New Regimens for Advanced Non-Small Cell Lung Cancer

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Disclosure and Off Label Use

- No financial conflict
- Off label discussion
  - Platinum analogs for NSCLC
  - Atezolizumab with chemotherapy as first line therapy

Objectives

1. Identify the appropriate place in therapy for new immunotherapy combination regimens. Discuss the benefit as compared to the standard treatment.
2. Describe common and unique toxicities associated with immunotherapy combination regimens to optimize monitoring and patient counseling.
3. Recommend appropriate toxicity prevention and treatment measures for new targeted therapies

Immunotherapy Expanding Role with Combination Therapy

<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local Dz Stage I/II (16%)</td>
<td>Surgery +/- adjuvant chemotherapy</td>
</tr>
<tr>
<td>Regional Disease Stage III (22%)</td>
<td>Surgery +/- chemotherapy +/- radiation</td>
</tr>
<tr>
<td>Non-resectable</td>
<td>Chemotherapy + radiation + maintenance immunotherapy</td>
</tr>
<tr>
<td>Distant Disease Stage IV (57%)</td>
<td>Chemotherapy and/or immunotherapy or targeted agent</td>
</tr>
</tbody>
</table>

Lung Cancer

Survival for all stages has improved since last year indicating better treatment

SEER Stat Fact Sheets: Lung and Bronchus Cancer.
Seer.cancer.gov/statfacts/html/lungb.html accessed 9/18/2018

Check Point Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atezolizumab</td>
<td>1200 mg IV over 60 min q3week</td>
<td>NSCLC*, Bladder CA*</td>
</tr>
<tr>
<td>Avelumab</td>
<td>10 mg/kg IV over 60 min q2week</td>
<td>Merkel Cell*, Bladder CA*</td>
</tr>
<tr>
<td>Durvalumab</td>
<td>10 mg/kg IV over 60 min q2week</td>
<td>NSCLC**, Bladder CA*</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>200 mg IV over 30 min q2week</td>
<td>Melanoma**, NSCLC**, Hodgkin Lymphoma*, Head and Neck CA*, Bladder CA*</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>240 mg IV over 30 min q2week or 480 mg IV over 30 min q4week***</td>
<td>Melanoma*, NSCLC**, Hodgkin Lymphoma*, Head and Neck CA*, Bladder CA*, MSI-H/dMMR CA*, Gastric CA*</td>
</tr>
</tbody>
</table>

* Used for therapy in the second line or beyond
** Used as first line therapy in specific patient populations
*** 4-6 week regimen approved for melanoma, NSCLC, RCC, classical Hodgkin Lymphoma, HNSCC, bladder CA, HCC players prescribing information for details.

Chemotherapy:
- Carboplatin (BDD-NAG)
- Paclitaxel (BDD-6)
- Bevacizumab (BCI-CF)
- Radiation Therapy (RT)
- Steroids (S)
- Hormone Therapy (HT)

NSCLC: Non-Small Cell Lung Cancer
MSI-H: High Microsatellite Instability
MSI-L: Low Microsatellite Instability
dMMR: Deficient Mismatch Repair
Non-Small Cell Lung Cancer: Immunotherapy approvals

<table>
<thead>
<tr>
<th>FDA Approvals</th>
<th>2015</th>
<th>2016</th>
<th>2017</th>
<th>2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>3/4/15</td>
<td>Approved for 2nd line therapy of mNSCLC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>10/2/15</td>
<td>Approved for 2nd line therapy of PD-L1+ mNSCLC</td>
<td></td>
<td></td>
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<tr>
<td>Pembrolizumab</td>
<td>10/24/16</td>
<td>Approved for 1st line monotherapy of PD-L1+ mNSCLC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>4/17/17</td>
<td>Approved for 2nd line monotherapy for mNSCLC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>5/10/17</td>
<td>Approved for 1st line with chemotherapy for mNSCLC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Durvalumab</td>
<td>2/16/18</td>
<td>Approved for 1st line with chemoradiotherapy for stage III NSCLC</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Drugs. www.fda.gov

Patient Case
SJ is a 61 yo WF who presents with NSCLC

HPI: After failing antibiotics a CXR revealed a left lower lobe mass – FNA confirmed adenocarcinoma of the lung

PMH: N/A

FH/Sh: Married w/ two sons 28 and 34 (none smoker)

Drug History: NKDA

PE: Findings consistent with lung cancer – otherwise WNL

Labs: Hepatic, renal, and chemistry levels WNL

Radiology: Lesions in the Left Lower Lobe – Negative for lesions in the liver, adrenal, and Brain

EBUS – 11L, 7, and 4 R positive (N3 disease)

Genetics: KRas – WT, EGFR WT, no ALK rearrangement, no ROS1 rearrangement, PD-L1 unknown

Localized Dz – Its in the Nodes

Chemoradiotherapy for N3 Disease

Pathology and Laboratory Medicine International 2015:7 83–93

Chemoradiotherapy Outcomes

Concurrent Results

- Median OS = 16.3 months
- 12 month DFS = 42%
- ORR = 49%
- CR, PR, SD = 84%


Chemotherapy, XRT and Immunotherapy

First-Line Treatment

Stage II/III NSCLC

Treated with Chemoradiotherapy (platinum-doublet) OR, TKI, or MP

Durvalumab 10 mg/kg IV q2 weeks

For up to 12 months N = 473

Placebo IV q2 weeks

For up to 12 months N = 236

Co-primary endpoint: PFS, OS

Secondary endpoints: 12 and 18 mo PFS, ORR


Durvalumab after chemoradiotherapy Stage III

11 month improvement in PFS

PD-L1 Expression subgroup

Analysis on bottom
Treatment for Advanced NSCLC

Newly Diagnosed Metastatic NSCLC

- No Targetable Driver Mutation, PD-L1 negative (50-60%)
- High PD-L1 Pembrolizumab (30%)
- Targetable Driver Mutation (EGFR, ALK, ...) (10-15%)

HIGH PD-L1 Pembrolizumab (30%)

Squamous Histology (15%)

Non-squamous Histology (40%)

1st line Platinum doublet, 2nd line PD-L1 i

1st line Platinum doublet and immunotherapy

No Targetable Driver Mutation, PD-L1 negative (55-60%)

Squamous Histology (15%)

Non-squamous Histology (45%)

1st line Platinum doublet, 2nd line PD-L1 i

1st line Platinum doublet and immunotherapy

HISTORY of 1st Line Platinum Doublets for Advanced NSCLC

- Newly Diagnosed Advanced NSCLC
- N=288-290 per group; 1155 in all
- Median OS = 7.4-8.1 months - NS
- ORR = 17-22%


Carbo-Taxol-Bevacizumab

Unresectable, Non-squamous cell NSCLC; N=842

Unresectable, Non-squamous cell NSCLC; N=842


IMpower150: Addition of Atezolizumab to Carbo/Pac + Bevacizumab in Advanced NSCLC

Patients with stage IV chemotherapy-naive NSCLC available tumor tissue (N = 1202)

Patients with stage IV chemotherapy-naive NSCLC available tumor tissue (N = 1202)

Atezolizumab 1200 mg IV Q3W + Carbo/Pac + Bevacizumab

Carbo/Pac + Bevacizumab

Atezolizumab 1200 mg IV Q3W + Carbo/Pac + Bevacizumab

Median PFS = 6.8 mo versus 8.3 mo

Median OS = 14.7 mo versus 19.2 mo

Median PFS = 6.8 mo versus 8.3 mo

Median OS = 14.7 mo versus 19.2 mo


**IMpower150: PFS by Subgroup**

First time immunotherapy is better than standard of care for EGFR or ALK


**Keynote -189: Addition of Pembrolizumab to Platinum/Pemetrexed**

Patients with stage IV Non-squamous NSCLC (N = 616)

- Pembrolizumab 200 mg IV Q3W + Carboplatin or Cisplatin + Pemetrexed
- Pemetrexed

4 cycles Maintenance of Pembrolizumab 200 mg IV Q4W

- 12 mo PFS = 4.9 vs 8.8 months
- 12 mo OS = 69% vs 49%

**Keynote 189 – PFS**

PFS = 4.9 vs 8.8 months 12 mo PFS = 34% vs 17%


**Keynote 189 – Overall Survival**


**Evaluating Overlapping Toxicity**

Table 3: Adverse Events of Any Grade in the Au-Treated Population

<table>
<thead>
<tr>
<th>Event</th>
<th>Pembrolizumab/Chemotherapy (N = 40)</th>
<th>Pemetrexed/Chemotherapy (N = 290)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>Any Grade: 13 (33%)</td>
<td>Any Grade: 41 (14%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Grade 3, 4 or 5: 5 (13%)</td>
<td>Grade 3, 4 or 5: 30 (10%)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Any Grade: 8 (20%)</td>
<td>Any Grade: 6 (2%)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Grade 3, 4 or 5: 2 (5%)</td>
<td>Grade 3, 4 or 5: 0 (0%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>Any Grade: 7 (18%)</td>
<td>Any Grade: 3 (1%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>Grade 3, 4 or 5: 2 (5%)</td>
<td>Grade 3, 4 or 5: 0 (0%)</td>
</tr>
</tbody>
</table>

Roughly 10% rash is due to pembrolizumab and 10% it is from pemetrexed


**Handling Toxicity per Protocol**

- Evaluation of any chemotherapy agent and not the other agent, appropriate if, in the opinion of the Investigator, the toxicity is clearly related to one of the chemotherapies, the toxicity is related to the combination of both chemotherapy agents, both drugs should be reduced according to recommended dose modifications.
- If the toxicity is related to the combination of three agents, all three agents should be reduced to the combination of three agents, if applicable.
- For subjects with discontinuation pembrolizumab/saline placebo and continuation of chemotherapy alone.


**– appendix –**

The Case of Rash

Evaluating Response

- "Per irRECIST, disease progression should be confirmed by the site at least 4 weeks after central verification of site-assessed 1st radiologic evidence of PD in clinically stable subjects. Subjects who have unconfirmed disease progression may continue on treatment at the discretion of the site investigator until progression is confirmed."

- "In subjects who have initial evidence of radiological PD by RECIST 1.1, it is at the discretion of the PI whether to continue a subject on study treatment until repeat imaging is obtained. This clinical judgment decision by the site should be based on the subject’s overall clinical condition, including performance status, clinical symptoms, and laboratory data. Subjects may receive study treatment and tumor assessment should be repeated ≥ 4 weeks later in order to confirm PD by irRECIST."

The Case of PJ

60-year-old man with stage IV adenocarcinoma of the lung. his PS is 1 and he is in relatively good shape.

TX: Carboplatin, Pemetrexed and Pembrolizumab

- Between his second and third dose (6 weeks out) he develops a rash (grade 2).
- Prednisone 80 mg po daily is started and pembrolizumab held.
- The decision was made to hold all treatment until toxicity (Rash) has improved to grade 1.
- Can we restart before the taper is complete?

Restarting ICI while on Steroids

- No recommendations in the skin toxicity section; however, the liver toxicity section states:
- "Should hold ICPi treatment temporarily and resume if recover to grade 1 or less on prednisone ≤ 10 mg/d".
- Seems reasonable given the difference in drug half life: 12-36 hours (biologic t½) vs 22 days.
Efficacy Summary

- **Local – Unresectable disease (Stage III)**
  - Durvalumab after chemoradiotherapy: increase PFS by almost a year (17 mo versus 6 months)
- **Advanced Stage Disease**
  - Platinum Doublet: PFS = 3.7 mo; OS = 8 mo
  - Bevacizumab and Carb/Tax: OS = 12.5 mo (12 mo PFS: 37% (+19%)
  - Pembrolizumab and Platinum/Pemetrexed: OS = 12 mo; PFS = 34% (+17%)


Patient and Family Education

- **Time to response differs from standard therapy**
  - Response in baseline lesions
  - Stable disease with slow decline in tumor volume
  - Response following initial increase in tumor volume or new lesion
  - Patients may develop signs of disease progression after treatment
  - Stable and partial responders in tumor size, rash, and pruritus can continue through the disease "pseudo-progression"

- **Different AE profile than chemotherapy**
- **Early recognition of irAEs is essential to effective treatment**
- **Patients must notify their care provider if their symptoms develop or they are admitted to local facility.**
- **irAEs are related to the mechanism of action of immunotherapies**
- **irAEs are treatable and respond well to steroids**

- AE, adverse event; irAEs, immune-related adverse events.

Communication Tool

All Routes Lead to ICI Therapy

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