Exciting New Data in Newly Diagnosed Multiple Myeloma

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2018-04 IFM: Quadruplet induction therapy, the next step for transplant-eligible, high-risk NDMM patients

The phase II 2018-04 study conducted by the Intergroupe Francophone du Myelome (IFM) group confirmed the efficacy and safety of quadruplet induction therapy in high-risk (HR), transplant-eligible (TE), newly diagnosed multiple myeloma patients (NDMM).[1] Previous studies investigating the triplet combination of carfilzomib, lenalidomide and dexamethasone (KRd) demonstrated a high efficacy with a favorable safety profile in TE-NDMM patients.[2] Furthermore, the addition of daratumumab (Dara) to front-line therapy resulted in a deep response and improved progression-free survival (PFS) in TE-NDMM patients, including HR patients.[3,4] The IFM study included TE-NDMM patients (age <66 years) with HR disease defined by cytogenic abnormalities such as translocation (t)(4;14), deletion (del)17p and t(14;16) detected by fluorescence *in situ* hybridization (FISH). The induction therapy consisted of 6 cycles of daratumumab, carfilzomib, lenalidomide and dexamethasone (Dara-KRd) given over 28 days, followed by stem cell collection and autologous stem cell transplantation (ASCT). Consolidation Dara-KRd was given in 4 cycles followed by a second round of ASCT, and finally, daratumumab and lenalidomide maintenance were administered over 2 years. The primary objective of this study was the feasibility of this treatment.

Overall, 50 patients (median age: 57 years) were included in the analysis and the revised international staging system (R-ISS) scores showed 76% of patients in stage 2 and 24% in stage 3. Over half of the patients (52%) had t(4;14), while 1q gain was observed in 50% of patients. Of note, 68% of the patients had 2 HR abnormalities defined by the presence of t(4;14), t(4;16), 17p del and 1q gain. The majority of patients (72%) are continuing this treatment, most of whom are in the maintenance phase, while the remaining 28% of patients discontinued treatment, the most common reason being stem-cell collection failure.

Regarding safety, neutropenia was the most common hematologic treatment-related adverse event (TRAE), with 40% of patients experiencing grade 3–4 neutropenia. The most common non-hematologic TRAEs included gastrointestinal (GI) disorders (any grade: 46%), infection (40%), skin rash (16%) and deep-vein thrombosis (14%).

The overall response rate (ORR) was high at 96%, while the very good partial response (VGPR) rate was 91%.[1] In addition, the minimal residual disease (MRD) negativity rate (threshold: 10^{-5}) was 62%. At a median follow-up of 19.4 months, the 18-month PFS rate was 92% and the 18-month overall survival (OS) rate was 96%. Despite the relatively short median follow-up, these results are in accordance with those obtained from the GMMG CONCEPT trial, supporting the use of the quadruplet induction regimen of Dara-KRd in high-risk transplant-eligible patients with NDMM. However, a longer follow-up is necessary to determine the efficacy and feasibility of this treatment strategy in this patient population.

Belantamab mafodotin in combination with lenalidomide and dexamethasone shows clinically meaningful responses with a manageable safety profile in transplant-ineligible patients with NDMM

A phase I/II dose and schedule evaluation study investigated the safety and clinical activity of belantamab mafodotin (belamaf) in combination with lenalidomide and dexamethasone (BelaRd) in transplant-ineligible patients with NDMM.[5] Historically, single-agent belamaf, a first-in-class immunoconjugate targeting B-cell maturation antigen (BCMA), has demonstrated clinically meaningful anti-myeloma activity, coupled with a manageable safety profile in heavily pretreated patients with relapsed/refractory multiple myeloma (RRMM).[6] This, as well as the findings that belamaf plus pomalidomide and dexamethasone resulted in a median PFS of 16.2 months in RRMM patients,[7] provides a strong rationale for investigating the clinical activity of belamaf plus lenalidomide and dexamethasone in transplant-ineligible NDMM patients. Overall, 36 patients who were ineligible for high-dose chemotherapy with ASCT and had an estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m^2 were included in this study. Patients were randomized 1:1:1 to receive either 2.5 mg/kg (cohort 1) or 1.9 mg/kg (cohort 2) or 1.4 mg/kg (cohort 3) of belamaf every 8 weeks plus lenalidomide and dexamethasone until progressive disease or unacceptable toxicity. The primary endpoint was to investigate the safety, tolerability and recommended phase II dose (R2D) for BelaRd.

Patient characteristics were well balanced between the three cohorts. All patients were ≥70 years of age, nearly 75% of patients had R-ISS stage 2 disease and about 90% of patients had an International Myeloma Working Group (IMWG) frailty score of 1. Of note, most patients had abnormal findings in the baseline ocular assessment. A relatively short treatment duration of 4–6 months was utilized, with a follow-up time between 6–9 months.

In terms of safety, treatment-emergent adverse events (TEAEs) across the three cohorts were considered manageable with no new safety signals, while there was a low frequency of grade 3–4 ocular TEAEs, especially in the 1.9 mg/kg cohort. Reduced visual activity was the only grade ≥3 ocular TEAE that was observed in ≥5% of all patients, with the lowest frequency in cohort 1.9 mg/kg observed for only 1 patient. In total, 3 deaths were reported during the study but were deemed unrelated to the study treatment. Quality of life analysis of these patients showed that the study treatment had a minor impact on daily life functioning, particularly in the 1.9 mg/kg and 1.4 mg/kg cohorts.

ORR across the three cohorts was >90%, and in spite of the short follow-up period, BelaRd showed rapid and clinically meaningful responses. Based on part I results, the recommended dose of belamaf is 1.9 mg/kg administered once every 8 weeks, and this dose will form the basis of further studies by these trial investigators.[8]

MajesTEC-1: Teclistamab has an early response which deepens over time in NDMM patients pretreated with BCMA-targeted therapies

The multicohort phase I/II MajesTEC-1 study investigated teclistamab, a bispecific antibody that binds BCMA and CD3 to redirect T cells to multiple myeloma cells, in patients with RRMM who had previously received ≥3 lines of therapy.[9] Efficacy and safety results from Cohort C of the MajesTEC-1 study were presented at EHA2022 for the use of teclistamab in patients with RRMM following exposure to other BCMA-targeted therapies.[10] Patients enrolled in Cohort C underwent step-up doses of teclistamab (0.06 and 0.3 mg/kg) during the first week of the trial, followed by weekly subcutaneous teclistamab (1.5 mg/kg) until the onset of progressive disease.

Overall, 40 patients were included in the study and 30% had extramedullary plasmacytomas and 1/3 of the patients had high-risk cytogenetics. About 85% of patients were triple-class

refractory and 35% of patients were penta-drug refractory. ORR was the primary endpoint of this study, which was recorded at 52.5% (21/40) for patients in Cohort C. Responses occurred early, which deepened over time, and maintained their durability. The median time to first response was 1.2 months, while the median time to best response was 2.9 months.[10] With a median follow-up of 11.8 months, 71.4% of patients maintained their response.

The safety profile for Cohort C was as expected based on prior MajesTEC-1 data.[11] Teclistamab was well tolerated with no dose reductions or adverse event-related discontinuations. Of the reported adverse events (AEs), cytopenia and cytokine release syndrome (CRS) (any grade) were the most common, the latter experienced by 65% (26/50) of all patients. The most common neurotoxic events were headache (12.5%) and immune effector cell-associated neurotoxicity syndrome (ICANS) (10.0%).

In conclusion, the effect of teclistamab occurred very early and deepened over time while also being safe and well-tolerated in heavily pretreated RRMM patients with prior exposure to BCMA-targeted agents.

DETERMINATION: Lenalidomide, bortezomib and dexamethasone plus ASCT and lenalidomide maintenance shows significant PFS improvement in patients with NDMM

The phase III DETERMINATION trial investigated the combination therapy of lenalidomide, bortezomib and dexamethasone (RVd), with or without ASCT, followed by lenalidomide maintenance in patients with NDMM.[12] The previous phase II study showed that RVd is highly efficacious with an ORR of 93–100% and a ≥VGPR rate of 61–74%.[13,14] The study included 722 patients, who received 3 cycles of RVd plus stem-cell mobilization and were randomized 1:1 to receive either 5 additional RVd cycles (the RVd-alone group) (n=357) or high-dose melphalan plus ASCT and 2 additional RVd cycles (the transplant group) (n=365). Patients in both groups received lenalidomide maintenance until disease progression, unacceptable side effects or both.

The primary endpoint of this study was met; the median PFS was 46.2 months in the RVd-alone arm versus 67.6 months in the transplantation arm (HR: 1.53 [95% CI: 1.23–1.91]; p<0.0001).[12] Comparable results were also reported in terms of responses. In total, 42.0% of patients in the RVd-alone arm and 46.9% of patients in the transplant arm achieved a complete response or better; VGPR or better rates were 79.6% and 82.7%, respectively. The rate of partial response or better was 95.0% with RVd alone and 97.5% with transplant plus RVd. In addition, the duration of response (DoR) was longer in the transplant arm than in the RVd-alone arm (56.4 months vs 38.9 months). The rate of MRD negativity (threshold: 10^{-5}) was 39.8% in patients without a transplant and 54.4% in patients who received a transplant. The 5-year PFS rate in MRD-negative patients was similar with RVd alone versus RVd plus ASCT (53.5% vs 59.2%). Additionally, OS outcomes did not differ between the two treatment arms, with estimated 5-year OS rates of 79.2% and 80.7% in the RVd-alone and transplant arms, respectively (HR: 1.10 [95% CI: 0.73–1.65]; p=0.99).

In terms of safety, rates of all grade ≥3 and hematologic grade ≥3 TRAEs during all treatment was significantly higher with RVd plus ASCT (both p<0.001). In general, there were no differences in the incidence of any second primary malignancies (SPMs) between the two treatment arms, but there was a significant difference in hematological SPM. In RVd alone arm, no patient experienced a hematologic SPM while 10% of patients in RVd plus ASCT arm did, this may have been due to the use of lenalidomide or melphalan.

In conclusion, RVd plus ASCT demonstrated significantly superior PFS versus RVd-alone, yet there was no difference in OS between the two groups. This treatment option offers a manageable safety profile despite a significantly higher rate of toxicity, plus a low overall rate of fatal AEs (RVd plus ASCT vs RVd-alone: 1.6% vs 0.3%).

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