a career in this specialty. Ultimately, these downstream effects may increase the pool of applicants in this underrepresented field.

Prior to 2017, our program did not have a formal application process for our single-board hematology track, and candidates were identified based on interest expressed during the fellowship interview. In 2017, we formalized a hematology track in ERAS to allow candidates to independently apply to a hematology and/or medical oncology track within our combined hematology/oncology fellowship structure. Of the 414 total applicants to our program for the 2018 season, 212 (45% female) applied to the hematology track, of whom 51 applied to the hematology track only. In addition, 26 candidates expressed an interest in benign hematology as assessed by overt mention in their personal statement. These numbers contradict the perceived lack of enthusiasm for hematology and likely underestimate the true number of candidates with an untapped interest in this field.

At Johns Hopkins, the Division of (benign) Hematology is a free-standing division in the Department of Medicine, which differs from most university programs. However, despite our unique division organization, our fellowship structure provides a widely applicable model for single-track hematology training within a dual-program structure. In many academic programs, fellows serve as an important workforce for patient care. The overlapping structure of our single-board hematology and medical oncology tracks preserves clinical training for hematologic malignancies for all fellows, which allows for extension of our structure to more traditional oncology programs. Furthermore, our structure preserves the option for dual certification from either track to allow flexibility in training.

In conclusion, our 10-year experience of a single-board hematology track demonstrates high retention in academic benign and malignant hematology, both in terms of clinical and research focus. Future efforts should be made to encourage academic programs to implement this system to help build and maintain the pool of academic hematologists in the United States.

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Authorship

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Correspondence: Rakhi P. Naik, Division of Hematology, Department of Medicine, Johns Hopkins University, 1830 E. Monument St Suite 7300, Baltimore, MD 21205; e-mail: rakhi@jhmi.edu.

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TO THE EDITOR:

The addition of IMiDs for patients with daratumumab-refractory multiple myeloma can overcome refractoriness to both agents

Maria Gavriatopoulou, Efstathios Kastritis, Ioannis Ntanasis-Stathopoulos, Despina Fotiou, Maria Roussou, Magdalini Migkou, Dimitrios C. Ziogas, Nikolaos Kanellias, Evangelos Terpos, and Meletios Athanasios Dimopoulos

Department of Clinical Therapeutics, National and Kapodistrian University of Athens, Athens, Greece

The survival of myeloma patients has doubled in the past decade, but patients refractory to both proteasome inhibitors (PIs) and immunomodulatory drugs (IMiDs) still have poor prognosis.[1] Immunotherapy with monoclonal antibodies targeting cell-surface antigens is a promising new treatment strategy with different mechanisms of action.[2,3] CD38, a transmembrane glycoprotein involved in adhesion, has enzymatic and receptor functions,[4-6] is highly expressed on myeloma cells, and represents an attractive target for myeloma immunotherapy. Monoclonal antibodies targeting CD38, such

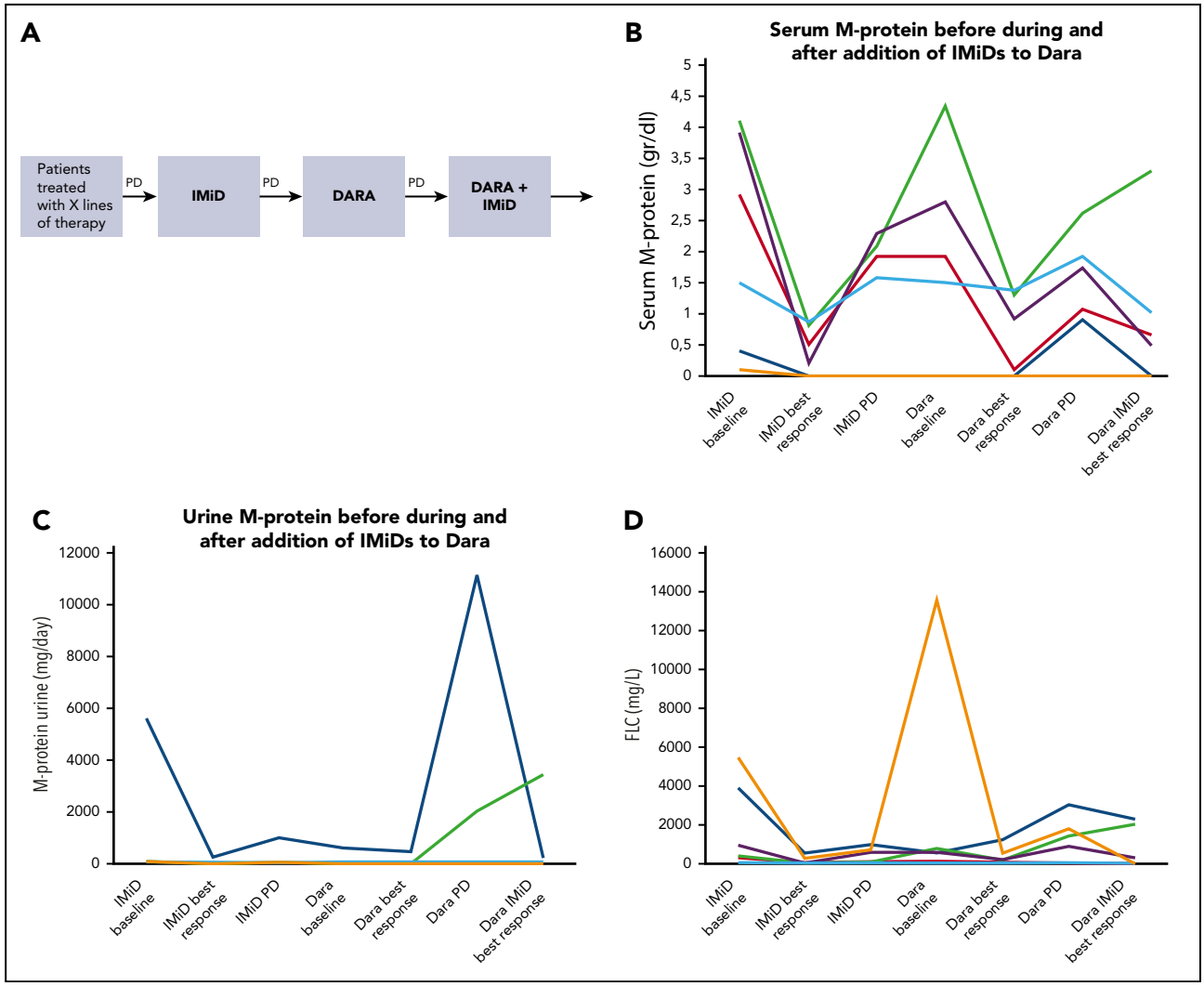

Figure 1. Patient flow and disease assessments before and after addition of IMiDs to daratumumab. (A) Patient flow and response monitoring of the daratumumab/IMiD/dexamethasone combination. (B-D) Each line represents an individual patient's serum M-protein (B), urine M-protein (C), and involved free light chain (D) values. FLC, free light chain; PD, progressive disease.

as daratumumab, can induce tumor cell killing via complement-dependent cytotoxicity, antibody-dependent cellular phagocytosis, and antibody-dependent cell-mediated cytotoxicity, although each anti-CD38 monoclonal antibody may have different properties with respect to each of these mechanisms.[7-9] In addition, immune modulation due to reduction of $CD38^+$ T-regulatory cells and $CD38^+$ myeloid-derived suppressor cells has been shown.[10] The US Food and Drug Administration approved daratumumab monotherapy in November 2015 for the treatment of myeloma patients who have received at least 3 prior therapies, including a PI and an IMiD, or who are double refractory to these drugs, based on the GEN501 and MMY2002 SIRIUS trial results.[11] These trials included heavily pretreated patients (prior therapies, median 5, range 2-14; 86.5% were double refractory to a PI and IMiD). The overall response rate, at the approved dose and schedule, was 31.1% (4.7% complete response or better and 8.8% very good partial response); the median duration of response was 7.6 months, and the median progression-free and overall survival were 4.0 months and 20.1 months, respectively. The exceptional efficacy of daratumumab monotherapy provided the rationale for the combination of daratumumab with other anti–multiple myeloma drugs. IMiDs (pomalidomide and lenalidomide) modulate immune response and enhance natural killer cell cytotoxicity directly or through T-cell stimulation; thus, they may interact with daratumumab and act more effectively when combined.[12-14] Furthermore, IMiDs have direct anti-myeloma activity and an indirect action via modulation of the microenvironment.[15] In the POLLUX trial, daratumumab with lenalidomide/dexamethasone was associated with a 63% reduction in the risk of disease progression or death compared with lenalidomide/dexamethasone alone in patients who had received ≥1 prior therapies.[16] In a phase 1b study, daratumumab with pomalidomide/dexamethasone was evaluated in 103 patients with ≥2 (median, 4) prior lines of therapy (71% were refractory to both PIs and IMiDs). The overall response rate was 60%, and median progression-free survival was 8.8 months.[17] The combination of pomalidomide/dexamethasone with daratumumab was recently approved by the US Food and Drug Administration and phase 3 studies of this combination compared with pomalidomide/dexamethasone are still ongoing. Nooka et al reported on the combination of daratumumab with

Table 1. Patient characteristics

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Sex	Male	Female	Female	Male	Male	Male
Age, y	58	79	51	60	58	66
MM subtype	IgGκ	IgGκ	IgGκ	λLC/BJ	IgGκ	κ LC
Prior ASCT	Yes	No	Yes	Yes	Yes	Yes
ISS prior to addition of IMiD to Dara	1	2	2	3	1	3
Time from diagnosis, y	11	8	8	6	9	4.5
Lines of prior therapies	13	8	4	4	3	4
Time from last exposure to IMiD to Dara/IMiD (mo)	13.2	16.3	20.7	15.8	37.1	13.9
Pomalidomide refractory	Yes, at 4 mg with weekly dexamethasone 40 mg	Yes, at 4 mg with weekly dexamethasone 20 mg and cyclophosphamide 50	Yes, at 4 mg with weekly dexamethasone 40 mg	No	No	Yes, at 4 mg with weekly dexamethasone 20 mg
Lenalidomide refractory	Yes, at 25 mg with weekly dexamethasone 40 mg	Yes, at 25 mg with weekly dexamethasone 40 mg	Yes, at 25 mg with weekly dexamethasone 40 mg	Yes, at 25 mg with weekly dexamethasone 40 mg	Yes, at 25 mg with weekly dexamethasone 40 mg	Yes, at 25 mg with weekly dexamethasone 40 mg
Best response to prior and current therapies						
Dara monotherapy duration, (mo)	11	17	6	6	10	8
Dara-IMiD-DEX	PD	MR	MR	VGPR	PR	VGPR
Dara + IMiD PFS, mo	2	3, ongoing	3, ongoing	4.5, ongoing	8, ongoing	8

ASCT, autologous stem cell transplantation; BJ, Bence Jones; BTZ, bortezomib; Dara, daratumumab; IgG, immunoglobulin G; MM, multiple myeloma; PD, progressive disease; PFS, progression-free survival; SD, stable disease; VGPR, very good partial response.

pomalidomide/dexamethasone in 41 patients who were naive to both drugs (n = 19), refractory to either (n = 10), or refractory to both (n = 12).[18] In this retrospective report, the response rate for naive patients was ~90%, whereas among patients who were refractory to both daratumumab and pomalidomide, 33% responded to the combination. Baertsch et al reported 2 patients refractory to both daratumumab and pomalidomide who were treated with the combination and achieved a minor response (MR) and partial response (PR), respectively.[19] However, in both reports, daratumumab administration was reintensified (ie, was initially given weekly for the first 2 cycles, every other week for cycles 2-6, and monthly thereafter). Therefore, it is unclear whether the observed responses were mainly due to daratumumab intensification, resensitization to pomalidomide, or both.

In order to answer this question and avoid the interference of a more intensified daratumumab administration, we analyzed 6 consecutive patients who progressed on daratumumab monotherapy and for whom the IMiD to which each patient was refractory prior to daratumumab was added (Figure 1). Daratumumab was continued at the dose of 16 mg/kg monthly, as our patients had progressed on this schedule. Pomalidomide and lenalidomide were administered at the standard doses and schedule (Table 1). All patients provided written informed consent, and approval by our institution's institutional review board was obtained for collection, analysis, and data publication. Prior to daratumumab monotherapy, 4 patients were refractory to pomalidomide and 2 were refractory to lenalidomide; therefore, pomalidomide was added to the 4 pomalidomide-refractory patients and lenalidomide to the 2 lenalidomide-refractory patients. All were heavily pretreated (had 3-13 prior lines of therapy). Four out of 6 had initially responded (ie, had at least a PR), and 2 had stable disease as their best response to daratumumab monotherapy. All were bortezomib refractory, and 3 were also carfilzomib refractory. Among patients for whom pomalidomide was added, 1 had no response to daratumumab/IMiD and progressed at the beginning of the third cycle; 1 responded for 8 consecutive cycles, achieving a VGPR, and then progressed; and 2 achieved an MR and are still on treatment after 3 cycles of therapy. Both patients for whom lenalidomide was added achieved a PR after the first cycle of therapy and are still on treatment (Figure 1). The duration of response was 2 to 8 months, and although the follow-up is relatively short, 4 patients are still on therapy. Thus, 5 out of 6 patients achieved at least a MR or better to the combination of 2 drugs to which they were previously refractory. No patient experienced significant toxicity with the combination.

This is the first report regarding the reintroduction of a previously failed IMiD in daratumumab-refractory patients while keeping daratumumab as a backbone, without changing its dose or schedule. Our patients had progressed on standard-dose IMiD/dexamethasone and not on lower doses (ie, maintenance). Although the numbers are small, the activity in patients refractory to both agents, including pentarefractory patients, was significant, providing a proof of principle of the potential synergistic

effect of IMiDs with daratumumab, which can potentially overcome refractoriness to both. By adding the most recent IMiD to which the patients were refractory prior to daratumumab, it was shown that it is the combination that is active and not the mere introduction of a more potent IMiD. IMiDs can potentiate the effect of monoclonal antibodies (ie, daratumumab or other antiCD38) by enhancing T-cell– and natural killer cell–dependent antimyeloma activity, but additional mechanisms may be involved. Reduction of CD38 expression may be a mechanism of resistance to daratumumab, but IMiDs may enhance plasma cell CD38 expression, leading to increased activity of anti-CD38 antibodies.[20] However, a recent study indicated that CD38 expression is reduced after daratumumab, even when lenalidomide is given, at least in part through trogocytosis, but is independent of the response; thus, CD38 reduction alone is probably not a sufficient mechanism of daratumumab resistance.[21] Another potential mechanism may involve CD38 as a marker or mechanism of resistance to immunotherapy. This hypothesis is based on recent observations in lung tumors in which increased CD38 expression acted as an additional checkpoint in patients treated with checkpoint inhibitors.[22] In this case, increased CD38 expression after IMiDs could be a mechanism or marker of resistance to IMiDs, and anti-CD38 may act by eliminating or diminishing this effect. Daratumumab induces clonal $CD8^+$ T-cell expansion that may contribute to clinical responses.[10] Potential loss of this response in progressing patients may be recaptured after the reintroduction of IMiDs. Another potential mechanism could involve the reemergence of IMiD-sensitive clones after an IMiD-free period. However, these hypotheses need to be further and prospectively investigated. Our report provides the first indication that daratumumab and IMiDs could act synergistically by unique mechanisms, overcoming resistance to both classes, and their combinations could be the backbone of myeloma therapy across several different lines of therapy, which should be explored further in future clinical trials.

Authorship

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ORCID profiles: E.K., 0000-0001-8191-5832; M.A.D., 0000-0001-8990-3254.

Correspondence: Meletios Athanasios Dimopoulos, Department of Clinical Therapeutics, National and Kapodistrian University of Athens, 80 Vas. Sofias Ave 11528, Athens, Greece; e-mail: mdimop@med.uoa.gr.

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