Challenges of Anti-Cancer Immunotherapy Development- Industry Perspective

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Key Challenges

• Unique mechanism of action and increasing commercial availability create a challenge for use of traditional efficacy endpoints to assess clinical benefit

• Biomarkers predictive of efficacy have been identified, but similar to other biomarkers used in cancer, are not completely accurate in identifying responders and non-responders
PD-1 and PD-L1/L2 Pathway

- PD-1 is an immune checkpoint receptor
- Binding of PD-1 by its ligands PD-L1 or PD-L2 leads to downregulation of T-cell function
- This mechanism is usurped by many tumors
- PD-1 blockade through mAb therapy can restore and reveal effective anti-tumor immunity

PFS in Assessing Clinical Benefit

• PFS may provide a more reliable assessment of clinical benefit than OS in certain scenarios
  – Crossover may confound OS comparison in a randomized study
  – OS effect may be diluted by multiple effective subsequent treatments

• PFS may not always indicate clinical benefit
  – Delay in disease progression may be offset by toxicity

• With increasing availability of highly effective immunotherapies and the resulting potential for crossover, PFS will likely become an increasingly important endpoint for assessing clinical benefit
Progression by RECIST vs “irRECIST”

• RECIST may “overcall” progression events for immunotherapy drugs, confounding PFS calculations
  – “new lesions” may represent immune cell infiltration rather than increased mass of tumor cells
  – Supported by biopsies of post-treatment metastatic lesions

• Regulators and IRBs have allowed treatment beyond RECIST progression in clinical studies, but PFS by “irRECIST” is not a recognized regulatory endpoint

• Little data on use of “irRECIST” for calculation of PFS with non-immunotherapy standard-of-care treatments
  – Investigators may not be willing to continue treatment with non-immunotherapy treatments beyond RECIST progression

• However, with recent and upcoming approvals, both arms of a randomized study may involve immunotherapy
  – “irPFS” may be important in assessing benefit in such studies
Example of Progression by RECIST, Followed by Response

Among 592 patients with melanoma who survived ≥ 12 weeks, 84 (14%) patients experienced progressive disease per RECIST v1.1 but non-progressive disease per irRC.

Hodi, et al., JCO 2016, in press
Not Unique to Melanoma: Pembrolizumab-Treated Head and Neck Cancer Patient

Baseline: Extensive skin infiltration and liver metastasis

Month 1: Marked local edema, hospital admission
Week 8 CT: PD by RECIST 1.1 due to non-target

Month 3: Clinical improvement
Week 12 CT: Stable disease

Month 6: Skin disease near CR
Week 40 CT head lesion almost resolved, liver lesion unchanged

Case courtesy of Dr. Tanguy Seiwert
Association of OS with irRC vs RECIST Progression Criteria – Ipilimumab Melanoma

Wolchok, et al. CCR 2009
Association of OS with irRC vs RECIST Progression Criteria – Pembrolizumab Melanoma

Hodi, et al. JCO 2016, in press
Melanoma Pembrolizumab (ASCO 2014)

RECIST by independent review, irRC by investigator

n=411

**Kaplan-Meier Estimate of PFS per RECIST 1.1, Independent Central Review**

<table>
<thead>
<tr>
<th>Population</th>
<th>Median (mo)</th>
<th>95% CI</th>
<th>Rate, 6 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>5.5</td>
<td>3.8-6.2</td>
<td>45%</td>
</tr>
<tr>
<td>IPI-N</td>
<td>5.6</td>
<td>3.7-11.0</td>
<td>49%</td>
</tr>
<tr>
<td>IPI-T</td>
<td>5.4</td>
<td>3.2-5.6</td>
<td>41%</td>
</tr>
</tbody>
</table>

**Kaplan-Meier Estimate of PFS per irRC, Investigator Review**

<table>
<thead>
<tr>
<th>Population</th>
<th>Median (mo)</th>
<th>95% CI</th>
<th>Rate, 6 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>8.3</td>
<td>(5.8-16.5)</td>
<td>55%</td>
</tr>
<tr>
<td>IPI-N</td>
<td>8.6</td>
<td>(5.5-19.3)</td>
<td>54%</td>
</tr>
<tr>
<td>IPI-T</td>
<td>8.2</td>
<td>(5.6-12.4)</td>
<td>55%</td>
</tr>
</tbody>
</table>

**Median PFS (mo)**

- RECIST: 5.5
- irRC: 8.3

**6 mo PFS**

- RECIST: 45%
- irRC: 55%
Using Biomarkers (Companion Diagnostics) to Select Patients for Treatment

- Histology is an imperfect biomarker that is used to select cancer patients for treatment
- “No test is perfect, but some tests are useful”
  - Imperfect HER2 IHC test allowed rapid development of an effective treatment for breast cancer patients
  - PD-L1 IHC test allowed accelerated development of PD-1 targeting in lung cancer
  - Companion diagnostics may be used to select among treatment options, vs excluding patients from an immunotherapy treatment
- Companion diagnostic development typically lags behind therapeutics, creating scientific and regulatory complexity
- Several biomarkers for PD-1 targeting agents have been identified that are predictive for efficacy, including PD-L1 protein expression, RNA signatures, and MSI/DNA mutation burden
Clinical Utility of PD-L1 Expression in Lung Cancer

• PD-L1 expression predicts survival outcome in lung cancer patients treated with PD-1 antibodies
  – In a pembrolizumab randomized study in 2L NSCLC, a survival benefit vs docetaxel was observed in patients with ≥1% PD-L1 tumor staining (Herbst, et al, Lancet 2015)
  – In a randomized study in 2L non-squamous NSCLC, survival was similar in patients with PD-L1-negative tumors treated with nivolumab vs docetaxel (Borghaei, et al, NEJM 2015)
Pembrolizumab vs Docetaxel in Previously Treated NSCLC Patients

OS, PD-L1 TPS ≥1% (Total Population)

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Median (95% CI), mo</th>
<th>Rate at 1 y</th>
<th>HR(^a) (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro 2 mg/kg</td>
<td>10.4 (9.4-11.9)</td>
<td>43.2%</td>
<td>0.71 (0.58-0.88)</td>
<td>0.0008</td>
</tr>
<tr>
<td>Pembro 10 mg/kg</td>
<td>12.7 (10.0-17.3)</td>
<td>52.3%</td>
<td>0.61 (0.49-0.75)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>8.5 (7.5-9.8)</td>
<td>34.6%</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

\(^a\)Comparison of pembrolizumab vs docetaxel. Analysis cut-off date: September 30, 2015.
Nivolumab vs Taxotere in Previously Treated Non-Squamous NSCLC Patients: OS by PD--L1 Status

- ≥1% PD-L1 expression level:
  - Nivolumab: 17.7 mo
  - Docetaxel: 9.0 mo
  - HR (95% CI) = 0.58 (0.43, 0.79)

- ≥5% PD-L1 expression level:
  - Nivolumab: 19.4 mo
  - Docetaxel: 8.1 mo
  - HR (95% CI) = 0.43 (0.30, 0.62)

- ≥10% PD-L1 expression level:
  - Nivolumab: 19.9 mo
  - Docetaxel: 8.0 mo
  - HR (95% CI) = 0.40 (0.27, 0.58)

- <1% PD-L1 expression level:
  - Nivolumab: 10.5 mo
  - Docetaxel: 10.1 mo
  - HR (95% CI) = 0.87 (0.63, 1.19)

- <5% PD-L1 expression level:
  - Nivolumab: 9.8 mo
  - Docetaxel: 10.1 mo
  - HR (95% CI) = 0.96 (0.73, 1.27)

- <10% PD-L1 expression level:
  - Nivolumab: 9.9 mo
  - Docetaxel: 10.3 mo
  - HR (95% CI) = 0.96 (0.74, 1.25)
Summary

• PFS Kaplan-Meier curves (and median PFS) for immunotherapies may be different when assessed by RECIST vs “irRECIST”
  – Patients with progression by RECIST but non-progression by irRC criteria have similar survival outcomes compared to patients with non-progression by RECIST
  – A uniform definition of “irRECIST” is needed
  – Analyses of immunotherapies across various cancer types are needed

• While not a perfect test, clinical utility of PD-L1 protein expression has been established in NSCLC
  – Additional predictive biomarkers involving RNA and DNA are under development – it remains to be determined whether these will have superior clinical utility relative to PD-L1 expression