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Navigating the Complexity of Cancer With Tumor Mutational Burden

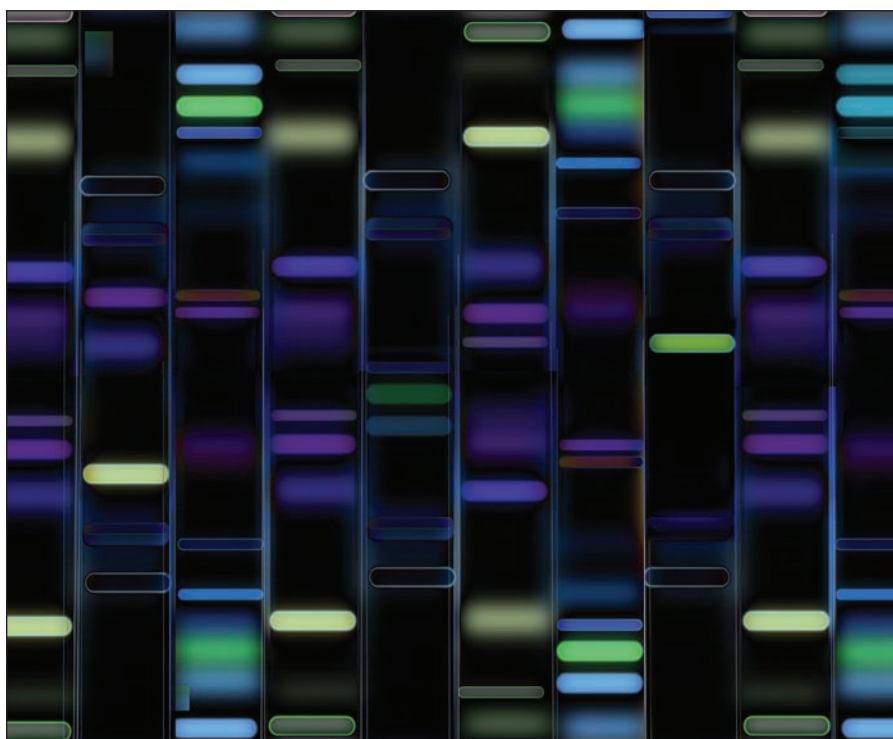
BY SAMUEL J. KLEMPNER, MD

The call to pursue oncology is different for everyone. For me, it was the field's immediacy: It stood out among medical subspecialties as a place where the bench and the bedside intersected frequently.

To make the biggest possible difference for patients, oncologists need to constantly bring the latest research, technology, and knowledge into the clinic. While we have made massive strides in our understanding of cancer biology, applying this knowledge to each of our patients on a daily basis is incredibly difficult.

New tools are needed to help oncologists select the best treatment in each case. The emergence of massively parallel DNA sequencing platforms, often called comprehensive genomic profiling (CGP), drastically increased the amount of tumor genomic data available to

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The Latest Clinical Trials Involving Targeted Therapies for NSCLC

BY RICHARD SIMONEAUX

According to the CDC, in 2013, the year for which the most recent data are available, 212,584 people in the U.S. were diagnosed with lung cancer. Additionally, that

year, 156,176 people in the U.S. died as a result of lung cancer. This disease causes more deaths in the U.S. than any other cancer. Data from the World Health Organization (WHO) similarly showed

that, in 2015, the leading cause of cancer deaths worldwide was lung cancer, with 1.69 million deaths, more than twice the amount of the second-leading cause, liver cancer, with 788,000 deaths.

Among lung cancers, the most common type is non-small cell lung cancer (NSCLC), which makes up approximately 80-85 percent of all lung malignancies. For NSCLC, the three most common subtypes are adenocarcinomas, squamous

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**CME
Article**

Hodgkin Lymphoma Survivors at High Risk of Second Cancers

Patients who are cured of Hodgkin lymphoma are at a high risk of developing a second type of cancer, particularly if they have a family history of the disease, a new study reports (*J Clin Oncol* 2017; doi:10.1200/JCO.2016.70.9709).

People who survived Hodgkin lymphoma were 2.4 times more likely to develop a second cancer of any type compared with people the same age and sex in the general population—and this risk remained high 30 years after treatment. But the risk was even greater in people who were treated for Hodgkin lymphoma and had a family history of those specific cancers.

Scientists found that patients treated for Hodgkin lymphoma were 3.5 times more likely to develop lung cancer if they had a close relative with lung cancer when compared to those without.

And those with a family history of breast or bowel cancer had around a two-fold increased risk of developing that cancer themselves.

The findings could help doctors identify patients most at risk of second cancers who might benefit from new risk-adapted treatment strategies, currently being evaluated in clinical trials, or increased monitoring for signs of specific second cancers.

Chances for Second Cancers

Scientists at The Institute of Cancer Research, London, along with researchers in Sweden and Germany, analyzed data from 9,522 patients with Hodgkin lymphoma and 28,277 relatives of the patients.

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cell carcinomas, and large cell carcinomas. Adenocarcinomas, which constitute nearly 40 percent of lung cancers, are often found in current or former smokers; however, it is also the subtype most frequently found in lifetime non-smokers. Squamous cell carcinomas account for 25-30 percent of lung cancers and are typically found in the central part of the lungs near the major airways and often occur in patients who have smoked previously. Approximately 10-15 percent of lung cancers are large cell carcinomas, which have a tendency to proliferate more rapidly than other NSCLC subtypes, thus making its treatment more difficult. Some less frequently encountered subtypes of NSCLC are sarcomatoid carcinoma and adenosquamous carcinoma.

When asked about the recent developments in NSCLC therapies, Ramaswamy Govindan, MD, Co-Director, Section of Medical Oncology, Professor of Medicine, Washington University School of Medicine in St. Louis and Clinical Advisory Editor for *Oncology Times*, replied, “We have seen promising results from several clinical trials of targeted therapies and immune checkpoint inhibitors in direct comparison with standard chemotherapy treatments.” He further added, “By far the biggest recent development in the treatment of NSCLC was the FDA approval of the checkpoint inhibitor pembrolizumab as a first-line therapy for PD-L1-positive patients, largely on the basis of results obtained for the landmark KEYNOTE-024 clinical trial.”

PD-1/PD-L1 Checkpoint Inhibitor Therapy

The programmed cell death-1 (PD-1) protein is a receptor present on the surface of many T cells and plays an important role as an immune checkpoint. Such checkpoints are important for immune system down-regulation and the prevention of autoimmunity. The mechanism by which this receptor affects immunosuppression is dual in nature, simultaneously inducing apoptosis in antigen-specific T cells and limiting apoptosis in the suppressive regulatory T cells. Anti-PD-1 monoclonal antibodies (e.g., pembrolizumab, nivolumab) inhibit the interaction of the PD-1 receptors on antigen-specific T-cells with its ligand,

PD-L1, which is often expressed on the surface of tumor cells. Alternatively, the PD-1/PD-L1 interaction may be disrupted by utilizing anti-PD-L1 antibodies such as atezolizumab, durvalumab, or avelumab.

KEYNOTE-021 Clinical Trial

In October 2016, results were reported for a phase II cohort of the KEYNOTE-021 clinical trial (NCT02039674) that evaluated the use of carboplatin and pemetrexed with or without the PD-1-selective monoclonal antibody pembrolizumab in patients with non-squamous cell NSCLC (*Lancet Oncol* 2016;17:1497-1508).

In that cohort, phase IIIB/IV non-squamous cell NSCLC patients without targetable anaplastic lymphoma kinase (ALK) or epithelial growth factor receptor (EGFR) genetic anomalies were randomized in a 1:1 manner to chemotherapy or pembrolizumab plus chemotherapy groups. Stratification of patients was performed using their PD-L1 tumor proportion scores (i.e., <1% or ≥1%). The chemotherapy group received four cycles of carboplatin area under curve (AUC) 5 mg/mL/min and 500 mg/m² pemetrexed every 3 weeks (day 1 IV dosing) with an indefinite period of pemetrexed maintenance therapy. The chemotherapy plus pembrolizumab group received the same chemotherapy regimen and 200 mg pembrolizumab for 24 months (IV dosing on day 1 of each 3-week cycle).

Patients in the chemotherapy group who displayed radiologically-determined disease progression were permitted to crossover and receive pembrolizumab after a period of 21 days if the relevant trial-specified safety criteria were met. The primary endpoint of the trial was the proportion of patients attaining a radiologically-confirmed objective response (complete or partial, using RECIST version 1.1 with independent and masked centralized review). Safety was assessed in all patients receiving at least one dose of experimental treatment.

From November 2014 to January 2016, 123 patients were enrolled and randomized to either the chemotherapy (n=63) or chemotherapy plus pembrolizumab (n=60) groups. For the pembrolizumab plus

chemotherapy group, 55 percent (95% CI-42-68%) of the patients attained a partial response, compared to 29 percent (95% CI-18-41%) for the chemotherapy group. No patients in this study showed complete response to the investigational treatments. Disease progression was observed in 17 percent of the chemotherapy group and in only 3 percent of the chemotherapy plus pembrolizumab participants. Grade 3 or worse treatment-related adverse events (AEs) were noted for 23 percent of the chemotherapy group and 39 percent of the chemotherapy plus pembrolizumab group.

For the chemotherapy plus pembrolizumab group, the most common grade 3 or worse AEs were anemia (12%) and lowered neutrophil count (5%). The most common treatment-related grade 3 or worse AEs in the chemotherapy group were anemia (15%), thrombocytopenia (3%), lowered neutrophil count (3%), and pancytopenia (3%). There were two treatment-related deaths in the chemotherapy group (1-sepsis; 1-pancytopenia) and one in the chemotherapy plus pembrolizumab group (sepsis). When commenting on this study's results, Govindan noted, “It has now been shown that the combination of platinum-based chemotherapy and checkpoint inhibitors is feasible.

“Clearly, the chemotherapy plus pembrolizumab group had a larger percentage of patients achieving a partial response and a smaller percentage showing disease progression,” he added.

KEYNOTE-024 Clinical Trial

In November 2016, the results were published for the open-label, phase III KEYNOTE-024 clinical trial (NCT02142738), which directly compared the use of standard platinum chemotherapies versus pembrolizumab as a therapy in those treatment-naïve NSCLC patients having PD-L1 tumor proportion scores >50 percent without treatable EGFR or ALK genetic aberrations (*N Engl J Med* 2016;375:1823-1833).

From September 2014 to October 2015, 305 patients were randomized to either the pembrolizumab (n=154) or the chemotherapy group (n=151). The pembrolizumab patients received 200 mg of the

“We have seen promising results from several clinical trials that evaluated targeted therapies in direct comparison with standard chemotherapy treatments.”

antibody IV on day 1 of every 3-week cycle (up to 35 or until disease progression), while the chemotherapy patients received 4-6 cycles of the clinician's choice of platinum doublet therapy (carboplatin or cisplatin + gemcitabine; carboplatin or cisplatin + pemetrexed; carboplatin + paclitaxel).

Patients in the chemotherapy group with non-squamous NSCLC were permitted pemetrexed maintenance therapy for the remainder of the study or until disease progression. Additionally, chemotherapy participants were also permitted to cross over to the pembrolizumab group if documented disease progression occurred (200mg IV, once every 3 weeks). The primary endpoint for this trial was progression-free survival (PFS), while secondary endpoints included objective response rate (ORR), overall survival (OS), and safety.

After a median follow-up period of 11.2 months, 48 percent of the pembrolizumab patients were still on that therapy; in contrast, only 10 percent of the chemotherapy group remained on the investigational therapy. Additionally, crossover to pembrolizumab was permitted for 44 percent of the chemotherapy group that experienced disease progression. A median PFS of 10.3 months was obtained for this pembrolizumab group (95% CI-6.7 months-not reached), while a figure of 6.0 months was determined for the chemotherapy patients (95% CI-4.2-6.2 months), thus affording a hazard ratio (HR) for death or disease progression of 0.5 (95% CI 0.37-0.68; P < 0.001). At 6 months,

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NSCLC

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the estimated OS for the pembrolizumab group was 80.2 percent, while for the chemotherapy group, the figure was 72.4 percent, giving an HR for death of 0.60 (95% CI=0.37–0.68; $P=0.005$). The ORR was also greater for the pembrolizumab group relative to the chemotherapy counterparts (44.8% and 27.8%, respectively), as was the duration of response (median value not reached [range=1.9+ months to 14.5+ months] vs. 6.3 months [range=2.1+ - 12.6+ months]).

Overall, fewer treatment-related AEs of any grade were obtained for the pembrolizumab group versus the chemotherapy group (73.4% and 90.0%, respectively). Only 26.6 percent of the pembrolizumab patients had grade 3-5 treatment-related AEs; however, 53.3 percent of the chemotherapy group had these grade AEs. When commenting on the results for this trial, Govindan observed, “This was clearly a landmark study; this trial validated the use of pembrolizumab as a first-line therapy for NSCLC. The investigational antibody showed greater PFS, OS, ORR, and duration of reaction while exhibiting a better safety profile.”

On Oct. 24, 2016, the FDA approved the use of pembrolizumab as a first-line therapy for the treatment of NSCLC patients having PD-L1 tumor proportion scores >50 percent and for patients having tumor proportion scores ≥ 1 percent in those NSCLC patients having undergone disease progression in prior platinum-based therapies. As with the previously-described clinical trials, this approval did not apply to NSCLC patients with targetable ALK or EGFR mutations. This marked the first time the FDA had approved the use of a checkpoint inhibitor for the first-line treatment of lung cancer.

ALK Inhibitor Therapy

Approximately 3-7 percent of NSCLC patients have an ALK rearrangement that serves as an oncogenic driver for their disease. These patients often have adenocarcinoma histology and are younger with a light- or non-smoking history. On Nov. 20, 2013, the FDA granted approval for crizotinib, an orally active tyrosine kinase inhibitor (TKI) of ALK, ROS1, and MET for the treatment of patients having ALK-positive NSCLC. Results obtained from the phase III, open-label PROFILE 1014 clinical trial (NCT01154140) showed crizotinib was superior to platinum-based doublet therapy, displaying a longer PFS (10.9 months vs. 7.0 months). However, most patients on this therapy do undergo disease progression, frequently as a result of CNS malignancies.

Ceritinib, the compound investigated in the ASCEND-4 clinical trial, is an orally available ATP-competitive selective next-generation ALK inhibitor that received accelerated FDA approval April 29, 2014, for the treatment of ALK-positive metastatic NSCLC for patients on or intolerant to crizotinib. Ceritinib showed an average 20-fold improvement relative to crizotinib for in vitro studies against a panel of three cell lines harboring crizotinib-resistant mutations. Additionally, ceritinib also showed enhanced blood-brain barrier crossing, giving an exposure ratio of 15 percent in a rat model.

Ascend-4 Clinical Trial

In March 2017, the results were published for the phase III, open-label ASCEND-4 clinical trial (NCT01828099) that compared ceritinib to standard platinum-based doublet therapy in treatment-naïve stage IIIB/IV non-squamous NSCLC patients with ALK-rearrangements (*Lancet* 2017;389:917-929).

From August 2013-May 2015, 376 patients were randomized to either the ceritinib group ($n=189$; 750 mg/day) or the chemotherapy group ($n=187$; AUC 5-6 carboplatin or 75 mg/m² cisplatin plus 500 mg/m² pemetrexed; four 3-week treatment cycles with additional pemetrexed maintenance therapy). Patient stratification was performed using the following criteria: WHO performance status (0 vs. 1-2); presence of brain metastases (determined by clinician at patient screening); previous adjuvant or neoadjuvant chemotherapy (yes vs. no). Primary endpoint was PFS, while secondary endpoints included OS, ORR, and patient-reported outcomes.

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Learning Objective for This Month's CME Activity: After participating in this CME activity, readers should be able to identify findings from recent clinical trials of targeted therapies for non-small cell lung cancer.

Across all patient groups, the median PFS, as determined by blinded independent review, was 16.6 months for the ceritinib group (95% CI=12.6-27.2 months) compared to 8.1 months for the chemotherapy group (95% CI=5.8-11.1 months) (HR 0.55–95% CI=0.42-0.73). For patients without brain metastases at the time of screening, the median PFS figures also favored the ceritinib group relative to the chemotherapy group (26.3 vs. 8.3 months; HR 0.48–95% CI=0.33-0.69). In patients with brain metastases at screening, the median PFS was 10.7 months in the ceritinib group and 6.7 months in the chemotherapy group (HR 0.70–95% CI=0.44-1.12). In patients who had not undergone adjuvant chemotherapy prior to this trial (i.e., treatment-naïve), the median PFS for the ceritinib group was 16.4 months (95% CI=12.1-27.2 months) and 7.5 months (95% CI=5.7-9.7 months) for the chemotherapy group (HR 0.55–95% CI=0.41-0.73).

Median OS was not reached for the ceritinib group (95% CI=29.3 months-not estimable) and was 26.2 months in the chemotherapy patients (95% CI=22.8 months-not estimable) (HR 0.73–95% CI=0.50-1.08). At 24 months, the estimated OS was 70.6 percent for the ceritinib group and 58.2 percent for the chemotherapy group. The centrally-determined ORR also showed a distinct advantage for the ceritinib patients. That group had an ORR of 72.5 percent (95% CI=65.5-78.7%) while the chemotherapy patients attained an ORR of 26.7 percent (95% CI=20.5-33.7%). Interestingly, in patients with measurable baseline brain metastases, the intracranial response rate for the ceritinib group was 72.7 percent (95% CI=49.8-89.3%), while the figure for the chemotherapy group was 27.3 percent (95% CI=10.7-50.2%).

The most common AEs reported for the ceritinib group were primarily gastrointestinal in nature: diarrhea (85%), nausea (69%), vomiting (66%), and increased alanine aminotransferase levels (60%). The chemotherapy group also reported a number of gastrointestinal side effects: nausea (55%), vomiting (36%), and anemia (35%). The investigators stated that attempts are being made to address some of the gastrointestinal issues with the empty-stomach ceritinib dosing utilized in this study (e.g., dose reduction and non-empty-stomach dosing).

Based on the results obtained in these studies, the investigators feel the use of ceritinib as a first-line therapy for ALK-positive NSCLC patients is warranted, especially when one considers the data for treatment-naïve patients included in this trial. The response rates shown by patients having measurable brain metastases were also encouraging for the ceritinib group in comparison to the chemotherapy group (72.7% vs. 27.3%). When asked about the results of this trial, Govindan stated, “Trials like this and encouraging results with a new generation of ALK inhibitors give us hope that we will continue to improve the outcomes in ALK-positive lung cancer.”

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Some 30 percent of people who had Hodgkin lymphoma in the study had one or more first-degree relatives with cancer.

Those with a family history of cancer were 2.8 times more likely to get a second cancer compared with 2.2 times more likely in patients with no first-degree relatives with cancer. People with two or more first-degree relatives with cancer were 3.4 times more likely to develop a second cancer.

The most common second cancers were non-Hodgkin lymphoma; leukemia; and lung, breast, bowel, and non-melanoma skin cancers.

The researchers also found increased risk of second cancer was linked to the age at diagnosis for both women and men.

Women diagnosed with Hodgkin lymphoma under the age of 35 had a 14 percent risk of developing breast cancer over the next 30 years, whereas for those over 35 at diagnosis the risk was only 3 percent.

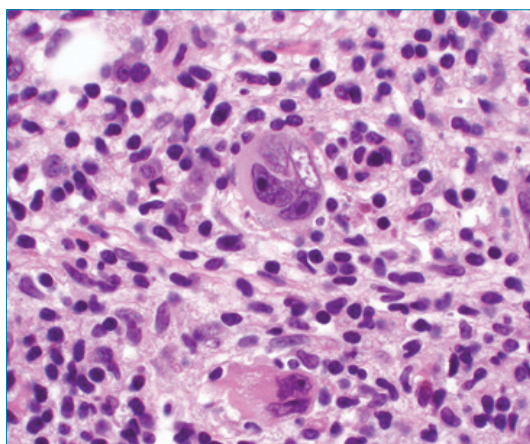
Screening Needed

“The vast majority of patients with Hodgkin lymphoma are cured with a combination of chemotherapy and radiotherapy. Our research

has shown that these patients are at substantially increased risk of a second cancer later in life—and particularly if they have a family history of cancer,” noted study author Amit Sud, MBChB (Hons), MRes, MRCP, Clinical Research Fellow at The Institute of Cancer Research, London.

“Younger women who have been treated with radiotherapy to the chest for Hodgkin lymphoma are already screened for breast cancer, but our study suggests that we should be looking at ways of monitoring survivors for other forms of cancer, too, and potentially offering preventative interventions.

“After patients are cured, they no longer encounter oncologists, so it’s important that other healthcare providers are aware of the increased risk to Hodgkin lymphoma survivors to improve early diagnosis of second cancers.”



Richard Houlston, MD, PhD, Professor of Molecular and Population Genetics at The Institute of Cancer Research, London, noted: “As cure rates for cancer improve, we are increasingly thinking about the long-term health of survivors, and how we can personalize the care they receive to take into account their own individual risks.

“This major new study has tracked the health of people who have survived Hodgkin lymphoma over several decades in order to provide a comprehensive assessment of the long-term risk of cancer. The research gives us invaluable information which we can look to use to tailor monitoring, screening, or preventative treatment.”

“People with Hodgkin lymphoma are at a greater risk of developing a second cancer, particularly in those who were treated with radiotherapy approach that was used a few decades ago,” Martin

“After patients are cured, they no longer encounter oncologists, so it’s important that other healthcare providers are aware of the increased risk to Hodgkin lymphoma survivors to improve early diagnosis of second cancers.”

Ledwick, Cancer Research UK’s head cancer information nurse, also noted. “A family history of breast cancer adds to their risk. This study is the first to show that a family history of lung and bowel cancer also play a role.

“The research shows that a family history of lung cancer carries the highest risk, and as the risk hasn’t decreased as treatment has changed to use less radiotherapy, there may be factors other than heredity, such as family smoking habits, that are influencing the risk.” **OT**

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EGFR Inhibitor Therapy

In the U.S., approximately 10-15 percent of NSCLC patients have a mutated EGFR oncogenic driver, while in East Asian patients, the figure is close to 35 percent. EGFR TKI drugs have been successfully developed to treat EGFR-mutant patients, including erlotinib and gefitinib; however, almost all of the patients who have initial success with these drugs will develop resistance to this therapy. For approximately 50 percent of the patients who develop resistance to EGFR TKI therapy, this is due to the T790M mutation on exon 20 of the EGFR gene.

To address the needs of patients with this mutation, efforts were made to find new TKIs that showed efficacy against those cancers driven by T790M-mutant EGFR. As a result, osimertinib was identified as a promising TKI candidate. Osimertinib is an orally-available irreversible TKI that shows effectiveness against the sensitized EGFR mutants as well as the resistant T790M mutant.

AURA-3 Clinical Trial

The results from the AURA-3 phase III, open-label clinical trial (NCT02151981), which compared the use of platinum-based doublet therapy with the TKI osimertinib, were published in February 2017 (*N Engl J Med* 2017;376:629-640).

In this trial, patients with metastatic or locally advanced NSCLC who had undergone previous EGFR TKI therapy with progression and who were T790M-mutant EGFR-positive were randomized in

a 2:1 ratio to either osimertinib (80 mg orally, once daily) or platinum-based doublet chemotherapy (carboplatin AUC-5 or cisplatin 75 mg/m² plus 500 mg/m² pemetrexed IV every 3 weeks for up to 6 cycles). Those patients from the chemotherapy group who experienced radiologically-confirmed disease progression (RECIST version 1.1) were permitted to cross over to receive osimertinib. The primary endpoint was PFS, while ORR was considered a secondary endpoint. In addition, safety measures (as determined by AEs) were obtained.

The researchers showed that PFS was considerably longer for the osimertinib group (10.1 months) than for the chemotherapy group (4.4 months), giving a HR of 0.30 (95% CI–0.23-0.42; P < 0.001). This trend was also observed for the PFS of patients having CNS-based metastases (osimertinib–8.5 months; chemotherapy–4.2 months; HR 0.32; 95% CI–0.21-0.49). ORR was significantly higher for osimertinib patients (71%; 95% CI–65-76%) than the chemotherapy patients (31%; 95% CI–24-40%). Safety, as measured by treatment-related grade 3 or higher AEs, were lower in the osimertinib group (23%) than the chemotherapy group (47%).

When asked to sum up the developments in NSCLC therapies over the past year, Govindan noted, “We have seen the continued trend of targeted therapies clearly outperforming standard chemotherapies in several clinical trials in molecularly-selected subgroups of NSCLC.” He reiterated the positive news concerning the landmark KEYNOTE-024 clinical trial. “The results obtained in this trial, along with the FDA’s approval for the first-line use of pembrolizumab will definitely change the way we approach NSCLC in those patients having PD-L1-positive disease.” **OT**

Richard Simoneaux is a contributing writer.