Immunotherapy and Targeted Therapy: Nibs and Mabs (and More)

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Disclosures

• Stock: McKesson

In the beginning...

Interferon:
• Family of naturally occurring proteins
• Mechanism of action:
  – Antiviral, antiproliferative, cytostatic, immunomodulatory, differentiating, and inhibitory of cellular genes, including oncogenes.
  – Direct effect on cancer cells
  – Influence on effector cells (e.g. NK cells, T cells, macrophages).
Immunotherapy 2016

Cancer immunotherapy is a rapidly evolving anticancer strategy that is based upon the evidence that **immune surveillance** and **immune tolerance** are key players in development and progression of cancer.


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Immunotherapy: Assessment of Response

- Progressive disease vs “flare response”
- Duration of response
- Retreatment benefit with immunotherapy

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Immunotherapy: Adverse Reactions

- Immune response adverse reactions
- Dose / regimen effect of adverse reactions
- Toxicity profile:
  - Immunotherapy + immunotherapy
  - Immunotherapy + chemotherapy(s)
  - Toxicity vs progression of disease
irAE with Checkpoint Inhibitors

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Typical Timing of Occurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatologic (Rash, pruritis, vitiligo)</td>
<td>2-3 weeks</td>
</tr>
<tr>
<td>Gastrointestinal (diarrhea, colitis)</td>
<td>5-6 weeks</td>
</tr>
<tr>
<td>Hepatic (elevated ALT, elevated AST)</td>
<td>7-8 weeks</td>
</tr>
<tr>
<td>Endocrine (hypothyroidism, hyperthyroidism, hypophysitis)</td>
<td>7-9 weeks</td>
</tr>
<tr>
<td>Pulmonary (pneumonitis)</td>
<td>unknown</td>
</tr>
<tr>
<td>Neurologic (neuropathy, arthralgia, myalgia)</td>
<td>unknown</td>
</tr>
</tbody>
</table>

* melanoma

Rubin KM. CJON 2015;19:709-717

Clinical Approach to irAEs

• Prevention and/or mitigation
  – Strategies impact on efficacy of agent
  – Evaluated vs. experienced
• Identification → detection
  – Clinical trials vs. post marketing
  – Single agent vs. combination
• Management of toxicity
• Coordination of care

What is the best strategy for immunotherapy in treatment?

• Multiple immunotherapy
  – combination
  – sequenced
• Immunotherapy + “targeted” therapy
• Immunotherapy + chemotherapy
• Immunotherapy + radiation therapy

Rini B. Semin Oncol 2014:S30-S40.
Considerations for Cost of Care

• Cost of immunotherapy
  – Single agent
  – Combination
  – Place in therapy
  – Duration of therapy
• Cost associated with management of immunotherapy complications
  – Prevention
  – Management

Targeting: PI3K δ

Phosphatidylinositol 3-kinases as a target:
PI3Ks regulate cellular function →
production PI3,4,5 triphosphates →
activate downstream serine-threonine kinase Akt →
cellular growth, proliferation and survival

Rationale as target for B-cell lymphoproliferative disorders:
  – Dysregulation of PI3K/Akt pathway seen in some malignancies
  – Expression of p110 isoform mainly seen in lymphoid cells

Therapeutic potential of applications of PI3K δ inhibition:
  – CLL
  – Follicular B-cell lymphoma
  – SLL

Bruton’s Tyrosine Kinase (BTK)

BTK as a target:
  • BTK is a non-receptor tyrosine kinase member of the Tec kinase family
  • BTK is important in B-cell development

Therapeutic potential of BTK inhibition:
  • BTK inhibition in CLL: inhibits binding, reduces cell migration, proliferation, and survival, disrupts integrin-mediated adhesion, DNA synthesis and cellular response to tissue chemokines
  • BTK inhibition in MCL: induces apoptosis, decrease levels of anti-apoptotic proteins and ultimately MCL growth and cellular migration.
Targeting Cyclin-Dependent Kinases

**CKD as a target:**
- Cyclin-dependent kinases (CDK) are critical regulatory enzymes that drive all cell cycle transitions.
- Integration of multiple signaling pathways through control of select CDK activation.
  - Crucial role in orderly and controlled progression through cell cycle
- Deregulation of select CDK dependent pathways associated with some malignancies.

**The therapeutic potential of CDK inhibitors:**
- First generation: relatively non-specific “pan CDK inhibitors”
- Second generation: target inhibition of select CDK
  - Single agent approach
  - Combination approach


Elotuzumab (Empliciti®)

Elotuzumab: Mechanism of Action

- **Target:** Signaling Lymphocytic Activation Molecule F7 (SLAMF7)
  - called CS1 [cell-surface glycoprotein CD2 subset 1]
  - SLAMF7 is a glycoprotein expressed on myeloma and NK cells
- Directly activates NK cells and mediates ADCC through the CD16 pathway
Elotuzumab: FDA Approval 2015

• Current FDA Labeling:
  – Elotuzumab is approved in combination with lenalidomide and dexamethasone for individuals with multiple myeloma who have received 1–3 prior regimens. (November 2015)

ELOQUENT-2: elotuzumab + lenalidomide + dexamethasone in myeloma

• Phase III open-label trial comparing elotuzumab + lenalidomide + dexamethasone to control (lenalidomide + dexamethasone)
• Patient Populations:
  – Adults with myeloma who had received 1-3 prior therapies and had disease progression after most recent therapy
  – CrCl of 30 mL/min or better
  – Prior treatment with lenalidomide was permitted
• Treatment:
  – Elotuzumab 10 mg/kg on D1, 8, 15 and 22 during first 2 cycles, then D1,15 for subsequent cycles
  – Lenalidomide 25 mg po daily D1–21 every 28 day cycle
  – Dexamethasone 40 mg po D1,8,15, 22
  – Supportive care medications
    • Premedication for elotuzumab: diphenhydramine, ranitidine, acetaminophen
    • Thromboembolic prophylaxis
• Endpoints:
  – Primary: PFS, ORR (partial response rate or better)
  – Secondary: OS, severity of pain or interference with daily life
  – Exploratory endpoints: TTR, duration response, HRQOL, safety

Elotuzumab: ELOQUENT-2

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>N=646</th>
<th>Elotuzumab+ lenalidomide + dexamethasone N=321</th>
<th>Lenalidomide + dexamethasone N=325</th>
<th>HR, p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS</td>
<td>19.4 mo</td>
<td>14.9 mo</td>
<td>0.7 (0.57 – 0.85), p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>79%</td>
<td>66%</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>1-yr PFS</td>
<td>68%</td>
<td>57%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-yr PFS</td>
<td>41%</td>
<td>27%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Elotuzumab: ELOQUENT-2

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Elotuzumab + Ld, n=318</th>
<th>Ld, n=317</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade (%)</td>
<td>Gr 3–4 (%)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>99</td>
<td>77</td>
</tr>
<tr>
<td>Anemia</td>
<td>96</td>
<td>19</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>84</td>
<td>19</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>82</td>
<td>34</td>
</tr>
<tr>
<td>Fatigue</td>
<td>47</td>
<td>8</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>37</td>
<td>3</td>
</tr>
<tr>
<td>Vomiting</td>
<td>15</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>47</td>
<td>5</td>
</tr>
<tr>
<td>Constipation</td>
<td>36</td>
<td>1</td>
</tr>
<tr>
<td>Cough</td>
<td>31</td>
<td>&lt;3</td>
</tr>
<tr>
<td>Headache</td>
<td>15</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Cataracts</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>27</td>
<td>4</td>
</tr>
</tbody>
</table>

Elotuzumab: ELOQUENT-2

- Administration: IV infusion over 60 minutes through separate line
  - Inspection for particulates and discoloration recommended prior to infusion
  - Flush with NS after infusion is complete

- Infusion reactions occurred in 10% of patients
  - Majority reactions grade 1 and 2
  - 70% of reactions seen with first dose

Ixazomib (Ninlaro®)
Ixazomib: Mechanism of action

• Reversibly binds and inhibits the 20S proteasome → proteasome inhibitor

Ixazomib: FDA Approval 2015

• Ixazomib is indicated in combination with lenalidomide + dexamethasone for patients with multiple myeloma who have received at least one prior therapy. (November 2015)

TOURMALINE-MM1:
ixazomib + lenalidomide + dexamethasone in myeloma

• Phase III trials comparing ixazomib + lenalidomide + dexamethasone to control (lenalidomide + dexamethasone)
• Patient Populations:
  – Adults with relapsed or refractory myeloma
• Treatment:
  – Lenalidomide 25 mg po daily D1-21 every 28 day cycle
  – Dexamethasone 40 mg po D1,8,15, 22
  – Ixazomib 4 mg po once weekly on D1, 8, 15
• Endpoints:
  – Primary: PFS
  – Secondary: OS, OS in high risk patients with del(17)

Moreau P, et al. ASH Annual Meeting December 7, 2015; Abst: 727
TOURMALINE-MM1: Interim Analysis

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Ixazomib + Lenalidomide + Dexamethasone (n=360)</th>
<th>Lenalidomide + Dexamethasone (n=360)</th>
<th>HR / OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS, months</td>
<td>20.6</td>
<td>14.7</td>
<td>HR 0.742 (0.587–0.939) p=0.012</td>
</tr>
<tr>
<td>ORR, %</td>
<td>78.3</td>
<td>71.5</td>
<td>OR 1.44; p=0.035</td>
</tr>
<tr>
<td>CR, %</td>
<td>11.7</td>
<td>6.6</td>
<td>OR 1.87; p=0.019</td>
</tr>
<tr>
<td>VGPR, %</td>
<td>48.1</td>
<td>39.0</td>
<td>OR 1.45; p=0.014</td>
</tr>
<tr>
<td>Median duration of response (PR), months</td>
<td>20.5</td>
<td>15.0</td>
<td></td>
</tr>
</tbody>
</table>

Moreau P, et al. ASH Annual Meeting December 7, 2015; Abst: 727

TOURMALINE-MM1

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Ixazomib + LL, n=360</th>
<th>LL, n=360</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any grade</td>
<td>Gr 3–4</td>
<td>Any Grade</td>
</tr>
<tr>
<td>Upper respiratory infection</td>
<td>19</td>
<td>14</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>28</td>
<td>21</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>42</td>
<td>36</td>
</tr>
<tr>
<td>Constipation</td>
<td>34</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Nausea</td>
<td>26</td>
<td>21</td>
</tr>
<tr>
<td>Vomiting</td>
<td>22</td>
<td>11</td>
</tr>
<tr>
<td>Rash</td>
<td>19</td>
<td>11</td>
</tr>
<tr>
<td>Back pain</td>
<td>21</td>
<td>16</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>25</td>
<td>18</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>26</td>
<td>16</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>78</td>
<td>54</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>67</td>
<td>66</td>
</tr>
</tbody>
</table>

Moreau P, et al. ASH Annual Meeting December 7, 2015; Abst: 727

Ixazomib: Drug interactions

- Metabolized by multiple CYP enzymes, including:
  - 3A4*, 1A2*, 2B6*, 2C8, 2D6, 2C19, etc
  - Avoid concomitant use of strong CYP3A inducers
    - St. John’s Wort; rifampin; phenytoin, carbamazepine, etc
- CYP3A inhibitors
  - Co-administration with clarithromycin did NOT result in clinically meaningful change in exposure
- CYP1A2 inhibitors
  - Co-administration did NOT result in clinically meaningful change in exposure
- Impact on other drugs:
  - Ixazomib is NOT a reversible or time-dependent inhibitor of CYPs 1A2, 2B6, 2C8, 2D6, 3A4
Ixazomib: Practical Consideration

- **Dose:**
  - 4 mg PO days 1, 8, and 15 of each 28-day cycle in combination with lenalidomide + dexamethasone
- **Availability:** Capsules 4 mg, 3 mg, 2.3 mg
- **Administration**
  - Take 1 hr before or 2 hrs after food
  - Do not crush, chew, open capsules
  - Do not take a missed dose within 72 hrs of next scheduled dose

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Daratumumab (Darzalex®)

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Target: CD38

- Transmembrane glycoprotein expressed on the surface of hematopoietic cells (including myeloma cells)
- **Functions:**
  - Receptor mediated adhesion
  - Signaling
  - Modulation of protein activity
Daratumumab: FDA Approval

- Daratumumab is approved as a **single agent** for the treatment of patients with myeloma who have received > 3 prior lines of therapy including a proteosome inhibitor (PI) and an immunomodulatory agent (IA) or who are double-refractory to both a PI and IA.
- Accelerated approval was based on response rate from the clinical trial.

Daratumumab: Clinical Trials

- Open label trial of daratumumab monotherapy in patients with relapsed or refractory myeloma who had received at least 3 prior lines of therapy including a PI and an IA or who were double-refractory to a PI and an IA. (MMY202)
- Open label dose escalation trial evaluating daratumumab monotherapy in patients with relapsed or refractory myeloma who have received at least 2 different cytoreduction therapy. (GEN501)

Daratumumab: Clinical Trials

<table>
<thead>
<tr>
<th>Response</th>
<th>MMY2002 n = 106 (%)</th>
<th>GEN501 Part 2 n = 42 (%)</th>
<th>Total n = 148 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stringent Complete Response (sCR)</td>
<td>3 (2.8)</td>
<td>0</td>
<td>3 (2.0)</td>
</tr>
<tr>
<td>Complete response (CR)</td>
<td>0</td>
<td>2 (4.8)</td>
<td>2 (1.4)</td>
</tr>
<tr>
<td>Very good partial response (VGPR)</td>
<td>10 (9.4)</td>
<td>2 (4.8)</td>
<td>12 (8.1)</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>18 (17.0)</td>
<td>11 (26.2)</td>
<td>29 (19.6)</td>
</tr>
<tr>
<td>Minimal response (MR)</td>
<td>5 (4.7)</td>
<td>4 (9.5)</td>
<td>9 (6.1)</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>46 (43.3)</td>
<td>22 (52.4)</td>
<td>68 (45.9)</td>
</tr>
<tr>
<td>Progressive disease (PD)</td>
<td>18 (17.0)</td>
<td>0</td>
<td>18 (12.2)</td>
</tr>
<tr>
<td>Overall response (sCR+CR+VGPR+PR)</td>
<td>31 (29.2)</td>
<td>15 (35.7)</td>
<td>46 (31.3)</td>
</tr>
</tbody>
</table>

**Daratumumab: FDA Approval**

- Daratumumab is approved as a **single agent** for the treatment of patients with myeloma who have received > 3 prior lines of therapy including a proteosome inhibitor (PI) and an immunomodulatory agent (IA) or who are double-refractory to both a PI and IA.
- Accelerated approval was based on response rate from the clinical trial.

<table>
<thead>
<tr>
<th>Response</th>
<th>MTD/200 (n = 123(%)</th>
<th>GEN501, Part 2 (n = 44(%)</th>
<th>Total n = 167(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response (CR + VGPR + PR)</td>
<td>31 (29.2)</td>
<td>15 (35.7)</td>
<td>46 (31.1)</td>
</tr>
</tbody>
</table>

**Daratumumab: Toxicities**

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion reaction</td>
<td>48 3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>39 2</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>21 1</td>
</tr>
<tr>
<td>Cough</td>
<td>21 0</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>27/14 0/0</td>
</tr>
<tr>
<td>Diarrhea/constipation</td>
<td>16/15 1/0</td>
</tr>
<tr>
<td>Headache</td>
<td>12 1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>10 5</td>
</tr>
<tr>
<td>Anemia</td>
<td>45 19</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>48 18</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>60 20</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>72 40</td>
</tr>
</tbody>
</table>

**Daratumumab: Infusion Related Reactions**

- Infusion related reactions are more common with the first infusion
  - 1st: 46%
  - Subsequent: 5% (none > grade 2)
- Median time of reaction
- Median duration of infusion
  - 1st: 7 hr
  - 2nd: 4.6 hr
  - 3rd: 3.4 hr
Daratumumab

Pre-medications:
- IV Corticosteroid (methylprednisolone 100 mg or equivalent)
- Oral antipyretic (acetaminophen 650 – 1000 mg)
- PO or IV antihistamine (diphenhydramine 25 – 50 mg or equivalent)

Post-medications
- PO Corticosteroid (methylprednisolone 20 mg or equivalent) on days 2-3
- Long-acting bronchodilators +/- inhaled steroids for individuals with history of COPD
  - May be discontinued after the first four infusions if no reactions
- Herpes Zoster reactivation:
  - Prophylaxis to start 1 week prior – 3 months post last dose

Daratumumab: Practical Considerations

- Dose: 16 mg/kg IV
  - Weekly: wk 1 – 8
  - Q2wk: wks 9 – 24
  - Q4wk: wk 25+
- Stability:
  - Following dilution, refrigerated at 2° to 8°C up to 24 hours
  - Use immediately after coming to room temperature
  - Infusion should be completed within 15 hrs
- Impact on laboratory tests
  - Impacts Ab screening and cross matching
  - Interference with tests to monitor M protein (e.g. SPE, IFE)

Melanoma: MAPK Signaling Pathway

- **BRAF inhibition:**
  - Vemurafenib (Zelboraf®)
  - Dabrafenib (Tafinlar®)

- **MEK inhibition:**
  - Trametinib (Mekinist™)
  - Cobimetinib (Cotellic™) (2015)

- **BRAF inhibition + MEK inhibition:**
  - dabrafenib + trametinib
  - vemurafenib + cobimetinib

**Cobimetinib (Cotellic™)**

- Potent, orally bioavailable small molecule
- Inhibitor of MEK-1
- Preclinical trials: activity in B-Raf and K-Ras mutant cancer cell lines
- Clinical development: melanoma, breast cancer, pancreatic cancer

**Cobimetinib**

- **Indication:**
  - Unresectable or metastatic melanoma with BRAF V600E or V600K mutation in combination with vemurafenib

**Cobimetinib (+ vemurafenib): Melanoma**

- Randomized Phase 3 study in previously untreated unresectable locally advanced or metastatic BRAF v600 mutation + melanoma.
- **Methods:**
  - Randomized phase 3 study evaluating combination cobimetinib + vemurafenib vs. vemurafenib (1:1)
  - Individuals with previously untreated unresectable locally advanced or metastatic BRAF V600 mutation + melanoma
  - Endpoints: investigator-assessed PFS
- **Treatment:**
  - Vemurafenib 960mg BID po + placebo (control)
  - Vemurafenib 960mg BID po + cobimetinib 60 mg daily po x 21 (7 days off)

Cobimetinib: Clinical Trial

<table>
<thead>
<tr>
<th>Study arm</th>
<th>MedPFS (investigator assessment)</th>
<th>95% CI (HR)</th>
<th>CR + PR</th>
<th>OS (9 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cobimetinib + Vemurafenib (N=247)</td>
<td>9.9 months</td>
<td>0.51, 0.39 – 0.68 (P&lt;0.001)</td>
<td>68%</td>
<td>81%</td>
</tr>
<tr>
<td>Vemurafenib + placebo (N=248)</td>
<td>6.2 months</td>
<td></td>
<td>45%</td>
<td>73%</td>
</tr>
</tbody>
</table>

Larkin J, et al. NEJM 2014;371:1867-6

Cobimetinib + Vemurafenib: Toxicities

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Grade 1 (%)</th>
<th>Grade 2 (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>diarrhea</td>
<td>19</td>
<td>11</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>nausea</td>
<td>10</td>
<td>9</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>vomiting</td>
<td>16</td>
<td>4</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>rash</td>
<td>22</td>
<td>11</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>photosensitivity reaction</td>
<td>19</td>
<td>3</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>hyperkeratosis</td>
<td>9</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>fatigue</td>
<td>19</td>
<td>9</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>arthralgia</td>
<td>21</td>
<td>9</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

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Cobimetinib: Clinical Trial

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>% of grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Photosensitivity</td>
<td>28%</td>
</tr>
<tr>
<td>Hyperkeratosis</td>
<td>10%</td>
</tr>
<tr>
<td>Cutaneous sq cell</td>
<td>2%</td>
</tr>
</tbody>
</table>

Larkin J, et al. NEJM 2014;371:1867-6
**Cobimetinib**

- **Availability:**
  - 20mg film-coated tablets (bottles of 63 tablets)
- **Dose:**
  - 60 mg (three 20 mg tablets) orally once daily x 21 days (every 28 days)
- **Administration:**
  - can be taken with or without food
- **Drug interactions:**
  - CYP3A4 inhibitors

**Venetoclax (Venclexta)**

- FDA approved for the treatment of patients with chronic lymphocytic leukemia (CLL) whose disease harbors the 17p deletion and who have received at least one prior therapy (June 2016)
- Approved under the FDA’s accelerated approval process based on response rate; continued approval may be contingent upon confirmatory results

**Venetoclax : Clinical Trial**

<table>
<thead>
<tr>
<th>Efficacy Outcomes</th>
<th>Venetoclax n=107</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Response Rate, %</td>
<td>79.4</td>
</tr>
<tr>
<td>Deep Response Rate (CR+PR+nPR), %</td>
<td>10</td>
</tr>
<tr>
<td>Median Time to First Response, mo</td>
<td>0.8</td>
</tr>
<tr>
<td>Median Duration of Response, mo</td>
<td>Not yet reached</td>
</tr>
<tr>
<td>Progression-Free Survival (12-mo), %</td>
<td>72</td>
</tr>
</tbody>
</table>

Venetoclax: Clinical Trial

<table>
<thead>
<tr>
<th>Week</th>
<th>Ramp-Up Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20 mg</td>
</tr>
<tr>
<td>2</td>
<td>50 mg</td>
</tr>
<tr>
<td>3</td>
<td>100 mg</td>
</tr>
<tr>
<td>4</td>
<td>200 mg</td>
</tr>
<tr>
<td>5</td>
<td>400 mg once daily Continuous until disease progression or toxicity</td>
</tr>
</tbody>
</table>

Venetoclax: Warnings

- **Tumor lysis syndrome (TLS)**
  - Somewhat mediated by the ramp-up dosing schedule
  - May see as early as 6 – 8 hours after the first dose and at each dose increase
- **Neutropenia**
  - Grade 3/4 = 41%
- **Live attenuated vaccines**
  - Do not administer prior to, during or after treatment with Venetoclax™ until B cell recovery
- **Embryo-fetal toxicity**
  - Advise patients to use effective contraception during treatment and for 30 days after the last dose

Talimogene laherparepvec (IMLYGIC™) (TVEC)
Talimogene laherparepvec (TVEC)

- Talimogene laherparepvec is a genetically modified oncolytic viral therapy.
  - Engineered, oncolytic herpes simplex virus type-1 (HSV-1)
  - Oncolytic viruses selectively recognize, infect and destroy malignant cells with minimal effects on normal cells.

Talimogene laherparepvec (IMLYGIC™)

- Indication:
  - Local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery.
  - Limitations per package insert: This therapy has not been shown to improve OS or have an effect on visceral metastases

Talimogene laherparepvec (TVEC)

- Phase III multicenter, open-label, randomized clinical study in patients with stage IIIB, IIC and stage IV melanoma that were not considered to be surgically respectable.(OPTIM)

### Talimogene laherparepvec (TVEC)

**Response**

<table>
<thead>
<tr>
<th>Response Description</th>
<th>TVEC (n=295)</th>
<th>GM-CSF (n=145)</th>
<th>Unadjusted relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Durable Response Rate (CR+PR for minimum of 6 months)</td>
<td>18.3%</td>
<td>2.1%</td>
<td>8.6 (2.4, 24.1)</td>
</tr>
<tr>
<td>CR</td>
<td>26.4%</td>
<td>5.1%</td>
<td></td>
</tr>
<tr>
<td>Median time to response</td>
<td>4.1 months (1.2-16.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median OS</td>
<td>22.9 months</td>
<td>19.0 months</td>
<td>P=0.116</td>
</tr>
</tbody>
</table>


### Talimogene laherparepvec: Toxicities

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>TVEC (n=292)</th>
<th>GM-CSF (n=127)</th>
<th>All Grade (%)</th>
<th>Grade 3 (%)</th>
<th>All Grade (%)</th>
<th>Grade 3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>50</td>
<td>2.1</td>
<td>36.2</td>
<td>&lt;1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chills</td>
<td>48.6</td>
<td>8.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>42.8</td>
<td>8.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Influenza-like illness</td>
<td>30.5</td>
<td>&lt;1</td>
<td>15.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection site pain</td>
<td>27.7</td>
<td>&lt;1</td>
<td>6.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>35.6</td>
<td>&lt;1</td>
<td>19.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>21.2</td>
<td>1.7</td>
<td>9.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>18.8</td>
<td>&lt;1</td>
<td>11.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>17.5</td>
<td>&lt;1</td>
<td>5.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>17.1</td>
<td>&lt;1</td>
<td>8.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>16.4</td>
<td>3.8</td>
<td>9.5</td>
<td>&lt;1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Numbness</td>
<td>18.8</td>
<td>&lt;1</td>
<td>9.5</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Talimogene laherparepvec (TVEC)

- **Contraindications:**
  - Immunocompromised patients
  - Pregnant patients

- **Warnings and Precautions:**
  - Accidental exposure ➔ may lead to transmission of herpetic infection
  - Herpetic infections
  - Injection site complications
  - Immune-mediated event
  - Plasmacytoma at injection site
Talimogene laherparepvec (TVEC)

**Availability:**
- 10^6 (1 million) PFU per mL, 10^8 (100 million) PFU per mL in single-use vial

**Dose:**
- Administered by injection into cutaneous, subcutaneous and/or nodal lesions that are visible, palpable or detectable by ultrasound
- 1 million PFU vials per mL for first dose only
- Dose volume is determined by lesion size
- Maximum injection volume per treatment visit

**Preparation:**
- Healthcare providers who are immunocompromised or pregnant should not prepare or administer
- Thawing of product required (30 minutes +)

Immune Checkpoint Blockade

- Activation of T cells to enhance antitumor response:
  - Antigen-specific signal mediated by the T-cell receptor (TCR)
  - Co-stimulatory signal mediated by stimulatory and inhibitory receptor and ligand pairs (immune checkpoints)
  - **Checkpoints:**
    - Cytotoxic T lymphocyte antigen-4 (CTLA-4)
      - Operational during early activation of T cells
    - PD-1/PD-L1 (PD-programmed death)
      - Operational during the effector phase of T-cell activation

Ipilimumab (Yervoy®)

**Melanoma:**
- Treatment of unresectable melanoma
- **Adjuvant treatment** of patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy. (Oct 28, 2015)
Nivolumab (Opdivo®)
- Unresectable or metastatic melanoma
  - Single agent for pt with BRAF v600 WT
  - Single agent pt with BRAF v600 mutation positive disease following ipilimumab and BRAF inhibitor (Dec 2014)
  - Combination with ipilimumab pt with BRAF WT disease (Sept 2015)
  - Combination with ipilimumab pt with BRAF WT and mutant melanoma (Jan 2016)

The Expanding Role of PD-1 Inhibitors
- Melanoma
- Metastatic non-small cell lung cancer (NSCLC)
- Renal cell carcinoma (RCC)
- Bladder cancer
- Non-Hodgkin’s lymphoma (NHL)
- Head and neck cancer
- Gastric carcinoma
- Merkel cell cancer

Programmed Death-Ligand 1
- Programmed death ligand-1
  - B7-H1
  - CD274
- PD-L1 is expressed on tumor cells (TC) and tumor-infiltrating immune cells (IC) in the tumor microenvironment
- PD-L1 negatively regulates T-cell proliferation and function → tumors evade immune surveillance and eradication

Inhibition of PD-L1 signaling has been shown to have activity in wide variety of solid tumors.
Atezolizumab: Anti-PD-L1 Antibody

Purpose:
• Determine safety and clinical activity in renal cell carcinoma (RCC)
• Evaluate biomarkers ↔ association with outcomes

Methods:
• RCC cohort was part of an ongoing phase Ia multicenter, dose-escalation and dose-expansion trial of atezolizumab
• Patients initially enrolled regardless of PD-L1 status → enrollment was limited to patients whose tumors expressed PD-L1 IC2 or IC3 (≥ 5% of ICS stained positive for PD-L1)


Atezolizumab: Anti-PD-L1 Antibody

Methods:
• Patients with either metastatic clear-cell RCC or non-clear cell histology
• Prior treatment allowed if treatments completed 3 weeks prior to starting (6 wks for interleukin-2)
  – VEGF tyrosine kinase inhibitors (TKI)
  – Bevacizumab
  – mTOR inhibitors
  – Interleukin-2


Atezolizumab: Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>Median: 61 years</td>
<td>Range: 33 – 81</td>
</tr>
<tr>
<td>Gender</td>
<td>Males: 77% Females: 33%</td>
<td></td>
</tr>
<tr>
<td>Performance status (ECOG)</td>
<td>PS 0: 57%</td>
<td>PS 1: 43%</td>
</tr>
<tr>
<td>PD-L1 IC Score</td>
<td>0 : 33%</td>
<td>1 : 23%</td>
</tr>
<tr>
<td>Histologic subtypes of disease</td>
<td>Clear cell: 90%</td>
<td>Non-clear cell: 10%</td>
</tr>
<tr>
<td>Prior regimen</td>
<td>Median: 2 (range 0-7)</td>
<td>no prior 13%, 1 prior 30%, ≥ 2 prior 57%</td>
</tr>
</tbody>
</table>

Atezolizumab: Published Results

- Maximum tolerated dose was not reached
- No dose limiting toxicities were observed
  - 84% experienced a treatment-related AE
  - Majority of adverse events where low grade (1,2)
  - Immune-mediated adverse events were reported in 43%
  - Adverse events led to discontinuation in 3 patients
    - Grade 2 gaze palsy → resolved with corticosteroids
    - Sudden death
    - Suicide attempt


<table>
<thead>
<tr>
<th>Treatment-Related AE</th>
<th>Any Grade (%)</th>
<th>Grade 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>84%</td>
<td>17%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>29%</td>
<td>4%</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>16%</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>14%</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>14%</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>13%</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>11%</td>
<td>4%</td>
</tr>
<tr>
<td>Chills</td>
<td>11%</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>11%</td>
<td>0</td>
</tr>
<tr>
<td>Influenza-like</td>
<td>11%</td>
<td>0</td>
</tr>
<tr>
<td>Pruritis</td>
<td>11%</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>11%</td>
<td>0</td>
</tr>
</tbody>
</table>

Optimization of Drug Targets

Targeting EGFR

- Activating mutations of the EGFR gene
  - 30-50% individuals with advanced NSCLC who are of east Asian ethnicity
  - 10-17% individuals with other ethnicity
- Classes of activating somatic EGFR mutations
  - Deletions of exon 19
  - Single point mutations in exon 20
- Predict sensitivity to EGFR TKI
  - 1st generation reversible TKI: erlotinib, gefitinib
  - 2nd generation irreversible TKI: afatinib

Remon J, Future Oncol 2015

Osimertinib: Mechanism of Action

- Small molecule TKI of EGFR
  - Irreversibly binds to mutant EGFR (less to wt EGFR)
    - T790M
    - L858R
    - Exon 19 deletion
Osimertinib (Tagrisso®): Mechanism

• Binds irreversibly to the EGFR kinase
• Developed to have activity against tumors
  — Bearing sensitizing EGFR mutations
  — T790M resistance mutations

Osimertinib was also called AZD9291 in clinical trials.

Osibertinib (Tagrisso®): Mechanism

• Binds irreversibly to the EGFR kinase
• Developed to have activity against tumors
  — Bearing sensitizing EGFR mutations
  — T790M resistance mutations

Osimertinib was also called AZD9291 in clinical trials.

Osibertinib: FDA Approval

• Metastatic EGFR T790M mutation-positive NSCLC after progression on or after EGFR tyrosine kinase inhibitor (TKI) therapy.
  — Accelerated approval based on RR and DOR
  — Full approval is pending clinical benefit per confirmatory trials

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study 1 (n=201)</th>
<th>Study 2 (n=219)</th>
<th>Combined (n=420)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>57%</td>
<td>61%</td>
<td>59%</td>
</tr>
<tr>
<td>Median f/u</td>
<td>4.2 months</td>
<td>4 months</td>
<td></td>
</tr>
</tbody>
</table>

TAGRISO prescribing information 12/2015
Osimertinib: Adverse Effects

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>All grades (%)</th>
<th>Grade 3 – 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>42</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>17</td>
<td>0.5</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>16</td>
<td>0.7</td>
</tr>
<tr>
<td>Constipation</td>
<td>15</td>
<td>0.3</td>
</tr>
<tr>
<td>Skin rash</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>41</td>
<td>0.5</td>
</tr>
<tr>
<td>Dry skin</td>
<td>31</td>
<td>0</td>
</tr>
<tr>
<td>Nail toxicity</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>Pruritis</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>18</td>
<td>0.2</td>
</tr>
<tr>
<td>Cough</td>
<td>14</td>
<td>0.2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>14</td>
<td>0.5</td>
</tr>
<tr>
<td>Back pain</td>
<td>13</td>
<td>0.7</td>
</tr>
<tr>
<td>Headache</td>
<td>10</td>
<td>0.2</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>4</td>
<td>2.2</td>
</tr>
<tr>
<td>VTE</td>
<td>7</td>
<td>2.4</td>
</tr>
</tbody>
</table>

Osimertinib: Adverse Effects

<table>
<thead>
<tr>
<th>Lab abnormality</th>
<th>All grade (%)</th>
<th>Grade 3 – 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyponatremia</td>
<td>26</td>
<td>3.4</td>
</tr>
<tr>
<td>Hypermagnesemia</td>
<td>20</td>
<td>0.7</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>63</td>
<td>3.3</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>54</td>
<td>1.2</td>
</tr>
<tr>
<td>Anemia</td>
<td>44</td>
<td>0.2</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>33</td>
<td>3.4</td>
</tr>
</tbody>
</table>

Osimertinib: Drug interactions

- Metabolized via oxidation (CYP3A)
  - Competitive inhibitor of CYP3A
  - Inducer of CYP3A and 1A2
    - Avoid concomitant use of strong CYP3A inducers
    - Avoid concomitant use of strong CYP3A inhibitors
- Substrate of P-glycoprotein
- Impact on other drugs:
  - Recommended to avoid concomitant administration with sensitive substrates of CYP1A2, BCRP (Breast cancer resistance protein) with narrow therapeutic indices
Dosing and administration

• Dose: 80 mg PO once daily
• Availability: 40 and 80 mg tablets
• Administration: 80 mg once daily
  Pts with difficulty swallowing:
  – Tablet may be dispersed in 50 ml (~4 TBLS) of non-carbonated water only. Stir until tablet is fully dispersed and then swallow (or via NG-tube) immediately.
  – Do not crush or heat.
  – Rinse container with additional 4 – 8 ml water and drink or administer through NG-tube
References


