Median number of DARA infusions was 10.5 vs 7.0, reflecting the more recent initiation of the 16 mg/kg cohort. Infusion times were 3.5 vs 3.4 hours in the 8 and 16mg/kg groups, respectively.	ORR: 7% 8 mg/kg n=30 ORR: 46% 16 mg/kg n=13	Not Evaluated	Most common AEs reported (in ≥20% of all pts) were pyrexia, allergic rhinitis, fatigue, upper respiratory tract infection, diarrhea, dyspnea and cough. Note that AEs less than 20% were not reported, and that may still be a significant # of AEs of concern. Only mild (Gr 1 and 2) infusion-related reactions (IRRs) were reported with 27% in the 16mg/kg group vs 20% in the 8mg/kg group. 2 SAEs, 1 in each group, were assessed as related to DARA (1 thrombocytopenia, 1 lymphocytopenia). One pt was withdrawn after 1st full dose due to thrombocytopenia Gr 3. Omission of the pre-dose increased neither the incidence nor the severity of IRRs.
Dara-LD *Daratumumab, lenalidomide, dexamethasone*	Daratumumab [DARA] + Lenalidomide (LEN)+dexamethasone [DEX]: (DARA [2-16 mg/kg] per week [8	All doses ORR 72% (8/11) VGPR: 45% (5/11)	Not Evaluated	One patient (2 mg/kg dose) withdrew from study due to recurrent grade 1 QT prolongation and hypokalemia. Most frequent (>40% patients) adverse events

Safety and efficacy of daratumumab with lenalidomide and dexamethasone in relapsed or relapsed, refractory multiple myeloma. [Plesner, 2014]	wks], twice a month [16 wks], then, once monthly until disease progression, unmanageable toxicity or ≤24 months; LEN [25 mg]; DEX [40 mg] once weekly). Cohort expansion (part 2) study explores testing of maximum DARA dose determined in part 1. Median prior therapies: 4 (2-4) Median ECOG status: 0.5 (0-1) Median DARA infusions: 14.5 (1-23) Median infusion time: 6.6 (5.9-7.3) hours. MTD was not reached. DARA+LEN+DEX PK-profile was similar to DARA alone suggesting LEN and DEX do not affect the DARA PK-profile.	MR: 18% (2/11)		were neutropenia and diarrhea; 17 were ≥ grade 3 with 70% hematological (neutropenia, thrombocytopenia, anemia).
SAR650984 [anti-CD38] A phase I trial of SAR650984, a CD38 monoclonal antibody, in relapsed or refractory multiple myeloma. [Martin TG, 2014a]	SAR was given by IV weekly (QW) or every 2 weeks (Q2W) Dose levels (DLs): 0.3, 1, 3, 5, 10, and 20 mg/kg Q2W and 10 mg/kg QW using 3+3 design (N=35) MTD was not reached at any dose level.	Overall all DLs ORR: 24% (N=34) CBR: 29% CR: 6% PR: 18% MR: 6% SD: 41% PD: 29% DL ≥ 10 mg/kg (n=18) ORR: 33% CBR: 39% CR: 11% PR: 22% SD: 39% MR: 5% PD: 22% Responses occurred at all dose levels ≥1 mg/kg. CBR(≥MR): 29% SD: 41%	Not Evaluated	Adverse events in ≥ 10% of pts at all DL, regardless of causality, were fatigue (48.6%), nausea (34.3%), pyrexia (28.6%), anemia (28.6%), cough (25.7%), headache (25.7%), upper respiratory infection and chills (22.9%), dyspnea (20%), constipation (17.1%), diarrhea and vomiting (14.3%) and bone pain, chest discomfort, muscle spasms, thrombocytopenia and hypokalemia in 11.4% of pts. SAR related ≥G 3 adverse events included pneumonia (n = 3), with hyperglycemia, hypophosphatemia, pyrexia, apnea, fatigue, thrombocytopenia and lymphopenia in 1 pt each.

SAR-LD *SAR650984, lenalidomide, dexamethasone* Phase Ib dose escalation trial of SAR650984 (Anti-CD-38 mAb) in combination with lenalidomide and dexamethasone in relapsed/ refractory multiple myeloma. [Martin, 2014b]	Three dose levels (DL) of SAR 3, 5 and 10 mg/kg were evaluated in combination with lenalidomide (LEN) and dexamethasone (Dex). LEN 25 mg was given on days (d) 1 – 21 and D 40 mg on d 1, 8, 15 and 22 every 28 days. SAR was given IV on d 1 and 15 and escalated using the classic 3+3 design. 13 patients (pts) with RRMM were treated Median age 61 yrs (48 - 73) Median prior treatment regimens 6 (2 - 12) 100% had received prior LEN 23% prior pomalidomide 92.3% previously received bortezomib 38.5% prior carfilzomib. Median time from diagnosis to first SAR dosing was 4.5 yrs (3 - 11). MTD was not reached. PK showed non linearity at select dose levels	ORR: 58% (n=12) Responses occurred at each DL of 3 mg/kg (1 PR), 5 mg/kg (1 PR, 1 VGPR) and 10 mg/kg (1 PR, 3 VGPR). CBR(≥MR): 67 % 1 MR at 3 mg/kg. Median time on treatment was 20.6 weeks (0 - 35); 7 pts remained on therapy.	Not Evaluated	The most frequent adverse events included nausea, cough (n = 6 each); fatigue, muscle spasm, infection (n = 5 each); vomiting, diarrhea, dehydration and insomnia (n = 4 each). Grade (G) ≥3 hematologic abnormalities were neutropenia (n = 4) and thrombocytopenia (n = 3). One pt discontinued therapy (cycle 1, d 1) due to an infusion reaction (bronchospasm G 3). No dose limiting toxicities were detected.

Note: Ixazomib, panobinostat, elotuzumab, daratumumab and SAR650984 are not approved by the United States (US) Food and Drug Administration (FDA) for the treatment of multiple myeloma (MM). Note: On November 6, 2014, ODAC voted 5-2 against the approval of panobinostat, stating that the risks outweighed the benefits regarding toxicities and only a demonstrated PFS benefit.