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A Joint Meeting by the Global Biomarkers Consortium and World Cutaneous Malignancies Congress

The Global Biomarkers Consortium (GBC) and World Cutaneous Malignancies Congress (WCMC) will be holding their fourth annual joint meeting focused on personalized and precision medicine in oncology (PMO) on July 22-25, 2015, in Seattle, Washington.

SCHEDULE OF EVENTS
July 22-24
A Focus on the Application of Molecular Biomarkers in Clinical Practice Across Multiple Tumor Types

July 24-25
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OUR MISSION
Personalized Medicine in Oncology provides the bridge between academic research and practicing clinicians by demonstrating the immediate implications of precision medicine – including advancements in molecular sequencing, targeted therapies, and new diagnostic modalities – to the management of patients with cancer, offering oncologists, oncology nurses, payers, researchers, drug developers, policymakers, and all oncology stakeholders the relevant practical information they need to improve cancer outcomes. This journal translates the new understanding of the biology of cancer into the day-to-day management of the individual patient with cancer, using a patient’s unique genetic makeup to select the best available therapy.

OUR VISION
Our vision is to transform the current medical model into a new model of personalized care, where decisions and practices are tailored for the individual – beginning with an incremental integration of personalized techniques into the conventional practice paradigm currently in place.
Providing Critical Insights for Clinical Application

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EBSCO research databases
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LETTER TO OUR READERS

Dear Colleague,

In this issue of *Immunotherapy in Oncology* (ITO), we continue to explore the many facets of immunotherapy, reaching beyond the basic science to bring you the practical implications of its usefulness. We are pleased to report that the FDA recently approved nivolumab injection, for intravenous use, for the treatment of patients with metastatic squamous non–small cell lung cancer with progression on or after platinum-based chemotherapy. This is good news, as nivolumab, a PD-1 (programmed death-1 receptor) therapy, demonstrated improved overall survival in this population. In light of this advance, we present additional articles exploring the need for immunotherapy options in lung cancer, specifically “The Need for Immunotherapeutic Approaches for Lung Cancer” (page 14) and “Immuno-Oncology Combination Approaches for Lung Cancer” (page 22). We will continue to explore this topic in future issues of ITO.

Also of interest is the business side of immunotherapy. In our Interview with the Innovators feature, titled “The Commercialization Process of Immunotherapies: An Interview with Olivier Lesueur and Rachel Laing, PhD,” we had the pleasure of talking with two experts from a consulting firm that specializes in bringing products to market (page 10). They compare the impact of immunotherapies in the current day to what chemotherapy agents were to cancer care in the 1970s. This comparison isn’t lost on pharmaceutical companies, who are focused on commercializing immunotherapy agents as quickly as possible.

Also in this issue, we present articles from meetings around the country monitoring the progress of immunotherapies. From FDA approvals to biomarkers, you’ll find an array of the most recent, groundbreaking events from the immunology field. We are greatly encouraged by the advances in cancer treatment that immunotherapy affords us, and it is our sincere hope this information assists you in providing the best care for your patients. We are pleased to be your source for information, and as always, we thank you for being part of our reading community.

Sincerely,

Sanjiv S. Agarwala, MD
Editor in Chief
*Immunotherapy in Oncology*

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**Exploring Advances in Immunotherapy**

We continue to explore the many facets of immunotherapy, reaching beyond the basic science to bring you the practical implications of its usefulness.
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The Academy of Oncology Nurse & Patient Navigators (AONN+) invites you to share your story of how cancer has affected you or a loved one. These stories will serve as a forum to build awareness and be a source of inspiration and reassurance to others. Select stories will be featured on the AONN+ website and in future issues of the Journal of Oncology Navigation & Survivorship®.

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The Commercialization Process of Immunotherapies

An Interview with Olivier Lesueur and Rachel Laing, PhD

The field of immunotherapy has made great strides in recent years, culminating in the FDA approvals of 3 checkpoint inhibitors: Yervoy, Keytruda, and Opdivo. For Big Pharma, this means the race is under way to investigate the potential of immunotherapies in as many indications as possible. The potential for blockbuster products looms large as the dawn of targeted therapies and companion diagnostics changed the way we thought of cancer treatments from “one-size-fits-most” to highly specialized, personalized treatments inherently removing the possibility of traditional blockbuster status. Enter immunotherapies, which have been touted as a revolution in oncology comparable to the advent of chemotherapies in the 1970s. As a result, the commercialization of immunotherapies presents a challenge to pharmaceutical companies, prompting partnerships with strategy consultants such as Bionest Partners to drive competitive differentiation. Bionest Partners is a global strategic consulting firm serving the pharmaceutical, biotechnology, medical device, and diagnostic industries. Further information about this consulting service is available at www.bionest.com.

In their recent paper published in IN VIVO titled “Immunotherapy: Big Pharma’s Seductive Embrace,” Olivier Lesueur and Rachel Laing, PhD, from Bionest Partners, along with science writer Mark Ratner, explore the emerging field of immuno-oncology, the revolution of immune checkpoint targeting, and the strategies Big Pharma is using to expedite the clinical trial process. The publishers of ITO had the pleasure of speaking with Mr Lesueur and Dr Laing. What follows is their insightful exchange.

ITO Thank you for taking the time to speak with us today. To begin, can you introduce us to Bionest Partners and your involvement in the field of immunotherapy?

Mr Lesueur Bionest is a strategy consulting firm based in New York and Paris with offices in San Diego, Tokyo, Munich, and London. For over a decade, we have specialized in providing consulting services to pharmaceutical, biotech, and diagnostic companies. In the immunotherapy space, we began work several years ago with a current leader in the field to look at their portfolio of checkpoint inhibitors because the science wasn’t providing obvious directions in terms of how to develop and prioritize the assets. At that stage, we felt the possibilities were wide open, much like the beginnings of chemotherapy. You could argue immunotherapies are somewhat like Avastin was; a ubiquitous asset that opened the field and raised many questions about the best path forward to commercialization—combination or monotherapy, what indication—without having a lot of mature scientific data directing that process. Since then, we have worked with several leaders in the field on a variety of topics, along with a number of companies looking to get into the immunotherapy field.

ITO Can you describe your observations of the progression of the immuno-oncology field?

Dr Laing It’s interesting when we think translationally and clinically about this field. If we go back in time, immunotherapy was traditionally thought to be limited to melanoma and renal cell carcinoma. Now we know it can be applicable to a number of different tumors beyond this.

From a clinical perspective, the types of responses we’re seeing are very different from what we’ve seen with targeted therapies. We have patients who were treated on the first Yervoy trial over 10 years ago, and they’re
still in remission. That’s really transformational.

In contrast to targeted therapies, we haven’t seen much in the way of acquired resistance to immunotherapy. In many cases with targeted therapies, you see acquired treatment resistance after a certain period, and there’s a new pool of targeted therapies to address that resistance. That’s not to say that we won’t have an issue with resistance to immunotherapy at some point, but we haven’t seen it yet.

With immunotherapies, there are cases where we have been able to induce long-term responses even after treatment has stopped because of the nature of the immune system. It’s like resetting that system, and those responses seem to endure. To us, these factors change the clinical landscape and then calls into question how to develop and commercialize the therapies.

ITO The paper you authored, called “Immunotherapy: Big Pharma’s Seductive Embrace,” describes holding the tumor at bay as being the distinguishing characteristic of checkpoint inhibitors from other therapies. Can you elaborate on this?

Dr Laing If you take targeted therapies as an opposite example, you’re specifically targeting pathways within the cell that the cell requires to stay alive. If you can hit those relevant pathways, the tumor cells will die, and you’ll have tumor regression. But in many cases, you can’t achieve that in every single tumor cell, so there will be some cells left behind. Once you stop therapy, the cancer grows back with new mutations, and the treatment that originally produced a response is no longer an option.

By contrast, immune checkpoint inhibitors target the tumor-immune interactions and are not just focused on the tumor itself. The immune system has the ability to kill tumor cells in a perfect world, but the tumor is often able to inhibit that function.

Regarding holding the tumor at bay, immune checkpoint inhibitors act as sort of a reset button, priming the immune system to recognize those tumor cells as foreign. You may eradicate the majority of the tumor and achieve remission, and even if you still have some residual cancer cells, you may also have developed memory T cells that remain primed to trigger an antitumor response in case the residual cancer cells try to grow back.

In many patients who respond, it appears that not only do they respond but that the duration of response is still ongoing. To us, this seems like a drastic change from what we’ve seen with many of the targeted therapies today.

ITO That is remarkable. What are you observing in terms of its diffusion into practice?

Mr Lesueur There are several diseases, such as melanoma and lung cancer, in which immunotherapies have established value. It would also make sense to approach cancers where established, foundational treatments do not exist, with the intent to become the foundational treatment, like Revlimid in multiple myeloma, for example.

Currently, immune checkpoint inhibitors are mostly employed as monotherapy in later lines of treatment. The big question is how to become first-line and foundational across many different tumor types.

So the applicability is wider than a few immune-driven indications that we identified in the past. As a result, there’s a race to get trials set up in as many indications as possible.

It would also make sense to approach cancers where established, foundational treatments do not exist, with the intent to become the foundational treatment.

Currently, there are trials focused on immunotherapies as monotherapy, and secondary trials testing immunotherapies in combination with other immunotherapies or targeted therapies sponsored either by a single company, companies in partnership, or investigators. Although proprietary combinations make the overall economics better for a pharmaceutical company, partnerships allow immunotherapy companies to rapidly penetrate a broad range of indications and across many lines.

ITO Please describe the drug commercialization process as one of the drivers of research in checkpoint targeting.

Mr Lesueur The many different stakeholders are pushing for broad acceptance of immunotherapy, including the investment community. The level of data required to get approved has changed over the past few years, with less and less being required of each subsequent approval. That changes the paradigm a bit from the development perspective and may convince more players to come into the immune checkpoint game.

From the commercial perspective, we see broad applicability across many indications, so mostly Big Pharma will be able to commercialize a PD-1 or PD-L1.

ITO How does the role of the pathologist play into the use of immunotherapies?

Mr Lesueur Pathologists certainly are a new consideration, and their role is changing. They will have to be educated in meeting the challenge of better qualifying patients who are more likely to respond. At some point, most likely when the competition among immunotherapy products is high, there will be some pushback from
Most tumors are “smart,” meaning that they are not dependent on just 1 pathway, but they’re dependent on a whole host of different things.

Mr Lesueur We’re still very much in the infancy of the immunotherapy era. Once the competition starts becoming fiercer and we have multiple PD-1 or PD-L1 assets approved for the same patient, then there will be a very strong drive to have better PD-1, PD-L1 value propositions, and that would include having a better diagnostic for determining the likelihood of response. There is a PD-L1 expression biomarker today that many agree is not a great test. But still, it’s something that will probably be used in the market.

There will be a requirement for more and better enrichment, and that creates a drive for innovation, and a number of small companies are looking at this. There are deals that are happening between diagnostic companies and Big Pharma. And that creates innovation and a better value proposition from the price perspective.

ITO Would you say the search for the diagnostic qualifier test is essentially linked to and dependent on the complexity of the cancer being treated?

Dr Laing Most tumors are “smart,” meaning that they are not dependent on just 1 pathway, but they’re dependent on a whole host of different things. Sometimes you get lucky and identify the driver mutations or specific targets. But more often than not, the tumor is pretty intelligent and can evade different therapies.

So, yes, I think it’s partly the tumor complexity, but it’s also the fact that these immune checkpoint inhibitors are part of a very complex and broader immune system response. So the PD-1 or the CTLA-4 pathway is 1 of many checkpoint pathways in the body. The immune system is so dynamic that to rely on 1 marker may not be a realistic goal. You’d be quite lucky to find that 1 marker when in reality there are a hundred things going on in that interaction.

Mr Lesueur I would add another layer of complexity. It’s not just about the tumor but also about the state of each patient’s immune system. If the patient is immunocompromised, they may not receive the same benefit as the patient who is not.

ITO Can you describe side effects from therapy?

Dr Laing We’ve seen side effects, but they’re different from what we’re used to seeing with targeted therapies. Mainly, we see side effects such as pneumonitis because of the continued activation of the immune system. These can be well controlled in most cases.

Oncologists are traditionally used to managing the side effects from chemotherapy and targeted therapies, and that side effect profile is very different from what we see with immunotherapies, which is more akin to what an immunologist would feel comfortable managing. So, if they aren’t already, oncologists will need to get comfortable managing these new types of side effects.

ITO What do you think we can expect as a next step in the life cycle of immunotherapies?

Dr Laing The combination therapy strategy is the way things are headed. There are a number of combination trials across a number of different indications under way.

Mr Lesueur It’s a bit of a Wild West now, which is actually very good. Everybody wants to try their drug with an immunotherapy. The market is full of possibility because there’s relatively low scientific rationale as to what you cannot try in combination with an immunotherapy. You have to start with the basic science as to why a combination might be synergistic.

Another point to consider is that immunotherapies will come to a stage where they may compete one versus the other without a clear understanding of their differentiating factors or predictive indicators for response. Introducing a targeted agent in combination with an immunotherapy may bring differentiation and competitive advantage to one immunotherapy versus another.

We address this concept in our article; that for a period of time, combination with targeted agents will be the driving force of competitive differentiation and market segmentation of immunotherapies, because the introduction of a targeted therapy introduces the possibility of a biomarker that sets apart the immunotherapeutic agent in a certain segment of the treatment population.

ITO Thank you so much for your time today. We really appreciate your insights into this exciting field.
The world of personalized medicine is a rapidly changing, ever-evolving state involving many stakeholders on the frontlines of its creation: physicians, industry, researchers, patient advocates, and payers. The publishers of PMO have the distinct honor of interviewing leaders in these sectors to bring you their game-changing strategies, missions, and impact on personalized oncology care.

Each year, we select the innovator whose contribution to the field of oncology represents the most profound impact on patient care. For 2015, it is our pleasure to award the distinction of Innovator of the Year to James Allison, PhD, of The University of Texas MD Anderson Cancer Center.

Dr Allison is the chairman of the Immunology Department and executive director of the immunology platform for the Moon Shots Program at MD Anderson in Houston. He is the recipient of numerous honors for biomedical research, including the inaugural AACR-CRI Lloyd J. Old Award in Cancer Immunology, the 2013 Innovations Award for Bioscience from The Economist, and a 2014 Breakthrough Prize in Life Sciences. He also coleads a Stand Up to Cancer Dream Team research project in immunotherapy.

Dr Allison is on a quest to train the immune system to attack cancer cells, eliminate tumors, and protect against recurrence. The strategy being employed is a new paradigm for cancer treatment called immune checkpoint targeting. This approach has proved effective in treating many different types of cancer and is now a standard of care for metastatic melanoma. To see our interview with Dr Allison, please visit us at www.PersonalizedMedOnc.com.

It is our pleasure to congratulate Dr Allison on his work to date and the profound impact it has had on the lives of patients. We wish him continued success in his quest to harness the power of the immune system to combat cancer.
The Need for Immunotherapeutic Approaches for Lung Cancer

Non–small cell lung cancer is one of the major cancer types for which new immune-based cancer treatments are currently in development.

Lung cancer is the second most common cancer in both men and women (not counting skin cancer); in men, prostate cancer is more common, whereas in women, breast cancer is more common. The American Cancer Society estimates that approximately 221,200 new cases of lung cancer (115,610 in men and 105,590 in women) will be diagnosed in the United States in 2015, and about 158,040 people (86,380 men and 71,660 women) will die of lung cancer this year. Lung cancer is by far the leading cause of cancer death among both men and women; each year, more people die of lung cancer than of colon, breast, and prostate cancers combined (Figure 1). Only 17.8% of all patients with lung cancer are alive 5 years or more after diagnosis; the lung cancer 5-year survival rate is lower than that of many other leading cancer sites, such as the colon, breast, and prostate (Figure 1). The 5-year survival rate for lung cancer is 54% for cases detected when the disease is still localized; however, only 15% of lung cancer cases are diagnosed at an early stage. For distant tumors, the 5-year survival rate is only 4% (Figure 1).

Approximately 85% to 90% of lung cancer cases are diagnosed as non–small cell lung cancer (NSCLC), which is further classified into 3 main histologies: adenocarcinoma, squamous cell carcinoma, and large cell carcinoma (Figure 2). Squamous NSCLC (which is closely associated with tobacco use) is a particularly aggressive form of lung cancer, for which there is a lack of effective and well-tolerated treatments.

Targeted Therapies for NSCLC

In recent years, a major paradigm shift has occurred in the management of NSCLC because of advances in the understanding of differences in therapeutic outcomes between tumors of squamous versus nonsquamous histology and the identification of driver mutations that can be targeted with novel agents.

Historically, patients with advanced NSCLC were treated with a platinum-based doublet chemotherapy without regard to histology. However,
in a phase 2 trial of bevacizumab, a monoclonal antibody against the vascular endothelial growth factor, a prohibitive rate of life-threatening pulmonary hemorrhages occurred in the subpopulation of patients with squamous histology.\textsuperscript{8} Consequently, patients with squamous histology were excluded from subsequent trials of bevacizumab, and the drug is approved by the FDA only for the treatment of nonsquamous NSCLC.\textsuperscript{7}

Advances in the treatment of patients with NSCLC over the past decade have largely involved the development of therapies directed at molecular targets such as mutations in the epidermal growth factor receptor (EGFR) gene or ALK rearrangements.\textsuperscript{8}

**Small-Molecule EGFR Inhibitors**

In 2004, insight was gained when treatment with the small-molecule tyrosine kinase inhibitor (TKI) gefitinib was associated with superior efficacy in a subgroup of patients with NSCLC whose tumors had certain mutations (ie, deletion of exon 19 or the L858R point mutation of exon 21) in the kinase domain of the EGFR gene.\textsuperscript{9,10} Mutations in EGFR are present in 10\% to 17\% of patients with NSCLC from a European background and are more common in women, patients who have never smoked, those of Asian heritage, and those with adenocarcinoma.\textsuperscript{11-14} Personalized therapy for patients whose tumors have activating EGFR mutations has resulted in better survival outcomes in these biologically selected subgroups.\textsuperscript{15} Currently, the EGFR TKIs are the standard of care for patients with locally advanced or metastatic NSCLC harboring activating EGFR mutations. A list of the TKIs targeting the EGFR that have been approved by the FDA is shown in Table 1.

Gefitinib was approved for marketing in May 2003 for patients with NSCLC under accelerated approval regulations that allow products to be approved on the basis of a surrogate end point for clinical efficacy. For gefitinib, the surrogate end point was tumor response rate. The response rate in patients taking the drug was approximately 10\%. The approved indication was for the treatment of patients who were refractory to chemotherapy (both a platinum drug and docetaxel). However, since the initial approval of gefitinib, erlotinib was approved based on the presence of EGFR at high levels appears to predict a good response to erlotinib. In the second trial in patients with stage III NSCLC, after completion of induction and consolidation chemotherapy and radiation therapy, patients were randomized to gefitinib maintenance therapy or placebo. No gefitinib survival benefit could be demonstrated.\textsuperscript{16}

In a randomized, open-label study (N = 174) conducted in Europe, the safety and efficacy of erlotinib as monotherapy were compared with standard platinum-based doublet chemotherapy (cisplatin plus gemcitabine, cisplatin plus docetaxel, carboplatin plus gemcitabine, or carboplatin plus docetaxel) for the first-line treatment of patients with metastatic NSCLC containing EGFR exon 19 deletions or exon 21 (L858R) substitution mutations. The median progression-free survival (PFS) of patients treated with erlotinib was 10.4 months compared with 5.2 months in the control group (hazard ratio [HR], 0.34; 95\% CI, 0.23-0.49; P < .001). The median OS of patients treated with erlotinib was 22.9 months compared with
In a randomized, multicenter, open-label study (N = 345), the efficacy and safety of afatinib were compared with pemetrexed/cisplatin chemotherapy in the first-line treatment of patients with EGFR mutation–positive, metastatic NSCLC. The median PFS of patients treated with afatinib was 11.1 months compared with 6.9 months in the control group (HR, 0.58; 95% CI, 0.43-0.78; \( P < .001 \)).

The median OS of patients treated with afatinib was 28.1 months compared with 28.2 months in the control group (HR, 0.91; 95% CI, 0.66-1.25; \( P = .55 \)).

Another study was conducted to evaluate the efficacy of afatinib in 96 patients with EGFR-mutant metastatic NSCLC with acquired resistance to erlotinib or gefitinib. Among the 86 patients evaluable for efficacy, the response rate was 11.6%, with a median PFS of 3.9 months and a median OS of 7.3 months. The authors concluded that these results showed that afatinib has only modest efficacy in a real-life population of patients with EGFR-mutant NSCLC with acquired resistance to erlotinib or gefitinib.

**Small-Molecule ALK Inhibitors**

More recently, another molecular abnormality, the ALK gene, that drives NSCLC in a different group of patients has been found in 2% to 8% of all patients with NSCLC, predominantly in young (\( \leq 50 \) years of age), never/former smokers with adenocarcinoma.\(^ {11-13,20,21} \) ALK rearrangements most often consist of a chromosome 2 inversion leading to a fusion with the EML4 gene, result-

19.5 months in the control group (HR, 0.93; 95% CI, 0.64-1.35) (Figure 3).\(^ {17} \)

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ing in the abnormal expression and activation of this tyrosine kinase in the cytoplasm of cancer cells. Two small-molecule ALK inhibitors are currently approved for the treatment of ALK-positive metastatic NSCLC (Table 2).

In a randomized, multicenter, open-label, active-controlled study (N = 347), the efficacy and safety of crizotinib as monotherapy were compared with chemotherapy (pemetrexed or docetaxel) for the treatment of patients with metastatic ALK-positive NSCLC who had been treated previously with 1 platinum-based chemotherapy regimen. The median PFS of patients treated with crizotinib was 7.7 months compared with 3.0 months in the chemotherapy group (HR, 0.49; 95% CI, 0.37-0.64; P < .001). The median OS of patients treated with crizotinib was 20.3 months compared with 22.8 months in the chemotherapy group (HR, 1.02; 95% CI, 0.68-1.54; P = .54) (Figure 4).

The efficacy of ceritinib was established in a multicenter, single-arm, open-label clinical study (N = 163) in patients with metastatic ALK-positive NSCLC who progressed while receiving, or were intolerant to, crizotinib. The major efficacy outcome measure was objective response rate (ORR) according to RECIST v1.0 as evaluated by both investigators and a blinded independent central review committee (BIRC). The ORR by investigator assessment was 54.6%, including 1.2% complete responses (CRs); the ORR by BIRC assessment was 43.6%, including 2.5% CRs. The median duration of response was 7.4 months by investigator assessment and 7.1 months by BIRC assessment.

**Monoclonal Antibodies**

Another strategy for treating NSCLC is the use of monoclonal antibodies to target angiogenesis (Table 3).

### Table 2 Small-Molecule ALK Inhibitors Approved by the FDA for the Treatment of Patients with NSCLC

<table>
<thead>
<tr>
<th>Targeted Agent</th>
<th>Target(s)</th>
<th>Approved Indication for NSCLC</th>
<th>Year of Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crizotinib</td>
<td>ALK, MET, ROS1, RON</td>
<td>Treatment of patients with metastatic NSCLC whose tumors are ALK positive as detected by an FDA-approved test</td>
<td>2011</td>
</tr>
<tr>
<td>Ceritinib</td>
<td>ALK</td>
<td>Treatment of patients with ALK-positive metastatic NSCLC who have progressed on, or are intolerant to, crizotinib</td>
<td>2014 (This indication is approved under accelerated approval based on tumor response rate and duration of response. An improvement in survival or disease-related symptoms has not been established.)</td>
</tr>
</tbody>
</table>

NSCLC indicates non–small cell lung cancer; RON, récepteur d'origine nantais; ROS1, proto-oncogene receptor tyrosine kinase.

![Figure 4](median_os_data_from_the_crizotinib_study_in_patients_with_metastatic_alk-positive_nsc_22.png)

**Figure 4 Median OS Data from the Crizotinib Study in Patients with Metastatic ALK-Positive NSCLC**

In a randomized, active-controlled, open-label, multicenter study (N = 878), the safety and efficacy of bevacizumab plus paclitaxel/carboplatin were compared with paclitaxel/carboplatin alone as first-line treatment of patients with locally advanced, metastatic, or recurrent nonsquamous NSCLC. The median OS was 12.3 months in the group treated with bevacizumab plus paclitaxel/carboplatin and 10.3 months in the control group (HR, 0.80; 95% CI, 0.68-0.94; P = .013) (Figure 5).

In another randomized, double-blind, placebo-controlled, 3-arm study (N = 1043), the safety and efficacy of bevacizumab (7.5 or 15.0 mg/kg) plus cisplatin/gemcitabine were compared with placebo plus cisplatin/
LUNG CANCER

**Table 3** Monoclonal Antibodies Approved by the FDA for the Treatment of Patients with NSCLC

<table>
<thead>
<tr>
<th>Targeted Agent</th>
<th>Target</th>
<th>Approved Indication for NSCLC</th>
<th>Year of Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab</td>
<td>VEGF</td>
<td>First-line treatment of patients with unresectable, locally advanced, recurrent, or metastatic, nonsquamous NSCLC in combination with carboplatin and paclitaxel</td>
<td>2004</td>
</tr>
<tr>
<td>Ramucirumab</td>
<td>VEGFR2</td>
<td>In combination with docetaxel, for treatment of metastatic NSCLC with disease progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving ramucirumab</td>
<td>2014</td>
</tr>
</tbody>
</table>

NSCLC indicates non–small cell lung cancer; VEGF, vascular endothelial growth factor; VEGFR2, VEGF receptor 2.

**Figure 5**

Median OS Data from the First-Line Bevacizumab Study in Patients with Locally Advanced, Metastatic, or Recurrent Nonsquamous NSCLC

<table>
<thead>
<tr>
<th>Median OS (Months)</th>
<th>Hazard Ratio</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab plus Paclitaxel/Carboplatin (n = 434)</td>
<td>12.3</td>
<td>0.80</td>
</tr>
<tr>
<td>Paclitaxel/Carboplatin (n = 444)</td>
<td>10.3</td>
<td></td>
</tr>
</tbody>
</table>

NSCLC indicates non–small cell lung cancer; OS, overall survival.

gemcitabine as first-line treatment of patients with locally advanced, metastatic, or recurrent nonsquamous NSCLC. PFS, the main efficacy outcome measure, was significantly higher in both bevacizumab groups compared with the control group; for the bevacizumab 7.5-mg/kg group, the HR was 0.75 (95% CI, 0.62-0.91; P = 0.0026); and for the bevacizumab 15.0-mg/kg group, the HR was 0.82 (95% CI, 0.68-0.98; P = .0301). The addition of bevacizumab to cisplatin/gemcitabine chemotherapy failed to demonstrate an improvement in the duration of OS, an additional efficacy outcome measure; for the bevacizumab 7.5-mg/kg group, the HR was 0.93 (95% CI, 0.78-1.11; P = .4203); and for the bevacizumab 15.0-mg/kg group, the HR was 1.03 (95% CI, 0.86-1.23; P = .7613).

In a multinational, randomized, double-blind study, 1253 patients with NSCLC who had disease progression on or after 1 platinum-based therapy for locally advanced or metastatic disease were randomized 1:1 to receive either ramucirumab plus docetaxel or placebo plus docetaxel. The median OS of patients treated with ramucirumab plus docetaxel was 10.5 months compared with 9.1 months in the control group (HR, 0.86; 95% CI, 0.75-0.98; P = .024). The median PFS of patients treated with ramucirumab plus docetaxel was 4.5 months compared with 3.0 months in the control group (HR, 0.76; 95% CI, 0.68-0.86; P <.001) (Figure 6).

**Unmet Need Despite Targeted Therapies**

Despite these targeted therapies, the OS in patients with metastatic disease continues to be poor, and the majority of patients with NSCLC are not candidates for these therapies. Patients with EGFR mutations or ALK rearrangements represent only a small percentage of the total population with NSCLC; thus, alternative treatment options are needed to improve the prognosis for patients with lung cancer.

**Immunotherapeutic Approaches**

Various immunotherapeutic options are being investigated in clinical studies. One approach is checkpoint inhibition, a strategy that involves “taking the brakes off” the immune system by blocking natural mechanisms that serve to limit the immune response. One checkpoint inhibitor, nivolumab, was approved by the FDA on March 4, 2015, for the treatment of patients with metastatic squamous NSCLC that had progressed on or after platinum-based chemotherapy. A number of other checkpoint inhibitors, including pembrolizumab, MPDL3280A, MEDI4736, ipilimumab, and tremelimumab, are...
under investigation. Another strategy is the use of therapeutic vaccines, such as MAGE-A3, PRAME, tecemotide, TG4010, epidermal growth factor vaccine, ratcemomab, and belagenpumatucel-L. Immunotherapy is starting to deliver promising results in lung cancer clinical trials, but it will be important to determine if immunotherapies are most effective when used alone or in combination with other agents.

**References**


FDA Approves Opdivo (Nivolumab) for the Treatment of Patients with Previously Treated Metastatic Squamous Non–Small Cell Lung Cancer

Bristol-Myers Squibb Company announced that the Food and Drug Administration (FDA) has approved Opdivo (nivolumab) injection, for intravenous use, for the treatment of patients with metastatic squamous non–small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy. Opdivo is the first and only PD-1 (programmed death-1) therapy to demonstrate overall survival (OS) in previously treated metastatic squamous NSCLC. Opdivo demonstrated significantly superior OS versus docetaxel, with a 41% reduction in the risk of death (hazard ratio, 0.59; 95% CI, 0.44-0.79; \( P = .00025 \)), in a prespecified interim analysis of a phase 3 clinical trial. The median OS was 9.2 months in the Opdivo arm (95% CI, 7.3-13.3) and 6 months in the docetaxel arm (95% CI, 5.1-7.3).

Opdivo is the first and only PD-1 therapy to demonstrate overall survival in previously treated metastatic squamous NSCLC. Opdivo demonstrated significantly superior overall survival versus docetaxel...

"Bristol-Myers Squibb is committed to patients with lung cancer, and we are pleased to offer Opdivo as the first immuno-oncology therapy for patients who have previously treated metastatic squamous NSCLC," said Lamberto Andreotti, Chief Executive Officer, Bristol-Myers Squibb. "Because lung cancer is one of the most commonly diagnosed cancers in the United States, with high mortality, there is a significant need for treatments that extend survival. We're thankful to the many patients and healthcare providers that partnered with us to develop a new treatment that has the potential to address that unmet need."

This approval is the second for Opdivo in the United States within 3 months and is based on the results of CheckMate -017 and CheckMate -063.

Opdivo is associated with immune-mediated pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, hypothyroidism and hyperthyroidism, other adverse reactions; and embryofetal toxicity.

Proven Superior Survival vs Standard of Care in a Phase 3 Clinical Trial

CheckMate -017 was a landmark phase 3, open-label, randomized, multinational, multicenter clinical trial that evaluated Opdivo (3 mg/kg intravenously over 60 minutes every 2 weeks) (\( n = 135 \)) versus standard of care, docetaxel (75 mg/m\(^2\) intravenously administered every 3 weeks) (\( n = 137 \)), in patients with metastatic squamous NSCLC who had progressed during or after prior platinum doublet-based chemotherapy regimen. This trial included patients regardless of their PD-L1 (programmed death ligand 1) status. The primary end point of this trial was OS.

In January, the trial was stopped based on an assessment conducted by the Independent Data Monitoring Committee, which concluded that the study met its end point, demonstrating superior OS in patients receiving Opdivo compared with docetaxel. The prespecified interim analysis was conducted when 199 events (86% of the planned number of events for final analysis) were observed (86 in the Opdivo arm and 113 in the docetaxel arm).

Opdivo is the only FDA-approved monotherapy to demonstrate proven superior OS compared with standard of care in more than 15 years in previously treated metastatic squamous NSCLC. The median OS was 9.2 months in the Opdivo arm (95% CI, 7.3-13.3) and 6 months in the docetaxel arm (95% CI, 5.1-7.3). The hazard ratio was 0.59 (95% CI, 0.44-0.79; \( P = .00025 \)). This hazard ratio translates to a 41% reduction in the
risk of death with Opdivo compared with docetaxel.

“The FDA approval of Opdivo introduces an entirely new treatment modality that has demonstrated unprecedented results for the treatment of previously treated metastatic squamous NSCLC, with the potential to replace chemotherapy for these patients,” said Suresh Ramalingam, MD, Professor and Director of Medical Oncology, Winship Cancer Institute of Emory University. “This milestone brings to fruition the long-held hope that immuno-oncology medicines can be significantly effective in this difficult-to-treat population.”

About the CheckMate -063 Trial and the Safety Profile of Opdivo

The safety profile of Opdivo in squamous NSCLC was established in CheckMate -063, a phase 2, single-arm, open-label, multinational, multicenter trial of Opdivo administered as a single agent in patients with metastatic squamous NSCLC who had progressed after receiving a platinum-based therapy and at least 1 additional systemic treatment regimen (n = 117). Patients received 3 mg/kg of Opdivo administered intravenously over 60 minutes every 2 weeks. This trial included patients regardless of their PD-L1 status. The most common adverse reactions (reported in ≥20% of patients) were fatigue (50%), dyspnea (38%), musculoskeletal pain (36%), decreased appetite (35%), cough (32%), nausea (29%), and constipation (24%). Serious adverse reactions occurred in 59% of patients receiving Opdivo. The most frequent serious adverse reactions reported in ≥2% of patients were dyspnea, pneumonia, chronic obstructive pulmonary disease exacerbation, pneumonitis, hypercalcemia, pleural effusion, hemoptysis, and pain. Opdivo was discontinued due to adverse reactions in 27% of patients. Twenty-nine percent of patients receiving Opdivo had a drug delay for an adverse reaction.

With at least 10 months of minimum follow-up for all patients, the confirmed objective response rate, the study's primary end point, was 15% (17/117) (95% CI, 9.9-22), of which all were partial responses. The median time to onset of response was 3.3 months (range, 1.7-8.8 months) after the start of Opdivo treatment. Seventy-six percent of Opdivo responders (13/17 patients) had ongoing responses with durability of response ranging from 1.9+ to 11.5+ months; 10 of these 17 patients (59%) had durable responses of 6 months or longer.

“The approval of Opdivo for the treatment of previously treated metastatic squamous non–small cell lung cancer is a major advancement in delivering extended survival for patients fighting this deadly disease,” said Andrea Ferris, President and Chairman, LUNGevity Foundation. “We are very excited for an immuno-oncology therapy to enter the market and offer options and hope for many of our patients. I applaud the FDA and Bristol-Myers Squibb for their work in making this important and first-of-its-kind treatment available to patients so quickly.”

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July 24-25, 2015
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Immuno-Oncology Combination Approaches for Lung Cancer

With the advent of new immunotherapeutic agents, including checkpoint inhibitors that target the programmed death-1 (PD-1) pathway and the cytotoxic T-lymphocyte antigen 4 (CTLA-4) pathway, investigations are being conducted to elucidate the potential combination of various therapies and their possible synergistic activity with chemotherapy.

Immune checkpoint blockade with monoclonal antibodies directed at the inhibitory immune receptors PD-1 (or one of its ligands, PD-L1) or CTLA-4 are showing some promise in clinical trials as monotherapy; however, there is evidence suggesting that these agents may be more effective as part of a combination regimen.1

In addition to CTLA-4 and PD-1/PD-L1, numerous other immunomodulatory targets have been identified preclinically, many with corresponding therapeutic antibodies that are being investigated in clinical trials.2 The majority of these targets are T-cell surface receptors, but targets in other immunologic cell populations are being investigated. For example, natural killer (NK) cells express killer immunoglobulin-like receptors (KIRs), which bind human leukocyte antigen class I molecules on target cells, thereby delivering an inhibitory signal preventing NK cell–mediated cytotoxicity. Anti-KIR antibodies may release these inhibitory KIR-mediated signals, thereby enabling tumor cytotoxicity and immune clearance.3 Another checkpoint protein target is lymphocyte activation gene 3 (LAG-3), a CD4-related inhibitory receptor coexpressed with PD-1.2 In animal models, inhibition of LAG-3 by a monoclonal antibody slowed the growth of established tumors, and it caused synergistic tumor regression when combined with an anti–PD-1 antibody.1 Dual checkpoint blockade strategies, such as those combining anti–CTLA-4, anti–PD-L1, anti–LAG-3, or anti-KIR, are being tested to increase the proportion and durability of tumor responses.

Clinical studies in NSCLC are exploring the dual T-cell checkpoint blockade with anti–CTLA-4 or anti–PD-L1 combined with anti-KIR or anti–LAG-3.

Dual Checkpoint Blockade

Some of the current clinical studies exploring the dual T-cell checkpoint blockade with anti–CTLA-4 and anti–PD-L1 are listed in Table 1.

Lirilumab, a fully human monoclonal antibody to KIR, in combination with nivolumab, has demonstrated an early efficacy signal in preclinical models.2 A trial of nivolumab with lirilumab in human solid tumors is under way, including 32 patients with non–small cell lung cancer (NSCLC).4 A similar trial is testing the combination of lirilumab with ipilimumab, accruing up to 20 patients with NSCLC in a dose-expansion cohort.5 Ongoing NSCLC clinical studies exploring the dual T-cell checkpoint blockade with anti–CTLA-4 or anti–PD-L1 combined with anti-KIR or anti–LAG-3 are listed in Table 2.

Checkpoint Blockade plus Targeted Therapy

In a study of 125 patients with NSCLC, including 56 (44.8%) whose tumors had epidermal growth factor re-
COMBINATION TREATMENTS

Table 1  Clinical Trials of Dual T-Cell Checkpoint Blockade (Anti–CTLA-4 plus Anti–PD-1/PD-L1) in Lung Cancer

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Patient Population</th>
<th>Study Phase</th>
<th>ClinicalTrials.gov Identifier</th>
<th>Estimated Study Completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab (anti–PD-1 mAb) alone or combined with ipilimumab (anti–CTLA-4 mAb)</td>
<td>Patients with advanced or metastatic SCLC</td>
<td>Phase 1/2 study</td>
<td>NCT01928394</td>
<td>March 2017</td>
</tr>
<tr>
<td>MEDI4736 (anti–PD-L1 mAb) alone (in NSCLC patients with PD-L1–positive tumors) or in combination with tremelimumab (anti–CTLA-4 mAb) (in NSCLC patients with PD-L1–negative tumors)</td>
<td>Patients with locally advanced or metastatic NSCLC (stage IIIB/IV) who have received ≥2 prior systemic treatment regimens, including 1 platinum-based chemotherapy regimen, and do not have known EGFR tyrosine activating mutations or ALK rearrangements</td>
<td>Phase 3 study (ARCTIC)</td>
<td>NCT02352948</td>
<td>September 2017</td>
</tr>
<tr>
<td>Tremelimumab (anti–CTLA-4 mAb) + MEDI4736 (anti–PD-L1 mAb)</td>
<td>Patients with advanced solid tumors, including NSCLC</td>
<td>Phase 1 study</td>
<td>NCT01975831</td>
<td>December 2016</td>
</tr>
<tr>
<td>Tremelimumab (anti–CTLA-4 mAb) + MEDI4736 (anti–PD-L1 mAb)</td>
<td>Patients with advanced NSCLC</td>
<td>Phase 1/2 study</td>
<td>NCT02000947</td>
<td>January 2018</td>
</tr>
</tbody>
</table>

CTLA-4 indicates cytotoxic T-lymphocyte antigen 4; EGFR, epidermal growth factor receptor; mAb, monoclonal antibody; NSCLC, non–small cell lung cancer; PD-1, programmed death-1; PD-L1, PD-1 ligand 1; SCLC, small cell lung cancer.

Table 2  Clinical Trials of Dual Checkpoint Blockade (Anti–CTLA-4 or Anti–PD-L1 plus Anti–KIR or Anti–LAG-3) in Lung Cancer

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Patient Population</th>
<th>Study Phase</th>
<th>ClinicalTrials.gov Identifier</th>
<th>Estimated Study Completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab (anti–PD-L1 mAb) + lirilumab (anti–KIR mAb)</td>
<td>Patients with advanced solid tumors, including NSCLC</td>
<td>Phase 1 study</td>
<td>NCT01714739</td>
<td>October 2017</td>
</tr>
<tr>
<td>Ipilimumab (anti–CTLA-4 mAb) + lirilumab (anti–KIR mAb)</td>
<td>Patients with advanced solid tumors, including NSCLC</td>
<td>Phase 1 study</td>
<td>NCT01750580</td>
<td>March 2016</td>
</tr>
<tr>
<td>Nivolumab (anti–PD-L1 mAb) + BMS-986016 (anti–LAG-3 mAb)</td>
<td>Patients with select advanced (metastatic and/or unresectable) solid tumors, including NSCLC</td>
<td>Phase 1 study</td>
<td>NCT01968109</td>
<td>May 2018</td>
</tr>
</tbody>
</table>

CTLA-4 indicates cytotoxic T-lymphocyte antigen 4; KIR, killer immunoglobulin-like receptor; LAG-3, lymphocyte activation gene 3; mAb, monoclonal antibody; NSCLC, non–small cell lung cancer; PD-L1, programmed death-1 ligand 1.

Receptor (EGFR) mutations, 29 (23.2%) with KRAS-mutated tumors, 10 (8.0%) with ALK translocations, and 30 (24.0%) whose tumors were EGFR/KRAS/ALK wild type (triple negative); PD-1/PD-L1 expression was assessed by immunohistochemistry. PD-1 positivity (+) was significantly associated with current smoking status (P = .02) and with the presence of KRAS mutations (P = .006), whereas PD-L1+ was significantly associated...
with adenocarcinoma histology ($P = .005$) and with the presence of $EGFR$ mutations ($P = .001$). Among the 95 patients treated with gefitinib or erlotinib (both $EGFR$ tyrosine kinase inhibitors [TKIs]), 49 patients (51.6%) were positive for PD-L1 expression. They achieved a significantly higher response rate (61.2% vs 34.8%; $P = .01$), a significantly longer time to progression (11.7 vs 5.7 months; $P < .0001$), and longer overall survival (OS; 21.9 vs 12.5 months; $P = .09$) compared with PD-L1–negative patients. In the subset of 55 patients with $EGFR$-mutated tumors treated with $EGFR$ TKIs, those who were PD-L1 positive (70.9%) showed a longer time to progression (13.0 vs 8.5 months; $P = .011$). The OS was 29.5 months in PD-L1–positive patients compared with 21.0 months in PD-L1–negative patients. However, no differences were identified in PD-1–positive versus PD-1–negative patients. These results suggest that PD-L1 expression is correlated with $EGFR$ mutation and support a rationale for checkpoint inhibitors combined with $EGFR$ TKIs in patients with $EGFR$-mutant NSCLC. Studies investigating this and other combinations of checkpoint inhibitors and targeted therapies are listed in Table 3.

One study is combining the anti–PD-L1 antibody MEDI4736 with the $EGFR$ TKI gefitinib; another study is evaluating MPDL3280A in combination with erlotinib.

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Patient Population</th>
<th>Study Phase</th>
<th>ClinicalTrials.gov Identifier</th>
<th>Estimated Study Completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEDI4736 (anti–PD-L1 mAb) + gefitinib (EGFR TKI)</td>
<td>Patients with NSCLC</td>
<td>Phase 1 study</td>
<td>NCT02088112</td>
<td>October 2017</td>
</tr>
<tr>
<td>Nivolumab (anti–PD-L1 mAb) + EGF816 (EGFR TKI) in patients with $EGFR$-mutated NSCLC and nivolumab (anti–PD-L1 mAb) + INC280 (MET inhibitor)</td>
<td>Previously treated patients with NSCLC</td>
<td>Phase 2 study</td>
<td>NCT02323126</td>
<td>August 2017</td>
</tr>
<tr>
<td>MPDL3280A (anti–PD-L1 mAb) in combination with erlotinib (EGFR TKI)</td>
<td>Patients with NSCLC</td>
<td>Phase 1b study</td>
<td>NCT02013219</td>
<td>August 2016</td>
</tr>
</tbody>
</table>

EGFR indicates epidermal growth factor receptor; mAb, monoclonal antibody; NSCLC, non–small cell lung cancer; PD-L1, programmed death-1 ligand 1; TKI, tyrosine kinase inhibitor.

One study is combining the anti–PD-L1 antibody MEDI4736 with the $EGFR$ TKI gefitinib; another study is evaluating MPDL3280A in combination with erlotinib.

Ipilimumab, a fully human monoclonal antibody that specifically blocks the binding of CTLA-4 to its ligands (CD80/CD86), was approved by the FDA for the treatment of unresectable or metastatic melanoma in 2011. Ipilimumab is being investigated in combination with the EGFR TKI erlotinib or the small molecule ALK inhibitor crizotinib.

The anti–CTLA-4 antibody tremelimumab is being studied in combination with the $EGFR$ TKI gefitinib in an open-label phase 1 study. The biologic rationale for such a study is that even though the disease is progressing, it is likely that $EGFR$-sensitive clones, although diminished under the pressure from the $EGFR$ TKI, are still present. Therefore, withdrawing the inhibitory pressure of the $EGFR$ TKI can potentially allow regrowth of the $EGFR$-sensitive cells. On the other hand, the proliferation of $EGFR$-resistant clones needs to be suppressed by another therapeutic approach. Therefore, the combination of gefitinib with immune checkpoint
COMBINATION TREATMENTS

### Table 4
Clinical Trials of Anti–CTLA-4 Checkpoint Blockade plus EGFR TKI–Targeted Therapy in Lung Cancer

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Patient Population</th>
<th>Study Phase</th>
<th>ClinicalTrials.gov Identifier</th>
<th>Estimated Study Completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab (anti–CTLA-4 mAb) + erlotinib (EGFR TKI) or crizotinib (small molecule ALK inhibitor)</td>
<td>Patients with EGFR- or ALK-mutated stage IV NSCLC</td>
<td>Phase 1b study with expansion cohorts</td>
<td>NCT01998126</td>
<td>December 2016</td>
</tr>
<tr>
<td>Tremelimumab (anti–CTLA-4 mAb) + gefitinib (EGFR TKI)</td>
<td>Previously treated NSCLC patients who have documented evidence of an activating mutation in the EGFR gene and have failed treatment with an EGFR inhibitor such as erlotinib or gefitinib</td>
<td>Phase 1 study</td>
<td>NCT02040064</td>
<td>January 2018</td>
</tr>
</tbody>
</table>

CTLA-4 indicates cytotoxic T-lymphocyte antigen 4; EGFR, epidermal growth factor receptor; mAb, monoclonal antibody; NSCLC, non–small cell lung cancer; TKI, tyrosine kinase inhibitor.

### Table 5
Clinical Trials of Checkpoint Blockade plus Targeted Therapy in Lung Cancer

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Patient Population</th>
<th>Study Phase</th>
<th>ClinicalTrials.gov Identifier</th>
<th>Estimated Study Completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab (anti–PD-L1 mAb) and afatinib (ALK and HER2 inhibitor)</td>
<td>Patients with NSCLC with resistance to erlotinib</td>
<td>Phase 1 study</td>
<td>NCT02364609</td>
<td>December 2018</td>
</tr>
<tr>
<td>Study assessing the efficacy of various sequences of either a small molecule gefitinib (EGFR TKI), AZD9291 (small molecule MET inhibitor), or selumetinib (small molecule MEK inhibitor) + docetaxel, or tremelimumab (anti–CTLA-4 mAb) followed by MEDI4736 (anti–PD-L1 mAb)</td>
<td>Patients with locally advanced or metastatic NSCLC (stage IIIb/IV)</td>
<td>Phase 2 study</td>
<td>NCT02179671</td>
<td>November 2017</td>
</tr>
<tr>
<td>Nivolumab (anti–PD-L1 mAb) + ceritinib (small molecule ALK inhibitor)</td>
<td>Patients with ALK-positive NSCLC</td>
<td>Phase 1 study</td>
<td>NCT02393625</td>
<td>June 2017</td>
</tr>
<tr>
<td>Nivolumab (anti–PD-L1 mAb) + varlilumab (anti–CD27 mAb)</td>
<td>Patients with advanced refractory NSCLC</td>
<td>Phase 1/2 study</td>
<td>NCT02335918</td>
<td>January 2020</td>
</tr>
</tbody>
</table>

CTLA-4 indicates cytotoxic T-lymphocyte antigen 4; EGFR, epidermal growth factor receptor; mAb, monoclonal antibody; NSCLC, non–small cell lung cancer; PD-L1, programmed death-1 ligand 1; TKI, tyrosine kinase inhibitor.

Blockade is very attractive and may result in clinical benefit in NSCLC with mutated EGFR. Examples of ongoing clinical studies combining anti–CTLA-4 antibodies with EGFR TKI–targeted therapy are listed in Table 4.

**Additional Studies of Checkpoint Blockade plus Targeted Therapy**

Numerous other studies are under way investigating various combinations of checkpoint inhibitors and targeted therapies (Table 5). Among these is a study com-
Combination Treatments

Combining the recently approved anti-PD-L1 molecular antibody nivolumab with varlilumab, a fully human monoclonal antibody that targets CD27, a critical molecule in the activation pathway of lymphocytes.

Some studies are investigating more complex interventions that involve not only checkpoint blockade and targeted therapy, but also chemotherapy.

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Patient Population</th>
<th>Study Phase</th>
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<tbody>
<tr>
<td>Pembrolizumab (anti–PD-L1 mAb) in combination with chemotherapy or immunotherapy (ie, paclitaxel, carboplatin, bevacizumab [VEGF mAb], pemetrexed, ipilimumab [anti–CTLA-4 mAb], erlotinib [EGFR TKI], gefitinib [EGFR TKI])</td>
<td>Patients with NSCLC</td>
<td>Phase 1/2 study (KEYNOTE-021)</td>
<td>NCT02039674</td>
<td>June 2019</td>
</tr>
<tr>
<td>Nivolumab (anti–PD-L1 mAb) alone or in combination with gemcitabine/cisplatin, pemetrexed/cisplatin, carboplatin/paclitaxel, bevacizumab (VEGF mAb) maintenance, erlotinib (EGFR TKI), or ipilimumab (anti–CTLA-4 mAb)</td>
<td>Patients with stage IIIB/IV NSCLC</td>
<td>Phase 1 study (CheckMate 012)</td>
<td>NCT01454102</td>
<td>November 2017</td>
</tr>
<tr>
<td>MPDL3280A (anti–PD-L1 mAb) in combination with carboplatin + paclitaxel with or without bevacizumab (VEGF mAb)</td>
<td>Patients with stage IV nonsquamous NSCLC</td>
<td>Phase 3 study</td>
<td>NCT02366143</td>
<td>August 2022</td>
</tr>
</tbody>
</table>

Table 6: Clinical Trials of Checkpoint Blockade plus Targeted Therapy plus Chemotherapy in Lung Cancer

CTLA-4 indicates cytotoxic T-lymphocyte antigen 4; EGFR, epidermal growth factor receptor; mAb, monoclonal antibody; NSCLC, non–small cell lung cancer; PD-L1, programmed death-1 ligand 1; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

Some studies are investigating more complex interventions that involve not only checkpoint blockade and targeted therapy, but also chemotherapy.

**Checkpoint Blockade plus Targeted Therapy plus Chemotherapy**

Some studies are investigating more complex interventions that involve not only checkpoint blockade and targeted therapy, but also chemotherapy (Table 6).

**Immunotherapy plus Chemotherapy**

The rationale for the use of immunotherapy in association with chemotherapy is based on the assumption that tumor-specific antigen released during chemotherapy-induced tumor necrosis may increase tumor-specific immunity and therefore enhance the immunotherapeutic efficacy. This hypothesis may explain the trend in favor of the sequential association of ipilimumab and chemotherapy in comparison with the concurrent association as highlighted in the phase 2 ipilimumab study reported below.

**Ipilimumab plus Chemotherapy**

Ipilimumab was investigated in a randomized, double-blind, phase 2 study that assessed the monoclonal antibody in combination with first-line chemotherapy in patients with advanced NSCLC (stage IIIB/IV) or extensive-stage small cell lung cancer (SCLC). Patients were randomized 1:1:1 to receive paclitaxel/carboplatin with either placebo or ipilimumab in 1 of 2 alternative regimens, concurrent ipilimumab (ipilimumab plus paclitaxel/carboplatin followed by placebo plus paclitaxel/carboplatin) or phased ipilimumab (placebo plus paclitaxel/carboplatin followed by ipilimumab plus paclitaxel/carboplatin). Treatment was administered intra-
venously every 3 weeks for 18 weeks. Eligible patients continued ipilimumab or placebo every 12 weeks as maintenance therapy. Tumor response was assessed via modified World Health Organization (mWHO) criteria and an immune-related response criteria to account for immune-related changes on scans. The primary end point was immune-related progression-free survival (irPFS). Other end points were progression-free survival (PFS), best overall response rate (BORR), immune-related BORR (irBORR), OS, and safety. The results for NSCLC and SCLC were reported separately.9,10

Results for the 204 patients with chemotherapy-naive NSCLC showed that the study met its primary end point of improved irPFS for phased ipilimumab versus the control (hazard ratio [HR], 0.72; \( P = .05 \)), but not for concurrent ipilimumab (HR, 0.81; \( P = .13 \)).9 Phased ipilimumab also improved PFS according to mWHO criteria (HR, 0.69; \( P = .02 \)). Phased ipilimumab, concurrent ipilimumab, and control treatments were associated with a median irPFS of 5.7, 5.5, and 4.6 months, respectively, a median PFS of 5.1, 4.1, and 4.2 months, respectively, an irBORR of 32%, 21%, and 18%, respectively, a BORR of 32%, 21%, and 14%, respectively, and a median OS of 12.2, 9.7, and 8.3 months (Figure 1A). Results from a subgroup analysis indicated a greater benefit to patients with squamous cell histology (HR, 0.55) than in patients with nonsquamous histology (HR, 0.82) in the group who received the phased schedule; however, in the group that received the concurrent schedule, differences in irPFS versus that in the control arm were similar between squamous and nonsquamous subsets (HRs, 0.85 and 0.77, respectively). Overall rates of grade 3/4 immune-related adverse events (AEs) were 15%, 20%, and 6% for phased ipilimumab, concurrent ipilimumab, and control, respectively. Two patients (concurrent, 1 patient; control, 1 patient) died of treatment-related toxicity.

Results for the 130 patients with chemotherapy-naive extensive-disease SCLC showed that phased ipilimumab, but not concurrent ipilimumab, improved irPFS versus control (HR, 0.64; \( P = .030 \)).10 No improvement was seen in PFS (HR, 0.93; \( P = .37 \)) or OS (HR, 0.75; \( P = .13 \)). Phased ipilimumab, concurrent ipilimumab, and control, respectively, were associated with median irPFS of 6.4, 5.7, and 5.3 months; median PFS of 5.2, 3.9, and 5.2 months; median OS of 12.9, 9.1, and 9.9 months (Figure 1B). Overall rates of grade 3/4 immune-related AEs were 17%, 21%, and 9% for phased ipilimumab, concurrent ipilimumab, and control, respectively.

Ongoing clinical studies of ipilimumab in combination with chemotherapy are listed in Table 7.

### Pembrolizumab plus Chemotherapy

Ongoing clinical studies of pembrolizumab in combination with chemotherapy are listed in Table 8.

### Nivolumab plus Chemotherapy

A phase 2 trial of nivolumab given after “epigenetic priming” with the chemotherapy drugs azacitidine and entinostat in patients with recurrent metastatic...
COMBINATION TREATMENTS

Table 7 Clinical Trials of Ipilimumab Immunotherapy plus Chemotherapy in Lung Cancer

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Patient Population</th>
<th>Study Phase</th>
<th>ClinicalTrials.gov Identifier</th>
<th>Estimated Study Completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab (anti–CTLA-4 mAb) + paclitaxel and carboplatin vs placebo + paclitaxel and carboplatin</td>
<td>Patients with squamous NSCLC</td>
<td>Phase 3 study</td>
<td>NCT01285609</td>
<td>December 2016</td>
</tr>
<tr>
<td>Ipilimumab (anti–CTLA-4 mAb) + paclitaxel and carboplatin vs placebo + paclitaxel and carboplatin</td>
<td>Patients with squamous NSCLC</td>
<td>Phase 3 study</td>
<td>NCT02279732</td>
<td>September 2019</td>
</tr>
<tr>
<td>Ipilimumab (anti–CTLA-4 mAb) + etoposide and platinum therapy vs etoposide and platinum therapy alone</td>
<td>Patients with extensive-stage SCLC</td>
<td>Phase 3 study</td>
<td>NCT01450761</td>
<td>March 2017</td>
</tr>
<tr>
<td>Ipilimumab (anti–CTLA-4 mAb) + carboplatin and etoposide chemotherapy</td>
<td>Patients with extensive-stage SCLC</td>
<td>Phase 2 study (ICE)</td>
<td>NCT01331525</td>
<td>May 2015</td>
</tr>
<tr>
<td>Standard treatment (chemotherapy and radiotherapy) alone vs standard treatment followed by ipilimumab (anti–CTLA-4 mAb)</td>
<td>Patients with limited-stage SCLC</td>
<td>Phase 2 study</td>
<td>NCT02046733</td>
<td>April 2020</td>
</tr>
</tbody>
</table>

CTLA-4 indicates cytotoxic T-lymphocyte antigen 4; mAb, monoclonal antibody; NSCLC, non–small cell lung cancer; SCLC, small cell lung cancer.

Table 8 Clinical Trials of Pembrolizumab Immunotherapy plus Chemotherapy in Lung Cancer

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Patient Population</th>
<th>Study Phase</th>
<th>ClinicalTrials.gov Identifier</th>
<th>Estimated Study Completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboplatin, nab-paclitaxel, and pembrolizumab (anti–PD-L1 mAb)</td>
<td>Previously untreated patients with advanced NSCLC</td>
<td>Phase 1/2 study</td>
<td>NCT02382406</td>
<td>November 2018</td>
</tr>
<tr>
<td>Pembrolizumab (anti–PD-L1 mAb) in combination with cisplatin/pemetrexed or carboplatin/paclitaxel</td>
<td>Patients with advanced NSCLC</td>
<td>Phase 1 study (KEYNOTE-011)</td>
<td>NCT01840579</td>
<td>June 2016</td>
</tr>
</tbody>
</table>

mAb indicates monoclonal antibody; NSCLC, non–small cell lung cancer; PD-L1, programmed death-1 ligand 1.

NSCLC and a phase 1 safety study of nivolumab plus nab-paclitaxel/carboplatin chemotherapy are under way (Table 9).

**MPDL3280A plus Chemotherapy**

The anti–PD-L1 molecular antibody MPDL3280A is being investigated in combination with chemotherapy in both squamous and nonsquamous NSCLC (Table 10). In one study, the MPDL3280A/chemotherapy combination is being studied both with and without the vascular endothelial growth factor–targeted antibody bevacizumab.

**Concluding Remarks**

With the advent of new immunotherapeutic agents, new options are available to patients with NSCLC. Although these agents are still under investigation,
they appear to have promising results—albeit in a minority of patients. Combinatorial strategies, including with novel immune checkpoint inhibitors, targeted agents, and chemotherapy, are undergoing investigation, and toxicity and efficacy results from these studies will help define the optimal role for immune-based therapeutics in NSCLC.

Table 9  Clinical Trials of Nivolumab Immunotherapy plus Chemotherapy in Lung Cancer

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Patient Population</th>
<th>Study Phase</th>
<th>ClinicalTrials.gov Identifier</th>
<th>Estimated Study Completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epigenetic priming with azacitidine and entinostat or oral azacitidine alone prior to nivolumab (anti–PD-L1 mAb)</td>
<td>Patients with recurrent metastatic NSCLC</td>
<td>Phase 2 study</td>
<td>NCT01928576</td>
<td>August 2015</td>
</tr>
<tr>
<td>Nivolumab (anti–PD-L1 mAb) plus nab-paclitaxel, and carboplatin</td>
<td>Patients with stage IIB/IV NSCLC</td>
<td>Phase 1 safety study</td>
<td>NCT02309177</td>
<td>July 2018</td>
</tr>
</tbody>
</table>

mAb indicates monoclonal antibody; NSCLC, non–small cell lung cancer; PD-L1, programmed death-1 ligand 1.

Table 10  Clinical Trials of MPDL3280A Immunotherapy plus Chemotherapy in Lung Cancer

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Patient Population</th>
<th>Study Phase</th>
<th>ClinicalTrials.gov Identifier</th>
<th>Estimated Study Completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPDL3280A (anti–PD-L1 mAb) in combination with carboplatin + nab-paclitaxel</td>
<td>Patients with non–squamous NSCLC</td>
<td>Phase 3 study</td>
<td>NCT02367781</td>
<td>July 2018</td>
</tr>
<tr>
<td>MPDL3280A (anti–PD-L1 mAb) in combination with carboplatin + paclitaxel or carboplatin + nab-paclitaxel vs carboplatin + nab-paclitaxel</td>
<td>Patients with stage IV squamous NSCLC</td>
<td>Phase 3 study</td>
<td>NCT02367794</td>
<td>February 2023</td>
</tr>
<tr>
<td>MPDL3280A (anti–PD-L1 mAb) in combination with carboplatin + paclitaxel with or without bevacizumab (VEGF mAb)</td>
<td>Patients with stage IV nonsquamous NSCLC</td>
<td>Phase 3 study</td>
<td>NCT02366143</td>
<td>August 2022</td>
</tr>
</tbody>
</table>

mAb indicates monoclonal antibody; NSCLC, non–small cell lung cancer; PD-L1, programmed death-1 ligand 1.

References
PD-L1: Promising MIUC Therapy for cNAC Nonresponders

There's hope for patients with muscle-invasive urothelial carcinoma (MIUC) who do not respond to cisplatin-based neoadjuvant chemotherapy (cNAC). According to data presented at the 2015 Genitourinary Cancers Symposium, patients with MIUC who are nonresponders to cNAC fare worse than patients undergoing radical cystectomy (RC) alone, but both groups exhibited similar rates of programmed death ligand 1 (PD-L1) positivity.

“Our results demonstrate that nonresponders to cNAC exhibit frequent PD-L1 tumoral staining,” noted Jen-Jane Liu, MD, Instructor of Urology at the Johns Hopkins School of Medicine in Baltimore, MD. “This suggests that neoadjuvant or adjuvant anti–PD-L1 therapy represents an attractive treatment alternative in MIUC patients whose tumors do not respond to cisplatin-based chemotherapy or in patients who cannot tolerate the therapy.”

As Liu explained, the 5-year cancer-specific survival (CSS) for nonresponders to cNAC is poor (27%) compared with the CSS in MIUC patients treated with RC alone (50%).

“The response rate to cNAC is 40% to 50%,” she reported, “which means that less than half of MIUC patients will benefit from cNAC. However, alternative systemic therapies are lacking.”

PD-L1 Shows Promise

According to Liu, anti–PD-L1 therapy has shown promising results in tumors with proven PD-L1 expression, including advanced-stage MIUC, by suppressing the immune response via T cells. To test the hypothesis that anti–PD-L1 therapy is a rational therapeutic option for patients nonresponsive to cNAC, researchers evaluated PD-L1 expression in MIUC in a cohort categorized by pathologic response to cNAC.

“We studied 150 patients who received cNAC followed by open radical cystectomy from 2000 to 2013,” said Liu. “Pathologic response (<pT1 N0 at RC) and CSS were compared to patients who had RC without cNAC.”

Tissue microarrays of MIUC specimens representing patients with and without response to cNAC were stained with PD-L1 and FOXP3, a marker for regulatory T cells, which help downregulate the immune system. A blinded pathologist then scored the degree of tumoral PD-L1 and tumoral lymphocyte FOXP3 staining. The primary outcome of the study was to determine the percentage of nonresponders to cNAC staining positive for PD-L1. Tumors with 5% and >15/hpf staining were considered positive for PD-L1 and FOXP3, respectively.

“Overall PD-L1 positivity was 38% (25 of 68) in patients receiving cNAC,” Liu observed, “and approximately 40% of both responders and nonresponders to cNAC were PD-L1 positive” (42% vs 37%, respectively).

As Liu noted, the similar rates of positivity between the 2 groups suggest that this mechanism is a potential therapeutic target for patients with MIUC.

PD-L1 also positively corresponded to FOXP3 positivity on tumor lymphocytes, implying that tumoral PD-L1 acts to circumvent the immune system by downregulating the T-cell immune response.

For Liu and colleagues, these findings indicate that anti–PD-L1 therapy could be effective in settings other than metastatic disease and is a reasonable therapeutic consideration for patients who do not respond to cNAC.

“It's worthy of prospective clinical trial testing,” she concluded. “Further studies are needed to evaluate the efficacy of anti–PD-L1 therapy in this context.”

Anti–PD-L1 therapy has shown promising results in tumors with proven PD-L1 expression, including advanced-stage MIUC, by suppressing the immune response via T cells.
Renal Cell Carcinoma Roundup

Immune checkpoint inhibitors show promise

A new class of cancer therapies has set its sights on immune checkpoints. A trio of studies presented at the 2015 Genitourinary Cancers Symposium offered a glimpse into the evolving landscape of treatment for metastatic renal cell carcinoma (mRCC), and the programmed death ligand 1 (PD-L1) and its receptor, programmed death-1 (PD-1), were primary targets.

The first study, presented by Brian I. Rini, MD, Associate Professor of Medicine at the Cleveland Clinic Taussig Cancer Institute in Cleveland, OH, attempted to show the association of PD-1 and PD-L1 protein expression in matched primary and mRCC tumors. As Rini noted, expression of PD-1 and PD-L1 on tumor and infiltrating immune cells in patients with mRCC is associated with a higher response to drugs inhibiting this pathway. However, these associations have been made based on primary tumor expression, whereas therapy is directed against metastatic deposits.

This study consisted of patients with mRCC and metastases who had undergone resection of both the primary and at least 1 metastatic tumor. Samples were evaluated for PD-1 and PD-L1 expression by immunohistochemistry.

“Fifty matched primary and metastatic RCC tissue sets were analyzed with 48 evaluable matched pairs,” reported Rini. PD-1 scores greater than 3 (considered positive) were detected in 9 primary tumors (18%) and 9 metastatic sites (18%). PD-L1 scores greater than 3 were detected in 9 primary tumors (18%) and 12 metastatic sites (24%).

“The expression of PD-1 and PD-L1 in primary clear cell RCC tumors is correlated with metastatic site expression,” concluded Rini, “although there is a substantial percentage of tumors with discordance.”

MPDL3280A plus Bevacizumab

Mario Sznol, MD, Professor of Medicine at Yale School of Medicine in New Haven, CT, presented the second study, a multicenter, phase 1b evaluation of anti-PD-L1 antibody MPDL3280A in combination with bevacizumab in patients with mRCC.

“The combination of MPDL3280A plus bevacizumab was well tolerated in clear cell mRCC patients,” noted Sznol, “and promising preliminary clinical activity and immune modulation of the tumor microenvironment were observed.”

As Sznol explained, MPDL3280A, a human anti-PD-L1 antibody engineered to remove Fc-effector function, prevents PD-L1 binding to the inhibitory receptors PD-1 and B7.1 on activated T cells. Bevacizumab was postulated to enhance the antitumor effects of MPDL3280A by blocking suppressive effects related to the vascular endothelial growth factor (VEGF) on immune function and lymphocyte traffic.

For this study, 10 patients with mRCC with clear cell histology and available pre-treatment tumor specimens were enrolled. Bevacizumab 15 mg/kg was given alone on cycle 1 day 1 and concurrently with MPDL3280A 20 mg/kg every 3 weeks thereafter. On-treatment tumor biopsy was performed during cycle 1 and 4 to 6 weeks after the start of cycle 2. The median duration of treatment for MPDL3280A was 288 days.

“Grade 3 to 4 adverse events included postoperative wound infection, hypercalcemia, tumor pain, acute respiratory failure in a patient with influenza (1 patient each), and hypertension (3 patients),” Sznol reported, but “no grade 3 to 4 adverse events were assessed as related to MPDL3280A.”

Among first-line mRCC patients with ≥1 tumor assessment (n = 10), the objective response rate was 40% at the time of data cutoff.

Bevacizumab was postulated to enhance the antitumor effects of MPDL3280A by blocking suppressive effects related to the vascular endothelial growth factor on immune function and lymphocyte traffic.

MPDL3280A treatment has been shown to increase CD8+ immune cell infiltration as well as expression levels of immune genes. Additionally, activated CD8+ T cells have been shown to transiently increase in blood (peaking at cycle 2) during treatment with MPDL3280A. Increases in immune activity were also detected in patients with mRCC receiving MPDL3280A plus bevacizumab.

A phase 2 trial of MPDL3280A with or without bev-
acizumab versus sunitinib in patients with previously untreated mRCC is ongoing.

**Efficacy of Targeted Therapies After PD-1/PD-L1 Inhibitors**

Finally, a multi-institution retrospective cohort, presented by Laurence Albiges, MD, Institut Gustave Roussy, Villejuif, France, sought to show the efficacy of targeted therapies after treatment with PD-1/PD-L1 inhibitors in patients with mRCC.

For this study, medical records of RCC patients treated with investigational PD-1 or PD-L1 inhibitors who received subsequent treatment with targeted therapies were reviewed in 4 institutions.

“This is the first report of targeted therapy efficacy after PD-1/PD-L1 inhibition,” noted Albiges. “In this selected population, median time to treatment failure [TTF] suggests a sustained benefit of both VEGF receptor [VEGFR] tyrosine kinase inhibitors [TKIs] and mTOR inhibitors after PD-1/PD-L1 inhibition.”

For this study, medical records of RCC patients treated with investigational PD-1 or PD-L1 inhibitors who received subsequent treatment with targeted therapies were reviewed in 4 institutions. Baseline characteristics at the time of subsequent therapy and outcome data including TTF, best response, and 1- and 2-year overall survival (OS) were retrospectively collected.

“Of the 99 patients who received PD-1/PD-L1 inhibitors,” Albiges reported, “56 patients have received a subsequent therapy after PD-1/PD-L1 blockade, while 7 patients are still on therapy, and 26 patients did not receive subsequent therapy. Among these 26 patients, 12 died of disease and 14 are still alive off systemic therapies.”

Forty-three patients received VEGFR TKIs and 13 received mTOR inhibitors as first subsequent targeted therapy. Median TTF was 6.6 months (range, 0.2-23.0), and was 6.9 and 5.7 months in patients who received VEGFR TKIs and mTOR inhibitors, respectively. One-year and 2-year OS from the initiation of subsequent targeted therapy was 58% and 36%, respectively.

Investigator-assessed best response to subsequent targeted therapy was evaluated in 53 of 56 patients. Partial response was found in 13% of patients (n = 7), stable disease in 62% (n = 33), and progressive disease in 25% (n = 13).

“Targeted therapy with VEGF and mTOR inhibitors may have significant activity after discontinuation of PD-1/PD-L1 inhibitors,” concluded Albiges, “but the potential sustained effect of PD-1/PD-L1 inhibitors after therapy discontinuation needs to be further characterized.”

---

**Cell Cycle Progression Test Impacts Treatment Decisions**

The cell cycle progression (CCP) test has the power to alter treatment decisions. Results from a prospective registry of newly diagnosed patients with prostate cancer showed that the CCP risk score led to an increase (12%) or decrease (31%) in actual treatment administered in 44% of patients, according to data presented at the 2015 Genitourinary Cancers Symposium.

“In this interim analysis,” said Neal Shore, MD, Medical Director for the Carolina Urologic Research Center in Myrtle Beach, SC, “the CCP risk assessment score had a significant impact in helping physicians and patients reach consensus on an appropriate personalized treatment decision, often with major reductions in interventional treatment burden.”

According to Shore, the CCP test is a validated molecular assay that assesses risk of prostate cancer-specific disease progression and mortality when combined with standard clinicopathologic parameters. Translated into the field at large, this can help deal with the pressing concerns of overdetection and overtreatment of prostate cancer that is unlikely to progress or metastasize.

“Because prostate cancer is a heterogeneous disease,”
said Shore, “adding novel prognostic markers like [the CCP score]...is a long-awaited step forward in making treatment decisions that match an individual’s cancer aggressiveness.”

PROCEDE-1000 is a prospective registry designed to evaluate the impact of the CCP test on personalizing prostate cancer treatment. It’s also the largest clinical utility trial to date for a genomic assay.

As Shore explained, the study enrolled 816 untreated patients diagnosed within the past 6 months with clinically localized prostate adenocarcinoma. One hundred five physicians in 20 states recorded their initial therapy recommendation (pre-CCP) on the first questionnaire. The CCP test was then conducted on prostate biopsy tissue.

“Three post-CCP questionnaires recorded the physician’s revised treatment recommendation, physician/patient treatment decision, and actual treatment administered,” Shore detailed. “Changes in treatments between the pre-CCP and post-CCP questionnaires demonstrated the impact of CCP testing on treatment decisions at each stage.”

The results were impressive.

“Visual analog scale measurements indicated a significant increase (P = .0125) in the physician’s likelihood of recommending noninterventional treatment post-CCP test,” said Shore. “There was an increase in active surveillance from the initial interventional therapy recommendation.”

From pre-CCP therapy recommendation, the CCP score led to a change in actual treatment administered in 44% of patients, with 72% of these changes being reductions in treatment. Reductions occurred in the following procedures: radical prostatectomy (27%), radiation therapy (44% primary; 56% adjuvant), brachytherapy (46% interstitial; 66% high-dose rate), and hormonal therapy (33% neoadjuvant; 68% concurrent).

Notably, for every 1-unit increase in mortality risk, researchers discovered an associated 3.3% rise in the odds of increase in treatment and a 3.3% drop in the odds of decrease in treatment.

PROCEDE-1000 is a prospective registry designed to evaluate the impact of the CCP test on personalizing prostate cancer treatment. It’s also the largest clinical utility trial to date for a genomic assay.

Whereas 35.9% of patients were recommended for conservative management pre-CCP testing, there was a 6.5% increase in noninterventional treatments during actual follow-up. Overall, however, there was a significant reduction in the number of treatment options at each successive evaluation (P < .0001).

“Results to date are compelling evidence that this genomic assay biomarker, when coupled with standard clinicopathologic parameters, can have a significant impact in personalizing treatment for men with localized prostate cancer,” Shore concluded. “Future analyses are likely to result in meaningful new insights about how patients and their providers use [CCP] to make treatment decisions.”

PROSTVAC plus Immune Checkpoint Inhibitors: Evidence of Improved Overall Survival in Prostate Cancer

The combination of active immunotherapy and immune checkpoint inhibitors shows signs of improved overall survival (OS) in patients with prostate cancer, according to data presented at the 2015 Genitourinary Cancers Symposium.

“The comparison of 3 independent trials of PROSTVAC active immunotherapy provides hypothesis-generating data that the addition of an immune checkpoint inhibitor may have a positive effect on OS through a potential synergy in mechanism of action,” said Harpreet
Singh, MD, a clinical research fellow at the National Cancer Institute, Bethesda, MD. “The updated long-term survival data are further evidence of improved OS with PROSTVAC.”

As Singh explained, the results of recent clinical trials have escalated interest in immunotherapy in oncology; a number of cancer immunotherapies have been approved recently, and others are in late-stage clinical development.

Ipilimumab, an approved immune checkpoint inhibitor in melanoma, is also being evaluated in a phase 3 trial in patients with chemotherapy-naive metastatic castration-resistant prostate cancer.

PROSTVAC, a poxvirus-based active immunotherapy, is currently under evaluation in a global, phase 3, randomized, placebo-controlled trial. Generally well tolerated, the vaccine expresses prostate-specific antigen (PSA) and 3 T-cell costimulatory molecules and has demonstrated evidence of clinical benefit in phase 1 and phase 2 studies. It is ready to use with minimal preparation and does not require blood cell collection from individual patients.

Ipilimumab, an approved immune checkpoint inhibitor in melanoma, is also being evaluated in a phase 3 trial in patients with chemotherapy-naive metastatic castration-resistant prostate cancer (mCRPC).

For this study, Singh compared the results of 2 phase 2 trials in men with mCRPC treated with PROSTVAC alone with results from a phase 1 combination study in mCRPC patients treated with PROSTVAC plus escalating doses of ipilimumab.

“In a multicenter phase 2 trial, 125 men were randomized 2:1 to receive PROSTVAC or placebo,” said Singh. “Patients treated with PROSTVAC had improved OS compared to placebo (25.1 vs 16.6 months; hazard ratio, 0.56; 95% CI, 0.37-0.85).”

Similar data were seen in a second phase 2 trial of PROSTVAC.

“Thirty-two patients with mCRPC had a median OS of 26.6 months,” said Singh, “when the predicted median OS by the Halabi nomogram was only 17.4 months.”

Combining Vaccines and Immune Checkpoint Inhibitors

In the phase 1 combination study conducted at the National Institutes of Health, 30 patients with mCRPC and similar baseline characteristics were treated with PROSTVAC plus escalating doses of ipilimumab. This study also produced encouraging results.

“The observed median OS was 31.3 months for all dose cohorts and 37.2 months for patients treated at 10 mg/kg based on updated overall survival data,” said Singh. “Again, treatment outperformed the predicted median OS of 18.5 months. Furthermore, there appears to be a tail on the curve with approximately 20% of patients at 10 mg/kg alive at 80 months.”

At this dosage, 73.3% of the patients were alive at 24 months. Fourteen of 24 patients (58%) who were chemotherapy-naive had a decline in their PSA, 6 of whom (25%) had a PSA decline >50%.

“The combination was well tolerated with not a lot of overlapping toxicity,” Singh concluded.

According to Singh, these data suggest that therapeutic vaccines may make T-cell–poor tumors into T-cell–inflamed tumors that are responsive to immune checkpoint inhibition. Future randomized trials are in development to prospectively evaluate this hypothesis.
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Best regards,

Lillie D. Shockney, RN, BS, MAS
Program Director, Academy of Oncology Nurse & Patient Navigators

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AONN+ is the largest national specialty organization dedicated to improving patient care and quality of life by defining, enhancing, and promoting the role of oncology nurse and patient navigators.
Among patients with advanced melanoma treated with immunotherapies, those whose tumors had NRAS mutations had better response and treatment outcomes than those whose tumors did not, according to new research.

Douglas B. Johnson, MD, and colleagues determined that 28% of patients with NRAS-mutant melanoma had complete or partial responses to various first-line immunotherapies, compared with 16% of those with wild-type NRAS (Cancer Immunol Res. 2015;3:288-295).

“In a retrospective study, we found that patients with NRAS-mutant melanoma seemed to respond better to immunotherapy compared with patients whose tumors had other genetic subtypes, and this was especially true for patients treated with anti–PD-1/PD-L1 therapies,” said Johnson.

The researchers evaluated the electronic medical records of 229 melanoma patients treated at Vanderbilt-Ingram Cancer Center, Memorial Sloan Kettering Cancer Center, and Massachusetts General Hospital. Patients were treated with ipilimumab (n = 143), interleukin-2 (n = 58), or inhibitors of programmed death 1 or its ligand (PD-1/PD-L1; n = 28).

The study sought to evaluate whether tumor genotype correlates with benefit from immune therapy in melanoma. The researchers identified NRAS mutations (n = 60), BRAF mutations (n = 53), and wild-type NRAS/BRAF status (n = 116) among the patients and compared clinical outcomes among these subsets.

**Responses Highest in NRAS-Mutant Tumors**

The NRAS-mutant cohort had superior or a trend toward superior outcomes compared with the other cohorts in terms of response to first-line immune therapy (28% vs 16%; P = .04); response to any line of immune therapy (32% vs 20%; P = .07); clinical benefit, that is, response plus stable disease ≥24 weeks (50% vs 31%; P <.01); and progression-free survival (median 4.1 vs 2.9 months; P = .09).

Benefit from anti–PD-1/PD-L1 therapy was particularly marked in patients with NRAS mutations, who had a clinical benefit rate of 73%, compared with 35% for NRAS wild-type patients. The researchers proposed these differences stemmed from the greater PD-L1 enrichment in NRAS-mutant tumors. NRAS-mutant tumors were more likely than wild-type tumors to demonstrate membrane staining ≥1% and staining ≥5%, “suggesting a potential mechanism for the clinical results,” the authors noted.

They noted “although only small numbers were treated, the clinical benefit rate was unexpectedly high with anti–PD-1 or anti–PD-L1, occurring in 8 of 11 patients with NRAS-mutant melanoma, compared with only 13 of 37 patients in the non–NRAS-mutant cohorts. This finding could have implications for molecular testing and treatment decision making and provides early insights into the complex relationship between tumor genetics and the immune response.”

“We studied a small group of patients, but the results were quite suggestive,” Johnson added.

The study, whose results need confirmation in a prospective trial, highlights the need to find predictive markers of response to immune therapies. “We are currently conducting studies to explain this finding,” he said. ◆

**Benefit from anti–PD-1/PD-L1 therapy was particularly marked in patients with NRAS mutations, who had a clinical benefit rate of 73%, compared with 35% for NRAS wild-type patients.**

NRAS Mutation Impacts Response to Immune Therapies in Melanoma

Douglas B. Johnson, MD

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"I want the country that eliminated polio and mapped the human genome to lead a new era of medicine, one that delivers the right treatment at the right time." So said the president of the United States in his State of the Union Address on January 20, 2015.

By calling attention to the promise of personalized medicine, the president underlined what has been the central contention of the Personalized Medicine Coalition for a decade: linking therapy to diagnostics and thereby targeting the right treatment to the right patient at the right time will lead to a paradigm shift in modern medicine, improving outcomes while lowering overall costs. To be sure, the road is long, opposition real, and the president’s proposed investment of $215 million in fiscal year 2016 relatively small, given the stakes and the opportunity.

But a closer look at the president’s Precision Medicine Initiative reveals its potentially transformative implications for the future of medicine. Even if small and only for 1 year, if Congress approves, the new program will transform the nature of the biomedical research enterprise, a fact not unnoted by the White House, which calls the initiative “a bold new research effort to revolutionize how we improve health and treat disease.”

In particular, the president wants to:

• Add $70 million to the budget of the National Cancer Institute (NCI) to study the genetic factors that cause cancer
• Add $10 million to the budget of the Food and Drug Administration (FDA) to develop new approaches for evaluating next-generation genetic tests
• Add $5 million to the budget of the Office of the National Coordinator for Health Information Technology to support the development of interoperability standards and requirements that address privacy and enable secure exchange of data across systems
• And, most importantly, add $130 million to the budget of the National Institutes of Health (NIH) to build a “voluntary national research cohort” of a million or more volunteers in order to better understand the etiology of health and disease.

According to the White House, “Most medical treatments,” as proponents of personalized medicine have argued for some time, “have been designed for the ‘average patient.’ As a result...treatments can be very successful for some patients but not for others.”

Advised by NIH Director Francis Collins, MD, PhD, and NCI Director Harold Varmus, MD, the president is proposing that we embark on a new era of discovery and delivery that places the individual at the center of his or her healthcare. It proposes creating, over time, a healthcare system that eschews one-size-fits-all, trial-and-error medicine in favor of a targeted approach that will deliver better results at a lower overall cost.

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What makes this vision possible and, in 2015, realistic, as Drs Collins and Varmus wrote in The New England Journal of Medicine for February 26, have been the creation of new methods of distinguishing among patients that include proteomics, metabolomics, genomics, and other molecular assays as well as computational tools that facilitate the development of large-scale databases, which can be used for research.

As they note, significant progress has already been made in understanding and therefore treating cancer as a genetic disease. The proposed additional investment in cancer research builds on ongoing success in developing targeted treatments.

With the declining cost of sequencing and the increased ability to integrate multipanel arrays to produce clearer and more informed analyses, diagnostics are becoming more sophisticated and important in the practice of medicine. Increasing investment, therefore, in regula-
tory science will help allow the FDA to keep up with a rapidly evolving field and thereby ensure that the new tests coming on the market are accurate and reliable.

Aggregating data from multiple sources provides a foundation for personalized medicine. Therefore, it also makes sense to invest in ensuring that those data can cross systems to inform treatment, as the president proposes.

But most importantly for the future of biomedical research is the proposed creation of, in Drs Collins and Varmus’ words, “a longitudinal ‘cohort’ of 1 million or more Americans who have volunteered to participate in research.” By collecting biological specimens, including DNA, combining them with environmental information, and linking the data to electronic medical records, researchers will finally have the instrument they need to understand individual variation. They will be able to ask the right questions and derive sophisticated answers that will produce individualized, and therefore more effective, treatments in the future.

Together, these 4 integrated programs put the federal government’s research agenda squarely on the side of finding the right treatment for the right patient at the right time. As the president said, “Something called precision medicine (in some cases, people call it personalized medicine) gives us one of the greatest opportunities for new medical breakthroughs that we have ever seen.”

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