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What is the future of immunotherapy in MM?

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Abstract:
The treatment of Multiple Myeloma (MM) is currently being redefined by humoral and cellular immunotherapies. For decades, there was limited believe in immune-based anti-MM therapy due to the moderate graft-versus-myeloma effect of allogeneic stem cell transplantation. Today, monoclonal antibodies are the new backbone of anti-MM therapy, and T-cell therapies targeting BCMA are emerging as the most potent single agents for MM treatment. Herein, we present our assessment and vision for MM immunotherapy in the short- and mid-term future.

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ABSTRACT

The treatment of Multiple Myeloma (MM) is currently being redefined by humoral and cellular immunotherapies. For decades, there was limited believe in immune-based anti-MM therapy due to the moderate graft-versus-myeloma effect of allogeneic stem cell transplantation. Today, monoclonal antibodies are the new backbone of anti-MM therapy, and T-cell therapies targeting BCMA are emerging as the most potent single agents for MM treatment. Herein, we present our assessment and vision for MM immunotherapy in the short- and mid-term future.

The future is now: antibody immunotherapy is the new backbone of MM therapy

After the approval of combination therapies with monoclonal antibodies (mAb) for patients with relapsed Multiple Myeloma (MM), the anti-CD38 mAb daratumumab (Dara) has become the new backbone of first-line therapy in transplant-eligible and -ineligible MM patients. In the CASSIOPEIA trial, a quadruple-regimen of Dara, bortezomib, thalidomide and dexamethasone (Dara-VTD) accomplished an overall response rate (ORR) and a progression free survival (PFS) of 93% and 93% vs. 90% and 85% in the control arm at 18-months[1], respectively, setting a new benchmark for efficacy in induction therapy. Minimal residual disease (MRD)-negativity was achieved in 64% of patients versus 44% in the VTD control arm, suggesting improved overall survival (OS) with longer follow-up. Based on these results, the U.S. (FDA) and EU (EMA) regulatory agencies approved Dara-VTD in early 2020.

Likewise, the induction regimen Dara-VRD, comprising lenalidomide instead of thalidomide, achieved compelling results in the GRIFFIN phase II study with PFS and OS rates of even ≥95% at 24 months[2]. Notably, PFS rates were not significantly different between Dara-VRD and VRD, but there was a marked difference in MRD negativity in the Dara arm (51.0% vs 20.4% at 22 months), which will likely translate into better PFS with longer follow-up [3]. The phase 3 study PERSEUS of Dara-VRD versus VRD has completed enrollment and results are expected to be reported in 2022. In transplant-ineligible MM patients, combination therapies that comprise Dara as backbone, i.e. Dara-VMP[4] and Dara-Rd[5], have recently been approved. Dara s.c. injection[6] has been approved lately and accordingly, Dara-VMP and Dara-Rd can be considered the new standard for transplant-ineligible patients with newly diagnosed (ND)MM.

Building on the successful clinical use of Dara, alternative anti-CD38 antibodies are entering the stage with isatuximab (Isa) being the most clinically advanced candidate. In the randomized IKARIA trial, the triple-regimen of isatuximab, pomalidomide and dexamethasone was superior to the control arm of pomalidomide and dexamethasone in relapsed refractory (RR)MM patients, with a PFS of 11.5 months and 6.5 months, respectively[7]. Based on this study, the FDA approved this regimen in March 2020 and we anticipate approval by EMA to occur in 2020 as well. In analogy to the PERSEUS trial, the GMMG HD7 trial evaluates induction therapy with Isa-VRD versus VRD in a randomized fashion. It is likely that both anti-CD38 antibodies – Dara and Isa – will be approved in combination regimen for use in first-line therapy. Numerous additional regimen with anti-CD38 antibodies, e.g. in combination with carfilzomib[8,9] or traditional chemotherapy[10] are being evaluated and will enrich the therapeutic armamentarium to achieve disease control in RRMM patients.

The primary mode of action of Dara and Isa is distinct however, the activity of both mAbs is in part dependent on the density of CD38 molecules on the myeloma cell membrane[11]. Accordingly, strategies to increase CD38-expression on MM cells, e.g. by epigenetic modulation are being investigated[12,13]. Of note, Dara also depletes CD38+ immunosuppressive cells, which is associated with an increase of cytotoxic T cells, potentially contributing to the activity of this antibody[14]. An unresolved question is whether prior therapy with an anti-CD38 mAb impacts on the subsequent efficacy of T-cell redirecting therapies. Because CD38 is expressed on activated T cells (and to a lesser extent on resting T cells and on NK cells), anti-CD38 mAbs may lead to pertubations in T cell composition and may interfere with the mode-of-action of chimeric antigen receptor (CAR) T-cell therapy and

T-cell engaging bispecific antibodies (bsAb). Careful investigations are warranted to determine the optimal sequence and timing of anti-CD38 therapy and T-cell redirecting therapies.

The role of elotuzumab (Elo), an anti-SLAMF7 mAb, in MM therapy is less clear. The anti-MM potency of Elo as a single agent is rather limited and therefore, Elo has been evaluated in combination with immune-modulating agents to augment activity. Recently, final data from the ELOQUENT-1 trial, that evaluated Elo, lenalidomide and dexamethasone (Elo-RD) versus RD in transplant-ineligible NDMM patients, did not report additive activity of Elo[15]. However, in the relapse setting, Elo-RD was superior to the RD control arm[16]. Furthermore, Elo in combination with pomalidomide and dexamethasone exerted significant clinical activity in the ELOQUENT-3 study with 40% of RRMM patients being in remission at 2 years[17]. Appreciating that Elo is well tolerated and has a favorable safety profile, this antibody may also play a role in the setting of maintenance therapy. Currently, Elo is evaluated in a quadruple induction and consolidation regimen in transplant-eligible patients with NDMM (Elo-VRd - HD6 trial, Elo-KRd - DSMMXVII trial). Notably, T-cells expressing a SLAMF7-CAR with a targeting domain derived from Elo are substantially more potent against MM than Elo in pre-clinical models in vitro and in vivo[18] and therefore, the results of phase I/IIA clinical trials with SLAMF7-CAR T-cells (CARAMBA and MELANI-01) are eagerly awaited.

A new future begins: the dawn of T cell redirecting therapies

Chimeric antigen receptor T-cells

T-cell redirecting therapies with gene-engineered CAR T-cells and T-cell engaging bsAb are currently the most exciting new developments in cancer immunotherapy and will change the treatment paradigm for MM (**Figure 1**). Idecabtagene-vicleucel (Ide-cel; bb2121) is a BCMA-CAR T-cell therapy that reported an ORR of 85%, with 45% of patients achieving complete response (CR) in heavily pretreated RRMM in a dose-escalating phase 1 study[19]. The pivotal phase 2 KarMMa study with Ide-cel has fully recruited and initial results were presented at the 2020 ASCO meeting showing an ORR of 73% and a median PFS of 8.6 months, and both increased with higher dose[20]. Thus, we are expecting FDA approval of Ide-cel for RRMM in 2020, which will constitute a landmark as the first gene-engineered T-cell therapy in MM.

LCAR-B38M (also known as JNJ-68284528) is another compelling BCMA-CAR T-cell product currently under investigation in phase I/II trials[21]. Interim results from the CARTITUDE-1 study showed an ORR of 100% with 76% stringent CRs for heavily pretreated RRMM patients[22]. Several other BCMA-CAR T-cell products are being investigated in phase 1 studies and collectively, the data support the notion that BCMA-CAR T-cells are highly effective and probably are the most potent single agent available in the RR disease setting[19,23,24]. However, duration of response is limited in these trials and the majority of patients ultimately relapse. In contrast to CD19 CAR T- cells in Non-Hodgkin lymphoma [25], there is no survival plateau in MM so far.

Overall, BCMA-CAR T-cell therapy displayed a favorable safety profile with lower incidence of cytokine release syndrome and neurotoxicity compared to CD19-CAR T-cell therapy in B-cell leukemia and -lymphoma[19,26]. However, the clinical experience with BCMA-CAR T-cells has also exposed several challenges associated with targeting this antigen, and potential mechanisms of relapse or resistance include antigen down-regulation or even loss [27] in a

small subset of patients, as well as limited persistence of BCMA-CAR T-cells, and limited fitness of T-cells in heavily pre-treated patients[19,21,23,24,28]. Several strategies are pursued to address these challenges, including the use of gamma-secretase inhibitors to enhance BCMA molecule density on MM cells and to reduce the amount of soluble BCMA in serum[29]; refined CAR T-cell manufacturing protocols to increase fitness, e.g. in the presence of PI3K inhibitors[30]; the use of CAR products with defined T-cell subset composition and humanized targeting domains to reduce immunogenicity and to promote engraftment and in vivo expansion[29,31,32].

Antibody drug conjugates

A subset of MM patients with significant comorbidities may be less able to tolerate the potential toxicity associated with T-cell redirecting therapies and for this patient population, BCMA-specific antibody drug conjugates (ADC) may be an alternative. A lead candidate in this class of compounds is belantamab mafadotin. Belantamab mafadotin eliminates MM cells by releasing the cytotoxic agent auristatin F and through antibody-dependent cellular cytotoxicity (ADCC). Belantamab mafadotin is administered i.v. every 3 weeks and is well tolerated except of corneal toxicity, which occurs in >70% of patients[33]. The ORR with belantamab mafadotin was around 30% in a phase 2 trial addressing patients refractory to Dara, IMiDs and proteasome inhibitors[34]. PFS was 2.8 months and 3.9 months in the 2.5mg/kg and 3.4 mg/kg dose group, respectively. In responding patients, PFS was not reached and 8.4 months in the 2.5 mg/kg and 3.4 mg/kg dose group, respectively[35]. Based on these results, we anticipate FDA approval in triple-refractory RRMM later in 2020. Intriguingly, belantamab mafadotin´s mode-of-action is independent of T-cell fitness and accordingly, this ADC is given consideration as one of the few remaining therapeutic options for patients that experience relapse after CAR T-cell therapy[36].

The future ahead: a race between BCMA-targeting agents to first-line therapy?

T-cell engaging bispecific antibodies

T-cell engaging bsAbs are another way to harness the power of a cellular immune response to combat MM (**Figure 1**). A first proof-of-concept for bsAbs in MM was recently provided with AMG420, a CD3xBCMA bispecific T-cell engager (BiTE) construct. At the dose of 400 µg/d, the response rate was 70% including 50% MRD-negative complete responses, with some responses lasting >1 year[37]. Recently, a pilot study with the asymmetric CD3xBCMA bsAb CC-93269[38] reported an 89% ORR and a 44% CR rate at the highest dose of 10 mg in heavily pre-treated MM patients[39]. Teclistamab and REGN5458 are two other BCMA/CD3 bispecific antibodies with promising preliminary results in early clinical trials [40,41].

A practical advantage of bsAbs over CAR T-cells is that they are ‘off-the-shelf’ products and can be administered repeatedly to sustain the therapeutic pressure against MM. A current focus in the field is to determine the most active bsAb compound that we anticipate will advance to pivotal trials within the next 1-3 years, and to derive detailed insights into potential mechanisms of resistance to bsAb therapy due to interference from soluble BCMA protein, BCMA down-regulation, as well as humoral and cellular immune responses against synthetic bsAb constructs[42].

We anticipate that T-cell redirecting therapies targeting BCMA (CART, bsAb) will rapidly move forward from late-stage RRMM to earlier treatment lines, and even to first-line therapy in difficult-to-treat MM patients. A key assumption supporting this strategy is that the fitness

of endogenous T cells at early disease stages is higher compared to later disease stages, when patents have received multiple rounds of cytotoxic therapy[43]. While data to support this hypothesis are still emerging in MM[44], we have recently shown in lymphoma that patient T cells acquire functional defects after chemotherapy, which impacts on activity of bsAbs[45].

A challenge for establishing BCMA-CAR T-cells and bsAbs in first-line therapy is the requirement to demonstrate superiority over standard-of-care, where Dara-based combinations have now set a high bar in efficacy and safety. Accordingly, several studies focus on subgroups of MM patients with suboptimal response to and outcome after conventional and Dara-based combination regimen, because these patients may particularly benefit from CAR T-cell and bsAb therapy. The randomized KarMMa 3 study evaluates Ide-cel versus standard-of-care in RRMM patients previously treated with Dara, an IMiD and a proteasome inhibitor, who have received at least 2 but not more than 4 prior regimen. The CARTITUDE-4 study investigates LCAR-B38M in patients with 1-3 prior lines of therapy, and pre-exposed to proteasome inhibitors and resistant to lenalidomide. Of note, there is limited safety data on BCMA CAR T-cell therapy in the transplant ineligible MM patient population. Similarly, there is a strategy to implement the ADC belantamab mafadotin earlier in MM treatment, e.g. the DREAMM 6 study evaluates belantamab mafadotin in combination with RD or VD in second line. The DREAMM 9 study will evaluate belantamab mafadotin together with standard of care as induction therapy for transplant eligible NDMM patients.

Key requirement: biomarkers to guide patient selection and choice of immunotherapy

Suboptimal response to and early relapse after induction therapy and high-dose chemotherapy with subsequent autologous stem cell transplantation[46] is another approach to define MM patients that may particularly benefit from CAR T-cell therapy as an element of first-line treatment. An alternative strategy is to identify high-risk MM patients at primary diagnosis using molecular markers, which is not without challenges due to the inter- and intra-patient tumor heterogeneity in MM[47,48]. We consider several markers as being potentially suitable for identifying high-risk patients for inclusion into CAR T-cell and bsAb therapy studies, including R-ISS stage 3[49], TP53 double-hit event[50,51], gene-expression profiling-defined high-risk status[52,53], and the presence of extramedullary MM disease[54,55]. The most recent FISH-based MM risk classifier is another promising tool for patient stratification[56]. We would consider an OS of ≥3 years in this MM patient subgroup a breakthrough that now seems accomplishable in the immunotherapy era.

MRD is another key marker defining a subgroup of MM patients with suboptimal response and outcome. The number of MRD-positive patients is significant and constitutes around 40% of NDMM patients after high-dose chemotherapy and autologous stem cell transplantation[1]. For these patients, the goal of administering CAR T-cell therapy is conversion to MRD-negativity with ensuing long-term disease-free survival and even cure. It is important to note that eradication of MM cells in the MRD setting is a prerequisite for cure. Recent data suggest that a primary mode-of-action of CAR T-cells against hematologic cancer cells is the induction of apoptosis[57], and it remains to be determined whether metabolically-inactive MM cells in MRD-positive patients can be sufficiently eliminated. Double-hit TP53 lesions are found in 4% of NDMM patients[58], increase in frequency in the course of disease[59,60] and provide another mechanism of apoptosis resistance. A recent study exposed that impaired FAS receptor signaling is associated with failure of CD19-CAR T-cell therapy in acute leukemia[61]. Noteworthy, genes involved in apoptosis induction are frequently altered due to mutations and chromosomal aberrations in MM[62,63].

Burning questions and outlook: The future is bright for immunotherapy in MM!

There are several burning questions centered around *i.* identifying biomarkers that predict outcome and identify patients that have the highest chance to benefit from T-cell redirecting therapies; *ii.* identifying the optimal single antigen or combination of antigens for T-cell redirecting therapies to consistently induce durable complete remissions; and *iii.* determine whether eventually, MM can be cured in a relevant subset (or even the majority) of patients (**Table 1**). At our institution, we have treated MM patients with biallelic TP53 inactivation and very aggressive disease and observed rapid and deep responses after BCMA-CAR T-cell therapy. This is in line with data from e.g. the KarMMa study, where the majority of patients with high-risk cytogenetics and extramedullary disease responded to CAR T-cell treatment[19]. These data suggest that current algorithms for staging and risk assessment in MM ought to be adapted in the immunotherapy era.

There is a rich pipeline of novel CAR T-cell products, bsAbs, and trispecific antibodies[64] that target alternative antigens including e.g. SLAMF7[18], CD44v6[65] and GPRC5D[66], as well as multi-specific CAR T-cells[67]. Indeed, it will be important to determine whether targeting two (or more) antigens can exert more therapeutic pressure to counteract down-regulation of a single antigen and clonal evolution of MM cells. In another approach, NK cells are used as effector cells and CAR-modified NK cells as well as bispecific killer cell engager (BiKE) targeting MM antigens showed encouraging results in preclinical studies [68,69]. A recent report on a Phase 1/2 trial evaluating CD19-CAR NK cells in patients with non-Hodgkin's lymphoma and chronic lymphocytic leukemia showed a high rate of initial responses and a favorable toxicity profile [70]. We have recently demonstrated that advanced microscopy techniques can be used to identify and monitor target antigens on MM cells to inform therapeutic decisions[71]. Significant efforts are undertaken to simplify the manufacturing and logistics around CAR T-cell therapy involving virus-free gene-transfer, automated point-of-care production and allogeneic cell products[72,73]. With these developments we are confident that the role of immunotherapy in MM will be manifested and the prospect of a chemo-free free, yet curative treatment for the majority of MM patients can become ‘real’ within the next decade.

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Author contributions

L.R., M.H. and H.E. wrote and approved the manuscript.

Conflicts-of-interest

L.R. participated in scientific advisory boards for Janssen, Celgene/BMS, GSK, Sanofi, and has received research support from Skyline Dx .
M.H. participated in scientific advisory boards for Janssen and Celgene/BMS; and is listed as an inventor on patent applications related to CAR technologies that have been filed by the University of Würzburg.
H.E. Scientific Advisory Board: Janssen, Celgene/BMS, Amgen, Novartis, Takeda. Research Support: Janssen, Celgene/BMS, Amgen, Novartis. Honorarium: Janssen, Celgene/BMS, Amgen, Novartis, Takeda

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Tables and Figures:

Table 1: Top 10 burning questions for immunotherapy in MM

Questions	Assessment and perspective in 2020
Will high-risk disease become standard-risk in the era of novel CAR T-cell therapy?	Potentially yes: BCMA-CAR T-cells are effective in patients with high-risk cytogenetics, incl. double hit TP53 mutation.
Is MRD negativity the best endpoint for immunotherapy trials?	Probably yes. Yet, there is an issue with obtaining high quality MRD samples shortly after CAR T due to hypocellular BM. Furthermore, MRD assessment should be combined with functional imaging to exclude residual focal lesions or extramedullary disease.
Should we deliver novel immunotherapies preferentially in early treatment lines (and what is the optimal sequence of novel immunotherapies)?	Probably yes. T cells from patients in early disease stages and early in the treatment course exhibit better fitness compared to late stages. Determining the optimal sequence of immunotherapy modalities is an open issue, e.g.: i. What is the optimal interval between Dara and Elo (because Dara diminishes NK cells that are required for Elo's mode of action? ii. If one BCMA-targeting agent fails, can another still work? iii. How soon after CAR-T therapy can bsAbs be considered (if lymphopenia after lymphodepletion has not resolved)?
Is relapse from immunotherapy more difficult to treat?	Probably no. Yet, the selective pressure of immunotherapies on tumor and microenvironment has yet to be defined.
Will we cure myeloma with CAR T-cells and T-cell engaging bispecific antibodies?	Probably yes, a subgroup of patients with low tumor burden and favorable biology will exceptionally benefit.
Will we deliver chemotherapy-free immunotherapy combos?	Probably yes. Strategies include combo of anti-CD38 mAbs with ADCs or bsAbs (anti-BCMA or anti-GPRC5D) or combo of T cell redirecting therapies with IMIDs to reprogram and improve fitness of endogenous T cells.
Do we need additional diagnostics in the era of immunotherapy?	Probably yes. There is a need and opportunity to implement advanced diagnostics into MM immunotherapy to guide patient and antigen selection, and to monitor disease response as well as advanced genomic analyses to monitor clonal composition and evolution, potential

	gene or even chromosomal loss.
Will targeting more than 1 antigen on MM cells improve response rates and durability of response?	Probably yes. Multi-antigen targeting is an appealing strategy to counteract antigen down-regulation and -loss that limits the efficacy of BCMA-CAR T-cells in a subset of of patients in current clinical trials.
Is there a place for immunotherapy in early asymptomatic stages of MM?	Probably yes, but these therapies need to be well tolerated.
Will the COVID 19 pandemic stop the success of novel immunotherapies?	Definitely no, but the timelines for completion of trials, approval of novel trials and reimbursement may decelerate.

Figure legend

Figure 1: A) Comparison of immunotherapy treatment modalities (CAR - chimeric antigen receptor; bsAb – bispecific (T-cell engaging) antibody; ADC – antibody drug-conjugate; mAb – monoclonal antibody). **B)** Potential therapeutic sequence for newly diagnosed multiple myeloma: Debulking with anti-CD38 antibody based regimen, consolidation and induction of MRD-negativity with T-cell redirecting therapy such as CAR T-cell therapy, followed by maintenance. Grey cells – multiple myeloma cells. Light cells – T cells.

Figure 1