ASH Highlights and Commentary: Multiple Myeloma

Abstract 3248

Patient-Reported Experiences During and Following Treatment With Belantamab Mafodotin (Belamaf) for Relapsed/Refractory Multiple Myeloma (RRMM) in the DREAMM-2 Study

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Introduction: Patients refractory to an immunomodulatory agent and a proteasome inhibitor, and relapsed/refractory to an anti-CD38 antibody, are a population with a high unmet need given the poor prognosis in this setting. Single-agent belamaf (GSK2857916), a B-cell maturation antigen-binding antibody-drug conjugate, has demonstrated deep and durable responses with a manageable safety profile in heavily pretreated patients with RRMM. We used qualitative interviews to understand the patient perspective on clinical benefits and tolerability of belamaf.

Methods: Patients enrolled in the DREAMM-2 study (NCT03525678) received single-agent belamaf 2.5 or 3.4 mg/kg once every 3 weeks until disease progression or unacceptable toxicity. All were invited to participate in interviews at Cycle 4 (C4) and end of treatment (EOT). If the patient discontinued treatment before C4, only one interview was conducted. Interview questions covered the patient symptom experience, treatment-related burden, and adverse events. Disease and treatment-related symptom severity and overall treatment satisfaction were rated 0-10 (0=not severe to 10=most severe/0=not at all satisfied to 10=extremely satisfied). Qualitative and quantitative analyses were conducted with interview results and select variables from the clinical trial dataset.

Results: A total of 104 patients (across both doses) participated in interviews before or at C4, with 56% (n=58) identified as responders to treatment (≥ partial response by International Myeloma Working Group criteria). Among the 104, the most commonly reported disease symptoms were fatigue (reported by 68% of patients), neuropathy (43%), and bone pain (37%). Responders reported a decrease in severity of these symptoms from the start of the study to the time of interview, with ratings changing from 6.9 to 3.6 (bone pain), 4.6 to 3.4 (fatigue), and 4.5 to 3.7 (neuropathy). The severity ratings for nonresponders increased slightly for fatigue (4.4 to 4.5) and decreased for bone pain (4.9 to 4.4) and neuropathy (3.9 to 2.8). Fifty-nine (57%) patients interviewed at or before C4 reported visual impairments, including poor vision, blurred vision, and sensitivity to light, while 42 (40%) reported symptoms of eye irritation, including irritated eyes, dry eyes, itchy eyes, and the feeling of something in the eye. Twelve (12%) patients reported eye pain, including sore eyes and burning at or before C4. Responders interviewed before or at C4 reported a mean treatment satisfaction of 8.5, while nonresponders reported their satisfaction at 5.1.

A total of 26 patients were interviewed at EOT after C4, 22 (85%) of whom were responders to treatment. Patients interviewed at EOT reported decreased severity in their ocular symptoms between the time when the symptoms were at their worst and the 2-week period prior to their interview. Between worst symptoms and interview, participant severity ratings showed a decrease from 8.0 to 0.0 (for eye pain; n=4), 7.2 to 1.8 (for eye irritation; n=11), and 8.1 to 2.9 (for visual impairment; n=17).
All 26 patients interviewed at EOT indicated they expected the ocular side effects they experienced. Six patients considered stopping treatment due to their ocular symptoms, two of whom reported their doctor discontinued treatment for this reason. At EOT, these 26 patients reported high treatment satisfaction, with responders rating their satisfaction higher than nonresponders (8.1 and 6.7, respectively).

**Conclusions:** Trial-embedded interviews provide valuable insights into the patient experience with their disease, the course of treatment-related side effects, and their overall impact on patient satisfaction with treatment. Overall, responders to treatment with single-agent belamaf reported more improvement than non-responders in key disease symptoms, including bone pain and fatigue. Many patients reported some type of ocular symptom, but these were shown to improve or resolve by EOT. Despite ocular symptoms, overall, patients reported high satisfaction while on treatment and a desire to remain on treatment, particularly in responders. These qualitative interviews, in addition to the efficacy data, support the use of belamaf in patients with RRMM.

**The Advanced Practitioner Perspective:**

Beth Faiman, PhD, MSN, APRN-BC, AOCN®, FAAN

Patients with relapsed and refractory multiple myeloma (RRMM) often experience a high burden of symptoms in advanced disease (Faiman et al., 2017; Faiman & Faiman, 2017; Faiman & Valent, 2016). An important aspect of patient care for advanced practitioners is to understand the burden of treatment in this patient population (Kiely et al., 2017).

One abstract presented the results of patient-reported experiences during and following treatment with belanamab mafadotin (belamaf). The DREAMM-2 study investigated belamaf, a B-cell maturation antigen targeting antibody-drug conjugate for use in patients with RRMM. A member of the tumor necrosis factor receptor superfamily, BCMA is highly expressed on malignant plasma cells collected from patients with MM compared with normal bone marrow mononuclear cells (BMMCs) from healthy donors (Shah et al., 2020). Belamaf is given at a dose of 2.5 mg/kg as an intravenous infusion once every 3 weeks as a single agent and has demonstrated deep and durable responses in patients with RRMM and with an overall manageable safety profile (Lonial et al., 2020).

Results of the DREAMM-2 study showed a duration of response of 11 months at the 2.5 mg/kg dose level; however, corneal events such as blepharitis and microcyst-like epithelial changes (MECs) can occur (Farooq et al., 2020; Lonial et al., 2020). Patients can report decreased visual acuity, which can be measured objectively by a Snellen chart, but most of these MEC changes are best seen under slit-lamp examination.

**Implications for the Advanced Practitioner**

This study is important for advanced practitioners to be aware of, as qualitative interviews were the method used to understand the valuable patient perspective on the clinical benefits and tolerability of belamaf. The interviews were conducted during and following treatment with belamaf as part of the DREAMM-2 study. Although participation in the substudy was voluntary, a total of 104 patients participated. Participants were grouped into two categories: responders to treatment and non-responders to treatment.

Keeping in mind that these patients were heavily pretreated and refractory to numerous prior therapies, the responders to belamaf recorded a decrease in the severity of various symptoms, including bone pain, fatigue, and neuropathy, compared with the non-responders who experienced a slight increase in fatigue (Lonial et al., 2020). Of note, 26 patients were interviewed at the end of treatment after cycle four. 22 of the 26 patients of whom were responders to treatment reported a decrease in the severity of their ocular symptoms between the time when the symptoms were at their worst and the 2-week period prior to the interval at the end of therapy.

What is most interesting about this study is not only the patient focus of the research but also the interviews that provided valuable insights into the experience of these heavily pretreated patients who received a novel class of drugs. One would assume that with numerous prior therapies, there would be little improvement of symptoms such as fatigue and bone pain, yet individuals who responded to...
belamaf reported an improvement in those symptoms. In addition, based on the results of the study, advanced practitioners can reassure patients that ocular effects such as blurred vision and decreased visual acuity can improve or resolve with relatively rapid improvement if belamaf is held or discontinued.

Future research will aim to evaluate those who are at risk for experiencing ocular events and interventions that might decrease one’s risk for developing visual changes.

Disclosure: Dr. Faiman has served as a consultant for Bristol Myers Squibb, Karyopharm Therapeutics, and Sanofi.

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Abstract 412

APOLLO: Phase 3 Randomized Study of Subcutaneous Daratumumab Plus Pomalidomide and Dexamethasone (D-Pd) Versus Pomalidomide and Dexamethasone (Pd) Alone in Patients (Pts) With Relapsed/Refractory Multiple Myeloma (RRMM)

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Introduction: Immunomodulatory drug (IMiD)-based regimens are a standard of care (SOC) for RRMM. Daratumumab (DARA) is a CD38-targeted mAb approved for treatment of pts with RRMM. The subcutaneous (SC) formulation of DARA has a similar safety profile as intravenous DARA, with a statistically significant reduction in infusion-related reaction (IRR) rates and a considerably shorter administration duration of 5 mins. DARA SC is approved for use in the US, EU, Canada, and Korea.

In the phase 1b study of DARA plus the IMiD pomalidomide, D-Pd induced deep responses and was well tolerated in pts with heavily pretreated RRMM, including those with prior lenalidomide (len) treatment. D-Pd is approved in the US for RRMM pts with ≥2 prior lines of therapy, including len and a proteasome inhibitor (PI).

APOLLO (NCT03180736) is a phase 3 study conducted in collaboration between European Myeloma Network investigators and Janssen to evaluate DARA SC plus Pd vs Pd alone in RRMM pts who had received ≥1 prior line of therapy in-
including len and a PI. We report the primary analysis of APOLLO.

Methods: In this open-label, multicenter study, eligible pts had RRMM and received ≥1 prior line of therapy including len and a PI, had responded to prior treatment and progressed on or after their last regimen; pts with only 1 prior line of therapy (1PL) were required to be refractory to len. Prior anti-CD38 or pomalidomide was not permitted. Pts were randomized 1:1 to Pd ± DARA SC. Stratification was based on International Staging System (ISS) disease stage (I, II, III) and number of lines of prior therapy (1, 2-3, ≥4).

All pts received 28-day treatment cycles (C). P: 4 mg (PO) QD on Days 1-21; d: 40 mg (PO) on Days 1, 8, 15 and 22 (20 mg for pts ≥75 years of age). For D-Pd pts, DARA was given QW for C 1-2, Q2W for C 3-6, and Q4W thereafter. Prior to protocol amendment, pts received DARA IV 16 mg/kg (n=7); after protocol amendment, all pts received DARA SC 1,800 mg co-formulated with recombinant human hyaluronidase PH20 (rHuPH20; ENHANCE® drug delivery technology, Halozyme, Inc.). All pts were treated until disease progression or unacceptable toxicity. The primary endpoint was PFS. Major secondary endpoints included overall response rate, rates of very good partial response or better and complete response or better, MRD-negativity rate, overall survival (OS), and safety.

Results: A total of 304 pts from 12 European countries were randomized (151 D-Pd; 153 Pd). The median (range) age was 67 (35-90) years, and 45%/33%/22% pts were ISS stage I/II/III. 35% had high cytogenetic risk (presence of del17p, t[14;16], or t[4;14]). 11% of pts had received 1PL (median [range] prior lines of therapy = 2 [1-5]). 82% of pts were refractory to len, 68% of pts were refractory to a PI, and 63% of pts were refractory to both. Median duration of treatment was 11.5 months with D-Pd vs 6.6 months with Pd.

The primary analysis was performed after 190 PFS events. The study met its primary endpoint of improved PFS; the hazard ratio (HR) was 0.63 (95% CI, 0.47-0.85; P=0.0018), representing a 37% reduction in the risk of progression or death in pts treated with D-Pd. The median PFS for the D-Pd vs Pd arms was 12.4 vs 6.9 months, respectively. With a median follow-up of 16.9 months, 99 pts (33%) have died; the HR for OS was 0.91 (95% CI, 0.61-1.35); survival data are immature and follow-up is ongoing. ≥CR rates for D-Pd vs Pd were 24.5% vs 3.9%; ≥VGPR rates were 51.0% vs 19.6%. The most common grade 3/4 adverse events with a >5% difference between D-Pd vs Pd were neutropenia (68% vs 51%), leukopenia (17% vs 5%), lymphopenia (12% vs 3%), febrile neutropenia (9% vs 3%), and pneumonia (13% vs 7%). The rate of IRRs with DARA SC was low (6%, all grade 1/2), and 2% of pts had local injection-site reactions (all grade 1). Median duration of injection was 5 mins. Rates of study treatment discontinuation due to TEAEs were similar for D-Pd vs Pd (2% vs 3%). The safety profile of D-Pd is consistent with known profiles of DARA SC and Pd.

Conclusion: In this phase 3 study evaluating DARA SC plus Pd, D-Pd significantly reduced the risk of progression or death by 37% in pts with RRMM who had received ≥1 prior line of therapy vs Pd alone. No new safety concerns were observed. The IRR rate was very low and administration duration short, thus increasing convenience for pts and decreasing treatment burden. Collectively, these data show that D-Pd is an effective and convenient treatment for pts with RRMM who received ≥1 prior therapy, including len and a PI.

The Advanced Practitioner Perspective: Beth Faiman, PhD, MSN, APRN-BC, AOCN®, FAAN

APOLLO is a phase III randomized study of subcutaneous daratumumab plus pomalidomide (D-Pd) and dexamethasone vs. pomalidomide and dexamethasone (Pd) alone in patients with RRMM. It has been described that immunomodulatory drug base regimens are the common standard of care for newly diagnosed and RRMM (Landgren et al., 2019; Noonan & Colson, 2017). The anti-CD38 targeted monoclonal antibody daratumumab is approved by the FDA for the treatment of patients with RRMM alone and in combination with various agents, such as bortezomib, lenalidomide, and carfilzomib (Janssen Biotech, Inc., 2020; Rajkumar, 2020).

The APOLLO study results were highly anticipated, as D-Pd was already approved based on results from a single-arm phase II study in...
the United States with daratumumab as an intravenous infusion. The use of subcutaneous daratumumab in the phase III APOLLO study helps further elucidate the safety and efficacy of subcutaneous daratumumab when added to Pd. Results of this study showed a 37% reduction in the risk of progression or death in patients who received D-Pd vs. Pd, and no new safety signals were identified.

**Implications for the Advanced Practitioner**
An important point for advanced practitioners to be aware of is the safety profile of subcutaneous daratumumab as it relates to the risk of infusion-related reactions, which are a major concern when starting patients on intravenous daratumumab. In this study, there was a lower incidence of infusion-related reactions compared with IV daratumumab. Therefore, not only does subcutaneous daratumumab provide a very short administration time, the low risk of infusion-related reactions decreases the patient’s treatment burden.

Another key practice-changing point for advanced practitioners to consider is that while the COLUMBA study looked at whether or not IV daratumumab was noninferior to subcutaneous daratumumab, the APOLLO study is the first phase III randomized study with mature data to support the use of subcutaneous daratumumab in combination with Pd in RRMM. In fact, this study demonstrated a high overall response rate and higher rate of minimal residual disease (MRD) negativity than Pd alone. As many of you are aware, MRD negativity in newly diagnosed myeloma is a surrogate marker for progression-free survival and overall survival (Avet-Loiseau et al., 2020; Diamond et al., 2020). Advanced practitioners should be on the lookout for additional updates on this APOLLO study, as with longer follow-up, the results of secondary endpoints such as progression-free survival, and overall survival benefit of the three drugs (subcutaneous D-Pd vs. Pd).

**Disclosure:** Dr. Faiman has served as a consultant for Bristol Myers Squibb, Karyopharm Therapeutics, and Sanofi.

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**Abstract 491**

**Impact of Minimal Residual Disease (MRD) By Multiparameter Flow Cytometry (MFC) and Next-Generation Sequencing (NGS) on Outcome: Results of Newly Diagnosed Transplant-Eligible Multiple Myeloma (MM) Patients Enrolled in the FORTE Trial**

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**Background:** In multiple myeloma (MM), the role of minimal residual disease (MRD) by multiparam-
eter flow cytometry (MFC) and next-generation sequencing (NGS) is well established (H. Avet-Loiseau et al. IMW 2019, S. Oliva et al. EHA 2020).

**Aims:** The aims of this analysis were the evaluation of (1) the rate of conversion from MRD-positivity (MRD-pos) to MRD-negativity (MRD-neg) with MFC and NGS during maintenance and (2) the impact on progression-free survival (PFS) and overall survival (OS) of MRD-neg with both techniques in different subgroups including different treatment arms.

**Methods:** Newly diagnosed (ND)MM patients (pts) aged ≤65 years were randomized (R1) to receive carfilzomib (K)-lenalidomide (R)-dexamethasone (d) induction followed by autologous stem-cell transplantation (ASCT) and KRd consolidation (KRd_ASCT), 12 KRd cycles (KRd12), or K-cyclophosphamide(C)-d induction followed by ASCT and KCd consolidation (KCd_ASCT). After consolidation, pts were further randomized (R2) to KR vs R maintenance. MRD was assessed every 6 months (m) by 8-color second-generation flow cytometry (sensitivity 10^-5) in pts with ≥very good partial response (VGPR). In pts achieving at least a complete response (≥CR), MRD was also assessed by NGS at the same time points (Adaptive Biotechnologies, Seattle, US-WA; sensitivity 10^-5-10^-6). Logistic regression analysis adjusted for International Staging System (ISS) stage (I vs II/III) and R1 was performed to evaluate the conversion rate from MRD-pos to MRD-neg during maintenance (KR vs R). PFS and OS of MRD-neg vs MRD-pos in the intention-to-treat (ITT) population were evaluated. For these analyses, MFC-pos pts included those who were positive by MRD plus those <VGPR, whereas NGS-pos pts included those who were MRD-pos plus <CR (excluding CR pts not evaluable by NGS). 1-year sustained MRD-neg by MFC and NGS was evaluated in pts with at least 2 samples available at least 1 year apart.

**Results:** Rates of MRD-neg by MFC and NGS before maintenance in the 3 induction/consolidation arms have been previously presented (S. Oliva et al. EHA 2020). At R2, 65% of randomized pts were MRD-neg by MFC (equally distributed in the 2 arms); 39% (48/123) of MRD-pos pts turned MRD-neg after a median of 7.6 m (IQR 6.5-12): 46% (29/63) in KR vs 32% (19/60) in R (OR 2.27; P=0.04) arms. At R2, 72% of pts evaluable for CR were MRD-neg by NGS (equally distributed in the 2 arms); 33% of MRD-pos pts (15/45) became MRD-neg at 10^-5: 39% (9/23) in KR vs 27% (6/22) in R arms (=NS).

In the ITT analysis, after a median follow-up of 45 m from R1, pts who were MRD-neg before maintenance by both techniques showed a superimposable prolonged PFS and OS vs pts who were MRD-pos: 3-year PFS was 80% vs 52% (HR 0.36, 95% CI 0.26-0.49 P<0.001) in MFC-neg vs MFC-pos pts and 83% vs 55% (HR 0.34, 95% CI 0.22-0.52, P<0.001) in NGS-neg vs NGS-pos pts (Fig. 1A); 3-year OS was 96% vs 79% (HR 0.24, 95% CI 0.14-0.42 P<0.001) in MFC-neg vs MFC-pos pts and 97% vs 82% in NGS-neg vs NGS-pos pts (HR 0.30, 95% CI 0.15-0.61, P<0.001). The favorable impact of MRD-neg on PFS was confirmed in all sub-

![Figure 1](image-url)
Numerous induction regimens are currently available for transplant-eligible patients with newly diagnosed multiple myeloma (NDMM), but the most effective regimen that achieves the deepest and most durable response remains to be determined. The impact of minimal residual disease (MRD) measured by multiparameter flow cytometry (MFC) and next-generation sequencing (NGS) on patient outcomes is highly relevant to the advanced practitioner audience.

The FORTE study aimed to assess the best induction and consolidation strategy for transplant-eligible patients with NDMM, as well as the significance of MRD-negative status by using two different MRD assessment techniques. In this randomized phase II trial with a total of three arms, patients with NDMM who were 65 years or younger were randomized to either carfilzomib (K), lenalidomide (R), dexamethasone (d) induction followed by autologous stem cell transplantation (ASCT) and KRd consolidation (KRd_ASCT), 12 KRd cycles (KRd12), or K-cyclophosphamide(C)-d induction followed by ASCT and KCd consolidation (KCd_ASCT). After consolidation, patients were further randomized (R2) to KR vs R maintenance.

Implications for the Advanced Practitioner
The MRD assessment occurred every 6 months by eight-color second-generation flow cytometry (with an MRD sensitivity $10^{-5}$) in patients with a very good partial response (VGPR) or better, and by NGS at the same time points (MRD sensitivity $10^{-5}$-$10^{-6}$). Importantly, in this FORTE study, both MFC and NGS provided comparable rates of MRD negativity. In addition, the progression-free survival in 1-year sustained MRD negativity patients, when assessed 1 year apart, was superimposable between MFC and NGS, and 90% of patients were alive and did not progress at 2 years. Results of this study support the use of both MFC and NGS techniques to calculate MRD negativity to $10^{-5}$ sensitivity. It is also important to emphasize that MRD negativity is an important endpoint to achieve, and MRD negativity can be used as a surrogate marker for survival.

Also noted in the results of the study is that in patients with a higher disease stage or risk status, the ongoing use of maintenance therapy can convert patients from MRD-positive status before maintenance to MRD-negative status with continuous therapy. Based on the findings of this study, advanced practitioners should consider the important role of ongoing therapy or continuous therapy in patients with newly diagnosed MM. While most providers will not stop or adjust therapy if one is MRD negative, findings from the FORTE study support continuing therapy to deepen one’s response in an effort to achieve MRD-negative status. Stay tuned for additional studies that investigate MFC and NGS, and patient-related outcomes in newly diagnosed and relapsed MM.

Disclosure: Dr. Faiman has served as a consultant for Bristol Myers Squibb, Karyopharm Therapeutics, and Sanofi.