**Non-Small Cell Lung Cancer (NSCLC)**

**PD-L1 by Immunohistochemistry**

**PD-1 and PD-L1**

Programmed death 1 (PD-1) is an immune inhibitory receptor expressed on the surface of activated T cells and mediates suppression of the immune system. PD-1 interacts with the immunosuppressive PD-L1 ligand which is expressed on tumor cells, inflammatory cells, and histiocytes, and inhibits T cell activation. A new class of immunotherapies, PD-1 and PD-L1 inhibitors, blocks the interaction between PD-1 and PD-L1 on the tumor cells and can enhance T cell responses and mediate anti-tumor activity.1,2

**PD-L1 Expression**

- Tumor PD-L1 expression levels have been shown to be a predictive marker with response to several anti-PD-1 antibodies.2,3
- PD-L1 expression can be measured by immunohistochemistry and detects PD-L1 expression in formalin-fixed, paraffin-embedded NSCLC tumor tissue samples

**Biomarker Assay**

**Cancer Type**

**Immunotherapy**

**Scoring Cut-off**

<table>
<thead>
<tr>
<th>Biomarker Assay</th>
<th>Cancer Type</th>
<th>Immunotherapy</th>
<th>Scoring Cut-off</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-L1 Dako® (22C3)</td>
<td>First-line treatment metastatic NSCLC</td>
<td>KEYTRUDA® (pembrolizumab)</td>
<td>High PD-L1 expression: TPS ≥50%8,9</td>
</tr>
<tr>
<td>COMPANION Diagnostic</td>
<td>Previously treated metastatic NSCLC</td>
<td>KEYTRUDA® (pembrolizumab)</td>
<td>PD-L1 expression: TPS ≥1%11,12</td>
</tr>
<tr>
<td>PD-L1 Dako® (28-8)</td>
<td>Previously treated metastatic adenocarcinoma NSCLC</td>
<td>OPDIVO® (nivolumab)</td>
<td>PD-L1 expression in ≥1% TC10,11</td>
</tr>
<tr>
<td>COMPLEMENTARY Diagnostic</td>
<td>Previously treated metastatic NSCLC</td>
<td>TECENTRIQ® (atezolizumab)</td>
<td>PD-L1 expression in ≥50% TC or ≥10% IC10,12,13</td>
</tr>
</tbody>
</table>

**NSCLC** - non-small cell lung cancer

*TPS – tumor proportional score

**TC – PD-L1 expressing tumor cells

**IC – PD-L1 expressing tumor-infiltrating immune cells

**REFERENCES**


9. PD-L1 expression can be measured by immunohistochemistry and detects PD-L1 expression in formalin-fixed, paraffin-embedded NSCLC tumor tissue samples.


11. Supplemental Appendix.


13. Non-Small-Cell Lung Cancer - N Engl J Med 2015; 372: 1820-30. However, in the context of this discussion, we refer to the PD-L1 expression cutoffs after the introduction of key clinical trials and subsequent FDA approvals.

**Lab Locations**

- Arizona Integrated Oncology
- 5005 South 40th Street
- Phoenix, AZ 85040
- 800-710-1800
- Fax 800-481-4151

- New York Integrated Oncology
- 521 West 57th Street, Sixth Floor
- New York, NY 10019
- 800-447-5816
- Fax 212-258-2143

- North Carolina LabCorp Center for Molecular Biology and Pathology
- 1912 Alexander Drive
- Research Triangle Park, NC 27709
- 800-345-4363
- Fax 919-361-7798

- Tennessee Integrated Oncology
- 201 Summit View Drive, Suite 100
- Brentwood, TN 37027
- 800-874-8532
- Fax 615-370-8074

**Menu of more than 450 genetic, pathology, IHC, and FISH tests, including 15 oncology-specific pharmacogenetic tests**

**Staff of more than 75 pathologists, PhDs, and genetic counselors dedicated to oncology and familial cancer testing**

More than 65 oncology- and pathology-specific publications and presentations since 2013

**THE PD-1/PD-L1 BLOCKADE**

The PD-1/PD-L1 interaction protects the cancer cell from immune destruction

Blocking the PD-1/PD-L1 interaction allows T cells to destroy tumor cells

**PD-L1 Dako® (22C3) Companion Diagnostic**

First-line treatment metastatic NSCLC

KEYTRUDA® (pembrolizumab)

High PD-L1 expression: TPS ≥50%

Previously treated metastatic NSCLC

KEYTRUDA® (pembrolizumab)

PD-L1 expression: TPS ≥1%

Previously treated metastatic adenocarcinoma NSCLC

OPDIVO® (nivolumab)

PD-L1 expression in ≥1% TC

Previously treated metastatic NSCLC

TECENTRIQ® (atezolizumab)

PD-L1 expression in ≥50% TC or ≥10% IC

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Clinical Studies in NSCLC

**KEYTRUDA®**

Several studies have assessed membranous PD-L1 expression (clone 22C3) and response to anti-PD1 immunotherapy KEYTRUDA (pembrolizumab) in metastatic NSCLC patients. The studies’ results include:

- **KEYTRUDA demonstrated a statistically significant improvement in progression free survival and overall survival compared to standard chemotherapy in patients with PD-L1 expressing tumors.**
- **KEYTRUDA has been FDA-approved as a first-line treatment option in patients with PD-L1 expressing tumors of ≥50%, and FDA-approved as a second-line or subsequent therapy option in patients with PD-L1 expressing tumors of ≥1%.

The Dako® PD-L1, IHC 22C3 pharmDx™ test is FDA-approved as a companion diagnostic assay to aid in identifying advanced NSCLC patients for treatment with KEYTRUDA® (pembrolizumab).

**Efficacy Results**

<table>
<thead>
<tr>
<th>First-line therapy – PD-L1 Expression levels ≥50% (Keynote 024 trial)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapy</td>
</tr>
<tr>
<td>KEYTRUDA 200 mg</td>
</tr>
<tr>
<td>Chemotherapy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Second-line or subsequent therapy – PD-L1 Expression levels ≥1% (Keynote 010 trial)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapy</td>
</tr>
<tr>
<td>KEYTRUDA 2mg/kg</td>
</tr>
<tr>
<td>KEYTRUDA 10 mg/kg</td>
</tr>
<tr>
<td>Docetaxel</td>
</tr>
</tbody>
</table>

OS - overall survival; HR - hazard ratio; PFS - progression free survival; ORR - objective response rate; DOR – duration of response; NR - not reached

**OPDIVO®**

A study of patients with advanced non-squamous NSCLC, PD-L1 expression (clone 28-8), and response to anti-PD1 immunotherapy OPDIVO (nivolumab) versus chemotherapy, included the following results:

- **PD-L1 expression was associated with improved efficacy across all endpoints (OS, PFS, DOR) at all expression levels. The most improvement was seen in patients with PD-L1 expression ≥5% and ≥10%, but was evident at PD-L1 expression levels as low as ≥1%.
- **Patients with tumors that had PD-L1 expression levels ≥1% were associated with a doubling of overall median survival.**

The Dako® PD-L1, IHC 28-8 pharmDx™ test is FDA-approved as a complementary diagnostic assay to help physicians determine which patients may benefit most with OPDIVO® (nivolumab).

**TECENTRIQ®**

A study of previously treated metastatic NSCLC patients, PD-L1 expression (clone SP142), and response to anti-PD1 immunotherapy TECENTRIQ (atezolizumab) versus docetaxel included the following results:

- **TECENTRIQ showed clinically relevant improvements in overall survival compared to docetaxel at all PD-L1 expression levels (high, medium, low, undetectable).**
- **However, patients with tumors with high expressing levels of PD-L1 (≥50% on tumor cells (TC)) or ≥10% on tumor-infiltrating immune cells (IC) derived the greatest benefit.**

The VENTANA® PD-L1, IHC SP142 test is FDA-approved as a complementary diagnostic assay to help physicians determine which patients may benefit most with TECENTRIQ® (atezolizumab).

**Specimen Requirement Options**

- **Global Only**
- **Tissue should be fixed in 10% neutral buffered formalin; alternative fixatives have not been validated and may give erroneous results**
- **A minimum of 100 cells is required**

1. **Fixed Paraffin Block with Corresponding H&E**
2. **Unstained Slides:**
   - Minimum of 4 slides (include additional slide for H&E per stain)
   - Pre-cut slides from paraffin block in 4-5 micron sections and mount on plus (+) slides
Clinical Studies in NSCLC

KEYTRUDA®

Several studies have assessed membranous PD-L1 expression (clone 22C3) and response to anti-PD1 immunotherapy KEYTRUDA® (pembrolizumab) in metastatic NSCLC patients. The studies’ results include:1

- KEYTRUDA demonstrated a statistically significant improvement in progression-free survival and overall survival compared to standard chemotherapy in patients with PD-L1 expressing tumors.

- KEYTRUDA has been FDA-approved as a first-line treatment option in patients with PD-L1 expressing tumors of ≥50%, and FDA-approved as a second-line or subsequent therapy option in patients with PD-L1 expressing tumors of ≥1%.

<table>
<thead>
<tr>
<th>Therapy</th>
<th>OS (mths)</th>
<th>HR</th>
<th>PFS (mths)</th>
<th>HR</th>
<th>ORR</th>
<th>DOR (mths)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KEYTRUDA 200 mg</td>
<td>NR</td>
<td>0.60</td>
<td>10.3</td>
<td>50</td>
<td>45%</td>
<td>NR</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>NR</td>
<td>---</td>
<td>6.0</td>
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<td>28%</td>
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<tr>
<td>KEYTRUDA 2mg/kg</td>
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<td>.88</td>
<td>18%</td>
<td>NR</td>
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<tr>
<td>KEYTRUDA 10 mg/kg</td>
<td>12.7</td>
<td>.61</td>
<td>4</td>
<td>.79</td>
<td>19%</td>
<td>NR</td>
</tr>
<tr>
<td>Docetaxel</td>
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<td>4</td>
<td>---</td>
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Efficacy Results2

First-line therapy – PD-L1 Expression ≥50% (Keynote 024 trial)

Second-line or subsequent therapy – PD-L1 Expression ≥1% (Keynote 010 trial)

OPDIVO®

A study of patients with advanced non-squamous NSCLC, PD-L1 expression (clone 28-8), and response to anti-PD1 immunotherapy OPDIVO® (nivolumab) versus chemotherapy, included the following results:1,11

- PD-L1 expression was associated with improved efficacy across all endpoints (OS, PFS, DOR) at all expression levels. The most improvement was seen in patients with PD-L1 expression ≥50% and ≥10%, but was evident at PD-L1 expression levels as low as ≥1%.

- Patients with tumors that had PD-L1 expression levels ≥1% were associated with a doubling of overall median survival.

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TECENTRIQ®

A study of previously treated metastatic NSCLC patients, PD-L1 expression (clone SP142), and response to anti-PD1 immunotherapy TECENTRIQ® (atezolizumab) versus docetaxel included the following results:2

- TECENTRIQ showed clinically relevant improvements in overall survival compared to docetaxel at all PD-L1 expression levels (high, medium, low, undetectable).

- However, patients with tumors with high expressing levels of PD-L1 (≥50% on tumor cells (TC) or ≥10% on tumor-infiltrating immune cells (IC)) derived the greatest benefit.

The Dako® PD-L1, IHC 22C3 pharmDx® test is FDA-approved as a companion diagnostic assay to aid in identifying advanced NSCLC patients for treatment with KEYTRUDA® (pembrolizumab).

The Dako® PD-L1, IHC 28-8 pharmDx® test is FDA-approved as a complementary diagnostic assay to help physicians determine which patients may benefit most with OPDIVO® (nivolumab).

OPDIVO®

The VENTANA® PD-L1, IHC SP142 test is FDA-approved as a complementary diagnostic assay to help physicians determine which patients may benefit most with TECENTRIQ® (atezolizumab).

Specimen Requirement Options

- Global Only
- Tissue should be fixed in 10% neutral buffered formalin; alternative fixatives have not been validated and may give erroneous results
- A minimum of 100 cells is required

1. Fixed Paraffin Block with Corresponding H&E
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Non-Small Cell Lung Cancer (NSCLC)

PD-L1 BY IMMUNOHISTOCHEMISTRY

PD-1 and PD-L1

Programmed death 1 (PD-1) is an immune inhibitory receptor expressed on the surface of activated T cells and mediates suppression of the immune system. PD-1 interacts with the immunosuppressive PD-L1 ligand which is expressed on tumor cells, inflammatory cells, and histiocytes, and inhibits T cell activation. A new class of immunotherapies, PD-1 and PD-L1 inhibitors, blocks the interaction between PD-1 and PD-L1 on the tumor cells and can enhance T cell responses and mediate anti-tumor activity.1,2

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PD-L1 Expression

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Biomarker Assay | Cancer Type | Immunotherapy | Scoring Cut-off
--- | --- | --- | ---
PD-L1 Dako® (22C3) Companion Diagnostic | First-line treatment metastatic NSCLC | KEYTRUDA® (pembrolizumab) | High PD-L1 expression: TPS ≥50%3,4
 Previously treated metastatic NSCLC | KEYTRUDA® (pembrolizumab) | PD-L1 expression: TPS ≥1%3,4
 PD-L1 Dako® (28-8) Complementary Diagnostic | Previously treated metastatic adenocarcinoma NSCLC | OSENO® (nivolumab) | PD-L1 expression in ≥1% TC22
 PD-L1 VENTANA® (SP142) Complementary Diagnostic | Previously treated metastatic NSCLC | TECENTRIQ® (atezolizumab) | PD-L1 expression in ≥50% TC or ≥10% IC23,24

NSCLC - non-small cell lung cancer

TPS – tumor proportional score

MC – PD-L1 expressing tumor cells

HC – PD-L1 expressing tumor-inhibiting immune cells

THE PD-1/PD-L1 BLOCKADE

The PD-1/PD-L1 interaction protects the cancer cell from immune destruction

Blocking the PD-1/PD-L1 interaction allows T cells to destroy tumor cells