

Clinical Trials Pushes the Treatment of Lung Cancer Forward

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NCCN Lists Duvelisib in Updated Clinical Practice Guidelines

Caroline Seymour

THE NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN) Clinical Practice Guidelines in Oncology has been updated to include duvelisib (Copiktra) as a category 2A designated option for second-line and subsequent treatment of patients with relapsed/refractory peripheral T-cell lymphoma (PTCL), regardless of intent to proceed to transplant.¹ “The NCCN guidelines provide a roadmap for treatment for patients with different diseases and they are useful for practicing community oncologists who may only see a few cases of different diseases every year. [The guidelines] bring [clini-

cians] up to date with the most recent references and the most recent recommendations that are evidence based. [The guidelines are] critical in terms of having some uniform pattern of treatment for our patients, especially when we have treatment algorithms that are highly effective for certain diseases,” Francine Foss, MD, professor of medicine, Yale School of Medicine, said in an interview with OncoLive®.

In October 2019, duvelisib, a dual PI3K-, inhibitor, received an orphan drug designation for the treatment of patients with T-cell lymphoma.² Duvelisib’s

orphan drug status succeeded its fast track designation, which was granted in September 2017 for patients with PTCL who have received at least 1 prior therapy.³

“[Because] duvelisib has not been approved yet for T-cell lymphoma, it’s not easy to get approval from payers. The fact that now duvelisib is listed in the NCCN guidelines can make things a little



FOSS

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Immunotherapy Continues to Touch All Areas of Lung Cancer Treatment

Caroline Seymour

ALTHOUGH TRIALS SUCH AS the phase 3 CheckMate 816 (NCT02998528) and POSEIDON (NCT03164616) studies are generating significant excitement for the future of neoadjuvant therapy and combination chemoimmunotherapy, respectively, it is the phase 3 IMPower010 trial (NCT02486718) that has made the largest splash in the field of non-small cell lung cancer (NSCLC), said David Spigel, MD.

“[IMpower010] is the biggest trial news because it led to a paradigm shift. Now we are talking about immunotherapy not just in advanced disease or unresect-

able stage III disease but in a curable setting of resected, stage II and III disease,” Spigel said in an interview with OncoLive® during an Institutional Perspectives in Cancer webinar on lung cancer, which he co-chaired.

In the interview, Spigel, chief scientific officer and director of the Lung Cancer Research Program and principal investigator at Sarah Cannon Research Institute, discussed the focus of each presentation, which centered on immunotherapy vs chemoimmunotherapy in the frontline metastatic setting, the surgical perspective of treatment in early-stage

NSCLC, best practices for molecular testing, and EGFR- and KRAS-targeted therapies for patients with advanced disease.

OncoLive®: What developments have been made with regard to frontline therapy for patients with advanced NSCLC without actionable genetic alterations?

Spigel: We had several great presentations at the Institutional Perspectives in



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bit easier for us,” Barbara Pro, MD, clinical director of the lymphoma program at the Herbert Irving Comprehensive Cancer Center at NewYork-Presbyterian/Columbia University Irving Medical Center, and a professor of medicine in the Department of Medicine and Division of Hematology/Oncology at Columbia University Vagelos College of Physicians and Surgeons, said in an interview with OncoLive®.

The agent is currently under study in patients with relapsed/refractory PTCL in the phase 2, open-label, multicenter PRIMO trial (NCT03372057), consisting of a dose-optimization and a dose-expansion phase.

Initial results of the dose-optimization phase (n = 33) demonstrated objective response rates (ORRs) of 54% and 35% in the 75-mg twice daily (n = 13) and 25-mg twice daily (n = 20) cohorts, respectively.

“The ongoing PRIMO trial, as well as an earlier phase 1/2 study shows high activity [with duvelisib] in T-cell lymphoma. We felt that the data were clinically significant enough that we should at least be able to offer this drug to our patients, so we did list it as one of the options for second-line therapy,” Foss said. “The significance of listing a drug in the guidelines is that it helps with third-party reimbursement, which is key for many of our patients, especially if there are high co-pays for some of these drugs. In addition, having it listed in the guidelines tells physicians that the drug is available and that the drug has activity.”

To be eligible for enrollment in the expansion phase, patients had to have histologically confirmed relapsed/refractory PTCL, measurable disease per International Working Group criteria, no prior history of allogeneic stem cell transplant or treatment with a PI3K inhibitor, and an ECOG performance status between 0 and 2.

Relapsed/refractory was defined such that patients had to have received at least 2 cycles of 1 prior regimen administered with curative intent and failed to achieve a partial response (PR) or better after at least 2 treatment cycles, or failed to achieve complete response (CR) after at least 6 treatment cycles, or progressed after initial response.

Based on the dose-optimization results, patients in the expansion phase receive duvelisib at 75 mg twice daily for 2 cycles. Patients who achieved CR, PR, or stable disease went on to receive 25 mg of duvelisib twice daily until progressive disease or unacceptable toxicity.

Disease response was evaluated by PET at the start of cycle 2 and every 2 months thereafter.

The primary end point was ORR by independent review committee assessment. Secondary end points included ORR by investigator assessment, duration of response (DOR), progression-free survival, overall survival (OS), disease control rate, and safety. All analyses consisted of patients who received at least 1 dose of duvelisib.

The median patient age was 66.5 years (range, 21-92), and approximately half of patients were male (52%). The median time from initial diagnosis was 2.74 years (range, 1.21-17.38).

Represented subtypes included PTCL not otherwise specified (n = 42; 53.8%), angioimmunoblastic T-cell lymphoma (n = 20; 29.6%), anaplastic large cell lymphoma (n = 11; 14.1%), and other (n = 4; 5.2%). The median number of prior therapies was 3 (range, 1-7).

In primary results of the expansion portion of the study, which included the first 6 months of data for 78 evaluable patients and were presented during the 2021 ASH Annual Meeting and Exposition, the agent demonstrated an ORR of 50% (n = 39), which also consisted of a CR rate of 32.1% (n = 25).⁴

The median time to response was 53 days (range, 15-114), and the median DOR was 233 days (range, 1+ to 420+).

At data cutoff, 82.1% (n = 64) of patients had discontinued treatment because of disease progression (n = 34; 43.6%), death (n = 4; 5.1%), transplant (n = 5; 6.4%), adverse effects (AEs; n = 14; 17.9%), and other (n = 7; 8.9%).

“This updated analysis continues to confirm the activity of duvelisib,” Pro said.

In terms of safety, any-grade treatment-emergent AEs (TEAEs) were infections (n = 31; 39.7%), colitis (n = 1; 1.3%), cutaneous reactions (n = 26; 33.3%), diarrhea (n = 20; 25.6%), neutropenia (n = 30; 38.5%), pneumonia (n = 2; 2.6%), pneumonitis (n = 2; 2.6%), and transaminitis elevation (n = 38; 48.7%).

Grade 3 or greater TEAEs were

infections (n = 9; 11.5%), cutaneous reactions (n = 6; 7.7%), diarrhea (n = 2; 2.6%), neutropenia (n = 17; 21.8%), pneumonia (n = 1; 1.3%), pneumonitis (n = 2; 2.6%), and transaminitis elevation (n = 21; 26.9%).

Alanine aminotransferase and aspartate aminotransferase elevations (n = 13) were the most common TEAEs leading to treatment discontinuation, followed by progressive disease (n = 3) and diarrhea (n = 2).

Serious TEAEs leading to death were pneumonitis, vascular dementia, suicide, pulmonary edema, Epstein-Barr virus-associated lymphoproliferative disorder, gastrointestinal hemorrhage, sepsis, febrile infection, infection, and disease progression.

“In our patients treated on the PRIMO trial, we have observed transaminitis, which is an expected and common toxicity with this class of drugs that we should try to pay attention to, because we need to stop the treatment or decrease the dose according to the guidelines,” Pro said.

“It’s important to recognize that patients with relapsed/refractory PTCL have a very poor prognosis, with an OS that is less than 6 months. A number of agents have been FDA approved for patients with this disease, but overall, the response rates have been quite modest, so targeting [the PI3K] pathway could be a very important strategy in this disease,” Pro concluded.

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Cancer webinar. My focus was on the state of affairs in the first-line setting for NSCLC and where we are at now with immunotherapy options and chemoimmunotherapy options in the first-line setting. I focused on our non-TKI targeted therapy options. We have a lot of regimens to choose from [in this setting]. Cemiplimab-rwlc [Libtayo] is a new PD-1 inhibitor that was FDA approved in the first-line setting as a monotherapy based on findings from the EMPOWER-Lung 1 trial [NCT03088540]. The study compared cemiplimab with platinum-doublet chemotherapy in patients with PD-L1 expression of 50% or higher. The results showed a survival advantage in the cemiplimab arm hence the FDA approval.

Now we have 3 monotherapies in the first-line setting with pembrolizumab [Keytruda], atezolizumab [Tecentriq], and cemiplimab. Each agent is approved for patients with high PD-L1 expression, and pembrolizumab is also approved for patients with PD-L1 expression of 1% to 49%.

In terms of chemotherapy combinations, the only thing that is new but not FDA approved yet is a regimen from the POSEIDON study. This was a trial that looked at a combination of dual immunotherapy with chemotherapy as first-line therapy. In the trial, patients with NSCLC with adenocarcinoma and squamous histologies were randomized to platinum-doublet chemotherapy, platinum-doublet chemotherapy with durvalumab [Imfinzi], which is a PD-L1 inhibitor, or platinum-doublet chemotherapy with durvalumab and tremelimumab, which is a CTLA-4 antibody. The take-home here is at the 2021 ESMO Congress we saw data presented by my partner, Melissa Johnson, MD, of Sarah Cannon Research Institute, showing a survival advantage for the 4-drug regimen compared with the platinum doublet. Will that lead to the FDA approval of that regimen? It seems like it should, but we don't have that approval yet.

Denis Gilmore, MD, of TriStar Medical Group, discussed the phase 3 CheckMate 816 and the IMpower010 trials. What has been most exciting about these studies?

Dr Gilmore is a thoracic surgeon I have the privilege of working with in Nashville. Dr Gilmore did a fantastic job summarizing 2 pivotal studies from this past year: the CheckMate 816 study and the IMpower010 study. The CheckMate 816 study evaluated preoperative chemoimmunotherapy, in this case, chemotherapy with nivolumab [Opdivo] in

patients with squamous and nonsquamous lung cancer that was deemed resectable, so stage 1B through stage IIIA disease. The IMpower010 study was an adjuvant trial, which evaluated patients with any histology of resected, early-stage lung cancer who received platinum-doublet chemotherapy where appropriate. Then, patients were randomized to 1 year of adjuvant atezolizumab or not.

CheckMate 816 was pivotal because it showed that pathologic complete response rates are significantly higher, approximately tenfold higher with chemoimmunotherapy vs just chemotherapy alone. Another interesting take-home is that operative outcomes don't appear to be negatively impacted by the introduction of immunotherapy. In fact, there's a suggestion or statistical improvement in the ability to do less surgery, so smaller surgeries, minimally invasive surgeries, and no worse outcomes with immunotherapy. This was a positive trial that hasn't yet led to an FDA approval. We did recently see a press release on disease-free survival [DFS] improvements with the nivolumab arm, so hopefully that will lead to an FDA approval.

The IMpower010 study did lead to an FDA approval recently. Patients with stage II to IIIA resected NSCLC with 1% or higher PD-L1 expression are now candidates for immunotherapy, because in that group in the study, there was a DFS advantage in favor of atezolizumab, which was the primary end point of the trial. Now, there's some caveats in that that benefit appears to be greatest or largely due to patients that have 50% or higher expression, but the approval is in patients with a PD-L1 expression level of 1% or higher. That's the biggest trial news because it led to a paradigm shift. Now we're talking about immunotherapy not just in advanced disease or unresectable stage III disease, but in a curable setting of resected, stage II and III disease.

Andrew McKenzie, PhD, of Sarah Cannon Research Institute, discussed testing for biomarkers. What mindset should be applied to molecular testing in NSCLC?

Dr McKenzie leads our personalized medicine program at Sarah Cannon Research Institute and is a fantastic colleague. I wouldn't add much else other than that everyone already appreciates, and that is the importance of testing. We certainly advocate for broad or comprehensive NGS [next-generation sequencing] testing in our patients with advanced disease, in this case, advanced NSCLC. I don't think that's limited to adenocarcinoma; testing should be done in squamous carcinoma, if for no other reason than to look for things

like MET exon 14 [skipping mutations], which you can see in squamous histology and even the rare things like RET and NTRK [alterations].

Ideally, the gold standard still is tissue, but if you can only [test] one thing, get whatever can be done that works for you, and largely that is turning into plasma-based testing. I recently met a woman with advanced disease, and [she and her family were] eager to get going [with treatment]. How do you make decisions based on somebody who has a new diagnosis? You need to know their molecular results, and the fastest way to get on that is plasma-based testing. That's become a standard

part of my workup with patients while tissue testing is cooking, and with that is PD-L1 testing.

Dr McKenzie gave a nice summary on that landscape of tissue- and blood-based testing, and they're not going away. We don't know a lot about how to use it, and understanding resistance mechanisms or minimal residual disease, but those are exciting emerging areas for everybody and likely will become new standards in the years to come. For now, we just kind of want to focus on getting testing done. There are so many markers, at least 8 that we want to know about in lung cancer. Knowing those will help guide the best treatment decisions for those patients.

Your co-chair, Melissa Johnson, MD, of Sarah Cannon Research Institute, shared insight into some of the more recently approved targeted therapies for patients with KRAS G12C mutations and EGFR exon 20 insertions. What has been learned about these agents in clinic since their approvals?

We're still talking about HER2, RET, and ROS alterations, and even sensitizing mutations in EGFR and what to do after [progression on standard therapy]. However, Dr Johnson's important message was that we had an FDA approval in 2021 in the treatment of KRAS G12C-mutant lung cancer with sotorasib [Lumakras], which selectively inhibits that genetic alteration, which can be found in plasma or tissue NGS testing. The agent is now approved for use in the refractory setting, so anything beyond first-line treatment, which often is chemoimmunotherapy based.

Sotorasib has an FDA approval now as an oral therapy for use in patients with KRAS G12C mutations, which speaks to the importance of testing and getting answers to try to be ready to use those therapies. We know sotorasib is associated with efficacy in the form of responses in about 40% to 50% of patients as well as extended durations of disease control that extend to



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a little bit under 1 year. Depending on the circumstance, some patients can get well beyond that, so that's a big story.

Dr Johnson talked also about another agent called adagrasib, which is an agent being developed that also is showing early promise in the same patient population. It's not yet FDA approved, but hopefully it will be soon.

The other big story has been in patients with EGFR exon 20 insertions. These molecular alterations can be found with NGS testing, and we know drugs like osimertinib [Tagrisso], which are ideal for patients with sensitizing mutations in exon 19 and 21 are not effective in exon 20 insertions although there has

been some data with high-dose osimertinib. The numbers are very small, but high-dose osimertinib may have benefit there. We have 2 FDA-approved drugs for patients with exon 20 insertions in EGFR: one is amivantamab-vmjw [Rybrevant], which is a bispecific antibody that targets EGFR and MET and then a TKI called mobocertinib [Ekivity], which is an oral agent. These 2 FDA-approved strategies are intravenous and oral, respectively, and are used in a post first-line setting, so a refractory setting in patients with EGFR exon 20 insertions, kind of like sotorasib's approval in KRAS G12C mutations.

These drugs are different; they aren't

the easiest to get used to administering. Amivantamab requires a stepped-up infusion, and specifically awareness of dealing with infusion-related reactions, which occur in just about everybody, so we are adjusting to that experience, including [that with] some pulmonary toxicity. Mobocertinib also has some unusual tolerability awareness that doctors need to get used to whether it's gastrointestinal or pulmonary in nature. The big take-home [message] is now we have 2 alterations, KRAS G12C and EGFR exon 20 insertions, for which a year ago we had no options. In terms of standards, now we have 3 and probably a forthcoming option, which is exciting.

A Wealth of Clinical Trials Pushes the Treatment Landscape Forward Across Lung Cancer

Ryan Scott

THE AVAILABILITY of chemoimmunotherapy regimens and dual checkpoint inhibition underscore the advances that have been made in immunotherapy options for patients with non-small cell lung cancer (NSCLC). Although these therapies have helped transform the treatment space, there is still potential for further improvement, according to David P. Carbone, MD, PhD.

"Immunotherapy has revolutionized the treatment of NSCLC, and, to a lesser degree, small cell lung cancer [SCLC]. We're getting long-term survivors that we've never seen before. [However,] the therapy is still far from perfect," Carbone said in an interview with OncLive® during an Institutional Perspectives in Cancer (IPC) webinar on lung cancer, which he chaired.

"There's a lot of room for improvement, with better matching of therapies, selecting [the right amount of therapy], and deciding who should get immunotherapy alone, combination immunotherapy, and combination chemoimmunotherapy," Carbone added.

In the interview, Carbone discussed the focus of each presentation, spanning the evolution of immunotherapy and targeted therapy in NSCLC and the importance of biomarker testing for personalized therapy. Carbone is a professor of internal medicine at The Ohio State University, the Barbara J. Bonner Chair

in Lung Cancer Research, co-leader of the Translational Therapeutics Program, and director of the Thoracic Oncology Center at The Ohio State University Comprehensive Cancer Center—James (OSUCCC—James).

OncLive®: You presented on the use of immunotherapy in lung cancer. How has immunotherapy carved out a role in patients with advanced NSCLC?

Carbone: [Immunotherapy] represents a new pillar of therapy available for treating patients with lung cancer. It started out in the second- and third-line [settings], and remarkably, it was better than available chemotherapies. It resulted in durable survival benefit, [extending several years].

These results appropriately moved [immunotherapy] to the frontline setting, in which it was shown to beat chemotherapy alone in many phase 3 trials. [Immunotherapy] is now the standard of care in the first line for non-driver mutant tumors. It is even being moved into early-stage disease in the perioperative setting.

You spoke about the phase 3 KEYNOTE-024 (NCT02142738), KEYNOTE-189 (NCT02578680), and KEYNOTE-407 (NCT02775435) trials, which all centered around pembrolizumab (Keytruda). How have data from these trials affected the treatment landscape?

[Pembrolizumab] totally transformed the landscape. Those were the definitive trials looking at immunotherapy in the first line, and they were all strongly positive studies.

I did point out that KEYNOTE-407 was less impressively positive, especially in [patients with] PD-L1-negative squamous [disease]. [However,] in the subset analysis, and in the overall analysis, [pembrolizumab] was still better than chemotherapy.

There has been a benefit with pembrolizumab in patients who have PD-L1 scores above 50%. How much of an indicator is PD-L1 in terms of making treatment decisions?

In adenocarcinomas, [PD-L1 status] may not be as important, in that chemoimmunotherapy is useful for all PD-L1 subsets. In my personal practice, in [patients with] high PD-L1, I use immunotherapy alone, without chemotherapy. In that respect, [PD-L1 status] important [when deciding to use pembrolizumab alone] in patients with adenocarcinoma and nonsquamous lung cancer.

In squamous [lung cancer], in KEYNOTE-407, [pembrolizumab plus chemotherapy] seemed to have an effect on patients with [high] PD-L1. In [patients who were] PD-L1 negative, the survival curves crossed, and there was no difference in the landmark survival past 2 years, which is disappointing because that's about one-third of the squamous patients. Even though squamous cell lung cancer is a smaller subset than nonsquamous, it's still a common diagnosis.

For the subset of patients with PD-L1-negative squamous cell lung cancer where

pembrolizumab and chemotherapy may not work, what other options would you consider?

In a subset analysis, the combination of ipilimumab [Yervoy] and nivolumab [Opdivo] showed a respectable threefold improvement in landmark survivals in PD-L1-negative squamous cell lung cancer. Unfortunately, it's not FDA approved in that setting. The same regimen with 2 cycles of chemotherapy is referred to as the [CheckMate 9LA (NCT03215706)] regimen, and that combination is approved for PD-L1-negative squamous cell lung cancer.

The benefit of the 2 cycles of chemotherapy is not entirely clear compared with the doublet immunotherapy regimen alone. The usage of that combination is not common. However, even with all those data, chemotherapy plus pembrolizumab is more frequently used.

What is the significance of the FDA approval of nivolumab and platinum-doublet chemotherapy for patients with resectable NSCLC in the neoadjuvant setting?

[Initial data] from the phase 3 CheckMate 816 trial [NCT02998528] showed remarkably high complete pathologic response rates with nivolumab and chemotherapy compared with chemotherapy alone. Those data are likely to transform the management of early-stage lung cancer.

Now we have approvals in the adjuvant and neoadjuvant settings with immunotherapy. They haven't been compared with each other [in a head-to-head trial], so we're forced to make cross-trial comparisons. In theory, the neoadjuvant approach may be better than the adjuvant approach. We will have to see what the data pan out to be and what the overall survival [OS] outcomes are down the road, but immunotherapy is here to stay in early-stage lung cancer.

In the phase 3 CheckMate 9LA trial, (NCT03215706), nivolumab and ipilimumab plus chemotherapy generated a benefit in patients with baseline brain metastases. What did those data suggest in terms of serving that population?

Brain metastasis is a huge problem in lung cancer. Most patients have brain metastases at some point in their [disease]. [Patients with brain metastases] have been a historically difficult-to-treat subset and have done worse than other subsets with chemotherapy. [Notably], the management with stereotactic radiation has aided that field.

We did a subset analysis of CheckMate 9LA looking at the outcomes of

patients with and without brain metastases. Remarkably, the chemotherapy control arm did far worse in patients with baseline brain metastases than patients without brain metastases, [meaning the addition of nivolumab and ipilimumab generated significant activity in these patients]. In the CheckMate 9LA treatment arm, the patients did about the same, whether they had brain metastases or not, in terms of OS. That is remarkable and implies significant brain activity [with nivolumab and ipilimumab plus chemotherapy].

Other parameters were impressive, [including] a doubling of the time to central nervous system [CNS] progression and the improvement in intracranial response rate with [nivolumab and ipilimumab plus chemotherapy]. There are signals that the combination may be active in the CNS. That has also been shown in melanoma, as well, so the results are consistent.

How important is biomarker testing in establishing individualized treatment for patients with lung cancer?

Biomarker testing, specifically testing for genetic drivers, is a crucial part of the workup for patients, especially those with nonsquamous lung cancer. The treatment and the optimal sequencing of therapies are completely different. The efficacy of immunotherapy in [patients with nonsquamous lung cancer] is low, except for the KRAS population, which seems to be about the same. The subset of BRAF-mutant tumors in patients who have smoked may respond to immunotherapy as well.

For the common drivers—EGFR, ALK, RET—those patients do better with first-line targeted therapies and may have more [adverse] effects [AEs] if [treatment] starts with immunotherapy and switches to a targeted therapy.

Many of the targeted therapies get into the CNS well. If you have a patient who has multiple asymptomatic brain metastases, especially in a non-smoker with a high likelihood of a driver mutation, we should do everything we can to avoid whole brain radiation until the genetics come back, because these patients are often effectively treated with systemic oral therapy and may completely avoid whole brain radiation. [These patients] may live for years on these targeted therapies, long enough to manifest the AEs and the long-term consequences of whole brain radiation. Doing reflexive whole brain radiation with multiple brain metastases in a [patient who has not undergone genotyping] is a huge mistake.

Your colleague, Erin M. Bertino, MD, of OSUCCC–James, discussed EGFR-mutant NSCLC. How has osimertinib (Tagrisso) affected the treatment landscape?

Some of the early drugs in that space, [including] gefitinib [Iressa], erlotinib [Tarceva], and afatinib [Gilotrif], had dramatic efficacy, but they were hampered by AEs, especially afatinib. Most patients couldn't tolerate the recommended dose of afatinib, and none of them got into the CNS very well, [which was problematic because] EGFR-mutant lung cancer often goes to the brain. Osimertinib is a selective inhibitor that had little EGFR wild-type effect. The toxicity was much less [than earlier-generation agents], and it got into the brain much better. It has [become] our standard of care in this space.

Kai He, MD, PhD, of OSUCCC–James, highlighted targeted therapy for NSCLC, including for ALK-positive disease. How has the emergence of ALK as a biomarker informed treatment decisions?

In a similar way to EGFR, ALK fusion-positive disease is effectively treated with the newer-generation drugs. Again, some of the older drugs, [such as] crizotinib [Xalkori] and ceritinib [Zykadia], had some activity. However, they were toxic, and the activity didn't last very long and didn't get into the brain well. Alectinib [Alecensa] gets into the brain well, has low toxicity, and recent data show a 65% 5-year OS rate. This is remarkable in metastatic disease when you consider that, historically, patients with metastatic disease had a 4- to 6-month survival. Now we're talking about more than half of patients [being] alive at 5 years. That's a major difference.

The activity [of alectinib] in the brain, similar to osimertinib, was a game changer. Half of patients treated with crizotinib would relapse in the brain within 2 years, whereas it's only 9% with alectinib. Some of the other agents in the field, [such as] brigatinib [Alunbrig] and lorlatinib [Lorbrena], have activity against some of the acquired resistance mutations to alectinib. We are doing resistance genotyping on these patients' tumors and picking second-line agents by virtue of the type of resistance mutation. These are patients where you want to avoid up-front whole brain radiation because of the efficacy of the newer-generation drugs in the brain.

The current management of SCLC was discussed by Asrar A. Alahmadi, MBBS, of OSUCCC–James. How has the space shifted?

When I was in training, SCLC was [previ-



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ously] the success story for lung cancer. We had an active regimen that resulted in responses in most patients, and survival went from 6 weeks to 12 months, and we thought that was great. Now, SCLC is the stepchild in lung cancer. NSCLC advances have outpaced those in SCLC.

We have some intriguing new therapies on the horizon. The addition of immunotherapy to chemotherapy in extensive-stage disease has made a definite advancement in the outcomes of patients. Better radiation therapy in limited-stage disease is improving outcomes in those patients.

We used to have common high-grade toxicities from radiation that now are

uncommon because of modern treatment-planning approaches. There are also new agents targeting various small-cell markers. For example, [the phase 2 TRINITY trial (NCT02674568)] used an antibody-drug conjugate [ADC] targeting DLL3, rovalpituzumab tesirine, that was not a huge success, mostly because of toxicity. There was a hint of activity, and now there are new ADCs and bispecific antibodies targeting DLL3 that are showing significant efficacy and may be part of our standard of care down the road.

There are other targets in SCLC that are being investigated. We are making progress in SCLC, but there's room for improvement.

Lurbinectedin (Zepzelca) has been tested as monotherapy and in combination in SCLC. What has been observed with this treatment?

Lurbinectedin is a chemotherapy, and it was found to be active in the second-line [setting] in SCLC therapy and represents a treatment option for our patients. We are now routinely using it in the clinic, and we're seeing significant activity.

It's not ideal. It has some toxicity, and the patients often progress after a few months. But in this population, any advance is welcome. Lurbinectedin is clearly an advance in chemotherapy for SCLC.

Systemic Advances Shine, But Multidisciplinary Approaches Remain at Core of Skin Cancer Treatment

Ashling Wahner

THE SKIN CANCER treatment landscape is evolving, with several new standards of care being introduced, including immunotherapy for basal cell carcinoma and checkpoint inhibitors such as the fixed-dose combination nivolumab plus relatlimab (Opdualag), explained Jason Luke, MD, FACP, who also emphasized the potential groundbreaking approval of tumor-infiltrating lymphocyte (TIL) therapy.

Although studies on these approaches have centered around skin cancer, they are opening the door for treatment in other tumor types, Luke added.

"It's very exciting to think about how [melanoma drug approvals] may be able to benefit more patients in the future of different cancer types," Luke said in an interview with OncoLive® following an Institutional Perspectives in Cancer webinar on melanoma, which he chaired.

In the interview, Luke, associate professor of medicine, director, Cancer Immunotherapeutics Center, Immunology and Immunotherapy Program, University of Pittsburgh Medical Center (UPMC) Hillman Cancer Center, reviewed key points from each presentation from the meeting and provided perspective on the practice-changing benefits of therapies moving into earlier lines of treatment. Luke also emphasized the importance of a multidisciplinary, team-

based approach in all stages of disease to provide quality patient care and support innovative treatment combinations.

OncoLive®: Starting with your presentation on basal cell carcinoma, what is important to know about the evolving treatment landscape in this space?

Luke: Basal cell carcinoma is an evolving space. We have had the use of hedgehog inhibitors for approximately the past 10 years. Hedgehog inhibitors are highly effective targeted therapies, albeit with a disadvantageous toxicity profile, such that more than half of patients end up stopping them because of adverse effects [AEs].

More recently, it's very exciting that we've had an approval of the PD-1 inhibitor cemiplimab-rwlc [Libtayo] as the first immunotherapy [agent] for basal cell carcinoma. That's a very attractive option, and the label is for patients who have progressed or were intolerant to hedgehog inhibitors. [That approval] is exciting because we know that many patients can benefit with durable control of their disease with immunotherapy.

All of this then sets up a future [question]: What about combinations of hedgehog inhibitors with immunotherapy? Those are the clinical trials that I

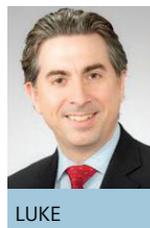
emphasized at the end of my talk, which are likely to get going within the next year or so.

Could you elaborate on some of those clinical trials that could be coming our way?

Clinical trials in basal cell carcinoma are really [in] two flavors right now. One is trying to optimize the use of hedgehog inhibitors [by evaluating] pulsatile dosing, sort of an on-off kind of an approach.

The other exciting approach would be the development of hedgehog inhibitors that are less toxic with or without anti-PD-1 immunotherapy. I've been working with a company called Endeavor [Biomedicines], which is developing a potential best-in-class hedgehog inhibitor called taladegib in PTCH1-mutant tumors, which would include basal cell carcinoma. We're also going to pursue a clinical trial combining that agent with anti-PD-1 immunotherapy, hoping to leverage the benefit of targeted inhibition of the hedgehog pathway along with the immunotherapy for long-term benefit.

Turning to the presentation given by John Kirkwood, MD, of UPMC Hillman Cancer Center, which focused on metastatic melanoma as the poster child for immunotherapy, have we seen the role of checkpoint inhibition grow within the



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advanced setting?

In the past couple of years, we've realized that the backbone of therapy for metastatic melanoma is immune checkpoint blockade, and several studies have shown this.

One study that has emphasized this is the DREAMseq trial [NCT02224781], which randomized patients to receive BRAF and MEK inhibition or [ipilimumab (Yervoy) and nivolumab (Opdivo)] as their first option. At the 2-year landmark, we observed a massive benefit to the [ipilimumab and nivolumab] combination such that the standard of care for metastatic melanoma really should be [a] checkpoint inhibitor and not BRAF inhibition in the frontline setting.

Also, we now have a third checkpoint inhibitor approved for melanoma. The combination of nivolumab and relatlimab received FDA approval [in March 2022], and that combination looks to be at least as potent as the combination of [ipilimumab and nivolumab], but with a much improved AE profile.

We're entering a space where the frontline treatment of metastatic melanoma should be dual checkpoint blockade. For many patients, that can be nivolumab and relatlimab as a high-benefit, low-toxicity [treatment].

I still plan to use [ipilimumab and nivolumab] in those patients who have very high-risk disease like brain metastases or liver metastases and high [lactate dehydrogenase (LDH)] because we have that long-term experience of knowing that [this regimen] can be an effective therapy for those patient populations.

What are your thoughts on the approval of relatlimab and nivolumab?

The approval of relatlimab in melanoma is a landscape shift for all of cancer. It shouldn't be underappreciated how big a deal this is. Essentially for anywhere that [anti-]PD-1 was approved previously, it makes sense to add relatlimab.

In melanoma, that's going to be in the frontline setting, but it also sets up the potential for triplets in melanoma. Therefore, what about [anti-]PD-1, LAG-3, and CTLA-4 inhibition?

Even in other diseases where immunotherapy is combined with chemotherapy, say, lung cancer, where we gave pembrolizumab [Keytruda] plus chemotherapy, now, should we consider giving PD-1 and LAG-3 inhibitors with chemotherapy? That's the kind of effect this approval is going to have.

Looking at the presentation given

by Diwakar Davar, MD, of UPMC Hillman Cancer Center, which centered on novel approaches for relapsed/refractory melanoma, how does the choice of frontline therapy affect subsequent treatment options for patients who progress?

In melanoma, we have an emerging landscape of treatment options for our patients, so the choice of first-line therapy can really dictate what happens afterwards.

There's been an argument about PD-1 inhibition alone vs the combination of PD-1 and CTLA-4 inhibition. It's important to point out that the combination has a fair amount of activity even in the

“All of this then sets up a future [question]: What about combinations of hedgehog inhibitors with immunotherapy? Those are the clinical trials that I emphasized at the end of my talk, which are likely to get going within the next year or so.”

[anti-]PD-1 refractory space. If your patient was to get [an anti-]PD-1 monotherapy for melanoma and progress, you can get about a 30% response rate by adding ipilimumab and continuing anti-PD-1.

More broadly, there's a whole host of developmental therapeutics that are in the pipeline now. If a patient progresses, please seek out clinical trials because there are many options that are on the horizon that may come into standard practice over the next year or so.

The last presentation, given by Yana Najjar, MD, of UPMC Hillman Cancer Center, centered on cutaneous squamous

cell carcinoma. What sort of multidisciplinary management is required within this disease?

The management of advanced squamous cell carcinoma requires an integrated multidisciplinary team. The disease most commonly is locally aggressive, and therefore we need help from our surgeons to manage that, but also radiation therapy to consolidate those surgeries, and possibly even to try to control refractory tumors.

That being said, [there's] really been a breakthrough with the development of PD-1 inhibitors in cutaneous squamous cell carcinoma, with response rates [of] more than 50%. Thinking about how and when to integrate surgery, radiation, and PD-1 inhibition [from] medical oncology is at the core of [our] management for every patient. Team therapy is the most important approach.

What forward-looking research across these diseases are you looking forward to seeing more of?

Since all skin cancers are, generally speaking, responsive to PD-1 inhibitors, we see fairly consistent themes of combining checkpoint inhibitors to try to augment response, but also to try to overcome resistance with therapies like intratumoral therapies, TLR9 [agonists] or oncolytic viruses being very obvious ones. There are also emerging data for small-molecule VEGF kinase inhibitors like lenvatinib [Lenvima] and others in combination with PD-1 inhibitors.

Finally, TILs, especially in melanoma, is a therapy that has been a historical legacy of our field, but [one that] is getting close to FDA approval. It's entirely possible that within the confines of 2022 there could be an FDA approval for TIL therapy, which really would be a ground shift in our landscape of therapeutics. Similar approaches are going to be thought about across all the cutaneous malignancies.

A key take-home, thinking about cutaneous malignancies, is the team-based oncology approach. That really goes from early-stage disease all the way through refractory metastatic disease because our therapies are moving into earlier lines of therapy. We have neoadjuvant presurgical trials, we have stage II approvals in melanoma, and obviously in stage III and in metastatic disease.

We really need input from dermatologists, surgeons, sometimes our radiation oncology colleagues, and obviously medical oncology, to help guide all of this. Don't lose sight of that. Get your colleagues involved early and keep them involved throughout the patient's care.

Advancements in Artificial Intelligence in Cancer Care to Be Highlighted at 2022 Capital Health Cancer Center Conference

Ryan Scott

MULTIMODAL STRATEGIES in the treatment of patients with lung cancer and applications for artificial intelligence in cancer care will be at the center of discussions at the 2nd Annual Capital Health Cancer Center Conference on March 25 and 26 in Atlantic City, New Jersey. The conference will aim to spread the cancer center's work and mission to practicing physicians and patients, according to Cataldo Doria, MD, PhD, MBA, FACS.

"Our objective is to continue to serve our patients with a better balance of technology and infrastructure. To do so, there are two major components," Doria said. "One is the investment done by the organization, and two is our ability to send this message outside of the walls of our organization. More people will know of our work and our outcomes, and more patients will benefit from it.

In an interview with OncoLive®, Doria, director of the Capital Health Cancer Center, and director of the Capital Health Center of Excellence in Robotic Surgery, discussed key presentations and objectives for the conference.

OncoLive®: What are the goals of the second annual Capital Health Cancer Center Conference?

Doria: The objective is to update colleagues and the public on the latest discoveries in cancer care for patients diagnosed with lung cancer. The second component of the conference will be focusing on the latest findings and the application of artificial intelligence to medicine, particularly cancer care.

What are some of the key topics that will be discussed at the conference?

There will be 2 major topics. One will be lung cancer, [and] this particular disease will be reviewed by specialists of different disciplines that treat [patients with] lung cancer in different ways, in what we generally describe [as a] multimodal approach to lung cancer. The second component will be geared on defining the latest updates in the application of artificial intelligence (AI) in cancer care.

The keynote speaker, Benny Weksler, MD, MBA, FACS, FACCP, of Allegheny Health Network Cancer Institute, will address disparities in cancer care. Why is this such a vital topic to be speaking on right now?

The Capital Health Cancer Center are at-

tentive to this topic. We are spending energy and resources in understanding disparity in cancer care. We have published [data] on the topic, and we are in the process of conducting other scientific experiments on making sure that this is a topic that is well addressed by our cancer center.

Since the COVID-19 pandemic has started, disparities in care have only become more pronounced. Can you elaborate on these existing disparities and some of the work that you are doing at Capital Health to address these?

In terms of work that has been done, we looked at how patients belonging to different socioeconomic statuses were receiving care when diagnosed with the pancreatic cancer. Everybody in [the pancreatic cancer] space knows that surgery is the single-most effective treatment for pancreatic cancer. However, we also found that in patients belonging to low socioeconomic statuses, patients who therefore have no insurance, were on charity care, or were on insurance products that were not comprehensive, that when they presented to major academic medical centers, they were denied the single-most effective treatment for pancreatic cancer, which is surgery.

At the other end [of the spectrum], that sequence of events [has] never really taken place in a cancer center, such as the one that we represent at the Capital Health Cancer Center. In part [due to] the talent, with decades of experience in major academic medical centers, we routinely offer the complicated surgery for this cancer to anyone, not just patients with commercial insurance, but to patients without insurance, on charity care, or with problems that are not particularly comprehensive.

Our conclusion is that the old paradigm that has been preached on for many years, is that patients diagnosed [with pancreatic] cancer should be taken care of at a major academic medical center. However, our research and science show that that old paradigm is fueling the disparity in health care, because those patients are deprived from the single-most effective treatment for pancreatic cancer.

What Capital Health has done is imported talented [doctors] with decades of experience in these major academic medical centers. We have better talents, better infrastructures, and better equipment. We have demonstrated that we are reversing the old paradigm with all the patients that we have treated in this

major center. To abate that disparity, Capital Health has made an amazing investment and is now capable of offering that specialized treatment for everyone.

As previously mentioned, there will be discussions on artificial intelligence in the treatment of cancer care. What are the opportunities or challenges that are presented in this space?

We decided to keep [this conference] to several key disciplines that are currently drilling down options [in artificial intelligence. The first consideration] is cancer radiology. AI applied to radiology will allow for a better, faster diagnosis that is precise and offered to everyone.

The second important field where [AI] can be applied is pathology. Diagnosis is most notably done by x-rays and by looking under the microscope at what we find in the tissues. Thinking about how much information can come out of 1 case, and how this information must be put all together and how all the dots need to be connected [before] we make the diagnosis. With the application of AI, this process can be automated and can be much more precise [to] benefit the patients.

[Additionally,] we decided to [present] one clinical example of the application of AI. We are going to have a urologist, [Eric Mayer, MD,] discuss the application of artificial intelligence to prostate cancer. Why prostate cancer? [About] 35 years ago when I trained, we used to remove the prostate, and the diagnosis was very subjective. Now, the algorithm to decide if an individual needs a prostatectomy is widely complex and is based primarily, though not exclusively, on objective data. [When put all together,] these objective data can be quite overwhelming, so the application of AI is an amazing advance in terms of outcomes for this deadly disease for men that are diagnosed with prostate cancer.

You will be delivering an address as the medical director of the conference. What will be your primary message to be when addressing to colleagues?

Our objective is to continue to serve our patients with a better balance of technology and infrastructure. To do so, there are two major components. One is the investment done by the organization, and two is our ability to send this message outside of the walls of our organization. More people will know of our work and our outcomes, and more patients will benefit from it.