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A GLOBAL CONGRESS DIGEST ON MULTIPLE MYELOMA

Report from the 19th European Multiple Myeloma Academy (EMMA) Meeting, 1st-2nd February 2019, Vienna, Austria

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Preface

Dear Colleagues,

There is increasing insight into the pathogenesis of monoclonal gammopathies and significant advancement in treatment options and therapy efficacy in multiple myeloma. Physicians need to stay up-to-date with the new developments and treatment strategies to offer the best possible care to their patients. Continuing education at increasingly shorter intervals has become a conditio sine qua non for health care professionals caring for patients with multiple myeloma.

Providing the newest information on key aspects of multiple myeloma is the main objective of European Multiple Myeloma Academy (EMMA) meetings. Early this year, the 19th EMMA meeting was held in Vienna, Austria, on February 1st and 2nd 2019. Three hundred eighty myeloma experts from 39 countries convened from all over the world and made this conference the largest annual EMMA meeting ever. As organizers of the meeting, we not only aim to provide a comprehensive update on the newest developments in basic research and treatment, but also aim to create an informal, friendly, collegial atmosphere, which facilitates the interaction between participants and panelists.

In this memo publication, you will find the summaries of five talks on current multiple myeloma treatment options and innovative agents. Although cure must still be considered an ambitious goal at present, the road ahead is promising as patient outcomes are continuously improving.

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Five steps to cure in multiple myeloma

Given the fact that recurrence represents an inherent feature of multiple myeloma (MM), cure seems to be an ambitious goal in this disease. However, Jesús San-Miguel, MD, PhD, Head of Clinical and Translational Medicine, University of Navarra, Navarra, Spain, expressed hope that achieving a normal life expectancy for a substantial proportion of MM patients might be within reach in the era of modern anti-myeloma drugs. For this purpose, MM should not be considered a single entity. „It is a complex disease, and treatment strategies should be adapted to the subtypes." Dr. San-Miguel suggested five steps to achieve cure: eradication of all tumor cells, use of highly sensitive tools for the evaluation of treatment efficacy, early detection and intervention, use of the most active treatments in standard-risk patients, and investigation of experimental therapies upfront in high-risk patients.

MRD is the key

The genomic complexity of MM is an obstacle to the eradication of all tumor cells. An interesting aspect arises from the monoclonal gammopathy of undetermined significance (MGUS) signature, as this predicts long-term survival at the time of diagnosis [1]. „We need to identify these patients", Dr. San-Miguel said. With respect to the assessment of treatment efficacy, Dr. San-Miguel pointed out that the definition of complete remission (CR) based on the percentage of plasma cells in the bone marrow is suboptimal due to lack of distinction between malignant and benign cells. Next-generation flow cytometry, which has a detection limit of 10^{-6}, has become available to the majority of patients [2].

The value of minimal residual disease (MRD) can hardly be overstated, as CR without MRD does not confer better outcomes than partial remission (PR) [3]. „Achieving MRD is important both in the transplant and non-transplant setting, as well as in the relapsed situation," Dr San-Miguel said. Pitfalls regarding MRD assessment include the quality of the bone marrow, the genetics of MRD clones, the immune reconstitution in patients with persistent MRD, and MRD outside of the bone marrow. Ideally, both MRD negativity and PET negativity should be obtained.

Hit fast and hard

Another crucial factor on the road to cure is early treatment of MM. Dr. San-Miguel challenged the concept of initiation of therapy only after the onset of symptoms. Arguments supporting this approach include the issue of clonal selection, long-term toxicity and considerable costs, among others. However, smoldering MM (SMM) shows less genomic complexity than the relapsed disease [4, 5], which facilitates eradication of all clones. Trials conducted in patients with high-risk SMM appear to support the concept of anti-myeloma treatment before the emergence of full-blown disease. A randomized phase III study revealed significant improvement of time to progression and overall survival (OS) with lenalidomide/dexamethasone compared to no treatment [6]. Likewise, autologous stem cell transplantation (ASCT) followed by consolidation and maintenance gave rise to a substantial progression-free survival (PFS) rate of 94 % at 28 months and MRD negativity in 55 % **(Table)** in the CESAR trial (7).

Finally, standard-risk patients should not be excluded from upfront intensive therapies, and high-risk patients need to be identified and treated appropriately. „The risk of undertreating low-risk patients who are in conventional CR might be a serious error," Dr. San-Miguel said. MRD negativity can be used as a guide for treatment decisions in both high-risk and low-risk disease. „If MRD negativity is achieved, the adverse prognosis of high-risk disease can at least partially be overcome." In patients with high risk and MRD positivity, innovative therapies are called for. ■

TABLE
Response rates and MRD status in the CESAR trial according to the updated results

Response category	Induction (n = 88)	ASCT (n = 83)
ORR	86 (98 %)	82 (99 %)
sCR	28 (31 %)	42 (51 %)
CR	8 (9 %)	10 (12 %)
VGPR	36 (40 %)	19 (23 %)
PR	13 (14 %)	11 (13 %)
SD	1 (%)	1 (1 %)
MRD negativity	27 (32 %)	43/78 (55 %)
PD	2 (3 %)	-

ORR, overall response rate; **sCR**, stringent complete remission; **CR**, complete remission; **VGPR**, very good partial remission; **PR**, partial remission; **SD**, disease stabilization; **PD**, progressive disease

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Induction & consolidation: where are we today?

In the treatment of MM patients eligible for ASCT, induction and consolidation represent important steps of high-dose therapy. While the former is aimed at providing fast control of the disease and allowing for an adequate stem cell harvest, the latter is supposed to increase the depth of response after transplantation.

Bortezomib-based induction is the treatment standard

In Europe, triplet regimens are commonly recommended for induction treatment. The ESMO guidelines list bortezomib/thalidomide/dexamethasone (VTd), bortezomib/cyclophosphamide/dexamethasone (VCd), bortezomib/lenalidomide/dexamethasone (VRd), and bortezomib/doxorubicin/dexamethasone (PAd) [1]. „With VRd induction followed by ASCT, VRd consolidation and lenalidomide maintenance for 1 year, the 4-year OS rate was higher than 80 % in the IFM 2009 study," reported Philippe Moreau, MD, Hematology Department, University Hospital Hôtel-Dieu, Nantes, France [2]. A meta-analysis of phase III trials showed that bortezomib-based induction regimens are more effective than those without bortezomib [3]. They gave rise to improvements in response rates, PFS (36 vs. 26.8 months; $p < 0.001$) and, importantly, OS (79.7 % vs. 74.7 % at 3 years; $p = 0.04$). „Bortezomib-based induction should therefore be the standard of care," Dr. Moreau stressed.

Only very few phase III comparisons exist for the triplets mentioned in the guidelines. „VTd and VCd are widely used in Europe," Dr. Moreau said. „VRd is used in the USA, and we are waiting for its European approval." The indirect comparison hints at higher response rates (RR) including improved MRD negativity with VRd compared to VTd, while VRd-mediated toxicity is markedly reduced, most notably regarding neuropathy [4-6].

Future perspectives

Potential future induction regimens include carfilzomib/lenalidomide/dexamethasone (KRd) and combinations of the anti-CD38 antibody daratumumab with VTd or VRd. The FORTE trial established significant superiority of KRd over carfilzomib/cyclophosphamide/dexamethasone (KCd) with respect to RR **(Figure)** and MRD negativity [7]. Daratumumab plus VTd and VRd as induction therapy is being tested in the Cassiopeia and PERSEUS trials, respectively.

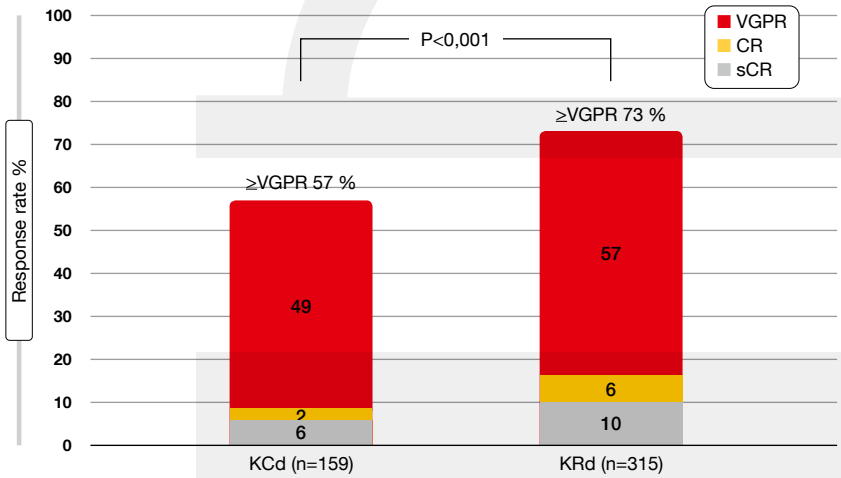
Triplets for consolidation

The optimal regimen and duration of consolidation therapy is still a matter of debate, as is the question of whether this part of the treatment is necessary in the first place. Dr. Moreau noted that several trials favor consolidation. Ten-year data of a phase II/III study testing 4 cycles of VTd after ASCT showed an impressive OS rate of more than 70 % in patients achieving MRD negativity [8]. The same triplet, when administered as both induction and consolidation, induced superior RR and PFS compared to Td after double ASCT in a GIMEMA trial [9, 10]. „Therefore, we trust the triplet consolidation in Europe," Dr. Moreau said.

Keep an eye on the big picture

In the EMN02/HO95 MM trial, VRd consolidation proved superior to no consolidation for PFS, albeit not for OS [11]. Long-term results need to be awaited here. In contrast to these findings, the US-based SCHEMA study yielded no PFS or OS advantage of consolidation with VRd compared to no consolidation [12]. „However, this trial has many biases," Dr. Moreau pointed out.

Improvement on the available options might once again arise from the Cassiopeia and PERSEUS trials as these are testing the addition of daratumumab to VTd and VRd, respectively, not only to induction, but also to consolidation. „MRD data will be presented for both studies," Dr. Moreau announced. However, induction and consolidation should only be viewed as segments of a global strategy. „We need to consider the entire concept including maintenance." ■



sCR: stringent complete remission; **CR**: complete remission; **VGPR**: very good partial remission

Figure: Response rates achieved with KRd vs. KCd as induction treatment

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The art of sequencing after relapse

Change of drug class as a principle

In the setting of relapsed and refractory MM (rrMM), several factors including different molecular and genetic types of MM and the so-called clonal tide (i.e., the appearance and disappearance of clones in the course of the disease) render the selection of subsequent treatments difficult. The multitude of available options plays an important role here, as it precludes head-to-head comparisons. „It is therefore impossible to acquire solid scientific evidence," stated Heinz Ludwig, MD, Wilhelminen Cancer Research Institute, Wilhelminenspital, Vienna, Austria.

Some basic recommendations have been framed. According to these, retreatment (including ASCT after an appropriate time interval) is feasible, although it depends on the quality of response, the tolerance to previous therapy, and available drugs. „Changes of drug classes are preferable in patients who demonstrated insufficient response or intolerance to their previous treatment," Dr. Ludwig explained. Aspects that require careful assessment include patient characteristics and preferences, biology and presentation of the disease, as well as availability of drugs.

The ESMO guidelines for rrMM recommend subsequent regimens according to the type of induction treatment [1]. After immunomodulatory drug (IMiD)-based induction, carfilzomib/dexamethasone (Kd)- or bortezomib/dexamethasone (Vd)-based therapy should be resorted to, while after bortezomib-based induction, lenalidomide/dexamethasone (Rd) is the backbone of choice. „Triplets are preferred for both groups," Dr. Ludwig said.

Patients who have been exposed to both IMiDs and proteasome inhibitors (PIs) should receive pomalidomide-based combinations. Of course, clinical trials are always an option.

Insights from studies

Trial findings leave no doubt about the potency of the novel agents. After the first relapse, the phase II MUK Five Study investigated KCd followed by carfilzomib maintenance *versus* VCd [2]. KCd gave rise to significantly improved RR in both standard-risk and high-risk patients. The carfilzomib maintenance was superior to observation with respect to PFS (11.9 vs. 5.6 months; p = 0.0086) and MRD negativity (24.4 % vs. 3.3 % at 6 months; p = 0.007).

Phase III trials have explored the PIs carfilzomib and ixazomib, the monoclonal antibody elotuzumab, the HDAC inhibitor panobinostat, the anti-CD38 monoclonal antibody daratumumab and the IMiD pomalidomide in addition to Rd or Vd; these regimens were compared to the backbones alone in patients with 1 to 3 prior lines of therapy **(Table)**. Also, elotuzumab plus pomalidomide/dexamethasone (EPd) was tested against pomalidomide/dexamethasone (Pd). „The hazard ratios for PFS were excellent for daratumumab plus Rd vs. Rd, daratumumab plus Vd vs. Vd, Kd vs. Vd, and EPd vs. Pd," Dr. Ludwig reported [3-6]. Significant OS benefits have been demonstrated for KRd vs. Rd, ERd vs. Rd and Kd vs. Vd [7, 8, 5].

Contrary to the rule of decreasing activity with increasing number of prior treatment lines, ixazomib in addition to Rd compared to Rd alone showed even greater PFS benefits in patients after 2 to 3 lines (not achieved vs. 12.5 months; HR, 0.58) than in the total study population (20.6 vs. 14.7 months; HR, 0.742) [9]. Moreover, the addition of ixazomib was shown to equalize the negative effect of high-risk cytogenetics [10], which is unique among the triplets. Other regimens to use in the high-risk setting include daratumumab plus Vd (DVd) or Rd (DRd), ERd, and Pd.

Choices in later lines

The Mayo recommendations for the treatment of second or later relapses suggest a change of treatment to DVd in

the IMiD-refractory setting, while DRd is indicated after PI failure [11]. For both dual-refractory and triple-refractory patients, pomalidomide-based treatment constitutes the first choice. „Pomalidomide is the optimal backbone for combinations with novel drugs," Dr. Ludwig explained. „Reasonable response rates and PFS improvement can be expected with this backbone irrespective of the type of combination partner."

In the triple-refractory setting after pomalidomide failure, daratumumab may be used, as well as alkylator-based therapies, PIs and panobinostat. Elotuzumab can be considered in daratumumab-resistant patients. In the ELOQUENT-3 trial, EPd caused remarkable PFS prolongation in patients with high-risk cytogenetics and in those with ≥ 4 prior lines of therapy [6]. Fit patients with quadruple-refractory disease are likely to respond to VDT plus cisplatin, doxorubicin, cyclophosphamide and etoposide (PACE) [11]. ASCT might be an option even in late stages, although only a small fraction of patients will be eligible. Alternatively, the Mayo Clinic recommendations list daratumumab-, panobinostat- or bendamustin-based treatment, besides alkylator-containing combinations or anthracycline-based therapy.

If conventional treatments have been exhausted, the remaining options comprise patient inclusion in clinical trials, chemotherapy with dexamethasone, cyclophosphamide, etoposide and cisplatin (DCEP), bendamustine combinations, melphalan or cyclophosphamide in combination with prednisone, radiotherapy, and the administration of BRAF inhibitors in the presence of the $BRAF^{V600E}$ mutation.

Refractoriness is not an entity

Although MM is basically a disease of the elderly, only few data are available for frail patients. Favorable PFS results for the elderly population have been obtained in the large trials for Kd vs. Vd, ERd vs. Rd, DRd vs. Rd, DVd vs. Vd, and PVd vs. Vd [5, 12, 3, 4, 6]. As many patients are not eligible for these regimens, reduced-intensity doublet therapy including Vd, Rd, melphalan/prednisone or cyclophosphamide/prednisone can be considered [13].

Generally, retreatment with agents of the same drug class is an option and may result in meaningful responses. Dr. Ludwig pointed out that the term ‚refractory' has weaknesses as it amalgamates clinical situations such as primary refractory disease and refractoriness occurring in later lines, which differ widely with respect to amenability to treatment. „The disease is changing all the time", Dr. Ludwig emphasized. Thus, the clonal tide may also promote the outgrowth of cells sensitive to a drug the patient has been resistant to previously.

Duration of treatment

To date, the duration of treatment has been insufficiently defined, but it is recommended to treat until progression or intolerance when high-risk cytogenetics with or without other high-risk features are present. „In patients with good prognosis and standard cytogenetics, the therapy can be discontinued after achievement of deep responses," Dr. Ludwig noted. Promising new drugs and treatment concepts are currently under clinical evaluation. ■

TABLE
Phase III trials in patients after pretreatment with 1 to 3 lines

	PFS		OS	Trial acronym
	HR	Δ months	Δ months	
Lenalidomide-based				
Carfilzomib-Rd vs. Rd	0.69	8.7	7.9	ASPIRE
Ixazomib-Rd vs. Rd	0.74	5.9	n. a.	TOURMALINE-MM1
Elotuzumab-Rd vs. Rd	0.71	4.5	8.0	ELOQUENT-2
Daratumumab-Rd vs. Rd	0.41	n. r.	n. a.	POLLUX
Bortezomib-based				
Carfilzomib-d vs. Vd	0.53	9.3	7.6	ENDEAVOR
Panobinostat-Vd vs. Vd	0.94	3.9	4.5	PANORAMA
Daratumumab-Vd vs. Vd	0.31	9.6	n. a.	CASTOR
Pomalidomide				
Pomalidomide-Vd vs. Vd	0.61	4.1	n. a.	OPTIMISMM
Elotuzumab-Pd vs. Pd*	0.54	5.6	n. a.	ELOQUENT-3

* ≥ 2 lines or prior ASCT

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The road ahead: innovative therapies

Novel alkylators & IMiDs

Any further improvement of the treatment of patients with rrMM will require new approaches. Enrique M. Ocio, MD, PhD, Marqués de Valdecilla University Hospital & Biomedical Research Institute, University of Cantabria, Santander, Spain, discussed innovative agents such as the novel alkylator melflufen. „This melphalan-derived prodrug is absorbed into the cells due its lipophilic nature, especially into tumor cells." In the OP-106 Horizon study, melflufen plus dexamethasone gave rise to a 33 % overall response rate (ORR) in a heavily pretreated population [1]. Combinations of melflufen with daratumumab and bortezomib are being tested. For EDO-S101, which is another agent that combines alkylating with deacetylase inhibiting activity, no clinical data have been obtained yet.

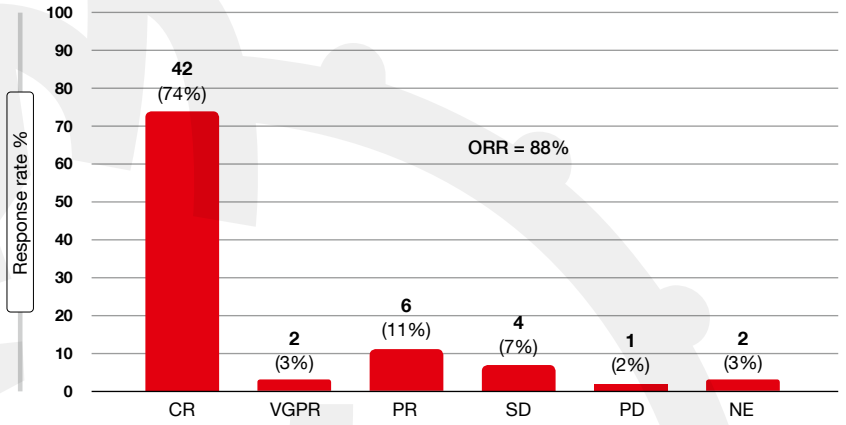
Likewise, IMiDs of the next generation, the so-called CELMoDs, are already at the doorstep. Here, several compounds have been developed, and clinical data are being generated.

Targeted agents on the rise

Pathogenetic features that can be targeted in MM include the RAS/RAF pathway, as the *RAS* family members are the most frequently mutated genes in MM. Heuck et al. reported reductions in MM protein and focal lesions with the MEK inhibitor trametinib as a single agent or combination partner in a substantial proportion of heavily pretreated patients [2]. „Responses were not durable, probably because this is not a driver mutation in MM," Dr. Ocio explained. „Probably trametinib can be combined with the established backbones." The selection of patients based on their genetic profile (e.g. oncogenic mutations of *KRAS*, *NRAS* or *BRAF*) appears to play an important role in the use of targeted treatment in MM.

The BCL-2 inhibitor venetoclax was shown to induce cell death in MM cell lines and primary samples, particularly in those positive for the translocation t(11;14), which correlates with higher ratios of BCL-2 to MCL-1 and BCL-2 to BCL2L1 mRNA [3, 4]. „Venetoclax monotherapy worked in rrMM patients with a median of five prior treatment lines," Dr. Ocio noted [5]. In the total population, the ORR was 21 %, but rose to 40 % in those with t(11;14) and was as high as 88 % in the group who had both t(11;14) and a high BCL-2:BCL2L1 ratio.

A trial combining venetoclax with Vd yielded ORRs of 67 % and 94 % in the overall population and the BCL-2-high patients, respectively [6]. In another study evaluating venetoclax plus Kd, 79 % of all patients and 100 % of those with t(11;14) responded [7]. Due to the connection of the BCL-2 and MCL-1 pathways, combined inhibition makes sense. Several MCL-1 inhibitors are currently being investigated in the phase I.



ORR: overall response rate; **VGPR**: very good partial response; **PR:** partial response; **SD:** stable disease; **PD:** progressive disease; **NE:** not evaluable

Figure: Response rates obtained in rrMM with a CAR construct containing two BCMA-targeting domains: LEGEND-2 trial

XPO1 & microenvironment

Another promising approach arises from the inhibition of exportin1 (XPO1), which is the main nuclear exporter for tumor suppressor proteins (TSPs) and other factors [8]. „The first-in-class XPO1 inhibitor selinexor induces nuclear retention and activation of TSPs and the glucocorticoid receptor in the presence of steroids," Dr. Ocio said. Oncoprotein expression is suppressed. The STORM study investigated selinexor plus dexamethasone in 122 penta-refractory MM patients who achieved an ORR of 26 % [9]. However, hematological and gastrointestinal toxicity must be dealt with, although Dr. Ocio stated that it is worth the effort in view of these results. Combinations of selinexor with PIs, IMiDs and daratumumab are under investigation.

Finally, targeting of the tumor microenvironment might prove a potent mechanism of action, as MM cells depend heavily on the stroma surrounding them. Research in this area is focusing on VEGF and HGF inhibitors, TGF-beta receptor inhibitors and anti-CXCR4 monoclonal antibodies.

Bispecific antibodies

Diminished or dysfunctional tumor-reactive T cells are typically found in cancer patients. Besides immune checkpoint inhibition, bispecific antibody therapy (bispecific T-cell engagers, BiTE®) and CAR T cell therapy are strategies to address this problem. „Bispecific antibody constructs allow for the detection of tumor cells irrespective of mechanisms used by tumor cells to escape from immune surveillance", said Hermann Einsele, MD, Medizinische Klinik und Poliklinik II, University of Würzburg, Germany.

The binding parts of bispecific antibodies connect the tumor cells to activated immune cells. „An immunological synapse is formed, and the T cell can eliminate the tumor cell," Dr. Einsele explained [10]. The first-in-class bispecific anti-CD19/CD3 antibody blinatumomab is currently being explored in MM, as is the anti-B cell maturation antigen (BCMA) BiTE® AMG 420. In a dose escalation phase I trial conducted in rrMM patients, the ORR obtained with AMG 420 at the maximum tolerated dose was 70 % [11]. „Most of the patients achieved stringent remissions, and MRD negativity was present in many," Dr. Einsele reported. Adverse events included mainly cytokine release syndrome and infections.

A phase I/II trial evaluating BCMA-bispecific antibody therapy with longer half-life is ongoing, and AMG 420 will be tested in earlier treatment lines.

Personalized immunotherapy: CAR T cells

In contrast to the BiTE® approach, the CAR T cell therapy does not rely on a preformed compound but on the integration of a chimeric antigen receptor (CAR) into the immune cell, enabling it to recognize surface antigens on tumor cells. Lentiviral or retroviral vectors perform the gene transfer into activated T cells that have been taken from the patient and are re-infused after cell expansion [12]. „This drug is called a living drug, because the quality of remission is improving over time," Dr. Einsele noted. Ideally, the cells should stay in the patient for life and eliminate tumor cells once they arise.

In MM, the target that is addressed most commonly in the context of CAR T cell therapy is BCMA as it is expressed on normal and malignant plasma cells. The investigational drug bb2121 was assessed in a phase I study in heavily pretreated patients who showed CR rates as high as 50 % at a dose level of > 150 x 10^6 cells [13]. At active dose levels, median PFS amounted to 11.8 months and was even longer at 17.7 months in patients achieving MRD negativity. „Surprisingly, cytokine-release syndromes and neurotoxicity, which are an issue in CD19-directed CAR T cell therapy, occurred less frequently," Dr. Einsele said.

The Chinese phase I LEGEND-2 study tested a CAR construct containing two BCMA-targeting domains in heavily pretreated rrMM patients [14]. Again, the treatment evoked only low rates of neurotoxicity and cytokine release syndrome. Eighty-eight percent of patients responded, with 74 % experiencing CR **(Figure)**. Remission lasted 16 months in the overall group and 22 months in the MRD-negative cohort.

Limitations of T-cell redirecting strategies

However, despite initial responses to CAR T cell therapy, the disease relapses in most patients. Reasons for this include a lack of persistence of CAR T cells, immune escape and upregulation of inhibitory receptors that leads to stealth. Potential solutions comprise the selection of more durable T cell subpopulations, increasing the target antigen expression, and combination with immune checkpoint inhibitors.

Long-term observations in other hematological entities imply that T-cell redirecting strategies are only curative in a minority of patients with refractory or heavily pretreated disease. „This has not been demonstrated for MM yet, however," Dr. Einsele pointed out. A clinical pilot study evaluated tandem ASCT and combined infusion of CD19- and BCMA-specific CAR T cells for high-risk MM patients [15]. The rate of MRD negativity increased from 44.4 % after transplantation to 60 % after CAR T cell therapy. Moving the novel therapies to the earlier treatment lines therefore appears reasonable. „Debulking with novel induction plus consolidation with redirected T cells might be an attractive option for MM patients, especially for those with high-risk disease," Dr. Einsele summarized. ■

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