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Abstract 2325

Carfilzomib, Dexamethasone, and Daratumumab Versus Carfilzomib and Dexamethasone in Relapsed or Refractory Multiple Myeloma: Updated Efficacy and Safety Results of the Phase 3 Candor Study

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Introduction: The randomized, open-label, multicenter, phase 3 CANDOR study compared carfilzomib, dexamethasone, and daratumumab (KdD) to carfilzomib and dexamethasone (Kd) in patients with multiple myeloma who have relapsed after 1–3 prior lines of therapy (ClinicalTrials.gov, NCT03158688). In the previously reported primary analysis (Dimopoulos et al, *Lancet* 2020), a significant progression-free survival (PFS) benefit was demonstrated in patients treated with KdD vs patients treated with Kd (hazard ratio [HR], 0.63 [95% CI, 0.46–0.85]; two-sided *P*=0.0027). However, after a median follow-up of 16.9 months, median PFS was not reached in the KdD arm. Here, we report updated efficacy and safety outcomes from the CANDOR study.

Methods: Adult patients with relapsed or refractory multiple myeloma (RRMM) received 28-day cycles of KdD or Kd (randomized 2:1). In the primary analysis, PFS was the primary endpoint and overall survival (OS) a key secondary endpoint. In this prespecified interim OS analysis, statistical testing was based on the actual number of OS events observed by the data cutoff (approximately 36 months after enrollment of the first patient); PFS was summarized descriptively. Disease progression was determined locally by investigators in an unblinded manner and centrally by the sponsor using a validated computer algorithm (Onyx Response Computer Algorithm [ORCA]) in a blinded manner. PFS and OS were compared between the KdD and Kd arms using a stratified log-rank test, and HRs were estimated by a stratified Cox proportional-hazards model.

Results: Patients were randomized to KdD (n=312) and Kd (n=154). Of all randomized patients, median age was approximately 64 years; 42% received previous lenalidomide, and 33% were lenalidomide refractory; 90% received previous bortezomib, and 29% were bortezomib refractory. At the data cutoff date of June 15, 2020, 199 (63.8%) patients in the KdD arm and 88 (57.1%) in the Kd arm remained on study. Among patients treated with KdD and Kd, 140 (44.9%) and 85 (55.2%) had PFS events, respectively; median follow-up was 27.8 months (KdD) and 27.0 months (Kd). Median PFS by ORCA was 28.6 months for the KdD arm versus 15.2 months for the Kd arm (HR, 0.59 [95% CI, 0.45–0.78]; **Figure**). OS data were not mature and will be updated at a future prespecified analysis. Median treatment

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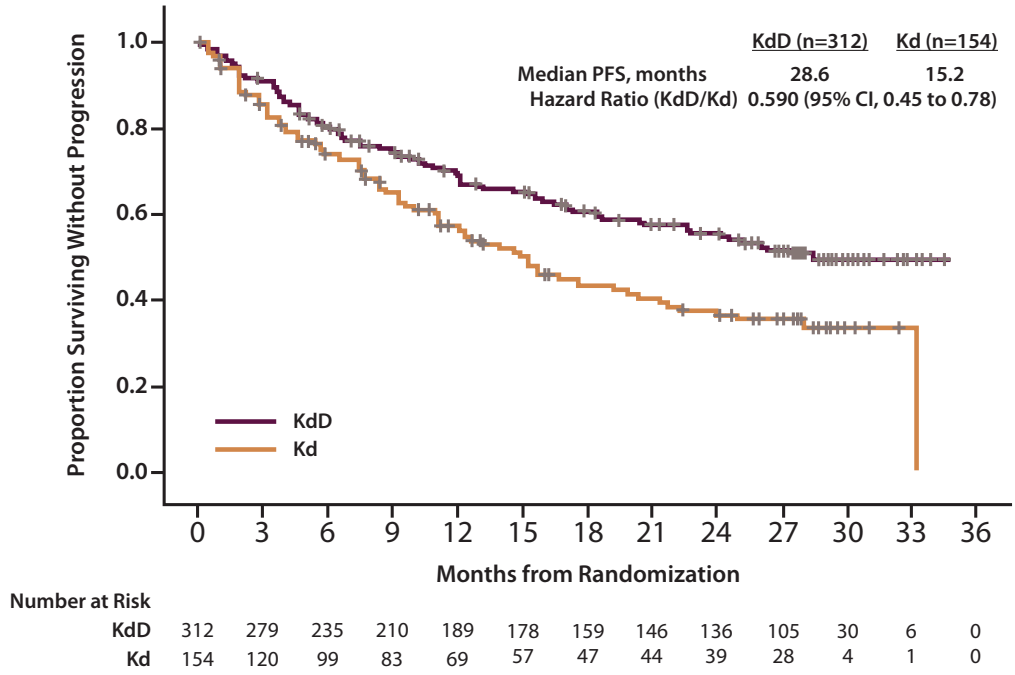
duration was 79.3 weeks with KdD versus 40.3 weeks with Kd. Grade ≥3 adverse events (AEs) occurred in 87.0% and 75.8% of patients in the KdD and Kd arms, respectively, and fatal AEs occurred in 8.8% and 4.6%; one fatal AE in the KdD arm (due to arrhythmia) and one fatal AE in the Kd arm (due to COVID-19 pneumonia) had occurred since the primary analysis. Carfilzomib treatment discontinuation rates due to AEs were 26.0% with KdD and 22.2% with Kd. Exposure-adjusted AE rates per 100 patient years were: 171.2 and 151.9 for grade ≥3 AEs and 6.9 and 5.6 for fatal AEs in the KdD and Kd arms, respectively. Updated data by key subgroups will be presented.

Conclusion: With approximately 11 months of additional follow-up, a 13.4-month improvement in median PFS was observed in patients treated with KdD (28.6 months) versus patients treated with Kd (15.2 months; HR, 0.59 [95% CI, 0.45–0.78]). Safety was consistent with previously reported results. KdD continues to show a favorable benefit-risk profile and represents an efficacious treatment option for patients with RRMM.



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Abstract 2287

Carfilzomib, Dexamethasone, and Daratumumab Versus Carfilzomib and Dexamethasone in Relapsed or Refractory Multiple Myeloma: Subgroup Analysis of the Phase 3 Candor Study in Patients with Early or Late Relapse

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Introduction: Although outcomes for patients with multiple myeloma (MM) have improved with recent advances in treatment, relapse is still frequent. Early relapse is associated with poorer outcomes (Majithia *et al.*, *Leukemia* 2016;30:2208–13) and is thought to reflect more aggressive disease, particularly within 12 months of autologous stem cell transplantation (ASCT). In the randomized phase 3 CANDOR study, progression-free survival (PFS) was significantly improved in patients with relapsed or refractory MM (RRMM) receiving carfilzomib, dexamethasone, and daratumumab (KdD) compared with carfilzomib and dexamethasone (Kd) (ClinicalTrials.gov, NCT03158688; Usmani *et al.*, *Blood* 2019;134:LBA-6). In this post hoc analysis of the CANDOR study, we studied the safety and efficacy of KdD vs Kd in patients with early or late relapse following the most recent therapy.

Methods: In the CANDOR study, patients with RRMM who received 1–3 prior lines of therapy were randomized 2:1 to receive KdD or Kd. The primary endpoint was PFS; secondary endpoints included overall response rate (ORR), rate of complete response or better (≥CR), and safety. In this analysis, subgroups were defined by relapse timing following the most recent therapy. Relapse <12 months from initiation of the most recent line of therapy was defined as early, and relapse ≥12 months from initiation of the most recent line of therapy was defined as late (except for the subgroup of patients who received only one prior line of therapy, where a cutoff of 18 months was used to define early and late relapse). For the subgroup of patients with prior ASCT, relapse <12 months following prior transplant was classified as early, and relapse ≥12 months following prior transplant was classified as late. Median PFS was estimated using the Kaplan-Meier method, while hazard ratios (HRs) and 95% CIs were estimated from a nonstratified Cox regression model. Response rates were defined per the International Myeloma Working Group Uniform Response Criteria.

Results: In total, 452 patients (156 of whom received prior ASCT) were included in this post hoc analysis; 210 patients received 1 prior line of therapy, and 242 patients received ≥2 prior lines of therapy. PFS HRs (KdD vs Kd) were consistent across subgroups regardless of early or late relapse, including in patients with prior ASCT (**Figure**). In patients who received 1 prior line of therapy, the ORR was 86.4% vs 57.6% for early relapsers in the KdD vs Kd arms and 93.9% vs 88.9% for late relapsers, respectively. The rate of ≥CR was 28.8% vs 3.0% for early relapsers and 39.0% vs 16.7% for late relapsers. In patients who received ≥2 prior lines of therapy, the ORR was 75.3% vs 65.1% for early relapsers in the KdD vs Kd arms and 82.9% vs 86.1% for late relapsers. The rate of ≥CR was 19.8% vs 4.7% for early relapsers and 28.0% vs 16.7% for late relapsers. The rates of grade ≥3 treatment-emergent adverse events (TEAEs) observed in the early and late relapse subgroups were similar to that in the overall CANDOR population.

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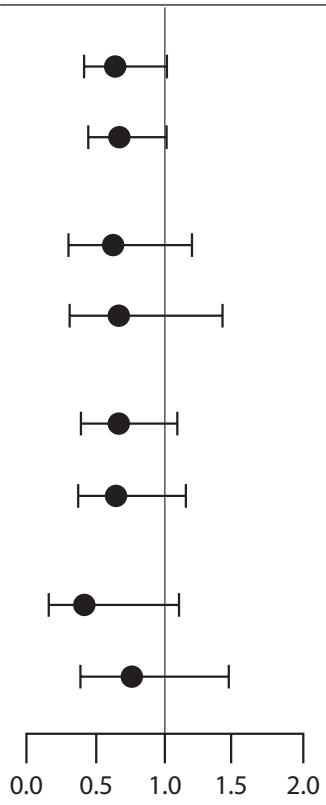
Conclusion: In this post hoc analysis from the phase 3 CANDOR study, efficacy results were generally consistent across early and late relapse subgroups. In particular, rates of ≥CR were higher with KdD vs Kd among patients with early relapse. The rates of grade ≥3 TEAEs were consistent with the safety profile of overall KdD and Kd cohorts. These results support the use of KdD in patients with RRMM, regardless of early or late relapse, prior ASCT, or whether patients relapsed after one prior line of therapy or 2 or more prior lines of therapy.

Figure

Subgroup	KdD (n=304)* Events/ Patients	KdD (n=304)* Median PFS (95% CI), months	KdD (n=148)† Events/ Patients	KdD (n=148)† Median PFS (95% CI), months	Hazard ratio (KdD/Kd) (95% CI)
≥1 prior line of therapy					
Early relapse (<12 months)	51/116	18.5 (12.1, NE)	32/64	11.1 (7.4, 17.6)	0.6 (0.4, 1.0)
Late relapse (≥12 months)	56/188	NE (NE, NE)	34/84	NE (15.2, NE)	0.7 (0.4, 1.0)
1 prior line of therapy					
Early relapse (<18 months)	23/59	NE (13.3, NE)	13/33	13.2 (5.7, NE)	0.6 (0.3, 1.2)
Late relapse (≥18 months)	17/82	NE (NE, NE)	11/36	NE (15.7, NE)	0.7 (0.3, 1.4)
≥2 prior lines of therapy					
Early relapse (<12 months)	38/81	18.5 (9.2, NE)	24/43	12.0 (7.4, 15.3)	0.7 (0.4, 1.1)
Late relapse (≥12 months)	29/82	NE (17.0, NE)	18/36	15.8 (9.3, NE)	0.6 (0.4, 1.2)
Prior ASCT‡					
Early relapse (<12 months)	12/25	16.0 (4.2, NE)	6/8	4.3 (0.5, 17.6)	0.4 (0.2, 1.1)
Late relapse (≥12 months)	27/92	NE (NE, NE)	12/31	NE (12.3, NE)	0.7 (0.4, 1.5)



ASCT, autologous stem cell transplantation; CI, confidence interval; Kd, carfilzomib, dexamethasone; KdD, carfilzomib, dexamethasone, daratumumab; NE, not estimable; PFS, progression-free survival.

*From the CANDOR intention-to-treat population, n=8 patients in the KdD arm had missing data or did not receive treatment per randomization and were excluded from this analysis.

†From the CANDOR intention-to-treat population, n=6 patients in the Kd arm had missing data or did not receive treatment per randomization and were excluded from this analysis.

‡Includes patients with ≥1 prior lines of therapy.

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OffLabel Disclosure: Carfilzomib is a proteasome inhibitor and daratumumab is an anti-CD38 monoclonal antibody, which can both be used to treat RRMM.

Abstract 2282

Evaluation of Minimal Residual Disease (MRD) Negativity in Patients with Relapsed or Refractory Multiple Myeloma Treated in the Candor Study

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Introduction: CANDOR is a multicenter, phase 3, randomized study of adult patients with relapsed or refractory multiple myeloma (RRMM) previously treated with 1–3 prior lines of therapy (NCT03158688). 466 patients received carfilzomib, dexamethasone, and daratumumab (KdD) or carfilzomib and dexamethasone (Kd) in 2:1 randomization (KdD: 312; Kd: 154). Based on the primary endpoint, KdD demonstrated superior progression-free survival (PFS) vs Kd (hazard ratio [HR], 0.63 [95% CI, 0.46–0.85]; *P*=0.0014). Deep responses and minimal residual disease (MRD) negativity have been associated with improved PFS for patients with RRMM. Herein, we present an analysis of MRD results from CANDOR.

Methods: Details of the dose and schedule were previously reported (Dimopoulos et al., *Lancet* 2020). The rate of patients with confirmed CR which were MRD negative (MRD[-]CR) in bone marrow aspirate at 12 months (± 4 weeks) measured by next-generation sequencing (NGS; threshold, 1 tumor cell/10^{-5} white blood cells) was a prespecified key secondary endpoint. Exploratory analyses included MRD[-]CR at increasing sensitivity (10^{-4}, 10^{-5}, 10^{-6}) and best overall response MRD[-] status at any time point. All reported responses were by Independent Review Committee and were analyzed for the Intent-to-Treat population. MRD[-] status is at $<10^{-5}$ unless otherwise specified.

Results: The best overall MRD[-]CR rate at any time was 13.8% vs 3.2% in the KdD vs Kd arm (Odds ratio [OR], 4.95; *P*<0.0001) and the MRD[-] rate regardless of overall response status was 22.8% vs 5.8% (OR, 5.15; *P*<0.0001). At the 12-month landmark, the MRD[-]CR rate was 12.5% vs 1.3% in the KdD vs Kd arm (OR, 11.3; *P*<0.0001) and the MRD[-] rate was 17.6% vs 3.9% (OR, 5.76; *P*<0.0001) with the proportion of patients with MRD[-]VGPR being 4.2% vs 2.6%, respectively. The MRD[-]CR rates at the 12-month landmark for KdD vs Kd were consistent across clinically relevant subgroups (**Table**).

At the 12-month landmark, KdD treatment resulted in a greater proportion of CR rates (26.9% vs 9.7%) and deeper MRD responses than Kd. Among patients in CR, the depth of response as measured by NGS MRD level at the 12-month landmark was deeper for KdD relative to Kd: cutoff of $>10^{-4}$, 36.9% vs 73.3%; 10^{-4} to 10^{-5}, 16.7% vs 13.3%; 10^{-5} to 10^{-6}, 23.8% vs 13.3%; $<10^{-6}$, 22.6% vs 0% for KdD vs Kd, respectively (**Figure**). Similar to the results at the 12-month landmark, MRD responses independent of the landmark were deeper among patients in the KdD compared to the Kd arm. With median follow-up of 6 months from the 12-month landmark, no patient with MRD[-]CR response progressed or died.

Additional post hoc analyses were conducted within patients randomized to KdD to explore prognostic characteristics for MRD[-]CR. Importantly, prior lenalidomide exposure did not meaningfully impact the MRD[-]CR rate at the

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12-month landmark; 13.2% (25/189), 11.4% (14/123), and 13.1% (13/99) for naïve, exposed, and refractory subgroups, respectively. For prior bortezomib, the MRD[-]CR rates were 24% (6/25), 11.5% (33/287), and 6.8% (6/88) for naïve, exposed, and refractory subgroups, respectively. The rates of MRD[-]CR at the 12-month landmark within the KdD arm were consistent across subgroups: patients refractory to the last prior therapy (yes vs no, 10.9% vs 14.3%), number of prior regimens (1–2 vs 3 prior regimens; 13.2% vs 10.1%), prior transplant (yes vs no, 11.8% vs 13.7%), duration of first remission (≤2 vs >2 years, 12.3% vs 13% and ≤1 vs >1 year, 10.7% vs 13.4%), baseline creatinine clearance (≥15 to <50, ≥50 to <80, and ≥80 mL/min, 10.5%, 14.4%, and 11.9%, respectively), age (≤75 vs >75 years, 12.9% vs 8.0%), or dose intensity (< vs ≥ median) for carfilzomib or daratumumab (10.5% vs 14.9% and 9.8% vs 15.6%, respectively). Data on cytogenetics will be included at the time of presentation.

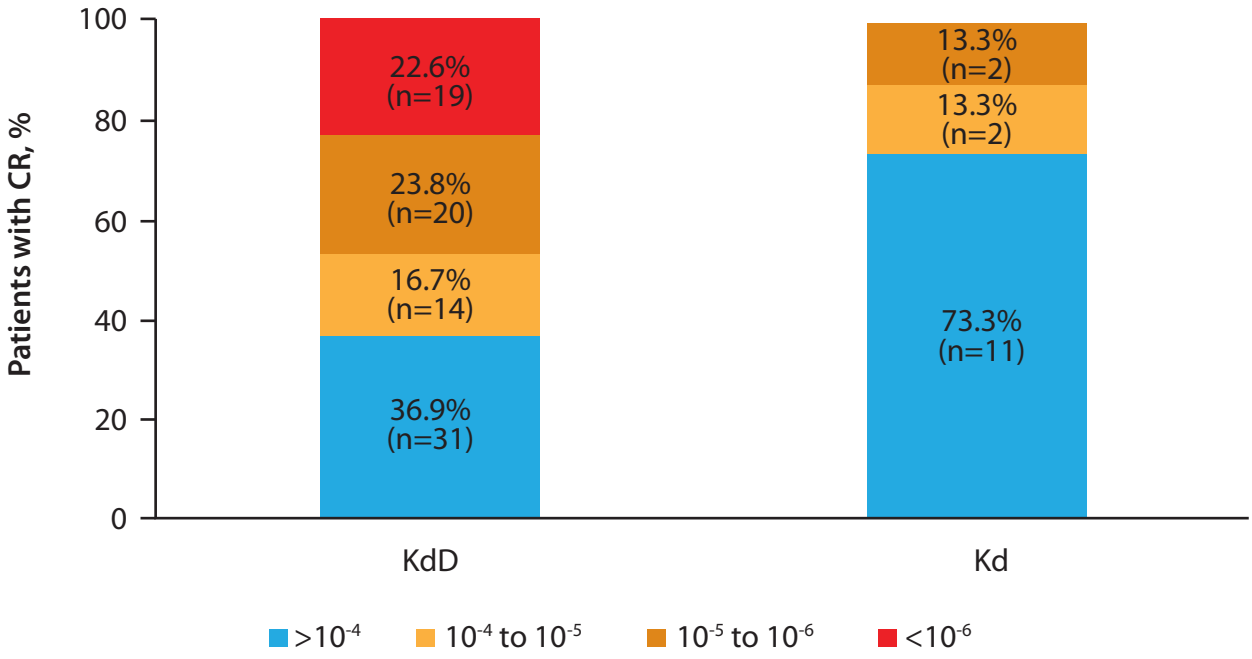
Conclusion: At the primary analysis, patients treated with KdD achieved significantly higher MRD[-]CR rates vs Kd at the 12-month landmark. Among patients with an MRD[-]CR, the depth of MRD was deeper with KdD vs Kd. With a median of 6 months follow-up, no patient with an MRD[-]CR has progressed; duration of response will be updated at time of presentation. Within the KdD arm, lenalidomide exposure or refractoriness did not diminish the MRD[-]CR rate. These findings support the efficacy of the KdD regimen as an effective treatment for RRMM, including patients who have become lenalidomide refractory.

Table. Subgroup Analyses of MRD-negative rates at 12 months for patients who had achieved complete response

		Kd		KdD	
Group	**n/N**	**MRD[-]CR**	**n/N**	**MRD[-]CR**	**Odds Ratio**
Prior lines of therapy per IXRS					
1	1/67	1.5%	22/133	16.5%	13.1 (1.7, 99.3)
≥2	1/87	1.1%	17/179	9.5%	9.0 (1.2, 69.0)
Age at baseline, years					
≤75	1/136	0.7%	37/287	12.9%	20.0 (2.7, 147.2)
>75	1/18	5.6%	2/25	8.0%	1.5 (0.1, 17.7)
Baseline CrCl, mL/min					
≥15 to 49	0/27	0.0%	4/38	10.5%	NE
≥50 to 79	1/50	2.0%	14/97	14.4%	8.3 (1.0, 64.8)
≥80	1//77	1.3%	21/176	11.9%	10.3 (1.4, 78.0)
Prior lenalidomide					
Yes	0/74	0.0%	14/123	11.4%	NE
No	2/80	2.5%	25/189	13.2%	5.9 (1.4, 25.7)
Refractory to lenalidomide					
Yes	0/55	0.0%	13/99	13.1%	NE
No	2/99	2.0%	26/213	12.2%	6.7 (1.6, 29.0)
Prior bortezomide or ixazomib exposure					
Yes	2/137	1.5%	34/289	11.8%	9.0 (2.1, 38.0)
No	0/17	0.0%	5/23	21.7%	NE
Refractory to bortezomide or ixazomib					
Yes	1/55	1.8%	7/100	7.0%	4.1 (0.5, 33.9)
No	1/99	1.0%	32/212	15.1%	17.4 (2.3, 129.4)
Prior IMiD exposure					
Yes	0/110	0.0%	24/206	11.7%	NE
No	2/44	4.5%	15/106	14.2%	3.5 (0.8, 15.8)
Refractory to IMiD					
Yes	0/65	0.0%	16/130	12.3%	NE
No	2/89	2.2%	23/182	12.6%	6.3 (1.4, 27.3)

Odds ratios and corresponding 95% CIs were estimated by unstratified analysis using the Mantel-Haenszel method as specified.

Figure. Level of Residual Disease in CR Patients at 12-month Landmark



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Abstract 2316

Isatuximab Plus Carfilzomib and Dexamethasone Vs Carfilzomib and Dexamethasone in Relapsed/Refractory Multiple Myeloma (IKEMA): Interim Analysis of a Phase 3, Randomized, Open-Label Study

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Background: Treatment of relapsed/refractory multiple myeloma (RRMM) has greatly improved, yet relapse is inevitable and additional effective treatments are needed. Isatuximab (Isa), a monoclonal antibody targeting a specific epitope on CD38, is approved in combination with pomalidomide and dexamethasone (d) in the United States, the European Union, Canada, Australia, Switzerland, and Japan for the treatment of adult patients with RRMM who have received at least two prior therapies including lenalidomide and a proteasome inhibitor.

Aim: Demonstrate benefit of adding Isa to carfilzomib (K) plus d (Kd) vs Kd in RRMM.

Methods: In this Phase 3 study (NCT03275285), pts with RRMM and 1–3 prior lines of therapy were randomized 3:2 and stratified by number of prior lines and R-ISS to receive Isa-Kd or Kd. Isa-Kd arm received Isa (10 mg/kg IV) weekly for 4 weeks, then every 2 weeks. Both arms received K (20 mg/m^2 Days 1–2, 56 mg/m^2 thereafter) twice-weekly for 3 of 4 weeks, and d (20 mg) twice-weekly. Treatment continued until disease progression or unacceptable adverse events (AE). Primary objective: demonstrate an increase in progression free survival (PFS) of Isa-Kd vs Kd, determined by an Independent Response Committee (IRC). Comparison between arms conducted through log-rank testing. Key secondary objectives: evaluation of overall response rate (ORR), rate of very good partial response (VGPR) or better, complete response (CR) rate, minimal residual disease (MRD) negativity rate (10^{-5} by NGS), and overall survival (OS). Key secondary endpoints tested with a closed test procedure. Safety data included treatment emergent adverse events (TEAE), and hematology and biochemistry results for all pts. Interim efficacy analysis was planned when 65% of the total expected PFS events were observed.

Results: 302 pts (179 Isa-Kd, 123 Kd) were randomized. Pt characteristics were well-balanced across arms. Median (range) age 64 (33–90) years; R-ISS I, II, III was 25.8%, 59.6%, 7.9% respectively; 44%, 33% and 23% had 1, 2 and ≥3 prior lines respectively; 90% and 78% had prior proteasome inhibitor and immunomodulatory drug (IMiD) respectively; 24% had high-risk cytogenetics. At a median follow-up of 20.7 months and with 103 PFS events per IRC, median PFS was not reached for Isa-Kd vs 19.15 months Kd; HR 0.531 (99% CI 0.318–0.889), one-sided p=0.0007. Thus, the pre-specified efficacy boundary (p=0.005) was crossed. PFS benefit was consistent across subgroups. ORR (≥partial response [PR]) was 86.6% Isa-Kd vs 82.9% Kd, one-sided p=0.1930. ≥VGPR rate was 72.6% Isa-Kd vs 56.1% Kd, p=0.0011. CR rate was 39.7% Isa-Kd vs 27.6% Kd. MRD negativity rate (10^{-5}) in the intent to treat population (ITT) was 29.6% (53/179) Isa-Kd vs 13.0% (16/123) Kd, descriptive p=0.0004. OS was immature (events 17.3% Isa-Kd vs

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20.3% Kd). 52.0% Isa-Kd vs 30.9% Kd pts remain on treatment. Main reasons for treatment discontinuation were disease progression (29.1% Isa-Kd vs 39.8% Kd) and AEs (8.4% Isa-Kd vs 13.8% Kd). Grade ≥3 TEAEs were observed in 76.8% Isa-Kd vs 67.2% Kd. Treatment-emergent SAEs and fatal TEAEs were similar in Isa-Kd and Kd: 59.3% vs 57.4% and 3.4% vs 3.3%, respectively. Infusion reactions were reported in 45.8% (0.6% Grade 3–4) Isa-Kd and 3.3% (0% Grade 3–4) Kd. Grade ≥3 respiratory infections (grouping) were seen in 32.2% Isa-Kd vs 23.8% Kd. Grade ≥3 cardiac failure (grouping) was reported in 4.0% Isa-Kd vs 4.1% Kd. As per lab results, Grade 3–4 thrombocytopenia and neutropenia were reported in 29.9% Isa-Kd vs 23.8% Kd and 19.2% Isa-Kd vs 7.4% Kd, respectively.

Conclusions: Addition of Isa to Kd provided a superior, statistically significant improvement in PFS with clinically meaningful improvement in depth of response. Isa-Kd was well tolerated with manageable safety and a favorable benefit-risk profile, and represents a possible new standard of care treatment in pts with relapsed MM.

Disclosures: Moreau: *Takeda:* Honoraria; *Sanofi:* Consultancy, Honoraria; *Abbvie:* Consultancy, Honoraria; *Celgene/Bristol-Myers Squibb:* Consultancy, Honoraria; *Janssen:* Consultancy, Honoraria; *Novartis:* Honoraria; *Amgen:* Consultancy, Honoraria. **Dimopoulos:** *Beigene:* Honoraria; *Janssen:* Honoraria; *Celgene:* Honoraria; *Amgen:* Honoraria; *Bristol-Myers Squibb:* Honoraria; *Takeda:* Honoraria. **Mikhael:** *Amgen, Celgene, GSK, Janssen, Karyopharm, Sanofi, Takeda:* Honoraria. **Yong:** *Janssen:* Honoraria, Research Funding; *GSK:* Honoraria; *Amgen Inc.:* Honoraria; *Takeda:* Honoraria, Research Funding; *Sanofi:* Honoraria, Research Funding. **Facon:** *Janssen, Takeda, Amgen, Roche, Karyopharm, Oncopeptides, BMS, Sanofi:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau. **Hajek:** *Amgen:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Pharma MAR:* Consultancy, Honoraria; *Takeda:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Janssen:* Consultancy, Honoraria, Research Funding; *BMS:* Consultancy, Honoraria, Research Funding; *AbbVie:* Consultancy, Honoraria, Research Funding; *Celgene:* Consultancy, Honoraria, Research Funding; *Roche:* Consultancy, Honoraria, Research Funding; *Oncopeptides:* Consultancy, Honoraria, Research Funding; *Novartis:* Consultancy, Honoraria, Research Funding. **Spicka:** *Celgene, Amgen, Janssen-Cilag, Takeda, Bristol-Myers Squibb, Novartis, Sanofi:* Consultancy, Honoraria, Speakers Bureau. **Risse:** *Sanofi:* Current Employment. **Asset:** *Sanofi:* Current Employment. **Macé:** *Sanofi:* Current Employment. **Martin:** *Roche:* Consultancy; *Juno Therapeutics:* Consultancy; *Amgen:* Research Funding; *Sanofi:* Research Funding; *Seattle Genetics:* Research Funding.

OffLabel Disclosure: Isatuximab, a monoclonal CD38 antibody, is approved in combination with pomalidomide and dexamethasone in the United States, the European Union, Canada, Australia, Switzerland, and Japan for the treatment of adult patients with relapsed/refractory multiple myeloma who have received at least two prior therapies, including lenalidomide and a proteasome inhibitor.

Abstract 414

Depth of Response and Response Kinetics of Isatuximab Plus Carfilzomib and Dexamethasone in Relapsed Multiple Myeloma: Ikema Interim Analysis

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Introduction: Achievement of minimal residual disease negative (MRD-) status in multiple myeloma (MM) is associated with improved progression-free survival (PFS) and overall survival (OS). Isatuximab (Isa) is an approved anti-CD38 IgG kappa monoclonal antibody. We analyzed the depth of response including MRD-, long-term outcomes, and kinetics of tumor response in the IKEMA study. Measurement by mass spectrometry of serum M-protein was also performed to overcome the interference with Isa in standard immunofixation assay.

Methods: IKEMA was a randomized, open-label, multicenter Phase 3 study that investigated Isa plus carfilzomib and dexamethasone (Isa-Kd) vs Kd in patients (pts) with relapsed MM who received 1–3 lines of therapy (NCT03275285). The primary endpoint of PFS and secondary endpoints of overall response rate (ORR), very good partial response or better (≥VGPR) and complete response (CR) rate were determined by an Independent Response Committee based on central data for M-protein, central imaging review and local bone marrow for plasma cell infiltration according to IMWG criteria. MRD was assessed in bone marrow aspirates from pts who achieved ≥VGPR by next generation sequencing at 10^{-5} sensitivity level. Mass spectrometry analysis was performed to measure serum M-protein without Isa interference. Hazard ratios and corresponding confidences interval were estimated using Cox proportional hazards model. Secondary endpoints were compared between treatment arms using Cochran Mantel Haenszel test. Per ITT, all randomized pts not reaching MRD- or without MRD assessment were analyzed as MRD+.

Results: 302 pts (179 Isa-Kd, 123 Kd) were randomized. At a median follow-up of 20.7 months deeper responses were observed in Isa-Kd vs Kd with ≥VGPR 72.6% vs 56.1% (nominal p=0.011) and ≥CR 39.7% vs 27.6%, respectively. MRD- occurred in 53/179 (30%) pts in the Isa-Kd arm vs 16/123 (13%) in the Kd arm (nominal p=0.0004) with 20.1% (36/179 pts Isa-Kd) vs 10.6% (13/123 pts Kd) reaching CR and MRD-. PFS by MRD status is shown in the **Figure**, HR favors Isa-Kd vs Kd in both MRD- pts (HR 0.578, 95% CI: 0.052–6.405) and MRD+ pts (HR 0.670, 95% CI: 0.452–0.993). MRD- pts had a longer PFS than MRD+ pts. Within Isa-Kd, MRD-negative status could be obtained in pts with renal impairment (26.5% MRD- vs 25.9% MRD+ with eGFR <60 mL/min/1.73 m^2); with ISS stage III at diagnosis (32.1% MRD- vs 27.8% MRD+); with t(4;14) [13.2% MRD- vs 11.9% MRD+], with gain(1q21) [45.3% MRD-

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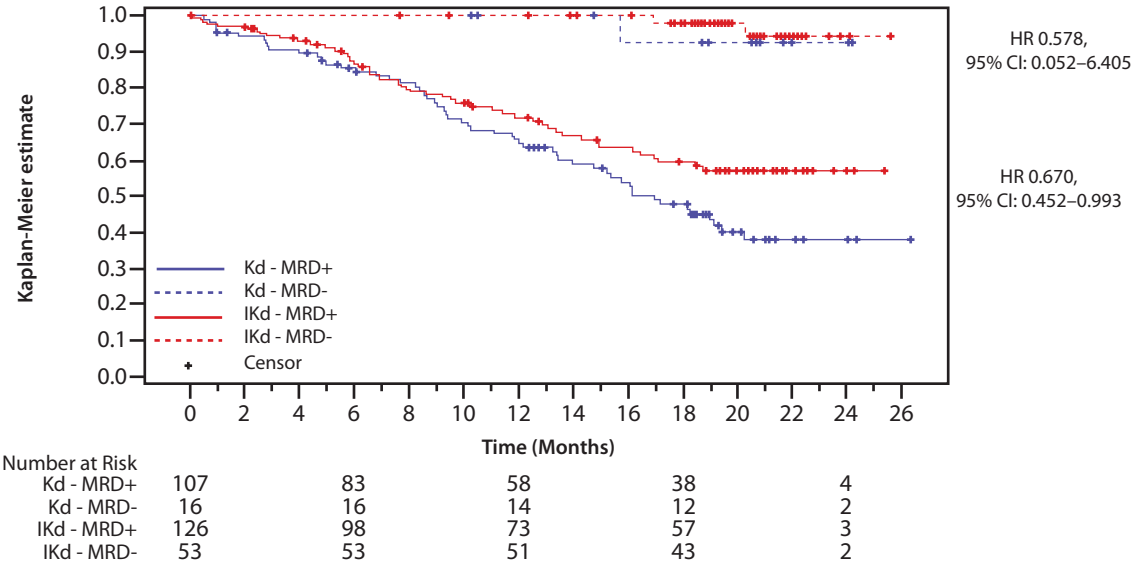
vs 40.5% MRD+]; in heavily pretreated ≥3 prior lines (22.6% MRD- vs 19.0% MRD+) or refractory to lenalidomide in last regimen (18.9% MRD- vs 20.6% MRD+). Within Isa-Kd, MRD-negative status was reached less frequently in pts refractory to a proteasome inhibitor (PI) [18.9% MRD- vs 36.5% MRD+) or with del(17p), [3.8% MRD- vs 12.7% MRD+].

Interference of Isa with M protein was explored: samples from 27 pts with near-CR (only serum immunofixation (IF) positive IgG kappa) or potential CR (serum remaining M protein ≤0.5 g/dL with IF positive IgG kappa) in the Isa-Kd arm were tested by mass spectrometry. Among them, 11 near-CR or potential CR pts had documented <5% plasma cells in bone marrow and were mass spectrometry negative (residual myeloma M protein level below LOQ of central lab immunofixation). In addition, 7/11 were also MRD-. These results support that both current CR rate and MRD- CR rate are underestimated (potential adjusted CR rate of 45.8%; potential adjusted MRD- CR rate 24%). Responses occurred quickly in both arms. The median time (Isa-Kd vs Kd) in responders to: first response was 32.0 (28–259) days vs 33.0 (27–251) days; best response 120.0 (29–568) days vs 104.5 (29–507) days; first CR 184.0 (30–568) days vs 229.5 (58–507) days; first ≥VGPR 88.0 (28–432) vs 90.0 (29–491) days, respectively. In addition to increased depth of response, quality of life as measured by QLQ-C30 Global Health Status scores was maintained with Isa-Kd per descriptive analyses.

Conclusions: There was a clinically meaningful improvement in depth of response in Isa-Kd vs Kd. CR rate in Isa-Kd of 39.7% was underestimated due to interference. Mass spectrometry results suggest that the potential adjusted CR rate could be reached for 45.8% of pts with 1 to 3 prior lines treated in Isa-Kd. More pts in Isa-Kd vs Kd reached MRD negativity (30% vs 13%) and at least twice as many reached CR MRD- (20.1% vs 10.6%; adjusted 24% vs 10.6%). Reaching MRD negativity was associated with longer PFS in both arms.

Figure. PFS by minimal residual disease (MRD) status



CI, confidence interval; d, dexamethasone; HR, hazard ratio; I, isatuximab; K, carfilzomib; MRD, minimal residual disease; PFS, Progression-free survival.

Disclosures: Martin: *Legend Biotech:* Consultancy; *Sanofi, Amgen, Seattle Genetics, JNJ – Janssen:* Research Funding. **Mikhael:** *Amgen, Celgene, GSK, Janssen, Karyopharm, Sanofi, Takeda:* Honoraria. **Hajek:** *Takeda:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Pharma MAR:* Consultancy, Honoraria; *BMS:* Consultancy, Honoraria, Research Funding; *AbbVie:* Consultancy, Honoraria, Research Funding; *Celgene:* Consultancy, Honoraria, Research Funding; *Amgen:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Janssen:* Consultancy, Honoraria, Research Funding; *Novartis:* Consultancy, Honoraria, Research Funding; *Oncopeptides:* Consultancy, Honoraria, Research Funding; *Roche:* Consultancy, Honoraria, Research Funding. **Kim:** *Amgen, BMS, Janssen, Sanofi, Takeda:* Consultancy, Honoraria, Research Funding. **Suzuki:** *Takeda, Celgene, ONO, Amgen, Novartis, Sanofi, Bristol-Myers Squibb, AbbVie and Janssen:* Honoraria; *Bristol-Myers Squibb, Celgene and Amgen:* Research Funding; *Takeda, Amgen, Janssen and Celgene:* Consultancy. **Hulin:** *Janssen:* Honoraria; *Celgene/Bristol-Myers Squibb, Janssen, GlaxoSmithKline, and Takeda:* Consultancy, Honoraria; *AbbVie:* Honoraria; *Amgen:* Honoraria. **Garg:** *Janssen, Takeda, Celgene, Novartis, Sanofi:* Honoraria. **Quach:** *GlaxoSmithKline, Karyopharm, Amgen, Celgene, Janssen Cilag:* Consultancy; *GlaxoSmithKline, Karyopharm, Amgen, Celgene, Janssen Cilag:* Honoraria; *Amgen, Celgene, Karyopharm, GSK, Janssen Cilag, Sanofi:* Membership on an entity's Board of Directors or advisory committees; *Amgen, Sanofi, Celgene, Karyopharm, GSK:* Research Funding. **Risse:** *Sanofi:*

Current Employment. **Asset:** *Sanofi:* Current Employment. **Macé:** *Sanofi:* Current Employment. **van de Velde:** *Sanofi:* Current Employment, Current equity holder in publicly-traded company. **Moreau:** *Celgene/Bristol-Myers Squibb:* Consultancy, Honoraria; *Janssen:* Consultancy, Honoraria; *Sanofi:* Consultancy, Honoraria; *Abbvie:* Consultancy, Honoraria; *Takeda:* Honoraria; *Novartis:* Honoraria; *Amgen:* Consultancy, Honoraria.

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Abstract 415

Randomized Phase 2 Study of Weekly Carfilzomib 70 mg/m^2 and Dexamethasone Plus/Minus Cyclophosphamide in Relapsed and/or Refractory Multiple Myeloma (RRMM) Patients (GEM-KyCyDex)

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Introduction: Carfilzomib dosed at 56 mg/m^2 twice a week in combination with dexamethasone (Kd) is a standard of care for RRMM after 1–3 prior lines (PL) based on the ENDEAVOR study. Later, the ARROW study showed Kd dosed at 70 mg/m^2 weekly to be superior to Kd dosed at 27 mg/m^2 twice a week on RRMM patients (pts) after 2–3 PL. On the other side, cyclophosphamide is an alkylating agent that has been widely combined with proteasome inhibitors and immunomodulatory drugs in MM, improving their efficacy with a good safety profile.

In this phase 2 randomized study, we have compared Kd plus cyclophosphamide (KCyd) with Kd in RRMM after 1–3PL, both with K dosed weekly at 70 mg/m^2.

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Patients and methods: RRMM after 1–3 PL of therapy were included in the trial. Consistently with the ENDEAVOR population, previous therapy with proteasome inhibitors was allowed but refractory patients were excluded.

Pts were randomized 1:1 to receive K at a dose of 70 mg/m^2 IV on days 1, 8 and 15 plus dexamethasone at a dose of 20 mg PO the day on and the day after K plus/minus KCyd at a dose of 300 mg/m^2 IV on days 1, 8 and 15 of each 28 days-cycle, as continuous treatment until progressive disease or unacceptable toxicity. The primary endpoint was PFS and key secondary endpoints included response rates, safety profile, and OS.

Results: Between January 2018 and February 2020, 198 RRMM pts were included. 97 pts were randomized to KCyd and 101 to Kd. The baseline characteristics of the patients were well balanced between both groups. The median age was 70 years, and 70% and 28% of pts were older than 65 and 75. The median number of PL was one; 61% of pts had received 1 prior line. 94% and 92% of patients had been exposed to bortezomib in the KCyd and Kd and all of them were sensitive. 72% and 67% of patients had been exposed to IMiD's and 51% and 55% of them were IMiD's-refractory in the KCyd and Kd. Only 4 and 6 patients in KCyd and Kd, had received anti-CD38 antibodies being all refractory.

After a median f/u of 15.6 months, median PFS was 20.7 m and 15.2 m in KCyd and Kd (p=0.2). In pts after 1PL, median PFS has not been reached in any arm (p=0.4) and in patients after 2–3PL, KCyd resulted in a median PFS of 20.7 vs 11 m for Kd (p=0.4). Of note, in the IMiD-refractory population, the addition of Cy to Kd resulted in a significant benefit in terms of PFS: 26.2 months vs 7.7 months in the Kd arm (p=0.01). OS is immature with 23 and 25 events so far in KCyd and Kd, respectively.

The ORR was 78% for KCyd and 73% for Kd: 20% of patients in both arms achieved at least complete response, 33% and 28% very good partial response, respectively, and 25% partial response in both arms. The MRD-ve rate was 4% and 5%.

As far as toxicity is concerned, neutropenia was the only hematological adverse event more frequently reported in KCyd compared with Kd, of any grade (24% vs 11%) and grade 3–4 (13% vs 7%). This did not translate into more infections and the rate was comparable in both arms (5% G3–4 in both arms). Thrombocytopenia of any grade and grade 3–4 occurred in 14%/1% and 18%/10% in KCyd/Kd. Cardiovascular events of any grade occurred in 22% and 30% of patients in KCyd and Kd. Nine pts in KCyd developed G3–4 cardiovascular events, these included atrial fibrillation (1 pt), cardiac failure (2 pts), myocardial infarct (2 pts), and hypertension (4 pts). In the Kd arm, 11 patients developed G3–4 cardiovascular events and consisted of hypertension in most of them (9 pts).

Conclusion: Cyclophosphamide added to Kd 70 mg/m^2 weekly in RRMM pts after 1–3 PL prolonged the PFS as compared to Kd particularly in the lenalidomide-refractory population. The administration of K at a dose of 70 mg/m^2 weekly was safe and more convenient and overall, the toxicity profile was manageable in both arms.

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Abstract 141

Survival Analysis of Newly Diagnosed Transplant-Eligible Multiple Myeloma Patients in the Randomized Forte Trial

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Background: Proteasome inhibitor (PI)-based induction/consolidation proved to be effective in newly diagnosed multiple myeloma (NDMM) patients (pts) eligible for melphalan 200 mg/m^2 plus autologous stem-cell transplantation (MEL200-ASCT). High response rates have been reported with carfilzomib (K) plus lenalidomide-dexamethasone (KRd) or cyclophosphamide-dexamethasone (KCd). Lenalidomide (R) alone is a standard of care for post-ASCT maintenance; K maintenance showed promising results in phase I/II studies, but no data on KR maintenance vs R are available.

Aims: The aims of this analysis were to evaluate the progression-free survival (PFS) of KRd induction-ASCT-KRd consolidation (KRd_ASCT) vs 12 cycles of KRd (KRd12) vs KCd induction-ASCT-KCd consolidation (KCd_ASCT) and the PFS of KR vs R maintenance. Secondary aims were efficacy in different subgroups of pts and safety of the maintenance phase.

Methods: NDMM pts ≤65 years were randomized [R1: 1:1:1, stratification International Staging System (ISS) and age] to: *KRd_ASCT*: 4 28-day cycles with KRd induction (K 20/36 mg/m^2 IV days 1,2,8,9,15,16; R 25 mg days 1–21; dexamethasone [d] 20 mg days 1,2,8,9,15,16) followed by MEL200-ASCT and 4 KRd consolidation cycles; *KRd12*: 12 KRd cycles; *KCd_ASCT*: 4 28-day induction cycles with KCd (K 20/36 mg/m^2 IV days 1,2,8,9,15,16; cyclophosphamide 300 mg/m^2 days 1,8,15; d 20 mg days 1,2,8,9,15,16) followed by MEL200-ASCT and 4 KCd consolidation cycles. Thereafter, pts were randomized (R2) to maintenance with KR (K 36 mg/m^2 days 1,2,15,16, subsequently amended to 70 mg/m^2 days 1,15 for up to 2 years; plus R 10 mg days 1–21 every 28 days until progression) or R alone (10 mg days 1–21 every 28 days until progression). Centralized minimal residual disease (MRD) evaluation (8-color second-generation flow cytometry, sensitivity 10^{-5}) was performed in pts achieving ≥very good partial response before maintenance and every 6 months (m) during maintenance. Data cut-off was June 30, 2020.

Results: 474 NDMM pts were randomized (KRd_ASCT, n=158; KRd12, n=157; KCd_ASCT, n=159) and analyzed. Pt characteristics were well balanced. Intention-to-treat (ITT) data of pre-maintenance MRD (KRd_ASCT, 62%; KRd12 56%, KCd_ASCT 43%) and safety of the induction/consolidation phases in the 3 arms were already reported (F. Gay et al. ASH 2018; S. Oliva et al. ASH 2019). After a median follow-up from R1 of 45 m, median PFS was not reached with KRd_ASCT, 57 m with KRd12 and 53 m with KCd_ASCT (KRd_ASCT vs KCd_ASCT: HR 0.53, *P*<0.001; KRd_ASCT vs KRd12: HR 0.64, *P*=0.023; KRd12 vs KCd_ASCT: HR 0.82, *P*=0.262). The benefit of KRd_ASCT vs both KCd_ASCT and KRd12 was observed in most subgroups (**Figure**). 3-year overall survival (OS) was 90% with KRd_ASCT and KRd12 vs 83% with KCd. 356 pts (KR, n=178; R, n=178) were randomized to maintenance; pt characteristics, pre-maintenance response (≥complete response [CR]: KR 62% vs R 59%; stringent CR: KR 50% vs R 48%) including MRD negativity (KR 65% vs R 66%) in the 2 groups were well balanced. After a median follow-up from R2 of 31 m and a median duration of maintenance of 27 m in both arms, 46% of MRD-positive pts at randomization turned negative in KR vs 32% in R (*P*=0.04). By ITT analysis, 3-year PFS from R2 was 75% with KR vs 66% with R (HR 0.63; *P*=0.026). The benefit of KR vs R was observed in most subgroups (**Figure**). 3-year OS was 90% in both arms.

During maintenance, a similar proportion of pts experienced ≥1 grade (G)3–4 hematologic adverse events (AEs)/serious AEs (SAEs) in the 2 arms (KR 22% vs R 23%); the most frequent were neutropenia (KR 18% vs R 21%) and thrombocytopenia (KR 3% vs R 3%). Rate of ≥1 G3–4 non-hematologic AEs/SAEs was higher with KR (27%) compared

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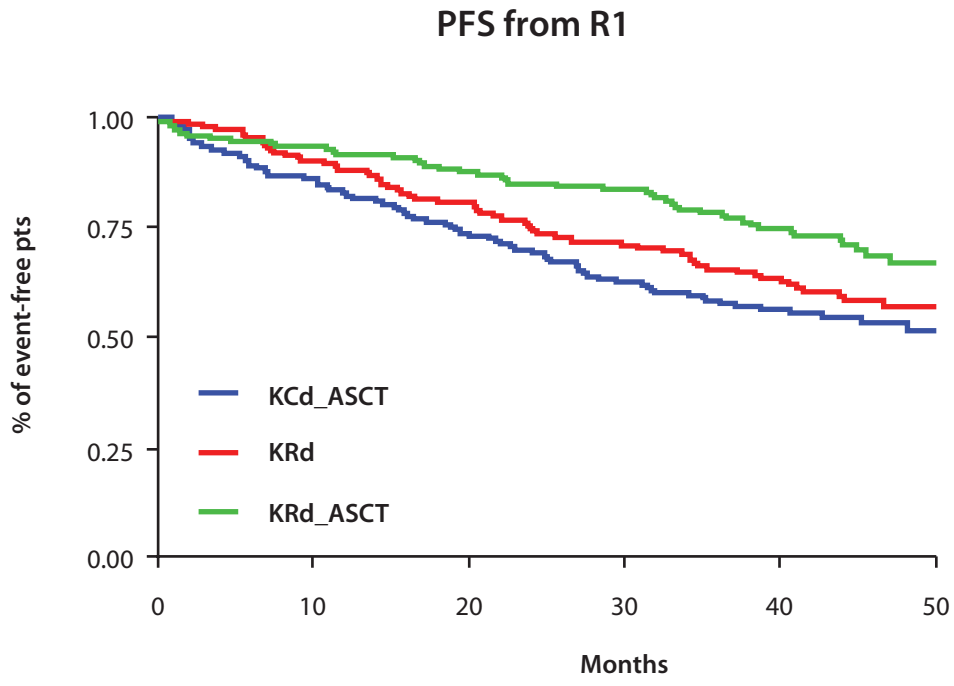
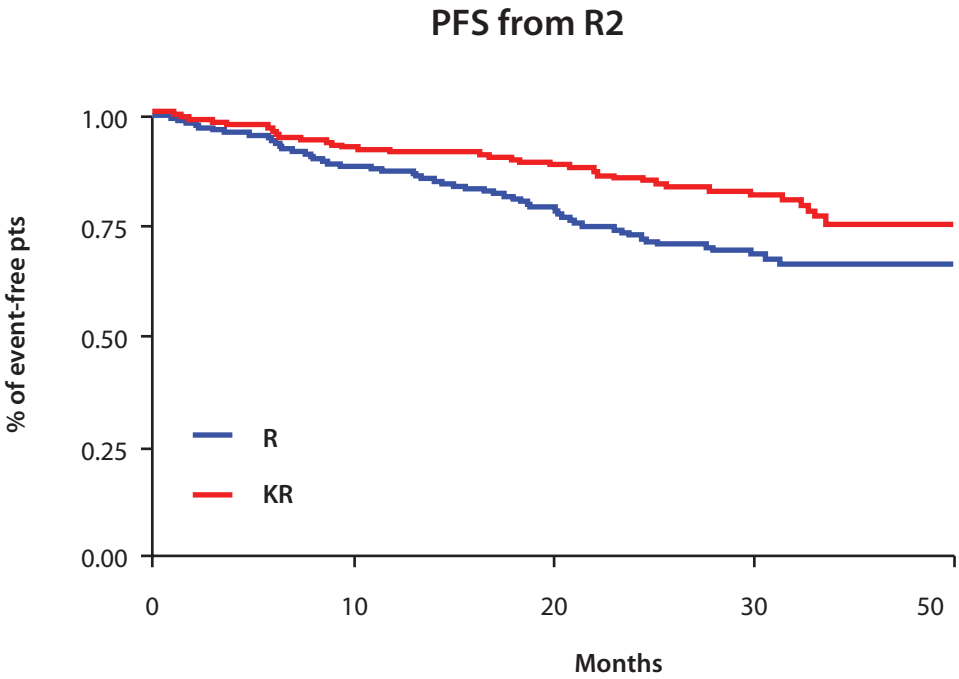
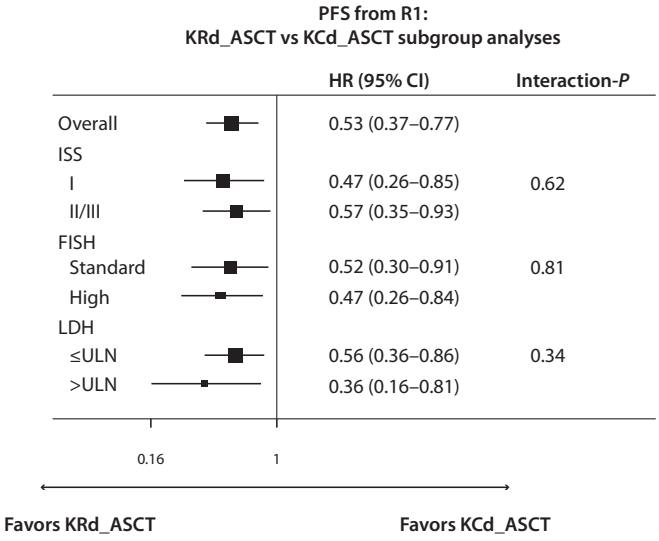
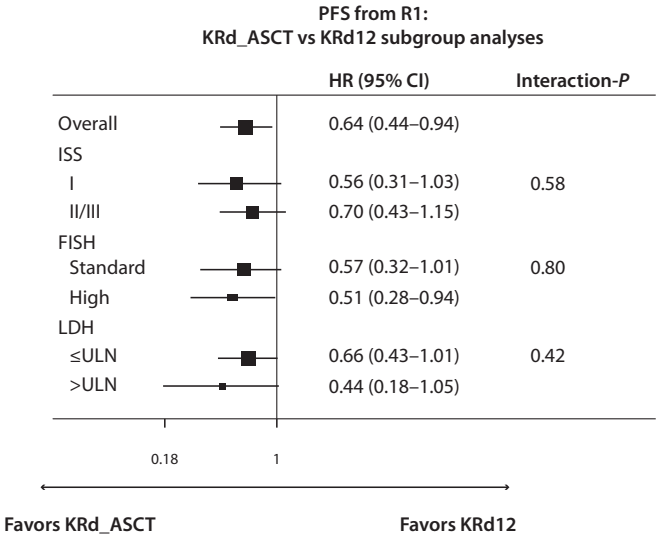
with R (15%), *P*=0.012; the most frequent were infections (KR 4% vs R 7%); all other events were reported in ≤5% of pts and included: gastrointestinal (KR 5% vs R 2%), cardiac (KR 4% vs R 1%), hypertension (KR 3% vs R 0%), and thrombotic microangiopathy (3% vs 0%). 4 pts developed a second primary malignancy in KR (breast 1 pt; thyroid 1 pt; myelodysplastic syndrome 1 pt; non-melanoma skin cancer 1 pt) vs 1 pt in R (acute lymphoblastic leukemia). Dose reductions of R were reported in 23% of KR and 29% of R pts; dose reductions of K were reported in 20% of pts. The rate of discontinuation due to AEs was similar in the 2 arms (KR 10% vs R 9%).

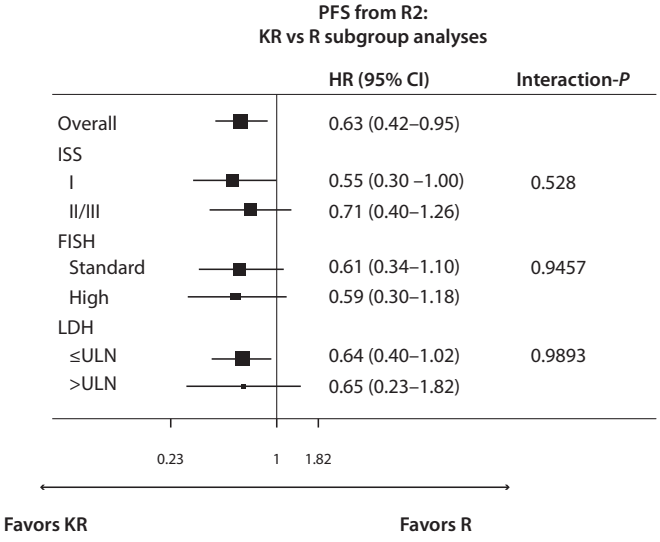
Conclusions: Treatment with KRd_ASCT significantly improved PFS compared with both KRd12 and KCd_ASCT. Maintenance with KR also improved PFS vs R.











Abbreviations. PFS, progression-free survival; R1, first randomization (induction treatment); R2, second randomization (maintenance treatment); pts, patients; K, carfilzomib; C, cyclophosphamide; R, lenalidomide; d, dexamethasone; KRd12, 12 cycles of KRd; ASCT, autologous stem-cell transplantation; HR, hazard ratio; CI, confidence interval; *P*, p-value; ISS, International Staging System stage; FISH, fluorescence *in situ* hybridization; LDH, lactate dehydrogenase; ULN, upper limit of normal.

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OffLabel Disclosure: The presentation includes discussion of off-label use of a drug or drugs for the treatment of multiple myeloma (including carfilzomib, cyclophosphamide, lenalidomide and dexamethasone).

Abstract 181

A Phase 1 First in Human (FIH) Study of AMG 701, an Anti-B-Cell Maturation Antigen (BCMA) Half-Life Extended (HLE) BiTE® (bispecific T-cell engager) Molecule, in Relapsed/Refractory (RR) Multiple Myeloma (MM)

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Aims: To evaluate AMG 701, a BiTE® molecule binding BCMA on MM cells and CD3 on T cells, in RR MM (Amgen, NCT03287908); primary objective was to evaluate safety and tolerability and estimate a biologically active dose; secondary objectives were to characterize pharmacokinetics (PK), anti-myeloma activity per IMWG criteria, and response duration.

Methods: Patients with MM RR or intolerant to ≥3 lines [proteasome inhibitor (PI), IMiD, anti-CD38 Ab as available] received AMG 701 IV infusions weekly in 4-week cycles until disease progression (PD). A 0.8-mg step dose was added prior to target doses ≥1.2 mg to prevent severe cytokine release syndrome (CRS). Target dose was achieved by day 8 or sooner with earlier escalation. Exclusion criteria included: solely extramedullary disease; prior allogeneic stem cell transplant (SCT) in the past 6 months; prior autologous SCT in the past 90 days; CNS involvement; prior anti-BCMA therapy. The first 3 cohorts (dose 5–45 μg) had 1 patient each, the next cohorts (0.14-1.2 mg) had 3–4 patients each, and subsequent cohorts (1.6–12 mg) were to have 3–10 patients each. Minimal residual disease (MRD) was measured by next-generation sequencing (NGS, $\leq 10^{-5}$ per IMWG) or flow cytometry ($\leq 3\times10^{-5}$).

Results: As of July 2, 2020, 75 patients received AMG 701. Patients had a median age of 63 years, a median time since diagnosis of 5.9 years, and a median (range) of 6 (1–25) prior lines of therapy; 27% of patients had extramedullary disease, 83% prior SCT, and 93% prior anti-CD38 Ab; 68% were triple refractory to a PI, an IMiD, and an anti-CD38 Ab. Median (Q1, Q3) treatment duration was 6.1 (3.1, 15.3) weeks and median follow-up on treatment was 1.7 (1.0, 3.7) months. Patients discontinued drug for PD (n=47), AEs (adverse events, n=4, 3 CRS, 1 CMV / PCP pneumonia),

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withdrew consent (4), other therapy (1), investigator discretion (1), and CNS disease (1); 17 patients remain on AMG 701.

The most common hematological AEs were anemia (43%), neutropenia (23%), and thrombocytopenia (20%). The most common non-hematological AEs were CRS (61%), diarrhea (31%), fatigue (25%), and fever (25%). CRS was mostly grade 1 (n=19) or 2 (n=21) per Lee Blood 2014 criteria. All grade 3 CRS (n=5, 7%) were assessed as dose-limiting toxicities (DLTs); all were reversible with corticosteroids and tocilizumab, with median duration of 2 days. CRS grade 3 drivers included transient LFT increases in 3 patients and hypoxia in 2 patients. Other DLTs were 1 case each of transient grade 3 atrial fibrillation, transient grade 3 acidosis, and grade 4 thrombocytopenia. Serious AEs (n=29, 39%) included infections (13), CRS (7), and asymptomatic pancreatic enzyme rise (2, no imaging changes, 1 treatment related). There were 4 deaths from AEs, none related to AMG 701 (2 cases of sepsis, 1 of retroperitoneal bleeding, and 1 of subdural hematoma). Reversible treatment-related neurotoxicity was seen in 6 patients, with median duration of 1 day, all grade 1–2, and associated with CRS in 4 patients.

The response rate was 36% (16/45) at doses of 3–12 mg; at ≤1.6 mg (n=27), there was 1 response at 0.8 mg in a patient with low baseline soluble BCMA (sBCMA). With earlier dose escalation with 9 mg, the response rate was 83% (5/6, 3 PRs, 2 VGPRs), with 4/5 responders being triple refractory and 1 DLT of grade 3 CRS in this group. Across the study, responses included 4 stringent CRs (3 MRD-negative, 1 not yet tested), 1 MRD-negative CR, 6 VGPRs, and 6 PRs (**Table**). Median (Q1, Q3) time to response was 1.0 (1.0, 1.9) month, time to best response was 2.8 (1.0, 3.7) months, and response duration was 3.8 (1.9, 7.4) months, with maximum duration of 23 months; responses were ongoing at last assessment in 14/17 patients (**Figure**). MRD was tested in 4 patients (3 sCR, 1 CR) and all were negative (3 by NGS, 1 by flow); MRD negativity was ongoing at last observations up to 20 months later. AMG 701 exhibited a favorable PK profile in its target patient population of RR MM, with AMG 701 exposures increasing in a dose-related manner. Patient baseline sBCMA levels were identified as a determinant of AMG 701 free drug exposures; at higher doses, encouraging preliminary responses were seen even at the higher end of baseline sBCMA values.

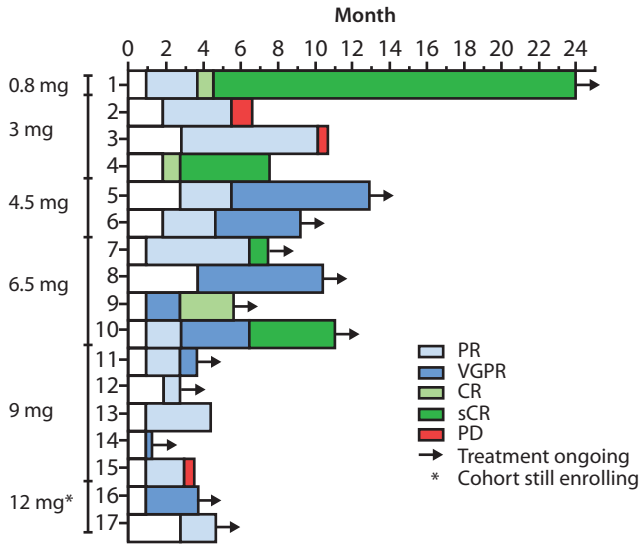
Summary: In this FIH study with ongoing dose escalation, AMG 701, an anti-BCMA BiTE® molecule, demonstrated a manageable safety profile, encouraging activity, and a favorable PK profile in patients with heavily pre-treated RR MM, supporting further evaluation of AMG 701.

Table. Cohorts assessed for confirmed responders ≥PR

Target dose (mg)	# responses/evaluable*	Responses
0.14	0/3	–
0.4	0/4	–
0.8	1/4	1 MRD- sCR†
1.6+	0/1	–
1.2+	0/4	–
1.6	0/8	–
3.0	3/11	2 PRs 1 MRD- sCR
4.5	2/7	2 VGPRs
6.5	All: 4/10 Earlier escalation: 2/5	1 VGPR 1 MRD- CR 1 sCR 1 MRD- sCR
9	All: 5/10 Earlier escalation: 5/6	3 PRs 2 VGPRs
12	All: 2/7 (cohort still enrolling)	1 PR 1 VGPR

*Table does not include single-patient cohorts (5, 15, and 45 μg) nor 1 patient at 12 mg not yet assessed. †Dosing frequency reduced to Q2W in Cycle 10 and Q4W in Cycle 18. +Save for 1 patient at 1.6 mg with the DLT of CRS, all patients at doses of ≥1.2 mg received a step dose of 0.8 mg prior to target dose.

Swimmer plot for confirmed responders (≥PR)



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OffLabel Disclosure: AMG 701, a half-life extended BiTE® (bispecific T-cell engager) molecule is an investigational agent for multiple myeloma.

Abstract 268

Superior Event-Free Survival with Blinatumomab Versus Chemotherapy in Children with High-Risk First Relapse of B-Cell Precursor Acute Lymphoblastic Leukemia: A Randomized, Controlled Phase 3 Trial

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Background: Children with high-risk (HR) first-relapse B-cell precursor acute lymphoblastic leukemia (BCP-ALL) are candidates for allogeneic hematopoietic stem cell transplant (alloHSCT) when a second complete morphological remission (CR2, M1 marrow) is achieved. Immuno-oncotherapy with blinatumomab, a bispecific T-cell engager (BiTE®) molecule, is efficacious in children with relapsed/refractory BCP-ALL. We conducted an open-label randomized, controlled phase 3 trial comparing blinatumomab with high-risk consolidation (HC) 3 chemotherapy as pretransplant consolidation therapy for children with HR first-relapse BCP-ALL.

Methods: Children with M1 (<5% blasts) or M2 (<25% and ≥5% blasts) marrow were randomized 1:1 after induction therapy and cycles of HC1 and HC2 chemotherapy, administered according to the IntReALL HR 2010, ALL-REZ BFM 2002, ALL R3, COOPRALL, and AIEOP ALL REC 2003 protocols, to receive a third consolidation course with blinatumomab (15 μg/m^2/day for 4 weeks) or HC3 (dexamethasone, vincristine, daunorubicin, methotrexate, ifosfamide, PEG-asparaginase); intrathecal chemotherapy (methotrexate/cytarabine/prednisolone) was administered before treatment. Stratification variables included age, marrow status at end of HC2, and minimal residual disease (MRD) after induction (evaluated in a local laboratory). Patients with CR2 (M1 marrow) after blinatumomab or HC3 proceeded to alloHSCT. The primary endpoint was event-free survival (EFS; from randomization until relapse date or M2 marrow after a CR, failure to achieve CR at end of treatment, second malignancy, or death from any cause). Secondary endpoints included overall survival (OS), cumulative incidence of relapse, MRD status (evaluated in a central laboratory by

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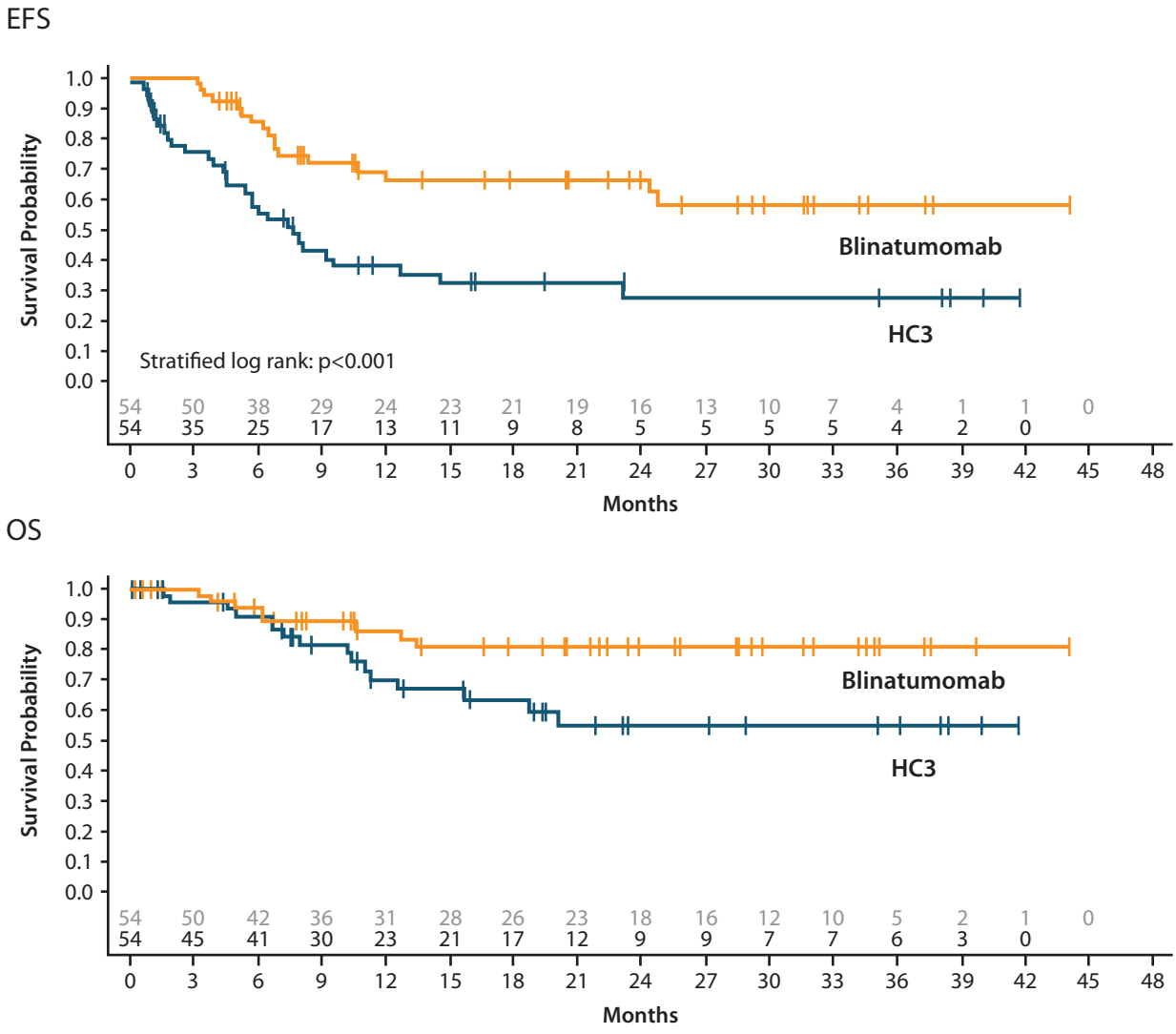
polymerase chain reaction), and incidence of adverse events (AEs). Two interim analyses were planned at approximately 50% and 75% of total EFS events.

Results: Enrollment was terminated for benefit (blinatumomab group) based on a predefined efficacy threshold at the 50% EFS events interim analysis. From November 10, 2015, to July 17, 2019 (data as-is snapshot), 108 patients were enrolled and randomized; 54 (50%) to blinatumomab and 54 (50%) to HC3. Patient baseline characteristics were comparable between treatment groups; most patients had completed treatment (blinatumomab, 91%; HC3, 89%). Events were reported for 18/54 (33.3%) and 31/54 (57.4%) blinatumomab- and HC3-randomized patients, with a median EFS of "not reached" and 7.4 months, respectively (**Figure**). Blinatumomab reduced the risk of relapse by 64% vs HC3 (hazard ratio 0.36, 95% confidence interval [CI] 0.19–0.66, p<0.001). In addition, OS favored blinatumomab vs HC3 (hazard ratio 0.43, 95% CI 0.18–1.01) (**Figure**). MRD remission (MRD<10^{-4}) was seen in 43/46 (93.5%) blinatumomab-randomized and 25/46 (54.3%) HC3-randomized patients. Grade ≥3 treatment-emergent AEs were reported by 30/53 (57%) and 41/51 (80%) patients in the blinatumomab and HC3 groups, respectively. As expected, grade ≥3 neurologic events occurred more frequently with blinatumomab than with HC3; no grade ≥3 cytokine release syndrome events were reported. Types of alloHSCT conditioning regimens received by patients as well as types of donors were balanced between groups.

Conclusions: Blinatumomab monotherapy as consolidation therapy before alloHSCT in children with HR first-relapse BCP-ALL leads to significantly better EFS, lower risk of recurrence, and fewer grade ≥3 treatment-emergent AEs vs HC3, suggesting a new standard-of-care treatment for these patients.



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Abstract 2795

Interim Results of a Multicenter, Single-Arm Study to Assess Blinatumomab in Adult Patients (pts) with Minimal Residual Disease (MRD) of B-Precursor (BCP) Acute Lymphoblastic Leukemia (GMALL-MOLACT1-BLINA)

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MRD in ALL is defined as the detection of leukemic cells in bone marrow below the microscopic threshold in complete remission (CR). Patients (pts) with molecular failure (MolFail) or molecular relapse (MolRel) after induction/consolidation therapy are at a high risk for hematologic relapse. Targeted therapies should prevent hematologic relapse, reduce MRD load and provide a bridging strategy to allogeneic stem cell transplantation (SCT) and thereby improve overall outcome of these pts. In pts without (wo) SCT option reduction of MRD load is an essential goal as well. Blinatumomab is an antibody construct that redirects CD3+ T cells to CD19+ target cells, resulting in a serial lysis of CD19+ B cells. In a study in pts with MRD ≥10–3, 78% achieved complete MRD response (Gökbuget N et al., Blood 2018). The MolAct1 trial was initiated by the GMALL study group to evaluate the efficacy and tolerability of Blinatumomab in MRD+ ALL including those with MRD below 10^{-3} and pts with MRD after SCT.

Adults (≥18 yrs) with CD19+, Ph-negative BCP ALL in CR after ≥3 chemotherapies with MRD ≥10^{-4} were eligible (NCT03109093). Recruitment of pts with MRD ≥10^{-3} was stopped after marketing authorization for this entity. After an amendment, which became effective after 44 recruited pts, pts with MRD below 10^{-4} or non-quantifiable (nq) MRD were eligible.

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Blinatumomab 28 µg/day was given as 4-wk infusion, followed by a 2-wk break (1 cycle). Responders could receive up to 4 cycles or undergo HSCT after ≥1 cycle. MRD after 1 cycle was the primary endpoint. MRD was centrally assessed by allele-specific quantitative real-time PCR of clonal rearrangements of immunoglobulin or T-cell receptor genes. For definition of MRD at inclusion and at response assessment see **table 1**.

64 pts with a median age of 44 (18–83) yrs were included from 19 centers and 60 were evaluable. 63 pts were treated in first CR (5 after SCT). Overall, 67% achieved MolCR, 10% had MolFail, 23% MolNE. MolNE identifies an intermediate response with different options clarified **table 1**. 81% of the pts included with MRD ≥10–4 had a molecular response i.e. MolCR or MRD<10^{-4}. No significant differences in terms of MRD response were observed according to MRD level at inclusion or other patient characteristics (**table 1**).

60 pts have completed study treatment (40 HSCT, 8 relapses during treatment, 4 completed 4 cycles wo SCT, 2 stopped earlier due to toxicities – 1 with subsequent SCT, 1 due to GvHD, 1 due to physicians' decision and 4 pts returned to standard treatment after 2 cycles).

SCT pts had a median age of 42 (18–66) yrs and follow-up is available in 37 / 41 pts (29 CCR, 3 relapse, 5 death in CR).

16 relapses occurred: 8 during treatment (1 after MolCR, 5 MolNE1-3 and 2 with MolFail resp); after SCT in 3/41 pts; 5/11 with CR at end of treatment wo subsequent SCT.

The median observation time of surviving pts is 12 (1–38) mo and the median survival is not reached. At 2 yrs the survival probability (OS) was 64%. OS was 70%, 64% and 43% in pts with MRD between 10^{-4}-10^{-3}, 10^{-3}-10^{-2} and >10^{-2} at inclusion, resp (p>.05; Fig.1). OS was 71% vs 54% in pts MolFail vs MolRel at inclusion (p>.05). OS was 72%, 40% and 56% in pts with MolCR, MolFail and MolNE after cycle 1 resp (P=0.02; Fig.2).

Overall, the results from previous trials were confirmed. In addition, it was demonstrated that pts with MRD between 10^{-4} and 10^{-3} had a similar response and a trend towards better outcome compared to pts with higher MRD levels >10^{-2}. So far only 7 pts with MRD below 10^{-4} were included; more data are needed to evaluate the impact of Blinatumomab in this population; GMALL does currently not recommend SCT for these pts unless there is an indication due to other risk factors. Interestingly, a significant proportion of pts (23%) had an incomplete MRD response and the outcome results indicate that these pts together with those with MolFail may have an inferior survival compared to those with MolCR. The results underline that the clear definition of MRD categories and consideration of level and sensitivity is essential for interpretation, which is possible due to well defined standards for the PCR method used here. 68% of the pts received SCT in CR after Blinatumomab with a so far limited mortality (13%). Further follow-up is certainly required. The GMALL will continue to recruit patients with MRD levels below 10^{-3} in order to improve their chances for long-term survival

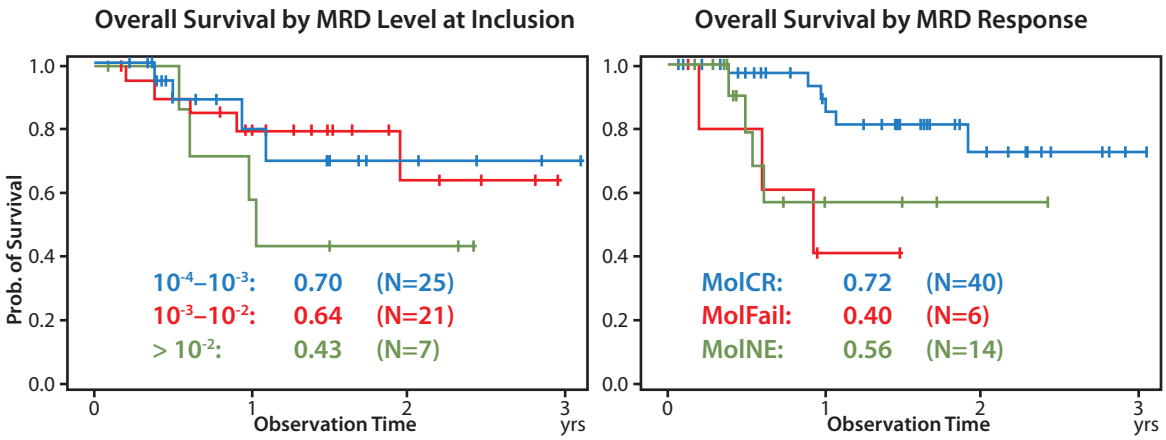
This study was supported by Amgen Inc.

Table 1. MRD Response after Cycle 1

Feature	Total n (%)	Complete MRD Response (MolCR)	MolFail	MolNE Total	MolNE Subgroups (1/2/3)	MRD Response
Total	**60**	**40 (67%)**	**6 (10%)**	**14 (23%)**	**7/2/5**	**49 (82%)**
MRD Level at inclusion						
$>10^{-2}$	7	5	0	2	0/1/1	
10^{-3}–10^{-2}	21	15 (71%)	3 (14%)	3 (14%)	1/0/2	6 (76%)
10^{-4}–10^{-3}	25	16 (64%)	2 (8%)	7 (28%)	4/1/2	21 (84%)
$<10^{-4}$ or nq.	7	4	1	2	2/0/0	6
Stage at inclusion						
CR1	54	34 (63%)	6 (11%)	14 (26%)	7/2/5	43 (80%)
After SCT (CR1)	5	5	0	0	0/0/0	5
Later CR	1	1	0	0	0/0/0	1
MRD Status at inclusion						
Mol Failure	38	25 (66%)	4 (11%)	9 (24%)	4/1/4	31 (82%)
Mol Relapse	15	11 (73%)	1 (7%)	3 (20%)	1/1/1	13 (87%)
Age						
18–35 yrs	23	13 (57%)	4 (17%)	6 (26%)	4/0/2	17 (74%)
36-55 yrs	22	15 (68%)	1 (5%)	6 (27%)	3/1/2	19 (86%)
>55 yrs	15	12 (80%)	1 (7%)	2 (13%)	0/1/1	13 (87%)

Definitions: MolCR=MRD negative with sensitivity of $\geq 10^{-4}$. MolFail=MRD above 10^{-4}; Complete MRD response=MolCR; MRD response=MolCR or MolNE1 or MolNE2; MolNE1=Positive MRD $<10^{-4}$, not quantifiable (nq); MolNE2=MRD $<10^{-4}$, quantifiable; MolNE3=Positive MRD nq. Molecular relapse: MRD $>10^{-4}$ after prior achievement of MolCR.

Figure 1 and 2



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OffLabel Disclosure: Blinatumomab in MRD positive disease below 10-3.

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