Supplementary Online Content


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This supplementary material has been provided by the authors to give readers additional information about their work.
**eTable 1. FDA Approval Language and Approval Dates by Cancer Type and Line of Therapy**

<table>
<thead>
<tr>
<th>Cancer Type [Subtype]</th>
<th>Line of Therapy</th>
<th>FDA Approval Language</th>
<th>FDA Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Melanoma</strong></td>
<td></td>
<td>Nivolumab</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2L+</td>
<td>After ipilimumab; and if BRAF V600 mutation positive, after a BRAF inhibitor</td>
<td>12-22-2014</td>
</tr>
<tr>
<td></td>
<td>1L</td>
<td>BRAF V600 wild-type in combination with ipilimumab</td>
<td>09-30-2015</td>
</tr>
<tr>
<td></td>
<td>1L</td>
<td>BRAF V600 wild-type as monotherapy</td>
<td>11-24-2015</td>
</tr>
<tr>
<td></td>
<td>1L</td>
<td>BRAF V600 mutation positive as monotherapy or in combination with ipilimumab</td>
<td>01-23-2016</td>
</tr>
<tr>
<td><strong>NSCLC [Squamous]</strong></td>
<td>2L+</td>
<td>Squamous histology, with progression on or after platinum-based chemotherapy</td>
<td>03-04-2015</td>
</tr>
<tr>
<td><strong>NSCLC [Non-squamous]</strong></td>
<td>2L+</td>
<td>Non-squamous histology, with progression on or after platinum-based chemotherapy, and (for eligible patients), FDA-approved therapy for EGFR or ALK genomic tumor aberrations</td>
<td>10-09-2015</td>
</tr>
<tr>
<td><strong>RCC</strong></td>
<td>2L+</td>
<td>After prior anti-angiogenic therapy</td>
<td>11-23-2015</td>
</tr>
</tbody>
</table>

| **Melanoma**           |                 | Pembrolizumab         |                   |
|                        | 2L+             | Unresectable or metastatic (no additional specifications) | 09-04-2014 |
|                        | 1L              | Unresectable or metastatic (no additional specifications) | 12-18-2015 |
| **NSCLC [PD-L1 Positive]** | 2L+     | With PD-L1 expression as determined by an FDA-approved test, and progression on or after platinum-based chemotherapy | 10-02-2015 |

*Defined as 1st line of therapy (1L) or 2nd line of therapy or greater (2L+).
**eTable 2.** Characteristics of Pivotal Trials for Each Cancer Type and Subtype

<table>
<thead>
<tr>
<th>Cancer Type [Subtype]</th>
<th>Pivotal Trial*</th>
<th>Publication Date</th>
<th>Study Design</th>
<th>Primary Outcome</th>
<th>Treatment Group Size, n</th>
<th>Treatment Group Outcome</th>
<th>Comparison Group Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nivolumab</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melanoma</td>
<td>Checkmate-037</td>
<td>03-18-2015</td>
<td>Randomized, Open-Label, Phase 3</td>
<td>ORR, 6-month</td>
<td>120</td>
<td>31.7%</td>
<td>10.6%</td>
</tr>
<tr>
<td>NSCLC [Squamous]</td>
<td>Checkmate-063</td>
<td>02-19-2015</td>
<td>Single-Arm, Phase 2</td>
<td>ORR, 1-year</td>
<td>117</td>
<td>14.5%</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Checkmate-017</td>
<td>05-31-2015</td>
<td>Randomized, Open-Label, Phase 3</td>
<td>OS, 1-year</td>
<td>135</td>
<td>9.2 months</td>
<td>6.0 months</td>
</tr>
<tr>
<td>RCC</td>
<td>Checkmate-025</td>
<td>09-25-2015</td>
<td>Randomized, Open-Label, Phase 3</td>
<td>OS, 1-year</td>
<td>410</td>
<td>25.0 months</td>
<td>19.6 months</td>
</tr>
<tr>
<td><strong>Pembrolizumab</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melanoma</td>
<td>Keynote-001</td>
<td>09-20-2014</td>
<td>Dose-Comparison, Phase 1</td>
<td>ORR, 6-month</td>
<td>89</td>
<td>26.0%</td>
<td>-</td>
</tr>
<tr>
<td>NSCLC [PD-L1 Positive]</td>
<td>Keynote-001</td>
<td>05-21-2015</td>
<td>Dose-Comparison, Phase 1</td>
<td>ORR, 6-month</td>
<td>61</td>
<td>45.2%**</td>
<td>-</td>
</tr>
</tbody>
</table>

ORR = overall response rate (%). OS = overall survival (months). Follow-up periods for each measure are rounded to nearest 6-month interval. 
*Primary source(s) of efficacy for initial FDA approvals for each cancer type according to FDA labels.
**For subset of n=61 patients with PD-L1 expression ≥50%, which supported FDA approval. For the full cohort, 6-month ORR = 19.4%.
eFigure 1. Melanoma Cohort Formation

**Advanced Melanoma EDM**
- Diagnosed with melanoma (ICD-9 172.x or ICD-10 C43x or D03x)
- 2 distinct visits after January 1, 2013 on distinct days
- Stage III or IV at initial diagnosis, or Stage I-II at initial diagnosis and develop a locoregional or distant recurrence on or after January 1, 2011
- Age 18 or older at advanced diagnosis

n = 3,471

**Limited to Melanoma as only primary**
n = 3,458

**Reasons for ineligibility**
- Final LOT received was prior to BRAF status-specific approval (n = 645)
- Received off-label therapy (n = 222)
- Unknown BRAF status (n = 179)

**Limited to those who received ANY systemic neoplastic therapy**
n = 1,601

**ELIGIBLE for anti-PD-1 therapy**
n = 555

**TREATED with anti-PD-1 therapy**
n = 439

- Treated with Nivolumab
  n = 259
- Treated with Pembrolizumab
  n = 153
- Treated with both
  n = 27

**Did not receive anti-PD-1 therapy**
n = 116

**EDM** = enhanced datamart (a dataset that includes both structured and unstructured data).

**LOT** = line of therapy (1st line of therapy, 2nd line of therapy, or 3rd line of therapy or greater).
eFigure 2. NSCLC Cohort Formation

- **Advanced NSCLC EDM**: Diagnosed with lung cancer (ICD-9 162.x or ICD-10 C34.x, or C39.9). Abstracter confirmed pathology consistent with NSCLC.  
  - **n = 29,710**

- **Limited to NSCLC as only primary**  
  - **n = 29,694**

- **Limited to those diagnosed at Stage IV**  
  - Age 18 or greater at metastatic diagnosis  
  - **n = 18,631**

- **Limited to those with 2 distinct visits after January 1, 2013**  
  - **n = 16,069**

- **Limited to those who received ANY systemic neoplastic therapy**  
  - **n = 12,291**

- **ELIGIBLE for anti-PD-1 therapy**  
  - **n = 2,159**

- **TREATED with anti-PD-1 therapy**  
  - **n = 1,417**

  - Treated with Nivolumab  
    - **n = 1,345**
  - Treated with Pembrolizumab  
    - **n = 52**
  - Treated with both  
    - **n = 20**

- **Did not receive anti-PD-1 therapy**  
  - **n = 742**

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**Definitions**

- **EDM** = enhanced datamart (a dataset that includes both structured and unstructured data).
- **LOT** = line of therapy (1<sup>st</sup> line of therapy, 2<sup>nd</sup> line of therapy, or 3<sup>rd</sup> line of therapy or greater).
- **1L** = 1<sup>st</sup> line of therapy
**eFigure 3. RCC Cohort Formation**

**Metastatic RCC EDM**
Diagnosed with RCC  
(ICD-9 189.x or ICD-10 C64x or C65x or C66x)  
Abstracter confirmed pathology consistent with RCC  
Diagnosed with Stage IV disease or metastatic recurrence on or after January 1, 2011  
2 distinct visits on or after January 1, 2013  
Age 18 or greater at metastatic diagnosis  
$n = 2,599$

Limited to RCC as only primary  
$n = 2,592$

Limited to those who received ANY systemic neoplastic therapy  
$n = 1,964$

**ELIGIBLE for anti-PD-1 therapy**  
$n = 375$

**TREATED with anti-PD-1 therapy**  
$n = 267$

**Reasons for ineligibility**
- Received only 1L therapy  
  $(n = 1,044)$  
- Final LOT received was prior to FDA approval  
  $(n = 447)$  
- Received off-label therapy  
  $(n = 98)$

Treated with Nivolumab  
$n = 267$

Did not receive anti-PD-1 therapy  
$n = 108$

**EDM** = enhanced datamart (a dataset that includes both structured and unstructured data).  
**LOT** = line of therapy.  
**1L** = 1st line of therapy.
eFigure 4. Schema for Dynamic Assessments of Eligibility for Anti-PD1 Treatment

**Determination of Eligibility**
For the purpose of this study, patients were considered eligible for anti-PD-1 therapy as of the date they started an approved (or later) line of any systemic therapy after the FDA approval date. For example, the FDA approved use of nivolumab in renal cell carcinoma (RCC) patients in the second line of therapy or later. The figure below illustrates hypothetical scenarios of eligibility assessments:

- **Ineligible** - The patient received only 1 line of therapy.
- **Ineligible** - The patient received only 1 line of therapy.
- **Eligible** - The patient was considered eligible at the start of the 2nd line.
- **Eligible** - The patient was considered eligible at the start of the 3rd line.

1L = 1\textsuperscript{st} line of therapy.
2L = 2\textsuperscript{nd} line of therapy.
3L = 3\textsuperscript{rd} line of therapy.