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Regorafenib for Metastatic Colorectal Cancer

Common Toxicities and Prevention Strategies

Amber Draper, PharmD, BCOP

Introduction
Regorafenib is a once-daily oral multikinase inhibitor approved for treatment of metastatic colorectal cancer following progression on chemotherapy, anti–vascular endothelial growth factor (VEGF) therapy, or anti–epidermal growth factor receptor therapy. The US Food and Drug Administration approved regorafenib based on the results of the 2012 CORRECT trial, which demonstrated an improvement in overall survival with this agent vs best supportive care in patients with metastatic colorectal cancer (6.4 months vs 5 months, respectively; hazard ratio, 0.77; 95% CI, 0.64–0.94; \( P = .0052 \)).

The most common grade 3 or higher adverse events associated with regorafenib use are palmar-plantar erythrodysesthesia (PPE; 17%), diarrhea (7%), and hypertension (7%). PPE is most likely to occur within the first 2 to 4 weeks of treatment and can be the most distressing adverse outcome to patients. Affected patients present with prodromal symptoms of dysesthesias in the palms and soles that progress to asymmetrical hyperkeratotic lesions. Lesions can be accompanied by redness, pain, and blisters, and escalation from grade 1 to 3 toxicity occurs quickly with continued dosing.

It is ideal for management of PPE to begin before symptoms appear. Prophylactic measures—such as removal of pre-existing hyperkeratotic lesions prior to treatment and assessing the need for orthotic devices in individuals with abnormal weight bearing—should be implemented. Patients can be educated to avoid activities that increase exposure of the hands/feet to heat and friction—such as washing dishes, taking hot showers, and exercising vigorously—and to wear non-constrictive clothing, thick socks, and padded shoes when needed.

Among the most common grade 3 or higher adverse events seen with regorafenib is palmar-plantar erythrodysesthesia, which occurs in 17% of patients.

Management of Regorafenib-Associated Toxicities

PPE
The mechanism of PPE is theorized to be a result of dual VEGF receptor and beta-type platelet-derived growth factor receptor inhibition, which interferes with vascular repair mechanisms in high pressure areas exposed to repeated friction or pressure.
and hepatotoxicity, should be assessed within the first month of treatment initiation and then on an ongoing basis.[1]

Hypertension
The overall incidence rate of regorafenib-related hypertension has been reported to be as high as 44%, demonstrating the need for close monitoring and management.[7] Providers should instruct patients to monitor their blood pressure daily for the first 6 weeks of treatment, as in the CORRECT trial. If blood pressure increases, there is no single preferred antihypertensive agent, and selection of therapy should take into consideration the patient's comorbidities. Diuretics should be avoided due to concern for dehydration in the setting of regorafenib-induced diarrhea. Pharmacologic treatment should be initiated for grade 2 or higher hypertension, and regorafenib should be discontinued if grade 4 toxicity occurs.[5,7]

Diarrhea
Grade 1 or 2 diarrhea has been reported in 34% of patients on regorafenib.[1] As with other toxicities, early management can prevent dose reductions and drug discontinuation. Management of mild-to-moderate diarrhea may include dietary changes, such as implementation of a lactose-free or high-fiber diet, as well as use of over-the-counter anti-diarrhea agents such as loperamide. Patients should be continually assessed and instructed to notify a provider if the number of stools increases by more than three daily, since severe diarrhea can lead to dehydration and electrolyte imbalances.[3]

Dosing Strategies
Although various dosing strategies have been employed in practice to ameliorate toxicities resulting from regorafenib, little data support such approaches. In the ReDOS trial, Bekaii-Saab et al investigated dose titration over the first cycle of treatment to optimize regorafenib dosing. They hypothesized that increasing the dose slowly in weekly increments would reduce adverse events during the first cycle and early discontinuation of therapy.[8]

Patients were randomized to 160-mg regorafenib daily for 21 days or a weekly dose escalation of regorafenib over 3 weeks (80-mg regorafenib daily for week 1, 120 mg daily for week 2, and 160 mg daily for week 3). The patient's tolerated dose at the end of cycle 1 became the starting dose for cycle 2. Within each treatment group, patients were further stratified to a preemptive strategy vs reactive strategy for PPE. The primary endpoint was the number of patients completing cycle 2 at 8 weeks. Secondary endpoints included overall survival (OS), progression-free survival, time to progression, cumulative dose, quality of life (QOL), and safety.[8]

At its conclusion, the study found that weekly dose escalation of regorafenib from 80 mg to 160 mg daily was superior to 160-mg regorafenib daily, with 43% vs 24% of patients, respectively, completing cycle 2 (P = .281). There was a trend for improved OS in the dose-escalation arm (9 months vs 5.9 months; P = .94). At 2 weeks following therapy initiation, the dose-escalation strategy did not appear to compromise QOL, unlike the standard-dose administration. Grade 3 and 4 toxicities were lower in the dose-escalation arm vs the standard-dose arm (PPE, 15% vs 16%; hypertension, 7% vs 15%; and fatigue, 13% vs 18%). The authors concluded that a dose escalation strategy optimizes regorafenib dosing and appears to be better tolerated than standard dosing, with fewer adverse events.[8]

Clinical Implications
The National Comprehensive Cancer Network (NCCN) Colon Cancer Guidelines Version 4.2018 include the dose titration schedule as an option for patients receiving regorafenib for metastatic colorectal cancer.[9] Data regarding the outcomes of preemptive vs reactive PPE prevention strategies are forthcoming.[8] In practice, the dose-escalation strategy may allow for early intervention during the escalation cycle, before drug discontinuation is warranted due to grade 3 or 4 toxicities. Combined with education and supportive measures, patients may be able to maintain treatment and achieve an improvement in OS when the dose-escalation strategy for regorafenib dosing is utilized.

FINANCIAL DISCLOSURE: Dr. Draper has no significant financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article.

Additional Considerations for Regorafenib Usage

- Although regorafenib has demonstrated an improvement in overall survival in metastatic colorectal patients, many patients discontinue therapy within the first treatment cycle due to adverse events.
- Providers should educate patients about common toxicities associated with regorafenib use, especially palmar-plantar erythrodysesthesia, hypertension, and diarrhea.
- Patient education should include preventative and supportive measures, as well as when to contact the provider.
- Monitoring within the first treatment cycle helps to optimize therapy and to provide an early intervention due to side effects.
- Implementing a dose escalation strategy optimizes dosing, improves overall survival, and results in fewer adverse events.

For references visit cancernetwork.com/regorafenib-mCRC

Dr. Draper is a Clinical Pharmacy Specialist at Winship Cancer Institute of Emory University, Atlanta, Georgia.
ABSTRACT: Despite advances in the treatment of castration-resistant prostate cancer (CRPC), options remain limited and non-curative; thus, prostate cancer remains one of the deadliest cancers in men. The discovery of novel therapeutic targets is needed to improve outcomes for men with metastatic CRPC. Precision/personalized medicine creates new opportunities to discover these targets. With an increase in the use of next-generation sequencing and tumor profiling, potentially clinically relevant tumor mutations are being identified. Here, we review the current use of and future direction for genetic testing and tumor profiling in patients with metastatic CRPC.

Introduction
Despite the success of androgen blockade, nearly all metastatic prostate cancer patients progress to castration-resistant disease. Although treatment of castration-resistant prostate cancer (CRPC) has improved substantially, most patients succumb to their disease. In Part 1 of this two-part review, we reviewed novel targeted therapies and immuno-oncology agents, as well as the future role of biomarker-driven studies in patients with CRPC (visit CancerNetwork.com/CRPC-part-1). As DNA sequencing techniques improve and become more available in the clinic, we have identified common mutations with predictive implications for the management of these patients. In Part 2, we review the current use of genetic and tumor profiling and its role in providing more personalized treatment strategies.

Microsatellite Instability
Pembrolizumab is the only immune checkpoint inhibitor that has been approved by the US Food and Drug Administration (FDA) across the spectrum of solid tumors, based on the presence of microsatellite instability (MSI). Defects in DNA mismatch repair (MMR) genes lead to an MSI-high phenotype that is associated with an increased mutational burden. Despite overall poor responses to anti–programmed death 1 (PD-1) therapy in colon cancer, a complete response was observed in a patient with metastatic colon adenocarcinoma and an MSI-high phenotype. [1] This finding led to a phase II study with pembrolizumab that demonstrated improved survival in mismatch repair-deficient colorectal cancer patients. This is thought to be secondary to an increased number of mutation-associated neoantigens seen in the mismatch repair-deficient population.[2] Subsequently, the efficacy of pembrolizumab in the MSI-high phenotype was investigated in five uncontrolled, open-label, single-arm trials, which led to its FDA approval in this setting. Of note, there were 2 patients with metastatic prostate cancer, 1 with stable disease, and 1 with a partial response.[3]

The correlation between MMR mutations and responses to immune checkpoint inhibition raises important questions for patients with prostate cancer. Pritchard et al demonstrated that 12% of patients with advanced prostate cancer have a hypermutated subtype, and that hypermutated cancers are associated with MMR mutations (MSH2 or MSH6).[4] In another study, the frequency of MSI in primary prostate cancer was investigated by immunohistochemistry and next-generation sequencing of MSH2; MSH2 loss was seen in 8% of Gleason pattern 5 (Gleason score, 9–10) primary adenocarcinomas of the prostate compared with 0.4% in all other Gleason scores. In addition, patients
with MSH2 loss were found to have an increase in CD8+ lymphocyte density, which may predict a response to immune checkpoint inhibition.

The actual prevalence of all MMR mutations in patients with Gleason score 9–10 is likely even higher than that seen with MSH2 mutations alone and supports the idea that screening for MSI should be performed in this patient population.[5] Early results from a study that included patients with either MSI or programmed death ligand 1 (PD-L1) positivity (> 1%) treated with either nivolumab or pembrolizumab have shown a biochemical prostate-specific antigen (PSA) response (> 50%).[6] An ongoing prospective clinical trial (ClinicalTrials.gov identifier: NCT02966587) will evaluate how patients with MSI respond to immune checkpoint inhibition with durvalumab. The National Comprehensive Cancer Network guidelines now recommend treatment with pembrolizumab for patients with metastatic prostate cancer with MSI who have progressed on prior systemic therapy.[7] Current FDA-approved second-line treatments for CRPC are summarized in Table 1.

**DNA Repair**

DNA repair is essential in maintaining the integrity of the genome. Defects in DNA repair promote carcinogenesis and have been identified in at least 20% to 25% of patients with metastatic CRPC.[8] Mutations in germline DNA repair genes have been associated with an increased risk of familial prostate cancer. These genes include BRCA1, BRCA2, MLH1, MSH2, PMS2, NBS1, BRIP1, PALB2, MUTYH, ATM, and CHEK2.[9]

In a study by Pritchard et al of 692 men with metastatic prostate cancer, DNA repair gene mutations were identified in 11.8%. This is significantly higher than the 4.6% prevalence seen among men with localized prostate cancer, which supports a link between mutations in DNA repair genes and a metastatic phenotype. Among these mutations, the most frequently identified was BRCA2 in 5.3% of men.[10] There is also evidence that the presence of BRCA1 or BRCA2 is associated with a high Gleason score (≥ 8), higher incidence of metastatic disease at diagnosis, and a decrease in cause-specific survival. The study by Castro et al found that cause-specific survival was 8.6 years among 61 patients with BRCA2 mutations and 18 patients with BRCA1 mutations compared with 15.7 years in patients without these mutations.[11] In a study of 67 patients definitively treated with either radical prostatectomy or external beam radiation, BRCA1/2 mutations were identified as an independent risk factor for metastasis-free survival, with a hazard ratio of 2.36 compared with non-carriers.[12] These data support that the presence of BRCA1 or BRCA2 is associated with an increased risk of metastasis and decreased survival in patients with prostate cancer.

When faced with a single-strand break in DNA, pathways exist to repair the error using the contralateral DNA strand. Repairing a double-stranded DNA break is achieved by the high-fidelity homologous recombination mechanism or the more error-prone nonhomologous end-joining pathway. If DNA repair is unsuccessful, cells enter programmed cell death.[13] Cells that are lacking DNA repair mechanisms will continue DNA replication without error correction, leading to increased carcinogenesis. It is by this mechanism that defects in DNA repair genes lead to an increased risk of cancer.

One of the proteins responsible for initiating repair of single-stranded DNA breaks is poly (ADP-ribose) polymerase (PARP). The PARP protein locates the DNA defect and binds at the replication fork until DNA repair is started.[14] PARP inhibition led to cellular toxicity in cell models deficient of BRCA1/2, this was not observed in cells with heterozygous or wild-type BRCA1/2.[15] It is hypothesized that single-stranded DNA breaks will progress to double-stranded breaks with PARP inhibition. In a system with BRCA-deficient DNA repair mechanisms, these double-stranded DNA breaks cannot be repaired and lead the cell into programmed cell death.[16] In patients with germline BRCA mutations, only the tumor itself is homozygous for BRCA. This allows for PARP-directed therapy against abnormal cancer cells that completely lack BRCA, without affecting normal host cells in patients with BRCA mutations.[17]

The first clinical trial of olaparib included 3 patients with CRPC, with 1 patient with a BRCA2 mutation who remained on the therapy with clinical benefit for over 3 years.[17] A phase II trial of olaparib in patients with metastatic CRPC included 50 patients who had previously progressed on standard therapy. All patients had received docetaxel, 49 had received either abiraterone or enzalutamide, and 29 had received cabazitaxel. Of these

<table>
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<td>MSI-high phenotype</td>
</tr>
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</table>

CRPC = castration-resistant prostate cancer; FDA = US Food and Drug Administration; MSI = microsatellite instability.

**TABLE 1 Ready-for-Practice Therapeutic Agents for the Second-Line Treatment of CRPC**
Cancer is a genetic disease. Carcinogenesis, response to therapy, and overall outcome are dependent on the complex interplay between the host and its environment. Many clues regarding these interactions exist within germline and somatic DNA. With the burgeoning research in prostate cancer, together with improved and lower-cost sequencing technologies, reading these genetic tea leaves is now becoming a reality. Considine and Petrylak do a wonderful job outlining the current and future state of genetic testing used to make treatment decisions for the second-line systemic treatment of men with advanced prostate cancer.

Practical application of these technologies can, however, be challenging. There are an increasing number of commercially available tests with variable coverage of known germline mutations. A well-validated companion diagnostic test is necessary for the ultimate success of these targeted therapies. In addition, due to the implications for the patient and his biologic relatives regarding risk of other malignancies, an informed conversation should be had with the patient prior to testing (preferably with a genetic counselor). Furthermore, the conversation should be had with the patient regarding risk of other malignancies, an informed conversation should be had with the patient prior to testing (preferably with a genetic counselor).

In short, the future is here! We are now able to rationally target cancerous mutations with currently available medicines, resulting in improved patient outcomes. However, this excitement needs to be tempered by a clear understanding of and communication about the limitations of this technology. Finally, outside of clinical trials, clinicians should offer this form of testing to only patients in whom actionable information may be gained.

**FINANCIAL DISCLOSURE:** Dr. Kader is the Chief Medical Officer of Stratify Genomics.

**Dr. Kader** is a Professor of Urology and the Director of Urologic Oncology at Moores Cancer Center, University of California San Diego Health System, San Diego, California.

patients, 16 (33%) had a response that met RECIST criteria, and 12 patients remained on the study for longer than 6 months. Next-generation sequencing was performed in 49 patients; defects in DNA repair genes, including *BRCA1/2*, *ATM*, Fanconi anemia genes, and *CHEK2*, were identified in 16 of these patients. Among these 16 patients, 14 had a response to olaparib, including all 7 of the patients with loss of *BRCA2*, and 4 of the 5 with an *ATM* mutation. Radiographic progression–free survival was 9.8 months in patients with DNA repair gene defects vs 2.7 months in patients without, and overall survival was 13.8 months vs 7.5 months, respectively.[18] These data support the clinical benefit of PARP inhibitors in patients with DNA repair gene mutations who have progressed on standard treatment for metastatic CRPC.

A potentially important treatment option that is currently being investigated is the concurrent use of platinum-based chemotherapy and PARP inhibition. DNA damage caused by the platinum in combination with PARP inhibition of DNA repair should lead to increased cell death. Olaparib in combination with cisplatin has had promising antitumor activity in patients with germline *BRCA1/2* mutations in breast and ovarian cancer; however, this combination was associated with significant hematologic toxicities, including neutropenia and anemia, limiting its clinical use.[19] Thus far, studies in patients with prostate cancer have not shown clinical benefit. Further investigation is warranted in this area.

The role of PARP in DNA damage repair is well established; however, it has also been directly associated with a protumorigenic effect via promoting androgen receptor (AR) transcriptional function in AR-positive prostate cells.[20] PARP also regulates prostate cancer cell growth through *ETS* gene fusion product *ERG*, since *ERG*-positive xenografts are sensitive to PARP inhibitors.[21-22] Asim et al demonstrated the role of the AR in maintaining homologous DNA repair gene activity in prostate cancer. With androgen blockade, PARP is upregulated in prostate cancer cells, and high PARP activity is seen in patients treated with androgen deprivation therapy. Synthetic lethality was observed with olaparib in combination with the anti-androgens bicalutamide and enzalutamide.[23] These findings have led to studies that are investigating whether a combination of PARP inhibitors and AR blockade have a role in the treatment of prostate cancer. In one study, 148 patients with metastatic prostate cancer were randomized to abiraterone alone or abiraterone and veliparib. Although a trend was identified favoring the combination, this was not found to have statistical significance.[24]

In a randomized phase II study, all patients received abiraterone combined with either olaparib 300 mg or placebo. The median progression–free survival was 13.8 months with olaparib and abiraterone compared with 8.2 months with abiraterone alone.[25] The combination of PARP and immune checkpoint inhibi-
Next-Generation Sequencing

Precision medicine powered by next-generation sequencing is a growing area of oncology as demonstrated by the focus on targeted and personalized cancer therapies. By identifying actionable mutations within a tumor, a treatment plan can be developed that targets this underlying driver mutation. This strategy has had success in non–small-cell lung cancer, with a tumor, a treatment plan can be developed to prolong survival and limit unnecessary testing and tumor profiling limits its availability upfront, the clinical benefit seen in many of these early trials is promising. In addition to patients with refractory disease, there are other patient populations that may benefit from upfront testing. In patients with a significant family history that supports a BRCA phenotype, genetic testing can identify these DNA repair mutations, which are associated with an unfavorable prognosis, and this will help identify patients who may benefit from PARP inhibition with olaparib. In addition to the discovery of DNA damage repair mutations, mutations in the AR, which lead to anti-androgen resistance, are being identified and may have therapeutic implications in the near future. Unlike with non–small-cell lung cancer, the molecular landscape of metastatic CRPC has had a limited effect on clinical outcomes for most men and remains a continued focus of further research.

Conclusion

Despite significant advances in the treatment of CRPC, most patients succumb to their disease. In the era of precision medicine and personalized cancer therapy, we are discovering genetic drivers of prostate cancer and uncovering novel therapeutic targets. More clinical trials have incorporated next-generation sequencing and tumor profiling (Table 2). Further characterization of the molecular landscape of prostate cancer has the promise to prolong survival and limit unnecessary treatments through a more personalized cancer treatment plan.

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For references visit cancernetwork.com/CRPC-part-2

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### Table 2 Selected Ongoing Clinical Trials for Patients With CRPC

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CAR = chimeric antigen receptor; CRPC = castration-resistant prostate cancer; PARP = poly (ADP-ribose) polymerase; PD-L1 = programmed death ligand 1; PFS = progression-free survival; PSMA = prostate-specific membrane antigen.

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Dr. **Considine** is a Clinical Fellow and Heme-Onc Medicine Fellow, Medical Oncology, at Yale Cancer Center, New Haven, Connecticut.
Recent Clinical Trials Explore Immunotherapies for Urothelial Carcinoma

Dr. Balar highlights promising evidence on the potential benefits of the use of immunotherapy in the advanced bladder cancer setting.

Urothelial carcinoma is the most common type of bladder cancer. Recently, two clinical trials explored the use of immunotherapy to treat patients with urothelial carcinoma. Additional research is also underway. In this interview, ONCOLOGY spoke with Arjun V. Balar, MD, the director of the Genitourinary Medical Oncology Program at New York University Langone’s Perlmutter Cancer Center. Dr. Balar, who specializes in the treatment of patients with bladder, prostate, kidney, and testicular cancers, discussed the treatment landscape for urothelial carcinoma, as well as promising advances that have the potential to change practice.

Q: Several immunotherapies have now been approved by the US Food and Drug Administration (FDA) for the treatment of urothelial carcinoma, both for treatment-naive patients and those with relapsed/refractory disease. Can you provide a brief overview of these therapies?

DR. BALAR: The current landscape of available immunotherapies for advanced bladder cancer can be broken down into two disease states. The first group, the disease state that was tested during initial development, includes patients who are refractory to platinum-based chemotherapy—including cisplatin- or carboplatin-based treatments. In this setting, five different FDA-approved agents are available: two agents that target the programmed death ligand 1 (PD-L1), which is the ligand for PD-1 (Figure). Essentially, these drugs lead to a range of responses from 15% to 21%.

There are two trials involving two agents that have shown a benefit vs chemotherapy, which was the standard of care be-
Immune checkpoint inhibitors have transformed the treatment landscape for urothelial cancers, with the approval of 5 different agents for patients with metastatic disease in less than 3 years. The enthusiasm for these therapies has been sustained by the potential durable response rates and tumor control combined with their safe and favorable adverse event profile. However, a wave of disappointment surged when one of the confirmatory phase III trials with atezolizumab (IMvigor211) failed to demonstrate a survival advantage vs chemotherapy for the second-line treatment of metastatic urothelial carcinoma.[1] And it persisted when the US Food and Drug Administration restricted the front-line use of pembrolizumab and atezolizumab to those with elevated programmed death ligand 1 (PD-L1) expression[2] following the decrease in survival observed in patients with low PD-L1 status in the single-arm atezolizumab study.[2] In theintent-to-treat analysis from an a study of pembrolizumab[1] and IMvigor130,[4] showed that immune checkpoint inhibitor–treated cohorts of the IMvigor130[3] and KEYNOTE-361[4] studies.

As it stands today, overall response rates are still relatively low for unselected patients. For those fortunate patients who respond, however, the durability of the responses is typically high. Additionally, our ability to predict responders is limited, and more research on predictive biomarkers is needed. Driven by our improved understanding of cancer immunology and the successful results seen in other diseases such as lung and kidney cancer, a wealth of very interesting clinical trials are currently testing immune checkpoint inhibitors in different clinical settings. This research is nicely summarized by Dr. Balar in this interview. Several studies are testing the combination of immunotherapy with chemotherapy, or with different immunotherapies, in the advanced-stage setting. Others are testing immune checkpoint inhibitors in curative stages, either as monotherapy or combined with other treatment modalities such as radiation therapy.

Preliminary efficacy data from these studies are very promising and open the door to significant changes in the management of this disease. Will immune checkpoint inhibitors replace chemotherapy as neoadjuvant therapy? Can we skip radical cystectomy in patients who achieve a complete response? Should we think about bladder preservation as a true alternative? Is a combination chemotherapy/immune checkpoint inhibitor regimen the next standard of care for metastatic cancer patients? We don’t know...yet.

**FINANCIAL DISCLOSURE:** Dr. Barata has no significant financial interest or relationship with the manufacturer of any product or provider of any service mentioned in this article.

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or metastatic urothelial carcinoma with a combination of NKTR-214 and nivolumab, which is approved on its own to treat bladder cancer. Can you tell us more about the design and results of PIVOT-02?

DR. BALAR: PIVOT-02 is a fairly large phase I study that served as the initial development platform for the agent NKTR-214. Specifically, this agent is essentially a reformulation of one of the oldest immunotherapy compounds to be tested in cancer, interleukin-2. Going back to the 1990s, interleukin-2 was administered as a high-dose intravenous bolus treatment for 5 consecutive days in a monitored intensive care treatment setting within the hospital because it causes an intense systemic immune response that causes patients to become quite sick; however, at the end of therapy, up to 10% of patients with advanced kidney cancer were essentially cured of their stage IV disease.

Now, fast forward to the 2010s, and this agent was reformulated by adding 6 polyethylene glycol (PEG) molecules to create a slow-release formulation. As the PEG molecules decrease from 6 PEGs down to 2, the active form of the cytokine is then present in the body, allowing immune stimulation, as well as preferential immune stimulation toward immune effector T cells, while minimizing stimulation of the suppressive T cells (regulatory T cells).

The PIVOT-02 study tested nivolumab in combination with NKTR-214, which was administered once every 3 weeks in the outpatient setting, so that the toxicities were much milder compared with patients receiving high-dose interleukin-2. In this particular study update, a cohort of 41 patients with advanced bladder cancer who were treatment-naive received first-line nivolumab and NKTR-214. The data were presented at the 2019 American Society of Clinical Oncology Genitourinary Cancers Symposium and included the 27 efficacy-evaluable patients, defined as those who had at least one response-evaluable imaging after starting protocol therapy. Essentially, the researchers found that up to 48% of patients achieved an objective response according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria, and 52% of patients had an immune-related RECIST response. Additionally, of the 15 patients with visceral metastases, 8 had responses to therapy. So, this agent seems to be quite active, even in patients with visceral metastases.[6]
Interestingly, 6 patients achieved a complete response, suggesting that NKTR-214 is quite active and may actually deepen responses in combination with nivolumab. A subgroup correlative analysis of this study found that, among patients who underwent an on-treatment biopsy vs a baseline biopsy, an influx of CD8+ T cells were present within tumors; in addition, the level of PD-L1 expression increased among patients who received combination therapy, suggesting that NKTR-214 can actually induce a more vigorous local immune response.[6] While these data are promising, they involve only the 27 efficacy-evaluable patients; the study is ongoing and will enroll more patients. Ultimately, randomized trials will be necessary to really understand what NKTR-214 truly adds to nivolumab monotherapy for patients with advanced bladder cancer.

Q: Pembrolizumab is now being tested in earlier stages of disease. The results of the phase II PURE-01 clinical trial of pembrolizumab as a neoadjuvant therapy before cystectomy in patients with muscle-invasive bladder cancer were reported last year. [7] Can you tell us about the results of this trial and their potential significance for early-stage disease?

DR. BALAR: PURE-01 was a very interesting study in that it tested neoadjuvant immunotherapy in patients with muscle-invasive bladder cancer who then underwent radical cystectomy. The historical standard of care for muscle-invasive bladder cancer is cisplatin-based chemotherapy for up to 4 cycles followed by a radical cystectomy. We use neoadjuvant therapy followed by cystectomy because we have level I evidence that the addition of chemotherapy in this setting improves survival and the rate of cure.

In the PURE-01 study, all patients were eligible for cisplatin-based chemotherapy but opted to participate in this trial; therefore, they received 3 doses of pembrolizumab immunotherapy administered every 3 weeks (6 to 9 weeks of treatment total) followed by a radical cystectomy, the standard-of-care surgical procedure with a curative intent. Essentially, the data showed that approximately 40% of patients achieved a complete pathologic response, suggesting that the addition of pembrolizumab elicited a significant local tumor immune response such that in 40% of patients, all cancer present in the bladder at the time of surgery was eradicated.[7]

These data are provocative because we have historically used the response rate to cisplatin chemotherapy as a surrogate for long-term survival. That is because data from the Southwest Oncology Group (SWOG) 8710 trial,[8] one of the pivotal studies that established cisplatin-based therapy as the neoadjuvant standard of care, showed that patients who achieved pT0 had a long-term cure rate of roughly 85% to 90%. The rate with which we see pT0 with cisplatin is estimated to be between 30% and 40%. So, to see a similar rate of pathologic complete response with neoadjuvant immunotherapy suggests that we may be able to see similar efficacy in the bladder.

These are promising data because more patients can tolerate pembrolizumab or immunotherapy in general compared with cisplatin. The challenge with this particular study is that it is a single-arm trial, so we don’t have any comparisons to other active treatments; furthermore, we don’t know whether the complete response in the bladder to pembrolizumab means the same thing as a complete response to cisplatin therapy. This is where long-term follow-up via randomized trials is absolutely necessary.

All of that being said, these data are very important and certainly lend a lot of background and evidence to support conducting larger randomized trials in which patients receive neoadjuvant immunotherapy followed by cystectomy and then are followed to see whether the rates of cure are improved compared with radical cystectomy alone. Not surprisingly, a subgroup analysis of the PURE-01 study showed that patients with high levels of PD-L1 expression in their baseline tumor sample were far more likely to achieve a pathologic complete response to immunotherapy,[7] which is in line with what we typically see in the metastatic setting. Additional data and analyses will be necessary to test if other biomarkers, such as tumor mutational burden or specific genetic mutations, might predict which patients will do best with neoadjuvant immunotherapy.

Q: Are there additional neoadjuvant studies utilizing immunotherapies in bladder cancer that are either ongoing or planned in order to better understand how these therapies fit into treatment?

DR. BALAR: Several randomized phase III trials testing immunotherapy in the neoadjuvant setting are either currently open or soon-to-be open. These include two studies focusing on pembrolizumab. The first is a randomized phase III trial evaluating cisplatin-based chemotherapy alone vs cisplatin-based chemotherapy plus pembrolizumab followed by radical cystectomy.[3] The second study is looking at neoadjuvant pembrolizumab alone followed by radical cystectomy.
cystectomy vs radical cystectomy alone in patients who have muscle-invasive bladder cancer but are not candidates for cisplatin-based chemotherapy (KEYNOTE-905; not yet listed on ClinicalTrials.gov). Lastly, a randomized phase III trial testing the PD-L1 antibody durvalumab in combination with cisplatin-based chemotherapy alone followed by radical cystectomy is underway (ClinicalTrials.gov identifier: NCT03775265). These three studies are just a sampling of the current trials that are better designed to ultimately answer the question, “How much does immunotherapy add to the neoadjuvant setting?”

**FINANCIAL DISCLOSURE:**
Dr. Balar has a speaking agreement with and serves on advisory boards and as a consultant for AstraZeneca, Genentech, Incyte, Merck, and Pfizer/EMD Serono.

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**KEY QUESTION**

**Besides the trials we already discussed, are there any additional ongoing trials focusing on immunotherapy for bladder cancer that you and your colleagues are excited about or that have the potential to be practice-changing?**

**DR. BALAR:** An additional area that I am particularly excited about is bladder preservation. The idea is definitive local treatment for muscle-invasive bladder cancer with a curative intent that does not require a radical cystectomy, which has a very high morbidity; up to two-thirds of patients who undergo radical cystectomy experience perioperative complications, and up to 1% to 2% of patients die from surgery-related complications. Trimodality bladder preservation is a well-established approach that first includes a maximal resection of the bladder, where the bulk of the tumor is removed. Patients are subsequently treated with a 4- to 6-week course of radiation; radiosensitizing chemotherapy is given concurrently to augment the effect of radiation, with the ultimate goal of curing the disease without having to surgically remove the bladder.

I am particularly interested in the addition of immunotherapy to trimodality bladder preservation. I am leading a phase II trial in which we are adding pembrolizumab in combination with trimodality bladder preservation (ClinicalTrials.gov identifier: NCT02621151). We have enrolled just over 30 patients in the last 2 years, and our goal is to enroll 54 patients total. So far, we are seeing encouraging outcomes and excellent safety results. The study is designed for patients who wish to preserve their bladder, as well as for older patients, who are commonly affected by this disease but are not surgical candidates.

A SWOG trial (ClinicalTrials.gov identifier: NCT03775265) is testing definitive chemoradiation and bladder preservation for muscle-invasive bladder cancer with and without atezolizumab as part of a randomized phase III trial that will enroll close to 500 patients. This study will activate in the coming months, and will more definitively test whether adding immunotherapy to chemoradiation will improve our ability to cure patients with muscle-invasive bladder cancer and, most importantly, help them to keep their bladders.

A great deal of evidence exists to support this strategy. Most recently, the PACIFIC trial evaluated patients with stage III non–small-cell lung cancer treated with definitive chemoradiation and then randomized to receive adjuvant durvalumab or adjuvant placebo. The updated data from that trial, published in the *New England Journal of Medicine* in fall 2018, showed significantly improved disease-free survival, with a hazard ratio close to 0.5, as well as significantly improved survival with the addition of durvalumab to chemoradiation.[9] These data suggest that immunotherapy truly does synergize with chemoradiation and hopefully induces a more potent and systemic immune response. This would allow us to eradicate not only the disease that is irradiated, but also systemic micrometastases, by initiating a more effective immune response.

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**NCCN: New Bladder Cancer Guidelines Include Updated Staging, Immunotherapy Options**

The updates reflect recent advances, including recommended immunotherapies and changes in tumor staging.

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Combining Chemotherapy and Immunotherapy for the Treatment of Triple-Negative Breast Cancer

Dr. McArthur discusses the latest results of immunotherapy trials in the treatment of triple-negative breast cancer.

Recently, various clinical trials have honed in on the use of immunotherapy to treat triple-negative breast cancer. The results of several such studies were presented at the European Society of Medical Oncology (ESMO) Annual Meeting and the San Antonio Breast Cancer Symposium (SABCS) in October and December of last year, respectively; results from several additional studies are anticipated in the next year. To identify key findings and their implications for clinical practice, ONCOLOGY spoke with Heather McArthur, MD, MPH, the Medical Director of Breast Oncology at the Samuel Oschin Comprehensive Cancer Institute at Cedars-Sinai Medical Center in Los Angeles.

Q: In December 2018, the results of the KEYNOTE-173 clinical trial—which tested pembrolizumab, an anti–programmed death 1 (PD-1) immune checkpoint antibody, as neoadjuvant treatment for triple-negative breast cancer—were presented at SABCS.

[1] Could you tell us about the design of the study and the results?

Dr. McArthur: KEYNOTE-173 is a relatively small neoadjuvant study that explored various chemotherapy backbones in combination with the PD-1–directed antibody pembrolizumab. There were 10 patients enrolled in each of the trial’s 6 arms, so a total of 60 patients were evaluated. All patients received pembrolizumab with a taxane (paclitaxel or nab-paclitaxel) with or without a platinum followed by 4 cycles of doxorubicin plus cyclophosphamide before surgery. In cohort A, pembrolizumab was administered in combination with nab-paclitaxel. In the other arms, nab-paclitaxel or paclitaxel plus carboplatin were administered at various doses with pembrolizumab. The study investigators found that the pathologic complete

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Jennifer M. Specht, MD, discusses remaining questions about immunotherapy on page 138.
The introduction and incorporation of immune checkpoint blockade into the treatment of many common cancers have revolutionized solid tumor oncology and solidified immunotherapy as the fourth pillar of oncology therapeutics. Breast cancer patients and advocates, as well as the breast oncology scientific community, celebrate the first US Food and Drug Administration–approved immune checkpoint inhibitor, atezolizumab, combined with nab-paclitaxel for the treatment of advanced triple-negative breast cancer—the most challenging breast cancer subtype.

In this interview, Dr. Heather McArthur articulately summarizes the current state and promise of immune checkpoint blockade in the neoadjuvant and advanced triple-negative breast cancer settings. The most immediate, practice-changing data come from the phase III IMpassion130 trial, presented in 2018 by Schmid et al, which shows prolonged progression-free survival with atezolizumab plus nab-paclitaxel vs placebo plus nab-paclitaxel (7.2 vs 5.5 months; hazard ratio, 0.80; 95% CI, 0.69–0.92; *P* = .002); further, it also demonstrated an impressive prolongation in overall survival, from 15.5 months to 25 months, with the addition of atezolizumab in patients with programmed death ligand 1 (PD-L1) expression in tumor immune cells.[1] As noted by Dr. McArthur, improvements in overall survival for patients with triple-negative breast cancer, even by an informal analysis, are noteworthy. These provocative results generate many questions. Which biomarker is best to identify tumors most likely to respond to immune checkpoint blockade? PD-L1 expression on tumor and immune cell infiltration are among the most common; however, there remain important considerations with regard to heterogeneity of expression, reproducibility, and need for harmonization. [2] As discussed by Dr. McArthur, the presence of stromal tumor–infiltrating lymphocytes (sTILs) is a known prognostic biomarker in early breast cancers associated with improved response to chemotherapy alone and in combination with immune checkpoint blockade.[3] Tumor mutational burden and genomic profiles are also being evaluated as surrogates for breast cancer immunogenicity. What about triple-negative breast cancers lacking PD-L1 immune cells, or sTILs, the “cold” or “immunologic desert” tumors? Leveraging our understanding of the many suppressive components of the breast tumor immune environment will be critical here. Combinations of checkpoint blockade agents, careful selection of chemotherapy, judicious use of radiation to modulate the microenvironment, intralesional therapies, and therapies targeting suppressive regulatory T cells and tumor-associated macrophages are all being evaluated as promising strategies to enhance endogenous cytotoxic T-cell response.

Beyond immune checkpoint blockade, a number of other exciting immuno-oncology modalities are under evaluation for triple-negative breast cancer that focus on enhancing immune response against tumor-associated antigens. These include vaccines, antibody-drug conjugates, oncolytic viruses, and, perhaps most directly, adoptive cellular immunotherapy using genetically modified T cells to directly interact with tumor antigens. T-cell receptors recognize tumor antigens in the context of major histocompatibility complex and chimeric antigen receptor (CAR) T cells, which combine the specificity of an antibody with the cytotoxic function of T cells. Our group is evaluating CAR T cells in ROR1-positive advanced triple-negative breast cancer (ClinicalTrials.gov identifier: NCT027068392).

It is a most exciting time in breast oncology, particularly for those impacted by triple-negative breast cancer. Continued advances for patients with triple-negative breast cancer will come with more sophisticated understanding of the breast tumor microenvironment and selection of rational and elegant immuno-oncology combinations.

**FINANCIAL DISCLOSURE:** Dr. Specht has no significant financial interest in or relationship with the manufacturer of any product or provider of any service mentioned in this article.

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**Dr. Specht** is an Associate Professor, Division of Medical Oncology, at the University of Washington, and an Associate Member, Clinical Research Division, at Fred Hutchinson Cancer Research Center, both in Seattle, Washington.
DR. MCARTHUR: Absolutely. We do already have some additional data from the neoadjuvant setting. For example, the I-SPY2 neoadjuvant trial has an adaptive design that allows for efficient evaluation of specific combinations and predicts for the success of these combinations in the phase III setting. This trial is not designed to look at various arms head-to-head, but rather to look for signals of promising combinations in individual arms. In one such arm, patients with triple-negative breast cancer treated with paclitaxel with or without pembrolizumab, followed by doxorubicin and cyclophosphamide, experienced a threefold improvement in overall survival had been seen with any prior strategies for the treatment of metastatic triple-negative breast cancer.

Q: Are there additional neoadjuvant trials in triple-negative breast cancer with immunotherapy agents that have been read out or trials that you and your colleagues are looking forward to reading out?

DR. MCARTHUR: Absolutely. We do already have some additional data from the neoadjuvant setting. For example, the I-SPY2 neoadjuvant trial has an adaptive design that allows for efficient evaluation of specific combinations and predicts for the success of these combinations in the phase III setting.

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Until the IMpassion130 trial, no improvement in overall survival had been seen with any prior strategies for the treatment of metastatic triple-negative breast cancer.

Q: There was also an accompanying presentation at SABCS about tumor-infiltrating lymphocytes (TILs) and their association with response to pembrolizumab. Was there anything illuminating in this analysis that could inform future trials, and are there larger follow-up trials that are now testing pembrolizumab in the neoadjuvant setting?

DR. MCARTHUR: You’re absolutely correct that there was a companion poster presented in which the researchers investigated the role of stromal TILs and stromal programmed death ligand 1 (PD-L1) expression as predictors of response to therapy. Pembrolizumab targets PD-1, and PD-1 interacts with PD-L1, so the idea is that with higher stromal PD-L1, patients might potentially be more responsive to the immunotherapy treatment. The investigators reported that the ability to achieve a pathologic complete response was much higher in patients who had high levels of pretreatment stromal TILs and high levels of stromal PD-L1 expression. Again, the analysis was limited by the number of treatment samples and the number of patients treated on the study. But, this is an encouraging and consistent signal that shows that there is a potential role for prospective biomarkers that will enable us to ultimately enrich for patients who are more likely to receive benefit from these therapies.

There are also a number of ongoing large randomized phase III studies in the curative-intent setting. For example, the I-SPY2 neoadjuvant trial has an adaptive design that allows for efficient evaluation of specific combinations and predicts for the success of these combinations in the phase III setting.

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Until the IMpassion130 trial, no improvement in overall survival had been seen with any prior strategies for the treatment of metastatic triple-negative breast cancer.
example, the IMpassion030 study will enroll 2,300 patients to receive adjuvant anthracycline- and taxane-based chemotherapy with or without atezolizumab (ClinicalTrials.gov identifier: NCT03498716). Another strategy is to enrich for patients who are at high risk of recurrence. The SWOG 1418 trial is doing that by enrolling patients with triple-negative breast cancer who have residual disease after standard chemotherapy and randomizing them to receive 1 year of pembrolizumab or no pembrolizumab (ClinicalTrials.gov identifier: NCT02954874). There are at least two studies that will be reported in the very near future, with highly anticipated results, and numerous global efforts in the curative-intent setting are currently underway. It’s a very exciting time.

Q: What is your perspective on immune checkpoint inhibitors in the neoadjuvant setting for patients with triple-negative disease? Are there already other neoadjuvant treatment options? How would these antibodies potentially fit into the treatment paradigm if larger studies show them to be efficacious?

DR. MCARTHUR: The standard curative-intent strategy for triple-negative breast cancer is chemotherapy. These newer strategies certainly build on that. The hope is that with more rational biologic combinations, we might be able to de-escalate the chemotherapy backbone. The whole idea of combining chemotherapy with immunotherapy is that if you can generate a robust tumor-specific immune response that is augmented by essentially killing tumor with chemotherapy, you can generate a long-term tumor-specific immune memory, so that if you are faced with that same information at a later date, in the form of a recurrence, ideally you wouldn’t even know it because your own immune system would recognize that tumor-specific information and go into attack mode to eliminate that recurrence.

The promise of immunotherapy is that it not only improves pathologic complete responses and early recurrences, but also translates into long-term meaningful improvements in cure rates. This is obviously so impactful for this disease specifically, because it affects so many young women and patients with BRCA deleterious mutations. The promise is incredible.

Q: Switching to immunotherapy agents in the metastatic triple-negative disease setting, the US Food and Drug Administration (FDA) just approved atezolizumab in combination with nab-paclitaxel for patients with PD-L1 positive tumors. The approval is based on the results of the phase III IMpassion130 trial that was published last October.[6] What are the key results from this trial?

DR. MCARTHUR: IMpassion130 focused on patients with newly diagnosed advanced triple-negative breast cancer who had not yet received chemotherapy in the palliative setting and who were at least 12 months from their adjuvant curative-intent chemotherapy. They were randomized to nab-paclitaxel with atezolizumab or placebo; the primary endpoint was progression-free survival, but the study was later expanded to allow for co-primary endpoints, including overall survival. In the intent-to-treat analysis, the 1-year progression-free survival rate was 24% for the atezolizumab arm vs 18% for the placebo arm, an almost 2-month improvement in progression-free survival for all patients.[6]

However, when you drill down into PD-L1-positive patients, the progression-free survival impact was much more pronounced, with an improvement from 5 months to 7.5 months. In the intent-to-treat population, there was an improvement in overall survival from 17.6 months to 21.3 months. However, this was not statistically significant because the investigators were unable to do an overall survival analysis in PD-L1-positive patients. In an informal analysis in the PD-L1-positive subset, the improvement in overall survival was almost 10 months (15.5 months vs 25 months with atezolizumab). It is worth noting that there has never been an improvement in overall survival with any prior strategies for the treatment of metastatic triple-negative breast cancer. To see this result, even in an informal analysis, is incredibly impactful.

KEY QUESTION

Lastly, what is the significance of the approval of atezolizumab? Could you place these trial results into context compared with currently used treatments?

DR. MCARTHUR: Given the results of IMpassion130,[6] and the recent FDA approval of atezolizumab with chemotherapy for the first-line treatment of PD-L1 positive metastatic triple-negative breast cancer based on the results of this study, this strategy will now be considered standard first-line therapy. It is exciting looking forward, since we are only starting to understand how to apply immunotherapy in the treatment of breast cancer.

FINANCIAL DISCLOSURE: Dr. McArthur serves on advisory boards for AstraZeneca, Genentech, and Merck. She also receives research funding (provided to institution) from Merck.

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What to Do When Anti–PD-1 Therapy Fails in Patients With Melanoma

Meghan J. Mooradian, MD, and Ryan J. Sullivan, MD

ABSTRACT: Monotherapy with immune checkpoint inhibitors, specifically those targeting programmed death 1 (PD-1), has revolutionized the treatment of metastatic melanoma: approximately 40% of patients achieve a partial or complete response, many of which are durable. However, a subset of patients who initially respond to therapy will progress, leaving the majority of patients in need of an effective second-line approach. While some standard therapies exist, there has been robust interest in utilizing targeted immunotherapy combinations in this population to overcome primary or acquired resistance. Other approaches include treatment with anti–PD-1 agents beyond progression; targeting oligometastatic disease with surgery, radiation, and/or intratumor injections; and the use of other approved systemic therapies. This review summarizes the current available treatment strategies for patients with advanced melanoma when PD-1–directed therapy is not enough.

Introduction

The use of immune checkpoint blockade has revolutionized the treatment of metastatic melanoma, with dramatic improvements in cancer-related outcomes since the advent of these agents. Long-term survival data demonstrate durable disease control in 20% and 30% of patients receiving the cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) antagonist ipilimumab and the programmed death 1 (PD-1) inhibitor pembrolizumab, respectively. [1,2] However, a subset of patients—approximately 40% to 45%—experience an initial response but ultimately progress months or even years later (acquired resistance). The mechanisms of acquired resistance, like primary resistance, are incompletely understood; however, they include loss of T-cell function through expression of alternative immune checkpoints (such as T-cell immunoglobulin and mucin domain 3 [TIM-3]), [6] disruption of interferon (IFN) gamma signaling via JAK2 mutations, [7,8] and impaired antigen presentation via altered expression of beta-2 microglobulin or major histocompatibility complex molecules. [8-10] Efforts to surmount acquired resistance include PD-1 inhibition coupled with agents targeting additional complementary immune checkpoints, such as TIM-3, CD137, and colony-stimulating factor 1 receptor (CSFR1). Advancements in deconstructing these resistance mechanisms have spurred the development of rational strategies to treat patients who have progressed on anti–PD-1 monotherapy, which will be highlighted in this review.
Moving Forward Post–PD-1 Therapy: Promising Data and Integrating Biomarkers

The past decade has seen a transformation in the field of melanoma treatment, with the introduction of both targeted therapies and immunotherapies. However, data on the efficacy of these treatments focus on only advanced disease in the front-line setting.[1] Broadly, these data highlight that primary resistance remains a major barrier to immunotherapy, while secondary resistance is a major obstacle for targeted therapies. While multidisciplinary approaches are essential for those with local-regional disease or isolated progression while on anti-programmed death 1 (PD-1) therapy, diffuse systemic progression on anti–PD-1 therapy requires a change in systemic therapy. Currently, the presumed approach is to switch the patient to targeted therapy; however, this strategy applies only to the 50% of patients who have a BRAF mutation.

Although multiple novel immunotherapy combinations (eg, LAG-3, TIM-3, and CD122 inhibitors; virotherapy; Toll-like receptor agonists; tumor-infiltrating lymphocytes; and more) are in clinical development, only early data series are yet available. We would note that, post–PD-1 therapy, the use of approved drugs (eg, BRAF/MEK inhibitors, ipilimumab) in standard practice is a priority because they are associated with important antitumor activity. For those already treated with BRAF-targeted therapies, the response rates seen after rechallenge with BRAF/MEK inhibition suggest that resistance may be transient in some cases. [2] With regard to immunotherapy, data from the KEYNOTE-006 study suggest that those who received ipilimumab post-pembrolizumab have response rates approaching or similar to front-line ipilimumab.[3] Further, a second-line combination of pembrolizumab plus low-dose (1.0 mg/kg) ipilimumab has also shown preliminary activity, with a response rate of 47% in a modest sample size, irrespective of programmed death ligand 1 staining, elevated lactate dehydrogenase levels, or liver metastases.[4]

While some patients clearly derive benefit from approved therapies post–PD-1 therapy, we currently lack biomarkers that allow us to optimize patient selection. It will be essential moving forward that we develop larger datasets and integrate biomarkers into clinical trial analyses to better determine which patients will benefit from which therapies. The T cell–inflamed tumor microenvironment, measured generally by gene expression profiling, is one such tool that may segregate patient tumors by their preexisting immune status and more optimally guide drug development.[5] Lastly, it will also be important to better define a common understanding of “PD-1–refractory” disease. It is unclear whether this means primary or acquired resistance, or how it applies to patients who progress after adjuvant anti–PD-1 therapy. We look forward to how such new frameworks may help to inform new treatment strategies to build upon our current therapies, and to help overcome the barriers to treatment with immunotherapy.

We currently lack biomarkers that allow us to optimize patient selection for approved therapies post–PD-1 therapy.

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For references visit cancernetwork.com/anti-PD1-melanoma
Post-Progression Continuation of PD-1 Inhibitors

Prior to transitioning to an alternative treatment approach, clinicians can consider continuing the use of PD-1 inhibitors after progression occurs. Whereas disease progression on chemotherapies and tyrosine kinase inhibitors (TKIs) almost uniformly results in treatment discontinuation due to futility of continued therapy, studies demonstrate the possibility of atypical and delayed response with immune checkpoint inhibitor therapy beyond Response Evaluation Criteria in Solid Tumors (RECIST)-defined progression in melanoma.\[11,12\] Mechanisms to account for these atypical presentations include delayed antitumor response, as well as “pseudoprogression,” in which a transient immune infiltration causes a paradoxical enlargement of the tumor with subsequent shrinkage and clinical benefit that transcends response rate (eg, overall survival (OS) benefit independent of response rate). Two retrospective studies evaluated the benefit of anti-PD-1 antibody therapy past progression in patients with metastatic melanoma.\[11,12\] Impressive response rates of 19% and 28% were seen in evaluable patients treated beyond progression, with these cases representing 4% and 5% of all patients who had received PD-1 inhibition in these studies, respectively.

Notably, delayed responses were rare after 6 months, with these events likely indicative of true progressive disease. In both studies, there was no increased safety signal for those treated beyond progression. Patients who derived the most benefit from continuation of immune checkpoint inhibitor therapy were more likely to be fit (Eastern Cooperative Oncology Group performance status of 0), with lower levels of lactate dehydrogenase. Though it remains difficult to identify patients who will derive benefit post-progression, in general, clinicians can consider PD-1 continuation with short-term follow-up in certain cases. Ideal candidates include those who appear to be deriving clinical benefit (eg, mixed response, slowed rate of progression, regression in critical areas with growth in non-critical areas), provided that they did not experience rapid progression, tolerated therapy well, are maintaining a good performance status, and would not experience an immediately life-threatening issue due to predicted further progression.

Oligoprogession

Patients who progress in a limited number of sites (four or fewer) while on immune checkpoint inhibitor therapy often benefit from a comprehensive, multidisciplinary approach—including incorporation of local therapy, such as surgical resection or ablative radiotherapy—to eradicate isolated site(s) of progressive disease and thereby render a more durable response.

Extracranial oligoprogession

Prior to the advent of effective immune checkpoint and targeted therapies, metastasectomy was often the only means of managing progressive disease.\[13,14\] Studies in the current era of immunotherapy continue to demonstrate improved outcomes of surgical resection in select cases, including in gastrointestinal (GI) tract-only disease,\[15\] large single brain metastasis,\[16\] and adrenal metastasis.\[17\] However, surgery is not feasible in all scenarios, and definitive radiation should be considered in such cases. Radiation
therapy provides not only the ability to palliate symptoms, but also to eradicate a resistant subclone when used at definitive doses. One appealing benefit of radiation therapy is its theoretical ability to modulate an immune response and thereby synergize an anticancer effect when used concurrently with immune checkpoint inhibitor therapy. The abscopal effect—a phenomenon in which local radiation therapy is associated with regression of metastatic sites distant from the radiated site—has been reported in patients treated with both radiation therapy and immune checkpoint inhibitor therapy.[18,19] However, it has yet to be prospectively validated.

The safety of radiation therapy in patients receiving immune checkpoint inhibitor therapy has been explored in various studies, with data demonstrating an acceptable safety signal with treatment of various extracranial sites of disease.[20-23] However, when considering the ideal combination of radiation therapy and immune checkpoint inhibitor therapy, there are several variables that require further investigation, including, but not limited to: the ideal dose, optimal timing of radiation therapy, and how much to fractionate. While certain preclinical studies highlight the immunogenic properties of an ablative radiotherapy dose of 15 to 25 Gy in a single fraction,[24] other studies show the potential immunosuppressive effects of radiation, particularly of prolonged fractionated radiation therapy, which depletes circulating lymphocytes.[25] Several prospective studies across tumor types have demonstrated that stereotactic body radiation therapy (SBRT), or a hypofractionated method of delivery, may reduce this iatrogenic effect and lead to a more effective antitumor response.[26-28] While the optimal combination regimen is unknown, the available data do demonstrate that immune checkpoint inhibitor therapy with radiation, particularly short-course SBRT, appears to be a safe and potentially synergistic treatment option for the management of melanoma.

Central Nervous System–only progression
Development of intracranial disease is a common cause of morbidity and mortality. Management entails a multidisciplinary discussion, since treatment options vary based on patient- and tumor-specific factors (Figure 1). Surgical resection is often beneficial in cases of a single surgically-accessible metastasis. [16] In cases where surgery is not permissible (eg, poor performance status, medical comorbidities, or metastases in critical locales such as the brain stem), stereotactic radiosurgery has been proven to be a highly effective local therapy. [29] Radiosurgery enables treatment of individual brain metastases using high-dose single-fraction radiation, while sparing the surrounding normal brain and thereby mitigating side effects. Based on the efficacy and acceptable side effect profile of stereotactic radiosurgery, this treatment modality is often pursued in cases of ≤ 4 brain metastases that are ≤ 3 cm in diameter.[30] The safety and efficacy of cranial radi-
ation therapy with concurrent administration of immune checkpoint inhibitor therapy has become an area of interest. Recent retrospective studies demonstrate an acceptable safety signal,[31,32] with favorable cancer-related outcomes (eg, reduced size of brain metastases and decreased number of new lesions) in patients who received radiation in combination with immune checkpoint inhibitor therapy compared with patients who received radiation alone.[33] A recently published meta-analysis examined a total of 534 patients with a collective 1,570 brain metastases who were treated with immune checkpoint inhibitor therapy and stereotactic radiosurgery; researchers examined the safety and efficacy of a concurrent vs sequential approach, with sequential defined as administration of stereotactic radiosurgery and immune checkpoint inhibitor therapy within 4 weeks of each other.[34] The primary endpoint was the 1-year overall survival rate with a secondary endpoint of necrosis incidence. The 1-year OS rate was 64.6% vs 51.6% for concurrent and non-concurrent therapy, respectively. Overall, the incidence of necrosis was 5.3%, with rates higher in patients receiving concurrent CTLA-4 antagonists vs PD-1 inhibitors.

In patients with multiple CNS lesions, local therapy options are limited. Strategies for these individuals include alternative systemic agents that penetrate the blood-brain barrier, such as ipilimumab,[35] and combination BRAF/MEK inhibitors in patients harboring an activating BRAF mutation. However, despite achieving high rates of intracranial disease control, the majority of patients have abbreviated progression-free survival (PFS) on targeted agents.[36,37] Notably, although research has been conducted on the efficacy of combination nivolumab and ipilimumab in treatment-naive brain metastases,[38] there are little data on the efficacy of salvage combination therapy in patients who develop CNS disease while on PD-1 inhibitors.

**Systemic Progression**

In cases of systemic progression, subsequent treatment selection depends on several factors, such as the molecular features of the tumor, site of progression, and clinical trial availability (Figure 2). The treatments mentioned here—which include standard therapies as well as investigational strategies—are categorized by the presence of injectable disease and BRAF status; the final subgroup highlights additional novel combination regimens under development.

**Progression in predominantly injectable disease**

**Oncolytic viruses.** The presence of accessible soft tissue lesions enables the use of injectable agents, such as oncolytic viruses. These innovative treatments, often compromised of wild-type and modified live viruses, favorably modulate the tumor microenvironment by increasing CD8+ T-cell infiltration and upregulating the IFN gamma gene signature.[39,40] Though research on the efficacy of oncolytic virus administration post–PD-1 progression is limited, some data have demonstrated the efficacy of these agents with and without immune checkpoint inhibitors in treatment-naive patients.[39,41,42] Talimogene laherparepvec was the first oncolytic virus to demonstrate efficacy in a phase III clinical trial.[41] It has since been studied in combination with pembrolizumab. In one phase Ib trial (N = 21), combination therapy was generally well tolerated; the overall response rate (ORR) was 62.3%, with 33% experiencing a complete response. Studies in a PD-1–resistant cohort are underway (ClinicalTrials.gov identifier: NCT02965716).

Positive results have also been seen with an alternative oncolytic virus, CAVATAK, which is a formulation of the naturally occurring virus responsible for the common cold (CVA21). The phase Ib MITCI study investigated the efficacy and safety of intratumoral CAVATAK with ipilimumab in both PD-1–naive and post–PD-1 cohorts (N = 13). Although the number of patients enrolled was small, combination therapy resulted in an ORR of 38%, with a disease control rate (DCR) of 88%, higher than expected for the CTLA-4 antagonist alone, especially since 54% of the group had previously received ipilimumab.[43]

**Toll-like receptor (TLR) agonists.** TLRs are pattern recognition receptors that, via activation, initiate the innate and adaptive immune response.[44] Due to their ability to enhance immune response, intratumoral administration of different TLR agonists has been incorporated into anticancer treatment strategies. Recent studies—particularly those involving the intratumoral TLR9 agonist SD-101 and CMP-001—have demonstrated encouraging preliminary results in treatment-naive and refractory patients with advanced melanoma. In a phase Ib trial comprised of patients resistant to anti–PD-1 therapy, CMP-001 in combination with pembrolizumab demonstrated an ORR of 22%.[45] Furthermore, the phase Ib study of combination SD-101 and pembrolizumab demonstrated an ORR of 78% in treatment-naive patients, and an ORR of 15% in anti–PD-1 resistant cases.[46] An increase in the expression of an IFN signature gene was detected in post-treatment biopsies in both clinical studies. The dose expansion phase of both trials is ongoing (ClinicalTrials.gov identifiers: NCT02680184 and NCT02521870).

**Ipilimumab.** Several studies have evaluated the role of ipilimumab after PD-1
monotherapy, with data demonstrating similar response rates in the post–PD-1 and treatment-naive settings. Notably, the response to PD-1 inhibition, or lack thereof, does not predict for subsequent response to ipilimumab. One of the earliest studies establishing the efficacy of post–PD-1 ipilimumab was CheckMate 064. This randomized phase II study examined the safety and efficacy of a planned switch from nivolumab to ipilimumab, or the reverse sequence, in patients with metastatic melanoma.[47] Although the rates of grade 3 to 5 treatment-related adverse events were similar in each cohort (50% vs 43%), the antitumor response rate (41% vs 20%) and 12-month OS rate (76% vs 54%) favored the nivolumab followed by ipilimumab arm. While the majority of patients had not progressed on nivolumab, these data established ipilimumab as a viable treatment option after anti–PD-1 monotherapy (though notably with substantial toxicity rates).[47,48]

Inhibition of the MAPK pathway. Mutations in the BRAF gene are present in approximately 50% of newly diagnosed melanomas and lead to constitutive activation of the MAPK pathway.[49] Successful inhibition of this pathway with combination BRAF and MEK inhibitors significantly altered the treatment paradigm of BRAF-mutant unresectable disease.[50] Although the National Comprehensive Cancer Network recommends immune checkpoint inhibitors as first-line therapy for this patient population, MAPK inhibitors remain an important treatment option for these patients. Importantly, the timing of BRAF-directed therapy (before or after immunotherapy) does not appear to impact response rates to TKIs.[51]; however, one study did demonstrate a longer OS when ipilimumab was used after TKI failure.[52]
munab was given prior to a BRAF inhibitor compared with a sequential BRAF inhibitor followed by ipilimumab, or with either agent alone.[52] The safety profile of MAPK inhibitors after immunotherapy is manageable, although data do demonstrate increased rates of TKI-related adverse events and dose interruptions in patients who receive TKIs after immune checkpoint inhibitors.[53]

There are little published data on the role of combination therapy (MAPK inhibition plus immunotherapy) as a way to overcome resistance; however, preclinical data support this combination.[54,55] The early combination of ipilimumab with dabrafenib/trametinib resulted in unacceptable rates of serious GI toxicity (colonic perforation); however, preliminary safety and efficacy results from KEYNOTE-022 are encouraging.[56] In this phase I/II study examining the use of combination dabrafenib, trametinib, and pembrolizumab in treatment-naive patients (N = 14), the safety profile was acceptable and efficacy data were promising: 5 patients achieved a confirmed response, 9 patients achieved an unconfirmed response, and 13 of the 14 patients experienced a reduction in tumor size. The randomized portion of the study is ongoing (ClinicalTrials.gov identifier: NCT02130466).

Key Points

- Although anti–programmed death 1 monotherapy renders a durable antitumor response in 30% to 40% of patients with metastatic melanoma, the majority will experience primary or acquired resistance to immune checkpoint inhibitors.
- Cases of progression, especially oligometastatic progression, require multidisciplinary management to discuss optimal treatment strategies, including metastasectomy and ablative radiotherapy.
- Post-progression treatment decisions should be based on both cancer- and patient-specific factors, such as the molecular features of the tumor (ie, BRAF mutation status), the site and extent of progression, the performance status of the patient, and clinical trial availability.

Additional Investigational Strategies

For motivated patients who are eligible for clinical trials, there are several investigational combinations currently in development (Figure 3). The following information highlights a subset of areas under active investigation, since a review of all ongoing studies is outside of the scope of this article.

Agonists of costimulatory molecules

Due to the demonstrated efficacy of CTLA-4 and PD-1 antagonists in blocking inhibitory pathways, enthusiasm surrounds the targeting of T-cell costimulatory molecules, such as OX-40 and CD137. A phase I trial of a monoclonal immunostimulatory antibody to OX-40 demonstrated antitumor activity across several cancer types, including melanoma,[57] with an acceptable safety profile. Current studies are evaluating the combination of an OX-40 fusion protein (MEDI6383) and the anti–programmed death ligand 1 (PD-L1) antibody durvalumab (ClinicalTrials.gov identifier: NCT02221960). CD137, also known as 4-1BB, is a potent T-cell and natural killer cell costimulatory receptor that functionally enhances cytotoxic T-cell responses. Due to its immunomodulatory effects, recent work has focused on combination therapy with immune checkpoint inhibitor therapy. The safety and efficacy of combination ulerumab, a monoclonal antibody agonist of CD137, and nivolumab was recently evaluated in a phase I/II study involving 138 patients with advanced hematologic and solid malignancies (ClinicalTrials.gov identifier: NCT02534506). In the 46 patients with unresectable melanoma, efficacy results were encouraging, with an ORR of 50%.[58]

Modulators of the tumor microenvironment

Primary and acquired resistance mechanisms are often mediated by the immunosuppressive elements of the tumor microenvironment; therefore, modulation of these factors with agents such as phosphoinositide 3-kinase (PI3K)-γ and CSF1R inhibitors is another area of intense study. Inhibition of PI3K-γ has been shown to affect immunosuppressive macrophages and myeloid-derived stem cells (MDSCs), leading to an increase in cytotoxic T-cell activity.[59] A clinical trial (ClinicalTrials.gov identifier: NCT02637531) is currently exploring the combination of PI3K-γ inhibition and immune checkpoint inhibitor therapy in advanced solid tumor patients, including those with metastatic melanoma, who have progressed on standard therapies. Preliminary data demonstrate evidence of immune modulation and early signs of clinical activity, with an acceptable safety signal.[60]

Additionally, targeting of CSF1R is an active area of interest. CSF1R-mediated signaling is crucial for the differentiation and survival of immunosuppressive macrophages.[61] A variety of small molecules and monoclonal antibodies directed at CSF1R or its ligand CSF1 are in clinical development, both as monotherapy and in combination with standard-treatment modalities such as pembrolizumab (ClinicalTrials.gov identifiers: NCT02975700, NCT02452424, and NCT02323191). The tumor microenvironment can also be altered via epigenetic modification of MDSCs. Entinostat, a histone deacetylase inhibitor, has been shown to suppress MDSCs,[62] and preliminary results from the phase II ENCORE trial of
combination entinostat and pembrolizumab demonstrated promising clinical activity and acceptable safety in PD-1–refractory melanoma.[63]

**Antiangiogenesis agents**

Targeting angiogenesis may also be an effective strategy to increase the efficacy of PD-1/PD-L1 inhibitors, since emerging data suggest that these agents possess immunomodulatory properties that may potentiate a durable immune response and/or overcome resistance.[64] A phase I study of combination bevacizumab and ipilimumab in patients with metastatic melanoma demonstrated a DCR of 67%, with provocative correlative data showcasing an intense immune infiltration in on-treatment tumor biopsies.[64] This prompted several additional trials across tumor types (ClinicalTrials.gov identifier: NCT02681549), including renal cell carcinoma: the phase II IMmotion150 trial demonstrated an improvement in PFS for PD-L1–positive patients (PD-L1 expression ≥ 1%) treated with combination atezolizumab/bevacizumab vs atezolizumab monotherapy.[65] The efficacy and safety of atezolizumab plus bevacizumab is currently under evaluation in untreated melanoma patients with brain metastases (ClinicalTrials.gov identifier: NCT03175432).

**Cytokines**

Cytokines, such as interleukin-2 (IL-2), are known stimulators of effector T-cell functions. High-dose IL-2 was the first immunotherapy regimen to be approved for use in patients with metastatic melanoma, providing up to a 10% durable response rate.[66] However, severe toxicities, coupled with potential immunosuppressive effects,[67] have limited its use. NKTR-214, a pro-drug of IL-2, has subsequently been developed to generate the immune stimulatory benefits of the IL-2 pathway to maximize antitumor responses and minimize adverse effects.[68] Combination NKTR-214 and nivolumab was recently examined in the phase I/II PIVOT-02 study. Impressive results were seen in the treatment-naive melanoma cohort, with a reported ORR and DCR of 52% and 78%, respectively, with no increased safety signal.[69]

There are several studies evaluating NKTR-214 with immune checkpoint inhibitor therapy in the first-line and second-line settings (ClinicalTrials.gov identifiers: NCT02983045 and NCT03138889).

**Adaptive T-cell transfer**

Adaptive T-cell transfer is a pioneering immunotherapy strategy and remains an innovative way to optimize T-cell immunity in metastatic melanoma. In this highly sophisticated technique, T lymphocytes are harvested from a patient, and tumor-specific T cells are generated, expanded in vitro, and ultimately re-infused into the patient, with the goal of eradicating tumor cells. Data demonstrate that these novel treatments can be an effective option for fit patients who have progressed on standard agents.[70]

Notably, although chimeric antigen receptor (CAR) T-cell therapy is an area of intense interest due to successes seen in hematologic malignancies, the complexity of identifying a target antigen and overcoming immunosuppressive effects of the tumor microenvironment has limited the effectiveness of this therapy in the treatment of solid tumors.[71] Studies of CAR T-cell therapy are ongoing across solid malignancies, including melanoma (ClinicalTrials.gov identifiers: NCT02830724 and NCT03060356).

**Conclusion**

Immunotherapy has changed the treatment landscape for unresectable melanoma. However, despite the successes of front-line immune checkpoint inhibitor therapy, most patients will eventually progress. Post-progression treatment decisions should be made based on the site of progression, extent of disease progression, and clinical status of the patient. In the setting of oligometastatic progression, employment of local therapy with surgical resection or ablative radiotherapy is often preferred with continuation of immune checkpoint inhibitors. In contrast, transition to an alternative standard or investigational systemic agent(s) is required in cases of diffuse progression. The decision regarding next-line therapy requires assessment of both cancer- and patient-specific factors, such as the molecular features of the tumor (eg, BRAF mutation status), the performance status of the patient, and clinical trial availability. Advancements in translational biomarker research are crucial in order to refine this treatment algorithm. Pre- and on-treatment biomarker discovery will hopefully aid clinicians in identifying patients who are likely to respond to front-line monotherapy with immune checkpoint inhibitors; importantly, it will also help to provide further insights into the optimal therapeutic strategies for individuals with primary resistance and those destined to develop acquired resistance.

**FINANCIAL DISCLOSURE:** The authors have no significant financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article.

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Multiple Myeloma With Extramedullary Disease: A Challenging Clinical Dilemma

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A 39-year-old woman with no significant medical history presented to the emergency department with progressive diffuse abdominal pain, involuntary weight loss, anemic syndrome, and limitation of mobility related to the presence of a right gluteal mass, all of which had persisted for the past 20 days. Physical examination revealed hepatomegaly, splenomegaly, ascites, right leg edema, and a palpable 6.0 × 5.3–cm mass in the right gluteus.

Blood tests were obtained following admission, revealing anemia (hemoglobin level, 9.9 g/dL), hyperglobulinemia (globulins level, 11.0 g/dL), hypercalcemia (calcium level, 14.15 mg/dL), and renal failure (creatinine level, 1.4 mg/dL), as well as coagulopathy with prolonged prothrombin time (PT), activated partial thromboplastin time (aPTT), and hypofibrinogenemia (fibrinogen level, 92.0 mg/dL). A CT scan showed ascites; splenomegaly; hepatomegaly dependent on multiple hypervascular intrahepatic tumoral lesions, the largest measuring 8.5 × 7.6 cm (segment 8 of Figure 1A); a solid soft tissue–dependent mass in the right iliac branch measuring 9.1 × 8.4 cm (Figure 1B); and multiple skeletal lytic lesions.

Due to clinical suspicion of monoclonal gammopathy, the following tests were performed: serum quantitative immunoglobulin (Ig) levels (IgA level, 14.0 mg/dL; IgM level, 20.0 mg/dL; IgG level, 6,842 mg/dL); beta-2 microglobulin level (10.5 mg/dL); serum free light chains (kappa level, 10.0 mg/L; lambda level, 7,500 mg/L; kappa/lambda ratio, 0.002); and serum protein electrophoresis and immunofixation, which showed an IgG lambda monoclonal paraprotein (6.8 g/dL).

Bone marrow trephine biopsy established the presence of 60% lambda clonal plasma cells (CD138-positive, CD56-negative, cyclin D1-negative; Figure 2), confirming a diagnosis of IgG lambda multiple myeloma. On cytogenetic analysis, the presence of chromosome 9 inversion and chromosome 17p11.2 deletion were identified: karyotype 5 = 46,XX,inv(9)(p13q13), del(17)(p11.2p11.2); karyotype 15 = 46,XX,inv(9)(p13q13). Fluorescence in situ hybridization from the bone marrow ruled out additional cytogenetic abnormalities. Peripheral blood immunophenotype ruled out plasma cell leukemia (4.8% CD138-positive plasma cells).

Regarding the presence of coagulopathy, additional tests were performed; the results of a thrombin time test were normal, and a mixing study found a correction of both PT and aPTT. Therefore, quantification of factor II (FII), factor V (FV), and factor X (FX) levels was com-
completed, all of which were low (FII, 26%; FV, 50.7%; FX, 27.5%). During the visit, the patient demonstrated mild mucocutaneous bleeding and was treated with fresh frozen plasma transfusion and cryoprecipitate without clinical instability.

Within days of the initial visit, the patient presented with clinical deterioration, including worsened renal failure requiring hemodialysis, coagulopathy, and disseminated candidiasis that led to death. After the patient passed away, a scientific medical autopsy was performed. Macroscopic findings complemented with histopathology tests were consistent with multiple myeloma with extramedullary disease (EMD) affecting the liver (Figure 3), gluteus muscle, ovaries, kidneys, and peritoneum.

**Discussion**

Multiple myeloma is a hematologic neoplasm characterized by a proliferation of clonal plasma cells, as well as evidence of related end organ damage. In most cases, the rapid reproduction of clonal plasma cells is restricted to the bone marrow; however, in some cases they can spread outside the bone marrow in patients diagnosed with multiple myeloma, which is recognized as EMD.[1-3] Currently, many questions remain regarding the clinical behavior, prognosis, and treatment of patients with EMD.

Over the last 2 decades, continuous debate has surrounded the definition of EMD. Initially, two clinical presentations were referred to as EMD: 1) a tumor mass adjacent to the bone that extends to the soft tissue and bone marrow (bone-related plasmacytoma), and 2) a tumor mass or diffuse infiltration by clonal plasma cells at a distant anatomical site not related to the bone.[4,5] In 2013, Weinstock and Ghobrial proposed that, taking into consideration the biological behavior and prognostic characteristics of this disease presentation, the term EMD should be restricted to the presence of EMD in patients with multiple myeloma, excluding bone-related plasmacytoma. [6]

The reported rate of patients presenting with EMD varies between 6% and 30%, depending on the time of EMD diagnosis, sites considered to be EMD, and the diagnostic method used for identification. When using adequate imaging techniques (ie, whole-body MRI or PET/CT), the incidence of EMD is approximately 7%.[2,5,7] In the relapsed/refractory setting, the prevalence of EMD has been reported to be as high as 10% to 30%; however, its real prevalence could be much higher when considering that autopsy studies have revealed extramedullary involvement in approximately 70% of suspected cases, with up to 40% infiltration to non–bone-related distant sites.[2,8-10]

To our knowledge, multiple myeloma with EMD affecting multiple distant-to-the-bone sites at diagnosis is rare; hepatic and ovarian involvement are particularly rare, with only a few cases reported in the literature.[11-13] In 2018, the European Society for Blood and Marrow Transplantation (EBMT) conducted a retrospective study that included 3,744 patients with multiple myeloma. Bone-related EMD was identified in 14.5% of the patients, only 3.7% of whom had non-paraskeletal involvement. The frequency of involved extramedullary sites was as follows: kidney (27.3%); skin (23%); lymph nodes (17.3%); central nervous system (10.1%); lung and respiratory tract (6.5%); gastrointestinal tract and liver (5.8%); pleura and heart (5.0%); and spleen, ovaries, and testicles (5.3%). In addition, 93.5% of patients presented with one involved site and only 6.5% with two or more.[7,14]

At the histopathology level, clonal plasma cells have an immature/plasmablastic appearance in patients with EMD,
while they have a mature/plasmacytic appearance in bone-related plasmacytoma. Differences in morphology, as well as the deleterious clinical impact of EMD, suggest that the pathogenesis of these two presentations is different. Although the exact mechanisms that contribute to the spread of clonal plasma cells is unknown, some pathophysiologic mechanisms have been proposed. Oncogene and tumor suppressor gene mutations that affect protein expression related to cell survival, migration, and invasion play a crucial role in patients with multiple myeloma.\(\text{TP53, RB1, FAK, and RAS genes, have been described in up to 50\% of patients with multiple myeloma with an EMD presentation.}\!^[2,4,6,15]\)

In EMD, migration of plasma cells to distant sites has also been related to the upregulation or downregulation of different molecules. Regarding adhesion molecules, CD56 and P-selectin promoters of the adherence of cells to the bone marrow are markedly unexpressed, while CD44—involved in proliferation, migration, and tumor metastasis—was found to have increased expression. Angiogenesis- and hypoxia-related factors (VEGF, MMP-9, angiopoietin-1, and CD31) and dysregulation of cytokines (CCR1, CCR2, and CXCR4/SDF-1) are still undergoing laboratory and clinical research, but have been described as specific pathogenic steps that limit or promote hematogenous dissemination of plasma cells.\!(15,16)\)

Multiple myeloma with EMD is known to have a highly aggressive disease presentation at both the time of diagnosis and relapse.\!(5,17)\) Usmani et al reported that EMD at diagnosis was associated with a significantly lower progression-free survival rate at 5 years compared with multiple myeloma without EMD, regardless of treatment modality (21\% vs 50\%; \(P < .001\)).\!(18)\)

More recently, the EBMT evaluated the impact of EMD on newly diagnosed multiple myeloma patients undergoing autologous hematopoietic stem cell transplantation (auto-HSCT). They found that patients with EMD had significantly lower rates of progression-free survival (39.9\% vs 47.9\%; \(P = .001\)) and overall survival (58\% vs 80.1\%; \(P < .001\)) at 3 years compared with patients without EMD. They also observed that the progression-free survival rate at 3 years was similar among patients with EMD with involvement of a unique site and patients without EMD (49.4\% vs 47.9\%, respectively; \(P = .36\)). However, when compared with cases involving multiple disease sites, patients with EMD had worse outcomes (47.9\% vs 22.7\%, respectively; \(P = .001\)).\!(14)\)

Considering the adverse impact that EMD has on clinical outcomes, the molecular and cytogenetic heterogeneity of multiple myeloma, and the lack of EMD-specific predictive scores, it is imperative that diagnostic strategies for this disease presentation be optimized. According to the current international recommendations, radiographs and MRI are acceptable methods for initial screening;\!(19,20)\) however, PET/CT has been recognized as a more effective technique, not only at diagnosis, but also during patient follow-up. Recent studies have demonstrated that PET/CT is a more sensible and specific tool to assess bone damage and extramedullary sites; distinguish between metabolically active and inactive disease; and determine response to therapy, including detection of minimal residual disease.\!(21-23)\)

Coagulopathy presenting in parallel with multiple myeloma has been described in 15\% to 40\% of cases.\!(24-26)\) Major hemorrhagic complications are rare, with clinically significant bleeding occurring in less than 15\% of patients, with no relation to the degree of laboratory test abnormalities. Risk factors related to bleeding include increased serum viscosity and levels of monoclonal paraprotein, as well as conditions that interfere with platelet function, coagulation factors, and fibrinolysis.\!(27,28)\) Incidence of coagulopathy in patients with EMD is unknown; nevertheless, previous reports have linked hemostatic disorders with high-risk multiple myeloma.\!(29,30)\)

Supportive care and timely control of primary neoplasia have been the only effective strategies to control related symptoms and complications.\!(24,31)\)

\![FIGURE 3 Macroscopic and Histopathologic Evaluation of Liver Autopsy Findings. (A) Multiple brown-colored nodular lesions in the liver parenchyma; (B) the major lesion measured 7.0 × 4.0 cm; (C and D) hematoxylin & eosin staining revealed a diffuse infiltration by clonal plasmablastic immature plasma cells related to multiple myeloma with extramedullary disease.](CANCERNETWORK.COM)
Targeted Therapy for Mutation-Driven Metastatic Non–Small-Cell Lung Cancer

Considerations for ALK-Rearranged Tumors

Kathryn F. Mileham, MD, FACP, Mufti N. Ahmad, MD, FACP, and Edward S. Kim, MD, FACP

A 64-year-old man ultimately diagnosed with ALK-rearranged non–small-cell lung cancer (NSCLC) with brain metastases initially presents to the emergency department with progressive dyspnea, a non-productive cough, and weight loss. His past medical history includes chronic obstructive pulmonary disease, nonalcoholic steatohepatitis, and non–insulin-dependent diabetes; he also has a 33 pack-year history of tobacco use, although he quit smoking 15 years prior to diagnosis. A chest x-ray is obtained, revealing questionable findings in the right hilum and a large right pleural effusion. A CT scan of the chest without contrast confirms right lung atelectasis, a large right pleural effusion, right lower lobe necrosis, and right hilar fullness.

Therapeutic and diagnostic thoracentesis was completed, with cytology positive for adenocarcinoma of the lung (thyroid transcription factor 1–positive, cytokeratin (CK)7-positive, CK20-negative, presence of WT-1, and calretinin-negative). Expression of programmed death ligand 1 (PD-L1) was 50%. ALK rearrangement was negative by fluorescence in situ hybridization (FISH) testing. The EGFR, ROS1, and BRAF genes were all wild-type. Due to rapidly reaccumulating symptomatic pleural effusion, video-assisted thoracoscopic surgery with right pleural tissue biopsy and talc pleurodesis were completed.

Pleural tissue was sent for pathology review and was once again consistent with adenocarcinoma of the lung. However, PD-L1 expression was 0%, and ALK rearrangement by immunohistochemistry was positive. ALK testing was repeated on this tissue sample with FISH (via the US Food and Drug Administration [FDA]-approved Vysis ALK Break Apart FISH Probe Kit), which detected the ALK (2p23) rearrangement in 52% of the cells analyzed.

Completion staging imaging was obtained, including a PET/CT scan and brain MRI with and without contrast. The PET/CT scan demonstrated a hypermetabolic lesion in the posterior right lower lobe, extensive hypermetabolic pleural-based disease in the right hemithorax with hypermetabolic right hilar and subcarinal lymph nodes, as well as lymph nodes at the left mediastinum and left neck base. Multiple foci of osseous metastases were visible, as was a possible small lesion in the left liver. Brain MRI revealed 3 metastatic lesions: a 12-mm lesion in the right caudate nucleus, a 10-mm lesion in the right temporal lobe, and a 3-mm lesion in the left cerebellar hemisphere.

The patient experienced an ongoing non-productive cough, dyspnea on exertion, right pleuritic pain, and back pain. He consulted with a radiation oncologist and received stereotactic radiosurgery to the right temporal lobe lesion (21 Gy) and the right parietal lobe lesion (21 Gy). The 3-mm lesion was not treated with radiation. First-line systemic treatment was initiated with 600-mg oral alectinib twice daily, which was well tolerated with no significant treatment-related toxicities. The patient’s disease-related symptoms improved. Imaging was repeated 6 weeks later. A brain MRI with and without contrast revealed a complete response in all 3 lesions, including the 3-mm lesion that was not initially treated with radiation. A CT scan of the chest/abdomen/pelvis with contrast exhibited a significant radiographic response in all previously identified sites of disease.

Treatment Considerations for ALK-Rearranged Metastatic NSCLC

The scope of treatment for ALK-rearranged metastatic NSCLC has substantially evolved since the initial identification of this aberration. Although ALK+ met-
Rationale Behind Targeted Therapy With Alectinib

The global phase III ALEX study compared alectinib with crizotinib in the first-line treatment of ALK+ metastatic NSCLC. The primary analysis showed a significant improvement in the study’s primary endpoint, median progression-free survival (PFS), with alectinib,[3] leading to its FDA approval in the first-line setting. In this patient’s case, first-line targeted therapy with alectinib was chosen based on the results of this trial. Moreover, the efficacy of alectinib in the CNS limited the need for whole-brain irradiation in the setting of few, small, and asymptomatic brain metastases.

At the 2018 American Society of Clinical Oncology Annual Meeting, the ALEX study was updated with 10 months of additional follow-up data.[4] Among the findings were an unprecedented investigator-assessed median PFS of 34.8 months and an updated hazard ratio (HR) of 0.43. The duration of treatment was also longer. In addition, the depth of response was deeper: > 40% of responders treated with alectinib demonstrated > 75% tumor reduction compared with ~25% of responders treated with crizotinib. Rates of significant adverse events were lower, and subsequent dose adjustments and treatment discontinuations were fewer. Notably, among the 303 patients included in this analysis, about 40% in each arm had baseline CNS metastases; 122 patients harbored baseline CNS metastases (alectinib arm, n = 64; crizotinib arm, n = 58), and 43 harbored measurable lesions (alectinib arm, n = 21; crizotinib arm, n = 22). In addition, 46 patients had received prior radiotherapy (alectinib arm, n = 25; crizotinib arm, n = 21).[4]
PFS with alectinib was comparable between patients with baseline CNS metastases (HR, 0.40; 95% CI, 0.25–0.64) and those without CNS metastases (HR, 0.51; 95% CI, 0.33–0.80), despite prior radiotherapy status. Time to CNS progression was significantly longer with alectinib versus crizotinib and was similar to that of patients with and without baseline CNS metastases (P < .0001).

In patients who were administered prior radiotherapy, the CNS objective response rate (ORR) was 85.7% with alectinib versus 71.4% with crizotinib. Among those who had not been administered previous radiotherapy, the ORR was 78.6% for alectinib versus 40.0% for crizotinib.[4]

Of high significance, the endpoints in the ALEX trial were also assessed based on CNS involvement. The median PFS, duration of response, and depth of response were all upheld regardless of baseline CNS metastases.[4] For patients with small and asymptomatic brain metastases in the setting of ALK-rearranged NSCLC, there is an opportunity to defer whole-brain irradiation until intracranial response to alectinib is assessed radiographically. With alectinib, assuming this clear position as the first-line treatment for ALK+ metastatic NSCLC, it will become even more important to understand ALK resistance patterns and appropriate drug sequencing when a patient progresses on alectinib.[3,4]

**Forgoing Immune Checkpoint Therapy**

The decision not to administer immunotherapy was based on previous research involving EGFR/ALK-mutated metastatic NSCLC with characteristics similar to the patient in this current case study, whose tumor harbored an ALK rearrangement. Trials of second-line or later treatments for metastatic NSCLC have shown that patients with EGFR-mutant tumors do not benefit from checkpoint inhibitors. This seems to be the case regardless of PD-L1 expression. In a meta-analysis,[5] Lee et al found that, in patients with driver mutations, immune checkpoint inhibitors do not lengthen overall survival (OS) any more than docetaxel. The three studies included in this meta-analysis compared immune checkpoint inhibitors (nivolumab [n = 292], pembrolizumab [n = 691], and atezolizumab [n = 144]) versus docetaxel (n = 776). In the overall population, immune checkpoint inhibitors resulted in longer OS compared with docetaxel (n = 1,903; HR, 0.68; 95% CI, 0.61–0.77; P < .0001). The same benefit was seen in the EGFR wild-type subgroup (n = 1,362; HR, 0.66; 95% CI, 0.58–0.76; P < .0001). However, in the EGFR-mutant subgroup, no increase in OS was observed (n = 186; HR, 1.05; 95% CI, 0.70–1.55; P < .81).[5]

The patient in this case study had a PD-L1 tumor proportion score (TPS) of 50% on pleural fluid but 0% on pleural tissue. In an abstract,[6] Hui et al showed that, among patients with a PD-L1 TPS higher than 50% treated with pembrolizumab, those with EGFR-mutant tumors had significantly reduced OS versus those with EGFR wild-type tumors (median OS, 6.5 versus 15.7 months). Furthermore, OS did not change significantly based on PD-L1 expression in the EGFR-mutant group (TPS > 50% vs < 1%; median OS, 6.5 versus 5.7 months). In the EGFR wild-type subgroup, however, a difference was observed (TPS > 50% vs < 1%; median OS, 15.7 versus 9.1 months). Notably, the patient’s tumor in this case study had an ALK rearrangement—not an EGFR mutation. However, similar results have been demonstrated for both and are anticipated regardless of the driver mutation (ie, EGFR or ALK).[6]

In a retrospective study,[7] Gainor et al found that NSCLC tumors possessing EGFR mutations or ALK rearrangements are significantly linked to lower ORR values when treated with programmed death 1 (PD-1)/PD-L1 inhibitors. The authors observed objective response rates in only 1 of 28 EGFR/ALK-mutant patients (3.6% vs 7 of 30 EGFR/ALK wild-type patients [23.3%; P = .053]). Additionally, the ORR among never- or light-smokers (≤ 10 pack-years) was 4.2% versus 20.6% among heavy smokers (P = .123). Not only did the patient in the current case study have ALK-rearranged NSCLC, he would also be considered a heavy smoker per these cut-
offs in pack-years, with a lower ORR in response to PD-1/PD-L1 inhibitors.[7]

Summary
Although immunotherapy has significantly impacted the treatment of metastatic NSCLC, regardless of the PD-L1 TPS, treatment with immunotherapy is not prioritized over targeted therapy in the first-line treatment of tumors with EGFR or ALK driver mutations. When a driver mutation is identified in metastatic NSCLC, such as the ALK rearrangement seen in this case study, targeted therapy provides the best outcomes on multiple levels. In an era of immune checkpoint inhibition, it is important to remember that the driver mutation—not the PD-L1 expression—determines first-line treatment. The benefit of agents penetrating the CNS is important, since it may provide alternatives to whole-brain irradiation, which has potentially unwanted toxicities.

FINANCIAL DISCLOSURE: Dr. Mileham is on the speakers’ bureau for Merck, Dr. Ahmad and Dr. Kim have no significant financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article.

For references visit cancernetwork.com/ALK-rearranged-NSCLC

Multiple Myeloma With Extramedullary Disease
Continued from page 151

One limitation of current therapy recommendations is that no prospective clinical trials have focused specifically on multiple myeloma patients with EMD. Expert opinion favors considering EMD to be a high-risk disease feature, and therefore to treat it with an intensive regimen. In this context, the preferred regimen for a newly diagnosed transplant candidate is triplet induction therapy including a proteasome inhibitor (bortezomib or bortezomib with lenalidomide/dexamethasone), followed by auto-HSCT with high-dose melphalan conditioning, triplet consolidation therapy, and maintenance therapy with lenalidomide (Answer A).[3] For non-transplant candidates, standard-of-care triplet therapy with an alkylating agent and proteasome inhibitor (bortezomib plus melphalan and prednisone), or continuous lenalidomide with dexamethasone, are the most effective therapies with high response rates.[32]

Routine use of tandem auto-HSCT (Answers B and D) has been proposed by some groups. Evidence in patients with EMD is scarce, since the evidence supporting its use was based on its utility in high-risk patients.[33] Allogeneic HSCT (Answer C) has been reserved for patients with disease that does not respond to therapy or those who experience relapse after initial therapy with auto-HSCT.[33,34]

Although there are no prospective data, current ongoing trials evaluating various upfront therapies have been integrating the use of PET/CT into the diagnosis and follow-up of patients—a strategy that will hopefully aid in more precisely analyzing response to therapy and clinical outcomes in patients with EMD.

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For references visit cancernetwork.com/MM-EMD-case
Supporting Data vs Patient Requests in Oncology: When the Two Don’t Coincide

Mehmet Sitki Copur, MD

ABSTRACT: Relationships between cancer patients and their oncologists flourish in a milieu of trust and goodwill. However, at times cancer patients may express strong preferences for medical tests, treatments, or other interventions that are not beneficial. Actively challenging these requests can be difficult and may threaten the patient–physician relationship. However, failure to discuss why specific diagnostic or therapeutic interventions are not appropriate may be harmful to the patient and lead to inefficient use or overuse of healthcare resources. It is therefore crucial that oncologists steer patients away from unnecessary or harmful tests and procedures in an eloquent and respectful manner. In addition to utilizing individualized clinical reasoning, clinicians can also consult clinical practice guidelines to help respond to these requests using an external source of authority. However, guidelines may not always be sufficient. This article reviews this topic and provides recommendations from a community oncology practice perspective.

Introduction
From diagnostic work-up and treatment through surveillance, cancer patients’ requests can influence management decisions. These requests may not always represent the oncologist’s first choice or be in line with established clinical guidelines. Practicing oncologists may have concerns about rejecting patient requests, in part because of the perception that rejection may lower patient satisfaction. Several studies, mostly in primary care, have reported rather conflicting results. While some found that refusal of patient requests was associated with lower patient satisfaction,[1-4] no such association was found in others.[5] Physicians have an ethical duty to maximize patient benefit and avoid doing harm. Refusal of patient requests may seem to conflict with respecting patient autonomy.[6,7] While consumer empowerment in healthcare is increasingly emphasized, physicians frequently find themselves as the target of cost-control measures and, as such, are being asked to restrain the use of expensive but marginally beneficial treatments.

Reported Data on Patient Requests

General medicine–specific data
Published data show that patient requests for clinical services are both inescapable and influential, and are more common in the primary care vs specialty medicine setting. Surveys show that 40% to 66% of physicians report having received patient demands or requests for tests or treatments, and 25% to 53% have complied at least once with such requests.[8-11] One quantitative study, which relied on the researchers’ interpretation of audiotapes, found the frequency of patient demands for a test, new prescription, or referral to be 23%.[12] In another study, phy-
Physicians’ approaches to denying requests for antidepressants were classified into patient perspective–based, biomedically based, or outright rejection as the primary denial reason. Higher visit satisfaction was reported by patients when the physician used a patient perspective–based strategy in order to refuse requests.[13]

Unmet requests may affect the physician–patient relationship, and physicians must learn to manage these requests in a reverent and clinically meaningful fashion. In a vignette-based study, researchers found that physician communication style, namely shared decision making, led to better evaluations of care in response to denial of a direct-to-consumer advertising-based request.[14]

In another study examining physician responses to patient requests for an expensive unindicated test, a few physicians ordered the test, but most referred the patient to a specialist.[15] The higher volume of patient requests in primary care vs specialty care may partly be attributed to the fact that scope of practice in primary care is broader, and primary care providers typically evaluate more conditions per visit than do specialty providers.

**Oncology-specific data**

Most of the reported data on patient requests comes from research conducted in non-oncology settings. A cancer diagnosis is almost always psychologically stressful, with chronic and disruptive changes to patients’ daily living. Cancer patients may spend a lot of their time feeling unhealthy, and the mental and physical tolls on them can be enormous. Due to the seriousness of their disease, the life-or-death motivation to find effective treatments, and the extensive information available on the internet, many cancer patients ask for high-cost and/or inappropriate imaging; genomic testing; and surgical, medical, or radiation therapies. They may request interventions based on media publicity about new research findings, sometimes even before their oncologists learn about them. Internet sources of clinical information on this often neglected topic in this article. The paper indicates that almost half (49.1%) of demands for tests were for imaging tests. One aspect of imaging tests that is often overlooked by patients is radiation exposure: I have found that patients grasp the importance of it when they compare the exposure with a more understandable and tangible reference. That is why the Wall Street Journal article’s summary of radiation levels for various medical procedures (Table), with a striking reference to atomic bomb exposure, is particularly relevant.

[1] When seen in this light, patients requesting repeated unnecessary CT scanning often find a more balanced view of the pros and cons of testing.

**TABLE Estimated Radiation Levels for Various Medical Procedures vs Atomic Bomb Radiation[1]**

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Exposure to intravenous contrast material can cause harm, such as kidney or lung damage resulting from iodine contrast, but other contrast materials may also be problematic. In 2017, the US Food and Drug Administration addressed the concern of such agents remaining in patients’ bodies for months to years after receiving scans by requiring a new class warning and other safety measures for all gadolinium-based contrast agents.[2]

Routine surveillance scans following cancer treatment are a frequent subject of discussion at oncology patient follow-up visits, and tools such as the National Comprehensive Cancer Network guidelines are helpful in following a reasonable plan.[3] It is worth remembering the experience of the National Surgical Adjuvant Breast and Bowel Project, which utilized routine repeat bone scans after breast cancer treatment. Their protocols required bone scans every 6 months for 3 years postoperatively and then yearly thereafter. The resulting data revealed that these tests were not helpful, and protocols subsequently required scans only as indicated by symptoms.[4]

Objective third-party, science-based published references that are available to patients can be powerful informational tools. In oncology practice, it is important to always balance the benefits and risks of interventions. In my experience, patient satisfaction is highest when patients are given helpful information that protects them from unnecessary harm, anxiety, and expenses.

**FINANCIAL DISCLOSURE**

Dr. Tchekmedyian has no significant financial interest in the manufacturer of any product or provider of any service mentioned in this article.

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**PERSPECTIVE BY**

Simon Tchekmedyian, MD, FACP

Utilizing Tangible Examples and Third-Party Data to Back Up Saying “No”

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tion increasingly empower cancer patients to make medical judgments independent of consultations with their oncologists. Furthermore, widespread direct-to-consumer advertising may prompt patients to ask for specific treatments that may not be appropriate. Fortunately, requests for nonbeneficial interventions can often be addressed by applying established practice guidelines. When guidelines recommend against a requested intervention, oncologists can respond to patients using external sources of authority and depersonalize potential conflict with the patient.

Understanding and addressing the patient’s role in making healthcare-related decisions as they relate to cancer care are crucial. Interestingly, however, surprisingly limited published data exist on this topic in the oncology practice setting. In one of these rare studies, Gogineni et al reported an 8.7% rate of patient demand or request. Of 5,050 oncology patient-clinician encounters involving 3,624 patients and 60 clinicians, a total of 440 patients requested or demanded a medical intervention. Oncology providers felt that 365 of these requests (83.0%) were clinically appropriate and thus complied with them. In only 50 of the 440 encounters (11.4%), the patient request or demand was deemed not clinically appropriate. However, 7 of these inappropriate demands or requests (14%) were granted, thus bringing the total compliance rate with inappropriate demands or requests to only 0.14% (7 of 5,050 total encounters). Of the 440 patient demands, 216 (49.1%) were for imaging studies; 68 (15.5%) were for palliative treatments, excluding chemotherapy or radiation; and 60 (13.6%) were for laboratory tests. In a multivariate model, having lung or head and neck cancer, receiving active treatments, and having a fair- or poor-quality patient-clinician relationship were associated with an increased likelihood of patient demands or requests (P < .01). Considering the high stakes of a cancer diagnosis and patients’ deep dependence on their oncologists, a nearly 9% rate of patient requests as reported here seems low. This may partly be due to the use of physician recall measure (up to 4 hours after the visit) utilized in this study, as well as the location of the study in large, tertiary, city-based cancer centers, which offer a full slate of aggressive diagnostic and therapeutic services.

Meaningful Use of Healthcare Resources

As science progresses and the ability to provide improved treatments increases, so does the cost of cancer care. Despite best efforts to improve efficiency, the effectiveness of therapy can be overwhelmed by the limited availability of clinical services and the pressure to provide them. Responsibly managing healthcare resources is critical and may require oncologists to oppose requests for nonbeneficial interventions. Several efforts to reduce such interventions have been initiated, such as the American Society of Clinical Oncology’s Choosing Wisely® campaign, which identified the top 5—and, subsequently, the top 10—tests that should never be ordered. [18-20]

On an individual level, stewardship is facilitated by evidence-based data. In some situations, however, available evidence may not provide a clear course. In an era of increased constraints on healthcare systems and practitioners, learning to say “no” to patient requests will become more important and more challenging.

How I Handle Nonindicated/Nonbeneficial Patient Requests

During my 23 years in community oncology practice, I have encountered my fair share of patient requests/demands that were not supported by the guidelines, not medically indicated, and, at times, that were even potentially harmful. In these situations, I first explore whether I might be missing any medical indications. Next, I try to understand why the patient is making the request. What is the driving force behind it? Once I figure that out, I take the time to provide education to correct or clarify any misunderstanding or misinformation the patient may have.

Before I decline a request, I make sure I take the necessary time to explain the reasoning behind my decision so that he does not suspect that I am merely ignoring her/his concerns, or acting in the interest of cost containment, rather than in his/her best interest. Most of the time, this approach is more than enough and resolves the conflict. However, the major hurdle with this approach, as you may predict, is time constraints, which we all have in our very busy and demanding daily practice. To get around this challenge, I frequently find myself making additional time during after hours, once my active immediate patient care duties have been completed for the day.

Cancer patients are special people. They are brave. They are rational. They are smart. They are resilient. Most of the time, they do have a special and cordial relationship with their oncologists. In my experience, cancer patients prove to be incredibly appreciative and trusting when their oncologist takes the time to build a confidence level with them that makes them realize they are truly and genuinely cared for. It just takes some extra time, empathy, and understanding.

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