MultipleMyelomaHub

General MM

Relapsed/refractory multiple myeloma: what can we target next?

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Nicola Giuliani, University of Parma, Parma, IT, and colleagues published a review article in the *Expert Review of Hematology,* which addressed current and novel targets for treating relapsed/refractory (R/R) multiple myeloma (MM, RRMM).

Immunomodulatory drugs (IMiDs), such as lenalidomide and pomalidomide, as well as proteasome inhibitors (PIs), like bortezomib, carfilzomib, and ixazomib, have become backbones of treating MM.

However, since MM is an incurable disease characterized by relapses and resistance to therapies, there is a high unmet need for targeted therapies that minimize or potentially eliminate the likelihood of relapse.

Therefore, drugs have been developed and tested which target both the MM cells directly and the tumor microenvironment.

Current models to explain drug resistance in MM cells:

- Plasma cells acquiring genetic abnormalities
- Clonal evolution – with drug-resistant clones emerging
- Persistence of MM cancer stem cells residing in the hypoxic bone marrow niche
- Immune escape
- Loss of microenvironment dependency

MM cells are predominantly found in the bone marrow (BM), which is a hypoxic microenvironment. This plays an important role in MM cell proliferation, survival and drug resistance. This is because MM cells highly express adhesion molecules. This, in turn, activates signal transduction molecules, enhancing pro-survival and anti-apoptotic pathways in MM clones. In R/R disease, the MM cells are less dependent on the microenvironment, as proliferative clones emerge and additional genetic lesions are acquired.

Identifying selectively expressed molecules on the surface of MM cells, as well as the key pathways involved in cell survival, helps to identify new druggable targets.

Anti-tumor drug targets in MM include: CD38, SLAMF7, B-cell maturation antigen (BCMA), programmed cell death protein 1 (PD-1) / PD ligand 1 (PD-L1), histone deacetylase (HDAC) inhibitors, B-cell lymphoma (Bcl)-2 family proteins, and nuclear transport protein exportin 1 (XPO1).

Therapeutic options to target these molecules include: monoclonal antibodies (mAbs), antibody-drug conjugates, bispecific T-cell engagers, chimeric antigen receptor (CAR) T-cells, immune checkpoint inhibitors, and selective small inhibitors.

Table 1. Summary of targets for RRMM

Target	Why target it?	Current drug options	Drugs (approved or in trials)
CD38	CD38 is a surface antigen and ectoenzyme expressed in high levels by MM cells	Anti-CD38 mAbs CAR T-cell therapy	DaratumumabIsatuximabMOR202
SLAMF7	Surface antigen with a high expression on MM cells	mAbs CAR T-cell therapy	Elotuzumab
BCMA	Surface antigen selectively expressed on plasma cells	mAb Antibody-drug conjugates Bispecific T-cell engager mAbs CAR T-cell therapy	BI 836909, EM801GSK2857916
PD-1/PD-L1	Immune checkpoint	mAbs	Pembrolizumab and nivolumab
HDAC inhibitors	Epigenetic regulators	Selective small inhibitors	PanobinostatDevelop pan-inhibitors or selective inhibitors of HDAC6Many HDAC inhibitorsRicolinostat
Bcl-2 family proteins	Anti-apoptotic protein	Selective small inhibitors	Venetoclax
XPO1	Nuclear export protein critical for the regulation of MM cell survival and intracellular protein transport	Selective small inhibitors	Selinexor

CD38

What is it and why target it?	· CD38 is a surface antigen and ectoenzyme expressed at high levels by MM cells and at lower levels by immune cells. Not expressed by early stem cells · Appears to be downregulated by plasma cells (PCs) by the administration of specific mAbs
What are the therapeutic options?	· Anti-CD38 mAbs: designed to kill MM cells via Fc-dependent immune effector mechanism · CAR T-cells targeting CD38-expressing cells
Daratumumab (mAb)	· Main mechanisms of action (MOA): complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP) and direct apoptosis after secondary cross-linking · Increasing NK cell number creates a synergistic effect with IMiDs and other anti-CD38 mAbs· Anti-CD47 mAbs potentiate the effects of anti-CD38 mAbs · Daratumumab eliminates $CD38^{+}$ immune-suppressor cells

· Treatment with daratumumab and lenalidomide leads to increased expansion of CD4 and CD8 T cells

· Clinical trials in patients with RRMM:

Ø Single-agent daratumumab: phase II GEN501 and SIRIUS

o Overall response rate (ORR): 31%

o The median duration of response (DOR): 7.6 months

o Median progression-free survival (PFS): 4 months

o Overall survival (OS): 20 months

Combination of daratumumab + lenalidomide + dexamethasone (dara-Rd) *vs* Rd tested in phase III POLLUX trial

o Median follow-up: 25.4 months

o PFS: not reached *vs* 17.5 months

o ORR: 92.9% *vs* 76.4%

o Minimal residual disease (MRD) negativity: 26.2% *vs* 6.4%

Combination of daratumumab + bortezomib + dexamethasone (dara-Vd) *versus* Vd tested in phase III CASTOR trial

o Median follow-up: 19.4 months

o PFS: 16.7 *vs* 7.1 months

o ORR: 83.8% *vs* 63.2%

o MRD-negative rates: >2.5x higher with daratumumab in all subgroup analyses

Isatuximab	· Isatuximab binding to CD38 has a strong direct pro-apoptotic effect, independent of cross-linking by activating caspase 3 and 7 pathways · Immunomodulatory effect: decreasing $CD38^+$ T_{reg} cells and increasing NK cells with a T-cell mediated immune response · Phase I-II clinical trial: Isatuximab monotherapy in patients with hematological malignancies, including MM Ø N= 97 patients Ø ORR: 24% Ø DOR: 6.6 months · Phase Ib clinical trial: Isatuximab combination with lenalidomide + dexamethasone for RRMM Ø N= 57 patients Ø ORR: 51% Ø Median PFS: 8.5 months
MOR202	· Moderate CDC potential
Limitations of target	· CAR T and bispecific mAbs may be challenging due to the expression of CD38 on activated T cells

SLAMF7

What is it and why target it?	· Cell-surface glycoprotein receptor also called CS1 · Interacts with an adaptor protein (EAT2) which is expressed by NK cells and regulates the activation signaling of SLAMF7. Acts as an adhesion molecule in the absence of EAT2 · Highly and uniformly expressed by MM cells
What are the therapeutic options?	· Antibodies · Immunotherapy e.g. CAR T-cells

Elotuzumab (mAb)	· Humanized antibody · Binds to the membrane-proximal motif of SLAMF7 on MM and NK cells Ø Activates NK cells with production of IFN-γ Ø Increase of ADCC-mediating killing of tagged MM cells · Effect potentiated by lenalidomide · Phase III trial in RRMM (ELOQUENT-2): Elotuzumab + Rd *versus* Rd Ø ORR 79% *vs* 67%, PFS 19.4 *vs* 14.9 months Ø Elotuzumab reduced risk of disease progression/death by 29% · Phase III trial in RRMM (ELOQUENT-3): Elotuzumab + pomalidomide + dexamethasone (elo-Pd) *vs* Pd alone Ø PFS: 10.3 *vs* 4.7 months Ø ORR: 53% *vs* 26%
Limitations of target	· SLAMF7 CAR T-cells can target and destroy healthy T and B cells with high SLAMF7 expression

BCMA

What is it and why target it?	· It is a tumor necrosis factor (TNF) receptor (TNFR) family, also known as TNFRSF-17 · Selectively expressed by plasmablasts and differentiated PCs · Not expressed by B lymphocytes, hemopoietic stem cells, and normal tissue cells

What are the therapeutic options?	· mAbs · Antibody-drug conjugates · Bispecific antibodies (BsAbs) · CAR T-cells
GSK2857916	· Humanized IgG1 anti-BCMA antibody conjugated with toxin monomethyl auristatin F (MMAF) via non-cleavable linker with high affinity for BCMA · Phase I trial as monotherapy: Ø ORR: 60% Ø Median PFS: 7.9 months Ø Toxicity: keratitis, thrombocytopenia, and infections · United States (US) Food and Drug Administration granted breakthrough therapy designation · European Medicines Agency granted priority medicine designation
AMG 420 **(BI 836909)**	· Bispecific T-cell engager (BiTE®) Ø Two linked single-chain variable fragments specific for BCMA and CD3ε · Phase I dose-escalation study is ongoing Ø Administered as a continuous infusion for 4 weeks every 6 weeks Ø ORR: 83% at 400µg/day · Read more about the phase I results of AMG 420 presented at the American Society of Clinical Oncology (ASCO) meeting here

EM801	· BsAb Ø Asymmetric two-arm IgG1-based human antibody Ø One arm has low affinity for CD3 with monovalent binding Ø The other has a high affinity for BCMA via divalent binding Ø Engineered Fc region to increase plasma half-life Ø Aim: reduce cytokine release syndrome (CRS) and excessive T-cell activation
Anti-BCMA CAR T-cell trials in RRMM	· National Cancer Institute (NCI) Ø Phase I trial Ø N= 24 Ø CAR T-cells: murine scFv and CD28 costimulatory domain, transduced with a γ-retroviral vector Ø Given after lymphodepleting chemotherapy Ø In patients (n= 16) treated with 9 x 10^6 CAR T cells/kg o ORR: 81% o Median event-free survival (EFS): 31 weeks · University of Pennsylvania Ø Phase I trial Ø CAR T: fully human anti-BCMA scFv and 4-1BB as costimulatory domain, transduced with a lentiviral vector Ø Group 1 (n= 9) received 1–5 x 10^7 cells Ø Group 2 (n= 5) received cyclophosphamide then 1–5 x 10^7 cells

	Ø Group 3 (n= 11) received cyclophosphamide then 1–5 x 10^8 cells Ø ORR (group 1 *vs* 2 *vs* 3): 44% *vs* 20% *vs* 64% Ø Median DOR (group 3): 125 days · bb2121 Ø Phase I, multicenter trial Ø N= 33 Ø CAR T: murine anti-BCMA scFv and 4-1BB costimulatory domain transduced with a lentiviral vector Ø ORR: 85% Ø Median PFS: 11.8 months Ø Read more here · LCAR-B38M Ø CAR T: binding domain for two separate BCMA epitopes and 4-1BB costimulatory domain Ø Cyclophosphamide conditioning Ø N= 57 Ø Dose: 0.07–2.1 x10^6 cells/kg: o ORR: 88% o Median PFS: 15 months · Read more about when to use CAR T in MM here and the latest data here
Limitations	· CAR-T-related toxicities

PD-1 and PD-L1

What is it and why target it?	· Inhibitory checkpoints include the PD-1 receptor and its ligands, PD-L1 and PD-L2 · PD-1 receptor is expressed by activated and exhausted T and B cells · PD-L1 and PD-L2 are expressed by MM cells to escape T-cell killing
What are the therapeutic options?	· mAbs against PD-L1 (durvalumab, atezolizumab) on MM cells and mAbs against the PD-1 receptor (nivolumab, pembrolizumab) restore immune activation and help in tumor destruction

Pembrolizumab (mAb)	· mAb against the PD-1 receptor · Phase III trial (KEYNOTE-183): Pembrolizumab in combination with dexamethasone + pomalidomide *vs* dexamethasone + pomalidomide Ø N= 249 RRMM patients Ø ORR: 34% *vs* 40% Ø Median PFS: 5.6 *vs* 8.4 months Ø Trial was prematurely halted by the FDA due to high toxicity Ø Read more about the trial here · Phase III trial (KEYNOTE-185): Pembrolizumab in combination with lenalidomide + dexamethasone *vs* lenalidomide + dexamethasone Ø N= 301 newly-diagnosed MM patients Ø ORR: 64% *vs* 62% Ø Median PFS: not reached *vs* not reached Ø Trial was prematurely halted by the FDA due to the high incidence of death Ø Read more about the trial here
Nivolumab (mAb)	· mAb against the PD-1 receptor · Clinical trial: Nivolumab + daratumumab with or without dexamethasone + pomalidomide Ø RRMM patients Ø Trial was placed on hold due to toxicity but has now resumed recruitment

Atezolizumab or durvalumab (mAbs)	· mAbs against PD-L1 · Clinical trials: Ø Atezolizumab or durvalumab in combination with IMiDs for MM patients Ø All trials were placed on hold due to toxicity
Limitations	· High toxicity rates with IMiD co-administration

HDAC inhibitors

What is it and why target it?	· Inhibitors of histone deacetylases · In general, HDAC inhibitors lead to DNA damage-mediated apoptosis by downregulating the anti-apoptotic Bcl-2 proteins and upregulating pro-apoptotic targets · HDAC inhibitors also reduce proteasome-related activities · High expression of HDACs has been associated with poor prognosis in MM · Aim: inhibition of tumor proliferation as well as tumor cell apoptosis
What are the therapeutic options?	· HDAC inhibitors together with bortezomib lead to enhanced MM cytotoxicity · HDAC6 specifically has been shown to kill MM cells successfully when combined with anti-PD-L1 drugs

Panobinostat	· Pan-HDAC inhibitor · Approved by FDA and EMA for the treatment of RRMM in combination with bortezomib · Phase III trial (PANORAMA 1): Panobinostat in combination with bortezomib + dexamethasone *vs* placebo + bortezomib + dexamethasone Ø N= 768 RRMM patients Ø PFS: 12.5 *vs* 4.7 months Ø OS: 25.5 *vs* 19.5 months Ø Incidence of grade 3-4 adverse events: 76.9% *vs* 51.2%
Ricolinostat	· HDAC6 inhibitor · Phase I/II trial: Oral ricolinostat (³160mg) in combination with bortezomib and dexamethasone in RRMM patients Ø ORR: 37% Ø Well tolerated, low toxicity · Phase Ib trial: Oral ricolinostat (160 mg) in combination with lenalidomide and dexamethasone Ø N= 38 RRMM patients Ø Response rate: 55% Ø Well tolerated, low toxicity
Limitations	· HDAC inhibitors as single agents are not as potent as when combined with other anti-tumor agents

Bcl-2 member proteins

What is it and why target it?	· Member proteins include Bcl-2, Bcl-xL, and MCL-1 · Critical for the survival of MM cell through prevention of apoptosis · Pro-survival cytokines, such as IL-6, regulate the expression of Bcl-2 proteins on MM cells, which in turn maintain MM cell homeostasis · MCL-1, a member of the Bcl-2 protein family, is overexpressed in patients with RRMM, while MCL-1 knockout induces MM cell apoptosis *in vitro*
What are the therapeutic options?	· Selective small inhibitors Ø Bcl-2 or Bcl-xL inhibitors (BH3 mimetics)
Venetoclax	· Bcl-2 inhibitor with an affinity for Bcl-xL but does not bind to MCL-1 · Induces MM cytotoxicity only in patients with the t(11;14) mutation that has a high Bcl-2:Bcl-xL: MCL-1 expression ratio · Phase I trial (M13-367): Venetoclax monotherapy Ø N= 66 RRMM patients Ø ORR: 21% (total cohort); 40% (t(11;14) patients) Ø Median DOR (t(11;14) patients): 9.7 months Ø Well tolerated · Phase Ib trial (M12-901): Venetoclax in combination with bortezomib + dexamethasone Ø N= 66 RRMM patients Ø ORR: 67% (total cohort); 78% (t(11;14) patients) Ø Median DOR (total cohort): 9.7 months Ø Read more about this trial here

	Ø Well tolerated · Phase III trial (BELLINI): Venetoclax in combination with bortezomib + dexamethasone *vs* placebo + bortezomib + dexamethasone Ø N= 291 RRMM patients Ø ORR: 82% *vs* 68% Ø Median PFS: 22.4 months *vs* 11.5 months Ø Patients with t(11;14) benefited the most from venetoclax treatment with median PFS: not reached Ø Incidence of deaths: 21% *vs* 11% Ø Based on the results of this trial, the FDA issued a hold on all trials involving venetoclax in MM due to the high death rate Ø Read more about the results of the trial here
AZD5991	· Highly selective MCL-1 inhibitor · Induces quick and potent MM cell apoptosis *in vitro* · Currently under development and pre-clinical investigation
Limitations	· High incidence of death when venetoclax is co-administered with bortezomib and dexamethasone for the treatment of patients with RRMM

XPO1

What is it and why target it?	· Nuclear export protein · Critical for the regulation of MM cell survival and intracellular protein transport · MM cells overexpress XPO1 · XPO1 blockade leads to MM cell death both *in vitro* and *in vivo*
What are the therapeutic options?	· Selective small inhibitors that bind covalently to XPO1 and block its nuclear transport

Selinexor	· First-in-class, selective, oral XPO1 inhibitor · Aim: blockade of XPO1-mediated nuclear transport activity · Phase IIb trial (STORM): Selinexor in combination with dexamethasone Ø N= 79 RRMM patients Ø ORR: 21% Ø Median PFS: 2.3 months Ø Median DOR: 5 months Ø Median OS: 9.3 months · Phase Ib/II trial (STOMP): Selinexor in combination with bortezomib + dexamethasone Ø N= 42 RRMM patients Ø ORR: 63% Ø Median PFS: 9.0 months · Phase III trial (BOSTON): Selinexor in combination with bortezomib + low-dose dexamethasone *vs* bortezomib+ low-dose dexamethasone Ø RRMM patients Ø Results not reported yet, anticipated by the end of 2019 · The FDA has recently delayed the approval of selinexor for RRMM until more safety data are available from the BOSTON trial. Read more about this here
Limitations	· More safety and efficacy data from phase III trials are needed to validate the potential of selinexor in RRMM

Conclusions

Although MM remains an incurable disease, the results and research involved in all of these targets discussed above are promising. Multiple novel anti-tumor targets have been identified and are currently being clinically evaluated for their efficacy and safety. Taking into consideration this broad range of targets for MM, it is possible that in the near future the successful anti-tumor drug, or more likely the correct combination of IMiDs, PIs, mAbs, CAR T-cells, or small inhibitors, will be identified to help alleviate the great unmet medical need that exists for this patient population.

References

1. Giuliani N. *et al.,* Novel targets for the treatment of relapsing multiple myeloma. *Exp Rev Hem.* 2019 Jun 03; 12(7):481–496. DOI: 10.1080/17474086.2019.1624158