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Winter Lung Cancer CONFERENCE™ UPDATE

A Message From the Chair

Heather A. Wakelee, MD

The field of lung cancer is always changing. With each passing year, the number of agents, lines of therapy, and targets for treatment grows. This year was no different.

2018 saw the approval of or expanded indication for the EGFR inhibitors afatinib, dacomitinib, and osimertinib, checkpoint inhibitors atezolizumab, durvalumab, nivolumab, and pembrolizumab, and the ALK inhibitor lorlatinib—to name a few.

Whether the change is to frontline treatment, metastatic disease, squamous or non-squamous non-small cell lung cancer (NSCLC), or small cell disease, every advancement made is an exciting time for our patients and another reminder of the importance of continued education.

With new approvals comes a multitude of data to decipher, recommendations to incorporate, practice changes to make, and patients to consider. Now, as the new year approaches it's time again for the **Winter Lung Cancer Conference™**. It's time to gather once again, review everything that's changed in 2018, and prepare for all the changes to come in 2019.

I can't wait to see you in Miami!

Sincerely,

Heather A. Wakelee, MD
Professor, Medicine (Oncology)
Stanford University Medical Center
Program Chair, Winter Lung Cancer Conference™
Stanford, CA

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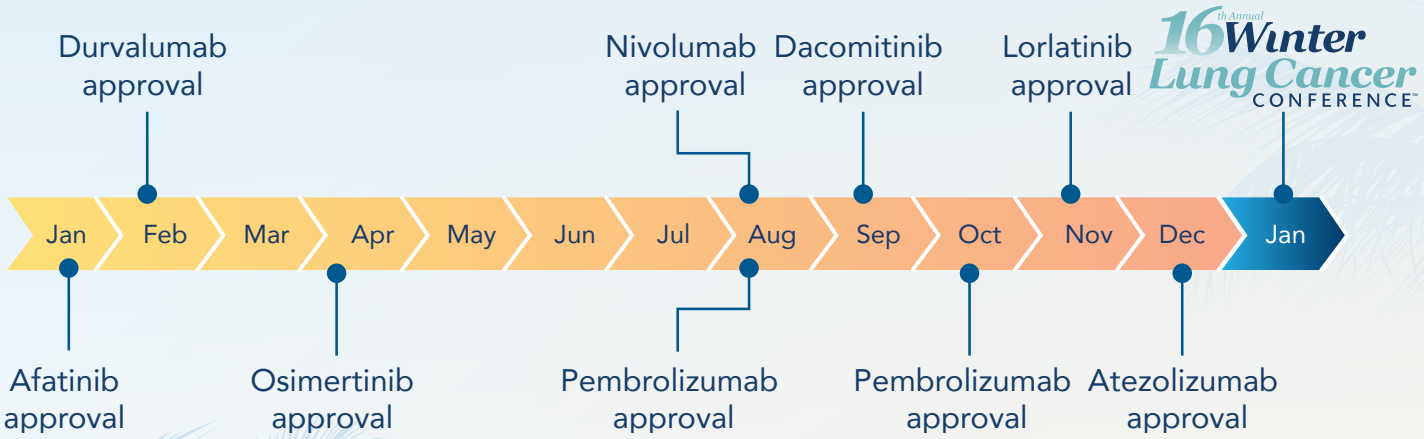

AFATINIB

After its initial approval in 2013 for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with exon 19 deletions or exon 21 L858R substitutions, **afatinib** was expanded to include patients with squamous histology following progression on a platinum-based chemotherapy in 2016.

Now in January of 2018, the FDA expanded the frontline indication for afatinib to include the treatment of patients with metastatic NSCLC whose tumors harbor the uncommon *EGFR* alterations: L861Q, G719X, and/or S768I.

This approval was based on findings from the phase II **LUX-Lung 2** trial (LL2) and the randomized phase III trials known as **LUX-Lung 3** (LL3) and LUX-Lung 6 (LL6). The objective response rate (ORR) across the 3 trials with **afatinib** was 66% (95% CI, 47%-81%). Among patients who responded, 52% had a duration of response (DoR) lasting longer than 12 months.

DURVALUMAB

In February of this year, the FDA approved the PD-L1 inhibitor **durvalumab** for the treatment of patients with locally advanced, unresectable stage III NSCLC who have not progressed following chemoradiotherapy.

This approval was based on the phase III **PACIFIC** trial, in which **durvalumab** improved median progression-free survival (PFS) by 11.2 months compared with placebo (16.8 vs 5.6 months). The 12-month PFS rate was 55.9% versus 35.3%, and the 18-month PFS rate was 44.2% versus 27.0%, for **durvalumab** and placebo, respectively.

OSIMERTINIB

In April, **osimertinib** was approved as a first-line treatment option for patients with *EGFR*-mutated NSCLC based on the phase III **FLAURA** study.

In this trial **osimertinib** reduced the risk of progression or death by 54% compared with standard therapy with erlotinib or gefitinib. In the study, the median PFS was 18.9 months (95% CI, 15.2-21.4) with **osimertinib** compared with 10.2 months (95% CI, 9.6-11.1) for standard therapy.

NIVOLUMAB

Then in August, the PD-1 inhibitor **nivolumab** was approved as a single agent for metastatic small cell lung cancer (SCLC) following progression on platinum-based chemotherapy and at least one other line of therapy.

The approval is based on the durability of responses in the phase I/II **CheckMate-032** trial, in which the ORR was 12% (95% CI, 6.5-19.5) for **nivolumab** following platinum-based chemotherapy and one other prior line. The median DoR was 17.9 months, with 62% of patients continuing to respond at 12 months. This was the first approval in SCLC in nearly 20 years.

PEMBROLIZUMAB

Checkpoint inhibitor approvals continued in lung cancer this year with an indication for **pembrolizumab**, another PD-1 inhibitor in chemotherapy combinations in the first-line for both squamous and non-squamous NSCLC.

In late August of this year, the FDA granted a full approval to frontline **pembrolizumab** in combination with platinum-based chemotherapy plus pemetrexed for patients with **non-squamous** NSCLC, based on findings from the phase III **KEYNOTE-189** trial. In this trial, the addition of **pembrolizumab** to pemetrexed and either cisplatin or carboplatin reduced the risk of death by 51%. At the time of approval, the median overall survival (OS) had not been reached with **pembrolizumab** compared with 11.3 months in the chemotherapy-alone arm. The estimated 12-month OS rate was 69.2% in the immune-chemotherapy combination arm compared with 49.4% for chemotherapy alone.

Then at the end of October, the FDA approved first-line use of **pembrolizumab** in combination with carboplatin and either paclitaxel or nab-paclitaxel for the treatment of patients with metastatic **squamous** NSCLC, based on results from the phase III KEYNOTE-407 trial. Here, **pembrolizumab** plus chemotherapy reduced the risk of death by 36% compared with chemotherapy alone in patients with metastatic disease. The median OS was 15.9 months with **pembrolizumab** versus 11.3 months with chemo alone Overall survival benefit was observed regardless of PD-L1 expression level, choice of chemotherapy, age, sex, or performance status.

DACOMITINIB

In late September, the FDA approved **dacomitinib** for the frontline treatment of patients with metastatic *EGFR*-mutated NSCLC based on the phase III **ARCHER 1050** trial. Investigators showed, **dacomitinib** resulted in an average 6.5-month improvement in response duration compared with gefitinib as a first-line treatment.

The median PFS was 14.7 months on **dacomitinib** compared with 9.2 months on gefitinib. The median DoR was 14.8 months versus 8.3 months, respectively.

LORLATINIB

Approvals for targeted therapies continued through the Fall with **lorlatinib** for the treatment of patients with *ALK*-positive metastatic NSCLC who have progressed following one or more ALK TKIs. Specifically following crizotinib and at least one other ALK inhibitor for metastatic disease or either alectinib or ceritinib as the first ALK inhibitor therapy for metastatic disease.

This approval was based on a nonrandomized, dose-ranging, phase II study that included a subgroup of 215 patients with *ALK*-positive metastatic NSCLC previously treated with one or more ALK kinase inhibitors. The ORR with **lorlatinib** in these patients was 48% including a complete response rate of 4%. The median DoR was 12.5 months.

ATEZOLIZUMAB

Finally, in early December, the PD-L1 inhibitor **atezolizumab** was approved for use in combination with bevacizumab, carboplatin, and paclitaxel for the first-line treatment of patients with metastatic non-squamous NSCLC without a sensitizing mutation.

The approval is based on findings from the phase III **IMpower150** trial, in which the combination regimen reduced the risk of death by 22% compared with bevacizumab and chemotherapy.

Additionally, the median OS with the addition of **atezolizumab** was 19.2 months compared with 14.7 months in the control arm.

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"THE TOPICS ARE VERY INTERESTING, COVERING EMERGING THERAPIES. I WILL BE BACK NEXT YEAR!"

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