Comment on Krejcik et al, page 384

**A new era of immune therapy in multiple myeloma**

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In this issue of Blood, Krejcik et al provide the first clinical data that describe unexpected immune stimulatory activity of the monoclonal antibody (mAb) daratumumab. By targeting CD38-expressing immune suppressive cells, clonal memory T-cell function is induced in heavily pretreated patients with relapsed and refractory multiple myeloma (MM).

Despite early disappointments, mAb's have now entered the clinical armamentarium for MM. They act via mechanisms distinct from currently available therapies and could complement other treatments at all stages of treatment. In particular, the development of immunotherapies targeting CD38 is based on its overexpression on malignant plasma cells (PCs) in all stages of MM. More than 2 decades ago, 2 preclinical studies reported a chimeric mAb or immunotoxin, providing evidence for CD38 as a promising target in MM. However, because of concerns about adverse effects related to CD38 expression on immune effector, endothelial, and committed hematopoietic progenitor cells, clinical development of anti-CD38 mAb therapy was delayed. Of note, CD38 is not expressed on primitive hematopoietic precursors (CD34+CD38+), suggesting that hematopoietic recovery would occur following CD38-targeted cytotoxic agents. Indeed, growth of burst-forming unit erythroid and granulocyte-macrophage colony-forming unit was unaltered or only moderately affected in these 2 early preclinical studies.

Promising preclinical data showing multiple Fc-dependent and immune-mediated mechanisms of MM cytotoxicity, coupled with single-agent activity in patients with heavily pretreated relapsed and refractory MM (RR MM), provided the framework for the anti-CD38 mAb daratumumab to be approved by the U.S. Food and Drug Administration in 2015. A second anti-CD38 mAb, isatuximab, also shows single-agent activity in patients with RR MM. Both anti-CD38 mAb's trigger antibody-dependent cytotoxicity, complement-dependent cytotoxicity, and antibody-dependent phagocytosis, as well as inhibition of the enzymatic activity of CD38. Moreover, even in the absence of Fc-receptor–expressing effector cells, both mAb's can induce direct apoptosis and lysosome-mediated cell death in MM cells harboring p53 mutations. Most importantly, this preclinical activity has translated to clinical utility as monotherapy even in high-risk, multiply relapsed MM.

What are the most important mechanisms underlying this impressive single-agent clinical activity of daratumumab? In particular, given that CD38 can be expressed on activated immune effector cells, what is the effect of daratumumab treatment on immune mechanisms of MM patients in vivo? In elegant correlative science studies, Krejcik et al collected peripheral blood mononuclear cells and bone marrow mononuclear cells pre- and postdaratumumab treatment from patients enrolled in 2 seminal trials to characterize immune inhibitory and stimulatory cells known to express CD38. They showed that CD38 expression is highest on MM cells, natural killer cells, and regulatory B cells (Bregs), followed by regulatory T cells (Tregs), B cells, and T cells, in both MM patients and healthy donors. CD38 expression on effector T cells is lower in MM patients compared with healthy donors. Myeloid-derived suppressor cells (MDSCs) were detectable at only low levels in fresh samples but highly express CD38 following expansion in cocultures with MM cell lines. Importantly, daratumumab depletes immunosuppressive CD38+Bregs, MDSCs, and Tregs in patient samples at 1 week after treatment. These Tregs...
expressing the highest levels of CD38 more significantly inhibited T-cell proliferation than CD38-negative Tregs. Furthermore, both helper and cytotoxic T cells were induced in daratumumab-treated patients, with interferon-γ and CD8+/Treg ratios increased in responders at week 8 following treatment. Most importantly, HLA-DR+CD38+ T cells, effector memory CD8+ T cells, and clonal T cells based on T-cell repertoire analysis were significantly increased during drug treatment and response. Conversely, effector memory CD8+ T cells returned to baseline levels at relapse.

These novel effects of daratumumab on multiple immune populations indicate that daratumumab overcomes immunosuppression by targeting Bregs, Tregs, and MDCs, which are elevated at diagnosis and increase the risk of disease progression and relapse. These cells express higher levels of CD38 and are therefore more sensitive to treatment than helper and effector T cells, which express lower levels or lack CD38. However, CD38 levels alone may not be the sole determinant of sensitivity to daratumumab, because CD38-negative Tregs were also reduced in responsive patients. These results suggest the potential benefits of combining daratumumab with other therapies targeting Tregs, including immune checkpoint inhibitors or immunomodulatory drugs, to further trigger a shift to positive vs negative regulators of anti-MM immune response. Importantly, these studies suggest that daratumumab may have even greater clinical activity when used in earlier stages of disease (ie, smoldering MM), when the patient immune repertoire is preserved and not impacted by therapy. Finally, long-lived and/or MM-initiating cells from which MM PCs are derived are CD38highCD19− PCs, suggesting that MM stem cells express high levels of CD38 and may also be susceptible to daratumumab therapy. Ongoing studies will define the impact of daratumumab, alone and in combination with other immune and targeted agents.

An overdue era of immune therapy in MM has begun, and the prospect of triggering long-term memory anti-MM immunity in patients at early stages of disease offers great potential for prolonged survival and potential cure.

Conflict-of-interest disclosure: K.C.A. serves on advisory boards to Onyx, Celgene, and Gilead, and is a scientific founder of Acteyon, Oncopep, and CH Therapeutics. Y.-T.T. declares no competing financial interests.

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Comment on Herling et al, page 395

Synergy: karyotypes and mutations in CLL

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In this issue of Blood, Herling et al present the first large, prospective clinical trial that integrates cytogenetic, next-generation sequencing (NGS), clinical, and laboratory data into a prognostic analysis.1 They demonstrate that karyotypic complexity is an independent prognostic factor of survival in chronic lymphocytic leukemia (CLL). They are also the first to show that mutations in KRAS or POT1 affect treatment response and survival after chemoimmunotherapy. Their results provide a strong rationale for incorporating the results of karyotypic and NGS analyses in clinical trial design and in routine practice.

Until relatively recently, the genomic landscape of CLL was considered to be characterized mainly by gains and deletions (del) of chromosomal material, rather than by translocations, unlike other hematologic malignancies. Because most peripheral blood (PB) CLL cells are in the G0/G1 phase of the cell cycle, under standard culture conditions most samples fail to undergo cell division. Stimulation with conventional B-cell mitogens, such as lipopolysaccharide, pokeweed mitogen, or phorbol 12-myristate 13-acetate, yields metaphases in fewer than half of cases. Under these conditions, the most commonly identified chromosomal abnormalities are trisomy of chromosome 12, followed by del in the long arms of chromosomes 13 and 11, and the short arm of chromosome 17; translocations are uncommon.2

In a landmark study published in 2000, Döhner et al demonstrated, by fluorescence in situ hybridization (FISH) analysis performed on interphase (nondividing) nuclei, that ~80% of CLL cases contained at least 1 of 4 recurrent chromosomal gains or del, most commonly del(13)(q14.1) (55% of cases; the site of the microRNA 15a and 16–1 genes), followed by trisomy 12 (16% of cases), del(11)(q22–23) (18% of cases; the site of the ataxia telangiectasia mutated [ATM] gene), and del(17)(p13.1) (7% of cases; the site of the tumor protein p53 [TP53] tumor suppressor gene).3 Further, these abnormalities were useful for risk stratification; patients with del(13q) had a good prognosis, whereas patients with del(17p) had a particularly poor prognosis characterized by rapid disease progression, treatment resistance, and poor survival. Based

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