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WEB EXCLUSIVE AJHO CONTENT

Oncology Briefings™: Overcoming Chronic Iron Overload in Pediatric AML and MDS

Elias Jabbour, MD, The University of Texas MD Anderson Cancer Center, and **Latika Puri, MD,** Le Bonheur Childrens Hospital and Saint Jude Childrens Research Hospital discuss the impact iron overload has on patients suffering from MDS and other hematologic malignancies.
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Chairman's Letter

Michael J. Hennessy, Sr

This issue of *The American Journal of Hematology/Oncology®* offers an in-depth look at the latest advances in immunotherapies and HER2-targeted therapies in colorectal, lung, and breast cancers, and original research about the knowledge and attitudes of women in Lebanon about breast self-examination (BSE) and clinical breast examination (CBE).

Despite the introduction of bevacizumab (Avastin) and cetuximab (Erbitux) as targeted treatment options in colorectal cancer in the early 2000s, over the past 15 years, the mainstay treatment option is still fluorouracil-based cytotoxic chemotherapy. However, with the advent of immunotherapies, checkpoint inhibitors offer new options for treatment, according to "Advances in Immunotherapy in the Treatment of Colorectal Cancer." Birendra KC, MD, and colleagues discuss the underlying molecular mechanisms and review published and ongoing clinical trials with immunotherapy in treatment of colorectal cancer.

In "Raising the Therapeutic Index for HER2-Targeted Therapy: Can We Safely Omit Anthracyclines in the Adjuvant Setting?" authors Kelly E. McCann, MD, PhD, and Sara A. Hurvitz, MD, note the dramatic improvements in outcomes for patients with HER2-positive breast cancer. Yet, the concurrent cytotoxic chemotherapy regimen is still debatable. Their article focuses on cardiac toxicities associated with concurrent use of anthracycline with trastuzumab (Herceptin) in the adjuvant setting.

The effect of immunotherapy in non–small cell lung cancer (NSCLC) has dramatically changed the treatment options available for clinicians and patients. Jeffrey Zweig, MD, and Sukhmani K. Padda, MD, note the rising role of pembrolizumab (Keytruda) for use in the first-line setting as a monotherapy and—with FDA-accelerated approval—in combination with carboplatin-pemetrexed chemotherapy. Could this hasten the demise of platinum-based therapy for patients with NSCLC? Not just yet, according to their article, "Frontline Immunotherapy in Non–Small Cell Lung Cancer: For Which Patients Is Platinum Passé?"

The last manuscript, an original research study, "Knowledge, Practices, and Attitudes of Women Toward Breast Cancer in Lebanon," presents the first national survey to study Lebanese women's knowledge of and attitudes toward breast cancer screening, and of their practice of BSE, CBE, and mammography. Myrna A. A. Doumit, PhD, MPH, BSN, and colleagues analyze the perceived barriers that women experience and that prevent them from implementing these breast health strategies.

In the CME article this month, Leora Horn, MD, MSc, associate professor of medicine in hematology and oncology at Vanderbilt University School of Medicine, discusses the use of immune checkpoint inhibitors of the PD-1/PD-L1 pathway in the treatment of NSCLC. Dr Horn discusses groundbreaking trials that led to the approval of atezolizumab (Tecentriq), pembrolizumab, and other practice-changing agents. The future of combinations with other therapies and ongoing trials are also discussed.

Michael J. Hennessy, Sr
Chairman and Chief Executive Officer

From the Editor

The landscape for lung cancer therapy has changed dramatically in the last 2 decades with the advent of antiangiogenic, growth factor receptor pathway, and, most recently, immunological targeting. Still a highly lethal disease, lung cancer has entered the realm of treatable cancers, notably with improvements in survival and quality of life.

Debu Tripathy, MD
Editor-in-Chief

Ironically, many postulate that the same factors that cause a majority of lung cancers—namely, carcinogenic products in tobacco—also increase the mutational burden compared with cancer in nonsmokers, making these cases more immunogenic and likely to respond to immunotherapy.

In the review by Drs Jeffrey Zweig and Sukhmani K. Padda, the new concept of first-line treatment with checkpoint inhibition is discussed, covering the latest data, with many more such trials pending. Although it is clear that immunotherapy is effective in this setting, the key questions are which checkpoint inhibitor will emerge as the most effective, what level of PD-L1 expression (or other biomarkers) identifies the most likely patients to benefit, and whether there is a role for combination chemotherapy and immunotherapy. At present, the situation is very fluid, with trials reporting results in rapid succession and the FDA approving drugs for defined situations with equal rapidity.

Non–small cell lung cancer (NSCLC) with druggable genomic alterations, specifically *EGFR* mutations and *ALK* rearrangements, are still treated with the appropriate targeted therapy initially. In this issue's review article, "Frontline Immunotherapy in Non–Small-Cell Lung Cancer: For Which Patients Is Platinum Passé?" the story is laid out as to how pembrolizumab demonstrated first-line efficacy as a single agent compared with standard chemotherapy while nivolumab did not. Are the outcomes due to differences in the drugs themselves or study design? The table included in the review points out the key differences in PD-L1 threshold and the percentage of patients who crossed over to immunotherapy upon progression in the control arm that could explain the divergent results.

What about the combination of chemotherapy and immunotherapy? This has been posited as a potential synergistic interaction, each helping the other be more effective through mechanisms that are not yet clear. However, no differences in survival were seen in cohort G of the phase II Keynote-021 trial, even though in the small subset of 50% PD-L1 expression, an 80% response rate was seen. Also, PD-L1 expression was not required in the Keynote-021 trial, so the improvement in the primary endpoint of overall response, as well as time to progression, led to accelerated FDA approval in all nongenomically altered cases of nonsquamous NSCLC. An ongoing phase III trial of similar design could lead to final approval, with other such trials testing newer biological combinations also in progress.

The dizzying speed continues and, most importantly, is offering wider and better options than would have been imagineable just a few years ago.

Advances in Immunotherapy in the Treatment of Colorectal Cancer

Birendra KC, MD; Jimmy J. Hwang, MD; Carol J. Farhangfar, PhD, MBA; and S. Jean Chai, MD

Abstract

Colorectal cancer (CRC) remains the third most common cancer in the United States, with a high mortality rate. In the early 2000s, there was significant excitement with the introduction of targeted agents like bevacizumab and cetuximab into the treatment of metastatic CRC. However, over the last 15 years, treatment options have been static and remain fluorouracil-based cytotoxic chemotherapy in moderately toxic combinations such as FOLFOX and FOLFIRI. The advent of immunotherapies—in particular, checkpoint inhibitors—has opened a potential new avenue of treatment. As with other targeted approaches, there may be specific populations who are more responsive to immunotherapy. Patients with defective DNA mismatch repair system (MMR)/microsatellite instability (MSI-high) may have immunogenic potential. Investigators have shown durable responses with immune checkpoint inhibitors in patients with CRC in small clinical trials, with larger studies ongoing. Currently, the National Comprehensive Cancer Network recommends pembrolizumab and nivolumab in the treatment of metastatic CRC in the second- and third-line settings for patients with defective MMR/MSI-high. Furthermore, the FDA recently has granted accelerated approval to pembrolizumab for any cancer with MSI-high or MMR-deficiency that has progressed on standard therapy. We will discuss the underlying molecular mechanisms and review published and ongoing clinical trials with immunotherapy in the treatment of CRC.

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Introduction

Colorectal cancer (CRC) is a leading cause of cancer mortality in the United States with an estimated incidence of 135,430, and causing the deaths of an estimated 50,260 people in 2017. With increasing acceptance of screening strategies, incidence rates have declined by 3% per year from 2004 through 2013.[1-3] Nevertheless, the median survival of patients with metastatic CRC not amenable to surgery remains less than 3 years. Survival improves significantly with resectable metastatic disease to a 5-year survival rate of 26% to 40%.[4] There have been modest advances since 2004, when targeted agents like VEGF and EGFR inhibitors were introduced. However, immunotherapy provides a promising avenue of therapy.

Molecular Drivers of CRC

Vogelstein and colleagues theorized a predictable progression from adenoma to carcinoma. They proposed a stepwise accumulation of genetic and epigenetic events. This model provides insights into the role of "driver" alterations in tumor suppressor genes that confer selective growth advantages and give rise to cancer. Genes with mutations include: adenomatous polyposis coli (*APC*), *TP53*, SMAD family member 4 (*SMAD4*), *BRAF* V600E, and oncogenes such as *KRAS* and *PI3K* catalytic subunit α.[5,6] About 85% of CRCs develop as a result of chromosomal instability due to allelic losses, loss of heterozygosity, chromosomal amplifications, and translocations.[7] These abnormalities may be inherited or sporadic.

The remaining 15% of CRCs have defective DNA mismatch repair systems (MMR) caused by inactivation of mutL homologue 1 (*MLH1*), *MLH3*, mutS homologue 2 (*MSH2*), *MSH3*, *MSH6*, or PMS1 homologue 2 (*PMS2*). This may occur through inherited or sporadic mutations, or through epigenetic silencing. These dominant genomic features give rise to hypermutations and microsatellite instability (MSI).[7]

Recently, the consensus molecular subtypes (CMS) of CRC have been defined, which reflect these differing etiologies. The 4 proposed CMS are: CMS1 (MSI immune: 14%, hypermutated, microsatellite unstable, strong immune activation and *BRAF* mutations); CMS2 (canonical: 37%, epithelial, marked Wnt and MYC signaling activation); CMS3 (metabolic: 13%, epithelial, evident metabolic dysregulation and *KRAS* mutations); and CMS4 (mesenchymal: 23%, prominent transforming growth factor-β, stromal invasion, angiogenesis, and worse overall survival). Samples with mixed features (13%) possibly represent a transition phenotype or intratumoral heterogeneity.[8]

MMR and MSI: Predictors of Benefit for Immunotherapy

The MMR system has long been an area of active research in CRC. It is of pivotal importance for the rectification of DNA sequence mismatches during DNA replication. The main function of MMR

proteins is maintenance of genomic stability by correcting for single base nucleotide mismatches, insertions, or deletions that arise during DNA replication.[9] Deficient MMR can be secondary to germline mutations or sporadic hypermethylation, which silences DNA in MMR genes.

Microsatellites are short DNA motifs of 1 to 6 bases that are repeated and distributed throughout the genome both in coding and noncoding regions. Owing to their repeated structures, microsatellites are particularly prone to replication errors that are normally repaired by the MMR system. Loss of function of 1 of the MMR proteins may lead to the accumulation of errors in microsatellites, resulting in genetic instability. Thus, defects in MMR lead to MSI, which may have oncogenic potential when errors occur in coding regions of crucial cellular functions and pathways.[10]

Many guidelines suggest universal screening of MSI to detect possible high risk for CRC. MSI can be tested by immunohistochemistry (IHC) and by polymerase chain reaction with excellent concordance, and most recently by next-generation sequencing.[11] CRCs can be classified as microsatellite instability-high (MSI-H), and microsatellite instability-low (MSI-L), depending on the percentage of loci with MSI. The MSI-H phenotype is defined by the presence of at least 2 unstable IHC markers among the 5 analyzed (or ≤30% of unstable markers if a larger panel is used). Patients who are MSI-H should be referred for further genetic testing and counseling for Lynch syndrome.

In addition to its utility in identifying patients and families who are at high risk for genetic cancers, MSI-H status in patients with stage II and III colon cancer has been shown to have prognostic impact. Ribic et al demonstrated that patients who were MSI-H had a better 5-year survival. Moreover, these patients did not have improvement in survival with the addition of adjuvant fluorouracil therapy, in part because their risk for relapse was lower than those who were MSI-L. The MSI-L population did benefit from adjuvant chemotherapy, as anticipated.[12] A meta-analysis confirmed a survival advantage in tumors with MSI-H (HR, 0.69; 95% CI, 0.56-0.85).[13]

MSI-H may be targeted for treatment using immunotherapy. In a phase I trial in 2012, Brahmer et al obtained a complete response in 1 patient with MMR-deficient CRC using the PD-1 inhibitor nivolumab. The response was durable for more than 21 months.[14] The authors suggested that MSI-H tumors are hypermutated and express numerous truncated proteins caused by frameshifts. These proteins act as neoantigens and elicit an immune response by tumor-infiltrating lymphocytes (TILs).[14,15] Thus, it was hypothesized that MSI-H tumors have a significant immunological response that is elicited by the neoepitopes created by increased DNA repair mistakes. These findings reinforced the practical importance of the MMR system not only in the development of cancer and as a prognostic marker, but also as a potential avenue in its treatment.

Immunotherapy in Colorectal Cancer

PD-1 is a transmembrane protein expressed on T cells, B cells, and natural killer cells. It is an inhibitory molecule that binds to PD-L1 and PD-L2. The PD-1/PD-L1/L2 interaction directly inhibits apoptosis of the tumor cell and promotes peripheral T-effector cell exhaustion and conversion of T effector cells to regulatory T (Treg) cells.[16] Blockade of this pathway with antibodies to PD-1 or its ligands have led to remarkable clinical responses in melanoma, non–small cell lung cancer, renal-cell carcinoma, bladder cancer, and Hodgkin lymphoma.

Two additional trials have suggested the activity of PD-1 blockade in metastatic CRC, and have led the National Comprehensive Cancer Center Network (NCCN) to recommend pembrolizumab and nivolumab for treatment of metastatic CRC in the second- and third-line setting.[17] In 2015, KEYNOTE-164[18] showed significant activity of pembrolizumab for second- or third-line treatment for MMR-deficient/MSI-H metastatic CRCs. Le et al conducted a phase II study of pembrolizumab (MK-3475), a PD-1 inhibitor, as monotherapy in a total of 41 patients with previously treated locally advanced unresectable or metastatic CRC with or without MMR deficiency. Pembrolizumab was administered intravenously at a dose of 10 mg/kg every 14 days to patients in 3 groups: those with 1) MMR-deficient CRCs (n = 11), 2) MMR-proficient CRCs (n = 21), and 3) MMR-deficient non-colorectal cancers (n = 9). The immune-related objective response rate (ORR) and 20-week progression-free survival (PFS) rate were 40% and 78%, respectively, for MMR-deficient CRCs compared with 0% and 11% for MMR-proficient CRCs. The median PFS and overall survival (OS) were not reached in patients with MMR-deficient CRC but were 2.2 and 5.0 months, respectively, for MMR-proficient CRC. A post hoc comparison of the cohorts with MMR-deficient and MMR-proficient colorectal cancers showed the HR for progression or death was 0.10 (P <.001), and HR for death was 0.22 (P = .05), respectively. Interestingly, patients with MMR-deficient non-CRC had responses smiliar to patients with MMR-deficient CRC (ORR, 71%; PFS, 67%). High somatic mutation loads were associated with prolonged PFS (P = .02). Whole-exome sequencing revealed a mean of 1782 somatic mutations per tumor in MMR-deficient tumors, as compared with 73 in MMR-proficient tumors (P = .007). Most common adverse events were fatigue (32%), rash or pruritis (24%), diarrhea (24%), abdominal pain (24%), constipation (20%), anemia/lymphopenia (20%), pancreatitis (15%), headache (17%), dyspnea (15%), arthralgia (17%) and hypothyroidism/thyroiditis (10%). Grade 3/4 adverse events included lymphopenia (20%), anemia (17%), hypoalbuminemia (10%), hyponatremia (7%), and diarrhea (5%).

CHECKMATE-142,[19] the third and largest trial to show the importance of immunotherapy in CRC, used nivolumab as second- or third-line treatment for MMR-deficient/MSI-H metastatic CRCs. Overman et al presented interim results of CHECKMATE-142 at the 2016 ASCO Annual Meeting. This phase II study used nivolumab with or without ipilimumab in treatment of patients with meta-

static CRC with and without high MSI-H. MSI-H patients received nivolumab (N) 3 mg/kg every 2 weeks (N3) or N 3 mg/kg + ipilimumab (I) 1 mg/kg every 3 weeks (N3+I1) x 4 doses followed by N3 until disease progression or other discontinuation. This was a small trial with 33 (N3) and 26 (N3+I1) MSI-H patients. There were 3 (N1+I1), 10 (N1+I3), and 10 (N3+I1) in the patients with non–MSI-H arm. The responses are shown in **Table 1**. Treatment-related adverse events (TRAEs) were in line with prior immunotherapy trials. These occurred in 26 (79%; N3) and 22 patients (85%; N3+I1); most common were diarrhea and fatigue (27% each; N3) and diarrhea (46%; N3+I1). The results were subsequently updated at the 2017 ASCO Gastrointestinal Cancers Symposium.[20] In the updated results, in MSI-H patients, the 74 patients who were treated with single-agent nivolumab had a centrally reviewed ORR of 27%, with stable disease in an additional 37.8%. The 12-month PFS rate was 48.9%, and the 12-month OS rate was 73.8%. Grade 3-4 TRAEs occurred in 20% of patients. TRAEs leading to discontinuation included acute kidney injury, increased alanine aminotransferase, colitis, and stomatitis (1 each). No treatment-related deaths occurred in this arm.

TABLE 1. Interim results of CHECKMATE-142.[19]

	MSI-H N	MSI-H N/I	MSS N1/I3	MSS N3/I1
ORR	12/47 (25.5%)	9/27 (33.3%)	1/10 (10%)	0/10 (0%)
Stable disease	29%	52%	N/A	N/A
Median PFS	5.3 months	NR	2.3 months	1.3 months
Median OS	17.1 months	NR	11.3 months	3.73 months

I indicates ipilimumab; MSI-H, microsatellite instability-high; MSS, microsatellite stable; N, nivolumab; N/A, not applicable; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

Based on these data, the FDA went a step further and granted the first-ever indication for a biomarker, rather than cancer type. The FDA granted accelerated approval to pembrolizumab for patients with MSI-H or MMR-deficient cancer that has progressed following standard treatment. The most common types of cancers with MSI-H were colorectal, endometrial, and other gastrointestinal cancers. Other cancers with MSI-H and activity with pembrolizumab were breast, prostate, bladder, and thyroid cancers.[21]

Several other clinical trials, mostly phase I and phase II, are ongoing using immunotherapy in metastatic CRCs (mCRCs) (**Table 2**). Hochster et al presented updated efficacy and safety of atezolizumab (atezo, PD-L1 inhibitor) and bevacizumab (bev) in a phase Ib study of MSI-high metastatic CRC.[22] Patients were treated with atezo 1200 mg every 3 weeks plus bev 15 mg/kg every 3 weeks. Ten patients with MSI-H were enrolled, with an ORR of 30% (95% CI, 6.7%-65.3%); the disease control rate was 90%. The median OS has not been reached with a median follow-up of 11.1 months. Initial clinical activity was observed in heavily pretreated patients with MSI-high mCRC receiving atezo plus bev. This combination was well tolerated with expected toxicities.

Unfortunately, only a minority of patients, perhaps 5% to 15%, have MSI-H/MMR-deficient mCRC. These patients are the clearest potential beneficiaries of immunotherapy with checkpoint inhibitors. An area of active exploration is the potential use of checkpoint inhibitors in the broader population of patients with MSI-L or MSS. Bendell et al presented the interim results of the phase I clinical trial of cobimetinib (cobi) and atezo in CRC at the 2016 ASCO Annual Meeting.[23] As of October 12, 2015, 23 patients with CRC (22 *KRAS* mutant, 1 wild-type) were enrolled during escalation and expansion. No dose-limiting toxicities were observed and expansion occurred at atezo 800 mg twice a week and cobi 60 mg daily (21 days on/7 days off). Three responses were ongoing (range, 4.0 to 7.7 months at time of data cutoff). Interestingly, 3 responders were MMR-proficient, and 1 was unknown. ORR in *KRAS*-mutated patients was 20% and stable disease was achieved in 20%. Median PFS was 2.3 months, and the 6-month PFS rate was 25%.

TABLE 2. Ongoing Checkpoint Inhibitors and Immune Modulators Phase II Clinical Trials in CRC.

Agent	Disease type	Study phase/ Estimated enrollment	Status	NCT number
Pembro	MSI-high mCRC	II/ 171	Recruiting	NCT01876511
Pembro + azacitidine	Chemorefractory mCRC	II/ 31	Ongoing; not recruiting	NCT02260440
Pembro + radiotherapy/ ablation	mCRC	II/ 48	Recruiting	NCT02437071
Pembro + mFOLFOX6	mCRC	II/ 30	Ongoing; not recruiting	NCT02375672
N and N combinations with I, cobi, daratumumab, anti-LAG-3 Ab	Recurrent and mCRC	II/ 340	Recruiting	NCT02060188
Durvalumab	mCRC	II/48	Recruiting	NCT02227667

Anti-LAG-3 ab indicates anti-lymphocyte activation gene-3 antibody; cobi, cobimetinib; I, ipilimumab; mCRC, metastatic colorectal cancer; mFOLFOX6, modified 5-fluorouracil, leucovorin, oxaliplatin; MSI, microsatellite instability; N, nivolumab; Pembro, pembrolizumab.

Conclusion

Immune checkpoint inhibition represents a breakthrough in cancer therapy, with durable responses and generally fewer adverse effects than conventional chemotherapy. However, immune-related adverse events (irAEs)

can be life-threatening, and include toxic epidermal necrolysis, colitis, hypophysitis, hepatitis, pancreatitis, iridocyclitis, neuropathies, and nephritis. Early recognition of irAEs and initiation of treatment are critical to reduce morbidity.

Predicting tumor responses to PD-1 blockade and selecting the optimal patient population remains a major challenge. A subset of patients with CRC who are MMR-deficient/MSI-high may be a target population for immunotherapy. Studies have demonstrated that the highest responses to PD-1/PD-L1 blockade occur in tumors with the highest mutational burden (melanoma, non–small cell lung cancer, squamous cell carcinoma of the head and neck, gastric cancer, and most recently urothelial cancer). Interestingly, MMR-deficient tumors were also noted to have high mutational burden and were associated with prolonged PFS.[18] In addition, identification of cytotoxic T-cell infiltration within tumors suggests pre-existing antitumor immunity and what has been found to predict response to PD-1/PD-L1 blockade. Identification of reliable biomarkers that will help identify the right patient population who would respond to immunotherapy needs further investigation.

Current success of immunotherapy is limited to only about 30% of MSI-H patients, which means only about 5% of all patients with CRC—a very small subset. Understanding why MSI-H tumors are responsive to immunotherapy will help develop better treatment options for all patients with CRC. One promising option would be to use immunotherapy in combination with agents that complement the cancer-immunity cycle. Using these agents in the right sequence could be a key to the success of immunotherapy. There has been a proposed stepwise immune response that occurs against tumors, which includes dendritic cell antigen presentation to T-cell priming and differentiation to effector and memory T cells. Throughout this process, T cells also must overcome tumor-derived immunosuppression including loss of *PTEN*, myeloid-derived suppressor cells, Treg cells, and tumor cell-secreted suppressive molecules. Combining therapies that enhance antigen presentation and boost T-cell priming—such as chemotherapy, ionizing radiation, and monoclonal antibodies—may help convert a cold (nonimmunogenic) tumor to a hot (immunogenic) tumor. At the same time, continuation of therapies that decrease tumor-derived immunosuppression (such as PI3K and BRAF inhibitors) throughout the treatment may further help lengthen immunotherapy's success.

Combination therapies may improve the outcomes in patients with CRC, but finding an effective combination for every patient will be a significant challenge. Additionally, combination treatments also have the potential for increased toxicity. Immunotherapies added to different targeted therapies, other immunomodulatory agents (eg, Wnt/β-catenin inhibitors), chemotherapy, and other modalities, such as radiation are being tested (**Table 2**). Better understanding of some important associated mutations like *KRAS*, *BRAF*, *PI3K*, *PTEN*, and β-catenin could help successful pairing of targeted therapies with immunotherapy.

Combination immunotherapy is a promising avenue of treatment for CRC. Its success will depend on identifying crucial molecular pathways and combining treatment modalities in the right sequence.

Author affiliations: All authors are with the Levine Cancer Institute, Carolinas Healthcare System, Charlotte, North Carolina.
Address correspondence to: S. Jean Chai, MD, Levine Cancer Institute, Carolinas Healthcare System, 1100 S. Tryon St., Suite 400, Charlotte, NC 28203. Tel: (980) 442-9100; Fax: (704) 446-4998; E-mail: Seungjean.Chai@carolinashealthcare.org.
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Raising the Therapeutic Index for HER2-Targeted Therapy: Can We Safely Omit Anthracyclines in the Adjuvant Setting?

Kelly E. McCann, MD, PhD, and Sara A. Hurvitz, MD

Abstract

The majority of patients who develop breast cancer are diagnosed with early-stage disease amenable to surgical resection. On a population basis, adjuvant therapies for curative intent provide a modest improvement in overall survival over resection alone, but the majority of individual patients are likely to be cancer-free after surgery and thus at risk of toxicity without benefit. For patients with HER2-positive disease, development of cardiomyopathy secondary to the combined effects of anthracycline-based therapy and the HER2-targeted antibody trastuzumab is especially worrying in the curative setting. In the absence of reliable clinical predictive tools for cardiomyopathy, it is reasonable to prioritize HER2-targeted treatment with adjuvant trastuzumab over anthracylines by using a non–anthracycline-based regimen of similar efficacy.

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Introduction

Gene amplification of *HER2* occurs in approximately 15% to 25% of breast cancers, resulting in overexpression of HER2 on the cell surface. Before the advent of trastuzumab (Herceptin; H), *HER2* amplification was associated with a more aggressive disease course and poorer overall survival.[1,2] Prognosis for patients with HER2-positive disease, defined by strong overexpression (3+) of HER2 by immunohistochemistry, or by a *HER2* to chromosome 17 copy number ratio of >2 by fluorescence in situ hybridization, dramatically improved with the advent of HER2-targeted therapy.[3] Trastuzumab was approved by the FDA in 1998 in combination with chemotherapy for metastatic HER2-positive breast cancer based on an improvement in overall survival (OS) compared with chemotherapy alone, and approved in 2006 for use in the adjuvant setting after joint analysis of interim results of National Surgical Adjuvant Breast and Bowel Project (NSABP) B31 and North Central Cancer Treatment Group (NCCTG) 9831 demonstrated a 52% reduction in relative risk of recurrence, second primary, or death (hazard ratio, 0.48) at a median follow-up of 2 years.[1,3-9] While the earliest adjuvant chemotherapy-trastuzumab combination regimens utilized an anthracycline, several non–anthracycline-based regimens have since been evaluated in clinical trials (**Table 1**). This paper will review the long-term benefits of trastuzumab-based adjuvant therapy and will consider the relative safety and efficacy of each of these regimens.

Outcomes for patients with HER2-positive breast cancer treated with HER2-targeted therapy are now similar to or better than outcomes for patients with HER2-negative disease.

Strong evidence indicates that in the absence of HER2-targeted therapy, patients with HER2-positive breast cancer have a significantly shorter survival compared with those with HER2-negative disease.[1,3,10,11] While the majority of published studies assessing trastuzumab in patients with early-stage HER2-positive breast cancer have only compared outcomes based on whether or not patients received trastuzumab, a handful of trials also provided disease-free survival (DFS) and OS for those with HER2-negative breast cancer. Collectively, these trials give us insights into how trastuzumab has altered the natural history of HER2-positive disease (**Table 2**).

Two concurrently run trials led by the Breast Cancer International Research Group (BCIRG), 1 of which enrolled patients with centrally confirmed HER2-negative disease (BCIRG-005)[12] and 1 of which enrolled patients with centrally confirmed HER2-positive disease (BCIRG-006),[13] have reported 10-year follow-up. Though these were 2 separate studies, they were run in parallel over a similar time period and at many of the same sites with patients triaged based on HER2 status. Thus for the purpose of this review, data from these 2 studies are considered together. BCIRG-005 was a phase III trial comparing adjuvant chemotherapy with 4 cycles of doxorubicin (Adriamycin; A) plus cyclophosphamide (C) followed by 4 cycles of docetaxel (Taxotere; T) (AC➔T) versus 6 cycles of doxorubicin plus cyclophosphamide plus docetaxel (TAC) in node-positive breast cancer.[12] BCIRG-006 was a phase III study in patients with HER2-positive stage I-III breast cancer treated in the adjuvant setting with AC followed by docetaxel with or without trastuzumab (AC➔T or AC➔TH) versus 6 cycles of docetaxel plus carboplatin plus trastuzumab (TCH).[13] At a median 10 years of follow-up, 86% of patients with HER2-positive disease treated with trastuzumab (BCIRG-006) were alive compared with 80% of patients with HER2-negative disease (BCIRG-005) and 81% of HER2-positive patients who did not receive trastuzumab (BCIRG-006).[13] Patients with HER2-positive disease treated with

TABLE 1. Dosages of Chemotherapy Regimens.

Regimen	Dosing
AC➔T	**Doxorubicin** 60 mg/m² + **cyclophosphamide** 600 mg/m² every 21 days for 4 cycles *Followed by:* **docetaxel** 100 mg/m² every 21 days for 4 cycles
AC➔P	**Doxorubicin** 60 mg/m² + **cyclophosphamide** 600 mg/m² every 21 days for 4 cycles *Followed by:* **paclitaxel** 80 mg/m² weekly for 12 cycles or **paclitaxel** 175 mg/m² every 3 weeks for 4 cycles
AC➔PH	**Doxorubicin** 60 mg/m² + **cyclophosphamide** 600 mg/m² every 21 days for 4 cycles *Followed by:* **paclitaxel** 80 mg/m² weekly for 12 cycles or **paclitaxel** 175 mg/m² every 3 weeks for 4 cycles + **trastuzumab** (4 mg/kg loading dose x1, then 2 mg/kg) weekly for 52 weeks
AC➔P➔H	**Doxorubicin** 60 mg/m² + **cyclophosphamide** 600 mg/m² every 21 days for 4 cycles *Followed by:* **paclitaxel** 80 mg/m² weekly for 12 cycles *Followed by:* **trastuzumab** (4 mg/kg loading dose x1, then 2 mg/kg) weekly for 52 weeks
TAC	**Doxorubicin** 60 mg/m² + **cyclophosphamide** 500 mg/m² + **docetaxel** 75 mg/m² every 21 days for 6 cycles
TCH	**Docetaxel** 75 mg/m² + **carboplatin** AUC 6 mg/mL/min every 21 days for 6 cycles + **trastuzumab** (4 mg/kg loading dose x1, then 2 mg/kg weekly) for 17 weeks *Followed by:* **trastuzumab** 6 mg/kg IV every 21 days to complete 1 year of treatment
EC➔T	**Epirubicin** 90 mg/m² + **cyclophosphamide** 600 mg/m² every 21 days for 4 cycles *Followed by:* **docetaxel** 100 mg/m² every 21 days for 4 cycles
EC➔TX	**Epirubicin** 90 mg/m² + **cyclophosphamide** 600 mg/m² every 21 days for 4 cycles *Followed by:* **docetaxel** 75 mg/m² every 21 days for 4 cycles + **capecitabine** 900 mg/m² twice daily on days 1 to 14 of a 21-day cycle
EC➔T➔X	**Epirubicin** 90 mg/m² + **cyclophosphamide** 600 mg/m² every 21 days for 4 cycles *Followed by:* **docetaxel** 75 mg/m² every 21 days for 4 cycles *Followed by:* **capecitabine** 900 mg/m² twice daily on days 1 to 14 of a 21-day cycle for 4 cycles
AP➔P➔CMF	**Doxorubicin** 60 mg/m² + **paclitaxel** 150 mg/m² every 21 days for 3 cycles *Followed by:* **paclitaxel** 175 mg/m² every 21 days for 4 cycles *Followed by:* **cyclophosphamide** 600 mg/m² + **methotrexate** 40 mg/m² + **5-fluorouracil** 600 mg/m² on days 1 and 8 of a 28-day cycle for 3 cycles
FEC	**5-Fluorouracil** 600 mg/m² + **epirubicin** 60 mg/m² + **cyclophosphamide** 600 mg/m² every 21 days (as described in FinHer study)
APT	**Paclitaxel** 80 mg/m² weekly × 12 weeks + **trastuzumab** (4 mg/kg loading dose x1, then 2 mg/kg weekly x11) *Followed by:* **trastuzumab** 6 mg/kg IV every 21 days to complete 1 year of treatment
TCHP	**Docetaxel** 75 mg/m² + **carboplatin** AUC 6 mg/mL/min + **trastuzumab** (8 mg/kg loading dose x1, then 6 mg/kg) + **pertuzumab** (840 mg loading dose x1, then 420 mg) every 21 days for 6 cycles *Followed by:* **trastuzumab** 6 mg/kg IV every 21 days to complete 1 year of treatment

A indicates doxorubicin (Adriamycin); AUC, area under the curve; C, cyclophosphamide or carboplatin as above; E, epirubicin; F, fluorouracil; H, trastuzumab (Herceptin); IV, intravenous; M, methotrexate; min, minute; P, paclitaxel or pertuzamab; T, docetaxel (Taxotere); X, capecitabine (Xeloda).

trastuzumab also fared better than those with HER2-negative disease in terms of OS in the retrospective Italian Registry study of patients diagnosed with stage I-III breast cancers in Parma, Italy, between 2004 and 2007.[14] The OS of patients with HER2-positive breast cancer treated with trastuzumab-based therapy was 98% compared with 87% for those with HER2-positive non–trastuzumab-treated disease and 93% for patients with HER2-negative disease.

The phase III NOAH[15] and GeparQuattro[16] trials investigated outcomes in patients treated with neoadjuvant chemotherapy with or without the addition of 1 year of perioperative trastuzumab. In NOAH, patients with locally advanced or inflammatory breast cancer were given neoadjuvant paclitaxel (P) plus doxorubicin every 3 weeks for 3 cycles followed by paclitaxel every 3 weeks for an additional 4 cycles followed by cyclophosphamide plus methotrexate (M) plus 5-fluorouracil (F) on days 1 and 8 of a 28-day cycle for 3 cycles (AP➔P➔CMF).[15] At 5.4 years of median follow-up in these high-risk patients, OS was 74% in the HER2-positive/trastuzumab arm and 76% in the HER2-negative arm. OS in the HER2-positive cohort randomized to neoadjuvant chemotherapy without trastuzumab was 63%, which is likely an overestimate of survival due to crossover. During the study, the NOAH protocol was amended to allow all patients with HER2-positive cancer to receive trastuzumab based on positive data from HERA17 and NSABP B-31,[8] discussed below. GeparQuattro explored the addition of capecitabine (Xeloda; X) to an anthracycline-taxane backbone of epirubicin (E) plus cyclophosphamide (EC) for 4 cycles followed by docetaxel (T) for 4 cycles (EC➔T) with or without 4 cycles of capecitabine given concurrently with docetaxel or following docetaxel (EC➔TX, EC➔T➔X).[16] Trastuzumab was given to all patients with HER2-positive breast cancer starting with cycle 1 for a year. At a median follow-up time of 5.4 years, OS was 88% in the HER2-positive/trastuzumab arm and 85% in the HER2-negative arm.

The FinHer trial was a phase III adjuvant study of node-negative tumors less than or equal to 5 cm but greater than 2 cm (T2) or node-positive breast cancers without distant metastases treated with adjuvant vinorelbine 25 mg/m² weekly for 9 weeks or docetaxel 100 mg/m² every 3 weeks for 3 cycles followed by fluorouracil, epirubicin, and cyclophosphamide (FEC).[18] Women with HER2-positive cancer were randomly assigned to receive or not receive trastuzumab for 9 weeks during vinorelbine or docetaxel therapy. At 5 years, 90% of women with HER2-positive disease treated with 9 weeks of adjuvant trastuzumab were alive compared with 92% of patients with HER2-negative disease who received the

TABLE 2. Overall Survival (OS) of Patients With HER2-Positive Breast Cancer.
The OS of those treated with adjuvant trastuzumab is similar to or better than the OS of those with HER2-negative disease.

Clinical study	Arms	Median follow-up (years)	HER2-positive disease				HER2-negative	
			Chemotherapy + trastuzumab		Chemotherapy, no trastuzumab		Chemotherapy	No trastuzumab
BCIRG 005/006[12,13†]	AC➔T AC➔TH➔H TAC TC_{AUC6}H➔H	10.3	1841/2149	% of Patients 86%	870/1073	% of Patients 81%	2647/3298	% of Patients 80%
NOAH[15*‡]	AP➔P➔CMF APH➔PH➔CMFH➔H	5.4	87/117	74%	74/118	63%	75/99	76%
Italian Registry[14†]	Regimens not described.	4.1	52/53	98%	140/161	87%	1108/1186	93%
GeparQuattro[16‡]	EC➔T EC➔TX EC➔T➔X ECH➔TH➔H ECH➔TXH➔H ECH➔TH➔XH➔H	5.4	392/446	88%	N/A	N/A	889/1049	85%
FinHer[18†]	T➔FEC V➔FEC TH➔FEC VH➔FEC	5	103/115	90%	95/116	82%	717/778	92%

A indicates doxorubicin (Adriamycin); AUC, area under the curve; C, cyclophosphamide; $CAUC_6$, carboplatin AUC_6; E, epirubicin; F, fluorouracil; H, trastuzumab (Herceptin); M, methotrexate; P, paclitaxel; T, docetaxel (Taxotere); V, vinorelbine; X, capecitabine (Xeloda).

* Crossover in HER2-positive arms allowed.
‡ Neoadjuvant chemotherapy + adjuvant trastuzumab to complete 1 year of therapy.
† Adjuvant therapy.

same cytotoxic regimen and 82% of HER2-positive patients who did not receive trastuzumab.

These studies, each utilizing different chemotherapy regimens, consistently demonstrated that the poor outcome associated with the HER2 alteration is improved by the use of trastuzumab. Based on survival benefits imparted by trastuzumab, current National Comprehensive Cancer Network guidelines recommend consideration of trastuzumab-based therapy for all HER2-positive tumors and as a standard-of-care therapy for HER2-positive tumors over the size of 1 cm.[19] The question is thus no longer "Should we use trastuzumab?" but is instead "Which chemotherapy regimen yields the best therapeutic index in combination with adjuvant trastuzumab?"

Why is therapeutic index so important when choosing an adjuvant regimen?

More than 60% of patients diagnosed with breast cancer in 2016 had disease localized to the breast.[20] While the DFS and OS clearly support the use of adjuvant trastuzumab, the risk of cardiotoxicity must be carefully considered in those with early-stage breast cancers, many of whom are potentially cured by local therapies alone and thus derive no benefit from adjuvant systemic therapy.[21] The 6-year cumulative incidence of congestive heart failure (CHF) or cardiac death in the NCCTG N9831 trial comparing AC followed by paclitaxel without trastuzumab (AC➔P), trastuzumab given with paclitaxel (AC➔PH), or AC➔P followed by trastuzumab (AC➔P➔H) was 0.6% in patients receiving AC➔P, 3.4% for AC➔PH, and 2.8% for AC➔P➔H.[22] Results were similar in the NSABP B-31, with a 7-year cumulative incidence of CHF or cardiac death of 1.3% in the AC➔P arm and 4.0% in the AC➔PH arm.[23]

The combination of anthracyclines and trastuzumab augments the risk of cardiomyopathy.

Anthracyclines are well known to be associated with cardiotoxicity in a cumulative, dose-related manner, necessitating lifetime dosage caps to minimize toxicity. In fact, myocardial depression can occur at any dosage of anthracycline, and patients must be carefully monitored for evidence of heart failure throughout their treatment courses, typically by assessment of left ventricular ejection fraction (LVEF) by echocardiogram or multigated acquisition.[24]

During the early trastuzumab monotherapy trials,[4,5] cardiac dysfunction similar to that related to anthracyclines was noted, leading to the establishment of an independent Cardiac Review

and Evaluation Committee to characterize the severity, treatment, and clinical outcomes of clinical trial patients treated with trastuzumab.[25] The risk of New York Heart Association functional classification III or IV CHF (NYHA III/IV CHF) with trastuzumab monotherapy is estimated to be 2% to 4%.[4,5,26]

In the pivotal trial of trastuzumab in combination with chemotherapy in patients with HER2-positive metastatic breast cancer, the incidence of NYHA III/IV CHF was 16% in those who received concomitant therapy with an anthracycline (doxorubicin or epirubicin), cyclophosphamide, and trastuzumab, compared with 3% for those who received the same regimen without trastuzumab.[5] This was surprisingly higher than the risk of doxorubicin-associated NYHA III/IV CHF, which was estimated to be about 7%,[27] and firmly established cardiotoxicity evaluation as an essential component of trastuzumab clinical trials. Moreover, based on these data, concurrent use of anthracyclines and trastuzumab was avoided in the majority of subsequent studies.

While the use of adjuvant trastuzumab has undoubtedly improved survival for early-stage disease, its use in conjunction with anthracycline-based chemotherapy leads to increased rates of cardiomyopathy. A meta-analysis of 8 adjuvant trastuzumab studies (N = 11,991) showed that the addition of trastuzumab to primarily anthracycline-based chemotherapy regimens increased the risk of CHF by more than 5 times and almost doubled the risk of decline in LVEF.[28] Analysis of the 4 largest of these studies suggests that while the rates of grade 3/4 heart failure are relatively low (<4%) with the use of adjuvant trastuzumab, a patient's ability to start or complete the full year of adjuvant HER2-targeted therapy and the rates of clinically occult cardiomyopathy may be affected by choice of chemotherapy backbone.[3,29,21,22] Data relating to these issues will be discussed below.

The problem with anthracyclines: Cardiomyopathy results in truncation of trastuzumab therapy.

The risk of cardiomyopathy has been partially ameliorated by temporally separating anthracycline administration from trastuzumab, hence the move to treatment regimens such as doxorubicin plus cyclophosphamide sequentially followed by taxane plus trastuzumab (AC➔TH or AC➔PH). Even with this amended treatment regimen, however, cardiomyopathy remains a challenging clinical problem. Patients with HER2-positive disease diagnosed with cardiomyopathy during their therapy typically receive a truncated course of trastuzumab. In 2 large studies of AC followed by paclitaxel with or without trastuzumab, 7% of patients in NSABP B-31 and 5% of patients in NCCTG N9831 were ineligible to receive trastuzumab due to decreased cardiac function after AC.[21,22,30] An additional 15.5% (n = 147) of patients in NSABP B-31 receiving AC➔PH stopped trastuzumab before completion of 1 year of therapy because of cardiac-related issues.[23] In the BCIRG-006 study, discussed in more detail below, 2.1% of patients randomized to adjuvant AC➔TH did not receive planned trastuzumab therapy due to cardiac dysfunction during or after AC. Fortunately, with discontinuation of cardiotoxic therapy and the addition of heart failure therapy (eg, beta blockers, angiotensin converting enzyme inhibitors, diuretics) for left ventricle (LV) dysfunction, recovery of pretherapy cardiac function is possible, typically over the course of years.[29]

Clinically occult cardiomyopathy: Are we appreciating the magnitude of toxicity?

The development of clinically silent cardiac dysfunction has been fairly well documented in the NSABP B-31 and N9831 trials with the use of serial cardiac function monitoring for 18 to 21 months. In B-31, 12% of patients came off trastuzumab due to asymptomatic declines in LVEF. In the N9831 trial, 26% of patients receiving AC➔P, 40% of those on AC➔PH, and 35% of those on AC➔P➔H experienced an LVEF decrease of ≥10 points with 12%, 24%, and 17% dropping below normal LVEF, respectively.[21] Unfortunately, these studies did not follow asymptomatic patients in the long term. Therefore, it is unknown if patients treated with an anthracycline-trastuzumab–based regimen have a higher long-term risk of asymptomatic or symptomatic cardiomyopathy 10 years after treatment.

It should be noted that rates of cardiotoxicity in the HERA trial were fairly low (4.1%) in patients receiving 1 year of trastuzumab after standard chemotherapy (94% of whom received an anthracycline-based regimen).[29] The rate of NYHA III/IV CHF was only approximately 1%, which is much lower than has been seen in other studies. These lower rates in comparison with those of other large trials may relate to the fact that patients with an LVEF below 55% after anthracycline-based therapy were excluded.

Non–anthracycline-based chemotherapy provides similar efficacy outcomes with less risk of cardiotoxicity.

In an effort to circumvent cardiac toxicity without compromising efficacy, alternative chemotherapy regimens have been actively sought. After preclinical data suggested synergy with the combination of trastuzumab and docetaxel or a platinum agent in vitro, 2 independent phase II adjuvant trials were performed demonstrating the efficacy of 6 cycles of docetaxel combined with carboplatin given concurrently with trastuzumab followed by trastuzumab to complete 1 year of therapy (TCH).[31,32]

BCIRG-006 was the first prospective randomized adjuvant trial that evaluated not only standard AC➔TH, but also a non–anthracycline-based regimen of TCH. These 2 regimens were compared with standard AC➔T.[3] In the final analysis after 10 years of follow-up, both trastuzumab-containing regimens yielded a significantly improved DFS (AC➔TH, 74.6%; TCH, 73.0%; AC➔T, 67.9%) and OS (AC➔TH, 85.9%; TCH, 83.3%; AC➔T, 78.7%). While the trial was not powered to test for noninferiority of TCH to AC➔TH, the DFS and OS were similar for the 2 arms in the overall population and in high-risk patients with lymph node–positive disease. Importantly, the rates of leukemia and cardiotoxicity were signifi-

cantly higher in the AC➔TH arm.[13] Heart failure (NYHA III/IV) developed in 2% in the AC➔TH arm versus 0.4% in the TCH arm, and 19.2% of patients had a sustained LVEF loss of more than 10 points on AC➔TH compared with 9.4% on TCH. Additionally, 7 patients on AC➔TH developed leukemia with anthracycline treatment versus 0 with TCH.[13] To date, more than 4700 patients have been treated with TCH-based therapy on neoadjuvant or adjuvant trials.[33-37] These studies have demonstrated consistently low rates of cardiac toxicity as well as high rates of DFS, OS, and pathological complete response (pCR) rates.

Additional anthracycline-free treatment regimens have also been reported. In a single-arm phase II adjuvant study of 12 weekly doses of paclitaxel combined with 1 year of trastuzumab for lymph node–negative, HER2-positive breast cancer (n = 406), Tolaney et al reported a 98.7% rate of survival free from invasive disease at 3 years of follow-up with a 0.5% rate of symptomatic congestive heart failure.[38] A single-arm phase II study of adjuvant docetaxel plus cyclophosphamide and trastuzumab for stage I or II patients with up to 3 positive lymph nodes (n = 493) reported a DFS of 94% in lymph node–positive disease and an OS of 98% at 3 years.[39]

The addition of a second HER2-targeted therapy, pertuzumab (P), to anthracycline-free trastuzumab-based regimens has also been evaluated in the neoadjuvant setting. Six cycles of combination therapy with docetaxel, carboplatin, trastuzumab, and pertuzumab (TCHP) yielded a 64% total pCR in TRYPHAENA (n = 75)[36] and TCHP x4 cycles resulted in a 41% pCR in patients with breast cancer co-expressing HER2 and hormone receptors in NSABP B52.[34] Positive results from the phase III adjuvant APHINITY trial (NCT01358877) investigating pertuzumab plus trastuzumab and chemotherapy with full results just published showing a small, but statistically significant, improvement in DFS with the addition of adjuvant pertuzumab to standard chemotherapy plus trastuzumab.[40]

Conclusion

HER2-directed therapy has resulted in dramatic improvements in outcomes for patients with HER2-positive breast cancers, becoming standard-of-care in the metastatic, neoadjuvant, and adjuvant settings, but the optimal concurrent cytotoxic chemotherapy regimen is still a matter of debate. In the adjuvant setting, there is no reliable way to separate those who will benefit from systemic therapy from those who will be cured with local therapy alone. Overtreatment is unavoidable, and there are those who incur the risks of treatment without benefit. Therefore, it is critical to weigh the risks of a regimen against the potential benefits. In the adjuvant setting, when trastuzumab is used with a non–anthracycline-based regimen, the risk of clinically evident cardiomyopathy is on the order of 0.5%, according to data from the BCIRG-006 and APT studies. In contrast, when trastuzumab is used in sequence with an anthracycline-based regimen, the rate of moderate to severe cardiac toxicity increases fivefold. Moreover, 2% to 7% of patients who start with an anthracycline are ineligible to ever receive trastuzumab due to a decline in cardiac function related to doxorubicin. Importantly, available data show numerically similar DFS and OS when comparing anthracycline and non–anthracycline-based regimens.

To conclude, treatment strategies to maximize efficacy and minimize long-term complications are particularly important in the curative setting, and replacement of anthracycline-based regimens is desirable and feasible.

Author affiliations: Drs Kelly E. McCann and Sara A. Hurvitz are both with the David Geffen School of Medicine at University of California Los Angeles.

Address Correspondence to: Sara A. Hurvitz, MD, Division of Hematology/Oncology, David Geffen School of Medicine at UCLA, 2825 Santa Monica Blvd, Ste 200, Santa Monica, CA 90404. E-mail: SHurvitz@mednet.ucla.edu.

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Frontline Immunotherapy in Non–Small Cell Lung Cancer: For Which Patients Is Platinum Passé?

Jeffrey Zweig, MD, and Sukhmani K. Padda, MD

Abstract

Immunotherapy in non–small cell lung cancer (NSCLC) is quickly changing the landscape of therapeutic options for patients with metastatic disease. In the frontline setting, the positive results of the KEYNOTE-024 trial demonstrated that pembrolizumab improved both progression-free survival (PFS) (HR, 0.50; 95% CI, 0.37-0.68; *P* <.001; median PFS, 10.3 vs 6 months) and overall survival (OS) (HR, 0.60; 95% CI, 0.41-0.89; *P* = .005; 1-year OS, 70% vs 54%) compared with standard platinum doublet chemotherapy, leading to FDA approval of pembrolizumab in the frontline setting for patients with NSCLC at least 50% programmed death ligand 1 (PD-L1) tumor expression and no *EGFR* mutation or anaplastic lymphoma kinase rearrangement. This is in contrast with the negative results of the CheckMate-026 trial with nivolumab, in which there was no difference in PFS (HR, 1.15; 95% CI, 0.91-1.45; *P* = .251; median PFS, 4.2 vs 5.9 months) or OS (HR, 1.02; 95% CI, 0.80-1.30; 1-year OS, 56.3% vs 53.6%) in patients with NSCLC with PD-L1 expression of at least 5% in comparison with standard platinum doublet chemotherapy. The KEYNOTE-021 (cohort G) phase II trial assessed the combination of carboplatin-pemetrexed chemotherapy with pembrolizumab in the frontline setting in 123 patients with nonsquamous NSCLC, demonstrating a 26% improvement in overall response rate compared with chemotherapy alone, as well as a PFS benefit as a secondary endpoint of 13 vs 8.9 months (HR, 0.53; 95% CI, 0.31-0.91). However, when last reported, there was no OS benefit seen with the combination (estimated 6-month OS >90% for both groups). Based on this phase II randomized study, pembrolizumab in combination with carboplatin and pemetrexed was approved by the FDA for upfront treatment of patients with metastatic nonsquamous NSCLC irrespective of PD-L1 expression. These 3 trials will be discussed in detail to better understand how immunotherapy is revolutionizing the frontline treatment approach in advanced NSCLC, and what questions remain to be answered.

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Introduction

Major advances have occurred over the last decade for the treatment of metastatic non–small cell lung cancer (NSCLC), including both molecularly targeted therapies and immunotherapies. Treatment algorithms for metastatic disease are rapidly changing, providing patients with enhanced clinical benefit. However, despite targeted therapies leading to increased options for subsets of patients with nonsquamous NSCLC, the majority of patients with advanced NSCLC will not harbor a "targetable" genetic aberration in *EGFR*, anaplastic lymphoma kinase (*ALK*), or *ROS1*. Until very recently, in the first-line setting, platinum-based chemotherapy (with or without the addition of angiogenesis inhibitors in nonsquamous NSCLC) has been the mainstay of treatment for these patients.[1]

In rapid succession, 3 immune checkpoint inhibitors have been approved by the FDA since 2015 for the treatment of advanced patients with NSCLC who have progressed on standard platinum-based chemotherapy and for patients with *EGFR* mutations or *ALK* rearrangements who have also progressed on an FDA-approved targeted therapy. These are the programmed cell death protein 1 (PD-1) inhibitors nivolumab and pembrolizumab, and the programmed death ligand 1 (PD-L1) inhibitor atezolizumab.[2-5] So far, pembrolizumab is the only immunotherapy that has received approval in the frontline setting, under 2 separate circumstances. The first approval was in October 2016 based on the randomized phase III KEYNOTE-024 study using pembrolizumab as monotherapy in 305 patients with NSCLC whose tumors demonstrated at least 50% expression of PD-L1 and did not harbor an *EGFR* mutation or *ALK* rearrangement.[6] The second approval was in May 2017, based on the randomized phase II KEYNOTE-021 (cohort G) study of 123 patients, for upfront use of pembrolizumab in combination with carboplatin and pemetrexed for patients with metastatic nonsquamous NSCLC, regardless of PD-L1 expression.[7] With several other checkpoint inhibitors in development, and trials ongoing of immunotherapy combinations as well as other chemotherapy plus immunotherapy combinations, it would be appropriate to say that a new revolution in frontline lung cancer treatment is underway. However, this revolution also raises questions about what treatment strategy is best for each patient, emphasizing the

great importance of a personalized approach.

The international KEYNOTE-024 trial of pembrolizumab was the first phase III trial to show that immunotherapy could replace chemotherapy in the frontline setting for a subset of patients.[8] The patients eligible for this trial had to meet the following criteria: be treatment-naïve, with metastatic nonsquamous or squamous NSCLC, have a PD-L1 tumor proportion score of at least 50% as determined by Dako immunohistochemistry (IHC) 22C3 pharmDx assay, and have no evidence of an *EGFR* mutation or *ALK* rearrangement. A total of 305 patients with these characteristics were randomized 1:1 to receive either pembrolizumab 200 mg intravenously (IV) every 3 weeks or investigator's choice of platinum-based chemotherapy for 4 to 6 cycles. Pemetrexed maintenance was allowed for those patients receiving a pemetrexed-containing regimen. Crossover was also allowed for patients who progressed on chemotherapy. The primary endpoint was progression-free survival (PFS) using RECIST v1.1 criteria, with secondary endpoints of overall survival (OS), objective response rate (ORR), and safety. Patient characteristics between the 2 arms of this study were well balanced. Of the 1653 patient samples eligible for PD-L1 testing, 30% screened positive for at least 50% PD-L1 expression. Although there was a relatively high prevalence of PD-L1 positivity, this did not necessarily mean that 30% of patients were eligible for pembrolizumab frontline therapy. For example, the trial excluded patients with untreated brain metastases, active autoimmune conditions, or active hepatitis B and C, and those with a requirement for steroids or immunosuppressive medications.

TABLE. Trial Comparisons, KEYNOTE-024 Versus CheckMate-026.[8,9]

	KEYNOTE-024	CheckMate-026
Primary endpoint	PFS (RECIST v1.1)	PFS (RECIST v1.1)
PD-L1 assay	22C3 clone (Dako)	28-8 clone (Dako)
PD-L1 cutoff	50%	5%
Tumor sample tested for PD-L1	Either at time of or after the diagnosis of metastatic disease	Archival tumor samples within ≤6 months of enrollment
Imaging interval	Every 9 weeks	Every 6 weeks until week 48, then every 12 weeks
Diagnosis to treatment time	Unknown	2 months
PFS	HR, 0.50 95% CI, 0.37-0.68; *P* <.001 10.3 vs 6 months	HR, 1.15 95% CI, 0.91-1.45; *P* = .251 4.2 vs 5.9 months
OS	HR, 0.60 95% CI, 0.41-0.89 1-year OS: 70% vs 54%	HR, 1.02 95% CI, 0.80-1.30 1-year OS: 56.3% vs 53.6%
ORR	NR	26%
DOR	NR	12.1 months
Crossover to immunotherapy	43.7%	57.5%

DOR indicates duration of response; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

The primary endpoint of the study was met, with significantly prolonged PFS in the pembrolizumab arm compared with the chemotherapy arm of 10.3 versus 6 months (HR: 0.50; 95% CI, 0.37-0.68; *P* <.001).[8] The ORR with pembrolizumab was 45% versus 28% with chemotherapy, and the median duration of response was not reached at the time of analysis with pembrolizumab versus 6.3 months with chemotherapy. Despite 44% crossover of the chemotherapy arm to the immunotherapy arm, at the second interim analysis, OS was significantly improved with pembrolizumab versus chemotherapy (HR, 0.60; 95% CI, 0.41-0.89; *P* = .005), with 70% versus 54% of patients alive at 12 months. This ultimately resulted in the early cessation of the trial by the data safety monitoring committee.

The quality-of-life results were later reported, using the validated European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ) Core 30 for global health status and EORTC QLQ-LC13 for lung-cancer–related symptoms, and again, pembrolizumab was significantly favored.[9] Fewer treatment-related adverse events (AEs) of any grade were observed in the pembrolizumab arm versus the chemotherapy arm (73.4% vs 90%), with expected autoimmune AEs similar to those previously reported with pembrolizumab. The benefit of pembrolizumab was seen across most subgroups, even when compared with those patients who received a pemetrexed-containing regimen. The hazard ratio (HR) point estimate was attenuated for subgroups of female patients and nonsmokers, though the latter group included smaller numbers of patients. The KEYNOTE-024 study provided the results to propel a novel treatment to replace chemotherapy in the first-line setting for a relevant subset of patients who were *EGFR*- and *ALK*-negative and had positive expression of the PD-L1 biomarker.

At the same time the KEYNOTE-024 trial was being conducted, the CheckMate-026 trial was underway, assessing nivolumab in the frontline setting in treatment-naïve patients with advanced NSCLC, no *EGFR* mutation or *ALK* rearrangement, and at least 1% PD-L1 expression as assessed by the Dako IHC 28-8 pharmDx assay.[10] The IHC antibody used and PD-L1 expression threshold used for testing differed from that of the KEYNOTE-024 pembrolizumab trial, which required at least a 50% cutoff. A total of 541 patients were randomized 1:1 to receive nivolumab 3 mg/kg IV every 2 weeks, or histology-dependent standard first-line platinum doublet chemotherapy. Crossover was allowed. The primary endpoint was PFS as determined by RECIST v1.1 criteria, though the criteria were examined using a 5% PD-L1 threshold instead of the 1% threshold required for eligibility. Secondary endpoints included PFS in PD-L1 expression greater than or equal to 1%, OS, and ORR. Baseline characteristics showed a higher female

predominance in the chemotherapy arm; otherwise, the treatment arms were well balanced.

The results of the trial were negative, with no difference in PFS at the 5% PD-L1 expression threshold. The median PFS was 4.2 months in the nivolumab arm versus 5.9 months in the chemotherapy arm (HR, 1.15; 95% CI, 0.91-1.45; $P = .251$).[10] There was also no difference in OS, with a median OS of 14.4 months in the nivolumab arm versus 13.2 months in the chemotherapy arm (HR, 1.02; 95% CI, 0.80-1.30). In patients with PD-L1 expression of at least 5%, ORRs were 26% and 34% in the nivolumab and chemotherapy arms, respectively. Also, more patients had a best response of progressive disease in the nivolumab arm versus the chemotherapy arm (28% vs 10%). Of patients who attained a response, however, the median duration of response was 12.1 months in the nivolumab arm versus 5.7 months in the chemotherapy arm, suggesting a prolonged benefit of immunotherapy in the patients who do respond. Interestingly, 60% of patients in the chemotherapy arm had subsequent nivolumab therapy versus only 44% in the nivolumab arm eventually receiving systemic therapy, suggesting that a majority of patients in the nivolumab arm did not have the opportunity to later receive a potentially effective treatment. The negative results for PFS and OS were seen across almost all subgroups, even in those patients with high PD-L1 expression of at least 50%, with unstratified HRs of 1.07 and 0.90 for PFS and OS, respectively.

KEYNOTE-024 and CheckMate-026

So how can the differences between the results of the KEYNOTE-024 pembrolizumab and CheckMate-026 nivolumab trials be explained? Although there is no clear explanation, several observations are important to consider. First, comparing the baseline characteristics of the trials, there was a higher percentage of nonsmokers in the immunotherapy arm of the CheckMate-026 trial than in the immunotherapy arm of the KEYNOTE-024 trial (11.1% vs 3.2%), although the percentage of nonsmokers was well balanced between the nivolumab and chemotherapy arms.[10] In other nonsmoker subgroup analyses, including in these studies, there is more limited benefit demonstrated for immunotherapy over chemotherapy. This may correlate to the hypothesis that a higher mutational burden is related to clinical benefit from immune checkpoint inhibitors in lung cancer.[11] Regarding radiation, in the CheckMate-026 trial, 38% to 40% of patients in both arms, surprisingly, had received prior radiation therapy, despite being systemic treatment-naïve in the advanced setting.[10] Prior radiation was not reported in the KEYNOTE-024 study, although patients who received thoracic radiation of greater than 30 Gy within 6 months of the trial start were excluded.[8] It is unclear how this may have played a role in the differences observed between the trial outcomes, but it is a notable difference.

Second, with regard to PD-L1 expression, in CheckMate-026, the threshold for positivity was lower than that of the KENOTE-024 trial. Despite the 5% threshold for PD-L1 expression being a stratification factor at randomization in the CheckMate-026 study and being balanced between both arms, there were a greater proportion of patients with high PD-L1 expression in the chemotherapy arm starting at the 25% threshold.[10] In the CheckMate-057 trial assessing nivolumab in the second-line setting in patients with nonsquamous advanced NSCLC, PD-L1 positivity was not required to enroll, and there was a significant correlation between a higher PD-L1 expression level and more pronounced benefit to immunotherapy starting at the 1% threshold.[3]

A thought-provoking exploratory subset analysis of 58% of patients in the CheckMate-026 study showed that high tumor mutation burden (TMB) might be a more effective biomarker.[12] In patients with high TMB (≥ 243 somatic mutations), nivolumab showed a trend for improved PFS (HR, 0.62; 95% CI, 0.38-1.00) and ORR compared with chemotherapy. The contrary was true for patients with low or medium TMB, in which nivolumab was inferior to chemotherapy for PFS (HR, 1.82; 95% CI, 1.30-2.55). Surprisingly, there was no association between TMB and PD-L1 expression for patients in this study who all had tumors with PD-L1 expression ≥1%, suggesting TMB may be a better biomarker. In addition, patients with both high TMB and high PD-L1 expression ≥50% derived the most benefit with nivolumab. OS, however, was similar regardless of TMB, although significant crossover may account for this. Additional biomarkers besides PD-L1 expression may be useful in the future as predictors of response to immunotherapy, and patient selection may remain critical in terms of which biomarkers are most applicable.

Furthermore, although both trials allowed crossover, in CheckMate-026, 58% of patients crossed over to the nivolumab arm versus 44% to the pembrolizumab arm in the KEYNOTE-024 trial, potentially attenuating survival data for the CheckMate-026 study. Other trial design factors that may have played a role include the time point at which PD-L1 was tested, imaging frequency for PFS endpoint, and the time from diagnosis to first treatment. The **Table** summarizes these trial comparisons and differences. Despite the results, nivolumab continues to remain a reliable option in the second-line setting and beyond, with other PD-1 and PD-L1 inhibitors currently being testing as frontline agents.[13]

With KEYNOTE-024 using a 50% PD-L1 cutoff and CheckMate-026 using a 5% cutoff for the primary endpoint analysis, an important question to be answered focuses on the patients who fall between these levels. Would an advanced NSCLC patient with PD-L1 expression of 40% benefit from frontline immunotherapy alone? This may remain an important consideration for future studies. Also, with a different PD-L1 assay used for each approved checkpoint inhibitor, how can accuracy and reproducibility among the assays be guaranteed? In the International Association for the Study of Lung Cancer's Blueprint PD-L1 IHC Assay Comparison Project, 39 NSCLC tumors were stained with 4 available PD-L1 IHC assays used previously in clinical trials (22C3 with pembroli-

zumab, 28-8 with nivolumab, SP142 with atezolizumab, and SP263 with durvalumab).[14] Analytical concordance was demonstrated among the 22C3, 28-8, and SP263 assays; however, the SP142 assay, used in trials with atezolizumab, stained fewer tumor cells, suggesting an underestimation of PD-L1 expression. In addition, for 37% of cases, depending on the assay used, a different PD-L1 classification was made. Though pembrolizumab is currently the only drug for which PD-L1 testing is a companion diagnostic, this will likely change in the future. Reproducibility among available assays is vital to avoid PD-L1 expression misclassification and, in turn, ensure the appropriate use of PD-1/PD-L1 checkpoint inhibitors. Other predictive biomarkers such as TMB may also become more relevant.

With the success of first-line pembrolizumab monotherapy in the KEYNOTE-024 trial, interest has risen significantly in combining immunotherapy with chemotherapy or with other immune therapies, such as CTLA-4 antibodies. The KEYNOTE-021 (cohort G) trial suggests that platinum-based chemotherapy in the frontline setting may not be so passé for a subset of patients with nonsquamous NSCLC. This was a phase II study of 123 patients with untreated stage IIIB/IV nonsquamous NSCLC without an *EGFR* mutation or *ALK* rearrangement and no PD-L1 requirement, randomized 1:1 to pembrolizumab plus 4 cycles of carboplatin plus pemetrexed versus 4 cycles of carboplatin plus pemetrexed alone, with pemetrexed permitted as maintenance therapy in both arms.[7] The primary endpoint was ORR, with secondary endpoints being PFS, OS, safety, and the relationship between response and PD-L1 expression. The results showed a significant (26%) improvement in ORR for the pembrolizumab plus chemotherapy combination compared with chemotherapy alone, at 55% versus 29% (95% CI, 9%-42%; $P = .0016$). The response rates were similar if patients were above or below the 1% PD-L1 threshold in the combination arm.

However, patients with 50% or greater PD-L1 expression in the combination arm had an ORR of 80%. On the other hand, this segment represented only 20 patients, and thus was too small from which to draw a definitive conclusion.

As a secondary endpoint, PFS was also significantly improved at 13 months in the combination arm versus 8.9 months in the chemotherapy-alone arm (HR, 0.53; 95% CI, 0.31-0.91). At a median follow-up of 10.6 months, OS was not improved, though a 52% crossover rate was noted. The incidence of grade 3 or worse treatment-related AEs was 39% in the combination group versus 26% in the chemotherapy group.[7] Under the FDA's accelerated approval regulation, the combination of pembrolizumab plus carboplatin and pemetrexed achieved first-line approval in May 2017, in patients with metastatic nonsquamous NSCLC regardless of PD-L1 expression. The confirmatory phase III KEYNOTE-189 trial, assessing the use of carboplatin or cisplatin and pemetrexed plus or minus pembrolizumab for nonsquamous histology, is underway, with continued approval of combination pembrolizumab contingent upon a demonstrated positive clinical benefit.[15] With regard to squamous histology, the phase III KEYNOTE-407 trial will assess carboplatin and paclitaxel or nab-paclitaxel plus or minus pembrolizumab in patients with advanced squamous NSCLC.[16]

It remains unclear at this time whether there will be great advantage to combining platinum-based chemotherapy and immunotherapy as first-line treatment rather than sequencing it, especially if there proves to be no OS benefit. It is also not known yet whether these results will translate in the phase III setting. Since the approval was granted for use regardless of the presence of PD-L1 expression, it is unclear if there will be an advantage to combination chemotherapy and pembrolizumab for patients who have tumor PD-L1 expression of at least 50% and who achieve reasonable response rates and PFS times with pembrolizumab alone. Nonetheless, the combination is a viable option for patients with nonsquamous histology. Important considerations for use include patient performance status and ability to tolerate a potentially higher chance of AEs, tumor burden, scenarios in which a patient with nonsquamous NSCLC has negative (<1%), or intermediate (1% to 49%) tumor PD-L1 expression and needs a rapid, higher chance of response in the frontline setting, and patient preference following an informed discussion.

Conclusion

The current landscape of frontline therapy for advanced NSCLC is evolving rapidly and now includes immunotherapy. The major breakthrough was pembrolizumab, now with FDA regulatory approval in the first-line setting as a monotherapy and with FDA accelerated approval in combination with carboplatin-pemetrexed chemotherapy. In the KEYNOTE-024 trial, pembrolizumab improved PFS and OS in the upfront setting in patients with at least 50% PD-L1 expression and no *EGFR* mutation or *ALK* rearrangement. This has had major treatment implications, now allowing a significant percentage of patients with metastatic NSCLC to proceed directly to immunotherapy alone. For patients with nonsquamous histology irrespective of PD-L1 expression, based on the phase II KEYNOTE-021 (cohort G) trial, pembrolizumab plus carboplatin and pemetrexed is now an option, showing improvement in ORR and PFS, but not in OS, compared with chemotherapy alone. Other early-phase combination immunotherapy trials with the CTLA-4 inhibitor ipilimumab have been promising, paving the way for several larger phase III combination trials that are actively recruiting or ongoing.[17,18] The disappointing results of nivolumab in the frontline setting can perhaps be explained by a host of factors, though there is not a single clear explanation. Patient selection may have been critical, and there may be better biomarkers to be identified, such as TMB. Improved standardization of PD-L1 assays will require future attention. All in all, though the use of platinum-only chemotherapy in metastatic disease is not passé, as almost all patients will receive and derive benefit from chemo-

therapy at some juncture in their disease course, this paradigm is certainly changing in the frontline setting at least.

Author affiliations: Sukhmani K. Padda, MD, and Jeffrey Zweig, MD, are with Stanford University and Stanford Cancer Institute in Stanford, California.
Address correspondence to: Sukhmani K. Padda, MD, Stanford University and Stanford Cancer Institute, Department of Medicine, Division of Oncology, 875 Blake Wilbur Dr, Stanford, CA 94305-5826. E-mail: padda@stanford.edu.
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Knowledge, Practices, and Attitudes of Women Towards Breast Cancer in Lebanon

Myrna A.A. Doumit, PhD, MPH, BSN; Suha Fares, PhD; and Mary Arevian, MPH, BSN

Abstract

Breast cancer is a major public health concern that affects both developed and developing countries. Its annual incidence is rising globally, accounting for 12% of all new cancer cases and 25% of all cancers in women as of 2012. Breast cancer is responsible for the most frequent malignancy-causing deaths and cancer-related mortality and morbidity in women, an epidemiological profile mirrored in almost every country. However, in developing countries, where health literacy, access to care, and resources are all scarce, these numbers become particularly alarming. They contribute to major health disparities between the developed and developing worlds, especially in that most women in developing nations who develop breast cancer seek healthcare only when the cancer is at an advanced stage.

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Introduction

Breast cancer is a major public health concern that affects both developed and developing countries.[1] Its annual incidence is rising globally, accounting for 12% of all new cancer cases and 25% of all cancers in women as of 2012. Annually, around 1.7 million women worldwide are diagnosed with breast cancer.[2] As such, breast cancer is responsible for the most frequent malignancy-causing deaths and cancer-related mortality and morbidity in women, an epidemiological profile mirrored in almost every country. However, in developing countries, where health literacy, access to care, and resources are all scarce, these numbers become particularly alarming. They contribute to major health disparities between the developed and developing world, especially in that most women in developing nations who develop breast cancer seek healthcare only when the cancer is at an advanced stage.

Breast cancer incidence is projected to rise in developing countries due to continued lack of awareness and resources for screening for women. Conversely, in developed countries, research and awareness campaigns have emphasized the necessity and importance of breast cancer screening. Successful efforts have also taken religious and cultural considerations into account to ensure the effectiveness and appropriateness of the teaching language and methods used.[3]

One country epitomizing an environment in urgent need of promoting knowledge about breast cancer to women, and how to detect it early, is Lebanon. This nation has a rising incidence of breast cancer, a fact compounded by political turmoil, religious specificities, decreased access to healthcare, and lack of sustained public health awareness campaigns. In Lebanon, breast cancer accounts for 42% of all cancers in women, with a median age at diagnosis of 52.5 years.[4] Lebanese data show that 1 in 5 cancers nationally is breast cancer but, even more significantly, breast cancer occurring in women aged younger than 40 years represents approximately 22% of the cases, while such scenarios represent about 6% of cases in Western populations.[5,6] These findings further emphasize the disparity between developing and developed nations in this area, and the need for breast cancer screening efforts in Lebanon.

Objectives

Using Champion's Health Belief Model Scale (CHBMS), the objectives of this study were to: 1) examine the knowledge of and attitudes about breast cancer in Lebanese women, and their practices of detection, and 2) identify potential barriers to breast cancer screening among Lebanese women.

Background

Overview of Lebanon

Lebanon, just 10,452 square kilometers in area, is in what's known as the Middle East, at the crossroads between the Mediterranean countries and the Arabian Peninsula. Because of its Mediterranean coastal location, the country has a rich history of religious and ethnic diversity, in addition to political turmoil and wars.

The total population of Lebanese people worldwide is estimated at 13 million to 18 million. Of these, the vast majority, 8.6 to 14 million, are in the Lebanese diaspora (ie, in countries around the world, outside of Lebanon), and about 4.3 million currently live in Lebanon itself.[7,8] Understanding what Lebanese women know about breast cancer, their attitude toward it, and how they act to protect themselves is important not only for the women residing in Lebanon today, but also for women of Lebanese origin living

internationally. More research about this population could help determine ways to promote and enhance early diagnosis and treatment of breast cancer, especially among young Lebanese women.

Breast Cancer Knowledge and Screening in the Middle East and Lebanon

There is universal consensus that early detection of breast cancer offers the greatest chance of long-term survival among women.[5,9-11] Early detection of breast cancer can be achieved by proper awareness about performing breast self-examination (BSE), and by accessing clinical breast examination (CBE) by health providers, along with mammography.[1] Bener and colleagues,[12] in a study assessing barriers to breast cancer screening in Qatar (a country in the Arab Gulf region), reported that despite having a sufficient level of knowledge about breast cancer, Qatari women had low rates of breast cancer screening. Fears of and worries about mammography's potential results were frequently reported as among the barriers to screening. Similarly, Petro-Nustus and Mikhail,[13] in a study of 519 Jordanian women that examined factors associated with BSE, found that although the majority (67%) of participants had heard or read about BSE, only 7% had performed it on a regular monthly basis. Confidence, motivation, benefits, susceptibility, and personal history of breast cancer were variables that had a positive association with BSE practice.[13] Montazeri and colleagues,[14] in a descriptive study with 410 Muslim women in Iran, investigated whether religious beliefs matter in BSE. Study findings suggested that most Muslim women do not perceive BSE as being against their Islamic beliefs and that they believe clinical breast examination by a male physician does not interfere with their religious beliefs.[14]

The results of other studies[15-21] have also emphasized that women's knowledge of and beliefs about breast cancer and its management may contribute considerably to health-related help-seeking behaviors. BSE training and adherence are the first steps for women seeking health-promotion behavior, and these set the stage for CBE and mammography screening guidelines later in life. Screening is associated with perceptions of risk, benefits, and barriers through a reasoning process that embraces personal and social influences and attitudes.[22] Arevian and colleagues,[23] in a study assessing beliefs related to breast cancer knowledge and screening among 94 Lebanese Armenian women aged between 26 and 68 years, noted that 80.9% of the women surveyed had heard of BSE and 76.6% had heard of mammography. Nevertheless, 53.2% had never practiced BSE and 79.6% had never undergone mammography. The authors suggested that low practice levels of BSE and mammography utilization were related to a multitude of factors, including fatalism, fear, and lack of guidance from a physician or primary care provider, as well as sociocultural beliefs and the meaning of breast cancer screening.[23] Recently, Hassoun and colleagues,[24] in a study examining the barriers to mammography screening in Lebanon, reported the 3 most common deterrents as lack of knowledge about breast cancer, social reasons, and lack of access. These researchers, despite naming somewhat different sets of barriers, agree and document that lack of knowledge and lack of practice are 2 major breast cancer screening barriers.

In 2002, Lebanese health experts and the Lebanese Ministry of Public Health began screening awareness campaigns about early detection to try to address the breast cancer taboo. Such campaigns are continuously being organized and conducted every year during October, November, and December, consisting of public awareness sessions about BSE, CBE, and mammography. The ministry also facilitated access to mammography for Lebanese women aged 40 years and older; it is offered free of charge in public hospitals and at discounted prices in some private hospitals and radiology centers. Despite these efforts, however, results of a survey of about 1200 women conducted between 2002 and 2005, to assess mammography utilization following breast cancer awareness campaigns showed disappointingly low rates of use—and those rates differed significantly between women in urban and rural locations. More than 50% of participants reported that they had heard about the campaign; however, just 12.7% of those who heard of the campaign were actually prompted to get mammograms in 2007.[25] More research is needed to understand why Lebanese women do not take advantages of available resources for breast cancer screening. Also, results of annual awareness campaigns for nurses and women across the country indicate that the majority of Lebanese women do not perform BSE or do not know how to do it. Although BSE alone does not decrease the risk of undetected breast cancer, the practice empowers women to take responsibility for their own health. Therefore, BSE is recommended for raising awareness among women at risk rather than as a screening method.[2]

To date and to our knowledge, no published studies exist that examine women's knowledge, practice, and beliefs related to breast cancer in Lebanon except for the Arevian et al[23] study, limited to 1 specific Lebanese Armenian group of women. Another study did focus on breast cancer from a different perspective—the lived experiences of Lebanese women with breast cancer. It highlighted their losses and feelings of guilt, fear, and uncertainty that they experienced during and after diagnosis.[26] The attitudes and knowledge base of Lebanese women must be taken into account when planning culturally appropriate health actions promoting breast cancer screening..

Methods

Study Design

A national cross-sectional descriptive survey design was used to examine the knowledge of, practice of, and attitudes toward breast cancer screening. Institutional Review Board approval from a major academic institution in Lebanon was obtained. Data collection was conducted by 24 certified female field surveyors. Trained by the researcher to standardize the data collection process, the data collectors were intentionally female to meet the cultural needs of Lebanese women and to avoid embarrassment when discussing intimate breast cancer screening concepts. A proportional sampling technique was used across all the governorates (Mohafaza) and women coming from different religious, educational, and social backgrounds in

Lebanon. The surveyors used the Kish grid approach for determining participant eligibility. A participant was eligible if she lived in a house that had more than 1 woman and if she were aged 40 years or older. We excluded women who were diagnosed with breast cancer or had a positive family history of breast cancer. Data collection was conducted in Arabic using translated instruments.

We calculated the sample size based on a 95% confidence level and a maximum 2.83% error ratio. The population of Lebanon is about 4 million and 52% are women[27]; therefore, the sample size was calculated to be 1200 participants.

Instruments

We used the revised version of the CHBMS questionnaire.[26] The CHBMS is composed of 53 items evaluating 8 dimensions: a) susceptibility (5 items), b) seriousness (7 items), c) benefits of BSE (6 items), d) barriers to BSE (6 items), e) confidence (11 items), f) health motivation (7 items), g) benefits of mammography (6 items), and h) barriers to mammography (5 items). Items are rated on a 5-point Likert scale ranging from strong disagreement (1 point) to strong agreement (5 points). We used the CHBMS after securing written approval from the author. In addition to CHBMS, we added sections on sociodemographic characteristics and on breast cancer screening behaviors to the instrument.

Translation and Pilot Testing

We followed the recommended back-translation procedure for translating research instruments.[28, 29] First, we translated the questionnaire from English to Arabic. Face validity and cultural validity of the translated questionnaire were examined by a group of experts (an oncology nurse, a breast cancer survivor, and an oncologist) with no recommendations for changes in translation. The Arabic version was back-translated to English by an independent translator with no prior knowledge of the original English version. The final version was pilot tested with 15 Lebanese women who met the eligibility criteria of the study. The purpose of the pilot was to assess for clarity, length, and comprehension of the translated survey. No further changes were recommended. Cronbach's alphas for the 8 dimensions ranged between 0.7 (benefits of mammography) to 0.97 (susceptibility). The Arabic-translated survey was thus deemed valid and reliable to be used in this study.

Analysis

Descriptive statistics were used to summarize the respondents' demographic characteristics, screening practices, and the CHBMS subscales. Simple and multiple logistic regression were used to determine the unadjusted and adjusted associations between the outcomes for BSE status (yes/no) and CBE status (yes/no) and independently selected predictors. Predictors included sociodemographic characteristics such as age, education, perceived socioeconomic status (SES), marital status, occupation, religion, governorate, and the CHBMS subscales. Crude and adjusted odds ratios and their 95% confidence intervals were reported. All tests were 2-tailed and *P* values <.05 were considered significant. Analyses were carried out using SPSS version 22 (IBM Corp; Armonk, NY).

Results

Sociodemographic Characteristics

A total of 1200 women participated in this study. Seventy-three percent were aged between 40 and 59 years with a mean age of 53.6 years (standard deviation, 11.2). More than half (67.3%) were married and 68.7% had an intermediate or secondary school education. Three-quarters (75.3%) were unemployed (not working outside the home) and 67.8% perceived their SES as middle income. More than half were Muslim (53.6%). Married women had a mean age at marriage of 21.5 years (SD, 5.7) and had on average 3 to 4 children (**Table 1**).

TABLE 1. Background Characteristics of the Study Sample.

	Count (n)	%
AGE (YEARS)		
40-49	504	42.0%
50-59	367	30.6%
60+	329	27.4%
MARITAL STATUS		
Single	149	12.4%
Married	808	67.3%
Widowed/divorced	243	20.3%
EDUCATION LEVEL		
Elementary	375	31.3%
Intermediate	347	28.9%
Secondary or above	478	39.8%
EMPLOYMENT		
Unemployed	903	75.3%
Employed	297	24.7%
PERCEIVED SES		
Low	266	22.2%
Middle	814	67.8%
High	120	10.0%
RELIGION		
Christian	456	38.0%
Muslim	643	53.6%
Druze	101	8.4%
GOVERNORATE		
Beirut	120	10.0%
Bekaa	240	20.0%
Mount Lebanon	360	30.0%
North	240	20.0%
South	120	10.0%
Nabatieh	120	10.0%
AGE AT MARRIAGE (YEARS): MEAN, SD	21.46	5.68
NUMBER OF CHILDREN: MEAN, SD	3.67	2.23

SD, standard deviation; SES indicates socioeconomic status.

Breast Cancer Screening Practices

The majority (83.5%) of the women had heard of BSE; among these women, 63.7% had conducted BSE; of the 83.5%, 71.1% said

they knew what CBE was, and 71.0% of those had conducted CBE. Overall, only 37.7% reported having had both CBE and BSE. The average responses of the Champion subscales are summarized in **Table 2.** Study participants were overall highly motivated, perceived high levels of benefit in performing both BSE and mammography, and had high levels of confidence in BSE. They perceived medium levels of susceptibility to breast cancer and seriousness of breast cancer. As for the barriers, participants perceived medium levels of barriers to performing mammography compared with low levels of barriers to performing BSE (**Table 2**).

TABLE 2. BSE, CBE, Mammography Knowledge, Practice, and Beliefs of the Total Sample (N = 1200).

Have you ever heard of breast self-examination? (count, %)	1002	83.5%
If yes, have you ever done breast self-examination?	638	63.7%
Do you know what a clinical breast examination is? (count, %)	853	71.1%
If yes, have you ever done clinical breast examination?	606	71.0%
Perceived susceptibility (mean, SD)	2.10	1.02
CHAMPION SUBSCALES (MEAN, SD)		
- Susceptibility to breast cancer	2.15	1.10
- Seriousness of breast cancer	2.82	1.11
- Health motivation	3.61	.86
- BSE barriers	1.88	.89
- BSE confidence	3.06	1.21
- BSE benefits	3.80	1.09
- Mammography benefits	3.86	1.06
- Mammography barriers	2.52	.98

BSE indicates breast self-examination; CBE, clinical breast examination, SD, standard deviation.

BSE Practices

Among women who knew and practiced BSE (n = 638), fewer than a quarter performed BSE every month (23.7%) and less than half performed BSE within the expected standard time, which is within 2 minutes (44.4%). Only 17.4% used the proper position of fingers to palpate the breast and 45.1% used 3 fingers while assessing their breasts. Only 34.3% used different types of pressure, whereas 76% followed a specific pattern, 39.0% used the proper hand to examine the breast, and 45.0 % always examined the entire area. Only 13.0% looked at the mirror when examining their breast and 17.8% of those always looked at the mirror with the 3 positions, whereas 27.4% always used small-circle motions and 51.3% examined both breasts (**Table 3**).

Factors Associated With BSE

To determine the factors associated with BSE practice, logistic regression analysis was conducted among women who knew what BSE is. In the unadjusted analysis, married women were more likely to practice BSE as compared with single women (odds ratio [OR], 1.79; 95% CI, 1.21-2.66). Women who perceived their SES as high were also more likely to perform BSE when compared with women perceiving their SES as low (OR, 3.45; 95% CI, 1.94-6.14). Across the 6 Lebanese Mohafaza, women living in the Bekaa, South, and Nabatieh Mohafaza regions were more likely to practice BSE than women living in the capital Beirut, which is also a Mohafaza (OR, 1.76; 95% CI, 1.10-2.84; OR, 3.17; 95% CI, 1.73-5.81; and OR, 2.11; 95% CI, 1.20-3.71, respectively). As for the Champion's subscales, health motivation, women with more confidence about their skills in performing BSE, and women who believed in BSE benefits were more likely to practice BSE (OR, 1.46; 95% CI, 1.25-1.70; OR, 2.65; 95% CI, 2.29-3.06; and OR, 1.42; 95% CI, 1.26-1.59, respectively).

TABLE 3. Percent of Correct BSE Practices Among Women Who Perform BSE (N = 638).

Practice	Correct	% Correct
1. During the past year, how many times have you examined your breasts?	Monthly	23.7
2. How long does it normally take to examine each breast?	1-2 minutes	44.4
3. When doing BSE, how do you feel your breasts?	Flat part of fingers	17.4
4. When doing BSE, how many fingers do you use?	3 fingers	45.1
5. When examining your breasts, how often do you use different types of pressure in each spot?	Always	34.3
6. When examining your breasts what type of pattern do you use?	Specific	76.0
7. What hand do you use to examine your breasts?	Proper	39.5
8. When examining your breasts, how often do you examine the entire area that extends from under the arm, across the bra line, and up the breast bone and across the collar bone	Entire area	45.0
9. When examining the breasts, how often do you look in the mirror?	Always	13.0
10. When looking in the mirror, how often do you view them from 3 positions–hands on your sides, hand on your hips, and hands on your head to assess your breasts?	Always	17.8
11. How often do you lie on your side when examining the outside area of your breasts?	Always	3.8
12. How often do you lie on your back to examine your breasts?	Depending on position of examination, the answers to this question are: never, sometimes, frequently, always	If always 7.4
13. When examining your breasts, how often do you move your fingers in small dime-shape circles?	Small circle	27.4
14.When examining your breasts how often do you examine both breasts?	Always	51.3

BSE indicates breast self-examination.

Women with high perception of the seriousness of breast cancer and those with high levels of BSE barriers were less likely to practice BSE (OR, 0.85; 95% CI, 0.75-0.95; and OR, 0.79; 95% CI, 0.69-0.92, respectively). Also, women with intermediate education were less likely to practice BSE compared with women with secondary education or above (OR, 0.62; 95% CI, 0.46-0.84). No significant differences were found related to age, employment, religion, and susceptibility.

In the adjusted analysis, women who were married; had secondary education and above compared with those with intermediate education; with high perceived SES; living in the Bekaa and the South Mohafaza compared with Beirut; and had high confidence in their own skills toward BSE practice remained more likely to practice BSE (**Table 4**).

TABLE 4. Adjusted Logistic Regression Analysis of the Factors Associated With Performing BSE (N = 1002).

	Adjusted OR	95% CI	*P*
MARITAL STATUS			
Single	Reference		
Married	1.70	(1.07-2.72)	.026
Widowed/divorced	1.37	(0.78-2.43)	.276
EDUCATION			
Secondary and above	Reference		
Elementary	1.34	(0.88-2.04)	.174
Intermediate	0.67	(0.46-0.96)	.031
Perceived SES			
Low	Reference		
Middle	1.14	(0.75-1.71)	.544
High	3.25	(1.63-6.52)	.001
GOVERNORATE			
Beirut	Reference		
Bekaa	1.83	(1.01-3.32)	.047
Mount Lebanon	1.07	(0.61-1.86)	.816
North	0.82	(0.45-1.48)	.508
South	3.56	(1.75-7.26)	<.001
Nabatieh	1.39	(0.70-2.76)	.342
CHAMPION SUBSCALES			
BSE confidence	3.02	(2.51-3.63)	<.001

BSE indicates breast self-examination, SES, socioeconomic status.

Factors Associated with CBE

To determine the factors associated with CBE practice, we carried out logistic regression analysis among women who knew what CBE was. In the unadjusted analysis, women aged between 50 and 59 years and women aged 60 years or more were more likely to perform CBE compared with women aged between 40 and 49 years (OR, 1.74; 95% CI, 1.23-2.47; OR, 2.10; 95% CI,1.43-3.10, respectively). Married or divorced women were more likely to practice CBE compared with single women (OR, 1.73; 95% CI, 1.09-2.75; and OR, 2.09; 95% CI, 1.19-3.67, respectively). Women perceiving their SES as middle or high were more likely to perform CBE as compared with women perceiving their SES as low (OR, 1.55; 95% CI, 1.07-2.26; and OR, 1.85; 95% CI, 1.06-3.23, respectively). Employed women were more likely to perform a CBE (OR, 1.80; 95% CI, 1.25-2.58) when compared with unemployed women. Muslim women (OR, 0.54; 95% CI, 0.39-0.74) and Druze women (OR, 0.48; 95% CI, 0.27-0.87) were less likely than Christian women to have a CBE. Across the 6 Lebanese Mohafaza, women living in the Bekaa, South, and Nabatieh were less likely to practice CBE than women living in the capital Beirut (OR, 0.25; 95% CI, 0.13-0.48; OR, 0.26; 95% CI, 0.13-0.54; and OR, 0.34; 95% CI, 0.17-0.70, respectively). Women with high perceived susceptibility were more likely to perform a CBE (OR, 1.29; 95% CI, 1.11-1.15). As for the Champion subscales, health motivation and women who had a high score on this subscale (OR, 1.33; 95% CI, 1.11-1.58) were more likely to practice CBE. No significant differences were found between women of different education levels and in those who had different perceptions of the seriousness of the condition.

In the adjusted analysis, women who were older; married or divorced; perceived their SES as middle or high; employed; had high perceived susceptibility; and were highly motivated remained more likely to have a CBE. Druze women and those living in Bekaa, South, and Nabatieh remained less likely to have CBE performed (**Table 5**).

TABLE 5. Adjusted Logistic Regression Analysis of the Factors Associated With Performing CBE (N = 853).

	Adjusted OR	95% CI	*P*
AGE			
40-49	Reference		
50-59	2.07	(1.41-3.04)	<.001
60+	3.06	(1.89-4.94)	<.001
MARITAL STATUS			
Single	Reference		
Married	2.57	(1.50-4.38)	.001
Divorced	2.26	(1.20-4.25)	.012
PERCEIVED SES			
Low	Reference		
Middle	1.53	(0.99-2.35)	.054
High	1.98	(1.05-3.72)	.034
EMPLOYMENT			
Unemployed	Reference		
Employed	1.89	(1.25-2.88)	.003
RELIGION			
Christian	Reference		
Muslim	0.99	(0.63-1.55)	.956
Druze	0.55	(0.28-1.07)	.08
GOVERNORATE			
Beirut	Reference		
Bekaa	0.25	(0.13-0.49)	<.001
Mount Lebanon	0.67	(0.33-1.34)	.255
North	0.73	(0.34-1.56)	.417
South	0.32	(0.14-0.69)	.004
Nabatieh	0.40	(0.19-0.87)	.02
CHAMPION SUBSCALES			
Health motivation	1.25	(1.02-1.53)	.03

CBE indicates clinical breast examination; SES, socioeconomic status

Discussion

As the incidence of breast cancer increases worldwide, understanding

women's knowledge of, attitude toward, and behaviors engaged in regarding breast cancer screening is essential, because screening is a first step toward early detection. Developed countries have recognized this for decades and have often created culturally specific awareness campaigns. However, a lack of similar research marks many developing countries, including Lebanon, to the detriment of women. With limited resources and access to healthcare, many developing countries may not have the luxury to plan several campaigns to make the required impact and reach women all over a given nation.

In Lebanon, the Ministry of Public Health and the National Breast Cancer Awareness Committee have tried to organize awareness sessions and campaigns to reach as many Lebanese women as possible, in different regions. However, studies have not been conducted to examine the post-campaign knowledge, attitudes, and practices of the women the campaigns sought to reach. Postcampaign studies are important to identify geographical areas that may have not been reached, messaging that needs to be modified, or remaining cultural barriers to this screening. Our study was timely to address these important issues to make breast cancer screening more widespread among Lebanese women, and our findings help us understand women's knowledge of, attitudes toward, and practices of BSE, CBE, and mammography.

Although strong evidence indicates that BSE does not reduce breast cancer mortality, it is still recommended that women know their breasts. Also, CBE is highly recommended for women in their 20s and 30s, every 3 years, and for women aged 40 and older on an annual basis.[1] Our study results showed that most of the surveyed women had heard of BSE but only a minority of women performed it monthly. Despite the acceptable rates of knowledge about BSE, its practice is unsatisfactory, given the intensive awareness strategy undertaken by the Lebanese Ministry of Health, which has been implemented on a yearly basis since 2002. The campaign uses a variety of media tools to enhance women's knowledge and practices regarding BSE, CBE, and mammography. Cancer-related anxiety and worry have been related with both the promotion and avoidance of breast cancer assessment.[24,30-31] This low percentage of practice of BSE among Lebanese women, which was also revealed by Arevian and colleagues[23] for Lebanese Armenian women, might be due to fear of breast cancer as mentioned in a study by Doumit and colleagues.[26] The low response could also be related to the type of message sent during the national campaigns. As emphasized by Champion and colleagues,[32] interactive tailored approaches are generally more effective than targeted messages, especially when addressing sensitive topics like breast cancer. As a comparison, results of a study done in Turkey[17] that involved 1344 women indicated that only 19.9% of the surveyed women practiced CBE, and almost half had heard or read about BSE. Furthermore, lower rates for BSE and CBE were reported in studies in Nigeria,[33] Qatar,[12] Jordan,[13] and Pakistan,[34] and among African American women as well.[10]

In our study, the characteristics of women who performed BSE and CBE compare well with the literature in terms of social status and perceived susceptibility to the condition and level of education.[35-36] These results are comparable to those of a study done in India[37] that reported that a higher level of education correlated to a higher level of knowledge about breast cancer screening. Women with secondary and university levels of education are better exposed to information related to health awareness.[37]

When comparing between Mohafaza, we noticed that the women in the South were around 4 times as likely to perform BSE compared with those living in Beirut. After investigating this finding, we learned that many nongovernmental organizations (NGOs) are extensively educating women in this area. The south of Lebanon has been known as a deprived and low-income area with a dense population. Lately, many efforts are in place to improve the health status of the people living in such areas. These efforts might explain our results for BSE, which does not require a physician's visit. Additionally, these results highlight the fact that these campaigns might not be speaking to the people living in major cities such as Beirut and others; the efforts should ensure that basic messaging is reaching women throughout Lebanon, with increased efforts for the areas in greatest need. Most people living in the South work or have parents who work in Africa, which explains the high perceived level of SES; it is attributed to finances and not to education. Data from the literature reveal that women of low SES seek help from health providers when sick, and presume they are healthy unless they feel sick.[36] Similarly, Lebanese women with perceived low SES practice significantly less BSE and CBE. The higher their perceived SES, the more they practiced BSE and CBE. This means that efforts need to target low-SES areas. CBE, done by a physician, is more common among employed women living in Beirut with middle-to-high SES, than among women elsewhere with low SES.

Techniques of practicing BSE were assessed in this study, but only a minority of women who practice BSE actually used the proper techniques. It is worth noting that none of the reviewed studies reported any data about techniques of performing BSE, which makes comparison with other studies challenging. However, these results about the techniques will enlighten physicians and nurses who are working in community centers or clinics to focus more on the "actual doing" techniques and not just be satisfied with the positive self-reporting about BSE.

It is well documented that the presence of role models and favorable perceptions in popular culture play a vital role in encouraging women to participate in breast cancer screening.[38] Research suggests that social structures influence the way in which women experience breast cancer, including their decision making in response to treatment options as well as their strategies for coping with and making sense of breast cancer.[39] Despite some changes in Lebanese society related to acceptance of breast cancer, the topic is still considered taboo; it has a direct connection with the perception of poor self-image and with negative repercussions on daughters in a family affected by the disease.[26] The situation would likely change for the better if more breast cancer survivors spoke about their positive expe-

riences in media outlets, and if more efforts were made to reverse the stigma. Hassoun and colleagues[24] reported that important barriers to mammography in Lebanese women are related to fear of knowledge of having breast cancer and to the anxiety experienced while waiting for the results of the mammography.

Based on the health belief model, perceived barriers are adversely associated with screening behaviors. Our results indicated that concepts of health motivation and confidence in performing BSE were significant at the multivariate level, and benefits were significant at the univariate level. Susceptibility, seriousness, benefits, confidence, and health motivation were positively associated with the practice of BSE. Lebanese women who were motivated toward maintaining good health, had confidence in doing BSE, and perceived the benefits of doing BSE had a higher rate of performance than others. These results compare with the outcomes of a study[17] with Turkish women. Other studies had similar results on the concepts of motivation, confidence, and benefits.[13,23] Moreover, Hassoun and colleagues[24] reported that anxiety while waiting for the results of mammography was the main barrier that socially prevented Lebanese women from participating in mammography screening.

Limitations

The limitations of this study relate to the design itself. A cross-sectional study such as this one is carried out at a single point in time, or over a short period of time at most. It provides a snapshot of the outcomes and its related characteristics, at that specific point, and results could have been different had another time frame had been chosen. Another potential limitation could be related to the interviews, because the interviewees might exhibit some bias (even inadvertently) in reporting information about themselves that they perceived as quite intimate.

Conclusions

Lebanon is currently actively involved in promoting awareness of breast cancer and the necessity of screening at a national level; however, our findings indicate that there remains a need for additional campaigns. Moreover, improvements that take educational, cultural, and behavioral factors into account would be beneficial.

Our conclusions do not only potentially benefit Lebanon, but other developing countries with which it shares certain characteristics. It is essential for healthcare providers to be aware of the barriers affecting breast cancer screening—mainly the educational and knowledge barriers. Understanding these barriers is the first step toward planning an enhanced educational message. Cultural factors should also be considered in planning awareness campaigns. More studies should be planned to gain in-depth understanding of the social and economic barriers to women's participation in breast cancer screening.

Lebanon, a developing country with a diverse population and limited resources, shares some similarities with numerous other countries. The population in Lebanon is religiously diverse, ranging from very liberal to very conservative. Therefore, educational national-level campaigns need to speak to different cultural preferences and practices of women. Other nations, too, have great sociodemographic variations and could benefit from the experiences of breast cancer awareness efforts in Lebanon.

This study presents the first national survey to study Lebanese women's knowledge of and attitudes toward breast cancer and screening, and of their practice of BSE, CBE, and mammography. By determining the perceived barriers to BSE, CBE, and mammography, we will be able to work with NGOs to plan a culturally appropriate strategic innovative approach to enhance women's compliance with screening measures.

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Author affiliations: Myrna Abi Abdallah Doumit, PhD, MPH, BSN, is with Lebanese American University, Alice Ramez Chagoury School of Nursing, Byblos, Lebanon; Suha Fares, PhD, and Mary Arevian, MPH, BSN, are with American University, Hariri School of Nursing, Beirut, Lebanon.

Send correspondence to: Myrna Abi Abdallah Doumit, PhD, MPH, BSN, Lebanese American University, Alice Ramez Chagoury School of Nursing, 5300 C Gilbert and Rose-Marie Chagoury Health Sciences Center, Byblos, Lebanon 36. E-mail: Myrna.doumit@lau.edu.lb.

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Checkpoint Inhibitors: Where Have We Been and Where Are We Going in Advanced NSCLC?

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Faculty

Leora Horn, MD, MSc
Associate Professor of Medicine
Ingram Associate Professor of Medicine
Director, Thoracic Oncology Research Program
Assistant Vice Chairman for Faculty Development
Vanderbilt University School of Medicine
Nashville, TN

Disclosure: *Consultant: AbbVie, BMS, Genentech, Merck, and AstraZeneca.*

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Overview

This activity is designed to inform physicians about the current availability and use of checkpoint inhibitors in advanced non–small-cell lung cancer (NSCLC).

Target Audience

This activity is directed towards medical oncologists, primary care physicians, nurses, and nurse practitioners who treat and/or manage patients with advanced non–small-cell lung 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 the PD-1/PD-L1 pathway and the rationale behind targeted inhibition in NSCLC
- Explain the development history leading to the approval of immune checkpoint inhibitors in NSCLC
- Discuss emerging treatment strategies and new indications in FDA-approved PD-1 or PD-L1 inhibitors

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Physicians' Education Resource®, LLC
2 Clarke Drive, Suite 110
Cranbury, NJ 08512
Phone: (888) 949-0045
E-mail: info@gotoper.com

Introduction

Lung cancer is the second most common cancer diagnosed in men and women in the United States, behind prostate cancer and breast cancer, respectively, and it is the most common cause of cancer-related mortality.[1] While the incidence rate has been decreasing and overall survival (OS) rate increasing over the last 2 decades, there are still more than 222,000 new cases of lung cancer expected in the United States in 2017, accounting for more than 13% of all new cancer cases.[2] Moreover, upwards of 155,000 people are expected to die from this disease, accounting for 25% of all cancer-related deaths in 2017. Overall, an estimated 525,000 people are living with lung cancer in the United States as of 2014; of those, 420,000 are living with NSCLC.[2] The incidence of lung cancer is highest in people aged 65 to 74 years, with a median age at diagnosis of 70, but it is observed commonly in people aged 45 to 84 years or older. In the past 40 years, the 5-year survival rate has nearly doubled; as of 2009, it was nearly 20%.[2]

The 2 main types of lung cancer are small cell lung cancer (SCLC), which accounts for approximately 10% to 15% of lung cancers, and non–small cell lung cancer (NSCLC), which accounts for the vast majority of lung cancer cases, between 80% and 85%.[1] NSCLC is further subcategorized into adenocarcinoma, squamous cell carcinoma, and large cell carcinoma, depending on the origin of the cancer cell. All histologic subtypes are seen in current and former smokers. However, small cell and squamous cell histology are more strongly associated with smoking, and adenocarcinoma is the predominant histology seen in nonsmokers. The distinctions between different histologic subtypes are critical in making treatment decisions, especially with respect to molecular testing and selecting the optimal platinum doublet therapy for patients without driver mutations. With the advent of immune checkpoint inhibitors in the treatment of all histologic subtypes, and the approval for their use in a select cohort of patients with NSCLC for first-line therapy, and in all patients as second-line therapy, immunotherapy has become increasingly prominent in the armamentarium of treatment options for patients with metastatic disease.

PD-1/PD-L1 Checkpoint Inhibitors

Checkpoint inhibitors, specifically of programmed cell death protein 1 (PD-1) and its ligand, programmed death ligand 1 (PD-L1), have been a focus of immunotherapy strategies in lung cancer. The PD-1/PD-L1 axis works primarily to mitigate the action of effector T cells as part of the body's defense against itself. The transmembrane protein and its ligand function to limit autoimmune responses of T cells, preventing potentially destructive self cannibalism.[3]

PD-1, a type 1 transmembrane protein, is a member of the immunoglobulin superfamily.[4] It is composed of an extracellular N-terminal immunoglobulin-variable-like domain, a transmembrane domain, and a cytoplasmic tail that contains an immunoreceptor tyrosine-based inhibitory motif as well as an immunoreceptor tyrosine-based switch motif.[5,6] Numerous splice variants of PD-1 have been identified, but have not been thoroughly studied.[3] In healthy individuals, PD-1 is minimally expressed in cells of the immune system including T cells, B cells, natural killer (NK) cells, NK T cells, and macrophages.[3,7] In specific tissues of individuals with an infection or inflammatory event, PD-1 is activated to limit immune-mediated tissue destruction.[3]

PD-1 binds 2 specific and distinct ligands: PD-L1 and PD-L2. While PD-L2 expression is limited to cells of the immune system, PD-L1 is constitutively expressed on hematopoietic and nonhematopoietic cells throughout the body.[8] PD-L1 is further induced by inflammatory cell signals, including interferons and TNF-α, regardless of cell type. PD-1/PD-L1 interactions promote downstream T-cell inhibition and T-cell apoptosis.[3] PD-L1 is also able to bind B7-1 and inhibit T cells independently of its interactions with PD-1, making the PD-1/PD-L1 axis a more complicated inhibitory receptor with a coinhibitory-ligand system.[3,9]

PD-L1 is primarily expressed on antigen-presenting cells and on tumor cells, including lung cancer.[3] Paired with the expression of PD-1 on tumor-invading lymphocytes, tumor cells are able to utilize the feedback inhibitory loop of the PD-1/PD-L1 axis as similarly observed in inflamed tissue. In addition, multiple oncogenic signaling pathways exist to increase the expression of PD-L1 on malignant cells following a host immune response.[3]

PD-1/PD-L1 Blocking Antibodies

The blocking of either PD-1 on immune cells or PD-L1 on cancer cells has the potential to restore normal host immune response and allow the body to fight the cancer itself. Immunotherapeutic options have become standard of care in the treatment of NSCLC with the approval of PD-1–targeted nivolumab in March 2015,[10] pembrolizumab in October 2015,[11] and PD-L1–targeted atezolizumab in October 2016.[12]

Nivolumab

Nivolumab is a human immunoglobulin G4 monoclonal antibody that targets and binds the PD-1 receptor on activated T cells; it completely blocks the interaction of the PD-1 receptor with both its ligands.[13] Nivolumab has a high affinity and specificity for PD-1 and is able to maintain a plateau of 70% PD-1 receptor occupancy, while serum nivolumab concentrations are nearly undetectable.[13,14]

The antitumor activity of nivolumab was first established in a phase I trial including 76 patients with advanced NSCLC; the response rate was 33% in squamous and 22% in nonsquamous NSCLC.[15] The randomized phase III CheckMate trials later led to the approval of nivolumab in advanced NSCLC following prior chemotherapy with a platinum doublet.

The phase III CheckMate 017 trial assessed nivolumab versus docetaxel in advanced squamous cell NSCLC.[16] A total of 272 patients were randomly assigned to the 2 treatment arms. Nivolumab was associated with a median OS of 9.2 months (95% CI, 7.3-13.3 months) compared with 6.0 months (95% CI, 5.1-7.3 months) with docetaxel,

resulting in a 41% lower risk of death while on nivolumab (HR, 0.59; 95% CI, 0.44-0.79; *P* <.001). At 1 year, the OS rate was 42% versus 24% for nivolumab and docetaxel, respectively. In this trial, expression of the PD-L1 was not a predictive factor of benefit from treatment.[16]

Simultaneously, the phase III CheckMate 057 trial assessed nivolumab versus docetaxel in patients with advanced nonsquamous NSCLC.[17] A total of 582 patients were assigned to receive either nivolumab or docetaxel. Nivolumab was associated with a median OS of 12.2 months (95% CI, 9.7-15.0 months) compared with 9.4 months (95% CI, 8.1-10.7 months) for docetaxel. OS at 1 year was 51% versus 39% for nivolumab and docetaxel, respectively. Patients with tumors that were PD-L1–positive had a higher response rate and improved OS with nivolumab compared with docetaxel, while those patients with tumors that were PD-L1–negative had a similar benefit.[17]

Since nivolumab's approval, CheckMate 017 and 057 have announced 2-year survival rates. For patients with nonsquamous NSCLC nivolumab was associated with a 2-year OS of 23%, compared with 8% with docetaxel. For patients with squamous NSCLC, nivolumab was associated with a 2-year OS of 29%, compared with 16% for docetaxel.[18]

Nivolumab has also been investigated as a first-line treatment option for patients with PD-L1–positive (1%) advanced NSCLC in the phase III CheckMate 026 trial. Regarding PD-L1 status, PD-L1–positive patients had expression on at least 1% of their tumor cells (TC) or tumor-infiltrating immune cells (IC). PD-L1–negative patients had >1% expression on their TC and IC. This trial did not meet its primary endpoint and nivolumab has not been approved for this indication.[19] Nivolumab has also been approved for use in melanoma, renal cell carcinoma, Hodgkin lymphoma, and head and neck cancer.[20]

Atezolizumab

Atezolizumab is a human immunoglobulin G1 monoclonal antibody that targets PD-L1 and has been shown to be effective in reinitiating an antitumor response. Atezolizumab was approved for use in NSCLC in October 2016, based on results from the OAK and POPLAR trials.[21]

The phase II POPLAR trial compared atezolizumab with docetaxel in patients with NSCLC who had progressed after receiving platinum-based chemotherapy.[22] A total of 287 patients were randomly assigned to the 2 treatment arms. Atezolizumab was associated with an improved OS of 12.6 months (95% CI, 9.7-16.4 months) compared with an OS of 9.7 months (8.6-12.0) with docetaxel. The benefit with atezolizumab was higher in patients with tumors that were PD-L1 positive, but was seen regardless of PD-L1 expression.[22]

Following the results of the POPLAR trial, 1225 patients were randomly assigned to receive either atezolizumab or docetaxel in the phase III OAK trial.[23] Patients receiving atezolizumab received 1200 mg every 3 weeks. OS for patients receiving atezolizumab was 13.8 months (95% CI, 11.8-15.7 months). OS for patients receiving docetaxel was 9.6 months (8.6-11.2 months). Similar to nivolumab, a more robust response was seen with atezolizumab in patients with tumors that were PD-L1 positive, a benefit was seen regardless of PD-L1 expression.[23] Atezolizumab has also been approved for use in urothelial carcinoma and advanced bladder cancer.[24]

Atezolizumab also showed clinical efficacy in chemotherapy-naïve patients with NSCLC in the phase II FIR trial,[25] and an ongoing phase III trial is comparing atezolizumab with platinum-based chemotherapy in patients with tumors that are PD-L1 positive. Also, multiple phase III trials are comparing platinum-based chemotherapy with or without atezolizumab in patients with treatment-naïve NSCLC with advanced stage disease.

Pembrolizumab

Like nivolumab, pembrolizumab is a highly selective immunoglobulin G4 monoclonal antibody that inhibits PD-1.

The phase I KEYNOTE-001 trial investigated pembrolizumab at multiple doses across multiple tumor types, including 495 patients with advanced NSCLC.[26] The overall response rate (ORR) was 19.4% across all NSCLC cohorts and correlated with PD-L1 expression levels. Dose and schedule did not dramatically affect ORR. Median duration of response was 12.5 months across all cohorts, but was lower (10.4 months) in previously treated patients and higher (23.3 months) in treatment-naïve patients. Current or former smokers had an ORR more than twice the rate of nonsmokers—a trend observed in nivolumab treatment as well.[26,27]

Pembrolizumab has also been approved for use in patients with advanced melanoma, head and neck cancer, Hodgkin lymphoma, and urothelial cancer. In October 2016, pembrolizumab was approved in the first-line setting, based on results from the KEYNOTE-024 trial.[28] In that study, patients received either pembrolizumab or physicians' choice of platinum-based chemotherapy. Median progression-free survival (PFS) was 10.3 months in the pembrolizumab arm compared with 6.0 months for chemotherapy; 6-month OS rates were 80.2% and 72.4%, respectively.[29] In May 2017, pembrolizumab was also approved as a first-line combination therapy for patients with nonsquamous NSCLC irrespective of PD-L1 expression.[30] This approval was based on results from the KEYNOTE-021 trial, cohort G1, in which pembrolizumab plus chemotherapy was associated with an ORR of 55% compared with 29% for chemotherapy alone; median PFS was 13.0 months for patients receiving pembrolizumab and 8.9 months for patients receiving chemotherapy alone.[31]

Durvalumab

Durvalumab, currently under investigation, is an immunoglobulin G1 monoclonal antibody that targets PD-L1. The phase II ATLANTIC trial demonstrated durvalumab's clinical benefit in patients with advanced or metastatic NSCLC. ORR increased with PD-L1 expression level.[32] Following these results, the phase III PACIFIC trial is now investigating durvalumab in patients with unresectable NSCLC who have not progressed following chemotherapy. In May 2017, it was announced that the trial reached its primary endpoint of improvement in PFS.[33] These data have not yet been presented. Durvalumab is also

being evaluated with or without tremelimumab versus platinum-based chemotherapy in patients with NSCLC in the phase III MYSTIC trial (NCT02453282)[34] and as a single-agent in the second- and third-line settings in advanced NSCLC in the phase II Abound2L+ trial (NCT02250326).[35] Both of these studies have completed enrollment and are awaiting follow-up.

The Future of Immunotherapy in NSCLC

The currently approved checkpoint inhibitors in NSCLC are nivolumab and pembrolizumab for PD-1 and atezolizumab for PD-L1. Investigations continue into additional agents, including durvalumab and avelumab. Other indications and combinations for these drugs are also being investigated, including in the first-line setting. Combinations with platinum-based chemotherapy, and combinations with ipilimumab—a checkpoint inhibitor of CLTA-4, a type 1 immunoglobulin protein that primarily functions to limit T cell activation and clonal expansion—are also being investigated. Leora Horn, MD, MSc, discussed the past and future of checkpoint inhibitor treatment in NSCLC.

Leora Horn, MD, MSc, is associate professor of medicine in hematology and oncology, and Ingram Associate Professor of Cancer Research, at the Vanderbilt Ingram Cancer Center, where she is also the clinical director of the Thoracic Oncology Research Program. She is the co-leader of the Schaffner Society and assistant vice chairman for faculty development at Vanderbilt University Medical Center, Nashville, TN.

Can you speak briefly about the mechanism of PD-1 and PD-L1 pathways?

PD-1 is expressed on T cells, and PD-L1 is expressed on tumor cells as well as on other cells in the body. In their normal interaction, they bind together to dampen an immune response. It is actually a negative regulator, acting so that if you get exposed to a virus or bacteria and your body is mounting an immune response, the immune response does not get out of control. PD-1 and PD-L1 bind together to act as a negative regulator.

It Is thought that by exploiting this negative interaction, you can actually make the body aware of cancer cells present within the body and make your own immune system fight against the cancer. The new agents, those that are currently in clinical development or are FDA-approved, block this negative interaction so that the immune system becomes activated and, as a result, can cause death of cancer cells and tumor shrinkage.

Can you discuss more specifically the roles of PD-1 and PD-L1 in NSCLC? What role do targeted therapies play in treating NSCLC?

The initial trials with both the anti–PD-1 and then anti–PD-L1 agents were conducted in patients both as first-line and second-line or beyond. When drugs are traditionally developed, we are often evaluating them first in patients who have exhausted all current standard therapies. Nivolumab was the first immune checkpoint inhibitor in the lung cancer space to enter clinical trials, and it was evaluated in patients who had progressed on multiple different prior lines of therapy regardless of PD-L1 expression status.

What we are still learning is how dynamic PD-L1 is as a biomarker. While there is fairly good concordance, it appears there is about 20% to 30% discrepancy between a fresh and an archival tissue sample. Many of the patients enrolled on the nivolumab study had PD-L1 expression assessed on archival tissue samples. And if you were using an older sample—such as an archival specimen—and treating a patient second- or third-line, there may have been a discrepancy calling a patient PD-L1–positive or PD-L1–negative, based on some of the data that have emerged.

Now what we do not know is this: is that discrepancy because there is a change in PD-L1 expression as a result of therapy, or are those expression data different because of where the patient was biopsied? For example, if you biopsy the primary site versus the metastatic site, we do not really know how good the concordance is between the 2. We also know tumors are heterogenous and we may see a positive result just because of where in the mass the tumor was sampled.

A lot of research is also being done in lung cancer patients in terms of targeted therapies and molecular testing. Generally, if a patient has a mutation, they are only going to have a single mutation. So, for example, if a patient is *EGFR*-mutation positive or has an *ALK* fusion, that is most likely to be the mechanism driving the growth of their tumor. PD-L1 is not necessarily a mutation, although it is something that we are testing for. For example, a patient can be EGFR-positive or *KRAS*-positive and PD-L1–positive.

Moving on to some of the checkpoint inhibitors and landmark trials that resulted in the original approvals, can we talk about the nivolumab data and its original indications? There was a 2-year follow-up of CheckMate 017 and CheckMate 057 presented at ESMO last year; can you comment on those findings as well, and the impact it may have on your use of nivolumab?

Both CheckMates 017 and 057, and for completeness 063, were the trials that led to the approval of nivolumab. CheckMate 063 was actually a third-line study for patients who had progressed following at least 2 lines of chemotherapy; it was not a randomized trial. CheckMate 017 and 057 had identical trial designs. Both were randomized phase III trials comparing nivolumab every 2 weeks until progression versus docetaxel in patients who had progressed on platinum-based therapy. The reason that nivolumab, unlike atezolizumab and pembrolizumab, was evaluated in 2 separate trials based on histology was due to data gleaned from a phase I trial, where it was thought that there was a difference in the benefit in squamous versus nonsquamous NSCLC.

Both studies met their primary endpoint with a significant improvement in OS for nivolumab compared with chemotherapy. Both had about a 3-month improvement in OS. There have been some discussions that the docetaxel arm in the CheckMate 017 underperformed, where the median OS of docetaxel was only around 6

months. Nevertheless, both trials led to approval for nivolumab in the second-line setting.

We had seen updated data presented twice. We saw data on 18-month survival at ESMO 2015, and then we saw data on 2-year survival at ASCO 2016, showing that this benefit is sustained, with a continued benefit for patients treated with nivolumab and a clear separation of the survival curves.

Now what is interesting about these trials is that the PD-L1 appears to have a differential role in squamous versus nonsquamous. What I mean by that is that in the CheckMate 017 trial, patients with squamous cell histology appeared to have a benefit with nivolumab regardless of level of PD-L1 expression. There was no differential if they were positive or nonexpressive, and there was no differential at 1%, 5%, or 10%.

Compare that with the CheckMate 057 trial, where there was a difference. Patients who were PD-L1–positive appeared to have a greater benefit with nivolumab, with a higher response rate and OS, whereas the benefit in OS was not seen for patients who were considered PD-L1–negative. That is not to say that nivolumab didn't work in the patients who were PD-L1–negative—it just was not better than chemotherapy. It was actually equal in terms of OS.

Now when you look at the difference in response to nivolumab between patients with tumors that were PD-L1 1%, 5%, and 10%, you do not really see a significant difference in terms of response rate. Responses range from 30% to 38% as the PD-L1 percentage increases. You also do not see a large difference in terms of OS, where it was between 17 and 19 months for patients treated with nivolumab. This was an improvement compared with OS of about 10 months with docetaxel in the PD-L1 expressers. Given that the trial was positive overall, nivolumab, similar to atezolizumab, is currently approved in the second-line setting regardless of PD-L1 expression.

CheckMate 026 was the first-line trial that ran at the same time as KEYNOTE-024. It compared nivolumab with platinum-based chemotherapy as first-line therapy for NSCLC patients with tumors that were *EGFR* and *ALK* wild type. Based on the data from CheckMate 057, the primary endpoint initially looked at patients with tumors that were greater than 5% PD-L1 positive. This trial did not meet its primary endpoint; there was no significant improvement in PFS for nivolumab compared with platinum-based chemotherapy. The response rates were low, around 28% for patients treated with nivolumab. We also saw that even in the patients who were strongly PD-L1–positive (>50%), if you used the pembrolizumab endpoint, then there was not a survival benefit.

There has been a lot of hemming and hawing about this subject. Even some patients who are on nivolumab at my institution, and doing well, have said, "Well, I want to switch over to pembrolizumab because it is a better drug," even though nivolumab is working. I think it was just an unlucky trial. There was some thought that maybe some of the nivolumab patients in the trial were sicker; there were maybe more patients with liver metastases in the nivolumab arm, more females in the chemotherapy arm, and more patients who were strongly PD-L1 positive in the chemotherapy arm. Regardless, it was a negative study and nivolumab remains an option only as a second-line therapy.

Atezolizumab was approved last year for the treatment of patients with metastatic NSCLC following progression from platinum-based chemotherapy based on results from the OAK and POPLAR clinical trials. Can you comment on these trials and how the approval of atezolizumab may be practice changing?

Atezolizumab was the third immune checkpoint inhibitor to receive approval for patients in NSCLC. We did see some indication from the phase I study that atezolizumab was an effective treatment in patients with NSCLC, particularly in patients with tumors that were PD-L1–positive. The first randomized study investigating atezolizumab was a small phase II trial, the POPLAR trial, a second-line trial that randomized patients who had progressed on platinum-based chemotherapy. If patients were *EGFR*- or *ALK*-positive, they also had to have progressed on a prior EGFR or ALK inhibitor. Patients were randomized to the flat dose of atezolizumab or docetaxel. The trial did show a significant improvement in OS by about 3 months for patients treated with atezolizumab compared with docetaxel.

This trial also looked at differences in benefit based on level of PD-L1 expression. Atezolizumab is being developed slightly differently than some of the other checkpoint inhibitors, in that we looked at not only PD-L1 expression within the tumor cells, but also at the immune infiltrate. The study also demonstrated that in patients with higher PD-L1 expression, there was an even greater benefit in terms of OS compared with patients who had lower PD-L1 expression or were PD-L1–negative.

The approval of atezolizumab did not come from the POPLAR trial, but from the phase III OAK trial. The OAK trial, again, randomized patients with similar criteria. They had to have progressed on a platinum-based chemotherapy regimen. If they were *EGFR*- or *ALK*-positive they had to have progressed on an EGFR or ALK inhibitor. And this trial randomized patients regardless of PD-L1 expression to atezolizumab or docetaxel. The primary endpoint of this study, again, was OS.

The OAK trial met its primary endpoint with a significant improvement in OS with patients treated with atezolizumab compared with docetaxel; the improvement was about 4 months. You do not often get a phase III trial looking better than the phase II, but the OS was 13.8 months for patients treated with atezolizumab and about 9.6 months for patients treated with docetaxel. This trial also looked at survival based on PD-L1 expression level and again found that in the patients who were PD-L1–positive, be it tumor-infiltrating immune cells (IC) 1, 2, or 3, that the stronger PD-L1–positive the patients were, the greater benefit they seemed to derive.

The OAK trial also showed that in patients whose tumors were considered to be PD-L1–negative, that there was an OS benefit with atezolizumab. This was not seen in the CheckMate 057. As a result of this trial, atezolizumab received FDA approval in the second-line setting for patients who have progressed on platinum-based chemotherapy regardless of a PD-L1 expression.

One thing to keep in mind when you are looking at the data from these different studies with atezolizumab, nivolumab, and pembrolizumab, is that the FDA Blueprint Project compared the PD-L1 expression with the different antibodies: SP142 with atezolizumab, 28-8 with nivolumab, and 22C3 with pembrolizumab. It found that there was fairly good concordance between the assays used to measure PD-L1 expression for therapy with nivolumab, pembrolizumab, and durvalumab, but found that the 1 outlier was the SP142 assay, which was used to assess PD-L1 expression for treatment with atezolizumab. This assay did not appear to be as sensitive. What that means is that in this trial, where we found that in patients who are PD-L1–negative, there was an OS benefit with atezolizumab compared with docetaxel, that might have been actually underreporting. And some of those patients who were called PD-L1–negative may actually have been PD-L1–positive, if the tumor had been measured with a different assay.

Nevertheless, atezolizumab at this time is FDA approved in the second-line setting for patients who progressed on chemotherapy.

In the frontline setting, atezolizumab is also being evaluated as a first-line therapy in the phase II FIR and BIRCH trials and the phase III IMpower trials. Can you provide us with a brief overview of the findings from these studies and what to expect in the future?

Yes. The FIR trial had multiple arms: there were patients who had prior treatment, patients who were previously untreated, and patients with brain metastases. This measured PD-L1 expression with the SP142 assays. The FIR trial did show us a nice response rate to atezolizumab and a fairly good PFS; OS data in this trial are still immature and pending.

BIRCH had 3 cohorts: first-line, second-line, and third-line. Patients who were enrolled were PD-L1–positive either on the immune infiltrate IC 2/3 or tumor cell (TC) 2/3. The assay used was SP142. Patients with brain or central nervous system metastases were excluded. The response rate was similar regardless of line of therapy, higher in the TC/IC groups compared with TC 2/3 or IC 2/3. The 6-month PFS and OS rates were higher in the untreated/first-line cohort.

Based on these data, the IMpower 110 trial was launched comparing atezolizumab as a single agent with platinum-based chemotherapy. The trial initially was restricted to TC/IC 3 but amended to included 1/2/3 patients. Enrollment in this trial is ongoing. The trial is excluding patients who are *EGFR*- and *ALK*-positive, partly because—from what we have seen from some of the phase III trials in the second-line setting, and other data—these agents do not appear to be as effective as targeted therapies in those specific patient populations.

In addition to the first-line single-agent trial, several IMpower trials are comparing chemotherapy to chemotherapy plus or minus atezolizumab or chemotherapy plus bevacizumab to chemotherapy plus or minus bevacizumab and atezolizumab in the first-line setting. Those studies are not restricting patients by PD-L1 expression but, again, they are excluding *EGFR*- and *ALK*-positive NSCLC patients. These trials are the IMpower 130, 131, 132, and 150 trials.

We are likely going to see a readout of many of these studies in the next 1 to 2 years. The primary endpoint of the majority of these studies is PFS, and the key secondary endpoint is OS. We've seen some long-term data presented at AACR earlier this year that looked at the 5-year OS of patients enrolled in the phase I study with nivolumab. And in that study we saw that the OS at 5 years was around 16%. That is pretty remarkable, when you consider that about a decade ago, the median OS for all of lung cancer patients—stage I through IV—was 16%. Now, we are saying the 5-year survival for stage IV disease alone is 16%, so we are definitely making progress.

With these trials we may see that PFS is better, but we do not yet know if OS is going to be improved. For example, if you look in the EGFR space, we know that with the EGFR TKIs PFS is improved if you get a first-line EGFR TKI, but OS is not improved, suggesting that it is just important that a patient gets a TKI at some point during their treatment course. We do not yet know if that is the same with the immune checkpoint inhibitors. We are seeing PFS is improved, but we do not know if OS is going to be improved if you use those agents first-line versus second-line.

Can we discuss pembrolizumab and durvalumab? Pembrolizumab has been approved based on the KEYNOTE trials. Can you comment on your usage of pembrolizumab and sequencing strategies you may employ?

Pembrolizumab initially got approval in the second-line setting for patients who were strongly PD-L1–positive (>50%). That was based on data from KEYNOTE-001 that showed a high response rate as well as durable response. There are 2 additional trials with pembrolizumab that have been reported to date, KEYNOTE-010 and KEYNOTE-024.

KEYNOTE-010 was a second-line registration trial. It was different from nivolumab and atezolizumab; this trial required patients to have tumors that were at least 1% PD-L1–positive. It randomized patients to pembrolizumab or docetaxel. Interestingly, the PFS was not dramatically different between the 2 arms. However, the OS was clearly better with pembrolizumab. Based on these data, pembrolizumab has been approved in the second-line setting for patients with tumors that have 1% or greater PD-L1 expression.

For a period of time, many providers were not necessarily testing for PD-L1 in the second-line, because nivolumab was available regardless of level of PD-L1 expression. In lung cancer, even *EGFR* and *ALK* testing are not performed in about 30% to 40% of patients in the United States. So adding another test like PD-L1 was unlikely. However, after ESMO 2016 we saw KEYNOTE-024, which looked at patients who were strongly PD-L1–positive (≥50%). The results showed a significant improvement in response rate and PFS, and a trend toward increased OS for patients treated with first-line pembrolizumab compared with platinum-based chemotherapy. Again, patients in this first-line trial had to be *EGFR*- and *ALK*-negative.

Based on these data, PD-L1 testing has become standard of care in the first-line setting. Pembrolizumab as a single agent, in my opinion, should be the preferred agent of choice in patients with tumors that are PD-L1 ≥50%. There was also a phase II trial that looked at combi-

nation carboplatin, pemetrexed, and pembrolizumab compared with chemotherapy alone that demonstrated an improvement in response rate and PFS regardless of PD-L1 expression but no improvement in OS. This was a small trial with response rate as the primary endpoint. Results of this study led to FDA approval of the combination of carboplatin, pemetrexed, and pembrolizumab in patients with nonsquamous NSCLC. I hope it does not stop people from testing for PD-L1 expression because what we do not know is this: do the patients who are strongly PD-L1–positive even need chemotherapy? Is pembrolizumab all that they need in terms of treatment to derive benefit? Which patients benefit from combination therapy? What is the long-term survival and toxicity from combination therapy?

The response rate for first-line pembrolizumab in patients who are strongly positive is around 50%. The response rate for the carboplatin/pemetrexed/pembrolizumab combination was 54%, so it is not dramatically improved. What we do not know is what was driving that response in the combination patients. Personally, I do not think that that trial was practice changing. I do not think that we should suddenly adopt carboplatin, pemetrexed, and pembrolizumab for all nonsquamous NSCLC patients. I think PD-L1 should still be tested. I think that if patients are strongly PD-L1–positive (≥50%) by the 22C3 assay, that they should get single-agent pembrolizumab.

I am waiting for the readout of the multiple phase III trials before I stop testing for PD-L1 and just routinely prescribe a checkpoint inhibitor plus chemotherapy. When you combine a checkpoint inhibitor with chemotherapy you are going through 2 lines of therapy upfront, so there is then not a lot for those patients when they progress. The standard of care, your next line of therapy, becomes docetaxel and ramucirumab. We do not know exactly which patients are going to benefit. With the larger ongoing phase III trials, if we see an overwhelming benefit, especially in the direction of OS, I think that that would be practice changing. To change treatment based on a response rate without OS data, especially a treatment that is significantly cost toxic, gives me pause prior to just blanket prescribing of this drug.

So what about durvalumab? Durvalumab has been investigated as a first-line or subsequent therapy for patients with advanced NSCLC. Can you comment on the role durvalumab may play in treating NSCLC going forward?

There was a press release of the PACIFIC trial investigating concurrent chemoradiation therapy for patients with locally advanced disease followed by 1 year of durvalumab compared with placebo. The PACIFIC trial had an announcement that the primary endpoint of PFS had been met for the study. The 1 cautionary tale I have is that PFS is not a good enough endpoint in patients where the goal is cure. So unless we see an improvement in OS, I do not think that that should become a standard of care treatment following concurrent chemoradiation therapy.

We are also waiting eagerly for the results of the MYSTIC trial. The MYSTIC trial is similar to KEYNOTE-024 and CheckMate 026, looking at first-line durvalumab or durvalumab and tremelimumab compared with platinum-based chemotherapy; it does not require patients to be PD-L1–positive. The primary endpoint is PFS, and the secondary endpoint is OS. We are expecting to see data from that trial potentially at ESMO 2017.

The big thing with these drugs is they are all fairly similar. Nivolumab and pembrolizumab are PD-1 inhibitors. Durvalumab, atezolizumab, and avelumab, which I haven't really talked about, are PD-L1 inhibitors. The big distinguisher in my mind between these drugs is frequency of administration. Even though they are similar, there are some patient convenience factors. For example, in the second-line setting if you are prescribing nivolumab versus atezolizumab, a patient may prefer atezolizumab because you only have to come in once every 3 weeks. If the MYSTIC trial is positive, durvalumab is only given once a month, which is even less frequent. Imagine with stage IV disease you only have to come to the cancer center 12 times a year for therapy. That can really have an impact on patients' quality of life and what they are able to do in between therapies, as we continue to look at lung cancer as a chronic disease.

How important of a role does PD-L1 expression play as an effective biomarker that will predict response to anti–PD-1 therapy?

Is PD-L1 the correct biomarker to use in selecting these agents? There was nice analysis that was preplanned for patients treated in the CheckMate 026 trial that looked at tumor mutation burden and how well that predicts response to nivolumab. What you saw from the data that was presented at AACR by Solange Peters, MD, PhD, is that high mutation burden was a better predictor of benefit from nivolumab than was PD-L1 expression. I think that the role of PD-L1 as a biomarker will continue to be explored and potentially in the next 5 to 10 years, hopefully sooner, PD-L1 may be replaced as the biomarker for selecting treatment.

This is the first time where we've seen a single class of drugs transcend so many tumor types. Lung cancer is the 1 tumor type where PD-L1 expression is required to be positive prior to administration of certain agents. These agents are approved in bladder cancer, melanoma, head and neck cancer, renal cell cancer, and lymphoma, and pembrolizumab just got approval in MSI-high [microsatellite instability] cancers. In my opinion, nobody knows exactly what the right biomarker is to screen for the optimal patient selection. A biomarker that predicts response in 30% to 50% of positive patients, but still has a 10% response in negative patients, is not a great biomarker, as opposed to an EGFR TKI, where if you are positive, you have a 70% chance of response, and if you are negative you have a 1% chance. And so I think a lot of research needs to be done in figuring out the appropriate and optimal biomarker in selecting patients for single-agent therapy as well as potentials for combination therapy.

It seems that the future of immuno-oncology (IO) is going to be in combination therapies. Is that how you see it? Will these therapies become the standard of care across multiple settings? What do we need to be aware of in managing treatment-related toxicity with these combinations?

There is clearly a group of patients who very much derive benefit from single agents, and we still are trying to figure out exactly who those patients are. Right now we are using PD-L1 expression as our best biomarker for benefit. The reality is, though, these drugs only benefit about 15% to 20% of patients when you look at the different ongoing studies. When you look at the long-term survival data, especially, you see they are similar among all trials. So combination therapies are definitely where we are headed.

The melanoma data that looked at nivolumab/ipilimumab compared with nivolumab alone showed that the combination was better initially, but now with longer-term follow-up, the OS is not that different. If you are combining nivolumab and ipilimumab, we are potentially subjecting patients to a higher level of toxicities, particularly with the CTLA-4 inhibitor, as opposed to using single-agent therapy.

Now some of the interesting results that are coming out are the combinations with the indoleamine-(2,3)-dioxygenase (IDO) inhibitors, as well as the histone deacetylases inhibitors and OX40 agonists. There were nice data at ASCO 2017 with pembrolizumab and an IDO inhibitor in NSCLC. There were also nice data with nivolumab and epacadostat in patients with melanoma where none of the patients in the phase I trial had progressed, which is pretty amazing. Further, what's interesting is the toxicities do not appear to be as significant as in previous combinations; for example, pembrolizumab combined with ipilimumab.

Hopefully, some of the new combination treatments will have less toxicity than those that combined a PD-1 or PD-L1 inhibitor with a CTLA-4 inhibitor. When you look at ipilimumab as an agent on its own—not to pick on that one, but it is the only CTLA-4 inhibitor that is approved—it is more toxic than nivolumab. When you look at epacadostat on its own, it is not as toxic as ipilimumab, so maybe that is a rational combination when you are combining it with atezolizumab or nivolumab or pembrolizumab. Then it is a matter of figuring out who the patients are who should receive those combinations versus a single agent. I'm still not excited about the combinations with chemotherapy. I do wonder if there is a group of patients who can be spared chemo and should never have received chemotherapy to begin with—if an IO/IO would make more sense for those patients.

When patients develop these toxicities, they have them sometimes for life. We do not know if there is a group of patients whom we are potentially harming with a checkpoint inhibitor because they are going to develop pneumonitis or colitis, which never completely goes away. If we could find the optimal biomarker in selecting patients for therapy, perhaps we could also potentially figure out some biomarkers that can predict for toxicity.

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