Update From ASCO: Advances in Immunotherapy for Non–Small Cell Lung Cancer and Melanoma

With Expert Commentary From Abraham Schwarzberg, MD

PER® Physicians' Education Resource, LLC

Dates of Certification:
August 29, 2014—August 29, 2015

Medium: *Print with online posttest, evaluation, and request for credit*

Faculty Author/Planner

Abraham Schwarzberg, MD
Chief of Oncology
Jupiter Medical Center
Managing Member, Cancer Center of South Florida
Disclosures: No relevant financial relationships with commercial interests to disclose.

Medical Writer

Kathleen Krafton
Disclosure: No relevant financial relationships with commercial interests to disclose.

The American Journal of Hematology/ Oncology Editorial Board

Debu Tripathy, MD
Professor of Medicine
University of Southern California
Norris Comprehensive Cancer Center
Los Angeles, CA
Disclosure: Grant/Research Support: *Genentech/ Roche, Pfizer, Puma, Inc. (clinical trial support contracted to University of Southern California);* Consultant: *Eisai, Novartis*

Staff/Planner Disclosures and Conflict of Interest Resolution

The staff of PER® (Debbie Augustus, Ann C. Lichti, CCMEP, and Megan O'Connell) as well as the editorial staff of The American Journal of Hematology/Oncology *(Devera Pine) have no relevant financial relationships with commercial interests to disclose.*

In accordance with ACCME's Standards for Commercial Support℠*, PER® resolved all conflicts of interest (COI) prior to the release of this CME activity using a multistep process.*

Overview

The 2014 American Society of Clinical Oncology (ASCO) Annual Meeting, widely regarded as the world's foremost event in oncology, convened on May 29 in Chicago, IL, where developments in immuno-oncology took center stage. Gains made in understanding tumor biology, immunology, and the underlying mechanisms of immunity in cancer have spurred the development of an increasingly broad range of immunotherapies, for an increasingly broad range of cancers. This activity will review key presentations in non-small cell lung cancer and melanoma. Commentary from a community-based medical oncologist will provide insight into how immunotherapy can have unique toxicities, and varying response times for different patients, contributing to important factors for determining appropriate patient selection.

Target Audience

This activity is directed toward medical oncologists and hematologists who treat patients with solid tumors and hematologic malignancies. Fellows, nurses, physician assistants, nurse practitioners, and other healthcare providers may also participate.

Learning Objectives

After participating in this CME activity, learners should be better prepared to:

- Review recent data on immunotherapies presented at national society meetings

Accreditation/Credit Designation

Physicians' Education Resource®, LLC, is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Physicians' Education Resource®, LLC, designates this enduring material for a maximum of 1.0 *AMA PRA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

No commercial support was received for this CME-certified activity. This activity was funded entirely by PER®.

Instructions for Participation/How to Receive *AMA PRA Category 1 Credit*™

1. Read the article in its entirety.
2. Use the QR Code or type http://www.gotoper.com/LINK/94 into your Web browser to access the posttest.
3. Complete and pass the posttest with a score of 70% or higher.
4. Complete the evaluation and request for credit. Participants may immediately download a CME certificate upon successful completion of these steps.

Off-Label Disclosure and Disclaimer

This CME activity may or may not discuss investigational, unapproved, or off-label use of drugs. Participants are advised to consult prescribing information for any products discussed. The information provided in this CME activity is for continuing medical education purposes only, and is not meant to substitute for the independent medical judgment of a physician relative to diagnostic and treatment options for a specific patient's medical condition.

Disclaimer

The opinions expressed in the content are solely those of the individual faculty members and do not reflect those of PER®.

Contact information for questions about the activity:
Physicians' Education Resource®, LLC
666 Plainsboro Road, Suite 356
Plainsboro, NJ 08536
Phone: (888) 949-0045
E-mail: info@gotoper.com

The 2014 American Society of Clinical Oncology (ASCO) Annual Meeting, widely regarded as the world's foremost event in oncology, convened on May 29 in Chicago, IL, where developments in immuno-oncology took center stage. Recent gains in the understanding of tumor biology, immunology, and the underlying mechanisms of immunity in cancer have spurred the development of an increasingly broad range of immunotherapies.[1] These novel agents and combinations are indicative of the promise of improved outcomes that immunotherapy holds for a widening array of cancers.

Select data on emerging therapies and key developments in the field are reviewed here; for complete meeting abstracts and posters, visit ASCO University at university.asco.org.

Non-Small Cell Lung Cancer

Non-small cell lung cancer (NSCLC) accounts for an estimated 85% of all lung cancer cases. Complete surgical resection remains the treatment of choice for early-stage NSCLC, with 5-year survival rates ranging from 73% for pathologic stage IA to 24% for stage IIIA; even in patients with completely resected NSCLC, a high risk of both local and distant failure exists.[2,3]

Numerous strategies have been studied in hopes of improving outcomes for patients with completely resected NSCLC, but with little success to date. Adjuvant radiotherapy is not currently recommended after the PORT meta-analysis in 1998 revealed that it offered no survival benefits and may, in fact, be deleterious in patients with early-stage NSCLC.[4] Although later studies have provided evidence of a possible benefit of adjuvant radiotherapy in patients with mediastinal nodal involvement, the issue remains controversial, and further investigations are under way.[3]

Adjuvant cisplatin-based chemotherapy has also been studied in this patient population. The International Adjuvant Lung Cancer Trial, which included 1867 patients, showed a fairly modest absolute survival benefit of 4% for adjuvant cisplatin-based chemotherapy. Given the high rate of NSCLC occurrence, the need for more effective novel treatment strategies is clear.[5]

Immunotherapy for NSCLC has not traditionally met with much success, as effective immune responses have been difficult to achieve. However, the identification of relevant target antigens, as well as the development of adjuvants and delivery systems that possess the ability to circumvent the immune-suppressive environment of NSCLC, have led to major advances in this arena,[6] a number of which were reported at the 2014 ASCO meeting.

Immunomodulatory agents that function as checkpoint inhibitors in the interaction between T cells and cancer cells appear to hold promise for the treatment of NSCLC. Therapies utilizing monoclonal antibodies targeting the programmed death 1 (PD-1) receptor have demonstrated meaningful responses in NSCLC, melanoma, and renal cell cancer (RCC) with both nivolumab and pembrolizumab (MK-3475; formerly known as lambrolizumab).[7,8]

Nivolumab is a fully humanized monoclonal antibody currently in development as a treatment for various solid tumors, including NSCLC. PD-1 receptors on T cells downregulate T-cell activation, similar to the activity of CTLA-4 receptors.[9] Correlative studies suggest that the mechanisms through which CTLA-4 and PD-1 inhibit T-cell activation are distinct and potentially synergistic.[10]

Published data from a large phase I trial of patients with advanced solid tumors have demonstrated durable clinical responses with nivolumab.[11] A subgroup analysis of patients with previously treated advanced NSCLC was presented at the 2014 ASCO meeting. Brahmer and colleagues[12] reported median overall survival (OS) by dosage and histology, as well as clinical activity of patient subgroups, including programmed death-ligand 1 (PD-L1) tumor status.

A total of 129 patients with refractory NSCLC were given intravenous nivolumab (1 mg/kg, 3 mg/kg, or 10 mg/kg) every 2 weeks for up to 96 weeks. Of these patients, 54% had received 3 or more prior therapies. Median OS ranged from 9.2 months to 14.9 months. One-year and 2-year OS rates were 32% to 56% and 12% to 45%, respectively, across dosages and histologies.

At the 3-mg/kg dosage, median OS was 14.9 months; 1-year and 2-year OS rates were 56% and 45%, respectively. The objective response rate (ORR) was 17% (22/129); mediation duration of response (DOR) was 17 months.

Clinical activity was observed across all patient subgroups, regardless of the number of prior therapies, and in patients with or without epidermal growth factor receptor (*EGFR*) or *KRAS* mutations. Median OS in patients with tumors expressing PD-L1 was 7.8 months (95% CI, 5.6-21.7) compared with 10.5 months (CI, 5.2-21.2) without expression. Median progression-free survival (PFS) was 3.6 months and 1.8 months, respectively. This suggests that PD-1 levels could identify responsive subsets of patients.

Fourteen percent of patients experienced grade 3/4 treatment-related adverse events (AEs). The most commonly reported AE was fatigue (3%).[12]

In another phase I trial, investigators studied nivolumab in patients with chemotherapy-naïve squamous or nonsquamous advanced NSCLC. Interim results for the first 20 patients were

presented at the ASCO Annual Meeting by Gettinger and colleagues.[13]

Nivolumab was administered to patients (3 mg/kg) every 2 weeks until disease progression or unacceptable toxicity. Post-progression treatment was allowed based on protocol-defined criteria.

After at least 6 months of follow-up, 17 patients (85%) experienced any-grade treatment-related AEs. Grade 3/4 treatment-related AEs included elevations of liver enzymes, hyperglycemia, and rash. There were no reports of pneumonitis.

The ORR for patients treated with nivolumab was 30%. Five of 6 responders (83%) achieved a response at the time of the first scan (week 11). Responses were durable and ongoing (median DOR not reached).

Of 15 evaluable tumor samples, 9 expressed PD-L1. The ORR was 67% in PD-L1-positive patients; no responses were observed in the 6 PD-L1-negative patients.

Nivolumab Plus Erlotinib

The EGFR tyrosine kinase inhibitor (TKI) erlotinib has been approved for first-line treatment of patients with advanced NSCLC with activating *EGFR* mutations.[14] Inspired by recently published data that suggest that constitutive oncogenic signaling through the EGFR pathway may promote tumor immune escape by inducing immune dysfunction in the tumor microenvironment,[15,16] Rizvi and colleagues[17] undertook a phase I study evaluating nivolumab plus erlotinib in chemotherapy-naïve patients with *EGFR*-mutated advanced NSCLC. Interim findings for 21 patients were presented.

Patients with stage IIIB and stage IV *EGFR*-mutated chemotherapy-naïve NSCLC who were either EGFR TKI-naïve or who had progressed after prior TKI therapy received nivolumab (3 mg/kg every 2 weeks) plus erlotinib (150 mg daily by mouth) until disease progression or unacceptable toxicity.

Only 1 of the 21 patients who received the combination had not received prior EGFR TKI therapy. Ninety-five percent of patients had stage IV disease; 5% had stage IIIb. All had nonsquamous histology and were *EGFR*-mutation positive.

The ORR was 19% (4 of 21 patients, all partial responses) and the 24-week PFS was 47%. Median DOR has not been reached.

Of the 20 patients who had relapsed after treatment with erlotinib, 3 (15%) achieved a partial response (PR; ongoing at the time of data analysis). Nine patients (45%) had stable disease (SD; 3 ongoing). One patient had an unconventional "immune-related" response (ongoing), with a 46% reduction in the target lesions after progression in the nontarget lesions. The EGFR TKI-naïve patient achieved PR with a duration of 24.3+ weeks (ongoing).

Although all patients experienced AEs related to treatment, only 2 discontinued as a result (grade 3 AST increase and grade 2 nephritis). There were no reports of pneumonitis.

Docetaxel Plus Ramucirumab

Results were also presented from REVEL, a randomized, double-blind, phase III study of docetaxel and the vascular endothelial growth factor receptor-2 (VEGFR-2) antibody ramucirumab (formerly IMC-1121B) versus docetaxel and placebo in the second-line treatment of stage IV NSCLC following disease progression after one prior platinum-based therapy.[18,19] Of the 1253 patients enrolled, 26.2% had squamous histology.

There was a statistically significant improvement in ORR (22.9% vs 13.6%; P <.001) with ramucirumab plus docetaxel compared with docetaxel alone. Median PFS was 4.5 versus 3.0 months (HR = .762; P <.0001) for the combination versus docetaxel alone, respectively. Median OS was 10.5 months in the ramucirumab-plus-docetaxel group compared with 9.1 months in the docetaxel-plus-placebo group (HR = 0.857; 95% CI, 0.751-0.98; P = .0235) Survival benefits were consistent in the major subgroups of patients, including patients with squamous cell and nonsquamous cell histology.

The most common grade 3 or higher AEs (>5% incidence) in the ramucirumab/docetaxel arm included neutropenia, febrile neutropenia, fatigue, leukopenia, hypertension, and pneumonia. The occurrence of pulmonary hemorrhage (any grade) was comparable between treatment arms (all patients, 2.1% vs 1.6%; squamous cell patients, 3.8% vs 2.4%).[19]

Melanoma

Dating back to the original use of high-dose interleukin-2 and high-dose interferon, the development of immunotherapy for advanced melanoma has been an area of tremendous progress and innovation. Historically, advanced melanoma has had a poor prognosis; however, advancements in immunotherapy are helping to pave the way for improved outcomes. In particular, adoptive-cell therapy has emerged as a promising area of investigation, with improvements in efficacy.[20]

Recently, clinical trials have demonstrated that immune checkpoint blockade of PD-1 or PD-L1 results in substantial antitumor activity. In particular, nivolumab and pembrolizumab, 2 PD-1-blocking monoclonal antibodies, have demonstrated robust ORRs in patients with melanoma, as well as in RCC and NSCLC. Additionally, rapid reductions in tumor burden, with limited immune-mediated AEs (less than that seen with the CTLA-4 checkpoint inhibitors such as ipilimumab) and highly durable responses have been demonstrated.[7,8,20]

At the 2014 ASCO Annual Meeting, Atkins and colleagues[21]

presented data from a phase II, open-label, multicenter, safety, and efficacy study of the anti-PD-1 antibody pidilizumab (CT-011) in patients with metastatic melanoma. Eligibility criteria included measurable disease, clearly progressive stage IV disease, and a minimum of 3 prior systemic therapies. Patients with stabilized brain metastases were allowed in the trial. Patients were required to be 6 weeks from treatment with ipilimumab; no prior treatment with PD-1, PD-L1, or PD-L2 inhibitors was permitted.[21,22]

Patients (N=103) were randomized to 2 dosage levels of pidilizumab: 1.5 mg/kg or 6 mg/kg by intravenous administration every 2 weeks for 27 weeks. Stratification by pidilizumab dosage and by prior ipilimumab receipt was also performed.

Using immune-related response criteria (irRC), the ORR for all patients was 5.9% (90% CI, 2.3-12.0); this increased to 10% in patients treated with 1.5-mg/kg pidilizumab who had received prior ipilimumab (90% CI, 1.8-28.3). Patients with prior ipilimumab had a slightly longer median PFS (2.8 months vs 1.9 months). OS at 12 months was 64.5% (90% CI, 55.6-72.0), with insignificant differences between pidilizumab dosages or *BRAF* mutation status, and irrespective of therapies given before entry or after withdrawal. In patients with M1c disease, 12-month OS was 67.2% (90% CI, 57.0-75.0).

Although response rates were low, pidilizumab therapy resulted in a substantial 12-month survival rate in heavily pretreated patients with metastatic melanoma. The most frequent AEs observed with pidilizumab in this large phase II trial included fatigue (43%), diarrhea (22.5%), and arthralgia (21%). Serious AEs included pneumonia (5%) and dyspnea (3%).[22]

Late-breaking data were presented by Ribas and colleagues[23] concerning the safety and efficacy of a novel humanized monoclonal IgG4 anti–PD-1 antibody, pembrolizumab, in metastatic melanoma. Pembrolizumab was evaluated in a pooled analysis of 411 patients with advanced melanoma. A total of 221 patients previously had been treated with ipilimumab, an anti-CTLA-4 antibody, and 190 were ipilimumab-naïve.

Overall, 34% of patients with metastatic melanoma experienced CR or PR to pembrolizumab. Response rates were 40% in patients who had not received ipilimumab and 28% in patients whose disease progressed after receiving ipilimumab, a difference that did not reach statistical significance. Responses were durable, with 88% ongoing at the time of analysis.

Activity of pembrolizumab was observed across all dosage levels and patient subgroups, regardless of ECOG performance status, lactate dehydrogenase levels, *BRAF* mutation status, melanoma stage, and number and type of prior therapies.

The 1-year OS rate in all patient subgroups and all pembrolizumab dosage schedules was 71%; at 18 months, this rate was an estimated 62%. Serious treatment-related AEs occurred in 8% of patients, but only half of these patients discontinued due to a treatment-related AE. Overall, drug-related grade 3/4 AEs were experienced by 12% of patients; 4% of patients discontinued due to a drug-related AE.[23]

Finally, Eggermont and colleagues[24] presented results from EORTC 18071, a phase III, randomized, double-blind, placebo-controlled study designed to assess the impact of ipilimumab on recurrence-free survival. In this study, a total of 951 patients with surgically treated stage III cutaneous melanoma, excluding in-transit metastases, were randomly assigned to receive ipilimumab or placebo. No patients had received prior systemic therapy for melanoma.

Ipilimumab was administered at 10 mg/kg every 3 weeks for 4 doses, followed by 10 mg/kg every 3 months for up to 3 years. Placebo was given using the same schedule. At median follow-up of 2.7 years, ipilimumab reduced the relative risk of melanoma recurrence by 25% compared with placebo. Three-year PFS rates were 46.5% and 34.8% in the ipilimumab and placebo groups, respectively (P = .0013).

Five treatment-related deaths occurred. A total of 52% of patients discontinued ipilimumab due to AEs, usually within 12 weeks of treatment. The most common grade 3/4 immune-related AEs in both arms were gastrointestinal (15.9% vs 0.8% for ipilimumab vs placebo), hepatic (10.6% vs 0.2%), and endocrine (8.5% vs 0%).[24]

Expert Commentary

By Abraham Schwarzberg, MD

Dr. Schwarzberg is Chief of Oncology, Jupiter Medical Center, Ella Milbank Foshay Cancer Center, Jupiter, FL.

This is a particularly exciting time in the field of immuno-oncology. The rapid pace of development and the promise of immunotherapy are evident in the sheer number of abstracts and posters presented at the ASCO Annual Meeting. There's been a reinvigoration of immune-based therapies which, with the exception of melanoma and kidney cancer, had not previously been in the forefront of solid tumor therapies or strategies. Immunotherapy is now being brought to a wide variety of solid tumors. The key, perhaps, to unlocking an effective immune response to tumors is to design studies with the right biomarkers, and targeting the critical pathways such as we are seeing with the use of PD-1/PD-L1 antibodies. Removing the brakes from the immune system at these specific checkpoints appears to yield meaningful activity in a broader range of malignancies with fewer side effects compared with established CTLA-4 blockade therapy for melanoma using

ipilimumab.

As much as we have learned about biomarkers and their potential role in developing new methods for diagnosis as well as treatment stratification, there is still much more to learn. Researchers and clinicians alike desperately want to have biomarkers so that we can know which immune-based therapy to give to which patients. Just as we have identified histologic subtypes that tell us which chemotherapy drugs are more effective in which subsets of cancers, biomarkers are becoming an important area of study as we develop and expand immuno-oncology.

First and foremost, clinicians want to be able to catch the right signal of efficacy by studying the right patient population. As an example of this, consider the use of trastuzumab in breast cancer trials. By understanding and looking for HER2-related targets, we were able to see that trastuzumab had robust clinical efficacy; had we only studied it in more general populations, however, we may have missed that signal. The same issue is true with immunotherapy, whether it's used in melanoma, kidney cancer, lung cancer, head and neck cancer, or bladder cancer. If we can find the right biomarkers, we can enhance and improve response rates, effectiveness, and, hopefully, the duration of response and improvement in survival.

On the other hand, the biggest concern with utilizing biomarkers to enrich patient selection for a treatment is that we don't want to leave people out who could be responders. If one day we are so specific with our biomarkers that we're able to home in on the patients with the highest response rates, we also want to make sure that we include patients who still might respond; even if they respond at a lower rate, we still want to make sure these patients have access to the drug.

For example, consider the data presented by Powles and colleagues[25] at the ASCO meeting on monotherapy with PD-L1 inhibitors in novel solid tumor indications, such as bladder cancer. Different response rates were demonstrated for high expressers of PD-L1 and low/nonexpressers. The idea behind these investigations was that tumors that have higher PD-L1 expression, such as head and neck cancers and bladder cancers, might be prime targets in which to utilize PD-L1 inhibitors. PD-L1 can have variable expression in tumors, however, which raises the concern: How do you reliably test the tumors? How do we reliably standardize the testing in clinical trials and in clinical practice when these drugs become available? A negative test result might not reflect the actual biology of the tumor if testing is not standardized in a reliable manner.

We need to better define how we're going to test the PD-L1 target and how we are going to define high expressers versus low or nonexpressers. Additionally, we need to establish whether or not there is a need for serial biopsies, and if a certain volume of tumor needs to be sampled. Certain drugs may work in different percentages in either nonexpressers or low expressers versus high expressers. These are the concerns about overanalyzing biomarkers, which will require further study before we can move these practices into the clinics.

The potential for improved outcomes versus the risk of toxicity with immunotherapy drug combinations is another subject that generates much debate. Consider the checkpoint inhibitors: the CTLA-4 antibodies, the PD-1 antibody inhibitors, and the PD-L1 inhibitors. All have shown activity individually as well as in combination, but the optimal dosing and schedule are still under investigation. What we don't know yet is if there are certain combinations that are perhaps more beneficial in certain cancer types than others. Will the combination yield improved overall survival and higher response rates to justify the increased risk in toxicity that appears to be generated when you combine these therapies concurrently? Will we achieve the same benefit if immune therapies are given sequentially and not concurrently with the potential benefit of less toxicity?

Concurrent immunotherapy with both CTLA-4 and PD-1 antibodies have been most extensively evaluated in advanced melanoma. Wolchok and colleagues[26] have demonstrated that concurrent therapy generates higher response rates than is typically seen with individual immune therapies. A phase III trial is currently under way to directly compare concurrent versus sequential approaches in advanced melanoma. While we don't have the answers yet, across the board, the combinations are exciting in a variety of tumor types. We have the most well-developed data for CTLA-4 plus PD-1 therapy, but that's really just because other combinations are still being explored in earlier phase trials. It's going to take time to identify the optimal combinations and dosing schedules.

As these drugs roll into the clinic and combination therapies are adopted, it's going to become important to educate clinicians on the autoimmune toxicities, which are very unique to immunotherapy. Community oncologists are of course extremely well versed with cytotoxic chemotherapy drugs and the types of side effects they engender. They're less familiar, however, with immune-based side effects and toxicities, such as endocrinopathies, autoimmune hepatitis, autoimmune colitis, and autoimmune pneumonitis. Those side effects are unique to these classes of drugs. Occasionally, they are seen in high-dose interleukin-2 and interferon, but those are not commonly used in a typical community oncology practice. Education about immune-related adverse reactions and how to catch and treat them before they accelerate and potentially become life-threatening will be needed.

A related issue is the clinical and radiographic assessments of a patient's response to immune treatment. Just as the side effects are unique, so are the timing and quality of the response to treatment. Patients may demonstrate pseudo-progression or "tumor

flares," which actually represent responses but radiographically might appear as progression initially. Response definitions may need to be altered as "immune-related response" criteria are adapted due to the fact that some tumors develop a "halo" on imaging, which can be misinterpreted.

Lastly, the kinetics of tumor response differ from traditional cytotoxic therapies, and therefore the time courses of responses vary with the different immune therapies. As we incorporate new immune therapies into our clinical practice, it's critical to realize that in the clinical trials, patients with the optimal circumstances are often selected because these are new drugs and it's important to evaluate the safety and the efficacy in a somewhat more pristine population. As new drugs get into the clinics, they are going to be applied to patients who may have a history of rheumatoid arthritis or patients who have a history of chronic lymphoma or other versions of immune dysfunction, and the efficacy and safety will not be well established in those settings. I think that it's going to be a challenge for clinicians and academicians to help define when we can apply the data from a more narrow population of study patients to a more general population that is seen in a typical clinical practice.

REFERENCES

1. Kirkwood JM, Butterfield LH, Tarhini AA, Zarour H, Kalinski P, Ferrone S. Immunotherapy of cancer in 2012. *CA Cancer J Clin*. 2012;62(5):309-335.

2. Vansteenkiste J, Zielinski M, Linder A, et al. Adjuvant MAGE-A3 immunotherapy in resected non–small-cell lung cancer: Phase II randomized study results. *J Clin Oncol*. 2013;31:2396-2403.

3. Le Péchoux C. Role of postoperative radiotherapy in resected non-small cell lung cancer: A reassessment based on new data. *Oncologist*. 2011;16(5):672-681.

4. PORT Meta-analysis Trialists Group. Postoperative radiotherapy in non-small-cell lung cancer: Systematic review and meta-analysis of individual patient data from nine randomised controlled trials. *Lancet*. 1998;352:257-263.

5. Liang Y, Wakelee HA. Adjuvant chemotherapy of completely resected early stage non-small cell lung cancer (NSCLC). *Transl Lung Cancer Res*. 2013;2(5):403-410.

6. Decoster L, Wauters I, Vansteenkiste JF. Vaccination therapy for non-small-cell lung cancer: Review of agents in phase III development. *Ann Oncol*. 2012;23(6):1387-1393.

7. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med*. 2012;366(26):2443-2454.

8. Hamid O, Robert C, Daud A, et al. Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. *N Engl J Med*. 2013;369(2):134-144.

9. Single-agent nivolumab in advanced NSCLC. http://www.valuebasedcancer.com/conference-correspondent/25379-single-agent-nivolumab-in-advanced-nsclc. *Value-Based Cancer Care*. July 30, 2014. Accessed July 30, 2014.

10. Parry RV, Chemnitz JM, Frauwirth KA, et al. CTLA-4 and PD-1 receptors inhibit T-cell activation by distinct mechanisms. *Mol Cell Biol*. 2005;25(21):9543-9553.

11. Topalian SL, Sznol M, Brahmer JR, et al. Nivolumab (anti-PD-1; BMS-936558; ONO-4538) in patients with advanced solid tumors: Survival and long-term safety in a phase I trial. *J Clin Oncol*. 2013;31(suppl; abstr 3002).

12. Brahmer JR, Rizvi NA, Lutzky J. Nivolumab (anti-PD-1, BMS-936558, ONO-4538) in patients (pts) with advanced non-small-cell lung cancer (NSCLC): Survival and clinical activity by subgroup analysis. *J Clin Oncol*. 2014;32(suppl 5s; abstr 8112).

13. Gettinger SN, Shepherd FA, Antonia SJ, et al. First-line nivolumab (anti-PD-1; BMS-936558, ONO-4538) monotherapy in advanced NSCLC: Safety, efficacy, and correlation of outcomes with PD-L1 status. *J Clin Oncol*. 2014;32(suppl 5s; abstr 8024).

14. Tarceva (erlotinib) [package insert]. Farmingdale, NY: OSI Pharmaceuticals, LLC; 2013.

15. Akbay EA, Koyama S, Carretero J. Activation of the PD-1 pathway contributes to immune escape in EGFR-driven lung tumors. *Cancer Discov*. 2013;3:1355-1363.

16. Rech AJ, Vonderheide RH. Dynamic interplay of oncogenes and T cells induces PD-L1 in the tumor microenvironment. *Cancer Discov*. 2013;3:1330-1332.

17. Rizvi NA, Chow LQM, Borghaei H, et al. Safety and response with nivolumab (anti-PD-1; BMS-936558, ONO-4538) plus erlotinib in patients (pts) with epidermal growth factor receptor mutant (EGFR MT) advanced NSCLC. *J Clin Oncol*. 2014;32(suppl 5s; abstr 8022).

18. Bath C. ASCO 2014: Second-line treatment with ramucirumab plus standard docetaxel extends overall survival in advanced lung cancer. http://www.ascopost.com/ViewNews.aspx?nid=16277. *The ASCO Post*. June 2, 2014. Accessed July 23, 2014.

19. Pérol M, Ciuleanu T-E, Arrieta O, et al. REVEL: A randomized, double-blind, phase III study of docetaxel and ramucirumab versus docetaxel and placebo in the second-line treatment of stage IV non-small cell lung cancer following disease progression after one prior platinum-based therapy. *J Clin Oncol*. 2014;32(suppl 5s; abstr LBA8006).

20. Recent explosion of progress in melanoma management catalyst for change in future directions for research. http://am.asco.org/recent-explosion-progress-melanoma-management-catalyst-change-future-directions-research. *ASCO Daily News*. June 1, 2014. Accessed July 23, 2014.

21. Atkins MB, Kudchadkar RR, Sznol M, et al. Phase 2, multicenter, safety and efficacy study of pidilizumab in patients with metastatic

melanoma. *J Clin Oncol.* 2014;32(suppl 5s; abstr 9001).
22. Pidilizumab in relapsed metastatic melanoma. http://value-basedcacer.com/conference-correspondent/25436-pidilizumab-in-relapsed-metastatic-melanoma. *Value-Based Cancer Care*. July 30, 2014. Accessed July 30, 2014.
23. Ribas A, Hodi FS, Kefford R, et al. Efficacy and safety of the anti-PD-1 monoclonal antibody MK-3475 in 411 patients (pts) with melanoma (MEL). *J Clin Oncol.* 2014;32(suppl 5s; abstr 9000).
24. Eggermont AM, Chiarion-Sileni V, Grob JJ, et al. Ipilimumab versus placebo after complete resection of stage III melanoma: Initial efficacy and safety results from the EORTC 18071 phase III trial. *J Clin Oncol.* 2014;32(suppl 5s; abstr LBA9008).
25. Powles T, Vogelzang NJ, Fine GD, et al. Inhibition of PD-L1 by MPDL3280A and clinical activity in pts with metastatic urothelial bladder cancer (UBC). *J Clin Oncol.* 2014;32(suppl 5s; abstr 5011).
26. Wolchok JD, Kluger H, Callahan MK, et al. Nivolumab plus ipilimumab in advanced melanoma. *N Engl J Med.* 2013;369:122-123.