Highlights in Multiple Myeloma from ASH 2021

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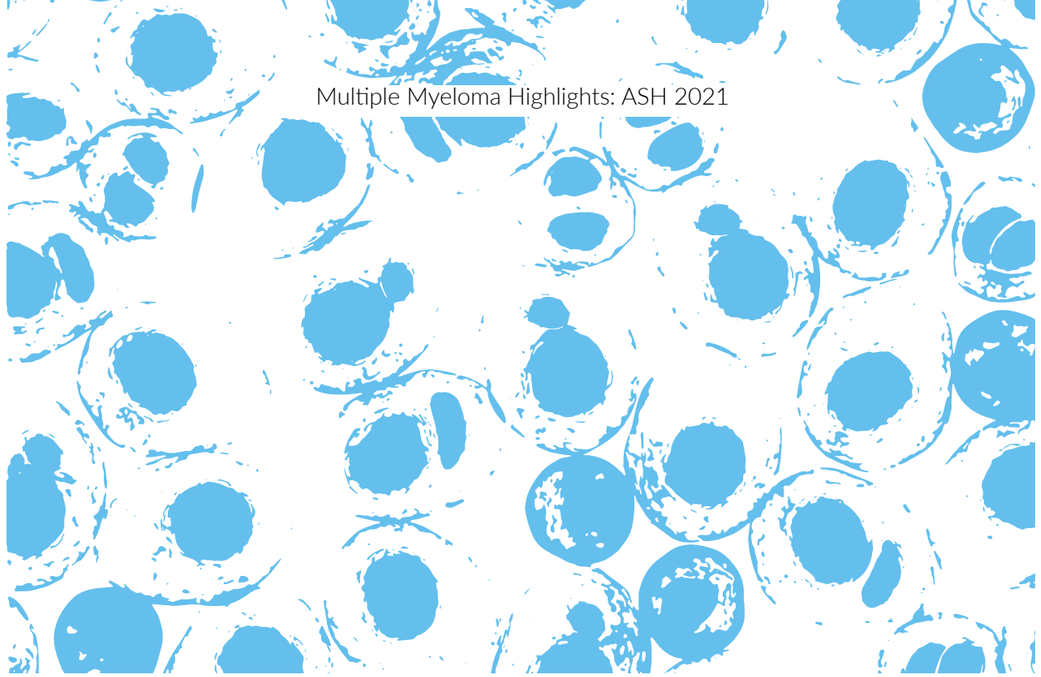
Quadruplet combination demonstrates superior MRD rate in transplant-eligible NDMM patients

In the phase III GMMG-HD7 trial, the anti-CD38 antibody isatuximab (Isa) is being assessed in a quadruplet combination with lenalidomide (R), bortezomib (V) and dexamethasone (d) in the induction and maintenance treatment of transplant-eligible newly diagnosed multiple myeloma (NDMM) patients.[1] Patients were randomized 1:1 to receive either Isa-RVd or RVd alone for three 6-week cycles as induction therapy before autologous stem cell transplantation (ASCT). In the second step, patients were randomized to either Isa-R or R maintenance therapy for 4-week cycles up to 3 years or until progressive disease. The baseline characteristics were well-balanced between both treatment arms, with about 20% of patients showing high-risk cytogenetics. The primary endpoint of minimal residual disease (MRD) negativity (threshold: 10^{-5}) by next-generation flow cytometry (NGF) after the end of induction was met in the intent to treat (ITT) population. MRD negativity after induction was achieved by 50.1% of patients with Isa-RVd versus 35.6% of patients with RVd alone (odds ratio [OR]: 1.83 [95% CI: 1.34–2.51]; p<0.001). This benefit was consistent throughout prespecified patient subgroups. While complete response (CR) rates were similar with Isa-RVd (24.2%) and RVd (21.6%), more patients achieved very good partial response or better (≥VGPR) with Isa-RVd (77.3%) versus RVd alone (60.5%). Regarding safety, a similar safety profile was observed in both groups, although the addition of isatuximab led to higher rates of leukocytopenia/neutropenia (26.4% vs 9.1%), which is consistent with the expectations based on reported safety results for anti-CD38 antibodies in phase III trials. In conclusion, Isa-RVd can induce MRD negativity (threshold: 10^{-5}) post-induction in transplant-eligible NDMM patients with a tolerable safety profile. Further follow-up is needed on the maintenance therapy after the second randomization. Besides the GMMG HD7 trial, several other studies assessing quadruple combinations were presented at ASH 2021, including the Griffin and the Cassiopeia trial.[2,3] The quadruple combination may be expected to become the standard of care (SOC) for induction of transplant-eligible patients with NDMM.

Promising results with bispecific antibodies in patients with RRMM

Regarding new targets in multiple myeloma (MM) the results from the phase I trial on cevostamab, an Fc receptor-homolog 5 (FcRH5)- and CD3-binding bispecific antibody, were presented by Dr Suzanne Trudel at ASH 2021.[4] FcRH5 is nearly ubiquitously expressed on myeloma cells.[5,6] By simultaneously binding to FcRH5 on myeloma cells and the membrane-proximal domain CD3 on T cells, cevostamab induces the T-cell-directed killing of myeloma cells. Heavily pretreated patients with relapsed/refractory multiple myeloma (RRMM) (n=161) were treated with either a single or double step-up expansion dosing to mitigate cytokine release syndrome (CRS). Patients received either 3.5 mg cevostamab on day 1 and 5.0 mg on day 8 of the first cycle and day 1 of all subsequent cycles or 0.3–1.2 mg on day 1, 3.5 mg on day 8 and 5.0 mg on day 15 of the first cycle and day 1 of the following cycles (21-day cycles). The median age of patients was 64 years. 70.5% of patients showed high-risk cytogenetics and the median time since diagnosis was 6.1 years. The median number of prior lines of therapy was 6 with 84.5% of patients being triple-class refractory and 68.3% being penta-drug-refractory. For triple-class refractory and penta-drug-refractory patients, a significantly reduced median overall survival (OS) has been reported as compared



to non-triple refractory patients (9.2, 5.2 and 11.2 months, respectively).[7] Overall, 161 patients were treated in this trial for a median time of 8.8 months.[4] Approximately 80% of patients experienced CRS (mostly grade 1 and 2), which was primarily observed in cycle 1, occurring within 24 hours of treatment and resolving within 48 hours. Serious adverse events (AEs) have been reported in 59.6% of patients and 6 patients (3.7%) experienced fatal grade 5 AEs, including 1 cevostamab-related death. CRS was more common in the single step-up dosing arm (88.4%) than in the double step-up dosing arm (79.5%) and the grade of CRS was generally lower with double step-up dosing. Regarding responses, the overall response rate (ORR) was higher with double step-up expansion in cycle 1 (54.8%) than with single step-up expansion in cycle 1 (29.0%). Patients with a dose level of 20–90 mg (n=83) achieved an ORR of 36.1%, while patients with a 132–198 mg dose level (n=60) achieved an ORR of 56.7%. The median time to first response was 1.0 months and the median time to best response was 2.1 months. Considering that these patients were heavily pretreated, responses were durable with a median duration of response (DOR) of 11.5 months. In conclusion, cevostamab showed an encouraging safety profile and a clinically meaningful activity in heavily pretreated RRMM patients.

The bispecific antibody talquetamab is a first-in-class antibody binding to targets G-protein coupled receptor class C group 5 member D (GPRC5D) and CD3 receptors to induce the T-cell-directed killing of myeloma cells expressing GPRC5D.[8] The phase I MonumenTAL-1 study assessed two different dosing schedules with subcutaneous (SC) talquetamab (405 μg/kg) once weekly (QW) in a 21-day cycle (n=30) or SC talquetamab (800 μg/kg) every second week (Q2W) in a 28-day cycle (n=25). The identified recommended phase II dose (RP2D) was 405 μg/kg (SC) weekly. Patients included in the trial were heavily pretreated with a median of 6.0 versus 5.0 prior lines of therapy in the 405 μg/kg (SC/QW) versus the 800 μg/kg (SC/Q2W) arm, including 27% and 16% who had received prior B-cell maturation antigen (BCMA)-targeted therapy. In fact, 77% and 76% of patients receiving 405 μg/kg (SC/QW) and 800 μg/kg (SC/Q2W) were triple-class refractory, while 20% and 24% were penta-drug-refractory, respectively. The safety profile was tolerable in both treatment arms with mainly grade 1 and 2 AEs. Cytopenias were mostly confined to cycles 1 and 2 and were reversible. Only one patient (1.8%) discontinued treatment due to AEs. Infections were reported in 33% of patients, including 5% with grade ≥3 infections (n=3). AEs of special interest included skin-related and nail disorder AEs which occurred in 75% of patients. 7.5% of patients experienced grade 3 rashes, but all patients were successfully rechallenged at the same (n=3) or a lower dose (n=1). No talquetamab-related AE leading to death has been reported. 76.7% and 72.0% of patients in the 405 μg/kg (SC/QW) and 800 μg/kg (SC/Q2W) arm, respectively, experienced CRS. Only one patient experienced grade 3 CRS and CRS was generally limited to step-up dosing and cycle 1. The ORR was comparable with both dosing schedules (70.0% and 66.7% with 405 μg/kg (SC/QW) and 800 μg/kg (SC/Q2W), respectively), including 10% and 9.5% of patients with stringent complete response (sCR) and ≥ VGPR in 53.3% and 52.4% of patients, respectively. The median DOR was not reached at a median follow-up of 10.1 months and 7.9 months with the lower and higher dosing, respectively, and 52% versus 86% of patients continued to receive treatment. Overall, responses were durable and deepened over time in this patient population.

Furthermore, talquetamab was assessed in combination with the anti-CD38 antibody daratumumab in patients with RRMM in the phase Ib TRIMM-2 trial.[9] The rationale behind this combination is the potential of daratumumab to enhance T-cell cytotoxic potential leading to T-cell expansion.[10] Preclinical studies have shown that daratumumab is able to enhance the talquetamab-mediated lysis of myeloma cells. Patients eligible for the TRIMM-2 trial had received ≥3 prior lines of therapy and had to be double refractory to a proteasome inhibitor (PI) and an immunomodulatory drug (IMiD).[9] Previous treatment with an anti-CD38 antibody ≥90 days prior to trial enrollment was allowed, regardless of refractoriness to anti-CD38 therapy. All patients (n=29) received daratumumab (1800 mg SC weekly in cycles 1 and 2, every second week in cycles 3–6 and once monthly from cycle 7 on) in addition to 400 μg/kg (SC/Q2W) (n=5), 400 μg/kg (SC/QW) (n=9) or 800 μg/kg (SC/Q2W) (n=15) talquetamab. Patients had received a medium of 6 prior lines of therapy, 79.3% of patients had been exposed to anti-CD38 therapy before, 65.5% were refractory to anti-CD38 therapy and 51.7% were triple-class refractory. Overall, hematological AEs were mainly grade 1 and 2 cytopenias that were mostly limited to step-up and cycles 1 and 2. No overlapping toxicities were observed, and AEs were consistent with those observed for the single agents. The most common hematological AE was neutropenia, occurring in 41% of patients. Similar to what has been previously observed for the single agent, 65% of patients experienced skin-related and nail disorder AEs with talquetamab plus daratumumab treatment. At a median follow-up of 4.7 months, 88% of responders (n=15) were still on treatment. The preliminary data suggest an ORR of 77–85%. In conclusion, talquetamab is a promising new treatment option both as monotherapy and in combination with daratumumab. Talquetamab was well tolerated and showed a manageable safety profile while providing encouraging early efficacy data.

CAR T-cell therapy shows durable clinical benefits in heavily pretreated patients with RRMM

At ASH 2021, Dr Thomas Martin presented an update of the phase Ib/II CARTITUDE-1 trial investigating the safety and efficacy of ciltacabtagene autoleucel (cilta-cel), a second-generation autologous chimeric antigen receptor (CAR) T-cell therapy with two BCMA targeting single domain antibodies in heavily pretreated patients with RRMM with a longer follow-up of approximately 2 years.[11] Eligible patients had progressive MM, had received ≥3 prior lines of therapy including a PI, an IMiD and an anti-CD38 antibody, or were double refractory. The median administered dose was $0.71x10^6$ (range $0.51–0.95x10^6$) CAR+ viable T cells/kg. At a median follow-up of 12.4 months, cilta-cel has demonstrated a manageable safety profile with an ORR and sCR of 97% and 67%, respectively.[12] Additionally, the 12-months progression-free survival (PFS) and OS rates with cilta-cel were 77% and 89%, respectively. With longer follow-up, the responses deepened, resulting in an ORR of 97.9% and an sCR of 83% at a median follow-up of 2 years. The 24 month PFS rate was 60.5%, and 24 month OS rate was 74% with both the median PFS and the median OS not reached. In patients with sCR, the 24-month PFS rate was 71.0% and the median PFS was not reached. Among patients evaluable for MRD (n=61), 92% were MRD-negative (threshold: 10^{-5}). No new safety signals have been observed with longer follow-up and cilta-cel continues to show a manageable safety profile. Over the course of the trial, 15 secondary or primary malignancies were reported in 11 patients, however, as assessed by the investigator all were unrelated to cilta-cel. In conclusion, with longer follow-up, the high efficacy of cilta-cel was confirmed, leading to impressive PFS and OS rates in heavily pretreated MM patients. This update on the encouraging efficacy of cilta-cel suggests its high potential as an important new treatment option for MM patients.

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