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 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; ENHANZE® 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]). 79.6% of pts were refractory to len, 48.0% of pts were

refractory to a PI, and 42.4% 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.

2314 Pomalidomide, Dexamethasone, and Daratumumab after Lenalidomide Treatment in Relapsed Refractory Multiple Myeloma: Updated Results from an Open-Label, Multicenter, Phase 2 Trial

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Introduction:

Lenalidomide (LEN), a standard of care for newly diagnosed multiple myeloma, is routinely administered until disease progression. However, patients with disease that has relapsed after or become refractory to LEN have been poorly represented in recent trials investigating triplet regimens after ≤ 3 prior treatment (Tx) lines. Consequently, patients who have exhausted the benefits of LEN in early relapse are a clinically relevant population in need of proven Tx options. The trial that led to approval of pomalidomide (POM) + dexamethasone (DEX) + daratumumab (DARA) evaluated patients with heavily pretreated (median of 4 prior lines of therapy) relapsed refractory multiple myeloma (RRMM; Chari et al. Blood 2017). The phase 2 MM-014 trial (NCT01946477), which is composed of 3 cohorts, was specifically designed to investigate the

outcomes of sequencing POM-based therapy immediately after first- or second-line LEN-based Tx failure in patients with RRMM. In an earlier report from cohort B of MM-014, POM + DEX + DARA demonstrated promising efficacy and safety results: the overall response rate (ORR) was 77.7%, and the 1-year progression-free survival (PFS) rate was 75.1% at a median follow-up of 17.2 months (Siegel et al. Leukemia 2020). Updated efficacy and safety results from cohort B are reported here.

Methods

Patients with RRMM treated with 1-2 prior Tx lines, LEN-based Tx as their most recent regimen, and progressive disease during/after their last line of Tx received POM + DEX + DARA. POM 4 mg/day was given orally on days 1-21; DEX 40 mg/day (20 mg/day in patients aged > 75 years) was given orally on days 1, 8, 15, and 22; and DARA 16 mg/kg was given intravenously on days 1, 8, 15, and 22 of cycles 1 and 2, days 1 and 15 for cycles 3-6, and day 1 for cycles 7+. ORR was the primary endpoint; secondary endpoints included PFS and safety.

Results

In the intention-to-treat (ITT) population of 112 patients, the median age was 66.5 years, all patients had prior LEN, and 77.7% had prior bortezomib. Overall, 84 patients (75%) had LEN-refractory MM and 28 (25%) had MM that relapsed after prior LEN Tx; most patients (70 [62.5%]) received 1 vs 2 (42 [37.5%]) prior Tx lines. As of March 24, 2020, 31 patients (27.7%) were still on treatment; median follow-up was 28.4 months. The most common reasons for discontinuation in 81 patients (72.3%) were progressive disease (46 patients [56.8%]), withdrawal by patient (19 patients [23.5%]), and adverse events (AEs; 7 patients [8.6%]). The efficacy-evaluable (EE) population comprised 109 patients who received ≥ 1 dose of study Tx and had ≥ 1 post-baseline assessment and was used for supportive efficacy analyses. ORR was 77.7% (≥ very good partial response [VGPR], 52.7%) and 79.8% (≥ VGPR, 54.1%) in the ITT and EE populations, respectively. ORR was similar in patients with LEN-relapsed and LEN-refractory disease (82.1% and 76.2%, respectively). The median PFS was reached: 30.8 months in both the ITT and EE populations (Figure). Overall, 97.3% of patients had ≥ 1 grade 3/4 AE, with neutropenia (64.3%; febrile 9.8%) being the most common grade 3/4 hematologic Tx-emergent AE, followed by anemia (17.9%) and thrombocytopenia (14.3%). Grade 3/4 infections were noted in 36.6% of patients, including 16.1% with grade 3/4 pneumonia.

Conclusions

POM + DEX + DARA administered in early-line Tx immediately after LEN failure continues to show a high response rate and a consistent safety profile, demonstrating the benefit of

maintaining continuous immunomodulation with POM following LEN. These updated results continue to demonstrate the efficacy and safety of POM-based therapy as early as second line in patients with RRMM, even immediately after LEN failure, indicating that switching from the immunomodulatory agent class is not necessary. Furthermore, these findings support the use of POM + DEX as the foundation of novel combinations in MM.