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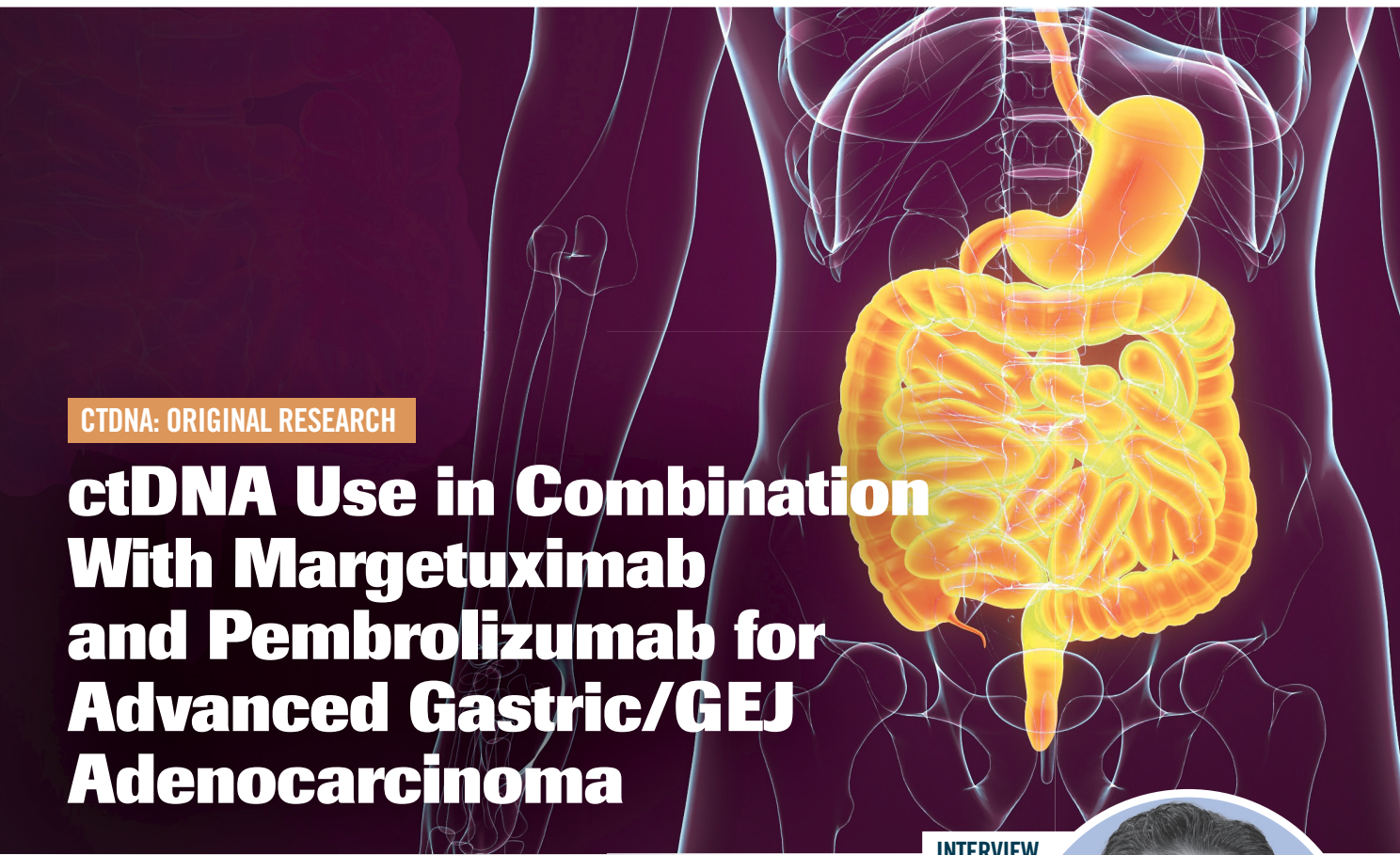

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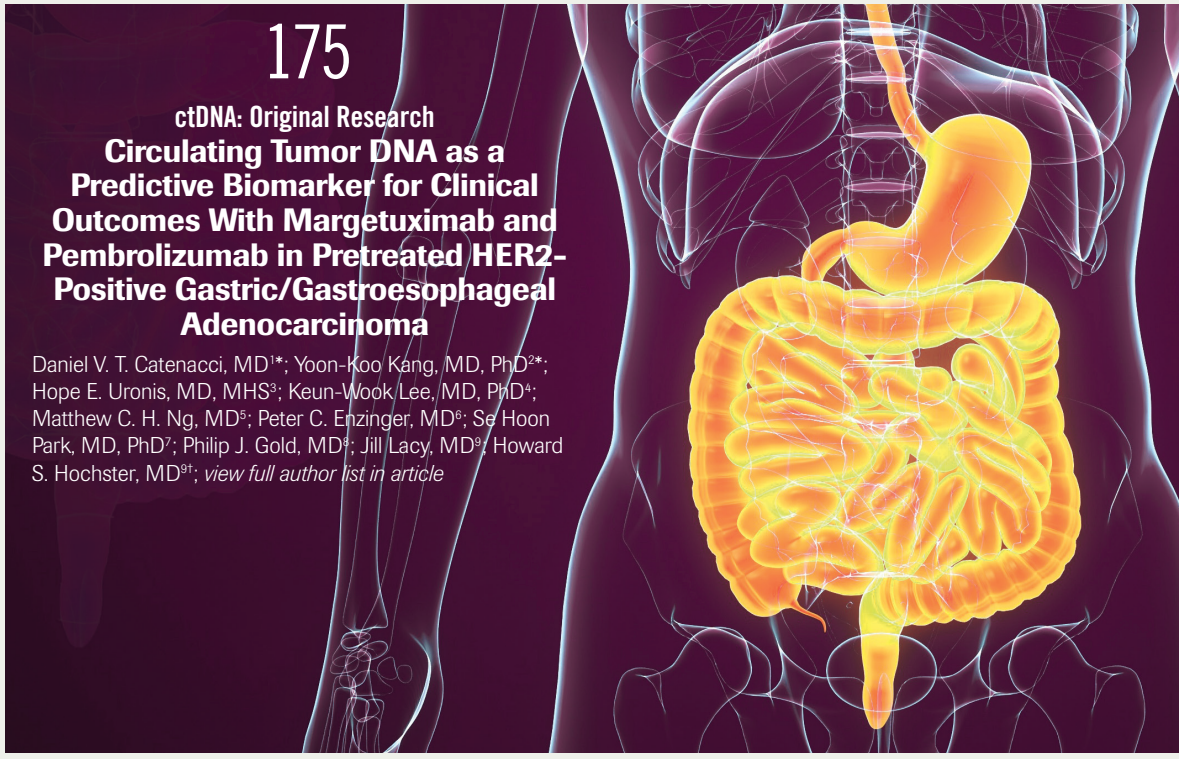

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OUR BOARD MEMBERS HAVE BEEN BUSY! TAKE A LOOK TO SEE WHAT THEY HAVE BEEN UP TO.

Hematologic Malignancies Tumor Chair

C. Ola Landgren, MD, PhD

Landgren recently published data that highlight whole-genome sequencing through genetic evolution for classical Hodgkin lymphoma. The study, which was published in *Blood Cancer Discovery*, found that when Hodgkin and Reed-Sternberg cells were isolated using fluorescence-activated cell sorting plus whole-genome sequencing may provide further insight into the disease.

Gynecologic Oncology Breast Cancer Editorial Board Member

Tari King, MD

During the 2023 International Conference on Surgical Cancer Care, King moderated the Breast Great Debate. The topic was on the surgeon's role in locoregional management of stage IV breast cancer. Anthony Lucci Jr, MD, was on the pro side and Mehra Golshan, MD, was on the con side.

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EDITORS NOTE

In the January issue, our Letter to Readers titled "Increasing Breast Cancer Diagnosis in Rural Areas and the Evolving Access to Health Care" incorrectly spelled Minh-Tri Nguyen, MD's, name. The correction has been made and updated on our website.

PRACTICAL, PEER-REVIEWED PERSPECTIVES
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Burnout: Which Way Out?

Burnout and the related morale injury it causes are characterized by physical and/or emotional exhaustion, depersonalization, and decreased effectiveness. Burnout is all too common in physicians and is estimated to affect at least 50% of physicians at some point in their career.[1] Many systemic risk factors contribute to this epidemic, including high patient volumes, increased administrative burden, lack of "user-friendly" electronic medical records, and lack of organizational infrastructure. Personal risk factors include being female, not having a spouse or partner, and being of younger age.

Oncologists are particularly at risk for burnout due to the difficult patient population we treat, continuous exposure to life-threatening illnesses, and psychological distress.

By now we can all identify burnout and stress. The more important question is what to do about it. Physician wellness starts with us: getting the rest we need, eating a healthy diet, exercising, doing activities that are not work related, and identifying and reducing unnecessary stress. The harder part is, how can we get the health care system to recognize stress in physicians and work with us on modifications to decrease the stress and burnout?

There is only so much any 1 physician can do on their own to reduce stress without infrastructure modifications. Research comparing the effectiveness of individual vs organizational interventions suggests that institutional interventions are much more effective than individual approaches alone, but both approaches when used together are the most effective in reducing burnout.[2]

How can health care professionals improve the systemic infrastructure that contributes to burnout? We need to work with the health care organization to build system-level interventions aimed at reducing environmental stressors and improve the workplace infrastructure support. One example of a program with such a design is the University of Colorado APEX (Awesome Patient Experience) teamwork model, which incorporates medical assistants to decrease administrative burdens on providers. After this system was implemented, the physician burnout rate was reduced from 53% to 13%.[3]

In addition, a thorough evaluation of the necessity of all online learning modules and excess meetings and committees and a reevaluation of patient volumes per provider are needed to move toward the future. Another example of an available program to help institutions is the American Medical Association STEPS Forward.[4] This program recommends 9 strategies—engagement of leadership, acknowledgment and routine of longitudinal burnout assessments, creation of infrastructure for implementation of individual and system-level interventions, workflow efficiency, reduction in administrative burdens, support for the health of the workforce, strengthening of local leadership, tracking organizational costs of burnout, and routine assessment of interventions—to promote organizational health and employee well-being.

The most important aspect of improving burnout is for physicians to work with the administrative and health care teams and to advocate for themselves. Medicine is a team sport, and all the players need to work together for the same goal. ■

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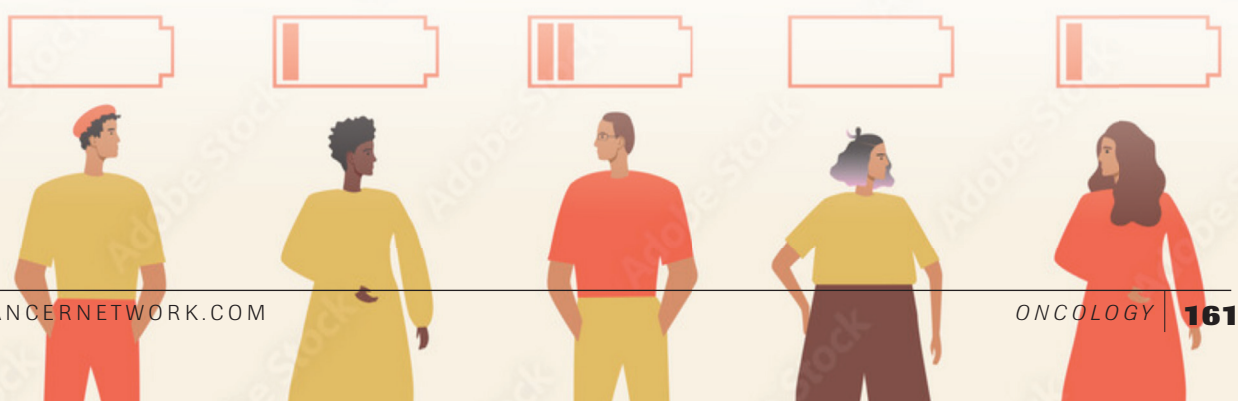

MEET OUR EXPERT

Robert L. Coleman, MD, FACOG, FACS, is a gynecologic oncologist at Texas Oncology, chief scientific officer at The US Oncology Network, and cochair of the Physicians' Education Resource® (PER®) *14th Annual* International Symposium on Ovarian Cancer and Other Gynecologic Malignancies ™.

Advancement Continues in 'Go-to' Strategies for Gynecologic Cancer

"Even in well-resourced countries, there are disparities in exposure to treatments; some of these are rooted deeply in social determinants of health and represent a very complex problem of providing equal access."

Future research efforts in the gynecologic cancer space should center on diversity in clinical trials, combined modality types, and surgical research, according to Robert L. Coleman, MD, FACOG, FACS.

In an interview with *ONCOLOGY*®, Coleman discussed the future of gynecologic cancers and the importance of attending and engaging in meetings such as the *14th Annual* International Symposium on Ovarian Cancer and Other Gynecologic Malignancies. Additionally, he touched upon the need for multidisciplinary care in the space and the barriers that need to be overcome before patients can receive the best possible care.

Q: What are the major trends in gynecologic cancer, and what do you think will be the overarching theme for the year?

COLEMAN: As in most years, [we will focus on the] continued evolution of more customized drug development as [new] treatments continue to populate the landscape of all our major diseases. I wouldn't want to diminish the other types of research that are ongoing right now, such as diversity and inclusion–type research, surgical research, and combined modality research. With respect to surgery, a lot of what we're doing is deescalating.

[With] the evolution of the PARP inhibitors, along with bevacizumab [Avastin] in ovarian cancer and cervical cancer, and then the arrival of immunotherapy for cervical cancer, we've seen a dramatic change in the way we approach these diseases. At the meeting, we'll have an opportunity to highlight new compounds and new approaches as we look at the antibody-drug conjugates, oncological viruses, and other more targeted, directed approaches based on genomic sequencing.

Q: How will newly approved agents in this space factor into testing and multidisciplinary approaches to care?

As [far as] testing goes, we do a poor job as a global medical community. For those of us who are close to this, it's hard to understand why patients don't [undergo] comprehensive genomic sequencing for every disease in every state setting.

In ovarian cancer, we've known for years that *BRCA* mutations such as *BRCA1/2* are important for familial-associated breast, ovarian, and prostate cancer, and maybe some other tumors such as pancreatic [cancer]. Even in the United States in 2023, we still know that a significant chunk of patients are not being tested [upon receiving] a new diagnosis. We have our work cut out for us.

Fortunately, education opportunities such as this [symposium] give us another venue [in which] to get in front of practitioners. I mean [all] practitioners: not just the doctors, but also the office staff and the nursing team, because frequently they're the ones on the front lines making a lot of recommendations and decisions on the approach to care for patients.

Q: What are some current barriers impeding access to optimal care?

Even in well-resourced countries, there are disparities in exposure to treatments; some of these are rooted deeply in social determinants of health and represent a very complex problem of providing equal access. We know that equal access does not occur, and there's not just 1 reason why that's the case.

In resource-constrained areas, where patients [do not] have access to those additional therapies after progression, it makes it very difficult to understand the long-term treatment effect for something that happened very early in the treatment [time span].

Q: Why should clinicians attend meetings such as the Ovarian Cancer Symposium?

The landscape is changing fast. One of the most important things we can do is to identify the knowledge and treatment gaps that exist. A lot of what we thought was the norm—the go-to strategies—are changing. Understanding the rationale for ongoing trials, understanding the implication of newly reported results, and understanding how clinical trials are constructed are all components of a conference that you can't get by reading a book; you need to hear the discussion.

That's what's beautiful about this meeting; there's an opportunity for experts to disagree on things that happen all the time in our group. At the Gynecologic Oncology Group Foundation, we frequently have conversations where we don't agree. [At these conferences,] we weigh the individual components outlined in a specific trial result, and [you] just can't get that [granularity] outside of venues [such as this] where you can have that kind of interaction. ■

The Management of Relapsed and Refractory Multiple Myeloma

Zhubin J. Gahvari, MD, MS[1]; and Natalie S. Callander, MD[1]

ABSTRACT

The treatment of patients with relapsed and refractory multiple myeloma has become increasingly complex due to the rising number of available therapies. Patients are also increasingly exposed to, and refractory to, multiple classes of therapy at the time of progression. Patients who are at an early point in their myeloma disease course are likely to have several effective options, but choices and prognosis are limited for relapsing patients who are more heavily pretreated, particularly if they are at least triple-class refractory. When selecting the next line of therapy, it remains essential to consider patient comorbidities and frailty as well as treatment history and disease risk. Fortunately, the myeloma treatment landscape continues to evolve with the development of therapies directed toward new biologic targets, such as B-cell maturation antigen. These new agents, including bispecific T-cell engagers and chimeric antigen receptor T-cell therapy, have shown unprecedented efficacy in late-line myeloma and will be increasingly used at earlier time points. Novel combinations of currently approved treatments, including quadruplets and salvage transplantation, also remain important options for consideration.

PERSPECTIVE

James J. Driscoll, MD, PhD; and James Ignatz-Hoover, MD, PhD page 166

Introduction

Multiple myeloma (MM) is a plasma cell malignancy that remains incurable, but survival is increasing due to ongoing development of new therapies. The median survival of a patient with newly diagnosed MM is estimated to be between 5 and 8 years.[1] Historically, the treatment of newly diagnosed MM has focused on fitness for autologous transplant, with recent changes due to the use of monoclonal antibodies, quadruplets, and intensified consolidation and maintenance to try to increase depth and duration of response and overcome high-risk disease features. The ever-expanding landscape of antimyeloma therapies provides more options for the next line of treatment at the time of disease relapse. It can be challenging for clinicians to integrate the results of clinical trials that have differing eligibility criteria from their patient's clinical situation to choose the "best" next line of therapy upon myeloma progression. This article will provide an overview of the current approach to treating patients with relapsed and relapsed/refractory multiple myeloma (RRMM), with a focus on practical decision-making and emerging therapeutic options.

Definition of Relapsed Myeloma

Relapsed myeloma is defined as disease progression after response to initial treatment.[2] The current standard definition for progressive myeloma was last updated by the International Myeloma Working Group (IMWG) in 2016.[3] Changes in laboratory parameters, imaging findings, or new clinical features can be utilized as criteria for progressive disease (**Table 1**).[3] IMWG guidelines state that, ideally, the documentation of progression involves consecutive discrete measurements of a parameter; they also suggest that serum free light chains be utilized only if serum and urinary monoclonal protein are unmeasurable. In practice, a patient who relapses with a new clinical feature, such as hypercalcemia or renal insufficiency, should be treated

urgently. Patients with low-risk MM, with low-level biochemical recurrence—ie, less than the IMWG bar—can often wait some time before new treatment begins. RRMM implies that a patient meets the definition of progression either during therapy or within 60 days of their last treatment.

Molecular Testing

Newly diagnosed MM has been clinically subclassified on the basis of recurrent cytogenetic abnormalities, some with prognostic implications.[4,5] Ultimately, the revised international staging system (R-ISS) incorporated deletion 17p, t(4;14), and t(14;16) as the relevant genetic markers for high-risk myeloma.[6] Additional abnormalities that convey poorer prognosis include t(14;20) and gain (≥3 copies)/amplification (≥4 copies) 1q.[7] Gene expression profiling can identify additional high-risk signatures, but it is not widely available.[8] Analysis of next-generation sequencing (NGS) of whole genome data from a data repository determined that patients with newly diagnosed MM with either biallelic inactivation of *TP53* or amplification of *CKS1B* in the setting of ISS3 disease had an extremely poor prognosis, with a median overall survival (OS) of 20.7 months. While this specific finding was coined "double-hit" myeloma,[9] this terminology can be generalized. Copresence of the other high-risk genetic features, including gain of 1q concurrent with t(4;14), t(14;16), or del(17p),[10] also has an additive deleterious prognostic effect.[11] Although some mutations appear to be "founder" events, patients can acquire new mutations, including deletions of p53 or gain of 1q, at relapse.[12-14] Furthermore, due to technical issues, important mutations with treatment implications, such as t(11;14), are sometimes missed, particularly if fluorescence in situ hybridization (FISH) testing is not performed on sorted plasma cells. Therefore, we recommend repeating FISH analysis at the time of relapse.

Minimal residual disease (MRD) testing in MM can be performed on bone marrow aspirate to assess for depth of disease response at an increased sensitivity.[3,15] As data regarding the importance of sustained MRD after initial treatment continue to grow, there is emerging evidence that attainment of MRD negativity following treatment for relapse appears to be important as well. Attainment of MRD negativity was associated with prolonged progression-free survival (PFS) and OS in patients with RRMM in a meta-analysis; MRD negativity may overcome high cytogenetic risk.[16] Achievement of sustained MRD negativity,[17] and the combination of MRD negativity with complete response,[18] are both associated with prolonged PFS in patients with RRMM. Loss of MRD negativity is associated with an increased risk of disease progression.[19,20] The optimal management of patients who have lost MRD negativity but have not yet met criteria for progression is unknown, and the role of preemptive therapy is being evaluated in clinical trials.[21,22]

Stratification for Treatment Selection

Both disease-related and patient-related factors must be considered when deciding on an approach to treatment at

TABLE 1. International Myeloma Working Group (IMWG) Criteria for Myeloma Disease Progression[3]

IMWG criteria for progressive multiple myeloma

Increase of 25% from lowest measured response value in:

- Serum M protein, absolute increase ≥0.5 g/dL
  - Absolute increase ≥1 g/dL if minimum M protein ≥5 g/dL
- Urine M protein, absolute increase ≥200 mg/day
- Difference between involved and uninvolved free light chains, absolute increase ≥10 g/dL
  - Light chain criteria can only be used if no measurable serum or urine M protein
- Bone marrow plasma cell percentage regardless of baseline status, absolute increase ≥10 %
  - Bone marrow criteria can only be used if no measurable light chains or serum or urine M protein

On imaging:

- Discovery of new lesions
- Increase of ≥50% in sum of products of maximal perpendicular diameters of more than 1 lesion
- Increase of ≥50% in the longest diameter of previous lesion that was >1 cm on short axis measurement
- Increase of ≥50% in circulating plasma cells (minimum of 200 cells/μL) if there are no other measures of disease

IMWG criteria for clinical progression of multiple myeloma

Detection of new or increasing end-organ dysfunction (such as CRAB: calcium elevation, renal insufficiency, anemia, bone abnormalities) related to underlying myeloma

- Hypercalcemia (>11 mg/dL)
- Rise in serum creatinine by ≥2 mg/dL
- Decrease in hemoglobin by ≥2 g/dL not related to another cause
- New bone lesions or soft tissue plasmacytomas
- Increase in size of bone lesion or plasmacytoma by ≥50% and ≥1 cm as measured by sum of products of maximal perpendicular diameter
- Hyperviscosity due to paraprotein

PERSPECTIVE BY

James J. Driscoll, MD, PhD[1,2]; and James Ignatz-Hoover, MD, PhD[1]

Emerging Strategies to Manage Relapsed and/or Refractory Multiple Myeloma

Multiple myeloma (MM) remains a malignancy that is largely incurable but highly treatable. The prognosis for patients with MM has improved substantially over the past 2 decades with the introduction of therapeutics that have improved patient quality of life and prolonged overall survival (OS). However, nearly all patients with MM ultimately relapse, including those who have experienced a complete response to initial therapy.[1,2] Clinicians are challenged to determine how to treat relapsed and/or refractory MM (RRMM) by integrating previously administered therapies, patient comorbidities, potential treatment-related adverse events, putative benefit of emerging agents, financial toxicity, and patient wishes. In the current issue, Gahvari and Callander provide a comprehensive overview of the current approach to treating patients with RRMM with a focus on practical decision-making and the role of emerging therapeutic options.

At diagnosis, the genetic, epigenetic, metabolic, and cellular architecture of MM is complex and heterogeneous across patients. Somatic mutations, chromosomal translocations, deletions, and epigenetic modifications within each patient are evident and drive clonal evolution. Clonal diversity continuously evolves throughout the treatment continuum, and patients harbor multiple subclones.[3] Disease progression leads to the emergence of drug resistance and eventually to relapsed/refractory disease.[4] Relapsed and progressive MM acquires additional mutations and genetic alterations that render the disease more resistant, leading to progressively shorter durations of remission or response to each salvage therapy. The heterogeneity of myeloma cells within each patient highlights the need to simultaneously target multiple pathways.

Selection of an optimal strategy at relapse is more complicated because at least 10 classes of drugs have been FDA approved for MM, including alkylators, steroids, proteasome inhibitors, histone deacetylase inhibitors, nuclear export inhibitors, immunomodulatory drugs (IMIDs), monoclonal antibodies (mAbs), peptide-drug conjugates, chimeric antigen receptor (CAR) T cells, and bispecific T-cell engagers (BiTEs). With the exception of CAR T cells and BiTEs, these antimyeloma drugs have been combined in doublet, triplet, or quadruplet regimens and have been delivered, when appropriate, antecedent to autologous stem cell transplantation (ASCT).[2]

As Gahvari and Callander point out, there is currently no consensus treatment for patients with RRMM. While multiple regimens have been approved, none have been evaluated head to head, and individual registry trials have enrolled different patient populations with dissimilar treatment histories. Collectively, these studies demonstrate the benefit of a triplet over doublet regimen at relapse. Based upon results from the phase 3 POLLUX study (NCT02076009), the addition of daratumumab to lenalidomide and dexamethasone significantly lengthened progression-free survival (PFS) among patients with RRMM.[5] For patients with newly diagnosed MM who were ineligible for ASCT, the risk of disease progression or death was significantly lower among those who received daratumumab, lenalidomide and dexamethasone than among those who received lenalidomide and dexamethasone alone.[6] While daratumumab/lenalidomide/dexamethasone demonstrated superior OS, the study utilized an IMID-naive patient population. Regimens that combined mAbs—isatuximab/carfilzomib/dexamethasone, and daratumumab/carfilzomib/

the time of myeloma progression. An important consideration is the potential harm to the patient from myeloma-related morbidity if a response is not achieved or is not durable. Patients with high-risk disease, or who are heavily pretreated, are at risk for early relapse and transient responses to systemic therapy, and they should be considered for clinical trials, novel agents, and cellular therapy, or the standard-of-care options with the highest probability of effectiveness. However, disease risk needs to be weighed against patient comorbidities, frailty, and patient preferences and goals.

dexamethasone—also demonstrated improved PFS in early-line relapsed disease. These regimens merit consideration in lenalidomide-refractory and mAb-naive patients. There are also limited data on the ideal or recommended sequence of mAbs in the RRMM setting. Isatuximab can directly induce apoptosis in myeloma cells, whereas daratumumab cannot induce cell death without being combined with cross-linking agents. Isatuximab also modulates CD38 enzymatic activity more effectively than daratumumab and may benefit daratumumab-refractory patients, whereas elotuzumab may have reduced efficacy following daratumumab-based therapy.

Patients who are actively relapsing after exposure to multiple lines of therapy (ie, late-line relapse) are likely to be at least triple-class refractory and penta-class exposed. Hence, historically, the likelihood of a response to the next line of therapy is low, regardless of the agent. Bendamustine, as monotherapy or combined with proteasome inhibitors or IMIDs, can elicit responses. Selinexor-based therapy has some benefit. Intensive regimens including PACE (cisplatin, doxorubicin, cyclophosphamide, and etoposide) or hyperfractionated cyclophosphamide-based regimens (with or without bortezomib or daratumumab) can serve as a temporizing bridge to the next line of therapy for aggressive relapses.

The scarcity of trials that have integrated the first salvage regimen into the assessment of frontline therapies to define optimal treatment sequencing in homogeneous or similar patient populations is also problematic. The management of RRMM is made even more complex with the advent of quadruplet therapy for transplant-eligible patients. The phase 2 GRIFFIN trial (NCT02874742) highlighted deeper and more sustained responses with upfront daratumumab plus lenalidomide, bortezomib, and dexamethasone than with lenalidomide, bortezomib, and dexamethasone alone.[7] Earlier exposure to daratumumab will significantly affect the approach to second-line therapy.

Gahvari and Callander highlight exciting cellular and immunotherapeutics that constitute the next frontier for the management of RRMM. Real-world experience with FDA-approved regimens in specific populations should further guide therapy beyond subgroup analysis of registry trials. For example, the management of patients with primary refractory MM vs those being treated for relapsed MM after a treatment-free interval is of particular importance and may mandate a more cellular immunologic approach compared with current approaches. Also, integrating high-risk cytogenetics (eg, 1q gain) into treatment decisions has not been uniformly applied in trials or real-world practice. Two B-cell maturation antigen (BCMA)-directed CAR T-cell agents, idecabtagene vicleucel and ciltacabtagene autoleucel, have shown efficacy in patients previously challenged with 3 lines or more of therapy.[8,9] Teclistamab is a BiTE that targets CD3-positive T cells and BCMA-positive myeloma cells and is now FDA approved for patients who have received 3 prior lines of therapy.[10] GC012F is an autologous BCMA-CD19 dual-targeting CAR T-cell therapy. In a phase 1 single-arm study, deep and durable responses as well as a favorable safety profile were reported with GC012F in patients with heavily pretreated RRMM. Based on these results, the safety and feasibility of GC012F were tested frontline for patients with newly diagnosed with MM who are high risk and transplant eligible.[11] Again, a favorable safety profile and high efficacy, with a 100% objective response rate and 100% minimal residual disease negativity, were reported.

Broader adoption of cellular therapies within the global immuno-oncology market requires careful consideration of costs, and unique toxicities, product quality standardization, and overcoming barriers to minimize production delays. It requires solving health care–related cost-to-value, coverage restrictions, and reimbursement issues. Finally, the broad administration of cellular therapies and the expansion of precision medicine approaches to treat MM will impact patient distribution to community oncologists, academic health centers, and specialized clinical centers that are designed to streamline CAR T-cell production, distribution, and administration. The past 2 decades have seen significant progress in MM, but the future therapeutic landscape may be even more promising, as more effective agents that overcome RRMM are developed and are better tolerated. ■

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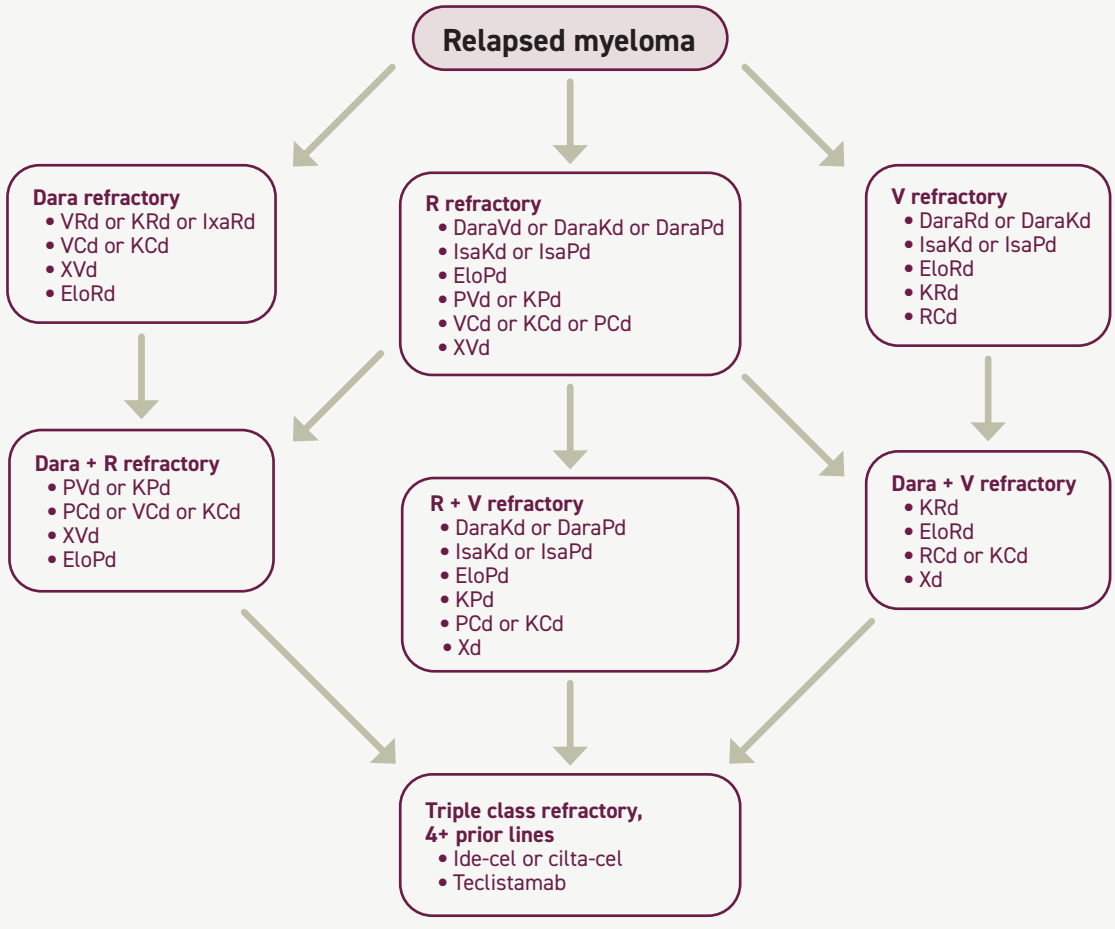
cancernetwork.com/4.23_Driscoll

High-risk Disease Features

Although myeloma risk stratification is traditionally performed at the time of diagnosis, the R-ISS classification has been shown to continue to convey prognostic information if recalculated in patients at the time of relapse.[23] In addition to R-ISS status, high-risk genetic features, and lactate dehydrogenase levels,[24] other findings associated with poorer prognosis at relapse include the presence of extramedullary disease,[25] circulating plasma cells and plasma cell leukemia,[26] and renal insufficiency.[27]

FIGURE. **Relapsed Myeloma Treatment Algorithm**



Relapsed myeloma considerations

- At any relapse: Evaluate for clinical trial.
- Elderly or frail: Consider starting with dose reduction or doublet and utilizing monoclonal antibody.
- Autologous stem cell transplant: Consider if no previous transplant or if time to progression is after first transplant at least 3 years.
- Aggressive relapse: If not refractory, consider K, Isa or Dara, immunomodulator.
- If t(11;14), then venetoclax.

C, cyclophosphamide; cilta-cel, ciltacabtagene autoleucel; d, dexamethasone; Dara, daratumumab; Elo, elotuzumab; ide-cel, idecabtagene vicleucel; Isa, isatuximab; Ixa, ixazomib; K, carfilzomib (Kyprolis); P, pomalidomide; R, lenalidomide (Revlimid); V, bortezomib (Velcade); X, selinexor (Xpovio).

An additional risk factor is rapid time to progression after previous therapy. Early relapse after induction therapy or transplant is ominous and portends a poor prognosis even when receiving modern antimyeloma therapy; this phenomenon can occur even in the absence of high-risk cytogenetics.[28] Relapse within 12 months of initial therapy has been associated with a median OS ranging between 21 months and 26 months in data from 2 different studies, compared with median OS of 91 months or longer for patients with later relapses.[29,30]

Effect of Previous Treatment History

Relapsed myeloma is characterized by a progressively shorter duration of response with each subsequent line of therapy.[31] However, as triplet combinations and maintenance therapy have become more common in

myeloma care, patients are more likely to be exposed or refractory to the main classes of antimyeloma treatment at the time of progression. Newer terminology to describe such patients includes (1) triple-class exposed or refractory, meaning exposed or refractory to an immunomodulator (IMID), proteosome inhibitor (PI), and anti-CD38 monoclonal antibody, and (2) penta-class exposed or refractory, meaning exposed or refractory to 2 IMIDs, 2 PIs, and an anti-CD38 antibody.[32] The prognosis of such patients is dismal: In a multicenter retrospective analysis, triple-class refractory patients experienced a median PFS and OS of 2.8 months and 10.3 months respectively, while penta-class refractory patients experienced a median PFS and OS of 2.5 months and 6.9 months, respectively.[33]

Elderly and Frail Patients

Frailty can be defined as an age-associated decline in multiple physiologic systems leading to increased vulnerability in the setting of stressors.[34] The optimal treatment of frail patients with relapsed myeloma can be challenging, and a balance needs to be struck between dose intensity and toxicity. Frail patients with myeloma are at increased risk for treatment-related adverse events causing premature treatment discontinuation and poorer survival.[35] Randomized prospective studies enrolling elderly, frail, and/or transplant-ineligible patients have focused on the newly diagnosed only. Although scoring systems have been developed to help clinicians assess frailty and guide treatment decisions, frailty scores have been validated only for survival outcomes in patients newly diagnosed with MM and not in those with relapsed disease.[36-39]

In recent clinical trials of RRMM, elderly and/or frail patients have benefited when newer therapies are added to established backbones. Separate subgroup analyses of trials comparing carfilzomib-, pomalidomide-, daratumumab-, and isatuximab-based triplets with doublets suggest a preserved efficacy and survival advantage.[40-43] However, it is possible that older patients enrolled in these trials are not particularly representative of the general elderly RRMM population, who would be less likely to meet the rigorous entry criteria for such trials.

Frail patients may lose the opportunity to benefit from the most effective therapies if those therapies are not offered early: A real-world study found an attrition rate of more than 40% at every instance of disease progression throughout the entire MM course of transplant-ineligible patients.[44] When in doubt regarding a patient's frailty, it may be preferable to start treatment at a lower dose or doublet and escalate if tolerated or there are improvements in functional status.[45]

Therapy Selection

Regimens for relapsed myeloma can be classified on the basis of their approval: for early-line relapse (1-3 prior lines of therapy) or late-line relapse (4 or more prior lines of therapy). Unsurprisingly, published clinical trial data that are used to guide treatment decisions are not applicable to all real-world situations.[46] If available, clinical trial opportunities should be pursued for all patients.

Early-Line Relapse

Most patients will have previously received induction therapy with a triplet combination containing steroids and 2 of the following: a PI, IMID, or anti-CD38 antibody. However, some patients are now receiving antibody-based quadruplets in the front line. Patients presenting with renal failure at the time of their myeloma diagnosis may have received a cyclophosphamide-based regimen. Some patients may have received up-front autologous transplant, and many will have received maintenance therapy regardless of whether they underwent transplant.[47]

The main principles of choosing a new regimen are to (1) utilize at least one therapeutic class not used in induction, (2) avoid agents to which a patient is not sensitive or is refractory, and (3) account for toxicities caused by previous treatment. Therapies that were previously effective and have not been utilized recently, to which the patient is not refractory, can be retrialed.[48] An algorithmic approach to selecting therapy is shown in the **Figure**.

Data from recent randomized phase 3 trials, all of which highlight approved combinations for early-line relapse, are shown in **Table 2**.[49-69] These regimens all demonstrate the benefit of utilizing a triplet over a doublet at relapse if tolerated. It is hard to directly compare the listed triplet regimens because none were evaluated head to head and the trials all enrolled at least somewhat different patient populations with different previous treatment histories. Daratumumab/lenalidomide (Revlimid)/dexamethasone (DaraRd), daratumumab/bortezomib (Velcade)/dexamethasone (DaraVd), carfilzomib (Kyprolis)/lenalidomide/dexamethasone (KRd), elotuzumab/lenalidomide/dexamethasone (EloRd), and isatuximab/pomalidomide/dexamethasone (IsaPd) all showed a benefit in median OS as compared with their control arms.[51,54,59,61,63] The other trials do not yet have mature OS data for reporting purposes, except for the comparison of lenalidomide/dexamethasone (Rd) with ixazomib/Rd, which showed a PFS but not an OS benefit to adding ixazomib, possibly due to differences in treatment received between the 2 arms after progression.[69] While DaraRd demonstrates the best OS outcome numerically, the study involved a patient population that was almost completely IMID unexposed, emphasizing why many expert panels recommend utilizing IMID-based combinations in patients sensitive to them. It should also be noted

that bortezomib in DaraVd was stopped after 8 cycles to minimize toxicity. Regimens combining monoclonal antibodies with carfilzomib—namely, isatuximab/carfilzomib/dexamethasone (IsaKd) and daratumumab/carfilzomib/dexamethasone (DaraKd)—demonstrated the second- and third-longest reported PFS, respectively, among patients with myeloma with early-line relapse, although OS data have yet to be reported for either combination. These 2 regimens merit strong consideration in patients who are lenalidomide refractory and have not yet been treated with a monoclonal antibody.

In general, if a patient has not been previously exposed or demonstrated resistance to a monoclonal antibody, they should receive one as part of their next line of therapy. However, there are limited data on the next best choice of regimen if a patient has previously received a monoclonal antibody. There are also limited data on the ideal sequencing of monoclonal antibodies. Isatuximab may have modest clinical benefit in daratumumab-refractory patients,[70] while elotuzumab-based regimens may display reduced efficacy when administered after daratumumab-based therapy.[71] Many experts recommend not re-treating with an anti-CD38 antibody, unless the patient is more than 6 months from the last dose and was not refractory.

Another area of uncertainty is selection of therapy for patients with high-risk disease, as not all trials incorporate the same definition of high-risk cytogenetics, use the same threshold for cytogenetic positivity, or utilize R-ISS staging. Many trials are also missing cytogenetic data on significant numbers of patients; for example, in the trial comparing carfilzomib/dexamethasone (Kd) with DaraKd, cytogenetic data were not available for more than 50% of enrolled patients. With the

TABLE 2. **Data From Recent Randomized Phase 3 Trials of Early-Line Relapsed Myeloma[46-69]**

Trial	Total pts[a]	Median (range) prior lines of treatment[a,b]	Prior treatments	ORR	Median PFS (mo)	Median OS (mo)
POLLUX: DaraRd vs Rd[49-51]	569	1 (1-11)	Refract IMID: 7.4% Refract PI: 21.8%	92.9% vs 76.4%	44.5 vs 17.5	67.6 vs 51.8
CASTOR: DaraVd vs Vd[52-54]	498	2 (1-10)	Refract R: 28.3% Prior PI: 68.5%	84.6% vs 63.2%	16.7 vs 7.1	49.6 vs 38.5
CANDOR: DaraKd vs Kd[55,56]	466	2 (1-3)	Refract R: 33.0% Refract V: 29.0%	84.3% vs 72.7%	28.6 vs 15.2	NR
APOLLO: DaraPd vs Pd[57]	304	2 (1-5)	Refract R: 79.3% Refract PI: 48.0%	68.9% vs 46.4%	12.4 vs 6.9	NR
ASPIRE: KRd vs Rd[58,59]	792	2 (1-3)	Refract IMID: 21.8% Nonresp PI: 14.9%	87.1% vs 66.7%	26.1 vs 16.6	48.3 vs 40.4
ELOQUENT-2: EloRd vs Rd[60,61]	646	2 (1-4)	Refract T: 9.9% Refract V: 21.8%	78.5% vs 65.5%	19.4 vs 14.9	48.3 vs 39.6
ICARIA-MM: IsaPd vs Pd[62,63]	307	3 (2-4)	Refract R: 92.5% Refract PI: 75.9%	63.0% vs 33.3%	11.5 vs 6.5	24.6 vs 17.7
IKEMA: IsaKd vs Kd[64,65]	302	2 (1-3)	Refract R: 32.8% Refract PI: 33.1%	86.6% vs 82.9%	35.7 vs 19.2	NR
OPTIMISSM: PVd vs Pd[66]	559	2 (1-4)	Refract R: 69.9% Refract PI: 13.2%	82.2% vs 50.0%	11.2 vs 7.1	NR
BOSTON: XVd vs Vd[67]	402	2 (1-3)	Prior R: 38.3% Prior V: 69.4%	76.4% vs 62.3%	13.93 vs 9.46	NR
TOURMALINE-MM1: IxRd vs Rd[68,69]	722	1 (1-3)	Refract T: 12.5% Refract PI: 1.7% Prior V: 69.0%	78.3% vs 71.5%	20.6 vs 14.7	53.6 vs 51.6

[a]Combined between experimental and control groups.
[b]Estimated.

d, dexamethasone; dara, daratumumab; elo, elotuzumab; IMID, immunomodulator; isa, isatuximab; ix, ixazomib; K, carfilzomib (Kyprolis); mo, months; nonresp, nonresponder to; NR, not reached; ORR, overall response rate; OS, overall survival; P, pomalidomide; PFS, progression-free survival; PI, proteosome inhibitor; pt, patient; R, lenalidomide (Revlimid); refract, refractory to; T, thalidomide; V, bortezomib (Velcade); X, selinexor (Xpovio).

TABLE 3. **Antimyeloma Regimens From Smaller Studies[75-81]**

Trial	Total pts	Median (range) prior lines	Prior treatment	ORR	Median PFS (mo)
Ven-d[75]	31	5 (2-12)	Refract IMID: 87.1% Refract PI: 87.1% Refract Dara: 87.1%	48.4%	10.8[c]
ELOQUENT-3: EloPd vs Pd[76,77]	117[a]	3 (2-8)[a,b]	Refract R: 87.2%[a] Refract PI: 80.3%[a]	53.3% vs 26.3%	10.3 vs 4.7
KPd[78]	47	2 (1-3)	Refract R: 100% Refract V: 44.7%	61.7%	10.3
PCd vs Pd[79]	70[a]	4 (2-12)[a,b]	Refract R: 100%[a] Refract V: 74.3%[a] Refract K: 41.4%[a]	64.7% vs 38.9%	9.5 vs 4.4
KCd[80]	75	2 (1-3)	Prior IMID: 81.3% Prior PI: 86.7%	85.3%	17.0
VCd vs RCd[81]	155[a]	1[a,b]	Prior IMID: 51.6%[a] Prior T: 42.6%[a] Prior V: 51.0%[a]	64.5% vs 79.7%	16.3 vs 18.6

[a]Combined between experimental and control groups.
[b]Estimated.
[c]Reported as TTP and not PFS.

C, cyclophosphamide; d, dexamethasone; Elo, elotuzumab; IMID, immunomodulator; K, carfilzomib (Kyprolis); mo, months; ORR, overall response rate; P pomalidomide; PFS, progression-free survival; PI, proteosome inhibitor; pt, patient; R, lenalidomide (Revlimid); refract, refractory to; TTP, time to progression; V, bortezomib (Velcade); ven, venetoclax; X, selinexor (Xpovio).

increasing recognition of the negative prognostic implications of gain 1q, more trials are incorporating this into their classification of high-risk cytogenetics. One post hoc subgroup analysis suggested that isatuximab may be able to overcome the negative impact of isolated gain 1q.[72] Other subgroup analyses have suggested that selinexor may be efficacious in patients with 17p deletions as well as in those with *RAS*-mutated myeloma; neither analysis was statistically powered.[73,74] While these findings are intriguing, they will need to be confirmed prospectively before they can be used to guide treatment decisions.

Other Regimens

Table 3 lists examples of other effective antimyeloma regimens that have not been studied in large or randomized trials.[75-81] Some have been studied at later relapse but can be effective earlier as well. Of note, venetoclax is highly active in myeloma with t(11;14), and venetoclax-based therapy should be strongly considered in this subset of patients. Although venetoclax with bortezomib and dexamethasone was associated with increased mortality among unselected patients with RRMM, it was recognized that the subset of patients with t(11;14) experienced improved outcomes.[82] These findings were later confirmed in a phase 1/2 trial of venetoclax and dexamethasone.[75]

The carfilzomib/pomalidomide/dexamethasone (KPd) regimen is efficacious in relapsed myeloma,[78,83,84] as are pomalidomide/cyclophosphamide/prednisone[85] or dexamethasone (PCd)[86-88] and carfilzomib/cyclophosphamide/dexamethasone (KCd),[80,89] but none have been analyzed in randomized controlled studies. Although frequently utilized in the first-line, bortezomib or lenalidomide can be used in relapsed disease, although they have rarely been compared prospectively. One phase 3 trial did compare fixed-duration bortezomib/cyclophosphamide/dexamethasone (VCd) with lenalidomide/cyclophosphamide + dexamethasone (RCd) in patients at first relapse; RCd had higher response rates but similar PFS.[81] Of the trials listed in **Table 2**, the only combination with a demonstrated OS benefit is elotuzumab pomalidomide/dexamethasone, which led to a median OS of 29.8 months compared with 17.4 months with pomalidomide/dexamethasone (Pd) alone.

Salvage Transplantation

For all patients who are candidates for autologous transplant and have not received this frontline therapy, transplant is recommended as second-line therapy based on data from multiple studies showing similar OS comparing delayed transplant with frontline transplant.[90-92] While a new course

TABLE 4. **Published Phase 2 Trial Results of BCMA-Directed Therapies**

Trial	Total pts	Median (range) prior lines	Prior treatment	ORR	Median PFS (mo)
DREAMM-2 Belantamab mafodotin[112,113]	97	7 (3-21)	TCR: 100%	32.0%	2.8
KarMMa Ide-cel[117]	128	6 (3-16)	TCR: 84.4% PCR: 25.8%	73.4%	8.8
CARTITUDE-1 Cilta-cel[118,121]	97	6 (4-8)	TCR: 87.6% PCR: 42.3%	97.9%	NR; 54.9% at 27 mo
MajestTEC-1 Teclistamab[124]	165	5 (2-14)	TCR: 77.6% PCR: 30.3%	63.0%	11.3

BCMA, B-cell maturation antigen; cilta-cel, ciltacabtagene autoleucel; dara, daratumumab; ide-cel, idecabtagene vicleucel; K, carfilzomib (Kyprolis); mo, months; NR, not reached; ORR, overall response rate; P, pomalidomide; PCR, penta-class refractory; PFS, progression-free survival; pt, patients; R, lenalidomide (Revlimid); TCR, triple-class refractory; V, bortezomib (Velcade).

of systemic therapy is often administered prior to salvage transplant, in retrospective studies the use of reinduction has not been associated with improved duration of response or OS after transplant.[93,94] Lack of response to reinduction may predict for poorer outcomes[94] and this knowledge may be helpful for planning therapy after transplant. However, even patients with chemorefractory disease can still derive benefit from salvage first transplant.[95]

Patients relapsing after an autologous transplant can sometimes benefit from a salvage second transplant, although prospective randomized data are limited. One UK study showed that second transplant was associated with superior OS compared with oral cyclophosphamide, but it did not utilize novel therapies as a comparator.[96] Data from a German study that enrolled patients relapsing after 1 to 3 prior lines showed no differences between Rd followed by second transplant vs Rd alone: Median PFS was similar at 20.7 months vs 18.8 months. However, 29% of patients assigned to second transplant did not receive it, potentially confounding results.[97] Retrospective analyses have indicated that a second transplant is more likely to benefit patients with treatment-sensitive disease and those who had a remission that lasted at least 36 months after first transplant[98,99]; it even can be efficacious in patients refractory to daratumumab.[100] It is important to develop a plan for the next therapy after recovery from second transplant to forestall disease relapse; for example, a Center for International Blood and Marrow Transplant Research analysis showed that maintenance therapy post second transplant was associated with significantly prolonged PFS and OS.[101]

For select patients, salvage allogeneic transplant can be considered, although its use may be declining given the continued new therapeutic options for myeloma. Longitudinal analyses of patients with newly diagnosed disease,[102,103] as well as of those with RR disease,[104] who receive allogeneic transplant show that a subset of patients experience long-term disease control. The first results of a prospective study of allogeneic transplant in high-risk MM, including relapsed disease, were recently published and demonstrated an estimated 24-month PFS of 52% and nonrelapse mortality of 11.7%.[105] While transplant-related morbidity and mortality remain a concern, allogeneic transplant should be considered for young and fit patients while their myeloma is still chemosensitive, given the expectation that all other treatment options will eventually be exhausted. Patients considering this option should be treated at transplant centers with experience in this clinical setting, ideally as part of a clinical trial.

Late-Line Relapse

Patients exposed to multiple lines of therapy who relapse are likely to be triple-class refractory and penta-class exposed. In this setting, the likelihood of a response to the next line of therapy historically has been low irrespective of the specific agent, although the response rate may be higher with carfilzomib- or alkylator-based therapy.[32]

Bendamustine has been studied as monotherapy as well as in combination with PIs and IMIDs and can be a useful option.[106] If not previously used, selinexor-based therapy was associated with an increased chance of benefit vs retrying classes of agents previously used.[107] For aggressive disease relapses, high-dose cytotoxic chemotherapy[108-110] can be employed to obtain temporary disease control as a bridge to the next line of therapy. In addition to pursuing clinical trial options, B-cell maturation antigen (BCMA)–directed therapy should be strongly considered if not already used, and will be discussed further in the next section.

Emerging and Novel Therapies

BCMA, a member of *TNFRSF17*, is highly expressed on MM cells, promotes MM cell survival and proliferation, and is minimally expressed elsewhere.[111] The first commercially available therapy targeting BCMA was belantamab mafodotin, an antibody-drug conjugate composed of a BCMA antibody linked to a microtubule-disrupting drug. As a single agent, belantamab mafodotin showed activity in a very heavily pre-

TABLE 5. **Select Ongoing Trials of Newer Antimyeloma Therapies in RRMM**

Trial	Trial identifier	Trial design	Patient population
KarMMa-2 Ide-cel	NCT03601078	Phase 2, multiple cohorts, including newly diagnosed and relapsed MM	For relapsed MM: TCE and at least 3 prior lines or 1 prior line with early relapse
KarMMa-3 Ide-cel vs SOC (DaraPd, DaraVd, IxaRd, Kd, or EloPd)	NCT03651128	Randomized phase 3	TCE and 2-4 prior lines
CARTITUDE-2 Cilta-cel	NCT04133636	Phase 2, multiple cohorts, including newly diagnosed and relapsed MM	For relapsed MM: 1-3 prior lines including PI and R or 1 line including PI and IMID with early progression or TCE and prior BCMA-directed therapy
CARTITUDE-4 Cilta-cel vs PVd or DaraPd	NCT04181827	Randomized phase 3, 2 arms	Refract R, 1-3 prior lines
MajesTEC-3 Teclistimab/Dara vs DaraVd or DaraPd	NCT05083169	Randomized phase 3, 2 arms	1-3 prior lines including PI and R, if only 1 prior line must be R refractory
MagnetisMM-3 Elranatamab	NCT04649359	Phase 2, 2 cohorts	TCR, cohorts stratified by exposure to prior BCMA-directed therapy
MagnetisMM-5 Elranatamab vs Elranatamab/Dara vs DaraPd	NCT05020236	Randomized phase 3, 3 arms	At least 1 prior line including PI and R
MonumenTAL-1 Talquetamab	NCT04634552	Phase 1/2, 3 cohorts	At least 3 prior lines; cohorts stratified by prior T-cell redirection therapy exposure
EXCALIBER-RRMM IberDara-d vs DaraVd	NCT04975997	Randomized phase 3, multiple iber dose levels	1-2 prior lines of therapy
CAMMA 1 Cevostamab Cevostamab-Pd Cevostamab-Dara-d	NCT04910568	Phase 1b, multiple cohorts	At least 1 or at least 2 prior lines depending on cohort

BCMA, B-cell maturation antigen; cilta-cel, ciltacabtagene autoleucel; d, dexamethasone; Dara, daratumumab; Elo, elotuzumab; iber, iberdomide; ide-cel, idecabtagene vicleucel; Ixa, ixazomib; K, carfilzomib (Kyprolis); MM, multiple myeloma; P, pomalidomide; PI, proteosome inhibitor; R, lenalidomide (Revlimid); RRMM, relpased/refractory MM; SOC, standard of care; TCE, triple-class exposed; TCR, triple-class refractory; V, bortezomib (Velcade).

treated population of patients with RRMM, with a median duration of response of 11.0 months, some deepening of response observed over time, and a median OS of 13.7 months. In patients who achieved at least a partial response, the median OS was not reached, with 88% alive at 1 year. The unique treatment-related toxicity is keratopathy, experienced by 72% of patients at any grade, with a grade 3/4 rate of 46%.[112,113] While numerous clinical trials are currently evaluating belantamab mafodotin in combination with other agents,[114,115] belantamab mafodotin was pulled from the US market in November 2022 due to failure of belantamab monotherapy to show significant improvement in PFS compared with Pd in a phase 3 randomized trial involving patients with RRMM.[116]

The next commercially approved BCMA-directed therapies were both chimeric antigen receptor (CAR) T-cell products: idecabtagene vicleucel (ide-cel) in March 2021[117] followed by ciltacabtagene autoleucel (cilta-cel) in February 2022[118]. Both ide-cel and cilta-cel demonstrated unprecedented outcomes compared with non–BCMA-directed therapies for such heavily pretreated patients[119,120] and demonstrated low rates of grade 3/4 cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS), although 6% of patients receiving cilta-cel suffered treatment-related parkinsonism.[121] An indirect comparison between the 2

CAR T-cell products suggests that cilta-cel has higher efficacy.[122] Availability for commercial ide-cel and cilta-cel remains very constrained, and most centers are not yet able to provide this therapy to the majority of eligible patients. Downsides to CAR T-cell therapy include the time delay required for manufacturing, during which time patients can experience disease progression and morbidity.[123] Furthermore, it remains to be seen whether real-world outcomes with ide-cel and cilta-cel match those reported in clinical trials. The authors' experience has been that patients with rapidly progressive MM do not experience meaningful or durable responses to ide-cel.

The first bispecific T-cell engager to treat myeloma, teclistamab, was granted accelerated approval in late 2022. Findings from a phase 2 study of teclistamab, which targets CD3 and BCMA, showed favorable outcomes compared with the other available BCMA-directed therapies, including an overall response rate of 63% and median duration of response of 18.4 months, with minimal rates of grade 3/4 CRS or ICANS.[124] Teclistamab, ide-cel, and cilta-cel are all approved for patients with RRMM who have been at least triple-class exposed with at least 4 prior lines of therapy.

Optimal selection and sequencing of BCMA-directed therapy remain to be determined, although BCMA-directed bispecific T-cell engagers have been shown to be efficacious in patients relapsing after a BCMA-directed CAR T product.[125] Patients who urgently need a response should be preferentially considered for teclistamab given the time delay from leukapheresis to manufacturing to receipt of a CAR T product, as well as current supply constraints. One potential advantage of ide-cel and cilta-cel is that they are a single treatment; patients will experience a treatment-free interval afterward.

Table 4 lists the reported pivotal trials for the aforementioned BCMA-directed therapies,[112,113,117,118,124] while **Table 5** lists ongoing clinical trials involving these and other novel agents, specifically evaluating their utility in earlier lines of therapy and in combination with other agents. Iberdomide is a modulator of cereblon with increased potency compared with lenalidomide and pomalidomide.[126] Talquetamab is a bispecific T-cell engager targeting CD3 and GPRC5D; the latter is a transmembrane protein with high expression in myeloma cells.[127] GPRC5D is also being evaluated as a target for CAR T.[128,129] Cevostamab is a bispecific T-cell engager targeting CD3 and FCRL5, which is a membrane protein restricted to B cells that has increased expression on MM cells.[130,131]

Another area of active interest is quadruplet therapy, particularly in patients with early-line relapse or high-risk disease before they have become multiclass refractory. Ongoing combinations under evaluation include elotuzumab with IsaPd (NCT04835129), elotuzumab with KPd, selinexor with DaraVd, daratumumab with KPd, and daratumumab with ixazomib and Pd.[132-135] Also, a series of selinexor-based combinations are under investigation as part of the multiarm phase 1b/2 STOMP trial (NCT02343042).[136-138]

Conclusions

The treatment of RRMM continues to evolve with the approval of new classes of therapy. Even so, certain principles stay constant, and it remains important to assess all patients on the basis of their disease risk as well as their fitness and comorbidities. The variety of approved anti-MM regimens means that patients with early-line relapses will have several effective regimens to choose among, although the lack of direct comparisons among regimens makes it hard to definitively rank regimens in terms of superiority. Frail patients can still benefit from triplet regimens, while patients with high-risk MM, including double-hit myeloma, continue to benefit less than standard-risk patients from the currently available regimens. Increased use of MRD-based end points to assess response and dynamically reassess risk, as well as the approval of quadruplets for relapsed disease, are likely, pending results of ongoing trials.

The management of late-stage RRMM remains challenging, as any response to therapy tends to be transient. BCMA-directed therapy has shown great promise, with some patients experiencing durable responses. As CAR T products remain very supply-limited, bispecific T-cell engagers and other off-the-shelf immunotherapy products will likely be increasingly employed. Current clinical trials are clarifying the optimal sequencing of these agents in the context of other anti-MM treatments, but it will not be surprising if therapies directed toward BCMA and other novel targets will be deployed at earlier time points and in combination with current standard-of-care agents. These advances indicate that the survival for patients with RRMM will continue to improve with time. ■

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Circulating Tumor DNA as a Predictive Biomarker for Clinical Outcomes With Margetuximab and Pembrolizumab in Pretreated HER2-Positive Gastric/Gastroesophageal Adenocarcinoma

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ABSTRACT

PURPOSE. To assess the ability of circulating tumor DNA (ctDNA)-based testing to identify patients with HER2 (encoded by *ERBB2*)-positive gastric/gastroesophageal adenocarcinoma (GEA) who progressed on or after trastuzumab-containing treatments were treated with combination therapy of anti-HER2 and anti–PD-1 agents.

METHODS. ctDNA analysis was performed retrospectively using plasma samples collected at study entry from 86 patients participating in the phase 1/2 CP-MGAH22-05 study (NCT02689284).

RESULTS. Objective response rate (ORR) was significantly higher in evaluable *ERBB2* amplification–positive vs –negative patients based on ctDNA analysis at study entry (37% vs 6%, respectively; $P = .00094$). ORR was 23% across all patients who were evaluable for response. *ERBB2* amplification was detected at study entry in 57% of patients (all HER2 positive at diagnosis), and detection was higher (88%) when HER2 status was determined by immunohistochemistry fewer than 6 months before study entry. ctDNA was detected in 98% (84/86) of patients tested at study entry. Codetected *ERBB2*-activating mutations were not associated with response.

CONCLUSIONS. Current *ERBB2* status may be more effective than archival status at predicting clinical benefit from margetuximab plus pembrolizumab therapy. ctDNA testing for *ERBB2* status prior to treatment will spare patients from repeat tissue biopsies, which may be reserved for reflex testing when ctDNA is not detected.

KEYWORDS. gastric/gastroesophageal adenocarcinoma; HER2; ctDNA; and margetuximab plus pembrolizumab

BACKGROUND

The human epidermal growth factor receptor 2 (HER2) protein is a receptor tyrosine-protein kinase, encoded by erythroblastic oncogene B2 (*ERBB2*), normally involved in the proliferation and division of cells. The *ERBB2* gene is often amplified and overexpressed in solid tumors, and solid tumors that are HER2-positive are aggressive. In patients with HER2-positive solid tumors, HER2-targeted therapies have become the standard of care in multiple tumor types, including breast, gastric and gastroesophageal (including gastric/

gastroesophageal adenocarcinoma [GEA]), salivary, and colorectal cancers. In GEA in particular, HER2-targeted therapies are associated with improved outcomes; however, patients eventually progress, often due to the loss of *ERBB2* amplification and subsequent loss of dependence on the *ERBB2*-signaling pathway.[1,2] As subsequent treatment options include both alternative HER2-targeted and nontargeted therapies, it is critical to distinguish between patients whose tumors retain HER2 dependence and those that are HER2 independent; therefore, repeated testing is necessary to determine *ERBB2* amplification status. Traditional assessment of *ERBB2* amplification—the most common cause of HER2 dependence in GEA—requires tissue samples, but repeated biopsies are not feasible for many patients. Moreover, HER2 status has been reported to vary among different regions in a tumor in an individual patient with GEA,[3-5] so HER2 status cannot necessarily be captured by a single tissue biopsy.

Cell-free DNA (cfDNA)-based liquid biopsies have the potential to address these limitations by assessing genomic information from across the entire tumor volume from a peripheral blood draw. The feasibility of such assessment specifically for tumor-derived *ERBB2* amplification has been previously demonstrated in multiple indications, including in GEA, both in terms of concordance with tissue-based testing and of predicting the clinical benefit of HER2-targeted therapies.[3-13] Moreover, circulating tumor–derived DNA (ctDNA) levels have also been shown to correlate with disease burden in GEA,[4] and changes in ctDNA levels are able to predict clinical benefit from both HER2-targeted therapies[7,10,12,14-16] and immunotherapies.[17-20] cfDNA is present in plasma and serum, and it is seen in higher quantities in patients with cancer.[21] ctDNA is the fraction of cfDNA shed into circulation by apoptotic and necrotic tumor cells in patients with cancer.[22] Approaches for detection of the ctDNA fraction in cfDNA include targeting of defined changes in single alterations or use of next-generation sequencing–based comprehensive genomic profiling (including targeted and whole exome/genome sequencing) to interrogate all possible aberrations in DNA; detection of the ctDNA fraction also permits assessment of clonal differences in tumor cell populations.[23]

Margetuximab is approved in combination with chemotherapy for patients with HER2-positive metastatic breast cancer who have received 2 or more prior anti-HER2 regimens, at least 1 of which was for metastatic disease. Margetuximab is also being investigated in patients with HER2-positive GEA. Margetuximab is an anti-HER2 monoclonal antibody that is designed to have increased binding to the activating fragment crystallizable (Fc) receptor FcγRIIIA (CD16A) and decreased binding to the inhibitory Fc receptor FcγRIIB (CD32B) compared with trastuzumab, delivering more potent antitumor responses via antibody-dependent cellular cytotoxicity.[6,24] Pembrolizumab is an anti–PD-1 monoclonal antibody approved in combination with trastuzumab-, fluoropyrimidine-, and platinum-containing chemotherapy for the first-line treatment of patients with locally advanced, unresectable or metastatic HER2-positive GEA.[7]

In this study, we assessed the ability of cfDNA-based testing to identify patients with HER2-positive GEA who progressed on or after trastuzumab-containing treatments and who were likely to benefit from combination therapy

TABLE. **IHC/FISH and ctDNA Results Are Concordant in Tissue and Liquid Biopsies Collected Less Than 6 Months Apart**

Subgroup analysis of PPA for ctDNA vs IHC/FISH		HER2+ by IHC/FISH		
		All patients	<6 months*	≥6 months*
		n = 86	n = 16	n = 70
PPA		**57%**	**88%**	**50%**
ctDNA detected	*ERBB2* amp+, n	48	14	34
	ERBB2 amp−, n	36	2	34
ctDNA not detected		2	0	2

amp, amplification; ctDNA, circulating tumor DNA; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; PPA, positive percentage agreement.

PPA was assessed for plasma-based *ERBB2* amp status relative to tissue-based HER2 status. All patients in this cohort (n = 86) were identified as HER2 positive by IHC or FISH at initial diagnosis. *ERBB2* amp (positive or negative [+ or −]) status was determined by Guardant360 CDx analysis of all patients from plasma samples collected at study entry, prior to treatment. Subgroups consisted of patients whose archival HER2 testing preceded study entry by <6 months (n = 16) or ≥6 months (n = 70). PPA is expressed as the percentage of *ERBB2* amp+ patients of all patients with ctDNA detected.

*Time interval between archival tissue testing and pretreatment ctDNA analysis.

of anti-HER2 and anti–PD-1 agents, based on pretreatment presence of *ERBB2* amplification and additional ctDNA-based biomarkers.

METHODS

Patients in CP-MGAH22-05 ctDNA study

We performed a retrospective ctDNA analysis on prospectively collected samples from patients with previously treated, locally advanced, unresectable or metastatic HER2-positive GEA in a single-arm, open-label, phase 1b/2, dose-escalation and cohort expansion study (CP-MGAH22-05; NCT02689284).[6] Patients must have had histologically proven unresectable locally advanced or metastatic HER2-positive GEA and received prior treatment with trastuzumab. Tissue biopsy HER2 status was based on local testing as described previously.[6] HER2 positivity was assessed using immunohistochemistry (IHC), defined as IHC3 positive or IHC2 positive, and amplified fluorescence in situ hybridization (FISH), defined as a HER2 to chromosome enumeration probe 17 ratio of 2.0 or more.[25] Tissue biopsy PD-L1 status, although not used for enrollment, was determined centrally by IHC, and PD-L1 positivity was defined as a combined positive score of 1 or greater.[6] In the dose-escalation phase, 9 patients were treated: 3 received margetuximab at 10 mg/kg intravenously (IV) plus pembrolizumab at 200 mg IV every 3 weeks, and 6 received the recommended phase 2 dose (RP2D) of margetuximab at 15 mg/kg plus pembrolizumab at 200 mg IV every 3 weeks. An additional 86 patients were enrolled in the phase 2 cohort expansion and received the RP2D. Plasma ctDNA was available from 86 of the 95 patients enrolled (the phase 2 cohort expansion), of whom 83 received the RP2D of margetuximab and pembrolizumab and 3 received margetuximab at 10 mg/kg and pembrolizumab.

The study was conducted according to International Conference on Harmonization Guideline for Good Clinical Practice and all applicable local and national regulations and ethical principles in accordance with the Declaration of Helsinki. All patients provided written informed consent. The protocol and the informed consent document were reviewed and approved by the institutional review board or independent ethics committee of each participating center before study initiation.

ctDNA analysis

Plasma samples collected from patients in the phase 2 cohort expansion were tested for ctDNA using the Guardant360 CDx.[26] Guardant360 is an FDA-approved[27] test that detects single nucleotide variants (SNVs; 73 or 74 genes), copy number amplifications (19 genes), insertion-deletion alterations (23 genes), and fusions (6 genes) in plasma from patients with solid tumors (full list of genes provided in the **Supplement**). ctDNA sequencing data was analyzed on the Guardant360 bioinformatics pipeline as previously described.[4,12] Briefly, gene-level copy number alterations were determined after probe-level unique molecule normalization, diploid baselining, background noise correction, and comparison with established reporting decision thresholds.[12] ctDNA detection was defined as presence of 1 or more somatic alterations per patient sample.

Statistical analysis

The objective response rate (ORR) was defined as the proportion of patients who achieved a confirmed complete response (CR) or confirmed partial response (PR). The clinical benefit rate (CBR) was defined as the proportion of patients who achieved a confirmed CR or confirmed PR or stable disease. The CBR was not a prespecified trial end point and was later selected as a marker of clinical benefit because this provided a larger sample size than the population of responders (CR/PR). Categorical data were summarized by the number and percentage of patients for each variable. Fisher's exact test was performed to compare binary end points between 2 groups divided according to ORR or CBR. A *P* value less than .05 was considered significant.

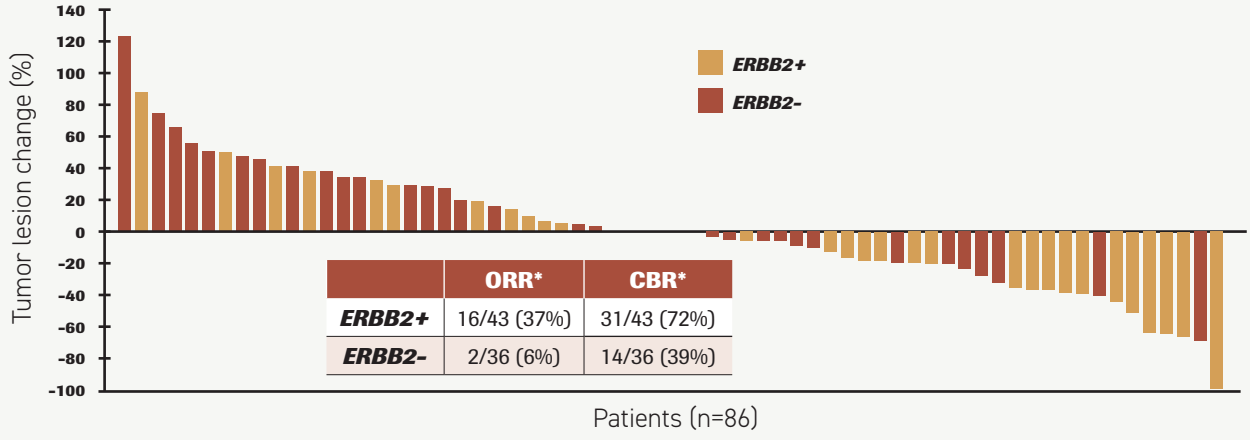
RESULTS

Concordance between *ERBB2* amplification detection using ctDNA and IHC/FISH

A total of 86 patients, 83 of whom received the RP2D of margetuximab (15 mg/kg) plus pembrolizumab and 3 of whom received margetuximab (10 mg/kg) plus pembrolizumab, had ctDNA testing at study entry, after progression on standard-of-care HER2-targeted therapy. At baseline, 84 of 86 patients (98%) had more than 1 reportable genomic alteration detected using ctDNA. As reported in the first publication from this trial,[6] *ERBB2* gene amplification was detected at study entry in ctDNA in 57% (48 of 84) of patients with *ERBB2* (HER2) amplification detected at the time of diagnosis using IHC or FISH (**Table**). The apparent lower rate of *ERBB2* gene amplification detection using ctDNA may reflect the loss of *ERBB2* amplification after progression on trastuzumab, which has been reported in 30% to 60% of initially HER2-positive gastric cancer cases, or it may reflect false-negative ctDNA results due to low tumor shedding.[4,28] To address the first possibility, we first asked whether the *ERBB2* amplification detection rate was higher among patients with HER2 IHC status determined from repeat biopsies collected post progression on trastuzumab. HER2 positivity for 9 of 86 patients had been determined from repeat tissue biopsies; these were not required but were performed following trastuzumab failure. This subset of 9 patients permitted a small but direct comparison of HER2 IHC and *ERBB2* amplification status due to lack of intervening trastuzumab treatment and

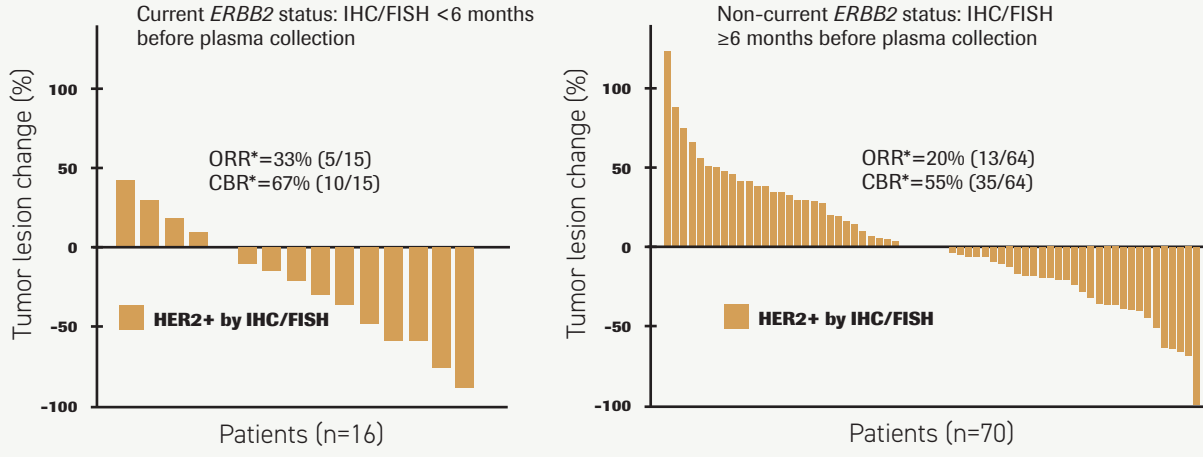
FIGURE 1.

1A. **Greater Clinical Benefit for *ERBB*-Postive and *ERBB*-Negative Patients by ctDNA at Study Entry**



	ORR*	CBR*
ERBB2+	16/43 (37%)	31/43 (72%)
ERBB2-	2/36 (6%)	14/36 (39%)

1B. **Greater Decrease in Tumor Lesion Change and Trend Toward Higher Clinical Benefit With Current vs Noncurrent *ERBB* Status**



Currency of *ERBB2* amplification testing is more important than the method for predicting clinical benefit. Analyses were performed for patients with an evaluable response and ctDNA testing at study entry (n = 79). (A) Clinical benefit was achieved in 72% (31/43) vs 39% (14/36) for patients who were *ERBB2* negative using ctDNA at study entry (P = .0058). (B) Clinical benefit was achieved in 67% (10/15) of patients who were currently *ERBB2* positive (using IHC/FISH) as determined at diagnosis and preceding M + P treatment initiation by less than 6 months, compared with 55% (35/64) of patients who were *ERBB2* positive (using IHC/FISH) as determined at diagnosis and preceding M + P treatment initiation by 6 or more months.

BOR, best overall response; CBR, clinical benefit rate (confirmed CR/PR + SD)/(confirmed CR/PR + SD + PD); CR, complete response; ctDNA, circulating tumor DNA; FISH, fluorescence in situ hybridization; receptor 2; IHC, immunohistochemistry; M, margetuximab; NE, not evaluable; ORR, objective response rate; P, pembrolizumab; PD, progressive disease; PR, partial response; SD, stable disease.

*Seven patients were not evaluable for radiographic response, so they were excluded from the calculation of ORR and CBR: four patients had no BOR (no postbaseline tumor assessment occurred) and 3 patients had BOR that was not evaluable (investigators of the postbaseline tumor assessment considered the tumor response to be NE).

short time interval between tissue and liquid biopsy (median, 19 days; range, 1-146). Amplified *ERBB2* was detected in ctDNA at study entry from 8 of the 9 patients for whom repeat tissue biopsies were HER2 positive. Maximum variant allele frequencies (maxVAFs) were 3% or higher for these 8 *ERBB2* amplification-positive cases vs 0.16% for the single *ERBB2* amplification-negative case, suggesting that the negative case was likely a false negative due to low tumor shedding.

Given the small sample size of paired tissue and liquid biopsies without intervening trastuzumab, we also asked whether the *ERBB2* detection rate was higher in patients with a short time interval between tissue testing and plasma collection for ctDNA analysis. True loss of *ERBB2* amplification is a time-dependent biological process, and this should result in a greater difference over time, whereas false negatives by ctDNA should be time-independent. The time between ctDNA testing at study entry and IHC/FISH at diagnosis ranged from a few days to more than 6 years, with some patients having progressed on trastuzumab with multiple combinations of chemotherapy between diagnosis and study entry. Across this range, tissue-ctDNA concordance demonstrated a strong dependence on the length of the interval between tests; the positive percentage agreement for tests performed less than 6 months apart was 88% (14/16) vs 50% (34/68) for tests performed 6 months apart or more ($P = .0099$).

Six months provided a sufficient sample size for the comparison and is aligned with the median progression-free survival (PFS) reported from the phase 3 ToGA trial (NCT01041404) of trastuzumab plus chemotherapy in patients with treatment-naive advanced GEA.[29] To address the question of whether *ERBB2* detection rate was higher among patients with higher tumor shedding, we explored maxVAFs across all 84 patients with ctDNA detected. The dependency of gene amplification detection on high tumor fraction is widely known, and the Guardant360 method for copy number assessment has been described previously, but a distinct ctDNA maxVAF threshold does not exist.[27] For simplicity and the purpose of our analysis, ctDNA maxVAFs below 1% were used to define low tumor shedding. Among patients with ctDNA detected, 42% (15 of 36) of *ERBB2* amplification–negative cases were associated with low tumor shedding (<1% ctDNA maxVAF) vs 10% (5 of 48) of *ERBB2* amplification–positive cases (Fisher exact test, $P = .0015$), confirming the relationship between tumor fraction and copy number. However, all but 1 patient with *ERBB2* amplification–negative tumors also had intervening trastuzumab-based treatment and a long time interval (median, 451 days; range, 167-2429) between HER2 IHC and ctDNA analysis; this makes it difficult to distinguish false negatives (due to low tumor shedding) from true negatives (due to HER2 loss).

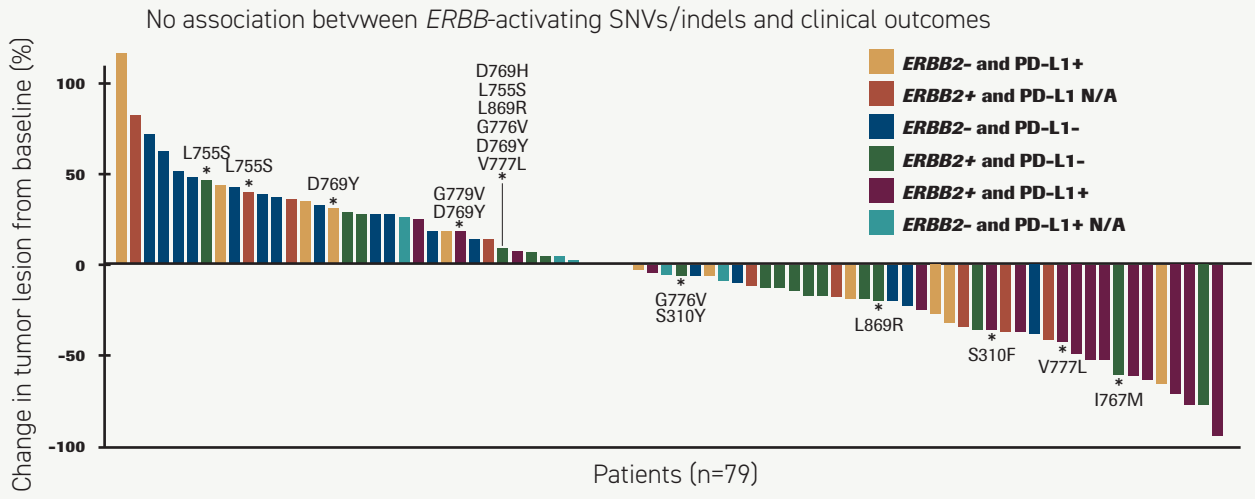
Current *ERBB2* status predicts response

Rates of objective response and clinical benefit from margetuximab and pembrolizumab combination therapy in patients from the CP-MGAH22-05 study were reported previously.[6] Updated treatment duration and outcome data became available in July 2021. Among the 79 patients who were evaluable for response and had ctDNA testing at study entry, ORR and CBR were significantly higher in patients who were *ERBB2* amplification positive than in those who were negative: ORR, 37% (16 of 43) vs 6% (2 of 36); $P = .00094$; CBR, 72% (31 of 43) vs 39% (14 of 36); $P = .0058$ (**Figure 1A**). To assess the importance of timing independent of the test method, we also compared the ORR between cases that were identified as HER2-positive less than 6 months before study entry vs the entire cohort, in which all cases were identified as HER2-positive at diagnosis or after progression on trastuzumab and in some cases years before study entry. Although ORR was numerically higher in cases with current HER2-positive status, the difference was not significant, as the full cohort likely includes cases with HER2 loss due to prior trastuzumab-based treatment (**Figure 1B**). These results suggest that the timing of HER2 or *ERBB2* amplification testing is more important than the method (IHC or ctDNA) for predicting clinical benefit.

VAFs and maxVAF

Baseline maxVAF values were explored for potential association with clinical outcomes. Negative correlations between maxVAF and PFS and between maxVAF and overall survival (OS) exist ($r = –0.229$ and $r = –0.270$, respectively) and are significant ($P = .0394$ and $P = .014$, respectively), indicating that lower tumor shedding, based on maxVAF as a proxy, is associated with longer PFS and OS. Numerically lower maxVAF at baseline (defined as ≤10% for the purpose of the analysis) was associated with longer median PFS and OS than higher maxVAF at baseline (defined as >10%), although the associations with PFS (median of 84 days vs 43 days, respectively) or OS (median of 423 and 221 days, respectively) were not statistically significant. A similar analysis was performed to ask whether longer PFS or OS were associated with baseline maxVAF of 1% or less. No significant differences in PFS or OS were observed between patients with baseline maxVAF greater than 1% vs 1% or less. Median PFS for patients with baseline maxVAF of 1% or less was 99 days vs 81.5 days for maxVAF greater than 1% (log rank test, $P = .87$). Median OS for maxVAF greater than 1% was 345 days, vs 404 days for maxVAF of 1% or less (log rank test, $P = .09$).

FIGURE 2. **Biomarker and Response**



There was no association between *ERBB2*-activating SNV/indels and clinical outcome. Colors of bars indicate *ERBB2* ctDNA amplification and PD-L1 status. Seven patients for whom the percentage change in tumor lesion from baseline was not calculated are not included in the waterfall plot.
ctDNA, circulating tumor DNA; *ERBB2–, ERBB2* negative; *ERBB2+, ERBB2* positive; indel, insertion-deletion; N/A, not available; PD-L1–, PD-L1 negative; PD-L1+, PD-L1 positive; SNV, single nucleotide variant.
gain-of-function mutation

Co-occurring *ERBB2* SNVs and clinical response

Using ctDNA analysis, all patients were assessed for mutations in 74 genes commonly mutated in cancer, in addition to *ERBB2* amplification. Gain-of-function *ERBB2* SNVs D769Y/H, S310F/Y, L755S, and V777L, may confer resistance to traditional antibody-based anti-HER2 therapies and were detected in 19% (16/84) of patients, all but 1 of whom retained *ERBB2* amplification (**Figure 2**; **Supplement Figure 2**). In the 13 patients evaluable for response, CBR was 69% (9 of 13), suggesting that the drug combination is effective in patients with both *ERBB2* amplification and *ERBB2*-activating SNVs.

Association between baseline ctDNA *ERBB2* amplification status and response

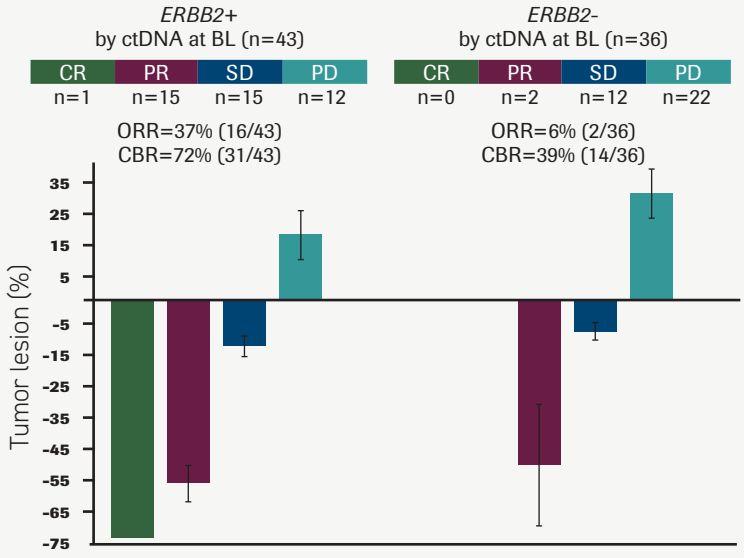
The ORR was significantly higher in patients who were *ERBB2* amplification positive vs negative at study entry (37% vs 6%, $P = .00094$; Figure 1A); however, the magnitude of the change in tumor lesion size was similar between patients who were *ERBB2* amplification positive and those who were *ERBB2* amplification negative at study entry (**Figure 3A**). Tumor shrinkage also was observed in a subset of 7 patients who were *ERBB2* amplification negative at study entry and experienced long treatment duration (**Figure 3B**). Of the 36 patients identified as being *ERBB2* amplification–negative at study entry, 7 were selected for analysis of ctDNA at later treatment time points.

Longitudinal analysis of ctDNA from selected patients

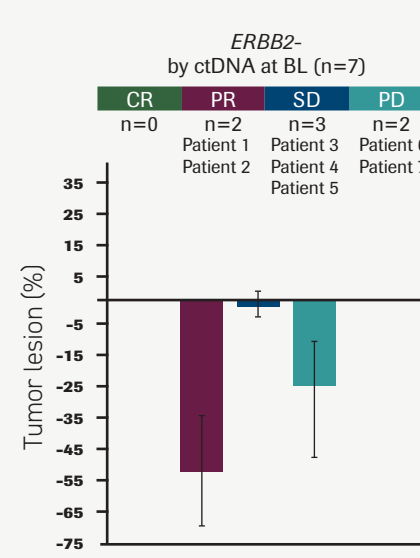
In the 7 selected patients for on-treatment ctDNA analysis, the best overall response varied, but they collectively had long treatment durations; PFS and OS were comparable with those achieved for patients who were *ERBB2* amplification positive at study entry. Statistical analysis of longitudinal ctDNA data vs response or outcomes was not possible due to the small sample size, but details from each case are summarized to speculate on potential explanations for the longer treatment durations of this subgroup. Longitudinal ctDNA fractions of these 7 patients are plotted graphically in **Supplement Figure 1**, and additional details are provided in the **Supplement Table** and the **Supplement**. In 4 of these patients (2, 3, 4, and 6), there was a net decrease or minimal net change in ctDNA from baseline to cycle 4 day 1 (C4D1), consistent with stabilization or tumor lesion shrinkage (best percentage tumor lesion change) and compatible with initial treatment effect. Among the 3 patients with a net increase in ctDNA from baseline to C4D1, the best percentage tumor lesion change was a small decrease (≤10%) for 2 patients (5 and 7) and a somewhat larger decrease (33%) for patient 1. For patients 5 and 7, a potential explanation for the net increase in ctDNA is the presence of additional tumors at C4D1 that were not yet measurable by RECIST v1.1 but, in the aggregate, meaningfully contributed to ctDNA levels, as

FIGURE 3.

3A. **Entire Response-Evaluable Cohort (n=79)**



3B. **Selected Cohort for Longitudinal Analysis**



Magnitude of tumor lesion change in any individual is independent of likelihood of clinical benefit. Shown are the changes in tumor lesion from BL in all response-evaluable patients (A) and in the 7 patients selected for longitudinal analysis (B). Means of best percent tumor lesion change values are shown. Error bars reflect SEM values.

BL, baseline; CBR, clinical benefit rate; CR, complete response; ctDNA, circulating tumor DNA; *ERBB2–, ERBB2* negative; *ERBB2+, ERBB2* positive; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; SEM, standard error of the mean.

has been previously reported.[14-18,30-32] For patient 1, who achieved PR, the apparent increase in ctDNA level was unexpected and should be viewed with caution, as the C4D1 sample input was below the range that is supported for clinical testing. Despite long treatment duration, subclonal *KRAS* and *TP53* SNVs at baseline emerged as dominant clones by end of treatment (EOT) and by C4D1, respectively, for 2 patients (6 and 7) whose best confirmed response was progressive disease (PD) per RECIST 1.1. Patient 6 developed a new lesion with substantial main tumor shrinkage (**Figure 3B**). The tumor of patient 7 enlarged at first assessment but shrunk during subsequent treatment that was received after radiographic PD (Supplement Figure 1; Supplement Table). It is noteworthy that patient 7 was *ERBB2* gene amplification negative before treatment but became positive after radiographic PD (C4D1) and at EOT.

DISCUSSION

Trastuzumab in combination with chemotherapy is the standard therapy for treatment naive HER2-positive GEA; however, most patients who initially benefit from trastuzumab-based therapy develop resistance. As the potential therapeutic options for such patients include both additional HER2-targeted and non-targeted therapies, it is critical to assess whether patients' tumors retain or have lost their HER2 dependence.

In this study, we assessed the ability of ctDNA testing for *ERBB2* amplification to identify previously treated patients with HER2-positive GEA who are likely to benefit from the combination of the anti-HER2 agent margetuximab and the anti–PD-1 agent pembrolizumab. Of all evaluable patients, all of whom were HER2 positive based on tissue biopsies at diagnosis or after progression on trastuzumab-based therapy, only 57% of patients retained detectable *ERBB2* amplification at study entry, consistent with previous reports of loss of HER2 positivity, which ranged approximately from 30% to 60% among previously treated patients with HER2-positive GEA.[33-36] Although a limitation of this study was that tissue-based biomarker information was established using diagnostic specimens obtained before and after trastuzumab treatment, *ERBB2* gene amplification in ctDNA was nevertheless associated with HER2 protein expression as

measured using IHC in a time-dependent manner, with more recent tissue testing demonstrating higher concordance regardless of testing modality. Importantly, we observed that patients with retained *ERBB2* amplification as measured using ctDNA at the time of study entry were more likely to experience an objective response from combined anti-HER2/anti–PD-1 therapy, consistent with previous reports of other anti-HER2 agents.[4,11,13] However, for patients with *ERBB2*-negative disease assessed by ctDNA, potentially because of low ctDNA shed, a biopsy would be preferable to further evaluate HER2 status.

On-treatment ctDNA dynamics have been reported as predictive of benefit from both anti-HER2 therapies[7,10,12,14-16] and immune checkpoint blockade.[17-20] We analyzed on-treatment ctDNA in selected patients without ctDNA *ERBB2* amplification at baseline, and although this analysis is limited by small sample size and lack of correlation to the primary end point of the clinical trial, we found that ctDNA VAF dynamics generally suggested a nonprespecified exploratory end point of clinical response in those patients. Validation in a larger, adequately powered cohort is needed to assess the benefit. In some cases, on-treatment changes in maxVAFs were more powerful predictors of both response and progression than radiographic response alone, consistent with previous reports of pembrolizumab treatment in HER2-positive gastric cancer.[14,17]

Known hotspot mutations reported in all cancers were observed in amplified *ERBB2* alleles in nearly 20% (16 of 84) of patients in this study of previously treated patients with HER2-positive GEA, including S310F, V777L, L755S, and D769Y, which are predicted to be driver mutations.[37,38] *ERBB2* S310F/Y mutations in particular have been associated with poor response to trastuzumab in lung cancer; however, we observed no diminution of efficacy in such patients with *ERBB2* comutated GEA, indicating that the combination of margetuximab plus pembrolizumab remains effective in patients with GEA with both *ERBB2* amplification and *ERBB2*-activating SNVs.[39]

An important limitation of this study is that concurrent ctDNA and tissue testing results were available only for a small subgroup of patients (tissue testing was performed at diagnosis for most of the cohort). As such, these data cannot inform a sufficiently powered comparison of testing methods; however, our primary results do suggest that the currency of testing is more important than the testing modality. In clinical practice, it is likely that the most appropriate testing modality may vary owing to patient- and situation-specific factors, such as access to current tissue and turnaround time.

The longitudinal ctDNA analysis described here for a small subset of patients who were *ERBB2* amplification negative at study entry revealed the emergence of additional alterations on treatment, which could be assessed for potential associations with response in a larger, adequately powered study. Based on The Cancer Genome Atlas classification, gastric cancer–overexpressed HER2 is more frequent in chromosomal instability subtypes, which show marked aneuploidy and focal activation of the receptor tyrosine kinases–RAS (RTK-RAS) pathway and high frequency of *TP53* mutations.[40] A previous study also showed that 5 genes (*CCNE1, PIK3CA, KRAS, CDK4*, and *CDK6*) were concomitantly co-amplified and that some genes, such as *TP53, CDKN2A, KRAS, KIT*, and *PIK3CA*, were concomitantly comutated in HER2-positive gastric cancer.[41] Acquired mutations in *KRAS* (G12D and T35A), *NF1* (N1503S), and *PIK3CA* (E542K and S1008T) and co-amplifications of *BRAF, KRAS, PIK3CA*, and *FGFR1* are believed to likely represent mechanisms of resistance to anti-HER2 therapy.[4]

In conclusion, our results suggest that a personalized treatment strategy based on testing for current *ERBB2* amplification status should be further explored for optimal selection of therapy in patients with GEA who are progressing on trastuzumab-based therapy, to successfully improve outcomes with targeted therapeutics in this disease. As a first choice of modality to identify persistent HER2-driven disease, ctDNA analysis will save patients from receiving repeat biopsies and will expand testing access to patients for whom repeat biopsies are infeasible. However, for patients with no ctDNA detected or patients with an *ERBB2* amplification–negative result and low tumor shedding, reflex testing to repeat tissue biopsy may be useful to further evaluate HER2 status. As such, the difficulty, invasiveness, and inconvenience of obtaining post-progression tissue biopsies, coupled with the predictive value of *ERBB2* amplification as assessed using ctDNA, support the practice of liquid biopsy molecular profiling to detect retention of HER2-driven disease for the continuation of HER2-directed therapies in patients with HER2-positive GEA who were previously treated with anti-HER2 agents. The findings from this report corroborate the prudence of this strategy. ■

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CONTINUING MEDICAL EDUCATION (CME)

Diversity, Equity, and Inclusion in Cancer Care: A Report Card

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Upon successful completion of this activity, you should be better prepared to:

- Review the impact of a lack of diversity in the hematology/oncology health care workforce on patient care
- Analyze gaps in the screening, diagnosis, treatment selection, and access to care in diverse populations with cancer
- Evaluate strategies to broaden oncology clinical trial opportunities and enrollment among diverse populations

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Diversity, equity, and inclusion are important goals in health care to ensure an appropriately diverse workforce, increase the inclusion of clinical trial participants, and provide culturally tailored care. Narjust Florez, MD, is a leader in the study of diversity, equity, and inclusion in United States health care. In this article, she grades different entities—from medical school applications to opportunities in hematology/oncology and care of cancer patients from different backgrounds—to show where good progress is being made, improvement of deficiencies is needed, or no change is evident. Further, Florez offers guidance on how to improve diversity, equity, and inclusion in health care.

Medical School Application Process

Grade: Needs Improvement/ Deficient

Q: The people entering medical training represent the first step in developing a diverse health workforce. How are we doing regarding diversity in the population accepted to medical school?

FLOREZ: This answer is somewhat complex. First, the number of minorities, or underrepresented groups in medicine, including Latinx, Hispanic, Black or African American, Native American, and members of the LGTBQ [lesbian, gay, bisexual, transgender, questioning] community, among others, have increased in terms of being accepted into medical school, compared with 20 years ago.[1] However, in the last 10 years, these numbers have stagnated, despite the increase in many underrepresented groups' corresponding US demographic changes.

Q: How does a person's financial standing influence their ability to apply to a medical school?

FLOREZ: Groups facing the most challenges in being accepted to medical schools are first-generation college graduates or those living in rural underserved areas of the United States.[2] Though medical school applications are often thought to solely be based upon merit, they are unfortunately associated with other subjective and objective factors that are financially influenced.[3] Let's start with the main one—the MCAT [Medical College Admission Test]. The MCAT is a nationwide test that is required to apply to medical schools, and applicants earn an arbitrary number. Two problems with this. One, first-generation graduates or students from underserved areas usually do not have the financial means to pay for widely utilized preparatory courses, which may range from $2000 to $3000.[4] Similarly, they lack the resources to pay for a tutor, which is often helpful because the MCAT is about test-taking skills, more than it is about straight knowledge.

Furthermore, due to these students' lack of generational wealth, many have to work a part-time or a full-time job in order to support themselves, which means that they have limited time when it comes to studying.[4]

A third, often-neglected factor related to the financial aspects of entering medical school is one's study environment. I have 2 mentees, the first being from a family of migrant farmers in California that pick blueberries. She needed to wake up at 3 in the morning, go to the field to work, and then after go study. Another student entered medical school without a laptop, and needed to access the library whenever a computer was necessary. These are examples of burdensome study environments resulting from a lack of financial resources.

Finally, interviews are so expensive. One of the silver linings about the COVID-19 pandemic is that some interviews became virtual, although many now are going back to being in person. When you are working a minimum wage job, studying for the MCAT, and need to go to 7 different cities for an interview, many students end up in a lot of credit card debt that only multiplies over time. So, though they are not often discussed, there are many financial aspects that affect minorities and underserved populations entering medical school.

Diversity in the Hematology-Oncology Workforce

Grade: Needs Improvement/ Deficient

Q: Could you please outline the findings of the study you reported in an abstract at the 2020 American Society of Clinical Oncology (ASCO) Annual Meeting regarding diversity in medical specialty training in hematology-oncology?

FLOREZ: The study was led by one of my mentees, Ana Velázquez Mañana, MD, MSc, from the University of California San Francisco.[5] Using the Western North Carolina Diversity Engagement Coalition of the American Association of Medical Colleges data, we investigated the demographics of the fellows that matched to hematology-oncology over the past 20 years. First, we found that in the last 10 years, there has been no improvement in diversity recruitment; we continue to recruit the same number of Hispanic, Latinx, African American, and Native American individuals into hematology-oncology.

Hematology-oncology continues to be one of the least diverse internal medicine specialties, even though it is known that cancer is the leading cause of death for Latinx and Hispanic people (even more so than cardiovascular diseases).[1] And something that is quite unique to hematologic oncologists is the relationships you have with your patients going through the hardest times of their health care journey, bringing attention to the importance of recruiting a diverse workforce.

Indeed, the importance of cultural concordance has been supported in *over 8 different studies*.[1] Cancer changes our patients' lives forever, and we need to make sure that their oncologists are able to provide practices and complementary support tailored to how these patients uniquely see their disease, as opposed to simply issuing therapy.

Q: There's an exodus of oncologists of color from academia to industry and into private practice right now. Why is this happening?

FLOREZ: The exodus was happening even before the COVID-19 pandemic, but the pandemic certainly accelerated it. From 2019 to 2020, we conducted the OCEAN study, in order to characterize women's choices regarding medical oncology careers–academia vs industry, vs practice vs community-based.[6] We learned that women's decisions, compared to men's, were influenced by a wide variety of external factors. Alarmingly, we also learned that 1 of 5 women in that study reported that they would leave academia within the next 5 years. We have worked so hard to incorporate women into the workforce and diversify faculty, but then they are not staying. Why is this? Because diversity without inclusion equals trauma.

I faced this myself. From the outside, it looked like I was thriving, the most productive resident, the most productive fellow who was traveling, winning awards. But I was trying to fit in to an environment that had *recruited* me but didn't *include* me. This lack of inclusion is due to multiple aspects of a workplace, including professionalism, which is weaponized against trainees of color. "Oh, your hair is so much better when it's straight." Or, "You shouldn't wear that African print because it's not professional enough."

Often, we are also charged with the minority tax, in which members of minority groups are responsible for fixing discrimination, fixing disparities, being on every hospital committee. But when the opportunities really come to make their suggested changes, it doesn't happen.

Populations of color are resilient, but there is a point in which the resiliency cup is emptied, and we fall back on self-preservation. Self-preservation often means going to industry or going to practice, because many of us have student loans and family responsibilities that don't stop. So, I train my mentees to be ready for an environment that wants to recruit them but not include them, in order to consider self-preservation along the way.

Cancer Diagnosis and Treatment in Underrepresented Populations

Grade: Good Progress Being Made

FLOREZ: This grade is based on 2 actions that have been taken. One is for lung cancer screening. We were only screening 6% of the patients who were candidates or who qualified for lung cancer screenings, but when changes were made to the eligibility criteria, changing age recommendations from 55 to 50 years, the amount of cigarettes to 30 pack-years, and medical histories from 30 to 25 years, eligibility criteria and subsequent screening improved for many women and minorities.[7]

Also, we saw progress in colorectal cancer screening. Changes to that age cutoff meant screening improvement, particularly among African Americans or Blacks, who are highly affected by this disease at a younger age.[8] So these are 2 changes that were made in the last 2 years, but there's still a lot of room for improvement when it comes to pap smears, the HPV vaccine, and mammograms.

Q: Screening for malignancy is less common in underrepresented populations. How does this impact the care of patients with cancer and their survival?

FLOREZ: Latinx, Hispanic, African American, or Black patients across all cancer types are most likely to be diagnosed with advanced stage cancer—stage IV—when the cancer is not curable and there are very limited treatment options.[9] A lack of adoption or lack of recommendation for screening is directly correlated to diagnosis at an advanced stage. Underrepresented populations or minority populations have several reasons for having lower rates of cancer screening, one being access to health care. They are less likely to be insured, despite working full-time jobs.[10] For example, in the food service industry, which is largely populated by Hispanics and Latinx individuals, many workers do not have benefits, despite working 40 to 50 hours a week.[11] A mammogram, out of pocket, is $1200 or more. Lung cancer screening costs about $4000 or $5000.[12] So, if you don't have health insurance, it's very hard to access this.

Another issue associated with employment is that many of these employees are paid hourly, so when they don't go to work, they don't make money. Most screening opportunities take place during working hours. So would you do a mammogram or feed your children?

Physician bias also plays a role here. One example of that is in lung cancer screening for women of color, who are 6 times less likely to be offered the opportunity for lung cancer screening compared with white males.[13] And this stands true for cross-matched cohorts, age, number of cigarettes, previous exposures. The only difference is race and gender.

Care of Patients From Underrepresented Populations with Cancer

Grade: Needs Improvement/ Deficient

FLOREZ: I would give it "needs improvement" to "deficient" for 3 reasons. First,

many studies on survivorship were done with majority White populations.[14] We have zero to little data about the survivorship experiences of populations of color, meaning that we are using data that's extrapolated from a majority White population to treat or understand these patients.

Second, the majority of available information about care and survivorship is only in English.[15] Immigrants, who make up a large population of patients, have very limited resources when it comes to reading educational materials in their language of preference. There have been increased efforts to improve information, but what I have seen is that often, the materials are inappropriately translated into other languages; when I read some of them as a native speaker, it's like, "This makes no sense." More so than increased effort, we need to ensure that the job is done appropriately.

Third, we lack cultural humility, a doctrine developed in the 90's: the belief in lifelong learning from each other and from our patients. Specifically, many assumptions are made regarding populations of color, and as a result, the care is suboptimal. In a study I did when I was at Mayo Clinic, we showed that if a woman of color did not show up to her mammogram after breast cancer, she would receive 1 to 3 phone calls as a follow-up to say, "Hey, you missed your mammogram." But when we looked at White women, they would receive 5 to 7 phone calls. These are cross-matched groups. So why are we calling one group more than another? The answer has to do with stereotypes—the women of color don't want to get care, so we are not going to bother them. But in reality, there is no data to back that up.

One last thing about follow-up care is that we often forget that our patients are more than their disease. We make appointments on arbitrary days and times that are inflexible, when in fact, patients have many, many responsibilities. Adapting to patient needs in follow-up care is very important, and we often fail to do that. Systemic change is needed.

Diversity of Populations in Clinical Trials

Grade: Needs Improvement/ Deficient

FLOREZ: In 2017, I published an article about the lack of patients belonging to a racial or ethnic group, women, and older adults in clinical trials that still remains true.[14] From 2005 to 2017, we found that the recruitment of members of minority groups actually has *declined* over time, instead of improved. People are becoming more interested in this now, but we still lack efforts to garner increased recruitment. Instead, we continue to extrapolate data from studies largely done in Asia. A study in 1000 patients may have 1 Black patient. How are we supposed to know about the efficacy and safety of these drugs in other populations, then?

Modern efforts have largely been about increasing the diversity of patient pictures on websites, but when studies open, there is no consent in Spanish, there is no consent in Mandarin, there is no consent in Portuguese.[14] There is no communication with community boards or community advisory boards, and they don't incorporate patient advocates in their study, all of which are necessary to diversify clinical trials.

Diversity, Equity, and Inclusion in the US Health Care System

Grade: Needs Improvement/ Deficient

FLOREZ: Diversity, unfortunately, doesn't exist. And the results of several studies published from my own laboratory show that only a minuscule number of deans are women, and that there remain significantly fewer female professors compared with professors who are men.[1] Leadership positions in hospitals of the US health care system, too, are mostly held by men.[16] This contributes to the salary gap in medicine. With cross-matched training, specialty, years in practice, and academy ranking, women are paid up to $100,000 less for the same job.[17]

That's only gender; so let's talk about members of minority groups , members of racial minorities, and intersectionality. When you're a woman of color, you have to deal with *both identities*, and the discrimination synergizes. A woman of color is more likely to not be promoted in the same amount of time compared with her other colleagues.[18] She is also very likely to pay the minority tax, in having a lower sign-on bonus or start-up salary, despite having the qualifications, and she is less likely to be given leadership opportunities outside of diversity, equity, and inclusion.

Another thing that contributes to the lack of inclusion is not bringing others to the table and presenting beneficial opportunities to them, instead of solely including them because you need a token woman or a token minority in your committee. Tokenism is using somebody for a secondary gain and not truly including that person, and it has negative repercussions for the person being tokenized.

Improving Disparity

Q: How can we address gaps in health care funding, including health insurance?

FLOREZ: Let's talk about accountability. One of the first things I do if I have a patient with insurance issues is to pick up the phone, but the health insurance industry has made this so difficult. For example, I have chemotherapies being approved without antiemetics. How can you give somebody chemotherapy without antiemetics? That's just unethical.

Then I have patients who get approved for one thing, such as a chest CT but I cannot look at the pelvis. They have liver

lesions, but we are only going to base decisions on the chest, because that's where the disease is. Also, insurance has loopholes in which the drug is approved, but the co-pay is $3000. The health care system has created patient navigators to help patients traverse these loopholes, but we are not fixing the root cause. Instead of creating more navigators, more programs, more alerts in EPIC [software (EPIC Systems Corp)] that just add burnout to the physician, what about transparency when it comes to insurance and preauthorizations? ASCO advocates strongly on Capitol Hill for the preauthorization of cancer drugs to allow us to give cost-effective treatments, but sometimes in cancer, the only treatment option *is* the expensive one. So, preauthorizations in cancer care do not have the same place that pre-authorizations have in other medical care, and often only delay care for our patients.

Then there are insurance companies that use peer-to-peer reviews, which is when I call somebody, often who's not trained in the field that I'm trained in, to get their authorization and explain why I need the drug. Once, I had to get a PET scan approved by a pediatric nephrologist. When I talked with her, I wanted to practice cultural humility, so I said, "Thank you for your help. I want to understand what is your specialty, before we move forward with this discussion." She said, "I'm a pediatric nephrologist." I said, "Oh, great, let me explain to you the following." I don't think that person is my peer, though, because she is not another oncologist. So, peer-to-peer review often ends up being just another obstacle.

Q: How can we improve screening rates in underrepresented populations?

FLOREZ: We need to adapt to the needs of the population. Mammograms have been proving to be successful because they *bring* the health care to patients in underserved areas. But in some places of the rural US, patients have to travel hundreds of miles before they can find a specialist, like a breast radiologist. For lung cancer screening, we're starting to bring the CT scan to communities that are underserved, but also need to remember that this can include urban areas, too. And we must ensure that all screening we bring is covered by insurance, which is not always the case. Preventive care or risk-reduction care is cheaper than cancer care. Finally, we need to explain to patients in their language why a screening is important, removing the stigma associated with it, which there is a lot of. The same is true in cervical cancer screening—that only very sexually active persons need to get a pap [Papanicolaou] smear. That's not true.

Q: How can we promote diversity in research populations?

FLOREZ: I would change the word *promote* to how to *include* minorities in research. The answer lies in understanding how these populations see research. There's a lot of myths out there that if you're in a clinical trial, you're a guinea pig, you're getting placebo.[14] That barely happens in oncology. So, when a patient of color is presented with a clinical trial and says no, it is important to go beyond the no. Last week, I presented a patient a clinical trial and before I even finished, she said no. I said, "Ok, let's figure out what concerns you about this and what doesn't fit your health care beliefs," and as it turned out, her main concern was that she thought she was going to get a placebo in a single-arm study. So, it's very important that we go beyond the no, especially when it comes to diverse populations for research. Also, that we do it for the right reasons: to provide our patients with therapies before approval, to give them that extra layer of support that comes from being in a clinical trial, and to generate good data.

Q: Beyond the health care system, how can we address broader social and economic factors, including exposure to environmental risks and disparities in behavioral risks?

FLOREZ: I strongly believe that the road to equity is everyone's responsibility. Everyone has been affected with a type of disparity in health care—some have to push and push and push to get pills, others have to call the insurance to argue why they were charged. But we all have faced disparities in health care in some way.

In order to create equity, we each have a role: in providing feedback, calling our lawmakers, advocating at the state level, at the federal level, and creating equity every day. As a health care provider, you can create equity every day without needing to run for office. Helping an older adult lost in the hospital get to the right place is creating equity. Their experience that day was improved compared with 2 weeks ago when they got lost and nobody helped them.

Ask your patients if they have food. Are they safe? Ask your neighbors. See patients not just as individuals, but as a member of our community. That's what we need to practice to create equity. We are the result of our environment, and we have the power to make it an equitable one. ■

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