What is the Role of Chemotherapy in the Era of Targeted Agents?

Gregory J. Riely, MD, PhD
Memorial Sloan Kettering Cancer Center

@RielyMD
Thesis Statements:

(1) Conventional chemotherapy remains important as initial therapy for the plurality of patients

(2) Conventional therapy is a critical, and often very effective, 2\textsuperscript{nd}/3\textsuperscript{rd} line treatment for patients who received targeted agents/immunotherapy
The Era of Targeted Agents

Stage IV NSCLC

Molecular Analysis + PD-L1 Testing

EGFR, ALK, ROS1

PD-L1 <50%

PD-L1 ≥50%
The Current Approach to NSCLC

Stage IV NSCLC

Molecular Analysis + PD-L1 Testing

Targeted Therapy
- EGFR, ALK, ROS1
- ~25% of patients

Platinum-based Chemotherapy (squamous vs non-squamous)
- PD-L1 ≥50%
- ~45% of patients

Pembrolizumab
- PD-L1 <50%
- ~30% of patients
Nivolumab vs Chemotherapy in First-line NSCLC

Key eligibility criteria:
- Stage IV or recurrent NSCLC
- No prior systemic therapy for advanced disease
- No EGFR/ALK mutations sensitive to available targeted inhibitor therapy
- ≥1% PD-L1 expression$^a$
- CNS metastases permitted if adequately treated at least 2 weeks prior to randomization

Randomize 1:1

**Nivolumab**
3 mg/kg IV Q2W
$n = 271$

Disease progression or unacceptable toxicity

**Chemotherapy** (histology dependent)$^b$
Maximum of 6 cycles
$n = 270$

Tumor scans Q6W until wk 48 then Q12W

Disease progression

Crossover nivolumab$^c$ (optional)

Socinski et al, ESMO 2016
Primary Endpoint (PFS per IRRC in ≥5% PD-L1+)
CheckMate 026: Nivolumab vs Chemotherapy in First-line NSCLC

No. of patients at risk:

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab</th>
<th>Chemotherapy</th>
</tr>
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<tbody>
<tr>
<td>n = 211</td>
<td>211</td>
<td>212</td>
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</table>

<table>
<thead>
<tr>
<th>Months</th>
<th>Nivolumab</th>
<th>Chemotherapy</th>
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<tbody>
<tr>
<td>24</td>
<td>211</td>
<td>212</td>
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<tr>
<td>21</td>
<td>144</td>
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Median PFS, months
Nivolumab: 4.2 (95% CI: 3.0, 5.6)
Chemotherapy: 5.9 (95% CI: 5.4, 6.9)

1-year PFS rate, %
Nivolumab: 23.6
Chemotherapy: 23.2

HR = 1.17 (95% CI: 0.95, 1.43), P = 0.2511

All randomized patients (≥1% PD-L1+): HR = 1.17 (95% CI: 0.95, 1.43), P = 0.2511

Socinski et al, ESMO 2016
### Summary of Response (≥5% PD-L1+)
CheckMate 026: Nivolumab vs Chemotherapy in First-line NSCLC

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab (n = 211)</th>
<th>Chemotherapy (n = 212)</th>
</tr>
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<tbody>
<tr>
<td><strong>ORR, % (95% CI)</strong></td>
<td>26.1 (20.3, 32.5)</td>
<td>33.5 (27.2, 40.3)</td>
</tr>
<tr>
<td><strong>Best overall response, %</strong></td>
<td></td>
<td></td>
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<tr>
<td>Complete response</td>
<td>1.9</td>
<td>0.5</td>
</tr>
<tr>
<td>Partial response</td>
<td>24.2</td>
<td>33.0</td>
</tr>
<tr>
<td>Stable disease</td>
<td>38.4</td>
<td>47.2</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>27.5</td>
<td>9.9</td>
</tr>
<tr>
<td>Could not be determined</td>
<td>8.1</td>
<td>9.4</td>
</tr>
<tr>
<td><strong>Median time to response, months (range)</strong></td>
<td>2.8 (1.2, 13.2)</td>
<td>2.6 (1.2, 9.8)</td>
</tr>
<tr>
<td><strong>Median duration of response, months (95% CI)</strong></td>
<td>12.1 (8.8, NE)</td>
<td>5.7 (4.2, 8.5)</td>
</tr>
</tbody>
</table>
The Current Approach to NSCLC

Stage IV NSCLC

Molecular Analysis + PD-L1 Testing

Targeted Therapy

~25% of patients

Platinum-based Chemotherapy (squamous vs non-squamous)

For patients with PD-L1 < 50%, NO EVIDENCE that immunotherapy is better

~30% of patients

Pembrolizumab

PD-L1 ≥50%

EGFR, ALK, ROS1

PD-L1 <50%
Front-line Pembrolizumab vs Chemotherapy

**Key Eligibility Criteria**
- Untreated stage IV NSCLC
- PD-L1 TPS ≥50%
- ECOG PS 0-1
- No activating *EGFR* mutation or *ALK* translocation
- No untreated brain metastases
- No active autoimmune disease requiring systemic therapy

R (1:1) N = 305

- **Pembrolizumab**
  - 200 mg IV Q3W (2 years)

- **Platinum-Doubllet Chemotherapy**
  - (4-6 cycles)

Reck et al, ESMO 2016
Progression-Free Survival
Chemotherapy vs Pembrolizumab

HR = 0.50, p<0.001

Reck et al, NEJM 2016
Response Rate
Pembrolizumab vs Chemo

Δ17%
P = 0.0011

CR
PR

45%
n = 6
n = 63

28%
n = 1
n = 41

Reck et al, ESMO 16
Response Rate
Pembrolizumab vs Chemo

More than half of PD-L1 highly positive patients don’t respond to pembrolizumab

Δ17%
P = 0.0011

CR
PR

60
45%
OR
The Current Approach to NSCLC

Stage IV NSCLC

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Targeted Therapy

~25% of patients

EGFR, ALK, ROS1

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Platinum-based Chemotherapy (squamous vs non-squamous)

PD-L1 ≥ 50%

Pembrolizumab

For patients with PD-L1 < 50%, NO EVIDENCE that immunotherapy is better

More than half of PD-L1 highly positive patients don’t respond to pembrolizumab
Targets in the Treatment of Lung Cancers

EGFR 17%
HER2 2%
KRAS 21%
RET fusions 2%
ROS1 fusions 2%
ALK fusions 2%
BRAF V600E 1%
MET exon 14 3%
Other 50%

MSK-IMPACT data, May 2015
Afatinib vs Cisplatin/pemetrexed

Progression-free survival (months)

<table>
<thead>
<tr>
<th></th>
<th>Afatinib n=230</th>
<th>Cis/pem n=115</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS event, n (%)</td>
<td>152 (66)</td>
<td>69 (60)</td>
</tr>
<tr>
<td>Median PFS (months)</td>
<td>11.1</td>
<td>6.9</td>
</tr>
<tr>
<td>Hazard ratio (95% confidence interval)</td>
<td>0.58 (0.43–0.78)</td>
<td>p=0.0004</td>
</tr>
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</table>

Yang et al ASCO 2012
How Do Tumors Become Resistant to EGFR Tyrosine Kinase Inhibitors

Yu et al, CCR 2013
Osimertinib in Patients With Acquired Resistance to EGFR TKI

Response Rate = 51%

Osimertinib in Patients With Acquired Resistance to EGFR TKI and $EGFR\ T_790M$

Response Rate = 61%

Osimertinib Progression-Free Survival by T790M

Janne et al, NEJM 2015
EGFR

Erlotinib, gefitinib, afatinib

EGFR T790M

Other

63%

After first generation EGFR TKI
1/3 of patients with EGFR mut NSCLC are best treated with chemotherapy
**EGFR** mut

**Erlotinib, gefitinib, afatinib**

**EGFR T790M**

**Other**

**Osimertinib**

After first generation EGFR TKI, 1/3 of patients with EGFR mut NSCLC are best treated with chemotherapy.

After osimertinib, there are no appropriate targeted therapies!
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EGFR, ALK, ROS1

Targeted Therapy

After progression on targeted therapies, all patients should be offered chemotherapy

For patients with PD-L1 < 50%, NO EVIDENCE that immunotherapy is better

More than half of PD-L1 highly positive patients don’t respond to pembrolizumab
Case

• 3 years after surgical resection of a stage IB EGFR mutant lung cancer, for which she received no adjuvant therapy, a 72 year old widow presents with 4 nodules in her right lung, with the largest 1.5 cm in diameter.
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• Biopsy is performed and pathology shows well-differentiated lung adenocarcinoma. Multiplexed genetic testing shows an EGFR exon 19 deletion.
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• Biopsy is performed and pathology shows well-differentiated lung adenocarcinoma. Multiplexed genetic testing shows an EGFR exon 19 deletion.

• She receives treatment with erlotinib and an IGF1R kinase inhibitor.
Case

- Two years after starting erlotinib, she develops progressive pleural based disease with significant chest wall pain.
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• Biopsy of a site of progressive disease shows EGFR exon 19 deletion and EGFRT790M.
Case

- Two years after starting erlotinib, she develops progressive pleural based disease with significant chest wall pain.

- Biopsy of a site of progressive disease shows EGFR exon 19 deletion and EGFRT790M.

- She starts on treatment with an experimental EGFR inhibitor with activity against T790M.
Case

• 12 months after starting the T790M-specific drugs, she develops progressive disease, with increasing pain and increased size of lung masses.

• She changes to osimertinib, with modest reduction in the size of the tumor, but progresses 3 months later with increasing chest pain.

• She starts carboplatin, pemetrexed, and bevacizumab
Case

• 3 weeks later, she returns to clinic for cycle 2 and she says “I haven’t felt this good since I was diagnosed with the lung cancer.”
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Targeted Therapy

PD-L1 ≥50%

Pembrolizumab

PD-L1 <50%

Platinum-based Chemotherapy (squamous vs non-squamous)

Second-line: Nivolumab, Pembrolizumab, Atezolizumab

Platinum-based Chemotherapy (squamous vs non-squamous)

Second-line Targeted Therapy

EGFR, ALK, ROS1