New Lung Cancer Treatment Strategies

Lung Cancer Initiative Advocacy Summit
Carrie Lee, MD, MPH
May 22, 2021
Advancing Survivorship
Overview

• Non-small cell lung cancer
  • Early stage
  • Spread to lymph nodes
  • Late stage

• Small Cell lung cancer
Non-Small Cell vs. Small Cell Lung Cancer

- Small cell lung cancer: 40%
  - Adenocarcinoma: 15%
  - Squamous cell carcinoma: 15%
  - Large cell carcinoma: 30%
Overview of Lung Cancer Stages

Stage I: Small, isolated to lung tissue

Stage II: Larger but isolated to lung +/- local lymph nodes

Stage III: Involving lung and more distant (but still regional) lymph nodes or invading critical structures

Stage IV: Distant spread to other organs, non-regional lymph nodes, the other lung, or malignant fluid
The cancer fighting toolbox

<table>
<thead>
<tr>
<th></th>
<th>Chemotherapy</th>
<th>Targeted Therapy</th>
<th>Immunotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>How does it work?</strong></td>
<td>Targets rapidly dividing cells (mostly cancer cells)</td>
<td>Targets Proteins required for cancer growth</td>
<td>Uses our immune system against cancer</td>
</tr>
<tr>
<td><strong>Side Effects</strong></td>
<td>Hair loss, intestinal damage, nausea</td>
<td>Liver problems, diarrhea, skin rash</td>
<td>Autoimmune effects</td>
</tr>
<tr>
<td><strong>Limitations</strong></td>
<td>Cancer cells develop resistance to chemotherapy, not specific</td>
<td>Cancer cells develop resistance</td>
<td>Tailored and expensive</td>
</tr>
</tbody>
</table>
Non-Small Cell Lung Cancer: Not One Disease, but Many!

Some DNA Mutations in Cancer Cells are Driver Mutations

NORMAL CELL

unfixable DNA damage

apoptosis

CANCER CELL

cell continues dividing

Adenocarcinoma

KRAS 25%

EGFR Sensitizing 17%

ALK 7%

MET 3%

> 1 Mutation 3%

HER2 2%

ROS1 2%

BRAF 2%

RET 2%

NTRK < 1%

PIK3CA 1%

MEK1 < 1%

No Known Oncogenic Driver Detected 31%
**Tissue Biopsy at Diagnosis is Essential**

**Subtype**
- NSCLC
  - Squamous or nonsquamous?[^1]

**For mutation testing:**
- Primary tumors and metastatic lesions equally suitable[^2]
- Liquid biopsies (cell-free DNA in plasma) when tissue not available[^3]

**Non-squamous (Adenocarcinoma)**

\[
\text{EGFR/ALK/ROS1/BRAF V600E}[^4]\]

Broad molecular testing by next-generation sequencing is preferred to detect a wider range of mutations[^4,5]

**Squamous**

At very least, consider molecular testing in young, never, or light smokers or if biopsy specimen is small or has mixed histology[^2]

**Determination of PD-L1 expression indicated in all NSCLC[^4]**

[^5]: Kalemkerian. JCO. 2018;36:911.
Liquid Biopsy

• What is liquid biopsy?
  • Blood sample containing cell-free DNA from multiple sources, including DNA shed from tumor

• When do we use liquid biopsy?
  • Molecular testing is needed but amount of available biopsy tissue is inadequate or tissue biopsy not possible
  • Resistance to targeted therapies

• Advantages
  • Minimally invasive

• Limitations
  • Sensitivity: 70%-80%; specificity: near 100%
  • Negative result is noninformative
Early Stage NSCLC
Chemotherapy has limited benefit in early stage/surgically removed NSCLC

- Meta-analysis: Lung Adjuvant Cisplatin Evaluation (LACE)
- 5 studies since 1995
  - Pooled individual data of 4585 patients
- Chemotherapy
  - ↓6.9% lung cancer death
  - ↑1.4% non-cancer death


HR 0.89 (95% CI 0.82 – 0.96); p = 0.005
Absolute benefit 5.4% at 5 years
New targeted therapy option in EGFR mutant NSCLC

ADAURA: Study Design

- International, randomized, double-blind phase III trial (data cutoff for interim analysis: 1/17/2020)
  - IDMC recommended early unblinding due to efficacy; at time of unblinding, trial had completed enrollment and all patients had ≥ 1 yr of follow-up

Patients with completely resected stage IB/II/IIIA NSCLC with negative margins; primary nonsquamous NSCLC with EGFR ex19del or L858R*; aged ≥ 18 yrs (≥ 20 yrs in Japan/Taiwan); WHO PS 0/1; brain imaging done; adj CT permitted; maximum time from surgery to randomization: 10 wks without adj CT, 26 wks with adj CT (N = 682)

- Stratified by stage (IB vs II vs IIIA), EGFR mutation (ex19del vs L858R), race (Asian vs non-Asian)

Osimertinib 80 mg QD (n = 339)

Placebo QD (n = 343)

Until 3 yrs, recurrence, or d/c criterion met*

- Primary endpoint: investigator-assessed DFS in patients with stage II/IIIA disease
  - Trial designed to test superiority with assumed DFS HR of 0.70

- Secondary endpoints: DFS in overall population; landmark DFS rates at Yrs 2, 3, 4, and 5; OS; HRQoL; safety

*Confirmed centrally in tissue. *Follow-up: until recurrence, Wks 12 and 24, then Q24W to 5 yrs, then yearly; after recurrence, Q24W for 5 yrs, then yearly.


Slide credit: clinicaloptions.com
ADAURA: DFS in Patients With Stage II/IIIA NSCLC (Primary Endpoint)

Adjuvant osimertinib significantly prolonged DFS vs placebo in stage II/IIIA disease \( (P < .0001) \)

- Median DFS, Mos
  - Osimertinib: 20.4 Mos
  - Placebo: NR

- HR: 0.17 (95% CI: 0.12-0.23)
  \[ P < .0001 \]

- Maturity: 33% (osimertinib, 11%; placebo, 55%)

Approved by FDA December 2020
ADAURA: Early OS in Patients With Stage II/IIIA NSCLC

Median OS, Mos

- **Osimertinib**: NR
- **Placebo**: NR

HR: 0.40 (95% CI: 0.18-0.90)

**Maturity**: 5% (osimertinib: 3%; placebo: 7%)

Stage III NSCLC
Ongoing immunotherapy benefit in Stage III NSCLC: PACIFIC

- Randomized, double-blind, placebo-controlled phase III trial

Stratified by age (< 65 vs ≥ 65 yrs), sex, and smoking history (current/former vs never)

- Adult patients with locally advanced, unresectable stage III NSCLC without PD after ≥ 2 cycles definitive platinum-based CT* concurrent with RT†; WHO PS 0/1; regardless of PD-L1 status‡ (N = 713)

- Tx initiation 1-42 days post concurrent CRT

Durvalumab 10 mg/kg IV Q2W for up to 12 mos (n = 473)

Placebo IV Q2W for up to 12 mos (n = 236)

Until disease progression or unacceptable toxicity

*Platinum-based CT contained etoposide, vinorelbine, paclitaxel, docetaxel, vinblastine, or pemetrexed.
†92% of patients received 54 Gy to 66 Gy RT dose. ‡If available, archived pre-cCRT tumor tissue tested for PD-L1.

PACIFIC: Overall Survival with Durvalumab at 4 Years

<table>
<thead>
<tr>
<th></th>
<th>No. of events/ total no. of patients (%)</th>
<th>Median OS (95% CI), months</th>
<th>12-month OS rate (95% CI) %</th>
<th>24-month OS rate (95% CI) %</th>
<th>36-month OS rate (95% CI) %</th>
<th>48-month OS rate (95% CI) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Durvalumab</td>
<td>247/476 (51.9)</td>
<td>47.5 (38.4–52.6)</td>
<td>83.1 (79.4–86.2)</td>
<td>66.3 (61.8–70.4)</td>
<td>56.7 (52.1–61.1)</td>
<td>49.6 (44.9–54.1)</td>
</tr>
<tr>
<td>Placebo</td>
<td>149/237 (62.9)</td>
<td>29.1 (22.1–36.1)</td>
<td>74.6 (68.5–79.7)</td>
<td>55.3 (48.6–61.4)</td>
<td>43.6 (37.1–49.9)</td>
<td>38.3 (30.1–42.6)</td>
</tr>
</tbody>
</table>

Stratified HR for death, 0.71 (95% CI: 0.57–0.88)

Stratified HR for death from the primary analysis, 0.68 (95% CI: 0.53–0.87)
Targeted Therapy in Stage IV NSCLC
Non-Small Cell Lung Cancer: Not One Disease, but Many!

NSCLC as one disease

Adenocarcinoma

No Known Oncogenic Driver Detected 31%
KRAS 25%
EGFR Sensitizing 17%
ALK 7%
EGFR Other 4%
MET 3%
> 1 Mutation 3%
HER2 2%
ROS1 2%
BRAF 2%
RET 2%
NTRK < 1%
PIK3CA 1%
MEK1 < 1%

Then  Histology-Based Subtyping  Now

## FDA Approved Agents for Advanced NSCLC

<table>
<thead>
<tr>
<th>Gene/Target</th>
<th>FDA-Approved Agent</th>
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<tbody>
<tr>
<td>ALK fusion</td>
<td>Alectinib, brigatinib, ceritinib, crizotinib, lorlatinib</td>
</tr>
<tr>
<td>BRAF V600E</td>
<td>Dabrafenib + trametinib</td>
</tr>
<tr>
<td>EGFR</td>
<td>Afatinib, dacomitinib, erlotinib, gefitinib, osimertinib</td>
</tr>
<tr>
<td>EGFR T790M</td>
<td>Osimertinib</td>
</tr>
<tr>
<td>MET exon 14</td>
<td>Capmatinib</td>
</tr>
<tr>
<td>NTRK1/2/3 fusions</td>
<td>Entrectinib†; larotrectinib†</td>
</tr>
<tr>
<td>RET fusions</td>
<td>Pralsetinib, selpercatinib</td>
</tr>
<tr>
<td>ROS1 fusion</td>
<td>Crizotinib, entrectinib</td>
</tr>
<tr>
<td>PD-1/PD-L1</td>
<td>Atezolizumab, durvalumab, nivolumab, nivolumab/ipilimumab, pembrolizumab</td>
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</tbody>
</table>

Amivantamab FDA approved 5.21.21
Poziotinib fast tracked 3.11.21
Some highlights...

- ALK positive
- MET exon 14 skipping mutation
- RET fusion
- KRAS G12C
Overall survival gains in ALK-Positive Disease

-Median Overall Survival from initial diagnosis = 81 mos (almost 7 yrs)

-Brain metastasis did not influence OS

Figure 1.
Overall survival from diagnosis of stage IV anaplastic lymphoma kinase gene rearrangement positive (ALK-positive) NSCLC. The 95% confidence interval is indicated by the shaded area.

Phase III CROWN Trial: First line Lorlatinib in ALK+ NSCLC

Approved by FDA for 1st line treatment March 2021

- Has not been compared to alectinib in front line
- Excellent CNS activity
- Toxicity profile; lipids, neurotoxicity
Phase II Lorlatinib: Efficacy in Patients With ≥ 2 Prior ALK TKIs (± CT)

- Pooled data from EXP4 (2 ALK TKIs ± CT), EXP5 (3 ALK TKIs ± CT)
  - 83 patients (75%) had brain metastases at baseline

<table>
<thead>
<tr>
<th>Outcome</th>
<th>n = 111</th>
</tr>
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<tbody>
<tr>
<td>ORR, n (%); 95% CI</td>
<td>43 (39; 30-49)</td>
</tr>
<tr>
<td>Intracranial ORR, n/N (%)</td>
<td>26/49 (53)</td>
</tr>
<tr>
<td>Median DoR, mos (95% CI)</td>
<td>NR (5.5-NR)</td>
</tr>
<tr>
<td>DoR ≥ 6 mos, n/N (%)</td>
<td>20/43 (47)</td>
</tr>
<tr>
<td>Median PFS, mos (95% CI)</td>
<td>6.9 (5.4-9.5)</td>
</tr>
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</table>

*Patients with ≥ 1 on-study target lesion assessment as per ICR were included in overall and intracranial tumor response analysis.


Slide credit: clinicaloptions.com
Phase II GEOMETRY mono-1: Efficacy With Capmatinib in METex14 Mutation–Positive NSCLC

Approved by the FDA in May 2020

- Durability of response by BICR
  - DoR
    - 1L: 11.1 mos
    - 2L/3L: 9.7 mos
  - PFS
    - 1L: 9.7 mos
    - 2L/3L: 5.4 mos
- 54% (7/13) with intracranial response
Phase II VISION: Efficacy With Tepotinib in METex14 Mutation–Positive NSCLC

<table>
<thead>
<tr>
<th>Tumor Response by IRC</th>
<th>ORR, %</th>
</tr>
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<tbody>
<tr>
<td>Pt group, n</td>
<td></td>
</tr>
<tr>
<td>Liquid biopsy, 66</td>
<td>48.5</td>
</tr>
<tr>
<td>Tissue biopsy, 60</td>
<td>50.0</td>
</tr>
<tr>
<td>Line of therapy</td>
<td></td>
</tr>
<tr>
<td>First, 43</td>
<td>44.2</td>
</tr>
<tr>
<td>Second, 33</td>
<td>48.5</td>
</tr>
<tr>
<td>Second or later, 56</td>
<td>48.2</td>
</tr>
<tr>
<td>Third or later, 23</td>
<td>47.8</td>
</tr>
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</table>

- **Durability of response**
  - Overall DoR (n = 99): 11.1 mos
  - By L biopsy (n = 66): 9.9 mos
  - By T biopsy (n = 60): 15.7 mos
  - PFS:
    - By L biopsy (n = 66): 8.5 mos
    - By T biopsy (n = 60): 11.0 mos

- Both patients with and without CNS mets achieved benefit from treatment

Approved by the FDA in Feb 2021

Paik. NEJM 2020. [online ahead of print].

Slide credit: clinicaloptions.com
Phase I/II LIBRETTO-001: Efficacy With Selpercatinib (LOXO-292) in RET Fusion–Positive NSCLC

- Durability of response in primary analysis set
  - DoR: 20.3 mos
  - PFS: 18.4 mos
  - ORR, DoR, and PFS similar regardless of prior therapy

- Treatment-naive (n = 34)
  - ORR: 85%
  - DoR and PFS not reached

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Drilon. WCLC 2019. Abstr PL02.08.

Approved by the FDA in May 2020
Phase I/II ARROW: Efficacy With Pralsetinib (BLU-667) in RET Fusion–Positive NSCLC

- Durability of response in response evaluable patients
  - DoR: not reached
- Anti-tumor activity regardless of prior ICI, RET fusion genotype, or presence of CNS mets
- 5/7 (71%) of treatment-naive patients had confirmed PR

<table>
<thead>
<tr>
<th>Best Response</th>
<th>All Patients (N = 48)</th>
<th>Prior Plt (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, % (95% CI)</td>
<td>58 (43-72)</td>
<td>60 (42-76)</td>
</tr>
<tr>
<td>CR*</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>PR*</td>
<td>27</td>
<td>20</td>
</tr>
<tr>
<td>SD</td>
<td>18</td>
<td>14</td>
</tr>
<tr>
<td>PD</td>
<td>2</td>
<td>--</td>
</tr>
<tr>
<td>DCR, % (95% CI)</td>
<td>96 (86-99)</td>
<td>100 (90-100)</td>
</tr>
</tbody>
</table>

Maximum % Reduction From Baseline Sum of Diameters of Target Lesions

Anti-Tumor Activity With Pralsetinib (BLU-667) 400 mg QD in Response Evaluable Population (N = 48)


n = 4 excluded. *Confirmed responses on 2 consecutive assessments as per RECIST 1.1.
Approx 13% of NSLC

Associated w/resistance to targeted therapies and more difficult to treat
**KRAS\textsuperscript{G12C} Inhibition with Sotorasib in Advanced Solid Tumors**

**Efficacy Outcomes for Evaluable Patients**

<table>
<thead>
<tr>
<th></th>
<th>All NSCLC Patients (n = 59)</th>
<th>Dose of 960 mg (n = 34)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Best overall response, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>19 (32.2)</td>
<td>12 (35.3)</td>
</tr>
<tr>
<td>SD</td>
<td>33 (55.9)</td>
<td>19 (55.8)</td>
</tr>
<tr>
<td>PD</td>
<td>5 (8.5)</td>
<td>2 (5.8)</td>
</tr>
<tr>
<td><strong>ORR, %</strong></td>
<td>32.2</td>
<td>35.3</td>
</tr>
<tr>
<td><strong>DCR, %</strong></td>
<td>88.1</td>
<td>91.2</td>
</tr>
</tbody>
</table>

**Planned dose:**
- 180 mg
- 360 mg
- 720 mg
- 960 mg

![Graph showing change in tumor size from baseline](image)

*Evaluable Patients With NSCLC (n = 57)*

*Hong et al. NEJM. Sept 2020.*
KRYSR1: Best Tumor Response in NSCLC Cohort

- Local radiographic scans every 6 wks in 51 evaluable patients

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>NSCLC</th>
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<tbody>
<tr>
<td>Number of evaluable patients, n</td>
<td>51</td>
</tr>
<tr>
<td>ORR, %</td>
<td>45</td>
</tr>
<tr>
<td>DCR, %</td>
<td>96</td>
</tr>
<tr>
<td>Patients continuing treatment, n</td>
<td></td>
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</tbody>
</table>

Adagrasib (MRTX849)

What if there is no “actionable” mutation?
Success!

The New England Journal of Medicine

Original Article

Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer

The New England Journal of Medicine

Original Article

Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC

The New England Journal of Medicine

Original Article

Pembrolizumab plus Chemotherapy for Squamous Non–Small-Cell Lung Cancer

The New England Journal of Medicine

Original Article

Nivolumab plus Ipilimumab in Advanced Non–Small-Cell Lung Cancer

The New England Journal of Medicine

Original Article
Small Cell Lung Cancer
Evolution of Systemic Therapy in Small-Cell Lung Cancer

1970s: Alkylating-Based Chemotherapy (CMV)

1980s: Anthracycline-Based Chemotherapy (CAV)

1990s: Platinum-Based Chemotherapy (EP)

Today: Immunotherapy + Chemotherapy

Extensive Stage Small Cell Lung Cancer

Lurbinectedin as second-line treatment for patients with small-cell lung cancer: a single-arm, open-label, phase 2 basket trial

- 105 patients with relapsed SCLC
- Overall response rate (ORR) of 35.2% at a median follow-up of 17.1 months.
- The ORR was 22.2% in patients with platinum-resistant disease and 45.0% in those whose disease was platinum sensitive.

Approved by the FDA in June 2020

Trilaciclib: First in Class bone marrow protective agent

Approved by the FDA in Feb 2021

Figure 1. Trilaciclib: A First-in-Class Transient Cell Cycle Inhibitor

Source: G1 Therapeutics
AND SO MUCH MORE...

More targeted therapies
Novel immunotherapies
Antibody drug conjugates