COLORECTAL CANCER
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HODGKIN LYMPHOMA
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Polycythemia Vera: Contemporary Updates in Diagnosis, Prognosis, and Treatment
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This issue of *The American Journal of Hematology/Oncology®* features insightful reviews on metastatic colorectal cancer, Hodgkin lymphoma, lung cancer, and polycythemia vera (PV). A common challenge addressed throughout the papers is the problem of resistance, which develops over time. It is the hope that these reviews, while providing the latest rationale for therapeutic options, at the same time spurs the innovative clinician to consider new approaches to managing these cancer types.

In “Targeted Therapy and the Use of Molecular Profiling in Metastatic Colorectal Cancer,” Dr Gagandeep Brar and colleagues comment on the role of predictive biomarkers in identifying subpopulations of patients who would benefit from appropriately targeted therapy and the magnitude of benefit of those therapies.

The field of Hodgkin lymphoma is rapidly changing. For example, in the treatment-naïve setting, Lorie A. Leslie, MD, and coauthors suggest that radiation therapy will be used more selectively, as novel agents are incorporated into upfront treatment regimens with the goal of decreasing long-term toxicity. In “Reshaping the Field of Hodgkin Lymphoma,” they discuss how to best use a PET-adapted approach to escalate versus de-escalate treatment.

In 1 of 2 lung cancer manuscripts in this issue, Luis E. Raez, MD, and Christian Rolfo, MD, PhD, MBA, discuss an interesting case involving a patient who developed a T790M mutation after erlotinib therapy. The use of liquid biopsy demonstrated this evolutionary genomic change after a tumor biopsy failed to do so. Another resistance mutation, c.797s, was discovered after osimertinib therapy. In the second manuscript, Drs Zweig and Wakelee review frontline trials of ceritinib and alectinib in ALK-positive non–small cell cancer, drawing comparisons with crizotinib, the only FDA-approved frontline choice until the recent approval of ceritinib. With several new promising options, they attempt to better answer the question of which ALK tyrosine kinase inhibitor should be favored upfront.

In “Polycythemia Vera: Contemporary Updates in Diagnosis, Prognosis, and Treatment,” Saba S. Shaikh, MD, and Brady L. Stein, MD, MHS, discuss recent developments in the epidemiology of PV. They note that the molecular pathogenesis of the condition continues to be characterized, and the diagnostic criteria allow for recognition of more subtle presentations of PV.

This month’s CME article features an interview with Angela DeMichele, MD, MSCE, the Jill and Alan Miller Endowed Chair in Breast Cancer Excellence at the Abramson Cancer Center at the University of Pennsylvania. She provides an overview of the current and emerging role of PARP inhibitors in breast cancer.

Michael J. Hennessy, Sr
*Chairman and Chief Executive Officer*
From the Editor

The summary of first-line therapy for the relatively uncommon set of genomic alterations of the ALK gene in non–small cell lung cancer (NSCLC) provided in this issue of the American Journal of Hematology/Oncology® by Wakelee et al demonstrates the clear and steady progress in genomically personalized cancer therapy. The initial presentation of the dramatic activity of crizotinib in ALK-rearranged lung cancer at the ASCO 2010 Plenary ushered in a new era of effective treatments for rare subsets of common cancers. It is also notable that this presentation came only 3 years after the initial discovery of the EML4-ALK fusion gene as a driver of lung cancer. Since this time, it is remarkable that for a rare cancer subtype there are now 4 approved agents for this genomic aberration, a necessary development because escape pathways invariably develop to most targeted agents. Some of these newer drugs will be shifted to when they should best be used—alecinitib was approved in 2015 for second-line treatment of ALK-positive lung cancer after progression on crizotinib, but with the recent demonstration of significant activity in untreated patients, and just-published (online) positive findings of the ALEX trial showing superior progression-free survival with alecinitib compared with crizotinib, it is now expected to be approved as frontline therapy. And an added bonus is less toxicity and fewer central nervous system progression events seen with alecinitib. It is encouraging that although these drugs are not curative, they are being rapidly developed and optimized in terms of sequence of use.

A case report by Raez and Rolfo also in this issue presents an interesting case of another mutation, T790M, that drives resistance in NSCLC to the first-line EGFR mutation–targeting drugs erlotinib and gefitinib. In this case, the use of liquid biopsy was able to show this evolutionary genomic change after a tumor biopsy failed to do so. Although there are no standards regarding multiple repeat biopsies, and the costs for doing this may prove untenable, we clearly need improvements in diagnostic sensitivity and several new technologies are attempting to do just that. In this case report, a response was seen to osimertinib, which is approved specifically for T790M mutation-associated NSCLC in second-line therapy. The FLAURA trial results recently released showed that osimertinib outperformed erlotinib or gefitinib as first-line therapy for EGFR-mutant NSCLC—so much shuffling is likely to ensue. And the beat goes on….

References
Targeted Therapy and the Use of Molecular Profiling in Metastatic Colorectal Cancer

Gagandeep Brar, MD; John L. Marshall, MD; and Michael J. Pishvaian, MD, PhD

Abstract

Metastatic colorectal cancer (mCRC) is the third leading cause of cancer-related mortality in the United States, but survival rates for advanced CRC have improved significantly in the past 15 years. This improved survival is due, in large part, to more effective chemotherapy, but improvements have also been attributed to the incorporation of therapies that either target, or are guided by, the multiple aberrant signaling pathways involved in the growth and spread of colorectal cancer cells, including the VEGF, EGFR, RAS/RAF, and HER2 signaling pathways, as well as genetic changes induced by mismatch repair enzyme deficits and the resultant microsatellite instability. Targeted treatments directed toward inhibiting these pathways have improved survival rates beyond those achieved with standard chemotherapy. This review provides an update on targeted agents used in mCRC and the impact that specific, defined predictive biomarkers have on patient selection and, ultimately, patient outcome.

AJHO. 2017;13(9):4-12

Introduction

Colorectal cancer (CRC) is the third leading cause of cancer-related death in the United States, affecting men and women equally. In 2017, there will be an estimated 135,430 new cases, with 50,260 deaths due to CRC. Approximately 20% of patients are diagnosed with advanced or metastatic disease on presentation, and 50% of all CRC patients will develop progressive disease and metastases over time. The prognosis for patients with advanced disease without treatment is poor, with a median overall survival of 6 months. However, advances in systemic therapy with combination chemotherapy using a fluoropyrimidine, irinotecan, and oxaliplatin have improved survival rates up to 20 months.

The development of targeted agents aimed at blocking key pathways involved in CRC cell growth and invasion further improved survival through the latter part of the first decade of the 2000s. The VEGF pathway inhibitors—primarily bevacizumab, but more recently ziv-aflibercept and ramucirumab—increased survival rates, compared with chemotherapy alone.

However, any predictive marker for selecting patients who would benefit most from VEGF pathway inhibitors has been elusive, and will not be discussed herein.

By contrast, other therapies, including those either targeting, or guided by, molecular abnormalities in the EGFR, RAS/RAF, and HER2 pathways, as well as immunotherapy for tumors with high levels of microsatellite instability, have defined predictive biomarkers, and they have demonstrated significant impact in well-selected patients.

This review will focus on molecularly targeted agents in metastatic colorectal cancer (mCRC) that have defined predictive biomarkers. We will also comment on the role of “molecular profiling” in identifying these subpopulations of patients who will benefit from appropriately targeted therapy, and the magnitude of benefit of those therapies.

Targeting the EGFR

The EGFR is overexpressed in approximately 60% to 80% of CRCs. Activation of the EGFR stimulates downstream signaling through the RAS, RAF, MAPK, and ERK pathways, leading to activation of several pathways involved in cell survival, proliferation, and the ability of cancer cells to metastasize.

Two anti-EGFR treatments have been approved for patients with mCRC: cetuximab and panitumumab. Both drugs are monoclonal antibodies that target the EGFR, preventing receptor activation and thereby inhibiting the signaling via the RAS/RAF/MAPK/ERK pathway (Figure). Both were first approved in the refractory disease setting with EGFR as the sole predictive biomarker of response.

Cetuximab was initially studied by Cunningham and colleagues. In the BOND trial, 329 chemotherapy-refractory patients with CRC were randomized to receive cetuximab and irinotecan versus cetuximab alone. To be eligible, either the primary tumor or a metastatic lesion must have expressed EGFR by immunohistochemistry (IHC). The objective response rate (ORR) was 22.9% (95% CI, 17.5%-29.1%) in the cetuximab-plus-chemotherapy arm and 10.8% (95% CI, 5.7%-18.1%) in the cetuximab-alone arm (P = .007). The progression-free survival (PFS) improved to 4.1 months in the combination arm, compared with 1.5 months with singleagent cetuximab. The overall survival (OS) rate did not improve when compared with cetuximab alone in EGFR-expressing patients who had progressed through irinotecan-based therapy. Of note, the degree of EGFR expression did not correlate with response, but patients with skin reactions after treatment with cetuximab had higher response rates than those without skin reactions. Grade 3 or 4 adverse
events (AEs) most commonly included diarrhea (21% in the combination arm vs 2% in the monotherapy arm) and neutropenia (9.4% in the combination arm vs 0% in the monotherapy arm).24

Panitumumab was shown to improve outcomes when compared with best supportive care (BSC) in the trial by Van Cutsem and colleagues.25 Randomization of 463 chemotherapy-refractory patients to single-agent panitumumab improved ORR and PFS but not OS (hazard ratio [HR], 1.00; 95% CI, 0.82%-1.22%; P = .81) when compared with BSC alone. The lack of OS benefit was thought to be due to the confounding variable of the crossover design of the study.25

The Impact of pan-RAS Testing
The above-mentioned trials, however, were done in the “pre-RAS” testing era.4,18,26 Posthoc analysis of these trials, as well as of several additional pivotal trials with cetuximab and panitumumab, have shown the benefit of KRAS testing, and more recently “pan-RAS” testing, on outcome in patients with mCRC (Table 1).

RAS and its subtypes, KRAS and NRAS (and likely HRAS), as well as the downstream signaling effector RAF, have been important markers in the treatment of CRC.18 When genetic mutations occur that result in constitutive activation of the RAS or RAF enzymes, signaling is activated down the RAS/RAF/MAPK/ERK pathway irrespective of inhibition of the EGFR, upstream of the active enzyme. Thus, logically, treatment with cetuximab or panitumumab on tumors with RAS or RAF gene mutations has generally demonstrated no benefit. This is true for other less-frequent RAS mutations, and may be the case for BRAF, but this has not been well established. KRAS mutations are present in approximately 40% of all CRC patients and can be seen in both early- and late-stage disease.21,22 The most common activating mutations occur in codon 12 and 13 of exon 2 of the KRAS protein. Within codon 12, the G12D and G12V mutations are the most common, occurring 13% and 9% of the time, respectively. In codon 13, G13D is the most frequent mutation, occurring in 8% of KRAS-mutated CRC. The frequencies of NRAS and RAF mutations are less common; they are seen in approximately 2% and 9% of patients, respectively.22 Altogether, “pan-RAS” wild-type (WT) tumors—those with WT KRAS, NRAS, likely HRAS, and RAF genes—make up only about 40% of CRCs, but there is a significant chance of benefit with anti-EGFR therapies in pan-RAS WT tumors.23

A number of studies have looked at mutations in the RAS pathway and their predictive and prognostic significance in colon cancer. When the initial anti-EGFR therapy trials were re-evaluated, taking into consideration pan-RAS status, it was clear that the magnitude of benefit of anti-EGFR therapy was much greater when restricted to patients with pan-RAS WT tumors only.

In a study by Jonker and colleagues (the joint Canadian/Australasian CO.17 trial) cetuximab was compared with BSC in EGFR-expressing mCRC and showed improved survival (HR for death, 0.77; 95% CI, 0.64-0.92; P = .005) in addition to improved PFS (HR, 0.68; 95% CI, 0.57-0.80, P < .001) and ORR.29 KRAS mutational status was not initially evaluated, but a posthoc analysis of the trial revealed that tumors with KRAS exon 2 mutations treated with cetuximab had a worse outcome compared with those without the mutation or with WT KRAS status, with an OS of 9.5 months for the patients with KRAS WT tumors versus 4.8 months for the patients with KRAS-mutated tumors (HR, 0.55; 95% CI, 0.41-0.74, P < .001).23

When KRAS mutational status was examined in the posthoc analysis of the Van Cutsem study of panitumumab versus BSC, PFS was significantly greater in the WT KRAS group (12.3 weeks; HR, 0.45; 95% CI, 0.34-0.59) compared with the mutated KRAS group (7.3 weeks; HR, 0.99; 95% CI, 0.73-1.36).28 The nonmutated KRAS group also had an improved OS compared with the mutated arm.18 Given the predictive value of identifying RAS mutations in mCRC, the concept of extended RAS analysis was first initiated by the PRIME and
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BSC indicates best supportive care; C, cetuximab; CAPOX, capecitabine and oxaliplatin; FLOX, bolus 5-fluorouracil with leucovorin and oxaliplatin; FOLFOX, 5-fluorouracil with leucovorin and oxaliplatin; FOLFIRI, 5-fluorouracil with leucovorin and irinotecan; FOLFOX/CAPDX, 5-fluorouracil with leucovorin and oxaliplatin; HR, hazard ratio; IRI, irinotecan; mut, mutant; NA, not available; OR, odds ratio; ORR, overall response rate; OS, overall survival; P, panitumumab; PFS, progression-free survival; RR, response rate; WT, wildtype.

PEAK studies. In the PRIME study, 512 patients with mCRC who were treated with FOLFOX4 (folinic acid, fluorouracil, oxaliplatin) with or without panitumumab were assessed according to RAS (KRAS or NRAS) or BRAF status. Patients who were WT for extended RAS analysis including KRAS and NRAS exon 2, 3, 4 had a 5.8-month OS benefit with the addition of anti-EGFR therapy compared with chemotherapy alone (26.0 vs 20.2; P = .04). The PEAK study looked at extended RAS analysis including exon 2, 3, 4 of KRAS and NRAS in patients with WT KRAS mCRC. It compared FOLFOX6 plus bevacizumab versus FOLFOX6 plus panitumumab in 278 patients with KRAS WT exon 2 mCRC. Like the PRIME study, the PEAK trial showed an improved PFS and OS in WT RAS compared with KRAS exon 2 mutated CRC for patients treated with panitumumab. In the RAS WT patients, improved PFS rates were seen with panitumumab (HR, 0.65; 95% CI, 0.44; 0.96; P = .029). OS was 41.3 months in the panitumumab arm versus 28.9 months in the bevacizumab arm (HR, 0.63; 95% CI, 0.39-1.02; P = .58). The results
of these 2 studies suggest that mutations in the RAS pathway, including those beyond KRAS exon 2 mutations, are predictive of a lack of response to anti-EGFR therapy for patients with mCRC.

Some data from Tejpar and colleagues suggest that patients with the KRAS G13D mutation may derive benefit when treated with cetuximab in combination with chemotherapy, compared with other KRAS mutations, but the effectiveness is still less than that seen in KRAS WT patients. Although this study highlights the variations in tumor biology seen in KRAS-mutated CRC, more clinical data are needed.

Interestingly, not all KRAS WT CRC responds to anti-EGFR treatment either, suggesting additional mutations also confer resistance. Emerging data indicate that the location of the primary tumor in mCRC has a role in predicting a response to EGFR inhibitors. Patients with left-sided KRAS WT tumors, located between the splenic flexure and rectum, were shown to have improved OS if first-line treatment included cetuximab compared with bevacizumab (37.5 vs 16.4 months; HR, 1.97; 95% CI, 1.56–2.48). A number of additional genes are known to be somatically mutated and have been studied in response to anti-EGFR therapy. A study by Peeters and colleagues used next-generation sequencing on mCRC tissue and found additional mutations in PTEN, TP53, EGFR, AKT1, and CTNNB1. Patients with WT KRAS but mutated NRAS or BRAF did not respond to panitumumab; however, if patients were WT for KRAS, NRAS, and BRAF, the ORR was 18%.

Fifteen years of clinical trials of anti-EGFR therapies, and more recent incorporation of RAS/RAF testing, have demonstrated that patients with pan-RAS WT tumors derive significant benefit from anti-EGFR therapy, while patients with RAS/RAF-mutated tumors derive little to no benefit. In fact, some studies have shown a detrimental effect and decreased OS (rather than just a lack of benefit) in patients with KRAS-mutated CRC who are treated with an EGFR inhibitor. Therefore, pan-RAS testing to evaluate mutations in KRAS, NRAS, and BRAF is an accepted standard-of-care practice in patients with mCRC. With 60% of tumors being RAS/RAF-mutated, the challenge in the coming years will be to identify novel therapies that target RAS/RAF-mutated tumors specifically.

**BRAF Mutations**

BRAF is a subset of the RAS family of oncogenes, which is mutated in approximately 10% of CRC cases and has been associated with decreased survival. The most common BRAF mutation is located in exon 15, resulting in a substitution from valine to glutamic acid at position 600 within the BRAF kinase domain (V600E). This leads to constitutive activation of the MAPK signaling pathway. Standard chemotherapy in combination with EGFR inhibitors in patients with mCRC who harbor the BRAF V600E mutation is less effective than in those with BRAF WT tumors. In patients with KRAS WT/BRAF-mutated tumors who were treated with FOLFIRI (5-fluorouracil with leucovorin and irinotecan) plus cetuximab, there was no statistically significant improvement in OS with the addition of anti-EGFR therapy. The lack of response is also seen with anti-EGFR inhibitors that are given without concurrent BRAF inhibition. In a retrospective analysis, patients with mCRC whose tumors were BRAF V600E-mutated were resistant to treatment with cetuximab or panitumumab, which was also confirmed in a cell-line model using colorectal tumor cells expressing the mutated BRAF V600E allele. However, when these cells were treated with a combination of cetuximab and sorafenib (an approved small molecule kinase inhibitor targeting BRAF), there was a synergistic effect causing cell death. Unfortunately, vemurafenib, another oral BRAF V600E inhibitor, showed disappointing results when used as a single agent in BRAF-mutated mCRC in the refractory setting. One patient had a confirmed partial response (PR) out of 21 patients who were treated. This is in stark contrast to the response rates of 60% to 80% seen in vemurafenib-treated patients with melanoma who harbor the identical BRAF V600E mutation. This resistance is thought to be due to inadequate suppression of the MAPK pathway by BRAF inhibition alone, due to an incomplete ERK suppression (located downstream of BRAF).

There was initial optimism for combining the BRAF inhibitor dabrafenib with trametinib, a MEK inhibitor that targets downstream of BRAF and MAPK, given that this combination has been effective in BRAF V600E-mutated melanoma. Forty-three patients with BRAF V600E-mutated mCRC were treated, and 5 patients (12%) achieved a PR, including 1 patient with a durable complete response (CR) extending over 36 months. The median PFS was 3.5 months, compared with 2.5 months seen with standard chemotherapy. Nine patients had biopsies during treatment, which revealed decreased levels of phosphorylated ERK, compared with pretreatment biopsies. However, there was not a more robust efficacy despite dual inhibition of BRAF and mitogen-activated protein kinase kinase (MEK).

More recent trials combining BRAF and EGFR inhibition have shown promising results (Table 2). When vemurafenib was combined with cetuximab and irinotecan, early-phase data demonstrated a promising PFS of 7.7 months in previously treated patients with BRAF V600E-mutated, KRAS WT tumors. There was a recent update of this initial trial at the 2017 Gastrointestinal Cancers Symposium (GI ASCO) conference by Kopetz and colleagues. One hundred and six patients with BRAF V600E-mutated extended RAS WT mCRC were randomized to irinotecan and cetuximab with or without vemurafenib. PFS in the vemurafenib arm was 4.4 months versus 2 months in the irinotecan and cetuximab-only arm, with response rates of 16% versus 4%, respectively. Updated analysis presented at GI

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**TABLE 2. BRAF and EGFR Inhibition**

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<tr>
<th>Study (citation)</th>
<th>Treatment</th>
<th>ORR</th>
<th>PFS (months)</th>
<th>OS</th>
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<td></td>
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<td>Panitumumab + dabrafenib + trametinib</td>
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</table>

ORR indicates overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; SD, stable disease.
ASCO 2017 revealed a median OS of 9.6 months in the vemurafenib arm versus 5.9 months in the irinotecan and cetuximab–only arm (HR, 0.73; 95% CI, 0.45-1.17; P = .19). The lack of survival benefit is thought to be due to crossover.

Another study evaluated the efficacy of combining panitumumab with dabrafenib and trametinib in BRAF V600E–mutated mCRC.44 Two of the 120 treated patients had concomitant BRAF V600E and RAS mutations at baseline. The combination of all 3 drugs achieved an 18% PR or better, with 67% of patients achieving stable disease. Comparatively, the PR/CR rate in the dabrafenib-and-panitumumab arm was 10%, but was 0% for the trametinib-and-panitumumab arm. Stable disease was seen in 80% and 53%, respectively. Median PFS for the triple combination had not been reached at the study end date. Of 12 patients with PR/CR or stable disease, 58% had a detectable RAS mutation on progression of disease. Updated analysis is pending.

It is important to note that BRAF mutations in mCRC confer a poor prognosis independent of the predictive value and possible efficacy of the combination with EGFR and MEK inhibitors, as discussed above.32,33 This worse prognosis will need to be considered as definitive trials are developed.

**MMR-Deficient CRC and Immunotherapy**

Tumors that have defects in the mismatch repair (MMR) system accumulate hundreds to thousands of somatic mutations in the microsatellite regions of DNA that are normally repaired.42,43 A defect in MMR (also called MMR deficient) is a surrogate for microsatellite instability (MSI), and MSI is further subdivided into MSI-high (MSI-H) and MSI-low (MSI-L). Tumors with an intact mismatch repair system (MMR proficient) are considered microsatellite stable (MSS). Dysregulation of the MMR system is caused primarily by mutations in the MLH1, MSH2, MSH6, and PMS2 genes (though other genes can be implicated as well).43,44 Hereditary forms of MMR deficiency can occur, which is known as hereditary nonpolyposis colorectal cancer or Lynch syndrome.45 This disorder is observed in 10% to 15% of sporadic cases of colon cancer; it is most commonly caused by a hypermethylation mutation in the MLH1 gene.45

Approximately 10% to 15% of sporadic GI cancers also carry the MSH-H phenotype.46,47 MSH-H is present in 15% of early-stage CRC.41 MSH-H is rare in metastatic disease, with incidence rates of about 4%, and the prognosis is unclear. MSH-H tumors typically lack mutations in TP53, KRAS, and APC, which are commonly mutated genes seen in MMR-proficient CRC.48,49 While MSI status is used as a prognostic marker in early-stage CRC, its role as a predictive marker for chemotherapy is conflicting. Typically, MMR-deficient (MSH-H) tumors are less aggressive than MMR-proficient (MSH-L, or MSS) tumors, with a better overall prognosis.46 Numerous studies have shown that patients with MSH-H tumors have better survival rates in early-stage disease. In a meta-analysis pooling 32 eligible studies including 1277 MSI samples, MMR-deficient (MSI-H) tumors were associated with a 35% reduction in the risk of death compared with those that were MMR-proficient (MSI-L).49 However, a study by Goldstein and colleagues showed that MSI-H mCRC did not have the improved outcome that was observed in early-stage CRC.46 Additionally, the BRAF V600E mutation is a poor prognostic factor that is seen in MSI-H mCRC.48 BRAF mutations are only seen in MSI-H sporadic CRC, and they can be used to differentiate between sporadic and hereditary forms of MSI-H CRC.48

Clinically, MMR-deficient (MSH-H) CRC has been shown to possess a highly activated lymphocyte microenvironment.33,35 MMR-deficient (MSH-H) tumors are also known to have an increased stromal inflammatory reaction.40 These tumors carry a higher number of cytotoxic lymphocytes that infiltrate the tumor architecture itself.40 These lymphocytes are seen in close proximity to tumor cells undergoing apoptotic death.40 The increased cytotoxic immune response against tumor cells is thought to be related to the increased mutational load in MMR-deficient (MSH-H) tumors, allowing for greater immunogenicity.45 The accumulation of irregular proteins provides a source of abnormal peptides to be presented to T lymphocytes.46 These cytotoxic T lymphocytes are also known to overexpress immune checkpoint–related proteins in the microenvironment, including PD-1, PD-L1, CTLA-4, lymphocyte-activation gene 3, and indoleamine-pyrirole 2,3-dioxygenase.50 The amount of lymphocyte infiltration into the tumor is an important predictor of relapse and OS.50 Cancer cells have an innate ability to maintain an immunosuppressive microenvironment, thus escaping the immune system mechanisms that target foreign cells for destruction.44 PD-L1 on tumor cells binds PD-1, which is expressed on the cell surface of T lymphocytes, thereby inhibiting the activation of PD-1 and evading tumor-cell killing.44 The expression of PD-L1 on the surface of tumor cells is a predictive marker that is used to predict response to PD-1 blockade.42 Preclinical data suggested that continuous antigen exposure to cytotoxic T lymphocytes may induce an exhausted or less vigorous state of activity in which T-cell effectiveness and transition to memory T cells are impaired.45 Inhibiting the PD-1 pathway with novel agents may restore T lymphocyte function, resulting in tumor-cell death by the immune system.43 The immune infiltration of cytotoxic lymphocytes is suggested to be a better predictor of survival than the current IHC methods used to stage colon cancer.51

Initial studies with PD-1 blockade in CRC were limited but promising.52 One of 33 patients treated with the humanized monoclonal immunoglobulin G4 (IgG4) anti–PD-1 antibody nivolumab had MSI-H mCRC. The patient had progressed through multiple lines of treatment and eventually was treated with single-agent nivolumab. The patient achieved a complete remission and showed no evidence of disease recurrence 3 years out from treatment. PD-L1 expression was seen in his original tumor tissue with evidence of infiltrating cytotoxic T cells.53 Pembrolizumab is a humanized monoclonal IgG4 kappa isotype anti–PD-1 antibody that was tested in a phase II study in patients selected specifically for their MSI-H mCRC status.53 When compared with patients with MSS tumors, MSI-H patients had an improved ORR (40% vs 0%) and PFS (78% vs 11%) at 20 weeks.50 Wholeexome gene sequencing also revealed that a high somatic mutational load was associated with improved PFS. This included patients with inherited and sporadic forms of MSI-H tumors.50 A similar study was more recently published in abstract form by Overman and colleagues.54 Nivolumab was tested in patients with mCRC.
with and without ipilimumab, a humanized anti-CTLA-4 monoclonal antibody. In patients with MSI-H tumors, initial results with nivolumab showed a PFS of 5.3 months and a median OS of 16.3 months. The combination arm had not reached either the PFS or OS endpoints. A pooled PFS of 1.4 months was seen in the non-MSH tumors. AEs included GI toxicity and fatigue. A recent update of the nivolumab monotherapy arm revealed an ORR of 31% with a 69% disease control rate. An updated PFS at 12 months was 48.4%. The duration of response and OS have not been reached. These responses are irrespective of PD-L1 expression or KRAS and BRAF mutation status.

The identification of MMR-deficient (MSI-H) CRC defines a subset of tumors that have specific molecular, pathologic, and clinical features that have shown to improve survival, and this justifies routine testing for MMR status in all patients with mCRC. The National Comprehensive Cancer Network guidelines recommend that all mCRCs be evaluated for MSI status, and both drugs, pembrolizumab and nivolumab, are approved treatment options.

**CRC and HER2-Targeted Treatment**

HER2 overexpression, which has a prevalence of 5% in CRC, has been identified as a novel potentially actionable molecular target. Previous trials that added HER2-targeted therapy to chemotherapy were inconclusive. One study evaluated the combination of 5-fluorouracil, oxaliplatin, and trastuzumab in patients with mCRC who had progressed on treatment containing 5-fluorouracil and/or irinotecan. It closed early due to insufficient accrual. Another study combined trastuzumab with irinotecan in HER2-overexpressing CRC. Nine patients out of 138 screened had tumors with HER2 overexpression. These 9 patients were enrolled into the study and only 7 were counted for data collection. Partial responses were seen in 5 of 7 patients. This study also closed early due to low accrual. Monotherapy with HER2-targeted treatment with a tyrosine-kinase inhibitor (lapatinib) or monoclonal antibody (trastuzumab) was also initially ineffective in early preclinical studies; however, the combination of the 2 showed sustained tumor control. The success of combination HER2-targeted therapy is thought to be related to the association of dual EGFR/HER2 inhibition by lapatinib and trastuzumab targeting the HER2 heterodimer.

Because the combination of trastuzumab and lapatinib has been used as a standard treatment option in HER2-positive breast cancer, Sartore-Bianchi and colleagues used trastuzumab and lapatinib in combination in patients who were KRAS exon 2 WT and HER2-positive in the HERACLES study. They defined HER2 positivity as either a 3+ score in more than 50% of cells by immunohistochemistry, or having a HER2:CEP17 (chromosome enumeration probe 17) ratio >2 in more than 50% of cells by fluorescence in situ hybridization. A total of 914 patients were screened, with 5% being identified as KRAS WT and HER2-amplified. Twenty-seven patients were eligible to enroll in the trial. These patients were heavily pretreated and had progressed through all prior standard chemotherapy including 5-fluorouracil, irinotecan, oxaliplatin, and anti-VEGF and anti-EGFR antibodies. Nevertheless, in this heavily pretreated population, the combination of trastuzumab and lapatinib resulted in a 30% ORR according to Response Evaluation Criteria in Solid Tumors v1.1 criteria, with durable responses, and a median duration of 38 weeks. HER2 is also suggested to be an early molecular alteration that persists during tumor progression, as Sartore-Bianchi and colleagues saw that HER2 was matched between the primary tumor and metastatic lesions. A follow-up study (HERACLES-RESCUE) is accruing to evaluate ado-trastuzumab emtansine (T-DM1) in patients who have progressed on trastuzumab and lapatinib. T-DM1 is an antibody–drug conjugate that binds HER2-expressing cells; the conjugate releases emtansine within the cell, resulting in cytotoxicity.

Hurwitz and colleagues have recently presented data from the MyPathway study, evaluating the combination of trastuzumab with pertuzumab in HER2-amplified or HER2-overexpressed mCRC. Pertuzumab is a monoclonal antibody that targets the HER2 dimerization domain. Inhibiting dimerization blocks downstream signaling, which inhibits cell growth and causes apoptosis. The 34 patients enrolled in the study received standard doses of trastuzumab and pertuzumab until disease progression or unacceptable toxicity. The ORR was similar to the HERACLES trial at 37.5%, with a median duration of response of 11.1 months.

Interestingly, amplification of the HER2 gene does not seem to be related to mutations in KRAS, NRAS, or BRAF, but it has been shown to confer some resistance to anti-EGFR therapy. Two recent studies showed that HER2 amplification allows for downstream signaling activation, even when EGFR inhibition has resulted in drug resistance. HER2 can therefore be considered a negative biomarker of anti-EGFR resistance but a positive marker of anti-HER2 targeted agents.

**Conclusion: The Need for Broad Molecular Testing in All Patients With mCRC**

Molecular profiling is an important tool in selecting the right patient for specific targeted agents. Pan-RAS testing that evaluates for KRAS, NRAS, and BRAF mutations is important to determine which patients are likely to derive benefit from EGFR inhibitors like cetuximab or panitumumab, and this testing is nationally recognized for mCRC prior to initiation of therapy. Only patients with WT RAS mCRC have seen significant improvement in PFS and OS, while treating mutated-RAS CRC has resulted in clear detrimental effects. Of those 7% to 10% of patients with mCRC who are BRAF V600E-mutated, initial results of combining BRAF and MEK inhibitors look promising. The addition of anti-EGFR therapy to overcome feedback activation of the RAS pathway is also being investigated in clinical trials. Similar improvements in efficacy are seen in patients with MMR deficiency who are treated with immunotherapy, as well as those with HER2 positivity who are treated with targeted anti-HER2 agents.

More recent efforts have been made to classify CRC genetically into different subgroups. However, while these subgroups have important prognostic implications, distinct connections have not been made between these subgroups and molecular predictive markers and targeted therapies.

Taken together, a large percentage of CRCs harbor specific molecular characteristics that define response (or lack of response) to therapy, and thus broad molecular testing has the potential to benefit the vast majority of patients with mCRC. The optimal sequencing of testing has yet to be determined.
defined, but future studies should incorporate broad molecular testing to identify additional patient subgroups, and to understand the optimal time for testing patients.

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**Disclosures:** John L. Marshall, MD, discloses being a board member of Caris Life Sciences, and he has received consultancies and has participated in paid advisory boards for Genentech, Amgen, Bayer, Celgene, and Taiho.

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50. Venook AP, Niedzwiecki D, Lenz FJ, et al. CALGB/SWOG 80405: phase III trial of irinotecan/5-FU/leucovorin (mFOLFOX6) with bevacizumab (BV) or cetuximab (CET) for patients (pts) with KRAS wild-type (wt) untreated metastatic adenocarcinoma of the colon or rectum (MCRC). J Clin Oncol. 2014;32(15 suppl; abstr LBA3).


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Reshaping the Field of Hodgkin Lymphoma

Lori A. Leslie, MD; Andre H. Goy, MD, MS; and Tatyana A. Feldman, MD

Background
Hodgkin lymphoma (HL) is the seventh most common subtype of lymphoma, with approximately 8500 new cases and 1120 estimated US deaths per year in 2016. The majority of US patients achieve cure, with a 5-year overall survival (OS) rate of more than 85%. However, up to 10% of patients are refractory to initial therapy, and up to 30% of patients will eventually relapse after frontline therapy, at which point the expectation of cure can be as low as 30% in patients with high-risk relapse or as high as 70% in patients without poor prognostic markers.

Currently, patients with treatment-naïve HL are classified as having early favorable, early unfavorable, or advanced disease based on several factors. These include: stage; presence or absence of B symptoms (ie, systemic symptoms of fever, night sweats, and weight loss); erythrocyte sedimentation rate elevation; number of nodal sites involved; and presence or absence of bulky disease. In the United States, standard chemotherapy for most patients includes a combination of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD), with or without consolidative radiation therapy (RT). Several studies have been performed to determine the optimal number of chemotherapy cycles and/or dose of RT for each group of patients.

The HD10, HD11, and EORTC 20012 trials suggest what standard therapy should be: For those with early favorable disease, 2 cycles of ABVD are followed by 20 gray (Gy) of involved site RT (ISRT); the associated OS is 97% and the progression-free survival (PFS) is 93%. For those with early unfavorable disease, 4 cycles of ABVD are followed by 30 Gy of ISRT; the associated OS is 94% and the PFS is 86%. For those with advanced disease, 6 cycles of ABVD are undertaken; the associated OS is 88% and the PFS is 74%.

Considering that HL occurs commonly in young patients and that the majority of patients are cured with standard therapy, recent studies have focused on developing algorithms to guide escalation versus de-escalation of treatment based on response, risk of treatment failure, and risk of long-term toxicity.

One evolving concept is the use of PET-adapted therapy. The Deauville score (DS) has become the standard way to evaluate PET response in HL. PET scan results are given a score of 1 to 5 based on a fludeoxyglucose (FDG) uptake compared with background mediastinal and liver uptake. A DS of 1, 2, or 3 is considered negative, and a DS of 4 or 5 is considered positive. In addition to the PET scans performed as a standard part of baseline and end-of-therapy evaluations, early interim PET scan performed after 2 cycles of chemotherapy (PET2) is emerging as a prognostic and predictive marker in HL. In a study of 206 patients with early unfavorable (n = 53) or advanced stage (n = 207) treatment-naïve HL, the 3-year PFS for PET2-negative patients was 95%, compared with 28% for those who were PET2-positive. Based on these data, there have been increasing interest in risk-adapted therapy based on PET2 results. In patients who achieve complete metabolic response at the end-of-therapy PET, routine PET surveillance is not recommended. Radiographic surveillance using CT scans no more frequently than every 6 months for the first 2 years following completion of therapy, followed by clinical surveillance only, is a common approach.

Updates in Frontline Therapy

Limited-Stage HL
PET2 has been used to investigate if RT may be omitted in subgroups of patients with limited-stage HL. The EORTC/LYSA/FIL H10 noninferiority trial evaluated whether RT could...
be omitted in patients with early-stage HL, achieving negative PET2 without compromising PFS. Patients with early favorable (HL-F) and early unfavorable (HL-U) HL and a negative PET2 received further ABVD (2 cycles in HL-F; 4 in HL-U) without RT or standard ABVD (1 cycle in HL-F; 2 in HL-U) plus 30 Gy of involved node RT (INRT). The study failed to show noninferiority of ABVD alone; 5-year PFS was 99% versus 87% in HL-F patients and 92% versus 90% in HL-U patients receiving INRT or no RT, respectively.5

In the RAPID trial, patients with early-stage HL received 3 cycles of ABVD, then those with a negative PET3 were randomized to no further therapy versus 30 Gy of involved field RT (IFRT). Five-year PFS was 97% in those who received IFRT versus 91% in the observation arm. However, 7 versus 2 patients died while in complete response (CR) and 5 versus 2 patients died of progressive disease in the IFRT and observation arms, respectively.7 Given the small PFS benefit and suggestion of increased toxicity in these trials, it is possible that IFRT may not be warranted in patients with early-stage HL who achieve a negative interim PET.

Given poor outcomes with continued ABVD therapy in patients with a positive PET2, another question is whether or not therapy should be escalated in patients with limited-stage HL and a positive PET2. In the experimental arms of the EORTC/LYSA/H10 trial, patients with early-stage HL-F or HL-U who were PET2-positive received 2 cycles of escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (eBEACOPP), followed by INRT. Compared with standard ABVD × 3 or 4 cycles plus INRT in HL-F and HL-U, respectively, pooled analysis revealed that intensification to eBEACOPP was associated with a statistically significant improvement in 5-year PFS from 77% to 91%.5 In the CALGB/ALLIANCE 50604 trial, 164 patients with early-stage HL were given 2 additional cycles of ABVD if PET2-negative (91%), and 2 cycles of eBEACOPP with 30 Gy of IFRT if PET2-positive (9%). With a median of 2 years’ follow-up, 3-year PFS was 92% in PET2-negative patients versus 66% in PET2-positive patients, and it was concluded that the protocol is unlikely to meet its secondary endpoint of improved PFS with eBEACOPP plus IFRT in patients with PET2-positive disease.7

Advanced-Stage HL

PET2 has also been investigated as a marker to identify patients who may benefit from intensification from ABVD to eBEACOPP in the advanced-stage setting. The SWOG 0816 trial included 358 patients with advanced-stage HL initially treated with 2 cycles of ABVD. PET2-negative patients (DS 1-3, 82%) were treated with an additional 4 cycles of ABVD for a total of 6 cycles of ABVD, and PET2-positive patients (DS 4-5, 18%) were intensified to receive 6 cycles of eBEACOPP after the initial 2 cycles of ABVD. With a median follow-up of 39.7 months, 2-year OS was 98% and 2-year PFS was 79% for the cohort. The 2-year PFS was 82% in PET2-negative patients and 64% in PET2-positive patients, significantly improved compared with historical controls treated who had continued ABVD after a positive PET2. Escalated BEACOPP was associated with increased grade 4/5 toxicity (86% vs 36%) and OS data are immature.8 While improved outcomes for PET2-positive patients who escalated to eBEACOPP cannot be ignored, given the absence of proven OS benefit and increased toxicity, whether or not intensification to eBEACOPP is warranted in patients with PET2-positive advanced-stage HL remains open to discussion. Trials exploring the incorporation of novel agents based on PET response are ongoing.

Another question is whether therapy can be safely de-escalated in patients with advanced-stage HL who achieve a negative PET2. The RATHL study included 1214 patients with treatment-naive bulky stage II or advanced-stage HL. All patients were treated with 2 cycles of ABVD, and the 952 who achieved negative PET2 were randomized to either receive an additional 4 cycles of ABVD or to omit bleomycin from subsequent doses and de- escalate to 4 cycles of AVD. Four percent of patients received consolidative RT at the treating physician’s discretion in both arms. There was no difference in PFS at 3 years (85.4% vs 84.4%) or OS (97% vs 97.5%) in ABVD versus AVD, and the risk of respiratory adverse events was reduced by omitting bleomycin.9 Based on these data, many have accepted that bleomycin may safely be omitted from ABVD in patients with advanced-stage HL who achieve negative PET2.

Treatment of First Relapse

Standard treatment of HL in first relapse currently includes salvage chemotherapy, such as ifosfamide, carboplatin, and etoposide (ICE), dexamethasone, cytarabine, and cisplatin (DHAP); gemcitabine, vinorelbine, and liposomal doxorubicin (GVD); and ifosfamide, gemcitabine, vinorelbine (IGEV); all are salvage chemotherapies and can be followed by autologous stem cell transplantation (autoSCT). Response rates to salvage therapy are in the 60% to 80% range; however, at about 20%, CR rates are low. Furthermore, approximately 50% of patients will relapse within 5 years of autoSCT. Patients with a late, localized relapse may instead be treated with a combination of chemotherapy and radiation. For those patients who relapse post autoSCT and are eligible, further salvage therapy followed by allogenic stem cell transplantation (alloSCT) is considered. With the development of novel agents, these historic treatment paradigms are rapidly changing, and currently there is no FDA-approved standard of care (Table 1).

Novel Agents

Brentuximab Vedotin

CD30 is universally expressed on Reed-Sternberg (RS) cells. It is a target of interest in HL due to its role in promoting RS cell survival through simulation of nuclear factor kappa-light-chain-enhancer (NF-kB) signaling, as well as its interaction with the tumor microen-
Brentuximab vedotin (BV) is an antibody-drug conjugate in which the microtubule-disrupting agent, monomethyl auristatin (MMAE), is linked via protease-cleavable linker to the anti-CD30 monoclonal antibody, brentuximab. In a pivotal phase II study, BV was administered to 102 patients with relapsed or refractory HL and a median of 3.5 prior therapies, all of whom had prior autoSCT. At a median of 18.5 months of observation, the overall response rate (ORR) was 75% with a median duration of response (DOR) of 6.7 months; the CR rate was 34% with a median DOR of 20.5 months. Longterm data published with a median of 69.5 months follow-up revealed a 5-year OS of 41% and 5-year PFS of 22%. For the 34 patients who achieved CR, OS was 64%, and 52% remained in CR at 5 years. Of the 13 patients in CR at study closure, 4 had undergone alloSCT and 9 remained in continued CR without further lymphoma-directed therapy. Based on these data, BV was approved by the FDA for use in relapsed or refractory HL in patients who have progressed after autoSCT or who are autoSCT ineligible. BV is also approved as early consolidation after autoSCT in high-risk HL were randomized to receive BV 1.8 mg/kg intravenously (IV) every 3 weeks versus placebo for 16 doses starting

- **Phase II Study**
  - **CD30+**
  - **BV 1.8 mg/kg q3wk + 4 cycles**
  - **AutoSCT**
  - **ORR %**
  - **CR %**
  - **PFS**
  - **OS**
  - **Ref**

- **Phase III Study**
  - **CD30+**
  - **BV 1.8 mg/kg q3wk + 4 cycles**
  - **AutoSCT**
  - **ORR %**
  - **CR %**
  - **PFS**
  - **OS**
  - **Ref**

- **Phase IV Study**
  - **CD30+**
  - **BV 1.8 mg/kg q3wk + 4 cycles**
  - **AutoSCT**
  - **ORR %**
  - **CR %**
  - **PFS**
  - **OS**
  - **Ref**

- **Phase V Study**
  - **CD30+**
  - **BV 1.8 mg/kg q3wk + 4 cycles**
  - **AutoSCT**
  - **ORR %**
  - **CR %**
  - **PFS**
  - **OS**
  - **Ref**

*Considered an off-label standard-of-care option.

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30 to 45 days after autoSCT. High risk was defined as primary refractory disease, relapse within 12 months of frontline therapy, or relapse with extranodal disease more than 12 months after frontline therapy. Median PFS was 42.9 months in the BV arm versus 24.1 months in the placebo arm. There were no statistically significant differences in 3-year OS (81% vs 79%), and treatment was well tolerated.11

**Immune Checkpoint Inhibitors**

PD-1 is a transmembrane protein that functions as a negative immunoregulator, promotes self-tolerance, and has been shown to be crucial in the pathobiology of classical HL. Amplifications of chromosome 9p24.1 in RS cells lead to overexpression of PD-1 ligands as well as JAK2, JAK/STAT pathway activation, further PD-1 ligand transcription, and subsequent immune evasion.14

Nivolumab is a fully human anti–PD-1 immunoglobulin G4 (IgG4) monoclonal antibody. In a phase I study, 23 patients with relapsed or refractory HL received nivolumab 3 mg/kg IV every 2 weeks. Seventy-eight percent were post autoSCT and 78% were previously treated with BV. Treatment was well tolerated, the ORR was 87% (CR, 17%) and the remaining 13% of patients had stable disease. Responses were durable, with 24-week PFS of 86%.15 In a single-arm phase II study, 80 patients with HL who were post auto-SCT and relapsed or refractory to BV were treated with nivolumab, resulting in an ORR of 66% (CR, 9%) with a median DOR of 7.8 months.16 Based on these results, nivolumab was granted FDA approval for use in patients with HL who have relapsed post autoSCT and post-transplant BV.

Pembrolizumab is a humanized mouse IgG4 anti–PD-1 monoclonal antibody. KEYNOTE-087 was a single-arm phase II trial in which 210 patients with relapsed or refractory HL received pembrolizumab at 200 mg every 3 weeks. Patients were heavily pretreated, 83% had received BV, and 61% were post autoSCT. The ORR was 69% (CR, 22%), median DOR was 11 months, and treatment was well tolerated.17 Based on these data, the FDA granted pembrolizumab accelerated approval for use in patients with HL that has relapsed after 3 or more lines of therapy.

**TABLE 2. Novel Upfront Treatment Strategies in Older Patients With Hodgkin Lymphoma**

<table>
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<tr>
<th>Regimen</th>
<th>Ph</th>
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<th>ORR %</th>
<th>CR %</th>
<th>18-mo PFS %</th>
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BV indicates brentuximab vedotin; CR, complete response; kg, kilogram; mg, milligram; mo, month; N, number of patients; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Ph, phase; q, every; ref, reference; wk, week.

**Treatment in Older Adults**

The incidence curve of HL is bimodal, with 1 peak around age 20 years and a second around age 65 years. Those diagnosed with HL over age 60 years are considered older and more likely to experience bleomycin lung toxicity, to have comorbidities limiting anthracycline use, and to have inferior outcomes compared with younger patients. Their reported 5-year PFS is 30% to 45%, with 5-year OS of 40% to 60%.19 As a number of novel agents are entering the HL armamentarium, several upfront alternatives to ABVD and less-toxic salvage regimens of interest have emerged, including BV monotherapy, BV-dacarbazine, BV-nivolumab, AVD-lenalidomide, and sequential therapy with BV-AVD. BV-bendamustine showed promising efficacy in this population, but further study has been halted due to unacceptable toxicity in older adults (Table 2).

**Future Directions**

The field of HL is rapidly changing. In the treatment-naïve setting, radiation therapy will be used more selectively, as novel agents are incorporated into upfront treatment regimens with the goal of decreasing long-term toxicity. The understanding of how to best use a PET-adapted approach to escalate versus de-escalate treatment will continue to evolve. Another area of investigation is the use of novel agents as consolidative therapy post autoSCT, including BV-checkpoint inhibitor combination therapy. AlloSCT will remain an option for eligible patients. With the availability of novel agents, outcomes in older and unfit patients with HL will continue to improve.

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References


Case Report: Detection of c797s as a Mechanism of Resistance in a Patient With Lung Cancer With EGFR Mutations

Luis E. Raez, MD, and Christian Rolfo, MD, PhD, MBA

Introduction
Non–small cell lung cancer (NSCLC) was the first epithelial neoplasm treated with targeted therapy, based on the discovery of EGFR mutations and their predictive value and response to tyrosine kinase inhibitors (TKIs). The prevalence of EGFR mutations is strongly correlated with ethnicity: 10% to 20% in Caucasians, 30% to 40% in Asians, and, as described in a recent study, 26% in Latin American patients.1

Despite the initial success of targeted therapy (overall response rate [ORR] 60% to 83% for erlotinib and 71% for gefitinib), patients will develop resistance generally after 1 year of treatment. The mechanism of resistance includes the acquisition of additional mutations in the EGFR receptor, such as T790M (60% of cases), the activation of additional driver genes, and histological transformation to small cell lung cancer.1

Abstract
We present here the case of a patient with exon 19 EGFR-sensitive mutation who, after months of experiencing benefit with tyrosine kinase inhibitors (TKIs), developed resistance to TKIs because of the development of EGFR T790M mutation that was initially missed. The patient was subsequently treated with palliative chemotherapy until he had disease progression (PD). However, after chemotherapy was initiated, the T790M mutation was identified by liquid biopsy and confirmed with a new tissue biopsy. Later, after starting osimertinib, the patient achieved disease stabilization until he developed a c797s mutation with PD. He did not respond to immunotherapy and subsequently died. Pertinent issues regarding diagnosis and therapy are discussed here.

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Case Report
The patient was a 54-year-old male nonsmoker with a past medical history significant for hypertension, hyperlipidemia, anxiety, and stage IV lung cancer (adenocarcinoma, with an EGFR mutation [exon 19 deletion]) diagnosed with tissue biopsy. He originally presented with multiple pulmonary nodules, multiple subcentimeter lesions on brain MRI, and metastatic lesions to the thoracic and lumbar spine. He was started on erlotinib 150 mg daily and received stereotactic brain radiation. Subsequent imaging revealed that the lesions in his chest and brain were stabilized or reduced in size for the next 10 months. The patient subsequently reported experiencing pain. MRI scan showed worsening on spine lesions (T11-L1), for which he underwent a short course of intensity-modulated radiation therapy; therapy with erlotinib continued. However, 3 months later an MRI of the brain revealed new brain metastases and systemic disease progression (PD) on PET scan.

The patient expressed interest in enrolling in a clinical trial: AURA 3 (NCT02151981) for osimertinib (Tagrisso) versus chemotherapy. His tumor was biopsied again and sent for central testing. It was reported that the tumor did not have the T790M mutation in tissue and he was not accepted in the clinical trial. We started him on palliative chemotherapy with carboplatin and pemetrexed for 5 cycles until he again had PD.

Next-generation sequencing (NGS) through a liquid biopsy revealed positive results for T790M. We conducted a second test of his previously negative tissue biopsy that also revealed positive results for T790M mutation. There were no other actionable mutations such as ALK or MET.

The patient was started on osimertinib and he was stable for 14 months until systemic and brain PD was exhibited in the PET scan and brain MRI. We found an EGFR c797s-resistance mutation in his blood. The patient was started on palliative nivolumab and ipilimumab; however, therapy eventually failed and he died from complications of pneumonia.

Discussion
Tyrosine kinases are part of a large multigene family that is
crucial for signal transmission cascades. Many extracellular receptors of growth factors have an intrinsic TKI activity that is triggered by the process of binding their ligands. Phosphorylation of downstream effectors usually produces conformational changes in the EGFR receptor and exposes catalytic sites with the effect of signal amplification. Docking of TKIs in the catalytic sites is either favored by some mutations (sensitizing mutations) or conversely disfavored (resistance mutations such as T790M and c797s). The study of resistance mutations led to the design of third-generation TKIs like osimertinib.

We classify resistance as primary or acquired. Primary resistance is present when the tumor cells bear an intrinsic mechanism of resistance, and therefore do not respond to the original treatment. In acquired resistance, the tumor cells develop mechanisms of resistance under forces of natural selection or selective pressure. Primary resistance is developed during the process of clonal evolution of cancer cells; it exists in the absence of or the modification of drug target or the expression of mechanisms to escape that create drug resistance. Although the process is not fully understood, several EGFR mutations exhibit ex novo resistance to EGFR TKI, including L747S and D761V in exon 19; T790M, V769M, and insertions in exon 20; and T854A and A871E in exon 21. T790M ex novo (before exposure to TKI) are variable in frequency, according to various studies, but the presence of this mutation before the treatment does not preclude the use of first-generation TKIs. The role that third-generation TKIs will play in this scenario is still not clear, beyond their potent activity in T790M-acquired mutation after TKI resistance. A prognostic role for T790M ex novo mutation was described together with a predictive value for a therapeutic benefit with pemetrexed. Jackman et al defined the criteria of acquired resistance for EGFR TKIs; they include prior monotherapy with EGFR TKIs in the presence of typical sensitizing mutations, or tumor progression within 30 days after achieving complete response, partial response (PR), or stable disease (≥6 months) to TKIs despite the uninterrupted treatment. In the clinical setting, treatment with TKIs could be continued after evidence of resistance, thus obtaining a prolonged period of disease control in some cases. Acquisition of T790M mutation is the most frequent mechanism of resistance; it occurs in about 50% to 60% of cases. Among other mechanisms that lead to resistance to EGFR TKI, it is important to consider c-MET amplification and the less-frequent presence of ALK translocations.

Finding the resistance mutation can be a challenge. First, we do not frequently perform biopsies in patients with lung cancer, and second, after several years of conducting small biopsies with endobrachial ultrasound, we are experiencing an increase in CT-guided core biopsies. We also have to consider costs and morbidity for the patients when we order tissue biopsies.

As an alternative, liquid biopsies are easier and cheaper, and results are reported more quickly. As such, there is a great interest among oncologists to further develop this field. Liquid biopsies represent a new technology, and we all need to feel comfortable learning its role in our practice, either by complementing or replacing tissue biopsies with liquid biopsies. Data from Lanman et al using NGS in plasma versus tissue sequenced at 5 institutions in stage III-IV solid-tumor cancers showed that cell-free plasma DNA NGS sensitivity is 85% of that found in tissue NGS, likely because not all tumor DNA may be shed into circulation. However, the tissue DNA NGS sensitivity is 80.7% versus that of cell-free DNA (cfDNA) in plasma NGS, likely because cfDNA picks up intra- and inter-tumor heterogeneity that is missed by needle or forceps biopsies of tissue. Specificity was 99.6% versus 99.7%, and accuracy was 99.3% for both.

During the American Society of Clinical Oncology 2016 Annual Meeting, Wakelee et al presented data comparing liquid biopsy results from blood and urine with tissue biopsy results; the patients had NSCLC with T790M treated with rociletinib. They reported that EGFR T790M sensitivity is 80.9% for blood and 81.1% for urine, with tissue biopsy as the reference. Notably, only 57% of the patients were positive by all 3 types of sampling: Some patients were detected only by urine, blood, or tissue. Another important finding was that the objective response rate (ORR) to rociletinib was similar in all 3 types of patients (32% to 36%).

Regarding the use of agents, among third-generation TKIs that are specific to T790M mutations, only osimertinib has received the approval by the US and European regulatory agencies. Despite osimertinib’s availability we still start therapy with the other TKIs, such as first-generation gefitinib or erlotinib, or second-generation afatinib, which has a dual EGFR/HER2 inhibition activity and it is approved for the treatment of lung tumors bearing the EGFR L858R mutation or exon 19 deletions. Osimertinib is still not approved for frontline therapy.

The LUX-Lung 5 trial showed that afatinib plus paclitaxel improved progression-free survival (PFS) (HR, 0.60; P = .003) and ORR (32.1% vs 13.2%; P = .005) compared with chemotherapy in patients with acquired resistance to TKIs and who progressed on afatinib after initial benefit. The specific activity against T790M mutation, however, is very limited. The LUX Lung 4 trial, which investigated patients who progressed while receiving the TKI afatinib, showed a confirmed ORR of 8.2%.

Osimertinib is a third-generation irreversible TKI with selective activity against T790M mutation. It was approved based on the results of 2 phase II trials (AURAex and AURA 2), achieving ORR of 66% among 411 patients with EGFR T790M; the median PFS was 11 months and the disease control rate was 91%. A phase III trial (FLAURA) comparing osimertinib versus gefitinib or erlotinib in patients with advanced NSCLC showed promising activity in treatment-naive patients with common EGFR mutations. Rociletinib (CO-1686) irreversibly binds mutant EGFR. In a phase I trial, rociletinib showed promising activity, with an ORR of 60% in T790M-positive patients versus 37% in the
T790M-negative group. However, the real-world ORR was less than described by authors (34% for the 625-mg arm and 28% for the 500-mg arm) and the pharmaceutical company stopped its development.22

New drugs such as olmutinib (BI 1482694), AP26113, ASP8273, EGFR816, and PF-06747775 are currently under development. Unfortunately, new mechanisms of resistance, such as the c797s mutation as seen in our patient, are also appearing. In a study by Oxnard et al, 15 out of 67 (22%) patients had detectable c797s mutations. These 15 patients had detectable T790M (T790-positive/c797s-positive). Additionally, this mutation was more common with EGFR exon 19 del (13/43; 30%) than those with L858R (2/24; 8%; P = .06).21 Among the patients, 32 out of 67 (48%) had no detectable T790M in plasma despite presence of the original EGFR mutation, suggesting overgrowth of an alternate resistance mechanism, such as MET or HER2 amplification or BRAF V600E mutation. MET amplification is found in 4% of new lung cancer tumors and is present in 20% of patients with acquired EGFR mutations.24

The case report presented here illustrates a typical case of a patient with exon 19 EGFR-sensitive mutation, who, after months of experiencing benefit with TKIs, developed resistance to TKIs because of the development of an EGFR T790M mutation. It was a challenge to confirm the diagnosis because the tissue biopsy was negative, and the patient had to endure chemotheraphy until a liquid biopsy found the EGFR T790M mutation; a second opinion from a tissue biopsy confirmed the mutation. Usually the patient would undergo another line of chemotherapy, without taking the extra step to get a second opinion or to order a liquid biopsy after negative tissue for T790M was reported. Repeat biopsy can reveal crucial information relevant to treatment decisions, but only, obviously, if it is performed. Fortunately, the use of liquid biopsy became an important tool in this case.21

It is worrisome that despite the fact that close to 60% of patients who fail TKI therapy have T790M, not all of these patients are currently being treated with osimertinib. This shortcoming might be due to not enough repeat biopsies being ordered, or due to the unavailability of liquid biopsy testing. Whatever the cause, there is much progress to be made in this regard for the benefit of our patients.

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Polycythemia Vera: Contemporary Updates in Diagnosis, Prognosis, and Treatment

Saba S. Shaikh, MD, and Brady L. Stein, MD, MHS

Introduction

Polycythemia vera (PV) is a myeloproliferative neoplasm characterized primarily by erythrocytosis and complicated by thrombosis, myelofibrosis, leukemic transformation, and increased mortality. PV also carries with it a significant symptom burden regardless of risk classification. The discovery of the \textit{JAK2} V617F mutation in 2005 has triggered a new era of scientific discovery, impacted diagnostic capabilities, and led to new developments in treatment. In this review, we address updates in molecular pathogenesis, including impact from non-\textit{JAK2} mutations on prognosis. Changes to the diagnostic criteria are reviewed, along with updates in treatment options. Finally, management of special situations that may arise in patients with PV, such as surgery and pregnancy, are discussed.

Epidemiology

The contemporary epidemiology of PV has been recently described, centered on a population-based study, using Surveillance, Epidemiology, and End Results program data from 2001 to 2012. Including MPN and MPN/myelodysplastic (MDS) overlap syndromes, PV was the most commonly identified myeloid neoplasm in this group, with an incidence of 10.9 per 1 million persons. Although described in all age ranges, the median age at presentation was 65 years, and a male predominance was noted.

Molecular Pathogenesis

The molecular basis of PV and the other MPNs was unknown until 2005, when the discovery of the \textit{JAK2} V617F mutation was made. This mutation leads to constitutive tyrosine kinase phosphorylation that promotes cytokine hypersensitivity and induces erythrocytosis. The erythroid progenitor cells that carry this acquired mutation are able to grow both in the presence and absence of erythropoietin, whereas wild-type progenitors are unable to grow without erythropoietin. This causal relationship was evidenced by the development of erythrocytosis in mice 4 weeks after transplantation of bone marrow cells infected with retrovirus containing mutant \textit{JAK2}, but not with wild-type \textit{JAK2} or an empty vector. This mutation has since been found to be present in most patients with PV and is located on exon 14 for 96% of patients and on exon 12 for 3% of patients with the mutation. In a comparison of

Abstract

Polycythemia vera (PV) is a myeloproliferative neoplasm characterized primarily by erythrocytosis and complicated by thrombosis, myelofibrosis, leukemic transformation, and increased mortality. PV also carries with it a significant symptom burden regardless of risk classification. The discovery of the \textit{JAK2} V617F mutation in 2005 has triggered a new era of scientific discovery, impacted diagnostic capabilities, and led to new developments in treatment. In this review, we address updates in molecular pathogenesis, including impact from non-\textit{JAK2} mutations on prognosis. Changes to the diagnostic criteria are reviewed, along with updates in treatment options. Finally, management of special situations that may arise in patients with PV, such as surgery and pregnancy, are discussed.

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patients with ET with and without the JAK2 mutation, it was found that those with the mutation had increased hemoglobin, increased neutrophil count, more venous thrombosis (VT), and a higher rate of conversion to PV.10 Some use this evidence as a hypothesis that PV and JAK2-positive ET exist on a continuum rather than as distinct disease processes.10 Approximately 30% of patients with PV experience loss of heterozygosity on chromosome 9p for the V617F mutation as a result of mitotic recombination. Homozygosity appears to modify the disease phenotype and clinical consequences.11

Some patients with PV may be genetically predisposed to developing JAK2-positive clonal hematopoiesis. A recent study performed genome-wide association analysis and confirmed a previously recognized association with a predisposition haplotype (46/1).12 These predisposition alleles are associated with the following genes: TERT, associated with myeloproliferation; SH2B3, which interferes with JAKSTAT activation; ATM, which is involved in DNA repair along with CHEK2, PINT, which is regulated by p53; and GFI1B, required for erythropoiesis and megakaryopoiesis.13 Individuals with these genes may be genetically predisposed to acquiring the JAK2 mutation and, subsequently, an MPN.

Other non-JAK2 mutations that may alter phenotype have been identified in patients with PV. Compared with MF, the average number of mutations in PV (and ET) is lower, which is consistent with MF being a more advanced stage of disease.14 One such mutation is TET2, which is present in approximately 10% of patients with the JAK2 mutation, as identified by genotyping hematopoietic colonies or through next-generation sequencing. Twenty-four patients of the 246 screened had both mutations, of which 11 had PV and the remaining had either ET or MF. The order by which JAK2 and TET2 mutations are acquired may affect phenotype. The JAK2-first patients presented at a younger age, were more likely to present with PV, were more likely to have a thrombotic event, and had a better in vitro response to ruxolitinib.15 Additionally, a recent study identified additional non-JAK2 mutations in patients with PV that may have prognostic value. In a study of 216 patients, 133 of whom had PV, a myeloid panel of 27 genes identified 3 particular genes, ASXL1, SRSF2, and IDH2, that were associated with worse overall survival and greater frequency of progression to MF.16 In a study of 19 patients, gene expression in circulating CD34-positive cells was evaluated and demonstrated specific differences in gene regulation based on gender; women with PV had fewer deregulated genes, but more molecular pathways activated compared with men. Further, there was a difference in gene expression patterns between those with indolent and aggressive disease courses.17

Diagnostic Criteria and Challenges
The World Health Organization (WHO) criteria for PV were updated in 2016 with some notable changes (Table). The hemoglobin threshold, which was previously greater than 18.5 g/dl in men and greater than 16.5 g/dl in women, is now 16.5 g/dl and 16 g/dl, respectively.17 This change may be based on a prior recognition of a “masked PV” phenotype, a recognition that came from a study suggesting that patients with PV features, especially those with consistent bone marrow morphology, despite having hemoglobin values below the prior diagnostic threshold, had worse overall survival.18 In a practical sense, this lower hemoglobin threshold allows for better differentiation between PV and JAK2-positive ET.19 This is an important distinction since the cornerstone of PV management and thrombosis risk reduction includes phlebotomy; those misclassified as having ET may miss out on this opportunity. Along these lines, patients with masked PV had higher rates of thrombosis compared with those with PV diagnosed based on the 2008 WHO criteria; these higher thrombosis rates were thought to be secondary to delays in treatment based on underrecognition of masked PV.20 Updated diagnostic criteria include the bone marrow findings as a major criterion for diagnosis, unless the hemoglobin is greater than 18.5 g/dl.21 Some patients with PV are found to have bone marrow fibrosis at diagnosis; if diagnostic criteria for PV are met, this diagnosis remains, rather than being changed to a diagnosis of MF, although this presentation influences prognosis. In a review of 260 patients with PV, those with grade 1 or higher bone marrow fibrosis at the time of diagnosis were more likely to have progression to MF, although there was not an effect on overall survival or leukemic transformation.22 These patients are commonly young women who are presenting with their first manifestation of MPN/PV.23

Prognosis/Risk Factors for Complications
The most well known complications associated with PV include its thrombotic tendency, a long-term possibility of evolution to MF or AML, and compromised longevity (Figure). It has also become clear that regardless of risk, patients with PV have a symptomatic burden that impacts quality of life.24

Thrombosis
The risk of thrombosis ascertained from the European Collaboration on Low-Dose Aspirin in Polycythemia Vera (ECLAP) data from 2004 was 4.4% of patients per year.25 The more recent Cytoreductive Therapy in Polycythemia Vera (CYTO-PV) study placed the risk of thrombosis at 2.7% of patients per year; this lower rate may be reflective of more aggressive treatment.26 Traditionally, thrombosis risk assessment has been based on age and thrombosis
Some younger patients have a unique predisposition to thrombosis. Karyocytosis as an additional risk factor for thrombosis. Notably, subanalysis of the CYTO-PV data identified leukocytosis as an additional risk factor for thrombosis. Additionally, an increased JAK2 V617F allele burden has been considered as a potential risk factor. Other contributing/emerging mechanisms for thrombosis may include inflammatory stress, activation of the endothelium and platelets, and activated protein C resistance.

While advanced age is an accepted risk factor for thrombosis, some younger patients have a unique predisposition to thrombosis. A long-term consequence of PV is evolution to post PV MF, which has a prevalence of approximately 5% at 10 years and 6% to 14% after age 65 years, the overall thrombosis rates were statistically similar (27% vs 31%), but younger patients, especially women, were much more likely to have VT involving abdominal veins. Further, these younger patients may experience a thrombotic event despite having lower leukocyte counts and JAK2 allelic burdens compared with those diagnosed at a typical age.

The associations among cardiovascular risk factors and vascular consequences in PV are becoming better appreciated. In a retrospective review of 604 patients, 75 patients (12%) experienced a thrombotic event within a median follow-up period of 4.9 years. A statistically significant association between hypertension and arterial thrombosis was found in this patient population that was otherwise deemed to have low risk for thrombosis. Of the cardiovascular risk factors, hypertension is more common in patients with PV, particularly those with higher hematocrit. In a prospective study of 3620 men who were followed between the years 1998 and 2009, every 1% increase in hematocrit was associated with a 7% increase in incidence of hypertension. This may be in part due to the effect of increased viscosity on resistance and the load that it subsequently places on the arterial system. If an antihypertensive agent is required in a PV patient, angiotensin-converting enzyme (ACE) inhibitors may be beneficial; they are also utilized after kidney transplants to reduce erythrocytosis.

The ECLAP database demonstrated that patients on ACE inhibitors required chemotherapy less frequently than those on different classes of antihypertensives; however, there were not significant differences in hematocrit or in thrombosis-free survival. This interesting question requires further study.

**TABLE. World Health Organization Criteria for Polycythemia Vera**

<table>
<thead>
<tr>
<th>2008 Criteria</th>
<th>2016 Criteria</th>
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<td><strong>Major Criteria</strong></td>
<td><strong>Minor Criteria</strong></td>
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| 1. a) men: hgb >18.5; women: hgb >16.5; OR  
  b) hgb or hct >99% reference range; OR  
  c) men: hgb >17; women: hgb >15, if ≥2 from baseline and not due to correction of iron deficiency; OR  
  d) red cell mass >25% baseline  
  2. Presence of JAK2 V617F | 1. Subnormal serum EPO level  
  2. Bone marrow biopsy with trilineage growth  
  3. Endogenous erythroid colony growth |
| **Diagnostic Requirements** |  |
| Both major criteria and 1 minor criterion, or first major criterion and 2 minor criteria | All 3 major criteria, or first 2 major criteria and the minor criterion |

EPO indicates erythropoietin; hct, hematocrit; hgb, hemoglobin. Adapted from Arber et al.

**FIGURE. Complications of Polycythemia Vera and Their Associated Risk Factors**

- **Thrombosis:** older age, history of thrombosis, leukocytosis, increased JAK2 V617F allele burden, inflammatory stress, gender (abdominal thrombosis), cardiovascular risk, JAK - before TET2 mutations
- **Myelofibrosis:** longer disease duration, older age, leukocytosis, splenomegaly, JAK2 V617F allele burden >50%, presence of ASXL1, SRSF2, and/or IDH2 mutations
- **Leukemic transformation:** older age, leukocytosis, abnormal karyotype, prior treatment with P-32, chlorambucil, or pipobroman
- **Mortality:** older age, leukocytosis, venous thrombosis, abnormal karyotype, presence of ASXL1, SRSF2, and/or IDH2 mutations
at 15 years. The diagnosis requires bone marrow fibrosis at least greater than grade 2 on a 3-point scale, and at least 2 of the following: anemia or no longer requiring treatment to maintain a hematocrit goal; a leukoerythroblastic peripheral smear; splenomegaly; or at least 1 constitutional symptom. In addition to disease duration, risk factors for progression to MF include older age, leukocytosis, splenomegaly, marrow fibrosis at diagnosis, and JAK2 allele burden greater than 50%. Allele burden does not portend a worse prognosis regarding survival or leukemic transformation.

The rate of leukemic transformation at 20 years is less than 10%. Younger patients (aged <45 years) transform to leukemia at a median of 19 years while older patients (aged >60 years) transform at a median of 7 years. Transformation to AML has a very poor prognosis. Transformation typically occurs through an MF phase, but can occur directly from a PV phase of the illness. Risk factors for transformation include leukocytosis, advanced age, and abnormal karyotype. An additional risk factor is prior use of agents such as radioactive phosphorus (32P), chlorambucil, or pipobroman. Of note, single-agent use of hydroxyurea (HU) or busulfan has a controversial association with leukemic transformation.

In a study of 826 patients with PV at Mayo Clinic, survival was 14 years for those older than 60 years and 24 years for those under 60 years. Risk factors for mortality and leukemic transformation in another recent study of 1545 patients with PV included older age, leukocytosis, thrombosis, and abnormal karyotype.

Impact on Quality of Life

It is also important to recognize that even in the absence of thrombosis, MF, or leukemic transformation, patients with PV can have a high symptom burden, independent of risk. Among 519 patients with PV, patients were clustered based on results of the Myeloproliferative Neoplasm Symptoms Assessment Form (MPN-SAF), a questionnaire that allows patients to rank symptoms and quality of life on a 10-point scale. No correlation was found between the total score collected from the form and risk category: In other words, even patients traditionally characterized as low risk could have significant symptoms. Symptoms that negatively impacted quality of life, with their associated prevalence based on survey data of 402 patients, included fatigue (97%), insomnia (58%), pruritus (40%), sexual dysfunction (51%), abdominal discomfort (45%), early satiety (62%), difficulty with concentration (58%), and sad mood (57%), among others. Another study further evaluated the symptomatic profile of patients with PV, and noted that the symptom burden was increased in those with splenomegaly, phlebotomy needs, and history of past or current HU use. Of note, in a recent survey of 813 patients with MPN and 457 hematologist/oncologist responders, discordance was noted between patients and physicians regarding evaluation of symptoms. Many patients reported being asked questions about general well-being rather than about specific symptoms, and they reported that they didn’t realize particular symptoms were associated with their underlying disease. Physicians underestimated the symptom burden of patients with MPN at the time of diagnosis. This study highlights the importance of recognizing and educating patients about the symptom burden associated with PV.

Treatment

Cornerstones of Therapy

Phlebotomy has been a cornerstone of therapy for PV since the 1900s. In a more recent randomized study of adults with PV treated with a target hematocrit of either less than 45% or 45% to 50%, the primary endpoint, which included thrombosis or cardiovascular deaths, was less prevalent in the group that maintained a hematocrit <45%. Thus, all patients with PV should utilize phlebotomy to maintain a hematocrit target of less than 45%.

Aspirin is another cornerstone of therapy. ECLAP evaluated the safety and efficacy of daily low-dose aspirin in a prospective study of 518 patients and favored once-daily dosing of low-dose aspirin for decreasing risk of thrombosis without a risk for significant bleeding. Microvascular disturbances involving platelet-rich arteriolar microthrombi can cause many symptoms, including lightheadedness, ocular/neurologic disturbances, tinnitus, chest discomfort, and erythromelalgia, but aspirin can help alleviate these symptoms. Since patients with MPNs and thrombocytosis may have more rapid turnover of platelets and an incomplete response to aspirin, patients who do not respond to once-daily dosing may benefit from twice-daily dosing, although this is clinically unproven and use would be extrapolated from a preclinical study with ET patients. Patients with platelet quantities greater than 1000 x 10^9 should be screened for ristocetin cofactor activity, which, if reduced, may compromise tolerability of aspirin and increase bleeding risk.

Cytoreductive Therapies

Traditional indications for cytoreduction include age over 60 years and thrombosis history. Either variable has historically suggested a higher risk for vascular complications. Consideration for cytoreduction can also be given with the presence of progressive leukocytosis, symptomatic or extreme thrombocytosis, symptomatic splenomegaly or other uncontrolled symptoms, or intolerance of phlebotomy. When cytoreduction is indicated, hydroxyurea (HU) has been considered frontline by most practicing hematologists. Use of HU as a first-line agent was established by the PVSG, although high-quality data in PV are actually scarce. In the study, there was a lower incidence of thrombosis with use of HU compared with a historical cohort treated with phlebotomy alone, and the incidence of AML was lower compared with treatment with both chlorambucil and radioactive phosphorus.

Second-line therapy is often considered in the presence of HU intolerance or resistance. In a study of 890 patients treated with HU, 15% of patients developed resistance/intolerance to HU. Resistance was defined as requiring phlebotomy to maintain the hematocrit goal; uncontrolled thrombocytosis and leukocytosis; failure to reduce massive splenomegaly by 50%; or related symptoms, despite
a sufficient dose and duration of therapy. A key aspect of intolerance included cytopenia(s) incurred with the lowest dose required to achieve a response. While previous HU resistance was thought to be associated with worse survival, the results of 1 study indicated that it was specifically the presence of intolerance due to cytopenias that is associated with worse prognosis regarding leukemic transformation, progression to MF, and mortality. Therefore, patients with this form of HU intolerance not only need a transition in treatment, but a reevaluation of their disease status.

While it is clear that patients with HU intolerance or resistance need to transition therapies, patients often continue treatment with HU despite having ongoing phlebotomy needs. The implications of an ongoing phlebotomy requirement despite HU therapy are under evaluation. A study found that patients treated with HU who required 3 or more phlebotomies per year had a higher risk for thrombosis compared with those who required 0 to 2 phlebotomies per year (20.5% vs 5.3% at 3 years; P <.0001). JAK2 Inhibition

In the RESPONSE study, ruxolitinib was evaluated as a second-line treatment after treatment failure with HU in a cohort of 222 patients; the endpoints were hematocrit control and reduction in spleen volume by at least 35%. In the ruxolitinib arm, 60% of patients had a reduction in hematocrit (vs 20% in the group receiving best available therapy [BAT], which was most commonly HU); 38% of patients had spleen volume reduction (vs 1% in BAT); and 49% of patients had better symptom control (vs 5% in BAT). After 32 weeks of treatment, patients originally in the BAT arm were able to crossover to ruxolitinib, which limits ability to make long-term comparisons between the groups. A subsequent report with follow-up at 80 weeks demonstrated durable responses regarding maintenance of hematocrit control and spleen volume reduction. Although not a prespecified endpoint, there was suggestion of lower thrombosis rates, which were 1.8 per 100 patient-years of exposure in those treated with ruxolitinib, 4.1 in ruxolitinib after cross over, and 8.2 in BAT. Additionally, the rate of MF progression in the ruxolitinib arm was 1.3 per 100 patient-years (2 after crossover, 1.4 in BAT), and the rate of leukemic transformation in that arm was 0.4 (0.7 after crossover, 0 in BAT). Notable adverse events (AEs) that were more common in the ruxolitinib arm compared with BAT included herpes zoster and nonmelanoma skin cancer.

Subsequently, the RESPONSE-2 study evaluated ruxolitinib as a second-line treatment option in 173 patients with HU intolerance and resistance, but without splenomegaly. The primary endpoint was hematocrit control at week 28, which was met by 62% of patients in the ruxolitinib arm compared with 19% in the BAT arm (P <.0001). The most common AEs included anemia (14% ruxolitinib vs 3% BAT), hypertension (7% vs 4%), and pruritus (0% vs 3%).

Interferons

Interferons are also considered first-line or second-line therapy for PV, although used less frequently in practice. Renewed interest in use of pegylated-interferon (peg-IFN) has come from phase II studies in newly diagnosed and previously treated patients with PV showing high rates of complete hematological response (CHR) and impressive rates of molecular responses. Recently, peg-IFN was compared in a randomized study with HU. In this study, presented at the 2016 American Society of Hematology Annual Meeting, 168 patients with high-risk PV who were newly diagnosed (<5 years) were randomized to peg-IFN or HU with a primary endpoint of CHR. Interim results of 75 patients after 12 months did not show a significant difference in the primary endpoint between the 2 treatment groups. CHR was seen in 33% of patients treated with HU and 28% of patients treated with peg-IFN. Normalization of spleen size was seen in 2 of 7 patients treated with HU and 5 of 7 patients treated with peg-IFN. Grade 3 hematologic and nonhematologic AEs occurred in 5 of 36 patients treated with HU and 16 of 36 patients treated with peg-IFN. Of the 75 patients enrolled, 66 completed questionnaires (MPN-SAF) to characterize symptoms and quality of life. The mean MPN-SAF was higher with HU compared with peg-IFN for the first 6 months; however, after 6 months patients treated with peg-IFN had worse total symptom scores, and the patients who achieved CHR reported a worse symptom burden compared with those who did not.

Novel interferons have also been developed, and 1 such form is rogeinterferon alpha-2b, which has a longer elimination half-life and can be dosed every 2 weeks. A trial of 51 patients began as a phase I study that demonstrated no dose-limiting toxicities. Subsequently, additional patients were enrolled during the phase II portion; results indicated that after 12 months of therapy, an overall hematologic response was observed in 82% of patients, with 29% experiencing a CHR. There was no association between treatment dose and hematologic response. A molecular response was observed in 33% of patients at 12 months, with 12% having a complete molecular response. Of note, patients who experienced a hematologic response were more likely to have a molecular response. Of the 51 patients, 13 discontinued at various points in the study—the earliest at week 10 and the latest at week 50. Four patients discontinued due to administrative/consent reasons, 1 patient discontinued due to lack of efficacy, and the remaining 9 experienced AEs, such as fatigue, deterioration of general well-being, depression, elevated thyroid antibodies, rheumatoid arthritis, and elevated antinuclear antibodies associated with hyperkeratosis. This agent is also being compared with HU in a randomized study of 257 patients. Twelve-month data from this phase III noninferiority trial were presented at the 2016 American Society of Hematology Annual Meeting, and preliminary data also suggested noninferiority between the rogeinterferon alpha-2b and HU groups.

Busulfan

Busulfan is an older agent, but one that can be considered as a second-line cytoreductive therapy for older adults with HU intolerance or resistance. A recent retrospective study of 36 patients (15 with PV,
21 with ET) with HU intolerance/resistance reported an 83% CHR durable at 1 year (87%).57 Partial MR was achieved in 3 of 9 patients; there were 8 (30%) discontinuations, an 11% thrombosis rate at 2 years, and 3 transformations to MDS or AML.

Additional Indications for Therapy
As mentioned, patients with PV can experience a considerable symptom burden, even in the absence of objective measures of disease severity. Lower-risk patients with a considerable symptomatic burden despite phlebotomy and aspirin may require additional therapies. One specific symptom that can negatively impact quality of life is pruritus, which can be severe and is often exacerbated by hot showers. Although the exact mechanism behind aquagenic pruritus is yet to be determined, many have hypothesized that it is related to histamine release from mast cell degranulation. Nonetheless, treatment with antihistamines has unreliable results.58 Treatments that have helped some patients with pruritus include paroxetine,59 JAK2 inhibitors,60 and narrow band ultraviolet B phototherapy.59,64

Special Situations
Hematologists also manage special situations, including pregnancy and surgery. Most information regarding management of MPN associated pregnancies pertains to ET, given a second peak incidence in women of childbearing age. In a recent prospective study of MPN pregnancies, among 58 patients, only 5 had PV.62 Including patients with ET and MF in this cohort, the miscarriage rate was 1.7%; 9% had pre-eclampsia or hemorrhage, and no thrombotic events were reported, although a significant number of patients were on aspirin, venous thromboembolism (VTE) prophylaxis, and/or cytoreduction.

There are consensus recommendations that advise on the hematocrit target (<45%), the use of aspirin, and VTE prophylaxis (typically postpartum or possibly antepartum in those who are at high risk or have had prior thrombosis).45 Consensus from European medical societies provide similar recommendations, and guidance from the National Comprehensive Cancer Network (NCCN) is anticipated.63,66 For patients requiring cytoreduction prior to pregnancy due to high risk, interferons are an option. Recombinant interferons have been utilized, as there have been limited data available regarding use of peg-IFN in PV pregnancies. A recent observational series has been published, describing use of peg-IFN, but this included only 10 patients with ET.56 The authors suggested that this option was safe and effective in this small series.

Another special situation includes management of the patient with PV around the time of surgery. A retrospective analysis included 105 patients with PV, as well as 150 patients with ET who underwent 156 minor and 155 major surgeries.66 Most patients were on cytoreduction and/or phlebotomy and had excellent hematocrit control, with a mean under 43%. Despite these measures and additional VTE prophylaxis, however, vascular occlusion still occurred in 7.7% of the cohort. In patients with PV, there was an increased hazard for VT (hazard ratio, 7.3). Guidelines are available, and guidance from the NCCN regarding perioperative management of PV is anticipated.63,64

Conclusion
The last decade of PV research has featured an abundance of discovery. Important recent developments include an updated description of the epidemiology of PV, with additional information to come from a large, natural history study of PV, which includes more than 2000 patients from academic and community medical centers.6 The molecular pathogenesis continues to be characterized, and diagnostic criteria allow for recognition of more subtle presentations of PV. There has been increasing awareness of risk factors for thrombosis beyond traditional ones such as advanced age and thrombosis history. Use of next-generation sequencing may help identify patients at higher risk for MF transformation. Further, the impact of PV on quality of life has been elucidated. Given that PV is a rare disease, it is expected that treatment practices are heterogeneous.66 However, the development of guidelines by the NCCN will provide a framework for decision making. This will be increasingly important as new therapies for PV are developed and the role and sequence of current therapies is better defined. In this regard, large-scale, randomized studies comparing peg-IFN with HU are underway. With ruxolitinib, PV finally has a specifically approved therapy. This agent is currently used for those with an inadequate response to HU. Given the efficiency and durability of hematocrit control, spleen volume reduction, and symptom management with JAK2 inhibitors, these therapies may eventually have a frontline role, though studies do not yet support this practice and this is not recommended.

Room exists for improved therapies and novel strategies. One could involve a combination of peg-IFN and ruxolitinib, which was presented at the 2015 American Society of Hematology Annual Meeting.67 The rationale for this combination is to utilize the anti-inflammatory properties of ruxolitinib to improve the efficacy of peg-IFN, which is thought to be limited in the setting of inflammation.69 Another combination involves the use of an MDM2 inhibitor and peg-IFN.69 MDM2 negatively regulates p53, which is more frequently mutated in MPN patients who experience leukemic transformation.69 Preclinical data demonstrated that JAK2 V617F upregulates La antigen, which increases translation of MDM2, thus decreasing apoptosis via p53. Peg-IFN was selected because it upregulates p53 and decreases JAK2 V617 hematopoietic progenitor cells. Additionally, using peg-IFN in conjunction with an MDM2 inhibitor may decrease the duration of treatment required by peg-IFN, which may limit AEs.70

Hopefully, the progress of PV research will continue to be as rapid in the next decade as it has been in the preceding one. If it is, we may be able to offer our patients therapies that are proven to modify the natural history of this myeloid neoplasm.

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The Evolution of Frontline Therapy in ALK-Positive Advanced NSCLC: Which ALK TKI to Use Upfront?

Jeffrey Zweig, MD, and Heather Wakelee, MD

Abstract
Therapeutic options for advanced anaplastic lymphoma kinase (ALK)-positive non–small-cell lung cancer have changed dramatically since the 2011 approval of crizotinib. Since then, 3 additional agents have received FDA approval for use in the second-line setting after progression on crizotinib: ceritinib, alectinib, and brigatinib. Other investigational ALK inhibitors are under evaluation. As these agents represent newer-generation, more potent ALK inhibitors, interest in their use in the frontline setting has quickly grown. Here, we review frontline trials of ceritinib and alectinib, with comparisons drawn with crizotinib, the only FDA-approved frontline choice until the recent approval of ceritinib. With several new promising options, we attempt to better answer the question of which ALK tyrosine kinase inhibitor (TKI) should be favored upfront.

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Introduction
The identification of the EML4-ALK fusion oncogene in 2007 as a driver of pathogenesis, in the 2% to 7% of patients with non–small-cell lung cancer (NSCLC) who express it, has led to the development over the last decade of several targeted anaplastic lymphoma kinase (ALK) inhibitors. The use of ALK inhibitors in advanced disease has transformed the treatment strategy of ALK-positive NSCLC, providing targeted therapeutic options that show significant progression-free survival (PFS) and overall survival (OS) benefit, with an impact on patients and their disease course. There are currently 4 approved agents—crizotinib (Xalkori), ceritinib (Zykadia), alectinib (Alecensa), and brigatinib (Alunbrig)—with several others in active development. Although crizotinib has historically represented the first-line agent of choice, it has quickly been challenged by the newer, more potent, second-generation ALK inhibitors ceritinib and alectinib, with ceritinib recently gaining FDA approval as a first-line option in May 2017. In order to best answer the question of which agent to use upfront, one must consider a variety of factors, including comparative trial data, adverse event (AE) profiles, and response rates, which will be reviewed here.

The use of crizotinib in ALK-positive lung cancer interestingly evolved when the drug, initially developed as a c-MET inhibitor, was in phase I development at the same time the EML4-ALK fusion oncogene was discovered. It was soon found that crizotinib was also a strong inhibitor of ALK phosphorylation and downstream signaling. Crizotinib was first tested in a phase I trial evaluating 143 ALK-positive patients treated with escalating doses, reaching a recommended dose of 250 mg twice daily. Results showed an overall response rate (ORR) of 60.8% (95% CI, 52.3%-68.9%), a median duration of response (DOR) of 49.1 weeks (95% CI, 39.3-75.4 weeks), and a PFS of 9.7 months (95% CI, 7.7-12.8 months), with a well-tolerated profile. In August 2011, crizotinib was granted accelerated approval by the FDA for treatment in patients with ALK-positive advanced NSCLC. Crizotinib was later tested in 2 landmark phase III trials. In the PROFILE 1007 trial, 347 previously treated ALK-positive patients were randomized to either crizotinib or single-agent pemetrexed or docetaxel. At a follow-up of 1 year, crizotinib showed a statistically significant PFS benefit of 7.7 versus 3 months for single-agent chemotherapy (HR, 0.49; 95% CI, 0.37-0.64; \( P < .001 \)) as well as improved ORR and DOR. Patients reported improved lung cancer symptoms and also greater global quality of life with crizotinib rather than chemotherapy. No significant difference in OS was found (20.3 vs 22.8 months; hazard ratio [HR], 1.02; 95% CI, 0.68-1.54; \( P = .54 \)), likely a result of 64% crossover.

With evident success in the second-line setting, crizotinib was then tested in the first-line setting in the PROFILE 1014 trial, in which 343 patients who were ALK-positive with no prior systemic treatment were randomized to crizotinib 250 mg twice daily or standard platinum doublet with cisplatin or carboplatin plus pemetrexed. The primary endpoint was PFS, which was met with a statistically significant benefit with crizotinib of 10.9 versus 7 months with chemotherapy (HR, 0.45; 95% CI, 0.35-0.60; \( P < .001 \)). The ORR was 74% for crizotinib versus 45% for chemotherapy (\( P < .001 \)), though the difference in OS was not significant (HR, 0.82; 95% CI, 0.54-1.26; \( P = .36 \)), again likely due to a high crossover rate of 70% of patients. The most frequently occurring AEs in the crizotinib arm compared with chemotherapy were visual disturbances (71%), diarrhea (61%), and edema (49%). Overall, there was less permanent discontin-
ulation of the drug compared with chemotherapy and a greater improvement in quality-of-life measures. This trial solidified crizotinib as the standard of care in the frontline setting of metastatic ALK-positive NSCLC, for which it was approved in November 2013 as the first-line agent of choice.

The success of crizotinib unfortunately is ultimately tempered by the development of drug-resistance mechanisms and disease progression, which on average occur toward the end of the first year of therapy, with central nervous system (CNS) metastasis being a common site of relapsed disease. These resistance mechanisms include secondary mutations within the ALK kinase domain, most notably the "gatekeeper" substitution L1196M, followed by a G1269A mutation, amplification of the ALK fusion gene, and activation of other receptor tyrosine kinase sites such as EGFR, cKIT, and IGF-1R. In contrast to EGFR tyrosine kinase inhibitor (TKI) resistance, in which approximately 50% of the time a specific mutation (T790M) develops, in ALK patients, there is significant tumor heterogeneity as well as the presence of varying point mutations that can occur at nonactive sites, with only one-third of crizotinib resistant cases being an on-target mutation.9,10

**Newer-Generation ALK Inhibitors**

Given that crizotinib targets not only ALK, but MET and ROS1, several newer-generation ALK inhibitors have subsequently been developed, with higher affinity for inhibiting ALK, auto phosphorylation, resultant downstream signaling, and improved CNS penetration. These include ceritinib, alectinib, and brigatinib, all of which are FDA-approved for treatment after progression on or intolerance to crizotinib, with ceritinib also approved in the upfront setting. Other investigational agents include lorlatinib and ensartinib, with lorlatinib having achieved a breakthrough FDA designation as a second-line agent.11,12 To further add to the complexity of ALK resistance, there are also differing activities of ALK inhibitors across ALK mutations, with varying selectivity profiles, making the understanding of the mechanism of resistance important to choosing an effective therapy.

The potency of ceritinib, alectinib, and brigatinib, and their demonstrated efficacy as second-line ALK inhibitors after progression on crizotinib, were shown in early phase I/II clinical trials, which led to approvals and also to interest in their use as first-line agents.13,14 In the ASCEND-4 trial, 376 treatment-naïve stage IIIIB/IV ALK-positive NSCLC patients were randomized to 750 mg daily of ceritinib or 4 cycles of platinum-based chemotherapy with cisplatin or carboplatin plus pemetrexed followed by pemetrexed maintenance. Crossover to the ceritinib arm was allowed if patients progressed on chemotherapy. ALK rearrangement was determined by immunohistochemistry. The primary endpoint was PFS, with secondary endpoints of ORR, DOR, OS, and intracranial response.15

The results showed a median PFS of 16.6 months in the ceritinib group versus 8.1 months in the chemotherapy arm (HR, 0.55; 95% CI, 0.42-0.73; P = .00001). This PFS benefit was observed in both patients with and without brain metastasis, with those without brain metastasis sustaining an impressive median PFS of 26.3 months versus 8.3 months in the chemotherapy group (HR, 0.48; 95% CI, 0.33-0.69). The ORR was also significantly improved for ceritinib (72.5% vs 26.7%) as well as the DOR (66.4 weeks vs 26.9 weeks). The OS data at the time of analysis were immature and did not cross the efficacy-stopping boundary, though it was not reached in the ceritinib group and was 26.2 months in the chemotherapy group (HR, 0.73; 95% CI, 0.50-1.08; P = .056). With regard to toxicity, notable AEs that were higher in the ceritinib arm compared with chemotherapy were diarrhea, nausea, and vomiting, as well as elevation in aminotransferases. Eighty percent of patients in the ceritinib group versus 45% in the chemotherapy group required dose adjustments or interruption of therapy, primarily as a result of gastrointestinal (GI) toxicity or liver function abnormalities. Five percent of patients discontinued therapy in the ceritinib group. Lung cancer–specific symptoms as evaluated by questionnaire were significantly improved for those randomized to the ceritinib arm versus chemotherapy arm.16

The study design of ASCEND4 closely mirrored that of the PROFILE 1014 study in terms of the comparator chemotherapy arm, with similar results of witnessed control-arm PFS between the trials. No new AEs using a more potent ALK inhibitor were observed, although GI toxicity with ceritinib was an issue for a significant number of patients, requiring dose reductions. Data have been reported that decreasing the dose of ceritinib to 450 mg daily and taking with food may mitigate many of the GI toxicities seen with 750 mg daily.17 The convincingly positive results of the ASCEND4 trial across all subgroups led to the recent frontline FDA approval of ceritinib. The updated National Comprehensive Cancer Network NSCLC guidelines now include ceritinib alongside crizotinib as a category 1 option in the frontline setting in ALK-positive metastatic disease.18

**J-ALEX**

The phase III J-ALEX trial was the first trial with data comparing 2 ALK inhibitors in the first-line setting. Conducted exclusively in Japan, this trial randomized 207 Japanese patients with stage IIIIB/IV ALK-positive NSCLC, previously given 0 to 1 lines of chemotherapy, but ALK TKI naïve, to alectinib 300 mg twice daily or crizotinib 250 mg twice daily. The primary endpoint was PFS with secondary endpoints of OS, ORR, DOR, time to onset of CNS lesions in patients without any at baseline, time to progression of CNS lesions in those with lesions present at baseline, and quality of life. At the time of analysis, median PFS was 26.2 months in the alectinib arm (20.3 months at the low end of the confidence interval) and was 10.2 months in the crizotinib arm (HR, 0.34; 99.7% CI, 0.17-0.70; P <.0001). The ORR of alectinib was 85.4% (95% CI, 78.6%-92.3%) versus 70.2%
(95% CI, 61.4%-79%) in the crizotinib arm. There was also an improved response to alectinib in the subgroup of patients with brain metastasis (HR, 0.08; 95% CI, 0.01-0.61). AEs of any grade favored alectinib, with the most common being constipation in the alectinib arm. In patients randomized to crizotinib, diarrhea, nausea, vomiting, visual disturbances, and transaminase elevations were significantly witnessed. No AEs resulting in a fatal outcome occurred. Survival data remain immature at present with only 9 events reported between the 2 groups.19

ALEX
With the J-ALEX trial conducted exclusively in Japan, the international ALEX trial was launched to assess whether these findings could be replicated on a global scale. Spanning 31 countries, the ALEX trial enrolled 303 treatment-naïve ALK-positive metastatic patients with NSCLC who were randomized to alectinib 600 mg twice daily or crizotinib 250 mg twice daily, with PFS as the primary endpoint. Secondary endpoints included OS, ORR, DOR, time to CNS progression, quality of life, and safety.20 In addition to being an international study, the ALEX trial design differed from J-ALEX in that the dose of alectinib used was 600 mg twice daily compared with 300 mg twice daily, and the patients were treatment-naïve, whereas about one-third of patients in the J-ALEX trial had previously received 1 line of chemotherapy.

The results, like those of J-ALEX, were again compelling. Median PFS was not reached in the alectinib arm (17.7 months at the low end of the confidence interval) versus 11.1 months in the crizotinib arm (HR, 0.47; 95% CI, 0.34-0.67; P <.001). Nearly all subgroups benefited, with the exception of smokers and patients with an Eastern Cooperative Oncology Group score of 2, although these patients were represented in small numbers. ORR was 82.9% (95% CI, 76%-88.5%) in the alectinib arm versus 75.5% (95% CI, 67.8%-82.1%) in the crizotinib arm. Of those patients without brain metastasis at baseline, time to CNS progression was significantly longer with alectinib, with a median of 14.8 months in the alectinib arm vs 7.1 months in the crizotinib arm. In patients randomized to crizotinib, diarrhea, nausea, vomiting, visual disturbances, and transaminase elevations were significantly witnessed. No AEs resulting in a fatal outcome occurred. Survival data remain immature at present with only 9 events reported between the 2 groups.19

Integrating the Results
So how can a clinician integrate the results of the PROFILE 1014, ASCEND-4, J-ALEX, and ALEX trials into deciding which ALK agent should be favored upfront? Crizotinib, ceritinib, and alectinib all show remarkable frontline overall response rates of 74%, 73%, and 80% to 85%, respectively.7-16,19,20 Refer to the Table for trial comparisons. When taking into account comparative toxicities, the above trials demonstrate that although the spectrum of AEs is similar, alectinib seems to be better tolerated overall than are crizotinib or ceritinib, with less GI toxicity, nearly no visual disturbances, and less transaminase elevation. Increased peripheral edema and skin rash can be seen, however, as well as some generally mild myositis.19

With regard to CNS penetration, even with good control of systemic disease, about 40% to 50% of patients on crizotinib will develop brain metastases. Nonetheless, crizotinib still has modest penetration in the CNS. As evidenced by the PROFILE 1014 trial, of the 23% of patients with brain metastases, there was a nonsignificant trend toward improved time for intracranial progression in the crizotinib versus chemotherapy arm (HR, 0.60). At 24 weeks of follow-up in the patients with previously treated brain metastases, 56% were controlled in those receiving crizotinib versus 25% in those receiving chemotherapy.7 The second-generation ALK inhibitors, however, have more robust CNS activity. In the ASCEND-4 trial, in patients with at least 1 brain metastasis, ceritinib had a 72.7% intracranial ORR versus 27.3% for chemotherapy.18 In both the J-ALEX and ALEX studies, alectinib was significantly favored over crizotinib in the subset of patients with brain metastases.19,20 It would thus seem reasonable that in patients who present with significant brain metastasis, an upfront second-generation agent should be considered over crizotinib. The survival data, when mature, will provide a more definitive answer.

| TABLE. Frontline ALK TKI Trials. |
|---------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Trial   | Treatment       | Number of Patients (N) | Median PFS (months) | ORR (%) | Median OS (months) |
| PROFILE 1014 | Crizotinib 250 mg BID vs Cisplatin/carboplatin + pemetrexed | 343 | 10.9 vs 7 (P <.001) | 74 vs 45 | No difference (P = .36) |
| ASCEND-4 | Ceritinib 750 mg daily vs Cisplatin/carboplatin + pemetrexed | 376 | 16.5 vs 8.1 (P <.00001) | 72.5 vs 26.7 | NR vs 26.2 (P = .056) |
| J-ALEX   | Alectinib 300 mg BID vs Crizotinib 250 mg BID | 207 | NR vs 10.2 (P <.0001) | 85.4 vs 70.2 | Data immature |
| ALEX     | Alectinib 600 mg BID vs Crizotinib 250 mg BID | 303 | NR vs 11.1 (P <.001) | 82.9 vs 75.5 | Data immature |

BID, twice daily; NR, not reached; PFS, progression-free survival; ORR, overall response rate; OS, overall survival
Certainly based on the head-to-head comparison posed in both J-ALEX and ALEX, alectinib demonstrated an improved PFS, ORR, and CNS response over crizotinib in the front line, and its toxicity profile was preferable. Even without mature OS data, it would be hard to picture alectinib not being granted FDA approval as a first-line option in the near future. It now represents a “preferred” frontline agent compared with crizotinib and ceritinib in the most recently updated NCCN guidelines. Both the 300 mg twice-daily dose as used in J-ALEX and the 600 mg twice-daily dose used in ALEX appear highly effective, with a response rate of more than 80% and median PFS that is yet to be reached. Like most drugs, higher dosages can come with higher toxicity, and alectinib at 300 mg twice daily appeared to be better tolerated than 600 mg twice daily. Twenty six percent of patients in J-ALEX experienced at least 1 grade 3 or 4 AE on alectinib 300 mg twice daily compared with 41% with at least a grade 3 AE on alectinib 600 mg twice daily in the ALEX trial. Despite encouraging CNS dosage used in ALEX appear highly effective, with a response rate of more than 80% and median PFS that is yet to be reached. Like most drugs, higher dosages can come with higher toxicity, and alectinib at 300 mg twice daily appeared to be better tolerated than 600 mg twice daily. Twenty six percent of patients in J-ALEX experienced at least 1 grade 3 or 4 AE on alectinib 300 mg twice daily compared with 41% with at least a grade 3 AE on alectinib 600 mg twice daily in the ALEX trial. Despite encouraging CNS response in both J-ALEX and ALEX, it is difficult to compare the 2 trials in this regard, because J-ALEX had significantly fewer patients with measurable brain lesions in comparison with ALEX (13.6% vs 42%). At present, alectinib 600 mg twice daily remains the recommended dose in the United States when used as a second-line agent.

With alectinib showing overall superiority to crizotinib, and being on pace to replace crizotinib as a new standard of care in the frontline setting, an important question arises: Is frontline alectinib better than sequential therapy with crizotinib followed by alectinib or another second-generation ALK TKI? One can conjecture that when assessing PFS, the answer depends on which drugs are used. Although PFS comparisons between trials should always be taken with caution, given that the low end of the confidence interval in ALEX with regard to PFS was 17.7 months with alectinib, this already is trending toward exceeding the median PFS of upfront crizotinib followed by alectinib or ceritinib in the second line, which is around 10 to 11 months for crizotinib® plus 7 to 8 months with alectinib or ceritinib. However, this calculation changes if the recently approved brigatinib is used as a sequential therapy to crizotinib, as it was the first ALK TKI to show more than a 12-month PFS benefit in the second-line setting. Therefore, it can be said that the verdict is still out on sequential therapy, regarding first-in-class crizotinib versus upfront use of the newer-generation ALK TKIs. Time and more mature survival data will likely settle this.

Conclusions

In sum, the current landscape of first-line treatment for ALK-positive stage IIIIB/IV disease is quickly, excitingly evolving. Several ALK TKIs are emerging as effective options, with crizotinib and ceritinib already FDA-approved in the frontline setting, and alectinib undoubtedly soon to follow. In addition, phase III trials of brigatinib versus crizotinib as well as ensartinib versus crizotinib in ALK treatment-naïve patients are underway, and their results are likely to eventually add to the pot of upfront therapies. The decision of which ALK inhibitor to use first has become complex, and without yet firm survival data to support 1 agent over another, it is fair to say that clinician decisions will vary, and drug tolerance, resistance patterns, quality-of-life measures, patient preference, accessibility, and cost should be carefully assessed and evaluated for each individual patient. Based on available data, alectinib appears to be the most promising agent of the group, and time will tell if it eventually wins out. One thing is for sure: There is indeed much hope for patients with advanced ALK-positive NSCLC who, before August 2011, were left with chemotherapy as their sole treatment choice. Now, just about 6 years later, they can take advantage of a list of effective ALK inhibitors that, as time progresses, only appears to be growing.

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Overview
This activity is designed to inform physicians about the current and developing strategies in using PARP inhibitors to treat patients with breast cancer.

Target Audience
This activity is directed towards medical oncologists, primary care physicians, nurses, and nurse practitioners who treat and/or manage patients with breast cancer. Surgical oncologists, radiation oncologists, pathologists, internists, fellows, physician assistants, and other health care providers are also invited to participate.

Learning Objectives
After participating in this CME/CE activity, learners should be better prepared to:

- Describe the biologic function of PARP, its role in DNA repair, and the rationale behind targeted inhibition in breast cancer
- Explain the developmental history of PARP inhibitors to date, including recently published clinical data
- Discuss emerging treatment options and ongoing trials of PARP inhibitors

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Introduction
Breast cancer is the most frequently diagnosed cancer in women. In 2017, an estimated 252,710 cases of breast cancer will be diagnosed in the United States, accounting for 15.0% of all new cancer cases. Breast cancer is most common in older women, with a median age at diagnosis of 62 years. However, about 32% of patients are aged less than 55 years at diagnosis.

Over the past 40 years, the incidence rate for breast cancer has generally remained the same. The 5-year survival rate, however, has increased more than 15%, to about 89.7%. Still, it is estimated that 40,610 women will die of breast cancer this year, accounting for 6.8% of all cancer-related deaths. The median age at death is 68 years. It is estimated that there are currently about 155,000 women alive with metastatic breast cancer in the United States. Overall, 12.4% of women will develop breast cancer at some point in their lifetime.

Standard therapies for breast cancer are dependent on estrogen receptor (ER) and progesterone receptor status (collectively referred to as hormone receptor status); human epidermal growth factor receptor 2 (HER2) status; and grade and stage. Treatment for nonmetastatic breast cancer can include a combination of chemotherapy, targeted therapy, and radiation therapy across the adjuvant and neoadjuvant settings, as well as surgical resection. Metastatic disease, which remains incurable, typically requires ongoing treatment with serial systemic therapies, due to the inevitable development of resistance.

DNA Repair Pathways
The cellular reaction to DNA damage is a complex process tailored to the type of damage that occurs. Proper repair of DNA damage is essential for preservation of the genetic information encoded by DNA, and it ensures accurate transmission to subsequent generations of cells. Interruptions of DNA repair mechanisms have been associated with an increased susceptibility to cancer.

The cell has 5 main pathways to repair DNA damage, each of which corresponds to certain types of damage. Base excision repair, in which small, non–helix-distorting errors are removed and replaced, is used to repair damage to base pairs caused by oxidation, alkylation, deamination, or single-strand breaks (SSBs). A similar pathway, nucleotide excision repair, in which bulky additions are removed and replaced, while conserving the overall structure of the DNA strand, is used to repair damage caused by UV light. Mismatch repair is a strand-specific repair mechanism to correct errors from replication; these include adenine-guanine and thymine-cytosine mismatch, as well as insertions and deletions (indels). Finally, double-stranded breaks (DSBs) are repaired by 1 of 2 mechanisms: homologous recombination (HR), in which the sister chromatid is used as a template to correct errant nucleotide sequencing; or nonhomologous end joining (NHEJ), in which blunt ends of DSBs are stitched together, disregarding original sequence. NHEJ is more prone to errors. The specific repair mechanism utilized is cell cycle–dependent. HR dominates throughout the S and G2 phases; NHEJ is present throughout the cell cycle.

BRCA1 and BRCA2 are critical elements in HR-based repair of DNA DSBs. When BRCA1 and BRCA2 genes are mutated in patients with breast cancer, cancer cells rely on alternative methods of DNA repair. By targeting and further inhibiting these alternative DNA repair mechanisms, synthetic lethality can be induced in cancer cells, inducing a second DNA repair defect, leading to cell death.

One such target is the poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP) family of proteins, which comprise 17 different enzymes. PARP plays a role in numerous cellular functions, ranging from DNA transcription/repair to genomic stability, cell cycle regulation, cell signaling, and programmed cell death. PARP-1 and PARP-2 are the most extensively studied members of the PARP family, specifically for their role in the repair of SSBs. PARP-1 detects SSBs, binds to DNA, catalyzes the polymerization of PARP to itself and other substrates, and recruits DNA repair proteins to the site of damage.

PARP inhibitors bind PARP-1 and PARP-2 to the sites of DNA damage, "trapping" them and thereby preventing DNA repair, replication, or transcription. This trapping of PARP to DNA induces a secondary DSB, a cytotoxic event for the cell. PARP itself is necessary for the cytotoxicity of PARP inhibitors: In other words, depletion of PARP proteins in the cell, or independent inactivation without DNA binding, is a nonlethal event.

An enhanced understanding of the role of PARP has led to investigations of PARP inhibitors in the clinical setting. While the development of PARP inhibitors has primarily focused on targeting tumors with BRCA1 or BRCA2 mutations, studies are also investigating the efficacy of PARP inhibition in non–BRCA-mutated tumors that harbor other DNA damage repair abnormalities.

PARP Inhibitors
Olaparib
Olaparib is an oral PARP inhibitor shown to have antitumor activity in HER2-negative metastatic breast cancer with a germline BRCA mutation. Following results from a proof-of-concept phase II trial, the phase III, open-label, randomized, controlled, multicenter OlympiAD trial (NCT02000622) compared olaparib monotherapy with standard chemotherapy in patients with germ-line BRCA-mutated, HER2-negative, metastatic breast cancer who had received fewer than 3 previous chemotherapy regimens and had not progressed on platinum-based chemotherapy.

A total of 205 patients were randomized to receive 300 mg of olaparib twice daily, while 97 were randomized to standard
chemotherapy of physician’s choice, consisting of either capecitabine, eribulin, or vinorelbine at standard doses. The primary endpoint of median progression-free survival (PFS) was significantly longer in patients receiving olaparib monotherapy than in patients receiving chemotherapy (7.0 months versus 4.2 months, respectively), resulting in a 0.58 hazard ratio for disease progression or death (95% CI, 0.43-0.80; P <.001). An overall response rate (ORR) of 59.9% was observed in the olaparib group versus 28.8% in patients receiving standard therapy.¹¹

Among secondary endpoints, median time from randomization to second progression or death following first progression was 13.2 months for patients receiving olaparib compared with 9.3 months for patients receiving chemotherapy (hazard ratio, 0.57; 95% CI, 0.40-0.83; P = .003). The median duration of response was 6.4 months in the olaparib group and 7.1 months in patients receiving chemotherapy.¹³

Overall survival (OS) was another secondary endpoint. At the time of primary analysis, 54.1% of patients receiving olaparib compared with 52.6% of patients receiving chemotherapy were still alive. Median time to death was 19.3 months compared with 19.6 months in the olaparib and chemotherapy groups, respectively. The difference in OS was not statistically significant between the 2 groups, with a hazard ratio for death of 0.90 (95% CI, 0.63-1.29; P <.001). An overall response rate (ORR) of 59.9% was observed in the olaparib group versus 28.8% in patients receiving standard therapy.¹¹

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The most common adverse events (AEs) in patients receiving olaparib were anemia, nausea, vomiting, fatigue, headaches, and cough. In patients receiving chemotherapy, AEs including neutropenia and palmar-planter erythrodysesthesia (hand-foot syndrome) were more common than in patients receiving olaparib. The rate of grade 3 or higher AEs was lower in the olaparib group (36.6%) than in the chemotherapy group (50.5%). Anemia was the most common cause of dose reduction in patients receiving olaparib (13.7% of patients), and that led to discontinuation of treatment in 2.0% of patients receiving olaparib.¹¹

A summary of outcome measures can be seen in the Table.

A phase III trial investigating olaparib as an adjuvant therapy for patients with germline BRCA-mutated, HER2-negative, primary breast cancer (OlympiA, NCT02032823) is currently active and recruiting participants.¹⁶

**Velparib**

Velparib is another PARP inhibitor that has shown success in phase II trials in combination with chemotherapy. The ongoing phase II I-SPY 2 trial (NCT0142379) randomized patients with stage II or stage III breast cancer with ER-positive/MammaPrint-high or triple-negative subtypes to veliparib in combination with carboplatin and paclitaxel versus paclitaxel alone followed by doxorubicin and cyclophosphamide.¹⁵ This adaptively randomized trial is designed to evaluate potential for success in a subsequent phase III evaluation; the primary endpoint is pathological complete response (pCR). In triple-negative patients receiving the veliparib/carboplatin combination, the predicted probability of pCR was 51% (95% Bayesian probability interval [PI], 36%-66%) versus 26% (95% PI, 9%-43%) for patients in the control group, resulting in an estimated phase III success of 88%.¹⁵

These promising results led to the randomized, placebo-controlled, double-blind phase III Brightness trial (NCT02032277), which also evaluated veliparib and carboplatin in the neoadjuvant setting for patients with triple-negative breast cancer, regardless of BRCA status.¹⁶ Patients were randomized 2:1:1 among 3 arms: veliparib plus carboplatin plus paclitaxel (arm A), placebo plus carboplatin plus paclitaxel (arm B), and placebo plus placebo plus paclitaxel (arm C). No significant difference was observed in pCR between arms A and B (53.2% and 57.5%, respectively); however, both arms were markedly improved over arm C, which had a pCR of 31.0% (P <.001). High-grade AEs were observed in both arms containing carboplatin (86% of patients in arm A and 85% of patients in arm B, versus 45% of patients in arm C). Velparib did not significantly impact toxicity. Common AEs included neutropenia, thrombocytopenia, anemia, nausea, and vomiting.¹⁶

Other evaluations of veliparib in combination with carboplatin have been performed in the metastatic setting, including the phase II, randomized BROCADE trial (NCT01506609). In this trial, patients with germline BRCA-mutated metastatic breast cancer were randomized to receive either veliparib plus carboplatin plus paclitaxel, placebo plus carboplatin plus paclitaxel, or veliparib plus temozolomide.¹⁷,¹⁸ For the veliparib/carboplatin/paclitaxel arm, the primary endpoint of PFS was 14.1 months and demonstrated a numerical improvement compared with 12.3 months in the placebo/carboplatin/paclitaxel arm. OS

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**TABLE. Summary of Primary and Secondary Outcome Measures From a Phase III Trial Comparing Olaparib With Standard Chemotherapy in Patients With HER2-Negative, Germline BRCA-Mutated, Metastatic Breast Cancer**²²

<table>
<thead>
<tr>
<th></th>
<th>PFS (months)</th>
<th>ORR (%)</th>
<th>Median Duration of Response (months)</th>
<th>Secondary Progression (months)</th>
<th>Grade ≥3 AEs (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olaparib</td>
<td>7.0</td>
<td>59.9</td>
<td>6.4</td>
<td>13.2</td>
<td>36.6</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>4.2</td>
<td>28.8</td>
<td>7.1</td>
<td>9.3</td>
<td>50.5</td>
</tr>
</tbody>
</table>

AE indicates adverse event; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.
was 28.3 months versus 25.9 months respectively. The ORR was 77.8% compared with 61.3%, reaching statistical significance. No significant increases in toxicity were observed.\(^{20,21}\)

Results from the phase II trial prompted a phase III investigation, Brocade 3 (NCT02163694), which is currently active and recruiting participants. This trial contains 2 arms, veliparib plus carboplatin plus paclitaxel, and placebo plus carboplatin plus paclitaxel. The primary outcome measurement is PFS.\(^{24}\)

\section{Talazoparib}
Talazoparib is a dual-mechanism PARP inhibitor that actively traps PARP on DNA.\(^{22-24}\) The 2-stage, 2-cohort phase II ABRAZO trial (NCT02034916) evaluated talazoparib in patients with germline BRCA-mutations and previously treated metastatic breast cancer. Forty-nine patients had previously been exposed to platinum-based chemotherapy (cohort 1) and 35 patients had been previously treated with 3 or more platinum-free cytotoxic regimens (cohort 2). Overall response rates of 21% and 37% were observed in patients in cohorts 1 and 2, respectively.\(^{20}\)

Following the success of ABRAZO, the phase III EMBRACA trial (NCT01945775) is evaluating talazoparib versus physician’s choice in patients with unresectable locally advanced or metastatic breast cancer. The primary outcome of EMBRACA is PFS. This trial is currently active and recruiting patients.\(^{25}\)

\section{Niraparib and Rucaparib}
Niraparib is another PARP inhibitor that has shown clinical benefit in germline BRCA-mutated recurrent ovarian cancer and is currently approved for that indication.\(^{26,27}\) BRAVO, a randomized, open-label, multicenter phase III trial (NCT01905592) is currently investigating niraparib in germline BRCA-mutated, HER2-negative breast cancer.\(^{28}\) Patients are randomized 2:1 to either receive 100 mg of niraparib once daily or physician’s choice of chemotherapy. The primary outcome measure of this trial is PFS. Secondary outcomes include OS and quality-of-life measurements. This study is ongoing, but not actively recruiting.\(^{24}\)

Like niraparib and olaparib, rucaparib is also approved in BRCA-mutated advanced ovarian cancer. RUBY, a single-arm, open-label phase II trial (NCT02505048), is currently investigating rucaparib in patients with a BRCA-like genomic signature.\(^{29}\) Patient will receive 600 mg of rucaparib daily, over 28-day cycles. The primary outcome measure is clinical benefit rate, and secondary outcome measures include PFS, OS, and AE measurements. This study is ongoing and actively recruiting.\(^{25}\)

For more information on the current and emerging use of PARP inhibitors in the treatment of breast cancer, see our interview with Dr DeMichele below.

Angela DeMichele, MD, MSCE, is a professor of medicine and epidemiology and holds the Jill and Alan Miller Endowed Chair in Breast Cancer Excellence at the Perelman School of Medicine at the University of Pennsylvania. Dr DeMichele is also the co-leader of the Breast Cancer Research Program at Penn Medicine’s Abramson Cancer Center.

\section{What makes BRCA-positive or “BRCA-like” breast cancer particularly susceptible to PARP inhibition? Are there differences in susceptibility for patients with germline or somatic BRCA mutations?}
Dr DeMichele: This is really an important question. Essentially, there are 5 major mechanisms of DNA repair that cells can use to repair the DNA damage that naturally occurs in our cells because of day-to-day wear and tear, exposure to things like UV light, and other toxins in our environment. Cells that are mutated in BRCA1 or BRCA2 have very specific defects in 1 such mechanism, homologous recombination. Tumors that have mutations in this particular mechanism of DNA repair have been very instructive to us in understanding carcinogenesis. It is from this understanding that the PARP inhibitors were developed as a way to take advantage of cells that already had 1 DNA damage repair mechanism knocked out. If we could then knock out others, then we could impair the cells from being able to survive.

The fact that a cell already has an intrinsic deficiency or impairment in the ability to repair its DNA is what makes it susceptible to PARP inhibition. Now, the difference between a BRCA-mutated cell and one that just has “BRCA-like” qualities is that cells are able to develop impairments in these mechanisms for reasons other than BRCA1 or BRCA2 mutations. If we could identify other mechanisms by which homologous recombination is impaired in cells, either through other mutations or by loss of heterozygosity, we could identify other tumors that would be sensitive to PARP inhibition.

Still, because these are different from BRCA-mutant tumors, we don’t know if they’re going to have the same sensitivity to PARP inhibitors that BRCA-mutant tumors have. Simply put, we don’t yet know if drugs in the PARP inhibitor family will also be effective in tumors that have impairments in DNA repair other than BRCA1/2.

Olaparib has been approved for use in ovarian cancer since December 2014. At ASCO this year, results from the phase III OlympiAD trial investigating olaparib in metastatic breast cancer were presented. Can you talk about the results and key takeaways from this trial?
This was a practice-changing study in the sense that it really showed definitive benefit of PARP inhibitors, olaparib specifically, in patients who harbor a germline BRCA1/2 mutation, over and above the benefits those patients would have received from chemotherapy. This trial was in a group of patients who had metastatic disease, but were also identified solely by the fact that they had germline BRCA1 or BRCA2 mutations. It was really agnostic about the subtype of breast cancer—-it had to be HER2-negative, but it could be ER-positive or ER-negative. I think that
including both of those patient groups was a strength of this study. Importantly, in order to be eligible, patients could not have progressed on a prior platinum therapy. This is incredibly important because we don’t yet know the relationship between sensitivity to platinum and sensitivity to PARP inhibitors. In many ways, these therapies operate similarly in terms of synthetic lethality in cells that have impaired DNA repair; thus, resistance to one may result in resistance to the other.

Patients were randomized to single-agent olaparib versus physician’s choice standard chemotherapy, a design which really now looks to be common for trials in this space. The results were quite impressive. There was a significantly longer median PFS in the patients in the olaparib group compared with the patients in the standard therapy group, which was 7 months versus 4.2 months. The hazard ratio for disease progression was also impressive at 0.58.

I think what this trial tells us is that these drugs have single-agent activity in tumors that are BRCA1/2-mutant regardless of whether they’re estrogen-receptor–positive or –negative. One other impressive result was that PARP inhibitor treatment was well tolerated and patients had a preserved quality of life. Especially given that the current standard of care here is single-agent chemotherapy—capecitabine, eribulin, or vinorelbine—which have substantial toxicities. The oral, well-tolerated drug olaparib, clearly shows benefit in terms of PFS, preserved quality of life, and tolerability.

Olaparib as another option for patients who have metastatic breast cancer, a currently incurable disease, is meeting a major unmet need in our field. This drug is giving people more time. This is giving us another treatment option in the armamentarium that is well tolerated, that allows patients to live their lives, to do the activities they like to do, and to really be able to live better with this disease. I think this was really groundbreaking and I think it bodes very well for the other PARP inhibitors that are being tested in a similar way. I anticipate that this will lead to FDA approval of the drug for this indication, and I think this was really a major breakthrough in this area.

What are some of the next steps following the results from this trial?

The results that were presented will likely lead the FDA to consider this drug for approval in breast cancer. As clinicians, we would really like to have access to this option for patients, and I hope that in the coming months that will occur. I also think that this should help bolster the enrollment in other clinical trials of PARP inhibitors in BRCA mutation carriers, because we now have demonstrated proof of principle. Further, there are ongoing trials in the adjuvant setting, particularly the OlympiAD trial, investigating if the drug is this effective in early-stage disease. We hope that PARP inhibition will actually be effective in this setting and potentially prevent a greater proportion of patients from ever becoming metastatic.

To recap, getting FDA approval for this drug so that it’s available to patients, providing the proof of concept to support the other clinical trials of other PARP inhibitors that are being tested similarly, and ultimately to be able to try to bring this earlier into the treatment trajectory to help prevent recurrence are all important consequences of these trial results.

Talazoparib has been shown to reduce tumor size in early-stage breast cancer and is currently being investigated in the phase III EMBRACA study. Does talazoparib have a role in the future of breast cancer treatment and what might we expect from this study?

Talazoparib is another promising agent in this space. Talazoparib is also targeting the trapping of PARP, and may even have enhanced trapping abilities. It was very exciting to see the neoadjuvant data presented at ESMO where, after 8 weeks of single-agent talazoparib, all patients in the study had tumor shrinkage, with an average of about 78%. This trial is another proof of concept that we’re seeing activity of this agent in actually shrinking tumors. The ABRAZO trial in metastatic patients, which was presented at ASCO, also showed response rates that were also very encouraging, with a 21% ORR in patients who had previously demonstrated platinum sensitivity.

So I think that these 2 trials, one in the neoadjuvant setting, one in the metastatic setting, provide us with some of the preliminary evidence that the EMBRACA trial may similarly show activity and potentially benefit patients. Whether the magnitude of that benefit will exceed the standard-of-care chemotherapy in that trial remains to be seen. I think it’s difficult to extrapolate from the data we have so far what the magnitude of the benefit will be. Certainly the OlympiAD data are encouraging, so if we have a drug that’s as efficacious as olaparib in this setting, my hope is that this will be a positive trial as well.

Veliparib has been shown to be highly responsive in combination with chemotherapy in the phase II BROCADE trial and had a high predicted probability of phase III success in the phase II I-SPY 2 trial. Can you comment on the role veliparib may have in the future of breast cancer treatment and what we may expect from the phase III Brightness and BROCADE 3 trials?

I think we can learn a lot from the neoadjuvant and metastatic settings. In the neoadjuvant setting, the data are somewhat mixed. In the I-SPY 2 trial, the comparison was between veliparib/carboplatin plus paclitaxel versus paclitaxel alone, followed by doxorubicin and cyclophosphamide. I-SPY 2 did not separate testing veliparib versus carboplatin versus the combination. As seen in the published data, there was a very high predictive probability of success for the triplet in a subsequent phase III trial, as well as a high predictive probability of an improvement of pathological complete response [pCR] over standard treatment, both of which were metrics of success in the I-SPY 2 trial.

Again, by its design, I-SPY 2 didn’t address whether the benefit was coming from the veliparib, from the carboplatin, or both. As I
said earlier, we have these questions about this interaction between PARP inhibitor activity and platinum activity and whether they are targeting the same processes. A potential answer to this was the phase III BROCADE trial in metastatic patients. In the BROCADE trial we have veliparib plus carboplatin plus paclitaxel compared with placebo plus carboplatin plus paclitaxel, and then the third arm being veliparib plus temozolomide.

Putting the temozolomide aside, if we simply look at this comparison of veliparib/carboplatin/paclitaxel versus placebo/carboplatin/paclitaxel, we saw a higher response rate to the veliparib-containing arm, 77% versus 61%, and a very small increase in PFS of 14.1 months versus 12.3 months. This was not statistically significant.

There is concern that perhaps we aren’t getting independent activity from veliparib and carboplatin—that giving carboplatin alone may be just as good, or close to as good, as giving it in combination with veliparib, potentially with less toxicity. We need to think about this in the context of the other trials. Many of the trials being done do not allow patients who have progressed on platinum before, for registration purposes. So the BROCADE trial is trying to separate out this issue, and I think it has given us food for thought about whether the PARP inhibitors will give us something independent of platinum. I don’t think we know that yet, but there may be an answer to the question in the Brightness trial.

In the Brightness trial, we see that they’ve broken it down even further. This trial compared veliparib/carboplatin/paclitaxel with placebo/carboplatin/paclitaxel or placebo/paclitaxel. This trial really helps us compare the effects of paclitaxel alone, paclitaxel with carboplatin, and paclitaxel with carboplatin and veliparib. In this trial, we really saw no difference between the veliparib/carboplatin/paclitaxel and the placebo/carboplatin/paclitaxel arms. It’s a similar situation to the BROCADE trial, but is now in the neoadjuvant setting. When we look at the pCR rates, we saw it was about 53.2% for veliparib/carboplatin/paclitaxel and 57.5% for placebo/carboplatin/paclitaxel. Again, this is not a large difference in terms of the addition of veliparib. But when you look at the paclitaxel alone without either drug, there was a pCR rate of only 31%. So, clearly, you’re getting more for the addition of the carboplatin or the veliparib, but it’s not clear that you’re getting more for the addition of both.

Niraparib and rucaparib are both approved for use in ovarian cancer. Is there a role for either of these agents for patients with breast cancer? What can we expect from the phase III BRAVO trial investigating niraparib in patients with germline BRCA-positive breast cancer?

Let’s take niraparib first. There were some nice data in phase I, BRCA1/2-mutated breast cancers, showing a response rate of 50%. So that was quite compelling in terms of thinking that this drug may have some activity in BRCA-mutation carriers. This ultimately led to the design of the BRAVO trial, which is very similar in design to the OlympiAD trial in that it is looking at single-agent niraparib versus physician’s choice chemotherapy. It also has the same caveat that it is only allowing prior platinum if the patients were sensitive and not allowing patients who have platinum-resistant cancer. We’re all very excited about seeing the results of the BRAVO trial and wondering if this drug also will have similar activity to olaparib as the results seen in OlympiAD. Moving to rucaparib, I think that this is a slightly different drug. It blocks PARP 1, 2, and 3 and right now is being tested in the phase II RUBY trial, which is for metastatic disease, enrolling patients who have the BRCA-ness profile. This trial is really looking at the group of tumors that may have some other DNA damage repair abnormalities, not patients who are mutation carriers. I think that this is another agent that looks potentially very interesting, and I think we’ll need to wait for those results to see if we can identify another group of noncarriers who may be particularly susceptible to PARP inhibitors.

Is there a role for PARP inhibitors as adjuvant therapy in breast cancer? What can we anticipate from the phase III OlympiAD trial?

Certainly when we see activity in the metastatic setting as impressive as what we saw with the OlympiAD trial, for any agent, we’re really anxious to look at whether that agent will actually have an effect in preventing patients with early-stage disease from recurring. It’s only natural that we would want to bring that agent forward into the adjuvant setting. Of course, primary tumors are, to some degree, biologically different than metastatic tumors, and the ability to eliminate micrometastatic disease and ultimately improve cure rates is certainly a very different bar to clear. It’s not a slam-dunk to assume efficacious drugs in the metastatic setting will provide event-free survival advantage in the adjuvant setting. It is essential to design trials to ask that question and, if they are successful, they will have a major impact on the prevention of a currently incurable disease—metastatic breast cancer.

I think it will also be very interesting to see whether we see reduction in additional primary breast cancers in patients with BRCA mutations who do not have a prophylactic mastectomy. It’s hard to look at this question because so many patients who are mutation carriers elect to have a bilateral mastectomy during primary treatment. We don’t know if PARP inhibitors have any primary preventative effect. To be able to look at whether there are any effects on local invasive recurrences will also be important. This is an incredibly important trial. It is focused on the highest-risk patients, those who are node-positive, and that’s important because those are the patients who have the most to gain. These patients have the highest risk of recurrence and it will help us get answers sooner than if a group of lower-risk patients had been included.
Are BRCA-mutation status or “BRCA-like” traits indicative of response to PARP inhibitor treatment? Is there a second-generation biomarker that better predicts susceptibility to treatment that accounts for germline BRCA-positive patients who do not respond to treatment?

I think this remains an open question. There have certainly been some interesting biomarker data to come out of some of these trials. From the I-SPY 2 trial, in the veliparib/carboplatin arm, there’s the PARPi 7 gene expression profile that further identified the group that was enriched for response to neoadjuvant veliparib in combination with carboplatin. These kinds of data can be very helpful in trying to understand somatic tumor changes that might be able to predict who will respond. Really very few trials, with the exception of the RUBY trial, have focused on that group. There are a few other trials that are focusing on other groups that may have BRCA-like changes that aren’t somatic. I think that we just need to wait to see.

Additional tests have been developed. On one hand, the question is whether there are there any other germline mutations that might be predictive. There are some data to suggest that RAD51, ATM, or ATR could have germline mutations that would predict response. Then, of course, things like loss of heterozygosity profiles and gene expression profiles will need to be tested. I think that it would be a shame to not take advantage of all of the knowledge we’ve gained from patients who have BRCA-mutated breast cancer to really try to find a broader group of patients who will respond even though they don’t have a germline mutation.

And then how can we understand the germline patients who don’t respond to treatment? I think that’s trickier. In general, we have considered germline BRCA1 or BRCA2 mutations to be drivers. By this I mean that in those patients, it is the loss of BRCA1 and BRCA2 that is solely driving tumor growth, and if you can exploit that, you will kill the tumors. It’s possible that there are other drivers in these tumors and that only targeting DNA damage repair is not enough to keep these tumors from growing. That led to some of the combination trials that are going on, looking at combining PARP inhibitors with other targeted therapies, for example with the PI3 kinase inhibitors, with HSP90 inhibitors, or even with immunotherapy.

Resistance really is a problem. Even patients who respond to PARP inhibitors ultimately become resistant, for the most part. Developing ways to get around that resistance by understanding those resistance mechanisms is incredibly important. Some of these trials are trying to address this. And so I think that these are very exciting avenues of inquiry in which we may be able to not only build on some of the successes, but also expand the group of patients who respond to PARP inhibition, and potentially be able to delay the time to development of resistance.

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