Immunotherapy: Nibs and Mabs

In the beginning…

Interferons:
• Family of naturally occurring proteins
• Mechanism of action:
  – Antiviral, antiproliferative, cytostatic, immunomodulatory, differentiating, and inhibitory of cellular genes, including oncogenes.
  – May act directly on cancer cells as well as effector cells (e.g. NK cells, T cells, macrophages).

The U.S. Food and Drug Administration New Drug Approvals in Oncology: 2015…

FEBRUARY
palbociclib
levatimib
panobinostat

MARCH
filgrastim-sndz
dinutuximab

JULY
gefitinib
sonidegib

SEPTEMBER
trifluridine/tipiracil
The U.S. Food and Drug Administration
NEW Anticancer Drugs Approvals in Oncology : 2015…

OCTOBER
irinotecan liposome
trabectedin

NOVEMBER
cobimetinib
osimertinib
daratumumab
ixazomib
nectumumab
elotuzumab

DECEMBER
alectinib

Identification of Targets in Cancer

Targeting: PI3K δ

• Role of Phosphatidylinositol 3-kinases:
  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 see in lymphoid cells

• Potential applications of this approach:
  – CLL
  – Follicular B-cell lymphoma
  – SLL

Keating GM. Targ Oncol 2015.
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 “panCDK inhibitors”
- Second generation: target inhibition of select CDK
  - Single agent approach
  - Combination approach
Elotuzumab (Empliciti®)

Elotuzumab: Mechanism of Action

- Humanized IgG1 immunostimulatory monoclonal antibody
- Targets Signaling Lymphocytic Activation Molecule F7 (SLAMF7), also called CS1 [cell-surface glycoprotein CD2 subset 1], 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


<table>
<thead>
<tr>
<th>Outcomes</th>
<th>N=544</th>
<th>Elotuzumab + Lenalidomide + Dexamethasone</th>
<th>N=321</th>
<th>HR, p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=321</td>
<td>N=325</td>
<td></td>
<td></td>
<td></td>
</tr>
<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>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>


<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>90</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>Pneumonia</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>38</td>
<td>1</td>
</tr>
<tr>
<td>Cough</td>
<td>31</td>
<td>&lt;1</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 (0.567–0.939) 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>Ld, n=360</th>
<th>Ld, n=360</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade</td>
<td>Gr 3–4</td>
</tr>
<tr>
<td>Upper respiratory infection</td>
<td>19 &lt;1</td>
<td>14 &lt;1</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>28 2</td>
<td>21 2</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>42 6</td>
<td>36 2</td>
</tr>
<tr>
<td>Constipation</td>
<td>34 &lt;1</td>
<td>25 &lt;1</td>
</tr>
<tr>
<td>Nausea</td>
<td>26 2</td>
<td>21 0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>22 1</td>
<td>11 &lt;1</td>
</tr>
<tr>
<td>Rash</td>
<td>10 3</td>
<td>11 1</td>
</tr>
<tr>
<td>Back pain</td>
<td>21 &lt;1</td>
<td>16 3</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>25 2</td>
<td>18 1</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>28 2</td>
<td>16 1</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>78 26</td>
<td>54 11</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>67 26</td>
<td>66 30</td>
</tr>
</tbody>
</table>

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

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

Daratumumab (Darzalex®)
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.
- Open label dose escalation trial evaluating daratumumab monotherapy in patients with relapsed or refractory myeloma who have received at least 2 different cytoreduction therapy.
### 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</td>
<td>3 (2.8)</td>
<td>0</td>
<td>3 (2.0)</td>
</tr>
<tr>
<td>Response (sCR)</td>
<td></td>
<td></td>
<td></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</td>
<td>10 (9.4)</td>
<td>2 (4.8)</td>
<td>12 (8.1)</td>
</tr>
<tr>
<td>response (VGPR)</td>
<td></td>
<td></td>
<td></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</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 reaction</th>
<th>Grade 1 (%)</th>
<th>Grade 2 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion reaction</td>
<td>48</td>
<td>3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>39</td>
<td>2</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>21</td>
<td>1</td>
</tr>
<tr>
<td>Chills</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Cough</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td>Nausea/pain/soreness</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>Back pain</td>
<td>23</td>
<td>2</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Upper respiratory infection</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>Neurological</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>Neurovascular</td>
<td>27/14</td>
<td>50</td>
</tr>
<tr>
<td>Dermatologic reaction</td>
<td>16/16</td>
<td>150</td>
</tr>
<tr>
<td>Headache</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>65</td>
<td>5</td>
</tr>
<tr>
<td>Anemia</td>
<td>45</td>
<td>19</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>48</td>
<td>18</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>80</td>
<td>20</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>72</td>
<td>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: 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)

The Evolution of Melanoma

Cobimetinib

- 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
Melanoma: MAPK Signaling Pathway

- **BRAF inhibition:**
  - Vemurafenib
  - Dabrafenib

- **MEK inhibition:**
  - Trametinib
  - Cobimetinib

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


Cobimetinib (Cotellic™)

- **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></th>
<th>Cobimetinib + Vemurafenib (N=247)</th>
<th>Vemurafenib (+ placebo) (N=248)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS (investigator assessment)</td>
<td>9.9 months</td>
<td>6.2 months</td>
</tr>
<tr>
<td>(HR: 0.51, 95% CI: 0.39 – 0.68; P&lt;0.001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR + PR</td>
<td>88%</td>
<td>45%</td>
</tr>
<tr>
<td>OS (6 months)</td>
<td>81%</td>
<td>73%</td>
</tr>
</tbody>
</table>

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

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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>39</td>
<td>11</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>nausea</td>
<td>30</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>7</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>

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

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Cobimetinib: Clinical Trial

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<thead>
<tr>
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<th>Cobimetinib + Vemurafenib (N=247)</th>
<th>Vemurafenib (+ placebo) (N=248)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% all grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>28%</td>
<td>19%</td>
</tr>
<tr>
<td>Hyperkeratosis</td>
<td>10%</td>
<td>29%</td>
</tr>
<tr>
<td>Cutaneous sq cell</td>
<td>2%</td>
<td>11%</td>
</tr>
</tbody>
</table>

Larkin J, et al. NEJM 2014;371:1867-6
Cobimetinib (Cotellic™)

- **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

Talimogene laherparepvec (IMLYGIC™) (TVEC)

- Talimogene laherparepvec (TVEC) 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™)

- 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)


<table>
<thead>
<tr>
<th>Response</th>
<th>TVEC (n=295)</th>
<th>GM-CSF (n=141)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Durable Response Rate (CR+PR for minimum of 6 months)</td>
<td>16.3%</td>
<td>2.1%</td>
</tr>
<tr>
<td>ORR</td>
<td>26.4%</td>
<td>5.7%</td>
</tr>
<tr>
<td>Median time to response</td>
<td>4.1 months (1.2-16.7)</td>
<td></td>
</tr>
<tr>
<td>Median OS</td>
<td>22.9 months</td>
<td>19.0 months</td>
</tr>
</tbody>
</table>

unadjusted relative risk 7.6 (95% CI: 2.4, 24.1)

P=0.116


<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>TVEC (n=292)</th>
<th>GM-CSF (n=141)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>50</td>
<td>2.1</td>
</tr>
<tr>
<td>Chills</td>
<td>48.6</td>
<td>8.7</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>42.8</td>
<td>8.7</td>
</tr>
<tr>
<td>Influenza-like illness</td>
<td>30.5</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>27.7</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Nausea</td>
<td>27.7</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>21.2</td>
<td>1.7</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>18.8</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Myalgia</td>
<td>17.7</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>17.1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>16.4</td>
<td>1.4</td>
</tr>
<tr>
<td>Headache</td>
<td>16.0</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

(All Grade (%) and Grade 3(%))
Talimogene laherparepvec (IMLYGIC™)

- **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

Evolving Indications for Cancer Drug Therapy

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
**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)

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**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)

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**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 (Tagrisso®)

Mechanism:
- Binds irreversibly to the EGFR kinase
- Developed to have activity against tumors
  - Bearing sensitizing EGFR mutations
  - T790M resistance mutations

Osimertinib: 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 duration of response
Necitumumab

- Recombinant human IgG1 monoclonal antibody to EGFR
- Mechanism of action:
  - Blocks EGFR binding to ligands

Necitumumab FDA Approval

- Approved in combination with cisplatin + gemcitabine for 1st line treatment of squamous non-small cell lung cancer
  - NOT indicated for non-squamous NSCLC histologic subtypes

Bibliography


