are we left to guess, "Which drug should I add?" We now have the potential to add in an agent that is specific for whatever is left. This is a huge step forward for the field and one that promises not only to increase the fraction of patients who achieve MRD negativity but also to ultimately increase the fraction of patients that are cured.

However, to date, most patients who achieve a CR, even MRD-negative CR, will continue to relapse. What is the limitation that these 3 methodologies share? They are all dependent upon measurement of disease burden at the site of marrow collection, and although this is a common source of disease when we are dealing with higher levels of residual disease, it does not represent the only site of potential disease. It has been shown by Barlogie and colleagues that even among patients who achieve a CR, there can be focal bone lesions that continue to harbor active disease,[7] and if they are not in the pelvis, then it is possible they will be missed no matter which sensitive MRD analysis method is used. Although we have been fortunate in myeloma to have a biomarker of activity, the paraprotein, it is increasingly clear that we will need to incorporate more than radiographs in our diagnostic toolbox as we seek the cure for myeloma.[8] Rather than being satisfied with an MRD-negative marrow by whatever test, imaging that is able to correctly identify the remaining areas of active bone disease is of critical importance if we are to eliminate all signs of residual disease. Thus, although sequencing or MFC is critical to assessing marrow-based disease, ultimately they need to be coupled with positron emission tomography/computed tomography imaging to demonstrate a true CR. Once the myeloma and oncology community incorporate both imaging and high-resolution sequencing technology to eliminate the last few remaining cells, we will be much closer to the bitter end of myeloma and a cure for our patients.

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● ● ● LYMPHOID NEOPLASIA

Comment on Tai et al, page 3128

Engineering more efficacious antibody therapy for myeloma

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In this issue of *Blood*, Tai et al describe a novel monoclonal antibody (mAb) for myeloma, which is both glycoengineered and conjugated to a cytotoxic agent. This mAb targets B-cell maturation antigen (BCMA) and has considerable preclinical activity, thus holding therapeutic promise. The outlook for myeloma patients has greatly improved over the past decade with the introduction of a number of novel agents. However, there is still a significant unmet need because many patients with gene expression profiling–defined good-risk disease eventually relapse and high-risk myeloma has poor long-term disease-free survival in the majority of patients.[1]

mAbs work through completely different mechanisms of action compared with currently available antimyeloma drugs and could complement their action at all stages of therapy. A prime example of a highly active mAb is rituximab, which has made a major impact on the management of non-Hodgkin lymphoma, chronic lymphocytic leukemia, and Waldenström macroglobulinemia. However, its target, CD20, is expressed by only 15% to 20% of myeloma patients belonging to the CD2 molecular subgroup and rituximab has limited activity in this setting. A number of mAbs are in various stages of development for myeloma. These mAb have assorted mechanisms of action and target the myeloma cell directly, induce immune responses, inactivate mediators of bone disease, neutralize growth factors, activate death receptors, and inhibit proangiogenic molecules. Promising mAbs for myeloma include the anti-CS1 antibody, elotuzumab, and the anti-CD38 mAb, daratumumab. Elotuzumab is in phase 3 trials in both the newly diagnosed and relapsed setting, and daratumumab has demonstrated single-agent activity in early studies.

Antibody-drug conjugates (ADCs) enhance the efficacy of native mAbs by delivering a cytotoxic agent directly to tumor cells. Brentuximab vedotin is the first US Food and Drug Administration (FDA)–approved novel agent for Hodgkin disease in over 30 years and induces impressive and durable responses in relapsed disease. Brentuximab also has significant activity in anaplastic large-cell lymphoma. Tai et al report that the humanized, antagonistic mAb, J6M0 (GSK2857916), which is directed at BCMA, has impressive activity both in vitro against myeloma cell lines and autologous primary myeloma as well as in mouse models.[1] BCMA

is a member of the tumor necrosis receptor superfamily and binds to a proliferation-inducing ligand (APRIL) and B-cell–activating factor (BAFF) with, as net effect, promotion of plasma cell proliferation and induction of antiapoptotic proteins.

Others have previously reported the targeting of BCMA with nonengineered mAbs.[2] BCMA is highly and homogeneously expressed in virtually all myeloma patients, with little or no expression in normal tissues including human $CD34^+$ cells, which should limit any mAb-mediated organ and hematopoietic toxicity. GSK2857916 is of particular interest because it displays multiple mechanisms of action and the potency of the native mAb is enhanced in several ways. First, defucosylation of the Fc region carbohydrates of the antibody increases the binding affinity to FcγRIII receptors and potentiates antibody-dependent cell-mediated cytotoxicity (ADCC). Similar glycoengineering helps to explain the enhanced efficacy of the novel anti-CD20 mAb, obinutuzumab.[3] Second, the mAb is conjugated via a noncleavable linker to its cytotoxic cargo, monomethyl auristatin F, which binds to tubulin and inhibits polymerization, thus disrupting mitosis through G_2/M arrest with induction of apoptosis. The use of a noncleavable linker has the advantage that GSK2857916 should be more stable in the blood with minimal spontaneous release of the cytotoxic conjugate. The experiments by Tai et al suggested that GSK2857916 is efficiently internalized and spares bone marrow stromal and effector cells. Further mechanisms of action include macrophage-mediated phagocytosis and the interruption of the BCMA/BAFF/APRIL pathway leading to inhibition of nuclear factor-κB signaling.

High levels of soluble BCMA (sBCMA) have been reported in the serum of myeloma patients and have been correlated with progressive disease and worse outcome.[4] Tai et al added MM1s cell supernatants (a source of sBCMA) to ADCC assays and noted some reduction in lysis of myeloma cell lines which was partly reversible by addition of lenalidomide. Clinical studies will have to establish whether a sBCMA "sink" could potentially interfere with the efficacy of GSK2857916. BCMA is expressed by plasma cells and B-cell subsets and anti-BCMA mAb therapy may affect these lineages. However, this potential toxicity is not likely to preclude clinical application. Two other nonglycoengineered ADCs, nBT062 (indatuximab ravtansine) and IMGN901 (lorvotuzumab mertansine), respectively, targeting CD138 and CD56, are presently in phase 1 clinical trial for myeloma. Dose-limiting toxicity of nBT02 was skin and gastrointestinal-related, and objective responses were observed in 2 of 20 patients.[5] IMGN01 elicited a partial response in 1 of 25 patients treated.[6]

BCMA is an interesting molecule from an immunotherapy perspective. Anti-BCMA antibodies have been detected as part of the graft-versus-myeloma response following donor lymphocyte infusion after allogeneic transplant, and patient-derived serum killed primary myeloma cells.[7] BCMA-derived peptides can generate antigen-specific T-cell responses and are candidates for future vaccination strategies.[8] T cells transduced with anti-BCMA chimeric antigen receptors have been reported to kill primary myeloma cells in vitro and in a mouse model, and will likely be tested in clinical trial.[9] GSK2857916 will be both the first defucosylated ADC compound tested in multiple myeloma and the first BCMA-based immunotherapy entering the clinical arena.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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● ● ● MYELOID NEOPLASIA

Comment on Nelson et al, page 3152

A(nother) RAF mutation in LCH

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In this issue of *Blood,* Nelson et al[1] describe a novel somatic *ARAF* mutation in a child with Langerhans cell histiocytosis (LCH) and demonstrate that the encoded protein has strong gain-of-function properties. Importantly, this mutant A-Raf molecule is sensitive to inhibition by vemurafenib, a potent and selective Raf kinase inhibitor that is Food and Drug Administration (FDA)-approved for the treatment of advanced melanoma.[2,3] This work thus identifies a new driver mutation in LCH that is potentially actionable in the clinic.

LCH is a rare hematologic disorder that is classified as a unified disease entity based on common histopathologic features and the proliferation of cells with phenotypic and cell surface marker expression characteristic of Langerhans cells.[4] However, the clinical presentation is highly variable, ranging from generally benign single system lesions to life-threatening multisystem disease with organ dysfunction. The antigen-presenting function of Langerhan's cells, mixed population of infiltrating leukocytes in pathologic specimens,