

# First-Line Therapy for Metastatic Non–Small Cell Lung Cancer: State-of-the-Art Targeted Therapy and Immunotherapy Approaches

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Presenters' disclosures of conflicts of interest are found at the end of this article.

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## Abstract

At JADPRO Live 2019, Joshua Bauml, MD, and Christina Knepley, CRNP, discussed how to devise treatment plans for patients with metastatic non–small cell lung cancer, including using biomarkers to guide treatment selection, understanding clinical data supporting the use of targeted and immune checkpoint inhibitor therapies, and managing adverse events.

**T**he treatment paradigm for metastatic non–small cell lung cancer (NSCLC) has changed dramatically in the past few years. At JADPRO Live 2019, Joshua Bauml, MD, and Christina Knepley, CRNP, of Penn Medicine, discussed the use of biomarkers to guide the selection of first-line therapy for metastatic NSCLC. The presenters also evaluated clinical data supporting first-line treatment with targeted and immune checkpoint inhibitors and outlined effective management strategies for adverse events associated with these agents.

## EPIDEMIOLOGY AND BIOMARKERS

Dr. Bauml, an Assistant Professor of Medicine at the Perelman School of

Medicine at the University of Pennsylvania and the Co-Deputy Director of Clinical Research for the airways program at the Abramson Cancer Center, highlighted the difference between the two main types of lung cancer: NSCLC, which accounts for 80% to 85% of cases, and small cell lung cancer, which accounts for 10% to 15%. As Dr. Bauml reported, adenocarcinoma is the most common subtype of NSCLC and is present both in smokers and among never and light smokers. Adenocarcinoma is also more common in women than men, younger people in general, and is typically found in the outer areas of the lung. Squamous cell carcinoma, on the other hand, tends to be central and is commonly associated with smoking.

“If someone has a diagnosis of squamous cell lung cancer, and they are a never smoker, I may doubt that pathologic diagnosis, so we really need go back to the biopsy to see whether it is accurate,” said Dr. Bauml.

As Dr. Bauml explained, National Comprehensive Cancer Network (NCCN) Guidelines recommend molecular testing for the following biomarkers in advanced or metastatic adenocarcinoma, large cell carcinoma, or NSCLC not otherwise specified:

- *EGFR* mutation testing (category 1)
- *ALK* testing (category 1)
- *ROS1* testing (category 2A)
- *BRAF* testing (category 2A)
- PD-L1 testing (category 1)
- Broad molecular profiling to identify rare oncogenic drivers for which targeted therapies are available

In advanced or metastatic squamous cell carcinoma, NCCN Guidelines recommend molecular testing for the following biomarkers in advanced or metastatic squamous cell carcinoma:

- PD-L1 testing (category 1)
- Consider *EGFR* mutation testing and *ALK* testing in never smokers or small biopsy specimens or with mixed histology (category 2A)
- Consider *ROS1* and *BRAF* testing in small biopsy specimens or mixed histology (category 2A)
- Testing should be conducted as part of broad molecular profiling (category 2A).

## EGFR OVERVIEW

As Dr. Bauml reported, *EGFR* inhibitors target *EGFR* mutations. Most patients with *EGFR* mutations are nonsmokers or former light smokers with adenocarcinoma histology, said Dr. Bauml, who noted that sensitizing mutations occur in approximately 10% to 15% of Caucasian patients with NSCLC and up to 20% to 30% of Asian patients (Choughule et al., 2013).

The most commonly found mutations include exon 19 deletion (approximately 45% of patients) and point mutation in exon 21 (L858R, approximately 40% of patients). G719X, S768I, and L861Q, on the other hand, are less common mutations, occurring in approximately 10% of patients. As Dr. Bauml explained, these sensitizing mutations result in constitutive activation of the kinase and are associated with sensitivity to small molecule *EGFR* tyrosine kinase inhibitors (TKIs).

“Patients with tumors that do not have sensitizing *EGFR* mutations should not be treated with *EGFR* TKIs in any line of therapy,” he emphasized (Table 1).

The 2018 approval of osimertinib was based on the FLAURA multicenter, international, randomized, double-blind, active-controlled trial, which enrolled 556 previously untreated patients with *EGFR* exon 19 deletion or exon 21 L858R mutation-positive, unresectable or metastatic NSCLC (Soria et al., 2018).

Patients with untreated sensitizing mutations in *EGFR* were randomized to osimertinib

**Table 1. Overview of *EGFR* Tyrosine Kinase Inhibitors**

Agent	Brand name	Approval in NSCLC	Indication in NSCLC
Gefitinib	Iressa	2003	First-line treatment: metastatic NSCLC with <i>EGFR</i> exon 19 deletions or exon 21 (L858R) substitution mutation
Erlotinib	Tarceva	2004	First-line, maintenance, or second-line or greater treatment: metastatic NSCLC with <i>EGFR</i> exon 19 deletions or exon 21 (L858R) substitution mutation
Afatinib	Gilotrif	2013	First-line treatment: metastatic NSCLC with nonresistant <i>EGFR</i> mutations Second-line treatment: metastatic squamous NSCLC progressing after platinum-based chemotherapy
Osimertinib	Tagrisso	2018	First-line treatment: metastatic NSCLC with exon 19 deletion or exon 21 (L858R) mutation Second-line treatment: metastatic <i>EGFR</i> T790M mutation-positive NSCLC progressing on or after <i>EGFR</i> tyrosine kinase inhibitor therapy
Dacomitinib	Vizimpro	2018	First-line treatment: metastatic NSCLC with <i>EGFR</i> exon 19 deletion or exon 21 L858R substitution mutation

or a standard EGFR TKI (investigators' choice of gefitinib or erlotinib), and the results showed a marked improvement in progression-free survival and overall survival with the use of osimertinib. Osimertinib was also better tolerated than gefitinib or erlotinib, said Dr. Bauml, who highlighted the significantly lower rates of rash, which is a "major problem" with other EGFR inhibitors.

### ALK/ROS1 OVERVIEW

As Dr. Bauml explained, most patients with *ALK* and *ROS1* rearrangements are light or never smokers. In addition, most patients with *ALK* rearrangements have adenocarcinoma histology, and *ROS1* rearrangements occur more frequently in patients who are negative for *EGFR*, *KRAS*, and *ALK* gene rearrangements. The NCCN Guidelines recommend that all patients with metastatic nonsquamous NSCLC be tested for *ALK* rearrangements, said Dr. Bauml, but testing may be considered in other patients with small biopsy specimens or mixed histology or those who are light or never smokers. *ROS1* testing is recommended in patients with metastatic nonsquamous NSCLC and can be considered in some patients with metastatic squamous cell carcinoma.

Current therapy for *ALK*-rearranged NSCLC is based on data from the ALEX study, which randomized patients with *ALK* translocated NSCLC to alectinib or crizotinib and demonstrated a marked improvement in progression-free survival (Camidge et al., 2019).

"Remarkably, the duration of response is still not at the median after 2 years of follow-up," said Dr. Bauml, who noted that both osimertinib and

alectinib have shown the ability to penetrate the blood-brain barrier and thus have efficacy against metastases in the central nervous system. "In addition, although both alectinib and crizotinib are well-tolerated drugs, the data showed improved safety outcomes for alectinib."

### BRAF AND NTRK OVERVIEW

Unlike in melanoma, where many *BRAF* mutations are sensitizing to *BRAF* inhibitors, said Dr. Bauml, in *BRAF*-mutant lung cancer, it is only V600E that should be clinically targeted, and dabrafenib and trametinib are FDA approved in this setting. For *NTRK*, there are now two drugs for the management of *NTRK*-fusion cancers.

"The latter occurs in less than 1% of patients, and there are now two drugs available in this space (larotrectinib and entrectinib), which shows just how exciting this field is," said Dr. Bauml (Table 2).

With multiple lines of therapy available for many mutations, Dr. Bauml emphasized the importance of reaching out to colleagues at other institutions for guidance.

"This is a complicated field for targeted therapies, so it's important to work as a community to figure out how to best take care of these patients," he said. "It's also important to note that while chemotherapy is still active for these diseases, immunotherapy tends not to be."

### PD-L1: IMMUNOTHERAPY OVERVIEW

In patients with NSCLC who don't have molecular targets, immune checkpoint inhibitors are available to target programmed cell death ligand 1 (PD-L1) and its receptor, PD-1. Dr. Bauml summarized

**Table 2. Emerging Targets in NSCLC**

Genetic alteration	Available targeted agents with activity in lung cancer	Other agents (not FDA-approved)
High-level <i>MET</i> amplification or <i>MET</i> exon 14 skipping mutation	Crizotinib	Tepotinib
RET rearrangements	Cabozantinib Vandetanib	Pralsetinib Selpercatinib
ERBB2 (HER2) mutations	Ado-trastuzumab emtansine	TAK-788
Tumor mutational burden (TMB)	Nivolumab + ipilimumab Nivolumab	N/A

*Note.* Information from Chandrashekhhar (2018); Drilon et al. (2019); European Society for Medical Oncology (2019); Paik et al. (2019); National Comprehensive Cancer Network (2019).

several key trials that have informed the use of immunotherapy in patients with NSCLC.

“If you don’t have molecular data back, you have to be hesitant about starting them on treatment, and specifically starting them on immunotherapy, regardless of PD-L1 status,” he emphasized. “If you start them on immunotherapy, sometimes you are unable to safely administer the targeted therapy, so it’s absolutely essential that you be aware of that before you start treatment.”

#### **KEYNOTE-024:**

##### **Pembrolizumab vs. Platinum Doublet**

In patients with advanced NSCLC and PD-L1 expression on at least 50% of tumor cells, pembrolizumab was associated with significantly longer progression-free and overall survival with fewer adverse events than platinum-based chemotherapy (Reck et al., 2019). Median progression-free survival was 10.3 months in the pembrolizumab group vs. 6.0 months in the chemotherapy group, and estimated overall survival at 6 months was 80.2% in the pembrolizumab group vs. 72.4% in the chemotherapy group. Based on these data, pembrolizumab was FDA approved for patients with greater than 50% PD-L1 expression.

#### **KEYNOTE-042:**

##### **Pembrolizumab vs. Platinum Doublet**

The benefit-to-risk profile suggests that pembrolizumab monotherapy can be extended as first-line therapy to patients with locally advanced or metastatic NSCLC without sensitizing *EGFR* or *ALK* alterations and with low PD-L1 expression. According to Dr. Bauml, however, even though this study led to an FDA approval for patients who have PD-L1 expression greater than or equal to 1%, there is no benefit over chemotherapy (Mok et al., 2019).

“For patients with less than 50% PD-L1 expression, I personally do not recommend pembrolizumab monotherapy over chemotherapy,” said Dr. Bauml. “In fact, in the early parts of the survival curve, pembrolizumab was actually worse, so this is an issue that we need to be aware of.”

#### **KEYNOTE-189:**

##### **Carboplatin/Pemetrexed ± Pembrolizumab**

However, there are still options for patients with lower PD-L1 expression. KEYNOTE-189 random-

ized patients with adenocarcinoma (excluding patients with NSCLC harboring a molecular driver) to carboplatin/cisplatin with pemetrexed with a placebo, or carboplatin/cisplatin with pemetrexed and pembrolizumab. The results showed an improved overall survival in the immunotherapy cohort over the platinum doublet regardless of PD-L1 status (Gandhi et al., 2018).

“This study makes it straightforward: For any patient who does not have a molecular driver and has adenocarcinoma, platinum, pemetrexed with pembrolizumab is a reasonable approach,” said Dr. Bauml.

#### **KEYNOTE-407:**

##### **Carboplatin/Taxane ± Pembrolizumab**

This study randomized patients to carboplatin and paclitaxel, either nanoparticle albumin-bound or solvent-based with pembrolizumab or a placebo. After 4 cycles, patients were placed on pembrolizumab or placebo maintenance. These results also showed an improvement in overall survival with the addition of pembrolizumab regardless of PD-L1 status (Paz-Ares et al., 2018).

“Based on this study, for a patient with squamous disease, regardless of their PD-L1 status, we can give them a combination of platinum, taxane, and pembrolizumab,” said Dr. Bauml. “For patients who have greater than 50% PD-L1 expression, we now have two options: We can still give them pembrolizumab monotherapy or we can give them histology-appropriate chemoimmunotherapy.”

#### **IMpower150: First-Line Atezolizumab**

Finally, the three-arm IMpower150 study randomized patients with squamous NSCLC to carboplatin, paclitaxel, bevacizumab, atezolizumab; or carboplatin, paclitaxel, atezolizumab; or carboplatin, paclitaxel, bevacizumab. The study also allowed patients with *EGFR* or *ALK* alterations provided they had failed a prior TKI. As Dr. Bauml reported, there was an improvement in overall survival with the use of the quadruplet regimen, and this is now FDA approved (Socinski et al., 2018).

## **IMMUNOTHERAPY-RELATED ADVERSE EVENTS**

Ms. Knepley, an oncology nurse practitioner at the Abramson Cancer Center Hospital at the

University of Pennsylvania, outlined the adverse events associated with immunotherapy. Although patients need not worry about the traditional chemotherapy side effects like nausea and vomiting, said Ms. Knepley, immunotherapy toxicity is real.

“Patients and providers need to watch out for pneumonitis, colitis, dermatitis, hepatitis, nephritis, and endocrinopathy,” she cautioned. “Basically, any symptom that ends in ‘-itis’ can occur” (Table 3).

According to Ms. Knepley, although manageable, immunotherapy toxicity often requires multidisciplinary care. However, the general approach is 1 mg/kg of steroids except for endocrine adverse events.

“We always involve appropriate specialties when we need help,” Dr. Bauml added. “If I have a patient who has hypophysitis, for example, I’m going to ask for help from doctors who have spent their whole lives thinking about endocrine and hormones.” ●

### Disclosure

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**Table 3. Management of Pneumonitis**

Grade	Treatment
1	<ul style="list-style-type: none"> <li>Increased monitoring</li> <li>If evidence of progression, treat at higher grade</li> </ul>
2	<ul style="list-style-type: none"> <li>Immunotherapy should be withheld and steroids (e.g., prednisone 1 mg/kg daily) administered</li> <li>If symptoms improve to ≤ grade 2, start slow steroid taper over &gt; 1 month</li> <li>If symptoms do not improve, or worsen, treat as grade 3–4</li> </ul>
3/4	<ul style="list-style-type: none"> <li>Permanently discontinue immunotherapy (except endocrinopathies and skin toxicity)</li> <li>Initiate methylprednisolone IV, 2 mg/kg/day; consider hospitalization and ICU care</li> <li>Taper steroids over &gt; 2 months</li> <li>If persistent with steroids, consider alternative immunosuppressive agents (infliximab at 5 mg/kg)</li> <li>Consider drug rechallenge on a case-by-case basis after discussions weighing risk/benefit with the patient and only if symptoms and imaging abnormalities resolve</li> <li>Permanently discontinue for grade 4</li> </ul>

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