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Immune status and selection of patients for immunotherapy in myeloma: a Proposal

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Abstract:
Newer immune-based approaches based on recruitment and redirection of endogenous and/or synthetic immunity such as chimeric antigen-receptor-T (CAR-T) cells or bispecific antibodies are transforming the clinical management of multiple myeloma (MM). Contributions of the immune system to the anti-tumor effects of myeloma therapies are also increasingly appreciated. Clinical malignancy in MM originates in the setting of systemic immune alterations that begin early in myelomagenesis and regional changes in immunity impacted by spatial contexture. Pre-existing and therapy-induced changes in immune cells correlate with outcomes in MM patients including following immune therapies. Here we discuss insights from and limitation of current data about immune status and outcomes following immune therapies in MM patients. Pre-existing variation in systemic and/or regional immunity is emerging as a major determinant of the efficacy of current immune therapies as well as vaccines. MM is however a multifocal malignancy. As with solid tumors, integrating spatial aspects of the tumor and consideration of immune targets with biology of immune cells may be critical to optimize the application of immune therapy including T cell redirection in MM. We propose 5 distinct spatial immune types of MM- immune-depleted, immune-permissive, immune-excluded, immune-suppressed, and immune-resistant, that may provide an initial framework for optimal application of specific immune therapies in MM. Such considerations may also help optimize rational patient selection for emerging immune therapies to improve outcomes.

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Immune status and selection of patients for immunotherapy in myeloma: a proposal

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Abstract

Newer immune-based approaches based on recruitment and redirection of endogenous and/or synthetic immunity such as chimeric antigen-receptor-T (CAR-T) cells or bispecific antibodies are transforming the clinical management of multiple myeloma (MM). Contributions of the immune system to the anti-tumor effects of myeloma therapies are also increasingly appreciated. Clinical malignancy in MM originates in the setting of systemic immune alterations that begin early in myelomagenesis and regional changes in immunity impacted by spatial contexture. Pre-existing and therapy-induced changes in immune cells correlate with outcomes in MM patients including following immune therapies. Here we discuss insights from and limitation of current data about immune status and outcomes following immune therapies in MM patients. Pre-existing variation in systemic and/or regional immunity is emerging as a major determinant of the efficacy of current immune therapies as well as vaccines. MM is however a multifocal malignancy. As with solid tumors, integrating spatial aspects of the tumor and consideration of immune targets with biology of immune cells may be critical to optimize the application of immune therapy including T cell redirection in MM. We propose 5 distinct spatial immune types of MM- immune-depleted, immune-permissive, immune-excluded, immune-suppressed, and immune-resistant, that may provide an initial framework for optimal application of specific immune therapies in MM. Such considerations may also help optimize rational patient selection for emerging immune therapies to improve outcomes.

Unmet needs for MM immunotherapy

Over the past two decades, the outcome for MM patients has improved considerably, first with the introduction of immune modulatory drugs and proteasome inhibitors, and then with monoclonal antibodies targeting CD38(1). For example, the great majority of newly diagnosed MM patients now experience tumor regression following modern induction regimens. More recently, T cell redirection with chimeric antigen receptor-T (CAR-T) cells and bispecific antibodies has also yielded high rates of tumor regression(2), leading to regulatory approvals for therapy of patients with relapsed MM following four or more prior lines of therapy(3-6). These therapies also lead to impressive responses in earlier lines of therapy, prompting ongoing consideration of their application earlier in the course of the disease. In spite of these advances, most MM patients eventually experience recurrent disease and eventually succumb to the underlying malignancy. Therefore there remains an unmet need to improve current therapies to achieve durable unmaintained responses and possibly cures. In view of ongoing challenges with cost, access, toxicity as well as variable durability of therapeutic benefit, it is desirable to better understand the mechanisms of resistance and optimize the application of immune therapy to maximize the potential to achieve cures. In addition, immune paresis, both from the underlying malignancy as well as effects of therapy is a major contributor to poor response to vaccines and ongoing risk of infections, which remain a major cause of mortality in MM patients, even in the setting of remission(7). While much progress in MM therapy has been achieved through application of “next effective line of therapy”, the premise of this review is the unmet need to maximize the curative potential of first line of therapy.

Implications of preexisting immune types on immunotherapy: lessons from solid tumors

Over the past decade, immune therapy has been firmly established as one of the pillars of cancer therapy(8). Blockade of inhibitory immune checkpoints (ICP) such as PD-1/PDL-1 led to durable remissions and cures in patients with some malignancies such as melanoma. ICP blockade by definition depends on preexisting endogenous immunity(9). Therefore the underlying immunogenicity of tumors reflected by the immune contexture such as the degree of T cell infiltration (e.g. hot tumors) or adaptive expression of PDL-1 has been correlated with responsiveness to these therapies. These concepts have led to biomarkers such as the expression of PD-L1 on tumor or immune cells, which serve as the basis of patient selection in some instances and have been incorporated into regulatory approval. It is also appreciated that such biomarkers are therapy-specific and may only apply to the specific immune therapy in question. PD-1 blockade did not improve outcomes in randomized trials with unselected MM patients(10), although some other checkpoints such as TIGIT and Lag-3 have been proposed in preclinical studies and show promise in early clinical trials(11, 12). In contrast to solid tumors, strategies for T cell redirection such as CAR-T and bispecific antibodies have proven highly effective in MM(2). Therefore we will focus on emerging data about how immune status might impact responsiveness to these therapies. As discussed further below, we suggest that while the overall strategies for immune therapy in MM differ considerably from that in solid tumors, the concept that preexisting

immune status may impact responsiveness to emerging immune therapies may apply in MM as well.

Systemic versus regional immune alterations in MM and MGUS

The concept that tumor cells from patients even in advanced MM remain sensitive to lysis by both innate and adaptive immune cells was demonstrated over 25 years ago(13, 14). All MM lesions are preceded by monoclonal gammopathy of undetermined significance (MGUS)(15). Prior studies have documented the capacity of the immune system to specifically recognize these earliest lesions(16, 17). However tumor recognition of MGUS occurs in the backdrop of underlying systemic immune dysfunction, which originates early during myelomagenesis(18, 19). Transition of MGUS to MM is associated with progressive attrition of TCF1+ T cells(20) previously shown to be capable of self-renewal and long-term persistence(18). Instead, MM bone marrow is characterized by an increase in more differentiated T cells, including granzymeB+ CD8+ T cells(18, 19). In some patients, this differentiated T cell compartment consists of large T cell clones that correlate with poor outcome(21, 22). In addition to adaptive immunity, MM bone marrow is also characterized by alterations in innate cells including NK and NKT cells as well as myeloid and other regulatory cells with immune-suppressive features(18, 23, 24). Systemic alterations of immune cells in the tumor microenvironment in both MGUS and MM have been analyzed with newer single cell technologies and linked to outcome(25-30). Changes in immune cells during early evolution to MM have been recently reviewed(31-33). Studies in preclinical models such as V-kappa myc mice have provided evidence for immune surveillance mediated by both T and NK cells(34). In this model, tumor immunity was enhanced by CD137 engagement(35) and impaired by IL-18 mediated effects(36). In another model, regulatory T cells (Tregs) were implicated in suppressing tumor immunity(37). The concept of tumor-extrinsic control in MM immune surveillance is also supported by the finding of progressive growth of preneoplastic cells in humanized models(38). In addition to immune cells, stromal compartment is also altered in MM and exhibits an inflammatory phenotype(39). The application of single cell genomics has also illustrated the transcriptional heterogeneity of T cells in the MM marrow microenvironment(19, 25, 26). It is important to note however that T cells isolated from marrow aspirates represent an admixture of several distinct populations including marrow resident(40, 41) and non-resident / in-transit cells, as well as contaminating T cells from blood(42). Several of these populations, except the truly marrow resident T cells are likely shared with circulating T cells. Another limitation of many of the current studies in MM is that they lack insights into antigen-specificity and functional aspects of T cells, particularly as only a proportion of T cells isolated from the bone marrow are expected to be tumor-specific(43, 44) and marrow aspirates may have varying degrees of hemodilution from blood.

A critical feature of malignant transition in MM is multifocal growth of tumors, accounting for the term “multiple” myeloma. Interestingly, this growth pattern is also observed in murine MM models suggesting that it is an intrinsic feature of tumor biology during malignant transition(45, 46). However, this feature creates the potential for distinct

aspects of spatial interactions in the malignant phase, with emergence of regions of immune exclusion. Recent studies with both *in-vitro* and *in-vivo* models have shown that the entry of antigen-specific T cells into MM clusters depends in part on *in-situ* stimulation by tumor-associated Clec9a+ DCs(45). These insights support regional regulation of tumor-specific immunity, which as discussed below, may be critical for achieving durable responses following immunotherapies. The concept that regional alterations in immune responses may be important in the context of myeloma immunotherapy is also supported by the emerging evidence from clinical trials that patients with high disease burden and extramedullary disease may be at an increased risk of recurrence following current T cell-based therapies, including bispecific antibodies(4, 6, 47). These considerations also urge the need to routinely include advanced imaging prior to initiation of these novel immune therapies.

Immune contributions to myeloma therapy and outcomes

It is now appreciated that the immune system may contribute to the effects of several current MM therapies. Immune-modulatory drugs such as thalidomide, lenalidomide, pomalidomide, as well as newer drugs such as iberdomide lead to activation of T and NK cells in vivo through de-repression of IL2 transcription due to cereblon-mediated degradation of ikaros(48). Notably, effects of these drugs on T cells as well as NK-T cells depend on signal 1 and TCR engagement, again emphasizing the need to understand antigen-specific responses(49, 50). Immune activation was linked to clinical responses to pomalidomide in early single agent studies(51). Proteasome inhibitors may lead to immunogenic cell death in MM tumors promoting the induction of tumor immunity via DCs(52) and signatures of immunogenic tumor cell death were correlated with outcome in MM patients receiving triplet therapies(53). Both daratumumb and isatuximab are monoclonal antibodies that engage Fc-dependent mechanisms such as antibody-dependent cytotoxicity to mediate anti-tumor effects and are now integral to MM therapy(54). Belantamab has also been shown to induce immunogenic cell death(55). These data underscore the possibility that immune system may play an important role in the anti-tumor effects of several MM therapies. This is also supported by studies correlating immune cell states with outcomes. As an example, differentiation states of T cells such as CD27+ T cells as well the presence of Tregs has been linked to outcome in large MM cohorts(21, 30, 56). An important message from these studies again is the high degree of variance in immune cell states and potential immune competence in MM cohorts. The impact of these differences in immune fitness and response to immune intervention was recently illustrated in studies documenting high variance in humoral and cellular immune response to SARS CoV-2 vaccines in MM(57, 58). Variance in immune status can not only impact response to therapy, but also other outcomes including overall survival and risk of infections in MM patients.

Immune correlates of response following T cell redirection in MM

CAR-T cells:

Two CAR-T products targeting B cell maturation antigen (BCMA), namely Idecel and Ciltacel have now been approved for therapy of relapsed MM following four or more lines of prior therapy(3, 4). In spite of high rates of remission, including MRD negativity, MM patients remain at risk of ongoing relapse. Understanding correlates of durable remissions following BCMA CAR-Ts is an area of active research and only some of the datasets have yet been fully published. Analysis of biospecimens from the first BCMA CAR-T clinical trial at University of Pennsylvania illustrated a dynamic crosstalk between CAR-T, endogenous T, myeloid cells/DCs and tumor cells that correlated with durable remissions(22). CAR-T infusion leads to expansion of endogenous T cells, predominantly in TCF1+CD27+ T cell compartment. Consistent with this, higher baseline TCR diversity was associated with longer progression free survival (PFS). PFS was also correlated with properties of the myeloid/DC compartment, with the presence of Baff+ myeloid cells correlating with shorter PFS and dendritic cell (DC)-like populations with longer PFS(22). Early correlative analyses from patients treated with Ciltacel and Idecel have also yielded similar findings. Among Idecel treated patients, increase in naïve and CD27+ early memory T cells correlated with longer PFS, while the presence of CD57+ senescent T cells correlated with shorter PFS(59). The expansion of CD8+ central memory T cells was correlated with longer PFS among Ciltacel treated patients(60). Properties of the drug product, likely reflecting immune state at the time of T cell harvest(61), also correlate with outcome. For example, higher proportion of CD8+ stem cell features and lower proportion of CD4+ Treg-like cells in the product correlated with improved outcome(60). Effector functionality of the CAR-T product, as reflected in target-specific interferon-g production has also been shown to correlate with improved outcome in treated patients(59).

T cell engagers (TCE):

Initial studies with single cell transcriptomics suggested that the presence of CXCR3+ effector CD8+ cells, but not other effector memory populations correlated with response to bispecific T cell engagers(62). In contrast, the presence of TOX+ CD8+ cells was correlated with lack of response. These elegant studies also described a correlation between early and sustained increase in clonality in CD8+ T cells following therapy and clinical response. Therefore the capacity of the TCE to engage and modify pre-existing endogenous T cells may be critical for their antitumor activity. TCE-mediated expansion of T cells in ex vivo cultures was inhibited by the addition of anti-MHCI antibody(62). Correlative analyses on patients treated with BCMA bispecific Teclistamab in MAJESTEC-1 trial suggested that higher proportion of naïve T cells correlated with improved response, while the presence of regulatory T cells and PD1+ Tim3+ T cells correlated with lack of response(63). In another analysis of MM patients treated with Teclistamab, higher proportion of effector memory T cells and lower proportion of regulatory T cells correlated with improved response to therapy(64). Together, these studies suggest that clinical response to TCE may be impacted by pre-existing properties of T cells. Some of the features relating to tumor burden including advanced stage, presence of extramedullary disease as well as excess soluble ligand (such as soluble BCMA) potentially providing a “sink effect” may also impact outcome in TCE treated patients(6, 47). Further studies are needed to better understand the

mechanisms by which TCEs redirect and sustain anti-MM immunity. Improved understanding of this biology may also allow strategies to reduce adverse events including the risk of infections following TCE therapy(65).

Limitations of current studies:

Most of the current studies evaluating correlates of response following T cell redirection in MM have been based on methods such as mass/flow cytometry and single cell transcriptomics from blood or bone marrow aspirates. In some studies, T cells from relatively small numbers of patients were pooled for comparisons, which may not meet the assumptions of the statistical tests employed. Analyses of functional aspects of immune cells in these studies are limited and assumptions based on T cell phenotypes in other models or tissues may not apply to redirected T cells. Importantly, spatial analyses of immune cells including redirected T cells (e.g. CAR-T cells or T cells bound to bispecific antibody) would be critical to understand the mechanisms underlying T cell redirection. Considering the emerging data that CAR-T therapy can lead to alterations in endogenous T cells(22), the capacity of long-term disease control or cures following these therapies may also depend on the induction of tumor-specific immune responses.

Vaccines- the next frontier?

Vaccines represent one of the greatest triumphs of modern medicine, but their application in cancer including MM remains yet unrealized. As discussed above, the appreciation that pre-existing durable tumor control may depend on pre-existing endogenous immunity has revitalized interest in vaccine-based approaches to boost endogenous responses. Initial studies have demonstrated the feasibility of boosting antigen-specific and tumor-specific T cell responses in vivo. These studies have targeted clinal immunoglobulin-associated idiotype, shared tumor antigens, plasma cell antigens or fusions of dendritic cells with whole tumor cells(66-69). DCs have also been utilized to boost innate immunity such as NKT cells in MM patients(70). Recent advances in understanding mechanisms of T cell infiltration also suggest that it may not be sufficient to simply elicit T cell responses via vaccines and it may be critical to actively drive vaccine-elicited T cells into tumors(71). Nonetheless, the stage is now set for future combinations of vaccines with strategies addressing immune suppressive factors or with immune redirection.

Integrating spatial biology of MM into immune types:

The importance of spatial biology has long been appreciated as being critical for the diagnosis and management of lymphoid tumors such as non-hodgkins lymphoma. Recent studies have illustrated the spatial heterogeneity of MM, both in terms of tumor genetics as well as changes in the immune microenvironment(45, 72). As discussed earlier, understanding spatial immune contexture has proven clinically useful for the application of immune checkpoint blockade in solid tumors(73). The principle of immune redirection therapy, by definition, relies on redirection and hence altering spatial

dynamics of immune cells. Therefore as these therapies gain prominence in MM therapeutics, we suggest that it would be critical for future studies to account for spatial immunobiology of MM to better interpret the results and improve outcomes associated with such immune therapies. The methods for spatial analysis of tumor tissues, as well as downstream analysis are rapidly evolving(74, 75). These advances include methods with greater depth and resolution, as well as advances in machine learning and the application of artificial intelligence tools(75). While the application of some of these methods on human bone marrow biopsies remains an area of active research, we emphasize the need to utilize whole-slide based approaches to study spatial aspects of myeloma. This is because of prior studies with MM biopsies showing that immunologically distinct lesions (e.g. T cell infiltrated as well as T cell poor) can coexist in the same biopsy(45). Integrating imaging-directed biopsies into clinical care may further improve our understanding of spatial heterogeneity in myeloma. Future clinical trials in MM should also try to harmonize initial processing of biopsies and prevent harsh decalcification methods that may impact downstream application of emerging spatial methods.

Below, we propose an initial framework for 5 major spatial immune types, based on analysis of MM tumors, as well as insights emerging from solid tumors(45, 76, 77). As has been observed in solid tumors, more than one type may co-exist in an individual patient and in that setting, the higher-risk lesion may impact clinical behavior or resistance to therapy. The proposal builds on some key findings from recent studies in MM including detection of areas of immune exclusion, role of DCs in T cell entry in model systems, correlation between proximity of DCs and T cells and outcome and impact of antigen-loss on efficacy of T cell redirection (45, 78). The proposed major immune types, as discussed below are immune-depleted, immune-permissive, immune-excluded, immune-suppressed and immune-resistant. The biologically defining features of these types are noted in Fig 1 and potential clinical implications in Table 1. We anticipate that application of newer artificial intelligence and machine learning tools may further refine these categories for clinical application.

Immune-permissive (IP):
T cells in these lesions typically lack terminally differentiated CD8+ T cell clones(21) and are instead enriched for TCF1+ cells with greater proliferative potential. T cells are enriched in hotspots proximate with Clec9a+ conventional type 1 DCs (cDC1)(45). T cells readily infiltrate these tumors. As such, these patients are likely excellent candidates for T cell redirection and may derive prolonged and potentially curative benefit from immune therapies. Early eradication of residual disease may be critical to achieving cures in this group(79). Tumors earlier in the course of evolution to MM may also fall into this group(18), and may provide the rationale for consideration of T cell redirection in earlier stages of MM development, if safety could be ensured.

Immune-excluded (IE):
While T cells abound in these lesions, they do not efficiently enter tumors, presumably due to lack of effective antigen-presentation via local DCs(45). Although T cell

redirection may theoretically overcome this limitation, durability of responses may be compromised if durable responses depend on both redirected and endogenous T cells. Combination approaches to enhance T cell infiltration, such as recruitment of DCs may particularly benefit this subset. The biology of such lesions also resembles those with extramedullary disease and may contribute to increased risk of recurrence.

Immune-suppressed (IS):
T cells in these patients can theoretically be suppressed by several distinct immune suppressive mechanisms including immune suppression by myeloid cells, or by regulatory T cells. Expression of inhibitory T cell checkpoints on these T cells may also represent a pathway-specific target to improve the efficacy of T cell redirection. Chronic and frequent dosing of TCE may itself promote T cell exhaustion and paradoxically create adaptive resistance.

Immune-depleted (ID):
The presence of systemic lymphopenia in these patients is a challenge to the efficacy of T cell redirection, particularly with bipecifics. The mechanisms underlying lymphopenia may be diverse and related both to malignancy as well as therapy (e.g. prior chemotherapy). These patients, and particularly those with lymphopenia may also be at an increased risk of CAR-T manufacturing failures(80).

Immune-resistant (IR):
While several of the mechanisms noted earlier (e.g. Tregs, T cell exhaustion, myeloid cells) may in principle contribute to immune resistance, we restrict this category to primary resistance of tumors mediated by inability to bind tumor-targeting moiety (such as by genetic loss(81) or mutation of target(78)) in the case of T cell redirection, or loss of TCR recognition (such as by MHC loss)(82) in the setting of endogenous immunity. As the binding epitopes for each of the bispecific antibodies may differ, this mechanism is expected to be both target (e.g. BCMA or GPRC5D) and agent-specific and can in principle only be overcome by switching targets or agents. A small proportion of immune therapy-naïve MM patients may carry monoallelic copy number losses in T-cell redirection targets such as BCMA. However BCMA antigen loss has been described in upto 40% of relapsing cases after TCE therapy(78, 81, 83-85). While the presence of antigen-loss/mutation can be detected genetically, recent data suggest that it may be more practical to test tumor binding of the bispecific antibody ex vivo, if available for diagnostic testing(78). Potential for emergence of immune resistant subclones is a strong argument for multi-epitope targeting in initial therapy, both for TCE and CAR-Ts in the future.

Integrating genetic and immune types:

It is well recognized that tumors co-evolve with changes in the immune system. Early studies of T cell redirection in MM already illustrate a dynamic cross-talk between tumors and redirected as well as endogenous T cells(22). At present, MM is classified based on cytogenetic changes in tumor cells, both for genetic subtypes as well as assessment of disease risk(1). The latter, along with eligibility for stem cell transplant

forms the basis of current therapy algorithms. However as immune-based approaches enter front-line, it is likely that these algorithms will need to be revisited, and risk-features may depend on specific therapies. Genomic changes in tumor cells are known to impact many aspects of response to immune therapies(86). These include features such as antigen-loss/mutations, defects in antigen presentation, susceptibility to immune-mediated cell death, expression of immune suppressive factors, capacity for excluding immune cells, expression and immunogenicity of neoantigens, plasticity and heterogeneity of tumors, to name a few. Some potential examples of genomic alterations with implications for immune microenvironment include alterations in wnt signaling/dkk1(18), c-myc or NF-kB signaling. As definitive studies in this regard will need adequate power, we urge the community to include spatial immunology together with genetic analyses and imaging in current clinical trials, to allow integration of genetic and immune types in the future.

Potential implications of immune types on patient selection and therapeutic approaches:

The primary impetus behind the immune types proposed above is that they may provide a framework for optimal application of immune therapies in the future. An early decision point may be identification of immune-resistant or immune-depleted phenotypes with direct implications for immune redirection. These patients are poor candidates for target-specific TCEs, but those with IR phenotype may benefit from TCE against alternate targets (e.g. GPRC5D in case of BCMA loss). Lesions with high risk for antigen-loss (e.g. monoallelic loss) are also prime candidates for multi-targeted therapies(87). Discovery of newer targets for CARTs targeting MM tumor cells and its precursor lesions remains a major unmet need and will be critical to overcome tumor heterogeneity and improve outcomes in IR lesions. ID lesions may initially require strategies that mediate immunogenic cell death as well improvement of cytopenias. IE lesions may benefit from combinations with strategies such as IMiDs (51) that engage innate cells to recruit DCs(88), vaccines(89) or approaches to induce immunogenic cell death(52, 53, 90). IS lesions may in addition, require strategies targeting suppressive elements such as targeting immune checkpoints(91) or immune suppressive cells(92). Finally, IP lesions may be most amenable to durable remissions with time-limited therapies and avoiding adverse effects of prolonged TCE.

While the utilization of immune therapy and particularly T cell redirection in MM in the immediate future is likely to be determined largely by global/regional access, cost and regulatory approvals, we posit that maximizing the curative potential of these highly effective therapies may be key to optimizing clinical benefit in the long-term. Factors that may impact these choices may include host and tumor genetics, tumor heterogeneity as well as immune contexture. In this regard, it may become essential to address the heterogeneity of tumors at the outset and better understand spatial immune types in an individual patient to maximize immune-mediated tumor lysis and early eradication of residual disease(93). Achieving this goal will require systematic integration of genomic analysis of tumors, imaging, immune monitoring, spatial biology

and emerging artificial intelligence and machine learning tools into the next phase of MM clinical research and eventually clinical care.

Contributions:

MVD wrote the paper.

Conflict of interest:

MVD has served on advisory board for BMS, Lava Therapeutics, Janssen, and Sanofi.

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References:

1. Kumar SK, Rajkumar V, Kyle RA, van Duin M, Sonneveld P, Mateos MV, et al. Multiple myeloma. Nat Rev Dis Primers. 2017;3:17046.
2. Cohen AD, Raje N, Fowler JA, Mezzi K, Scott EC, Dhodapkar MV. How to Train Your T Cells: Overcoming Immune Dysfunction in Multiple Myeloma. Clin Cancer Res. 2020;26(7):1541-54.
3. Munshi NC, Anderson LD, Jr., Shah N, Madduri D, Berdeja J, Lonial S, et al. Idecabtagene Vicleucel in Relapsed and Refractory Multiple Myeloma. N Engl J Med. 2021;384(8):705-16.
4. Berdeja JG, Madduri D, Usmani SZ, Jakubowiak A, Agha M, Cohen AD, et al. Ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): a phase 1b/2 open-label study. Lancet. 2021;398(10297):314-24.
5. 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.
6. Lesokhin AM, Tomasson MH, Arnulf B, Bahlis NJ, Miles Prince H, Niesvizky R, et al. Elranatamab in relapsed or refractory multiple myeloma: phase 2 MagnetisMM-3 trial results. Nat Med. 2023;29(9):2259-67.
7. Terpos E, Neri P, van de Donk N, D'Agostino M, Parekh S, Jagannath S, et al. Immune Reconstitution and Vaccinations in Multiple Myeloma: A Report From the 19th International Myeloma Society Annual Workshop. Clin Lymphoma Myeloma Leuk. 2023;23(6):413-9.
8. Sharma P, Allison JP. Immune checkpoint therapy: Forging ahead. Sci Transl Med. 2022;14(670):eadf2947.
9. Zou W, Wolchok JD, Chen L. PD-L1 (B7-H1) and PD-1 pathway blockade for cancer therapy: Mechanisms, response biomarkers, and combinations. Sci Transl Med. 2016;8(328):328rv4.
10. Lesokhin AM, Ansell SM, Armand P, Scott EC, Halwani A, Gutierrez M, et al. Nivolumab in Patients With Relapsed or Refractory Hematologic Malignancy: Preliminary Results of a Phase Ib Study. J Clin Oncol. 2016;34(23):2698-704.
11. Guillerey C, Harjunpaa H, Carrie N, Kassem S, Teo T, Miles K, et al. TIGIT immune checkpoint blockade restores CD8(+) T-cell immunity against multiple myeloma. Blood. 2018;132(16):1689-94.
12. Jing W, Gershan JA, Weber J, Tlomak D, McOlash L, Sabatos-Peyton C, Johnson BD. Combined immune checkpoint protein blockade and low dose whole body irradiation as immunotherapy for myeloma. Journal for immunotherapy of cancer. 2015;3(1):2.
13. Dhodapkar MV, Krasovsky J, Olson K. T cells from the tumor microenvironment of patients with progressive myeloma can generate strong tumor specific cytolytic responses to autologous tumor loaded dendritic cells. Proc Natl Acad Sci. 2002;99:13009-13.
14. Dhodapkar MV, Geller MD, Chang D, Shimizu K, Fujii SI, Dhodapkar K, Krasovsky J. A reversible defect in natural killer T cell function characterizes the

progression of premalignant to malignant multiple myeloma. J Exp Med. 2003;197:1667-76.
15. Dhodapkar MV. MGUS to myeloma: a mysterious gammopathy of underexplored significance. Blood. 2016;128(23):2599-606.
16. Dhodapkar MV, Krasovsky J, Osman K, Geller MD. Vigorous premalignancy-specific effector T cell response in the bone marrow of patients with monoclonal gammopathy. J Exp Med. 2003;198(11):1753-7.
17. Spisek R, Kukreja A, Chen LC, Matthews P, Mazumder A, Vesole D, et al. Frequent and specific immunity to the embryonal stem cell-associated antigen SOX2 in patients with monoclonal gammopathy. J Exp Med. 2007;204(4):831-40.
18. Bailur JK, McCachren SS, Doxie DB, Shrestha M, Pendleton KE, Nooka AK, et al. Early alterations in stem-like/resident T cells, innate and myeloid cells in the bone marrow in preneoplastic gammopathy. JCI Insight. 2019;5.
19. Zavidij O, Haradhvala NJ, Mouhieddine TH, Sklavenitis-Pistofidis R, Cai S, Reidy M, et al. Single-cell RNA sequencing reveals compromised immune microenvironment in precursor stages of multiple myeloma. Nature Cancer. 2020;1(5):493-506.
20. Wu T, Ji Y, Moseman EA, Xu HC, Manglani M, Kirby M, et al. The TCF1-Bcl6 axis counteracts type I interferon to repress exhaustion and maintain T cell stemness. Sci Immunol. 2016;1(6).
21. Botta C, Perez C, Larrayoz M, Puig N, Cedena MT, Termini R, et al. Large T cell clones expressing immune checkpoints increase during multiple myeloma evolution and predict treatment resistance. Nat Commun. 2023;14(1):5825.
22. Dhodapkar KM, Cohen AD, Kaushal A, Garfall AL, Manalo RJ, Carr AR, et al. Changes in Bone Marrow Tumor and Immune Cells Correlate with Durability of Remissions Following BCMA CAR T Therapy in Myeloma. Blood Cancer Discov. 2022;3(6):490-501.
23. Görgün GT, Whitehill G, Anderson JL, Hideshima T, Maguire C, Laubach J, et al. Tumor-promoting immune-suppressive myeloid-derived suppressor cells in the multiple myeloma microenvironment in humans. Blood. 2013;121(15):2975-87.
24. Ramachandran IR, Martner A, Pisklakova A, Condamine T, Chase T, Vogl T, et al. Myeloid-Derived Suppressor Cells Regulate Growth of Multiple Myeloma by Inhibiting T Cells in Bone Marrow. 2013;190(7):3815-23.
25. Pilcher W, Thomas BE, Bhasin SS, Jayasinghe RG, Yao L, Gonzalez-Kozlova E, et al. Cross center single-cell RNA sequencing study of the immune microenvironment in rapid progressing multiple myeloma. NPJ Genom Med. 2023;8(1):3.
26. Yao L, Jayasinghe RG, Lee BH, Bhasin SS, Pilcher W, Doxie DB, et al. Comprehensive Characterization of the Multiple Myeloma Immune Microenvironment Using Integrated scRNA-seq, CyTOF, and CITE-seq Analysis. Cancer Res Commun. 2022;2(10):1255-65.
27. Parmar H, Gertz M, Anderson EI, Kumar S, Kourelis TV. Microenvironment immune reconstitution patterns correlate with outcomes after autologous transplant in multiple myeloma. Blood Adv. 2021;5(7):1797-804.
28. Kourelis TV, Villasboas JC, Jessen E, Dasari S, Dispenzieri A, Jevremovic D, Kumar S. Mass cytometry dissects T cell heterogeneity in the immune tumor microenvironment of common dysproteinemias at diagnosis and after first line therapies. Blood Cancer J. 2019;9(9):72.

29. Sklavenitis-Pistofidis R, Aranha MP, Redd RA, Baginska J, Haradhvala NJ, Hallisey M, et al. Immune biomarkers of response to immunotherapy in patients with high-risk smoldering myeloma. Cancer Cell. 2022;40(11):1358-73 e8.
30. Maura F, Boyle EM, Coffey D, Maclachlan K, Gagler D, Diamond B, et al. Genomic and immune signatures predict clinical outcome in newly diagnosed multiple myeloma treated with immunotherapy regimens. Nat Cancer. 2023;4(12):1660-74.
31. Dhodapkar MV. Role of Natural Killer T (NKT) Cells in Myeloma Biology and Therapy. Crit Rev Oncog. 2024;29(1):63-8.
32. Dhodapkar MV. Immune-Pathogenesis of Myeloma. Hematology/oncology clinics of North America. 2024;38(2):281-91.
33. Dhodapkar MV. The immune system in multiple myeloma and precursor states: lessons and implications for immunotherapy and interception. Am J Hematol. 2022;Oct 4. doi: 10.1002/ajh.26752.
34. Guillerey C, Ferrari de Andrade L, Vuckovic S, Miles K, Ngiow SF, Yong MC, et al. Immunosurveillance and therapy of multiple myeloma are CD226 dependent. J Clin Invest. 2015;125(7):2904.
35. Guillerey C, Ferrari de Andrade L, Vuckovic S, Miles K, Ngiow SF, Yong MC, et al. Immunosurveillance and therapy of multiple myeloma are CD226 dependent. J Clin Invest. 2015;125(5):2077-89.
36. Nakamura K, Kassem S, Cleynen A, Chretien ML, Guillerey C, Putz EM, et al. Dysregulated IL-18 Is a Key Driver of Immunosuppression and a Possible Therapeutic Target in the Multiple Myeloma Microenvironment. Cancer Cell. 2018;33(4):634-48 e5.
37. Larrayoz M, Garcia-Barchino MJ, Celay J, Etxebeste A, Jimenez M, Perez C, et al. Preclinical models for prediction of immunotherapy outcomes and immune evasion mechanisms in genetically heterogeneous multiple myeloma. Nat Med. 2023;29(3):632-45.
38. Das R, Strowig T, Verma R, Koduru S, Hafemann A, Hopf S, et al. Microenvironment-dependent growth of preneoplastic and malignant plasma cells in humanized mice. Nat Med. 2016;22(11):1351-7.
39. de Jong MME, Kellermayer Z, Papazian N, Tahri S, Hofste Op Bruinink D, Hoogenboezem R, et al. The multiple myeloma microenvironment is defined by an inflammatory stromal cell landscape. Nat Immunol. 2021;22(6):769-80.
40. Sercan Alp O, Durlanik S, Schulz D, McGrath M, Grun JR, Bardua M, et al. Memory CD8(+) T cells colocalize with IL-7(+) stromal cells in bone marrow and rest in terms of proliferation and transcription. European journal of immunology. 2015;45(4):975-87.
41. Boddupalli CS, Nair S, Gray SM, Nowyhed HN, Verma R, Gibson JA, et al. ABC transporters and NR4A1 identify a quiescent subset of tissue-resident memory T cells. J Clin Invest. 2016;126(10):3905-16.
42. Puig N, Flores-Montero J, Burgos L, Cedena MT, Cordon L, Perez JJ, et al. Reference Values to Assess Hemodilution and Warn of Potential False-Negative Minimal Residual Disease Results in Myeloma. Cancers. 2021;13(19).
43. Dhodapkar MV, Krasovsky J, Olson K. T cells from the tumor microenvironment of patients with progressive myeloma can generate strong, tumor-specific cytolytic responses to autologous, tumor-loaded dendritic cells. Proc Natl Acad Sci U S A. 2002;99(20):13009-13.

44. Perumal D, Imai N, Lagana A, Finnigan J, Melnekoff D, Leshchenko VV, et al. Mutation-derived Neoantigen-specific T-cell Responses in Multiple Myeloma. Clin Cancer Res. 2020;26(2):450-64.
45. Robinson MH, Villa NY, Jaye DL, Nooka AK, Duffy A, McCachren SS, et al. Regulation of antigen-specific T cell infiltration and spatial architecture in multiple myeloma and premalignancy. J Clin Invest. 2023;133(15).
46. Akhmetzyanova I, McCarron MJ, Parekh S, Chesi M, Bergsagel PL, Fooksman DR. Dynamic CD138 surface expression regulates switch between myeloma growth and dissemination. Leukemia. 2020;34(1):245-56.
47. 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.
48. Gandhi AK, Kang J, Havens CG, Conklin T, Ning Y, Wu L, et al. Immunomodulatory agents lenalidomide and pomalidomide co-stimulate T cells by inducing degradation of T cell repressors Ikaros and Aiolos via modulation of the E3 ubiquitin ligase complex CRL4(CRBN.). Br J Haematol. 2014;164(6):811-21.
49. LeBlanc R, Hideshima T, Catley LP, Shringarpure R, Burger R, Mitsiades N, et al. Immunomodulatory drug costimulates T cells via the B7-CD28 pathway. Blood. 2004;103(5):1787-90.
50. Chang DH, Liu N, Klimek V, Hassoun H, Mazumder A, Nimer SD, et al. Enhancement of ligand dependent activation of human Natural Killer T cells by Lenalidomide: Therapeutic Implications. Blood. 2006;108(2):618-21.
51. Sehgal K, Das R, Zhang L, Verma R, Deng Y, Kocoglu M, et al. Clinical and pharmacodynamic analysis of pomalidomide dosing strategies in myeloma: impact of immune activation and cereblon targets. Blood. 2015;125(26):4042-51.
52. Spisek R, Charalambous A, Mazumder A, Vesole DH, Jagannath S, Dhodapkar MV. Bortezomib enhances dendritic cell (DC) mediated induction of immunity to human myeloma via exposure of cell surface heat shock protein 90 on dying tumor cells: therapeutic implications. Blood. 2007;109(Jun 1):4839-45.
53. Gulla A, Morelli E, Samur MK, Botta C, Hideshima T, Bianchi G, et al. Bortezomib induces anti-multiple myeloma immune response mediated by cGAS/STING pathway activation. Blood Cancer Discov. 2021;2(5):468-83.
54. Krejcik J, Casneuf T, Nijhof IS, Verbist B, Bald J, Plesner T, et al. Daratumumab depletes CD38+ immune regulatory cells, promotes T-cell expansion, and skews T-cell repertoire in multiple myeloma. Blood. 2016;128(3):384-94.
55. Montes de Oca R, Alavi AS, Vitali N, Bhattacharya S, Blackwell C, Patel K, et al. Belantamab Mafodotin (GSK2857916) Drives Immunogenic Cell Death and Immune-mediated Antitumor Responses In Vivo. Mol Cancer Ther. 2021;20(10):1941-55.
56. Coffey DG, Maura F, Gonzalez-Kozlova E, Diaz-Mejia JJ, Luo P, Zhang Y, et al. Immunophenotypic correlates of sustained MRD negativity in patients with multiple myeloma. Nat Commun. 2023;14(1):5335.
57. Azeem MI, Nooka AK, Shanmugasundaram U, Cheedarla N, Potdar S, Manalo RJ, et al. Impaired SARS-CoV-2 Variant Neutralization and CD8+ T-cell Responses Following 3 Doses of mRNA Vaccines in Myeloma: Correlation with Breakthrough Infections. Blood Cancer Discov. 2023;4(2):106-17.

58. Nooka AK, Shanmugasundaram U, Cheedarla N, Verkerke H, Edara VV, Valanparambil R, et al. Determinants of Neutralizing Antibody Response After SARS CoV-2 Vaccination in Patients With Myeloma. J Clin Oncol. 2022:JCO2102257.
59. Lin Y, Raje NS, Berdeja JG, Siegel DS, Jagannath S, Madduri D, et al. Idecabtagene vicleucel for relapsed and refractory multiple myeloma: post hoc 18-month follow-up of a phase 1 trial. Nat Med. 2023;29(9):2286-94.
60. Montes de Oca R, Gu J, Zhao H, Zelinsky K, Wu D, Davis C, et al. Biomarker Correlates of Response to Ciltacabtagene Autoleucel in Patients with Relapsed or Refractory Multiple Myeloma from CARTITUDE-1, a Phase 1b/2 Open-Label Study, at the ~3 Year Follow-up. Blood. 2023;142:2099.
61. Garfall AL, Dancy EK, Cohen AD, Hwang WT, Fraietta JA, Davis MM, et al. T-cell phenotypes associated with effective CAR T-cell therapy in postinduction vs relapsed multiple myeloma. Blood Adv. 2019;3(19):2812-5.
62. Friedrich MJ, Neri P, Kehl N, Michel J, Steiger S, Kilian M, et al. The pre-existing T cell landscape determines the response to bispecific T cell engagers in multiple myeloma patients. Cancer Cell. 2023;41(4):711-25 e6.
63. van de Donk N, Cortes-Selva D, Casneuf T, Vishwamitra D, Stein S, Perova T, et al. P32 MAJESTEC-1: CORRELATIVE ANALYSES OF TECLISTAMAB, A B-CELL MATURATION ANTIGEN (BCMA) X CD3 BISPECIFIC ANTIBODY, IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA (RRMM). Hemasphere. 2023;7(Suppl).
64. Firestone RS, McAvoy D, Shekarkhand T, Serrano E, Hamadeh I, Wang A, et al. CD8 effector T cells enhance response in BCMA-exposed and -naive multiple myeloma. Blood Adv. 2023.
65. Lancman G, Sastow DL, Cho HJ, Jagannath S, Madduri D, Parekh SS, et al. Bispecific Antibodies in Multiple Myeloma: Present and Future. Blood Cancer Discov. 2021;2(5):423-33.
66. Nooka AK, Wang ML, Yee AJ, Kaufman JL, Bae J, Peterkin D, et al. Assessment of Safety and Immunogenicity of PVX-410 Vaccine With or Without Lenalidomide in Patients With Smoldering Multiple Myeloma: A Nonrandomized Clinical Trial. JAMA Oncol. 2018;4(12):e183267.
67. Chung DJ, Shah N, Wu J, Logan B, Bisharat L, Callander N, et al. Randomized Phase II Trial of Dendritic Cell/Myeloma Fusion Vaccine with Lenalidomide Maintenance after Upfront Autologous Hematopoietic Cell Transplantation for Multiple Myeloma: BMT CTN 1401. Clin Cancer Res. 2023;29(23):4784-96.
68. Freeman CL, Atkins R, Varadarajan I, Menges M, Edelman J, Baz R, et al. Survivin dendritic cell vaccine safely induces immune responses and is associated with durable disease control after autologous transplant in patients with myeloma. Clinical Cancer Research. 2023.
69. Qazilbash MH, Saini NY, Cha SC, Wang Z, Stadtmauer EA, Baladandayuthapani V, et al. A randomized phase 2 trial of idiotype vaccination and adoptive autologous T-cell transfer in patients with multiple myeloma. Blood. 2022;139(9):1289-301.
70. Richter J, Neparidze N, Zhang L, Nair S, Monesmith T, Sundaram R, et al. Clinical regressions and broad immune activation following combination therapy targeting human NKT cells in myeloma. Blood. 2013;121(3):423-30.

71. Dhodapkar MV. Harnessing Dendritic Cells: Next Frontier for Durable Immune Control in Myeloma. Clin Cancer Res. 2023;29(22):4524-6.
72. Rasche L, Chavan SS, Stephens OW, Patel PH, Tytarenko R, Ashby C, et al. Spatial genomic heterogeneity in multiple myeloma revealed by multi-region sequencing. Nat Commun. 2017;8(1):268.
73. Zhang Y, Chen L. Classification of Advanced Human Cancers Based on Tumor Immunity in the MicroEnvironment (TIME) for Cancer Immunotherapy. JAMA Oncol. 2016;2(11):1403-4.
74. Lee S, Kim G, Lee J, Lee AC, Kwon S. Mapping cancer biology in space: applications and perspectives on spatial omics for oncology. Mol Cancer. 2024;23(1):26.
75. Schafer PSL, Dimitrov D, Villablanca EJ, Saez-Rodriguez J. Integrating single-cell multi-omics and prior biological knowledge for a functional characterization of the immune system. Nat Immunol. 2024;25(3):405-17.
76. Galon J, Bruni D. Tumor Immunology and Tumor Evolution: Intertwined Histories. Immunity. 2020;52(1):55-81.
77. Angelova M, Mlecnik B, Vasaturo A, Bindea G, Fredriksen T, Lafontaine L, et al. Evolution of Metastases in Space and Time under Immune Selection. Cell. 2018;175(3):751-65 e16.
78. Lee H, Ahn S, Maity R, Leblay N, Ziccheddu B, Truger M, et al. Mechanisms of antigen escape from BCMA- or GPRC5D-targeted immunotherapies in multiple myeloma. Nat Med. 2023;29(9):2295-306.
79. Paiva B, Manrique I, Rytlewski J, Campbell T, Kazanecki CC, Martin N, et al. Time-Dependent Prognostic Value of Serological and Measurable Residual Disease Assessments after Idecabtagene Vicleucel. Blood Cancer Discov. 2023;4(5):365-73.
80. Hansen DK, Sidana S, Peres LC, Colin Leitzinger C, Shune L, Shrewsbury A, et al. Idecabtagene Vicleucel for Relapsed/Refractory Multiple Myeloma: Real-World Experience From the Myeloma CAR T Consortium. J Clin Oncol. 2023;41(11):2087-97.
81. Samur MK, Fulciniti M, Aktas Samur A, Bazarbachi AH, Tai YT, Prabhala R, et al. Biallelic loss of BCMA as a resistance mechanism to CAR T cell therapy in a patient with multiple myeloma. Nat Commun. 2021;12(1):868.
82. Sari G, Rock KL. Tumor immune evasion through loss of MHC class-I antigen presentation. Curr Opin Immunol. 2023;83:102329.
83. Truger MS, Duell J, Zhou X, Heimeshoff L, Ruckdeschel A, John M, et al. Single- and double-hit events in genes encoding immune targets before and after T cell-engaging antibody therapy in MM. Blood Adv. 2021;5(19):3794-8.
84. Da Via MC, Dietrich O, Truger M, Arampatzi P, Duell J, Heidemeier A, et al. Homozygous BCMA gene deletion in response to anti-BCMA CAR T cells in a patient with multiple myeloma. Nat Med. 2021;27(4):616-9.
85. Derrien J, Gastineau S, Frigout A, Giordano N, Cherkaoui M, Gaborit V, et al. Acquired resistance to a GPRC5D-directed T-cell engager in multiple myeloma is mediated by genetic or epigenetic target inactivation. Nat Cancer. 2023;4(11):1536-43.
86. Spranger S, Gajewski TF. Impact of oncogenic pathways on evasion of antitumour immune responses. Nat Rev Cancer. 2018;18(3):139-47.

87. Hou J, Li Y, Lin Q. Bispecific antibodies and dual-targeting CAR-T cells for multiple myeloma: latest updates from the 2023 ASCO annual meeting. Exp Hematol Oncol. 2023;12(1):74.
88. Bottcher JP, Bonavita E, Chakravarty P, Blees H, Cabeza-Cabrerizo M, Sammicheli S, et al. NK Cells Stimulate Recruitment of cDC1 into the Tumor Microenvironment Promoting Cancer Immune Control. Cell. 2018;172(5):1022-37 e14.
89. Avigan DE. Advances in the development of vaccines and other immunotherapies for multiple myeloma. Clin Adv Hematol Oncol. 2019;17(12):670-3.
90. Chesi M, Mirza NN, Garbitt VM, Sharik ME, Dueck AC, Asmann YW, et al. IAP antagonists induce anti-tumor immunity in multiple myeloma. Nat Med. 2016;22(12):1411-20.
91. Ribrag V, Avigan DE, Green DJ, Wise-Draper T, Posada JG, Vij R, et al. Phase 1b trial of pembrolizumab monotherapy for relapsed/refractory multiple myeloma: KEYNOTE-013. Br J Haematol. 2019;186(3):e41-e4.
92. Meermeier EW, Welsh SJ, Sharik ME, Du MT, Garbitt VM, Riggs DL, et al. Tumor burden limits bispecific antibody efficacy through T cell exhaustion averted by concurrent cytotoxic therapy. Blood Cancer Discov. 2021;2(4):354-69.
93. Guerrero C, Puig N, Cedena MT, Goicoechea I, Perez C, Garces JJ, et al. A Machine Learning Model Based on Tumor and Immune Biomarkers to Predict Undetectable MRD and Survival Outcomes in Multiple Myeloma. Clin Cancer Res. 2022;28(12):2598-609.

Table 1. Potential clinical implications of MM immune types for application of immune therapy

	Immune - permissive	Immune-excluded	Immune-suppressed	Immune-deplete	Immune-resistant
Proposed Defining Feature(s)	T cell hotspots with infiltration and Clec9a DCs, lack of terminal diff. T cell clones	T cells at tumor margins without infiltration, lack of Clec9a DCs	Inhibitory myeloid infiltration, immune suppressive cells, T cell exhaustion	Systemic and regional lymphoid depletion	Loss of T cell redirection target, Resistance to immune recognition
Clinical Aspects	Expected favorable course, earlier in disease evolution.	? biology similar to extramedullary plasmacytomas	Potentially diverse mechanisms	Lymphopenia, ? with impaired hematopoiesis, extreme age, frailty, prior extensive chemotherapy	Target-specific loss or mutations in targets for T cell redirection.
Response to T cell redirection	Yes. Durable responses	Yes, but may not be durable	Yes, but not durable	Unlikely. High risk of CAR-T manufacturing failure.	No, but resistance may be limited to specific therapies
Possible solutions / therapeutic goals	Target early eradication of residual disease.	Enhance T cell entry, DC or NK recruitment	Combinations to overcome suppression. Optimal combinations may be pathway/mechanism specific.	Direct tumor targeting, restore lympho-hematopoiesis.	Alternate targets or combinatorial targeting. Alternate immune cells (e.g. NK/NK-T)

Figure Legends:

Figure 1. Proposed spatial immune types of myeloma. Development of myeloma is characterized by clustered growth of tumor cells which creates distinct spatial immune types as shown. These immune types may impact optimal application of immunotherapy in MM.

Figure 1

Fig1