short review

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ASH highlights 2022—multiple myeloma

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Summary The 64th annual meeting was held in New Orleans, Louisiana from December 10–13, 2022. More than 150 abstracts concerning multiple myeloma have been presented, mirroring the rapid progression, and deepening of our understanding of this disease. Evolution in treatment options includes new therapeutic regimens incorporating established drugs as well as entirely newly discovered substances, targeting malignant plasma cells utilizing the power of the immune system. In the following, a personal shortcut of hot topics is presented, focusing on data from large clinical trials which have the potency to change clinical practice as well as on new treatment options which may impact future strategies to achieve deep and durable responses aiming to pave the way to potential cure.

Keywords American Society of Hematology · Multiple myeloma · CD38 antibodies · Bispecific antibodies · Anti-BCMA directed therapy · CAR-T cells

Newly diagnosed multiple myeloma—patients not eligible for ASCT

Defining the optimal *first-line therapy* for patients *not eligible for ASCT (TNE)*, both the *MAIA trial* [1] and the *IFM 2017-03 trial* [2] have been conducted. Data from MAIA were already presented during the last years' ASH meetings; in 2022 important updates regarding long-term treatment, tolerability and quality of life (QoL) were presented.

The MAIA trial [1] evaluated patients with newly diagnosed multiple myeloma (NDMM) not eligible for autologous stem cell transplantation (ASCT). In the experimental arm, patients were treated with daratumumab/Lenalidomide/dexamethasone (D-Rd), while the comparison cohort received the then-standard therapy consisting of Lenalidomide and dexamethasone (Rd).

In previous years, the MAIA trial was able to show that triple therapy (D-Rd) is superior to the previous standard therapy (Rd). Based on the results of the MAIA trial, the latest guidelines have already been updated and since then, triple combination therapy has become the standard induction for patients not eligible for ASCT. Now, after more than 5 years of observation, we have deep insights into the side effect profile, safety and tolerability. It is reasonable to assume that triple therapy is associated not only with an improved response but also with an increased risk of side effects. Contrary to this assumption, the D-Rd cohort's quality of life was significantly improved in all patients, including frail patients. Moreover, a reduction in pain symptoms and improvement of physical functioning was observed. Overall, there are no new additional safety concerns, and the results support the first-line use of D-Rd in transplant-ineligible multiple myeloma patients, also in patients considered as frail.

The International Myeloma Foundation (IFM) 2017-03 survey (*IFM 2017-03*) [2], a phase III clinical trial where the use of daratumumab and Lenalidomide (DR) versus Lenalidomide and dexamethasone (Rd) for the treatment of TNE, frail NDMM patients was evaluated. The comparison of Dara-Rd (as in the MAIA trial) versus steroid-sparing Dara-R was not ad-

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dressed because Dara-Rd was not a standard therapy at the baseline of this study.

But still, the data from this trial should gain insights into the importance of corticosteroids on treatment outcome and on the risk of infections when using daratumumab combined with Lenalidomide without corticosteroids. The safety data for both treatments are comparable. The DR cohort showed significantly more cases of neutropenia. There was no increased risk of infection or pneumonia. At the same time, the overall response rate (ORR) in the DR cohort was significantly higher than in the Rd cohort (ORR: 89% vs ORR: 77%). The dexamethasone-sparing regimen (DR) demonstrated deep and rapid responses as well as a favorable safety profile. It is hypothesized that the follow-up data on efficacy and safety will show further advantages of corticosteroid-sparing therapy possibly as first-line therapy.

Newly diagnosed multiple myeloma—patients eligible for ASCT

The optimal *first-line therapy* for patients with NDMM *eligible for ASCT (TE)* was evaluated in the *Myeloma XI trial* [3] and in the *GRIFFIN trial* [4].

The Myeloma XI trial [3] among other study goals aimed to find the optimum duration of lenalidomide maintenance therapy after ASCT. Lenalidomide maintenance therapy is the standard of care for myeloma patients after ASCT and is administered as long-term therapy until progression of the disease.

The most recent data from the Myeloma XI study were analyzed to answer two main questions: Is fixed duration maintenance therapy as effective as maintenance therapy until progression? Do different risk groups benefit differently from maintenance therapy?

Patients with NDMM were randomized after ASCT to receive either lenalidomide maintenance (until disease progression) or observation. Progression-free survival (PFS) data were analyzed 2, 3, 4, and 5 years after the time of maintenance randomization. The analyzed data provide strong evidence that in the overall cohort, continuation of lenalidomide maintenance therapy for 4–5 years is associated with improved PFS and that the benefit of lenalidomide maintenance therapy diminishes thereafter. In patients who are minimal residual disease (MRD) positive, data support continuing lenalidomide until disease progression. Even in patients with persistent MRD negativity, there is evidence of benefit from continued lenalidomide maintenance therapy for a total of at least 3 years. Controlled randomized trials are needed to investigate whether it is really safe to subsequently discontinue maintenance therapy in this cohort.

The *phase II GRIFFIN trial* [4] evaluated the effects of Dara-VRD (daratumumab–bortezomib–lenalidomide–dexamethasone) compared to VRD as induction therapy before ASCT followed by D-VRD or VRD consolidation and later on Dara-R vs R maintenance. Past analyses of the GRIFFIN study have already shown a significant increase in stringent complete remission (sCR) with the addition of daratumumab [5]. Among other studies, the GRIFFIN study paved the way for the inclusion of CD-38 antibodies in induction therapy. Also, it was analyzed whether Dara-VRD quadruple combination would lead to increased side effects and reduced quality of life. Therefore, in the latest update of the GRIFFIN study, the side effect profile of these quadruple combinations was examined after a longer follow-up. It was shown that therapy with Dara-VRD is not associated with a reduced quality of life but—on the contrary—with an improvement in quality of life. Again, pain reduction over time was significant as well as reduction of fatigue after therapy with the quadruplet. Furthermore, the subgroup of high-risk patients (cytogenetic high-risk aberrations present) benefited from the quadruple therapy. The only subgroup that did not benefit from quadruple therapy is the ultra-high-risk group with ≥2 high-risk aberrations. There are still no optimal therapy concepts for these patients.

High-risk and ultra-high-risk patients

Therapy options for patients with *high-risk (HR)* or even *ultra-high-risk (UHiR) cytogenetics* were examined in the *GMMG-CONCEPT trial, OPTIMUM trial* and a study by Tan et al.

The *GMMG-CONCEPT* [6] trial investigated quadruplet therapy with isatuximab, carfilzomib, lenalidomide, and dexamethasone (Isa-KRd) for high-risk NDMM as induction and consolidation including TE and TNE patients. High-risk MM was defined by the presence of del17p or t(4;14) or t(14;16) or >3 copies 1q21 in combination with ISS 2 or 3-stage disease.

The presented data showed high response rates in this very difficult-to-treat population, in TE patients (91% ≥VGPR; 68% MRD-neg) as well as TNE patients (89% ≥VGPR; 54% MRD-neg). These data are of pivotal importance since the presented MRD-negativity rates are unique so far and, as has already been shown in other trials, may have an essential impact on overall clinical outcome and survival.

Since the debate about optimal combination of proteasome inhibitors during induction is still ongoing, the retrospective study by Tan et al. [7] may add important information to the topic. Although only retrospectively analyzed, induction with KRd and VRd was compared in the management of HR-NDMM. The phase III Endurance trial [8], published 2020 showed no difference between the two combinations but excluded patients with HR-NDMM. On the other hand, in the FORTE trial by Gay et al. the use of KRd + ASCT was superior compared to control arms and a significant clinical benefit could be shown for patients with high-risk cytogenetics. Confirming these data, the data by Tan et al. showed

significant improvement in PFS among HR-NDMM patients who received KRd (median PFS 71 months) compared to VRd induction (median PFS 41 months). Taken together, the debate about using KRd or VRD as induction is still going on.

The *OPTIMUM trial* [9, 10] examined the use of a quintuple therapy for *ultra-high-risk and plasma cell leukemia* patients. Patients received induction therapy with up to 6 cycles of daratumumab, bortezomib, cyclophosphamide, lenalidomide, and dexamethasone (Dara-CVRd) then V-ASCT, followed by Dara-VRd consolidation for 6 cycles (Cons1), Dara-VR consolidation for 12 cycles (Cons2) and monthly Dara-R maintenance until progression. Data after quintuple therapy induction were released in 2021 [10].

In 2022 the data after Cons2 were presented. Patients in Cons2 demonstrated a 30 month PFS of 77%. For context, PFS at 30 months for UHiR patients in Myeloma XI trial was significantly lower (34% CRd cohort). Relevant adverse events (neutropenia and infection) were higher but manageable with extended Dara-VR consolidation. The OPTIMUM trial results support extended, risk-stratified post-ASCT therapy for these ultra-high-risk patients since optimal treatment options are lacking. However, benefit and risk must be weighed against each other when intensive strategies with quintuplets are administered.

Triple-class refractory patients

The prognosis of *triple-class refractory patients* is extremely poor with a median overall survival of 13 months [11]. Therefore, the identification of more effective therapeutic strategies for this patient population has emerged as a key priority for multiple myeloma (MM) research.

Tackling this topic, special attention of this year's ASH meeting was on *bispecific antibodies* and their use in the relapsed/refractory setting.

Teclistamab is the first T-cell redirecting bispecific antibody approved for MM. It targets CD3 on cytotoxic T cells and B-cell maturing antigen (BCMA), which is overexpressed on the surface of MM cells. Teclistamab is extremely effective when administered as a single agent in RRMM as we have learned from the pivotal MajesTEC-1 trial [12]. Now, results from the *MajesTEC-2* [13] trial were presented, where teclistamab was tested in combination with daratumumab and lenalidomide (Tec-dara-len). The triple combination showed even better ORR (ORR 94%) than teclistamab-mono (ORR 65%) with a safety profile consistent with tec or dara-len individually.

Elrantamab was investigated in the *MAGNETISMM-3 study* [14]. This humanized bispecific antibody also targets BCMA and CD3 and showed promising ORR (61%).

Due to the BCMA expression on healthy plasma cells, the main observed adverse event in both elrantamab and teclistamab treatment is hypogammaglobulinemia. Intravenous or subcutaneous immunoglobulin therapy was used to treat hypogammaglobulinemia in 39% (teclistamab-mono) [15] and 41% (elrantamab-mono) [14] of patients, respectively.

The *MonumenTAL trial* [16] investigated the bispecific antibody *talquetamab* in patients with RRMM. Talquetamab is a first-in-class, off-the-shelf, T-cell redirecting bispecific antibody targeting both GPRC5D and CD3 receptors. Because GPRC5D is not expressed on B cells, therapy with talquetamab results in fewer cases of hypogammaglobinemia and a lower rate of severe infections. Of note, treatment response was 74% in the overall cohort and is still 62.7% in patients who received prior T-cell redirecting therapies (other bispecific antibodies, ADCs or CART cells). Side effects seem to be mild, and focus on dysgeusia, hair and nail changes. However, longer follow-up for more detailed information on safety and tolerability is needed.

First in human

New, so-called 2+1 bispecific antibodies are *alnuctamab* and *forimtamig*.

These bispecific antibodies have two possible binding sites and are thus expected to be even more effective. *Alnuctamab* [17] is a 2+1 BCMAxCD3 T-cell engager. In a phase 1 first-in-human study, alnuctamab has demonstrated clinical effectivity in RRMM patients. To reduce CRS risk, the study protocol pivoted from intravenous to subcutaneous administration. One special feature of this antibody is that it has to be administered weekly (first 2 cycles) at the beginning, but then only once a month.

Forimtamig [18] (also known as RG6234) is a novel 2+1 GPRC5DxCD3 T-cell engaging bispecific antibody. Showing similar effectivity, again, an advantage seems to be the prolonged dosing intervals.

Modakafusp alfa [19] is a first-in-class, innate immunity enhancer. It binds with high affinity to CD38 and signals through IFNRa (attenuated IFNa is coupled at the Fc part of the immunoglobulin). Efficacy data are promising and again, administration seems convenient with application subcutaneously every 3–4 weeks.

Mezigdomide [20] is a novel oral agent with enhanced tumoricidal, and immune-stimulatory effects compared to immunomodulatory drugs (IMiDs). Activity is promising in triple-refractory patients as well as those with extramedullary disease or prior anti-BCMA therapy.

And finally, updates regarding CART cells were presented [21]. Apart from subgroup analyses and efficacy data after longer follow-up, the most important aspect relates to accelerating the manufacturing process. Data from different groups were presented and showed manufacturing procedures completed in up to 5 days [22]. If a shorter manufacturing process

of CARTs would be possible, bridging therapy will no longer be necessary.

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Conflict of interest L.Z. Rüsing, H. Agis and M. Krauth declare that they have no competing interests.

References

1. Perrot A, Facon T, Plesner T, Usmani S, Kumar SK, Bahlis NJ, et al. Health-related quality of life for frail transplant-ineligible patients with newly diagnosed multiple myeloma treated with Daratumumab, Lenalidomide and Dexamethasone: subgroup analysis of MAIA trial. Blood. 2022;140(Supplement 1):1142–5.
2. Manier S, Corre J, Hulin C, Laribi K, Araujo C, Pica G-M, et al. A dexamethasone sparing-regimen with daratumumab and lenalidomide in frail patients with newly-diagnosed multiple myeloma: efficacy and safety analysis of the phase 3 IFM2017-03 trial. Blood. 2022;140(Supplement 1):1369–70.
3. Pawlyn C, Menzies T, Davies FE, de Tute RM, Henderson R, Cook G, et al. Defining the optimal duration of lenalidomide maintenance after autologous stem cell transplant—data from the myeloma XI trial. Blood. 2022;140(Supplement 1):1371–2.
4. Chari A, Kaufman JL, Laubach JP, Sborov DW, Reeves B, Rodriguez C, et al. Daratumumab plus lenalidomide, bortezomib, and dexamethasone (D-RVd) in transplant-eligible newly diagnosed multiple myeloma (NDMM) patients (pts): final analysis of griffin among clinically relevant subgroups. Blood. 2022;140(Supplement 1):7278–81.
5. Voorhees PM, Kaufman JL, Laubach J, Sborov DW, Reeves B, Rodriguez C, et al. Daratumumab, lenalidomide, bortezomib, and dexamethasone for transplant-eligible newly diagnosed multiple myeloma: the GRIFFIN trial. Blood. 2020;136(8):936–45.
6. Leypoldt LB, Besemer B, Asemissen AM, Hänel M, Blau IW, Görner M, et al. Isatuximab, carfilzomib, lenalidomide, and dexamethasone (Isa-KRd) in front-line treatment of high-risk multiple myeloma: interim analysis of the GMMG-CONCEPT trial. Leukemia. 2022;36(3):885–8.
7. Tan CR, Derkach A, Nemirovsky D, Ciardiello A, Diamond B, Hultcrantz M, et al. Bortezomib, lenalidomide and dexamethasone (Vrd) vs carfilzomib, lenalidomide and dexamethasone (Krd) as induction therapy in newly diagnosed multiple myeloma. Res Sq. 2023. https://doi.org/10.21203/rs.3.rs-2583053/v1.
8. Kumar SK, Jacobus SJ, Cohen AD, Weiss M, Callander N, Singh AK, et al. Carfilzomib or bortezomib in combination with lenalidomide and dexamethasone for patients with newly diagnosed multiple myeloma without intention for immediate autologous stem-cell transplantation (ENDURANCE): a multicentre, open-label, phase 3, randomised, controlled trial. Lancet Oncol. 2020;21(10):1317–30.
9. Kaiser MF, Hall A, Smith I, de Tute RM, Roberts S, Ingleson E, et al. Extended intensified post-ASCT consolidation with daratumumab, bortezomib, lenalidomide and dexamethasone (Dara-VRd) for ultra-high risk (UHiR) newly diagnosed myeloma (NDMM) and primary plasma cell leukemia (pPCL): the UK optimum/Muknine trial. Blood. 2022;140(Supplement 1):1833–5.
10. Kaiser MF, Hall A, Walker K, Newnham N, de Tute RM, Roberts S, et al. Daratumumab, cyclophosphamide, bortezomib, lenalidomide, dexamethasone (Dara-CVRd), V-augmented Autologous stem cell transplant (V-ASCT) and Dara-Vrd consolidation in ultra-high risk (UHiR) newly diagnosed myeloma (NDMM) and primary plasma cell leukemia (pPCL) compared with myeloma XI/XI+ trial treatment for Uhir MM: the UK optimum/Muknine trial. Blood. 2021;138(Supplement 1):465.
11. Kumar SK, Dimopoulos MA, Kastritis E, Terpos E, Nahi H, Goldschmidt H, et al. Natural history of relapsed myeloma, refractory to immunomodulatory drugs and proteasome inhibitors: a multicenter IMWG study. Leukemia. 2017;31(11):2443–8.
12. Usmani SZ, Garfall AL, van de Donk N, Nahi H, San-Miguel JF, Oriol A, et al. Teclistamab, a B-cell maturation antigen x CD3 bispecific antibody, in patients with relapsed or refractory multiple myeloma (MajesTEC-1): a multicentre, open-label, single-arm, phase 1 study. Lancet. 2021;398(10301):665–664.
13. Searle E. Teclistamab in combination with subcutaneous daratumumab and lenalidomide in patients with multiple myeloma: results from one cohort of MajesTEC-2, a phase1b, Multicohort study. American Society of Hematology Meeting. 2022.
14. Bahlis NJ. Efficacy and safety of elranatamab in patients with relapsed/refractory multiple myeloma naïve to B-cell maturation antigen (BCMA)-directed therapies: results from cohort a of the magnetismm-3 study. American Society of Hematology Meeting. 2022.
15. Moreau P, Garfall AL, van de Donk N, Nahi H, San-Miguel JF, Oriol A, et al. Teclistamab in relapsed or refractory multiple myeloma. N Engl J Med. 2022;387(6):495–505.
16. Chari A, Touzeau C, Schinke C, Minnema MC, Berdeja J, Oriol A, et al. Talquetamab, a G protein-coupled receptor family C group 5 member D x CD3 bispecific antibody, in patients with relapsed/refractory multiple myeloma (RRMM): phase 1/2 results from MonumenTAL-1. Blood. 2022;140(Supplement 1):384–7.
17. Wong SW, Bar N, Paris L, Hofmeister CC, Hansson M, Santoro A, et al. Alnuctamab (ALNUC; BMS-986349; CC-93269), a B-cell maturation antigen (BCMA) x CD3 T-cell engager (TCE), in patients (pts) with relapsed/refractory multiple myeloma (RRMM): results from a phase 1 first-in-human clinical study. Blood. 2022;140(Supplement 1):400–2.
18. Carlo-Stella C, Mazza R, Manier S, Facon T, Yoon S-S, Koh Y, et al. RG6234, a GPRC5dxCD3 T-cell engaging bispecific antibody, is highly active in patients (pts) with relapsed/refractory multiple myeloma (RRMM): updated intravenous (IV) and first subcutaneous (SC) results from a phase I dose-escalation study. Blood. 2022;140(Supplement 1):397–9.

19. Bruins WSC, Rentenaar R, Collins S, Sampson JF, Van De Donk NW, Zweegman S, et al. Modakafusp alfa (TAK-573), a novel CD38-targeting attenuated interferon-alpha immunocytokine, kills MM cells via NK cell activation. Blood. 2022;140(Supplement 1):4236–7.
20. Richardson PG, Trudel S, Quach H, Popat R, Lonial S, Orlowski RZ, et al. Mezigdomide (CC-92480), a potent, novel cereblon E3 Ligase modulator (CELMoD), combined with dexamethasone (DEX) in patients (pts) with relapsed/refractory multiple myeloma (RRMM): preliminary results from the dose-expansion phase of the CC-92480-MM-001 trial. Blood. 2022;140(Supplement 1):1366–8.
21. Usmani S, Patel K, Hari P, Berdeja J, Alsina M, Vij R, et al. KarMMa-2 cohort 2a: efficacy and safety of Idecabtagene vicleucel in clinical high-risk multiple myeloma patients with early relapse after frontline autologous stem cell transplantation. Blood. 2022;140(Supplement 1):875–7.
22. Costa LJ, Kumar SK, Atrash S, Liedtke M, Kaur G, Derman BA, et al. Results from the first phase 1 clinical study of the B-cell maturation antigen (BCMA) Nex T chimeric antigen receptor (CAR) T cell therapy CC-98633/BMS-986354 in patients (pts) with relapsed/refractory multiple myeloma (RRMM). Blood. 2022;140(Supplement 1):1360–2.