

# 2019 ASCO Annual Meeting Highlights for the Advanced Practitioner: Non–Small Cell Lung Cancer

Options for patients with non–small cell lung cancer have expanded following trials studying the safety and efficacy of checkpoint inhibitors and targeted therapies. **Elizabeth S. Waxman, RN, MSN, AOCN®, ANP-BC**, of MD Anderson Cancer Center reviews the major abstracts from the 2019 ASCO Annual Meeting using coverage by *The ASCO Post* and offers considerations for advanced practitioners in this field.

## Abstracts 9007 and 9008

### Advances in Targeted Therapy for Non–Small Cell Lung Cancer

By Alice Goodman

Visit <https://meetinglibrary.asco.org/record/174631/abstract> and <https://meetinglibrary.asco.org/record/174550/abstract> to read the full abstracts and view disclosures.

**T**argeted therapies for non–small cell lung cancer (NSCLC) are a hotbed of investigation. Two new targeted therapies are promising for patients with lung tumors that are either *EGFR* exon 20 insertions or *RET*-rearranged. At the 2019 ASCO Annual Meeting, attendees heard early data on therapies targeted to these complex driver alterations.

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In the first study, TAK-788 achieved a confirmed objective response rate of 43% and a disease control rate of 86% in pretreated patients with advanced NSCLC and *EGFR* exon 20 insertions (Jänne et al., 2019). Responses were seen in patients with and without brain metastases at baseline.

The second study found that BLU-667 yielded an objective response rate of 58% and a disease control rate of more than 90% in patients with *RET* fusion–positive advanced NSCLC (Gainor et al., 2019). In patients who received prior platinum-based chemotherapy, the overall response rate was 60%, and the disease control rate was 100%.

### TAK-788: Study Details

“*EGFR* mutations are relatively common in patients with lung cancer. Exon 20 is the third most common alteration in *EGFR*, and unlike exons 19 and 21, it is associated with resistance to available tyrosine kinase inhibitors [TKIs] used to treat NSCLC,” explained Gregory Riely, MD, of Memorial Sloan Kettering Cancer Center, New York, who was filling in for lead author Pasi Jänne, MD, in presenting the data. “TAK-788 has potent and selective preclinical inhibitory activity against *EGFR* exon 20 insertions compared with other TKIs such as afatinib and osimertinib,” he noted.

For phase II, the recommended dose carried forward from phase I was 160 mg/d. Of 7 phase II cohorts with different disease characteristics, Dr. Riely presented efficacy data on cohort 1 alone, which comprised 28 patients treated at the 160-mg/d dose: 22 from the dose-expansion phase and

6 from the dose-escalation phase. Safety data were presented for 2 cohorts: 137 patients ever treated with TAK-788 and 72 patients treated at 160 mg/d across all cohorts.

In cohort 1, the median patient age was 62 years; 79% had an Eastern Cooperative Oncology Group performance status of 1; 43% had brain metastases at baseline (largest tumor allowed was up to 1 cm); the median number of prior systemic anticancer regimens was three (including prior checkpoint inhibitors in 61% and EGFR- or HER2-directed TKIs in 18%).

The median time on treatment was 7.9 months. Seven patients had progressive disease, three patients discontinued treatment due to an adverse event, three patients discontinued treatment due to physician's decision, and one patient died. "About half the patients are still on study, including those with brain metastasis," Dr. Riely noted.

At the time of data cutoff, the best radiographic response in patients with EGFR exon 20 inserts was 43%; 12 were confirmed responses and 3 were unconfirmed responses.

The confirmed objective response rate in patients with baseline brain metastases was 25%, with a disease control rate of 67%. In patients without baseline brain metastases, the objective response rate was 56%, and the disease control rate was 100%. Median progression-free survival in cohort 1 was 7.3 months (3.7 months for patients with brain metastases at baseline and 8.1 months for those without brain metastases at baseline). "Patients with brain metastases had lower response rates and shorter progression-free survival," Dr. Riely said.

### **TAK-788: Safety**

Grade 3 or higher treatment-emergent events occurred in 63% of patients treated at the 160-mg dose and in 61% of those who received the drug at any dose; 25% required dose reductions for treatment-related adverse events, and 14% discontinued therapy.

The most common adverse events were grade 1 and 2. The most common grade 3 or higher adverse events were diarrhea (18%), nausea (6%), increased lipase (6%), stomatitis (4%), and increased amylase (4%).

"Treatments such as EGFR TKIs [afatinib, osimertinib] have limited potency against exon

20 insertion variants. Another drug in development, poziotinib, has limited selectivity for exon 20 compared with TAK-788," Dr. Riely said.

TAK-788 is being studied further. The EXCLAIM expansion cohort (using TAK-788 at 160 mg/d) is currently ongoing in patients with locally advanced or metastatic NSCLC with exon 20 insertion mutations. So far, 91 patients are enrolled.

### **Background on RET Inhibitors**

"BLU-667 is a highly potent and selective RET inhibitor under study in patients with advanced *RET* fusion-positive NSCLC," explained lead author Justin F. Gainor, MD, of Massachusetts General Hospital, Boston.

Genetic alterations in *RET* drive the pathogenesis of various solid tumors, including lung, thyroid, esophageal, and breast cancers as well as melanoma, he noted. About 1% to 2% of lung cancers harbor *RET* fusion, and there is no approved RET inhibitor to date. Although available TKIs may include *RET* fusion as an off-target effect, they are not selective for it.

Two selective RET inhibitors have been granted Breakthrough Therapy designation by the U.S. Food and Drug Administration: BLU-667 and LOXO-292. BLU-667 is designed to inhibit *RET* alterations and resistance mutations. It is 90-fold more selective for *RET* than for *VEGFR2*, a common target in NSCLC.

### **BLU-667: Study Details**

The ongoing ARROW study is currently enrolling patients into seven cohorts. The data Dr. Gainor presented were based on cohorts 1 and 2, which included 131 *RET* fusion-positive patients: 41 platinum-naive and 90 previously treated with platinum. The safety analysis was based on 120 patients.

Forty percent of patients in cohort 1 had brain metastases at baseline. These patients were heavily treated, with a median of two prior lines of therapy (chemotherapy, 77%; checkpoint inhibitor, 39%; and multikinase inhibitor, 18%). The most common fusion partner was KIF5B (66%).

A majority of responses were seen on the first scan, and 82% remain on treatment as of the data cutoff of April 2019. The median duration of response has not yet been reached, and many patients continue to respond for more than 24

months, Dr. Gainor said. Responses occurred regardless of the *RET* fusion partner, brain metastases, and prior front-line therapy.

Among nine patients with measurable untreated brain metastases, 78% had tumor shrinkage, including tumors that had *CCDC6b* and *KIF5B* as fusion partners. No patient experienced disease progression due to new central nervous system involvement. Dr. Gainor showed scans of two patients who had complete resolution of brain metastases on treatment with BLU-667.

Treatment-related toxicity was generally low-grade and reversible; the adverse events included constipation, neutropenia, fatigue, hypertension, and alanine transaminase elevation. Grade 3 neutropenia was reported in 13% and grade 3 hypertension, in 10%. Treatment discontinuation due to treatment-related toxicity was reported in 7%.

“BLU-667 has activity in other *RET* fusion-positive malignancies, including genitourinary and papillary thyroid cancers,” Dr. Gainor said. “The broad and durable activity of BLU-667 in patients with *RET* fusion-positive NSCLC supports the expansion of the ARROW trial and studies in other malignancies.” ●

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### The Advanced Practitioner Perspective

Elizabeth S. Waxman, RN, MSN, AOCN®, ANP-BC, MD Anderson Cancer Center

The results of these new agents in Abstracts 9007 and 9008 present interesting data and exciting news for patients with NSCLC who have exon 20 insertion and *RET*-fusion mutations.

#### Study Results

It is important for the advanced practitioner (AP) to keep in mind that these drugs will be effective in a small percentage of patients with NSCLC. Additionally, in the TAK-788 presentation, the results were from one cohort with 28 patients, which is a small sample. It is good news to see that TAK-788 has efficacy in treating brain metastases. Toxicity management and prompt intervention is crucial for the patients to remain on treatment.

BLU-667 is a drug with activity in NSCLC and other malignancies. It is interesting that

the median duration of response has not yet been reached and patients continue to respond for more than 2 years on treatment. It is important for APs to be aware of the toxicities with BLU-667.

#### Safety

Treatment for lung cancer is becoming more personalized, with treatment decisions based on the presence (or absence) of mutations. These oral treatments are not without toxicities, although they are different from those with chemotherapy and immunotherapy. For APs, thorough assessments are needed while the patient is on treatment, and knowledge of side effects and their management is essential. Drugs such as TAK-788 and BLU-667 give hope to patients with rare mutations and their families.

**Disclosure:** Ms. Waxman has no conflicts of interest to disclose.

## Abstracts 8503 and 8504

**Neoadjuvant Immunotherapy May Benefit Patients With Early-Stage NSCLC**

By Alice Goodman

Visit <https://meetinglibrary.asco.org/record/173482/abstract> and <https://meetinglibrary.asco.org/record/173490/abstract> to read the full abstracts and view disclosures.

**N**eoadjuvant immunotherapy had encouraging activity and demonstrated favorable safety in patients with resectable early-stage NSCLC, according to two studies presented at the 2019 ASCO Annual Meeting (Cascone et al., 2019; Kwiatkowski et al., 2019). This approach has the potential to boost the survival rate in resectable early-stage NSCLC, according to experts.

In an interim analysis of the Lung Cancer Mutation Consortium's LCMC3 study, neoadjuvant monotherapy with the programmed cell death ligand 1 (PD-L1) inhibitor atezolizumab led to a major pathologic response in 19% of patients as well as a pathologic complete response in 5% of patients who went on to complete surgical resection (Kwiatkowski et al., 2019). The checkpoint inhibitor was well tolerated. A placebo-controlled phase III trial is currently testing this strategy.

In the NEOSTAR study, both monotherapy with the programmed cell death protein 1 inhibitor nivolumab and the combination of nivolumab plus ipilimumab (a cytotoxic T-lymphocyte-associated protein 4 inhibitor) achieved favorable results as neoadjuvant therapy (Cascone et al., 2019). The combined major pathologic response rate and pathologic complete response rate was 17% with monotherapy and 33% with the combination.

Although the findings are encouraging, additional research is needed before neoadjuvant immunotherapy is accepted as a standard of care in this setting, according to the speakers who presented these studies.

**LCMC3 Study**

"Small pilot studies suggest there may be a benefit for neoadjuvant immunotherapy in treatment-naïve patients with potentially resectable, early-stage NSCLC," said lead author David J.

Kwiatkowski, MD, PhD, Professor of Medicine at Harvard Medical School and Senior Physician at Dana-Farber/Brigham and Women's Hospital, Boston. "Immune checkpoint inhibitor therapy is included as a standard of care for patients with advanced metastatic lung cancer, and this study suggests that it may also have a benefit in earlier-stage disease when it is operable."

LCMC3 is currently enrolling patients with stage IB to IIIB NSCLC with a planned goal of 180. At the ASCO Annual Meeting, Dr. Kwiatkowski presented an interim analysis of 101 patients treated with two cycles of atezolizumab prior to surgery and up to 12 months of postoperative atezolizumab. The primary endpoint of the study is major pathologic response, defined as no more than 10% viable tumor cells at surgical resection. This endpoint has been adapted for neoadjuvant immunotherapy trials.

Patients enrolled in the trial were typical for those with NSCLC: median age was 65 years, one-third had squamous histology, 90% were current or former smokers, and 46% had either stage III or IIIB disease based on presurgical staging. About 50% of patients were negative for PD-L1 staining, 7 patients were *EGFR*-positive, and 1 patient had an *ALK* translocation.

The primary efficacy population included 77 patients who underwent surgery and had no known molecular drivers of disease. Among them, 19% had a major pathologic response, 5% had a pathologic complete response, and 49% had greater than 50% tumor shrinkage.

The researchers were unable to identify biomarkers of response. Neither PD-L1 expression nor tumor mutational burden were associated with response or pathologic regression. Based on an analysis of 40 patients, no significant associations were found between gene alterations and major pathologic response.

The safety analysis included all 101 patients. Almost all of them (97%) experienced an adverse event. Serious adverse events occurred in 30%, and 5% of patients discontinued atezolizumab due to toxicities. Two deaths were reported; neither was deemed treatment-related.

**NEOSTAR Study**

"More than 50% of patients with stage I to III resectable NSCLC will relapse, and postopera-

tive chemotherapy is associated with an absolute 5-year overall survival benefit of only 5.5% vs surgery alone,” explained NEOSTAR lead author Tina Cascone, MD, PhD, Assistant Professor at The University of Texas MD Anderson Cancer Center, Houston.

NEOSTAR was a multiarm phase II study of checkpoint blockade for untreated stage I to IIIA NSCLC amenable to surgical resection. Patients in arm A were treated with nivolumab, and those in arm B received the combination of nivolumab plus ipilimumab, based on preclinical studies showing synergy for this combination. All patients were scheduled for surgery within 3 to 6 weeks of the last dose of neoadjuvant therapy.

Dr. Cascone presented the final results of NEOSTAR at the ASCO meeting. Of 53 patients screened, 44 were assigned and treated; 39 underwent surgery (including 2 who had surgery off of the trial) and 5 did not undergo curative surgery due to treatment-related adverse events.

The mean age was 65.6 years; most patients were male, Caucasian, and had a history of smoking. Two-thirds had adenocarcinoma, 98% had invasive mediastinal staging, and 92% completed planned neoadjuvant chemotherapy. The resectability rate was 89%.

“Twenty-two percent of surgeries were delayed beyond 42 days. These findings will be reported in the future,” Dr. Cascone said.

In an intent-to-treat analysis, the combined major pathologic response rate and pathologic complete response rate (ie, cure rate) was 25%. That combined rate was 17% in the nivolumab

arm and 33% for the combination immunotherapy arm.

Dr. Cascone pointed out that 11% of patients had apparent radiographic disease progression after neoadjuvant immune checkpoint inhibitor therapy. “These patients had evidence of granulomas—a phenomenon called nodal immune flare. The clinician needs to distinguish between nodal immune flare and progressive disease,” she advised.

Most treatment-related adverse events were grade 1 or 2. The most common treatment-related adverse events were fatigue in the nivolumab monotherapy arm (35%) and rash in the combination immunotherapy arm (52%). Grade 3 to 5 treatment-related adverse events included hypermagnesemia, hypoxia, pneumonitis, and pneumonia (4% each) in the combination arm.

“Preliminary analysis suggests that elevated baseline PD-L1 may be associated with radiographic responses and greater tumor regression,” Dr. Cascone said. ●

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**The Advanced Practitioner Perspective**  
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In these two studies on neoadjuvant immunotherapy prior to surgical resection, it is important to note that major pathologic response (MPR) was the primary endpoint. In neoadjuvant studies, pathological response (or MPR) can be a substitute for survival. An MPR of 10% or less residual viable tumor after neoadjuvant therapy is associated with improved survival and reflects treatment efficacy.

**LCMC3 and NEOSTAR**

Advanced practitioners need to be mindful that in these two presentations, immunotherapy was used in the neoadjuvant setting. In LCMC3, atezolizumab was given as monotherapy in the neoadjuvant setting, with an MPR of 19%. Interestingly, MPR was observed regardless of PD-L1 expression. The phase II

NEOSTAR trial had two arms: nivolumab vs. nivolumab plus ipilimumab, and MPR was the primary endpoint. There were 23 patients in the nivolumab arm and 21 patients in the combination arm, for a total of 44 patients. Thirty-nine patients went on to have surgery. Major pathologic response was 17% in the nivolumab arm and 33% in the nivolumab/ipilimumab arm.

**Immune-Related Adverse Events**

In both studies, patients experienced immune-related toxicities, and a small number of patients withdrew from the LCMC3 trial due to toxicities. These studies demonstrate that immunotherapy can be given in the neoadjuvant setting with responses (MPR), and subsequent definitive therapy. Advanced practitioners need to be aware of immune-related toxicities and their management so patients can stay on effective treatment.

**Disclosure:** Ms. Waxman has no conflicts of interest to disclose.

**Abstract LBA9015**

**KEYNOTE-001 Shows Long-Term Survival Benefit With Pembrolizumab in Advanced NSCLC**

By Alice Goodman

Visit <https://meetinglibrary.asco.org/record/175606/abstract> to read the full abstract and view author disclosures.

**B**efore the introduction of immunotherapy with checkpoint inhibitors, the 5-year life expectancy for patients with advanced non-small cell lung cancer (NSCLC) was 5.5%. This dismal outlook has changed. Treatment with the immune checkpoint inhibitor pembrolizumab dramatically improved overall survival in this group of patients, according to 5-year follow-up data from the phase Ib KEYNOTE-001 clinical trial. The greatest benefit of pembrolizumab was observed in patients with high programmed cell death ligand 1 (PD-L1) expression ( $\geq 50\%$ ; Garon et al., 2019a).

For chemotherapy-naïve patients at the time of treatment with pembrolizumab, the estimated 5-year survival was 23.2%. For previously treated patients, the estimated 5-year survival was 15.5%.

In patients with PD-L1 expression of at least 50%, the 5-year overall survival was 29.6% in treatment-naïve patients and 25% in previously treated patients. For patients who received pembrolizumab for 2 years or more, the 5-year survival was 75%.

These data represent the longest follow-up study to date of people with advanced NSCLC treated with pembrolizumab, and they are expected to change the discussion oncologists have with their patients who have lung cancer, experts agreed. The study was presented at the 2019 ASCO Annual Meeting and published simultaneously online in the *Journal of Clinical Oncology* (Garon et al., 2019b).

“The uniformly negative outlook that has been associated with a diagnosis of advanced non-small lung cancer is certainly no longer appropriate. The fact that we have patients on this trial who are still alive after 7 years is quite remarkable. We also have evidence that most patients who are doing well after 2 years on pembrolizumab live for 5 years or more,” said lead author Edward B. Garon, MD, Associate Professor of Medicine at UCLA, Los Angeles.

ASCO expert David L. Graham, MD, FASCO, of the Levine Cancer Institute, Charlotte, North Car-

**KEYNOTE-001: 5-Year Results**

- These findings provide the longest-term data on patients with advanced lung cancer treated with pembrolizumab.
- The findings demonstrate greatly improved survival on pembrolizumab compared with historical expectations.
- Survival is related to PD-L1 expression level, but responses are seen at all levels.

olina, commented: “These data are similar to what we have seen in other cancers treated with immunotherapy in that there is a population of patients who can live for 5 years or more. It’s truly remarkable that for more patients than ever before, we no longer have to count survival in months.”

“We used to have to tell patients their chances down the road were uniformly bad. Now one in four of them will be around in 5 years. This changes our mind set,” Dr. Graham added.

“Another important point is that appropriately funded studies are needed to gather data like these over time. Without such funding, we would not have learned that this group of people were alive at 5 years. This highlights the theme of our meeting. We are learning from our patients every day,” Dr. Graham said.

“We still have a long way to go to improve outcomes for all patients with advanced NSCLC. We look forward to more research that will help us determine the best way to select patients for treatment,” Dr. Graham added.

**KEYNOTE-001**

The patients enrolled in KEYNOTE-001 were the first cohort to receive pembrolizumab for advanced lung cancer, and the 5-year results presented at the 2019 ASCO Annual Meeting represent mature overall survival.

“The phase I trial enrolled more than 1,000 patients and led to approval for melanoma and the PD-L1 diagnostic assay,” Dr. Garon reminded the audience.

In 2016, pembrolizumab was approved as first-line treatment for advanced NSCLC that lacked *EGFR* or *ALK* mutations but expressed PD-L1 on 50% or more of tumor cells. Expanded approval was granted for the front-line treatment of patients with stage III NSCLC who are not amenable to surgery or radiation or who have

NSCLC with PD-L1 expression of more than 1% and no *EGFR* or *ALK* mutation.

KEYNOTE-001 included 550 patients with advanced lung cancer; 449 received previous systemic treatment and 101 were treatment-naive. Patients were treated with pembrolizumab at 2 mg/kg body weight every 3 weeks or 10 mg/kg every 2 or 3 weeks. The protocol has been changed, and now the typical regimen is a single dose of 200 mg regardless of body weight every 3 weeks.

At a median follow-up of 60.6 months, 100 patients enrolled in KEYNOTE-001 were still alive. The median duration of treatment was 3.3 months (range, 1 day–75.9 months). A total of 60 patients were treated with pembrolizumab for 2 years or longer (14 [14%] in the treatment-naive group and 46 [10%] in the previously treated group).

**Key Findings**

The median overall survival was 22.3 months for treatment-naive patients and 10.5 months for previously treated patients. Among treatment-naive patients, the 2-year overall survival rate was 49%, the 3-year overall survival rate was 37%, and the 4-year overall survival rate was 31%. Among previously treated patients, the overall survival rates at 2, 3, and 4 years were 30.1%, 20.9%, and 18.2%, respectively.

PD-L1 expression of at least 50% was associated with longer overall survival. Among treatment-naive patients with PD-L1 expression of at least 50%, the median overall survival was 35.4 months, and the 5-year overall survival rate was 29.6%. Among patients with PD-L1 expression between 1% and 49%, the median overall survival was 19.5 months, and the 5-year survival was 15.7%.

Among previously treated patients with PD-L1 expression of at least 50%, the median overall survival was 15.4 months, and the 5-year overall survival was 25% compared with 8.5 months and 12.6% among patients with PD-L1 expression between 1% and 49%, and 8.6 months and 3.5% among patients with PD-L1 expression up to 1%.

Of the 100 patients alive at the data cutoff, 78% had an objective response, and complete responses were seen in 1 treatment-naive patient and 5 previously treated patients.

“These data are encouraging,” Dr. Garon stated. “Taken together with data from other randomized controlled trials, efficacy outcomes and the observed association between PD-L1 expression and overall survival are consistent. The results highlight the potential for long-term benefit that may be realized through individualized treatment selection.”

### Safety Profile

Treatment-related adverse events were reported in 71% of patients with lung cancer. Grades 3 to 5 treatment-related adverse events occurred in 13%. After the first report of safety in 2015, just three additional treatment-related grade 3 to 5 adverse events occurred—hypertension, glucose intolerance, and hypersensitivity reaction—as reported at a median of 3 years’ follow-up (Leighl et al., 2019).

Serious adverse events occurred in 42%, including 9% with treatment-related serious adverse events. A total of 31 patients discontinued pembrolizumab due to treatment-related adverse events, and 9 are still alive (7 in ongoing response). Two deaths due to treatment-related adverse events were reported, both within the first 32 days of treatment.

A total of 17% of patients experienced an immune-related adverse event, and 32 of these 92 patients were still alive at data cutoff. The most common immune-mediated adverse events of all grades included hypothyroidism (9%), pneumonitis (5%), and hyperthyroidism (2%). Grade 3 to 5 immune-related adverse events were reported in 4%.

### The Advanced Practitioner Perspective

Elizabeth S. Waxman, RN, MSN, AOCN®, ANP-BC, MD Anderson Cancer Center

This is very exciting news regarding the improved survival rate with an immunotherapy drug, pembrolizumab. All of the survival data show the benefit from treatment on KEYNOTE-001. Also, the data from KEYNOTE-001 demonstrate that immunotherapy is still tolerated and effective, with 60 patients on the clinical

### Additional Commentary

At an ASCO press conference, Senior Vice President and Chief Medical Officer of ASCO, Richard L. Schilsky, MD, FACP, FASCO, FSCT, commented on the phenomenon of the apparent lack of association of complete response with survival in patients treated with checkpoint inhibitor therapy. “There is a great deal of literature on the importance of achieving complete response in association with long-term outcomes in patients with cancer. This appears to be different with checkpoint inhibitor therapy. The lesion improves but does not go away completely,” Dr. Schilsky noted. Dr. Garon agreed and said it is not completely clear why this occurs.

Among 60 patients taking pembrolizumab for 2 or more years, the estimated 5-year survival was 78.6% in the treatment-naïve group and 75.8% in the previously treated group. ●

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trial treated over 2 years, and at median follow-up of 60.6 months (5.5 years), 100 patients were alive. Chemotherapy clinical trials did not have such results. The benefit of pembrolizumab was not confined to patients with high PD-L1 overexpression. KEYNOTE-001 demonstrates how immunotherapy has changed the treatment paradigm for NSCLC.

**Disclosure:** Ms. Waxman has no conflicts of interest to disclose.