Pretest Question #1

Pembrolizumab was approved in September 2014 for treatment of unresectable metastatic melanoma. Which of the following adverse effects is a potential immune-mediated side effect that is related to this particular drug, which may require management with high-dose systemic corticosteroids followed by a taper dose should it occur?

A. Hyperthyroidism  JL434
B. Reversible posterior leukoencephalopathy  JL435
C. Thrombocytopenia  JL436
D. Dysrhythmia  JL437
Pretest Question #2

Olaparib was initially approved for use in patients diagnosed with which of the following malignancies?

A. Advanced breast cancer  JL438
B. ALK-positive NSCLC  JL439
C. BRCA1 and BRCA2 advanced ovarian cancer  JL440
D. Non-Hodgkin lymphoma  JL441

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Financial Disclosure

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Learning Objectives

1. Discuss the pharmacology and indications of medications approved from late 2014 to 2015 for the management of patients with cancer and/or hematologic diseases

2. Describe recommended monitoring and management of toxicities associated with these agents

3. Describe the impact of these agents in advanced practice
New Agents in Oncology

- Sonidegib
- Gefitinib
- Dinutuximab
- Lenvatinib
- Palbociclib
- Lanreotide
- Olaparib
- Nivolumab
- Pembrolizumab

Sonidegib

(LDE225)
July 24, 2015
The Hedgehog Pathway

Sonidegib Mechanism of Action

Audience Response Question

Which laboratory value may necessitate a dosage decrease when initiating sonidegib?

A. Elevated serum creatinine  JL442
B. Elevated bilirubin   JL443
C. Elevated creatinine kinase  JL444
D. Elevated prothrombin (PT) time  JL445
Sonidegib

- **Mechanism:** SMO (smoothened) inhibitor
  Somatic mutations in PTCH have been identified in > 90 of sporadic basal cell carcinoma (BCC) and in ~20% of medulloblastoma

- **Indication:** Adult patients with locally advanced BCC that has recurred following surgery or radiation therapy or those who are not candidates for surgery or radiation therapy

Sonidegib (cont)

- **Dose:** 200 mg orally once daily taken on an empty stomach at least 1 hour before or 2 hours after a meal (no renal or hepatic dose adjustments noted)
  - Hold for:
    - Severe or intolerable musculoskeletal adverse reactions
    - First occurrence of serum creatinine kinase (CK) elevation between 2.5 and 10 × upper limit of normal (ULN) or recurrent serum CK elevation between 2.5 and 5 × ULN
  - Permanently discontinue for:
    - Serum CK elevation greater than 2.5 × ULN with worsening renal function or serum CK elevation greater than 10 × ULN; recurrent serum CK elevation greater than 5 × ULN
    - Recurrent severe or intolerable musculoskeletal adverse reactions
Sonidegib (cont)

- **Toxicities**: The most common adverse reactions occurring in ≥ 10% of patients are muscle spasms, alopecia, dysgeusia, fatigue, nausea, musculoskeletal pain, diarrhea, decreased weight, decreased appetite, myalgia, abdominal pain, headache, pain, vomiting, and pruritus.
  - Avoid donating blood
  - Obtain serum CK and creatinine levels prior to initiating therapy and periodically during treatment

Sonidegib (cont)

- **Drug-drug interactions**
  - CYP3A4 substrate
    - Avoid concomitant administration with moderate to strong CYP3A inhibitors, including but not limited to saquinavir, telithromycin, ketoconazole, itraconazole, voriconazole, posaconazole, and nefazodone
    - Avoid concomitant administration with strong and moderate CYP3A inducers, including but not limited to carbamazepine, efavirenz, modafinil, phenobarbital, phenytoin, rifabutin, rifampin and St. John’s wort

Sonidegib (cont)

- Embryo-fetal death or severe birth defects when administered to a pregnant woman. It is embryotoxic, fetotoxic, and teratogenic in animals.
- Verify the pregnancy status of females of reproductive potential prior to initiating therapy. Advise females of reproductive potential to use effective contraception during treatment with sonidegib and for at least 20 months after the last dose.
- Advise males of the potential risk of exposure through semen and to use condoms with a pregnant partner or a female partner of reproductive potential during treatment with sonidegib and for at least 8 months after the last dose.
Treatment With Two Different Doses of Sonidegib in Patients With Locally Advanced or Metastatic Basal Cell Carcinoma (BOLT): A Multicentre, Randomized, Double-Blind Phase II Trial

Sonidegib Efficacy

Gefitinib

(ZD1839)
July 13, 2015
**Gefitinib**

- **Mechanism:** EGFR tyrosine kinase inhibitor
- **Indication:** First-line treatment of patients with metastatic non–small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations
- **Dose:** 250 mg orally, once daily with or without food
  - Obtain periodic liver function testing. Withhold for grade 2 or higher ALT and/or AST elevations. Discontinue for severe hepatic impairment.
- **Warnings**
  - Interstitial lung disease (ILD); hepatotoxicity; GI perforation (discontinue); diarrhea (hold for grade 3 or higher); ocular disorders including keratitis (hold); bullous and exfoliative skin disorders (hold for grade 3 or higher); embryofetal toxicity

ALT = alanine aminotransferase; AST = aspartate aminotransferase.

Gefitinib (cont)

- **Toxicity**: Skin reactions and rash occurred in greater than 20% of patients
  - Treat rash aggressively with antibiotics (e.g., doxycycline), topical medications (e.g., hydrocortisone, clindamycin, erythromycin), and systemic steroids if grade 3 or higher

- **Drug-drug interactions**
  - CYP3A4 inducers: Increase to 500 mg daily in patients receiving a strong CYP3A4 inducer
  - CYP3A4 inhibitors: Monitor adverse reactions if concomitant use
  - Avoid concomitant use with proton pump inhibitors
  - Monitor changes in prothrombin time or international normalized ratio if on warfarin

Phase IV IFUM (IRESSA Follow-Up Measure) Study

Gefitinib IFUM Results

- ORR 69.8% (95% CI 60.5%–77.7%)
- PFS 9.7 mo (95% CI 8.5–11.0 mo)
- Median OS 19.2 mo (95% CI 17.0–NC; 27% maturity)
- Most common AEs (any grade): Rash (44.9%), diarrhea (30.8%)

ORR = overall response rate; CI = confidence interval; PFS = progression-free survival; OS = overall survival; AE = adverse event.

**EGFR Mutations in NSCLC**

Positive predictors of response
- Exon 19 deletions or exon 21 (L858R) substitution mutations

Predictor of resistance
- Exon 20 T790M mutation

Dinutuximab
(ch14.18)
March 10, 2015
Dinutuximab

- **Mechanism:** See upcoming slides
- **Indication:** In combination with granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-2 (IL-2), and 13-cis-retinoic acid (RA), for the treatment of pediatric patients with high-risk neuroblastoma who achieve at least a partial response to prior first-line therapy.
- **Dose:** 17.5 mg/m²/day as a diluted IV infusion over 10 to 20 hours for 4 consecutive days for up to 5 cycles (not studied in hepatic or renal failure)
  - Prehydrate with normal saline 10 mL/kg over 1 hour
  - Administer morphine (50 μg/kg) IV immediately prior to initiation and then continue as a drip at rate of 20–50 μg/kg/hr during and for 2 hours after completion
  - Administer diphenhydramine IV prior to initiation and as tolerated every 4 to 6 hours during infusion
  - Administer acetaminophen along with diphenhydramine
  - Dose may need to be held or drug permanently stopped for adverse reactions noted in warning section

Dinutuximab (cont)

- **Warnings**
  - Capillary leak syndrome and hypotension: Administer required prehydration and monitor patients
  - Infection
  - Neurologic disorders of the eyes: Interrupt for dilated pupil with sluggish light reflex
  - Bone marrow suppression
  - Electrolyte abnormalities (hyponatremia, hypokalemia, and hypocalcemia)
  - Atypical hemolytic uremic syndrome
  - Embryofetal toxicity
Dinutuximab (cont)

- **Toxicities:** Occurring ≥ 25%: Pain, pyrexia, thrombocytopenia, lymphopenia, infusion reactions, hypotension, hyponatremia, increased ALT, anemia, vomiting, diarrhea, hypokalemia, capillary leak syndrome, neutropenia, urticaria, hypoalbuminemia, increased AST, and hypocalcemia
  - The most common serious adverse reactions (≥ 5%) are infections, infusion reactions, hypokalemia, hypotension, pain, fever, and capillary leak syndrome

- **Drug-drug interactions:** None reported

ALT = alanine aminotransferase; AST = aspartate aminotransferase.

Dinutuximab (cont)

**Serious Infusion Reactions**
- Serious and potentially life-threatening infusion reactions (facial and upper airway edema, dyspnea, bronchospasm, stridor, urticaria, and hypotension) occurred in 26% of patients
- Administer required prehydration and premedication including antihistamines prior to each infusion

**Neuropathy**
- Causes severe neuropathic pain in the majority of patients
- Administer intravenous opioid prior to, during, and for 2 hours after completion of infusion
- Severe (grade 3) peripheral sensory neuropathy ranged from 2% to 9% in patients with neuroblastoma
- Resolution of motor neuropathy was not documented in all cases
Dinutuximab History and Mechanism of Action

- GD2 expressed on the surface of 99% of neuroblastoma cells
- Also found on nerve, skin, and brain tissue
- Earliest antibodies were generated from mice (14G2A, 3F8)
- A chimeric antibody against GD2
- Lab work late 1970s to mid 1980s
- Investigational New Drug Application process begun in 1989

Mechanism of GD2 Antibody–Targeted Destruction of Neuroblastoma by CDC and ADCC

Dinutuximab (cont)

Lenvatinib

(E7080)
February 13, 2015
Lenvatinib (cont)

- **Mechanism:** VEGFR tyrosine kinase
  - Also inhibits fibroblast growth factor (FGF) receptors, platelet-derived growth factor receptor alpha (PDGFRα), KIT, and RET

- **Indication:** Treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer

- **Dose:** 24 mg orally, once daily (decrease to 14 mg in patients with severe renal or hepatic impairment)

Lenvatinib (cont)

- **Warnings**
  - Typical VEGF inhibitor effects: Hypertension, cardiac failure, thromboembolic events, proteinuria, GI perforation, reversible posterior leukoencephalopathy syndrome (RPLS), bleeding
  - Hepatotoxicity, QT interval prolongation, hypocalcemia, fetal harm, impairment of thyroid-stimulating hormone suppression (monitor TSH levels monthly and adjust thyroid replacement medication); all of them require monitoring and dose adjustments or holding the dose until corrected
Lenvatinib (cont)

- **Toxicities:** Common adverse reactions (incidence greater than or equal to 30%) are hypertension, fatigue, diarrhea, arthralgia, decreased appetite, weight decreased, nausea, stomatitis, headache, vomiting, proteinuria, hand-foot syndrome, abdominal pain, and dysphonia

- **Drug-drug interactions:** No clinically significant interactions reported
# Baseline Characteristics in the Intention-to-Treat Population


<table>
<thead>
<tr>
<th>Variable</th>
<th>Lenvatinib (N = 261)</th>
<th>Placebo (N = 131)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age — yr</td>
<td>64</td>
<td>61</td>
</tr>
<tr>
<td>Male sex — no. (%)</td>
<td>125 (47.9)</td>
<td>75 (57.3)</td>
</tr>
<tr>
<td>Region — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>131 (50.2)</td>
<td>64 (48.9)</td>
</tr>
<tr>
<td>North America</td>
<td>77 (29.5)</td>
<td>39 (29.8)</td>
</tr>
<tr>
<td>Other†</td>
<td>53 (20.3)</td>
<td>28 (21.4)</td>
</tr>
<tr>
<td>ECOG performance status — no. (%)‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 or 1</td>
<td>248 (95.0)</td>
<td>129 (98.5)</td>
</tr>
<tr>
<td>2 or 3</td>
<td>13 (5.0)</td>
<td>2 (1.5)</td>
</tr>
<tr>
<td>One prior treatment regimen with a tyrosine kinase inhibitor — no. (%)§</td>
<td>66 (25.3)</td>
<td>27 (20.6)</td>
</tr>
<tr>
<td>Histologic subtype of differentated thyroid cancer — no. (%)¶</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Papillary</td>
<td>132 (50.6)</td>
<td>68 (51.9)</td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>28 (10.7)</td>
<td>19 (14.5)</td>
</tr>
<tr>
<td>Follicular, not Hürthle cell</td>
<td>53 (20.3)</td>
<td>22 (16.8)</td>
</tr>
<tr>
<td>Hürthle cell</td>
<td>48 (18.4)</td>
<td>22 (16.8)</td>
</tr>
<tr>
<td>Metastatic lesions — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With bony metastases</td>
<td>104 (39.8)</td>
<td>48 (36.6)</td>
</tr>
<tr>
<td>With pulmonary metastases</td>
<td>226 (86.6)</td>
<td>124 (94.7)</td>
</tr>
</tbody>
</table>

* There were no significant differences between the groups in any of the characteristics listed in this table.

† Other regions include Brazil, Chile, Japan, South Korea, Russia, and Thailand.

‡ Eastern Cooperative Oncology Group (ECOG) performance status scores range from 0 to 5, with higher scores indicating increasing disability.

§ Further information is provided in Table S4 in the Supplementary Appendix.

¶ Histologic findings were determined from investigators’ reports.
Kaplan-Meier Estimate of PFS in the Intention-to-Treat Population

Median (95% CI)
- Lenvatinib: 18.3 mo (15.1–NE)
- Placebo: 3.6 mo (2.2–3.7)

Hazard ratio for progression or death:
- 0.21 (99% CI, 0.14–0.31)
- P<0.001

<table>
<thead>
<tr>
<th>Months</th>
<th>Lenvatinib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>261</td>
<td>131</td>
</tr>
<tr>
<td>2</td>
<td>225</td>
<td>71</td>
</tr>
<tr>
<td>4</td>
<td>198</td>
<td>43</td>
</tr>
<tr>
<td>6</td>
<td>176</td>
<td>29</td>
</tr>
<tr>
<td>8</td>
<td>159</td>
<td>19</td>
</tr>
<tr>
<td>10</td>
<td>148</td>
<td>13</td>
</tr>
<tr>
<td>12</td>
<td>136</td>
<td>11</td>
</tr>
<tr>
<td>14</td>
<td>92</td>
<td>5</td>
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<tr>
<td>16</td>
<td>44</td>
<td>4</td>
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<td>18</td>
<td>24</td>
<td>2</td>
</tr>
<tr>
<td>20</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>22</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>24</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

### Table 3. Adverse Effects.

<table>
<thead>
<tr>
<th>Effect</th>
<th>Lenalidomide (N=261)</th>
<th>Placebo (N=131)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade ≥3</td>
</tr>
<tr>
<td>Any treatment-related adverse effect — no. of patients (%)</td>
<td>254 (97.3)</td>
<td>198 (75.9)</td>
</tr>
<tr>
<td>Adverse effect developing during treatment — no. of patients (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>130 (49.8)</td>
<td>30 (27.9)</td>
</tr>
<tr>
<td>Treatment-related</td>
<td>70 (10.3)</td>
<td>8 (1.1)</td>
</tr>
<tr>
<td>Fatal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total†</td>
<td>20 (7.7)</td>
<td>6 (4.6)</td>
</tr>
<tr>
<td>Treatment-related</td>
<td>6 (2.3)</td>
<td>0</td>
</tr>
<tr>
<td>Treatment-related adverse effect of any grade in ≥10% of patients, of grade ≥3 in ≥2%, or both — %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>67.8 (41.8)</td>
<td>9.2  (3.1)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>59.4 (8.0)</td>
<td>8.4  (1.1)</td>
</tr>
<tr>
<td>Fatigue or asthenia</td>
<td>58.0 (9.2)</td>
<td>27.5 (4.6)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>50.2 (5.4)</td>
<td>11.5 (0.8)</td>
</tr>
<tr>
<td>Decreased weight</td>
<td>46.4 (9.6)</td>
<td>9.2  (1.1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>41.0 (2.3)</td>
<td>13.7 (0.8)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>35.6 (4.2)</td>
<td>3.8  (0.8)</td>
</tr>
<tr>
<td>Palmar–plantar erythrodysaesthesia syndrome</td>
<td>31.8 (3.4)</td>
<td>0  (0.8)</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>31.0 (10.0)</td>
<td>1.5  (0.8)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>28.4 (1.9)</td>
<td>6.1  (0.8)</td>
</tr>
<tr>
<td>Headache</td>
<td>27.6 (2.7)</td>
<td>6.1  (0.8)</td>
</tr>
<tr>
<td>Dysphonia</td>
<td>24.1 (1.1)</td>
<td>3.1  (0.8)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>18.8 (0.8)</td>
<td>0  (0.8)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>16.9 (0.8)</td>
<td>1.5  (0.8)</td>
</tr>
<tr>
<td>Rash</td>
<td>16.1 (0.4)</td>
<td>1.3  (0.8)</td>
</tr>
<tr>
<td>Constipation</td>
<td>14.6 (0.4)</td>
<td>0.8  (0.8)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>14.6 (1.5)</td>
<td>2.3  (0.8)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>13.8 (0.4)</td>
<td>3.8  (0.8)</td>
</tr>
<tr>
<td>Upper abdominal pain</td>
<td>13.0 (0.4)</td>
<td>3.8  (0.8)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>11.5 (0.4)</td>
<td>0.8  (0.8)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>11.1 (0.4)</td>
<td>0  (0.8)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>11.1 (0.4)</td>
<td>3.8  (0.8)</td>
</tr>
<tr>
<td>Dyspnnea</td>
<td>10.0 (0.4)</td>
<td>0  (0.8)</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>10.0 (0.4)</td>
<td>0.8  (0.8)</td>
</tr>
<tr>
<td>Hypoesthesia</td>
<td>6.9 (2.7)</td>
<td>0  (0.8)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>2.7 (2.7)</td>
<td>1.5  (0.8)</td>
</tr>
</tbody>
</table>

* A complete list of serious adverse effects is provided in Table S2 in the Supplementary Appendix.
† A complete list of fatal adverse effects that developed during treatment is provided in Table S3 in the Supplementary Appendix.
Lenvatinib (cont)
Palbociclib

(PD0332291)
February 3, 2015
Palbociclib

- **Mechanism:** Inhibitor of cyclin-dependent kinase (CDK) 4 and 6
- **Indication:** In combination with letrozole for the treatment of postmenopausal women with estrogen receptor (ER)–positive, HER2-negative metastatic breast cancer as initial endocrine-based therapy
  - Data exist with other ER receptor antagonists
- **Dose:** 125 mg once daily taken with food for 21 days followed by 7 days off treatment (in combination with daily letrozole)
  - Dose reduce for grade 3 or greater nonhematologic or hematologic toxicity (100 mg)
  - No known hepatic or renal adjustments

Which of the following clinical parameters is NOT required to be checked in patients receiving palbociclib?

A. White blood cell count  JL446
B. Renal function  JL447
C. Platelet count  JL448
D. Estrogen receptor status  JL449
Palbociclib (cont)

- **Warnings**
  - Neutropenia may occur (check CBC prior to therapy and every 2 weeks for first 2 cycles)
  - Infections
  - Embryofetal toxicity

- **Toxicities**: Most common adverse reactions (incidence ≥ 10%) were neutropenia, leukopenia, fatigue, anemia, upper respiratory infection, nausea, stomatitis, alopecia, diarrhea, thrombocytopenia, decreased appetite, vomiting, asthenia, peripheral neuropathy, and epistaxis

CBC = complete blood cell count

Palbociclib (cont)

- **Drug-drug interactions**
  - Avoid concurrent use with strong CYP3A inhibitors. May require dose decrease (to 75 mg)
  - Avoid concurrent use with strong and moderate CYP3A inducers
  - The dose of sensitive CYP3A4 substrates may need to be reduced when given concurrently with palbociclib
Palbociclib: PALOMA-1/TRIO-18

PALOMA-1/TRIO-18

- Phase II, randomized, open-label trial
- Two arms (2:1 randomization)
  - Palbociclib 125 mg daily (3 wk on/1 wk off) + letrozole 2.5 mg daily
  - or
  - Letrozole 2.5 mg daily

Efficacy results: Investigator assessment of PFS in intent-to-treat population

<table>
<thead>
<tr>
<th>Progression-free survival</th>
<th>Palbociclib + letrozole (n = 84)</th>
<th>Letrozole (n = 81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of PFS events (%)</td>
<td>41 (48.8%)</td>
<td>59 (72.8%)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.488 (0.319–0.748)</td>
<td></td>
</tr>
<tr>
<td>Median PFS (95% CI)</td>
<td>20.2 mo (13.8–27.5 mo)</td>
<td>10.2 mo (5.7–12.6 mo)</td>
</tr>
</tbody>
</table>

**Palbociclib: PALOMA-1/TRIO-18 (cont)**

<table>
<thead>
<tr>
<th>Event</th>
<th>Palbociclib + letrozole (%) (n = 83)</th>
<th>Letrozole (%) (n = 77)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>74*</td>
<td>5</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>43</td>
<td>3</td>
</tr>
<tr>
<td>Anemia</td>
<td>35</td>
<td>6</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>25</td>
<td>7</td>
</tr>
<tr>
<td>Nausea</td>
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<td>13</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>21</td>
<td>10</td>
</tr>
<tr>
<td>Alopecia</td>
<td>22</td>
<td>3</td>
</tr>
<tr>
<td>Hot flashes</td>
<td>21</td>
<td>12</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>23</td>
<td>16</td>
</tr>
<tr>
<td>Fatigue</td>
<td>40</td>
<td>23</td>
</tr>
</tbody>
</table>

*54% grade 3/4

CDK4 and Cyclin D Drives Progression Through the Cell Cycle

- Phosphorylates Rb and drives progression through the cell cycle
- Activated by p16 loss, CDK4 amplification, cyclin D overexpression, or Rb loss in many cancers
- Also activated by upstream signal transduction
  - ER receptor
  - EGFR receptor
  - MAPK pathway

Lanreotide

December 16, 2014
Lanreotide

- **Mechanism:** Analog of natural somatostatin
- **Indication:** Retreatment of patients with unresectable, well- or moderately differentiated, locally advanced or metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs)
- **Dose:** 120 mg administered every 4 weeks by deep subcutaneous injection
  - No renal or hepatic dose adjustments for GEP-NETs noted

Lanreotide (cont)

- **Warnings**
  - Gallstones
  - Hypo- and/or hyperglycemia may occur; glucose monitoring is recommended and antidiabetic treatment adjusted accordingly
  - Decrease in heart rate

- **Adverse effects:** Most common adverse reactions (> 10%) are abdominal pain, musculoskeletal pain, vomiting, headache, injection-site reaction, hyperglycemia, hypertension, cholelithiasis

- **Drug-drug interactions**
  - Antidiabetic medication
  - May decrease the bioavailability of cyclosporine

- **Drugs affecting heart rate:** Can lower heart rate; use with caution with other drugs that lower heart rate
Progression-Free Survival (Intention-to-Treat Population)

- Progression-free survival at 24 mo was 65% with lanreotide and 33% with placebo.
- Tumors were grade 1 or 2 (Ki-67 < 10%).

Baseline Demographic and Disease Characteristics
(Intention-to-Treat Population)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lanreotide (N = 101)</th>
<th>Placebo (N = 103)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex — no. (%)</td>
<td>53 (52)</td>
<td>54 (52)</td>
</tr>
<tr>
<td>Age — yr</td>
<td>63.3±9.8</td>
<td>62.2±11.1</td>
</tr>
<tr>
<td>Time since diagnosis — mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>32.6±46.1</td>
<td>34.4±41.4</td>
</tr>
<tr>
<td>Median</td>
<td>13.2</td>
<td>16.5</td>
</tr>
<tr>
<td>Prior treatment for neuroendocrine tumor — no. (%)</td>
<td>16 (16)</td>
<td>16 (16)</td>
</tr>
<tr>
<td>Primary tumor resected — no. (%)</td>
<td>40 (40)</td>
<td>39 (38)</td>
</tr>
<tr>
<td>Origin of neuroendocrine tumor — no. (%)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>42 (42)</td>
<td>49 (48)</td>
</tr>
<tr>
<td>Midgut</td>
<td>33 (33)</td>
<td>40 (39)</td>
</tr>
<tr>
<td>Hindgut</td>
<td>11 (11)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Unknown or other</td>
<td>15 (15)</td>
<td>11 (11)</td>
</tr>
<tr>
<td>Tumor progression — no. (%)</td>
<td>4 (4)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Tumor grade — no. (%)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1: Ki-67 0–2%</td>
<td>69 (68)</td>
<td>72 (70)</td>
</tr>
<tr>
<td>2: Ki-67 3–10%</td>
<td>32 (32)</td>
<td>29 (28)</td>
</tr>
<tr>
<td>Data missing</td>
<td>0</td>
<td>2 (2)</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. Additional baseline data are provided in Table S3 in the Supplementary Appendix.
Post hoc analyses confirmed that there were no significant between-group differences at baseline. The midgut was defined as the small intestine and appendix, and the hindgut was defined as the large intestine, rectum, anal canal, and anus.
† Two patients in each group had gastrinomas.
‡ Ki-67 thresholds for the tumor grade index were based on the World Health Organization 2010 classification. Patients who had Ki-67 values greater than 2% and up to 10% in the present study were classified as having grade 2 disease.
Targeting Critical Signaling Pathways in NETs

Blocks sst2 and sst5, effectively reducing the release of bioactive peptides and neuroamines.
Lanreotide: Medical Management

- Managing hormone excess
- Somatostatin analogs (SSAs): Octreotide (PROMID trial) 30 mg IM injection every 28 days or lanreotide (CLARINET trial) 120 mg once in 28 days, targets somatostatin receptors that are overexpressed on most pNETs (except insulinomas)
- SSAs also seem to have cytostatic effects that can stabilize metastatic disease without tumor regression in most cases
- The effect of these agents is most pronounced in tumors with a low proliferative index, as they have a higher burden of somatostatin receptors

Olaparib

(AZD-2281)
December 19, 2014
Olaparib

- **Indication(s):** Monotherapy in patients with deleterious or suspected deleterious germline *BRCA* mutated (as detected by an FDA-approved test) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy

- **NCCN:** Recurrent ovarian targeted therapy (category 2A)

- **Cost:** $12,000/month

- **How supplied:** 50-mg capsules

Olaparib (cont)

Multicenter, single-arm, phase II study

Advanced ovarian cancer with deleterious or suspected deleterious germline BRCA-mutated advanced
• > 3 prior lines of chemotherapy

Olaparib 400 mg bid (n = 137)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>34% (26, 42)</td>
</tr>
<tr>
<td>PFS</td>
<td>7 mo</td>
</tr>
<tr>
<td>PFS at 6 mo</td>
<td>54.6%</td>
</tr>
<tr>
<td>Median OS</td>
<td>16.6 mo</td>
</tr>
<tr>
<td>OS at 12 mo</td>
<td>64.4%</td>
</tr>
<tr>
<td>Duration of response</td>
<td>7.9 mo (5.6, 9.6)</td>
</tr>
</tbody>
</table>

Olaparib (cont)

- **Dose:** 400 mg twice daily until progressive disease or unacceptable toxicity

- **Dose adjustments**
  - Renal impairment (moderate/severe): Not recommended
  - Hepatic impairment: Not recommended with serum bilirubin > 1.5 × ULN

- **Pharmacokinetics**
  - CYP3A4 strong/moderate inhibitors: Avoid
    - If unavoidable strong inhibitor: Reduce the dose to 150 mg twice daily
    - If unavoidable moderate inhibitor: Reduce the dose to 200 mg twice daily
  - CYP3A4 strong/moderate inducers: Avoid; if cannot avoid, be aware of potential for decreased efficacy
  - Avoid grapefruit and Seville oranges
## Olaparib: Adverse Reactions

<table>
<thead>
<tr>
<th>Adverse reactions &gt; 20% of patients with gBRCA-mutated advanced ovarian cancer (%)</th>
<th>Olaparib (n = 53)</th>
<th>Placebo (n = 43)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Anemia</td>
<td>25</td>
<td>4</td>
</tr>
<tr>
<td>Nausea</td>
<td>75</td>
<td>2</td>
</tr>
<tr>
<td>Vomiting</td>
<td>32</td>
<td>4</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>Upper respiratory infection</td>
<td>43</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>32</td>
<td>4</td>
</tr>
<tr>
<td>Rash</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>85</td>
<td>8</td>
</tr>
<tr>
<td>Decreased ANC</td>
<td>32</td>
<td>8</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>26</td>
<td>0</td>
</tr>
</tbody>
</table>

ANC = absolute neutrophil count.
Olaparib: Tips

Counseling
- Weakness, weight loss
- Fever
- Signs or symptoms of infection
- Blood in urine or stool or bleeding/bruising more easily
- Shortness of breath

Monitoring
- Monitor CBC at baseline and monthly thereafter: *For prolonged hematologic toxicities, interrupt and monitor counts weekly until recovery*
- Signs/symptoms of pneumonitis

Nivolumab

(ONO-4538/BMS-936558 or MDX1106)
Nivolumab

- **Indication(s)**
  - Unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation–positive, a BRAF inhibitor
  - Metastatic squamous non–small cell lung cancer with progression on or after platinum-based chemotherapy

- **NCCN**
  - Melanoma: preferred regimens (category 2A)
  - Non–small cell lung cancer: subsequent therapy (category 1)

- **Cost:** $12,500/mo or $150,000/yr
  - Bristol-Myers Squibb Access Support

Anti–PD-1: Mechanism of Action

Nivolumab: CheckMate-037
Multicenter, open-label phase III, randomized

Unresectable or metastatic melanoma (n = 405)

R 2:1

Nivolumab 3 mg/kg IV q2wk (n = 272)

Investigators’ choice chemotherapy, ICC (n = 133)
- Dacarbazine 1,000 mg/m² IV q3wk OR
- Carboplatin (AUC 6) IV + paclitaxel 175 mg/m² IV q3wk

Exclusion Criteria
- Autoimmune disease/concurrent immunosuppression/ocular melanoma, history of grade IV ipilimumab adverse reactions (except endocrinopathies)/grade 3 ipilimumab adverse reactions not resolved or inadequately controlled within 12 weeks of initial events

Co-primary Endpoints
- Overall response rate in first 120 patients with ≥ 6 months of follow-up
- Overall survival to ICC

Nivolumab: CheckMate-037 (cont)

Interim Baseline Characteristics
(n = 405)

- No prior anti-CTLA-4 benefit: 64%
- BRAF V600 mutation positive: 49%
- H/O Brain mets: 72%
- M1c disease: 51%
- Age > 65 years: 65%

Nivolumab: CheckMate-037 (cont)

Results from interim analysis, 120 patients

- Overall survival 12.3 mo vs. 8 mo ICC*
- ORR 31.7% nivolumab (n = 120)
  - 4 CR + 34 PR, 28 stable, 42 PD, 12 unknown
  - 36/38 ongoing responses (95%)
- ORR 10.6% chemotherapy (n = 60)
  - 0 CR + 5 PR, 16 stable, 15 PD, 11 unknown

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median time to response (range), mo</th>
<th>Median duration of response (range), mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>2.1 (1.6, 7.4)</td>
<td>NR (1.4+, 10+)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>3.5 (2.1, 6.1)</td>
<td>3.6 (1.3+, 3.5)</td>
</tr>
</tbody>
</table>

* Interim analysis and had not met power for proper analysis

Nivolumab: CheckMate-017 (cont)

Multicenter, open-label phase III, randomized

Exclusion Criteria
Autoimmune disease / concurrent immunosuppression, CNS metastases (eligible if treated and returned to baseline), carcinomatous meningitis, treatment with PD-L1 or PD-L2 inhibitor, CTLA-4 inhibitor, anti-CD137, interstitial lung disease, prior docetaxel

Primary Objective: Overall survival

Secondary Objectives: Overall response rate (ORR), progression-free survival (PFS), efficacy by PD-L1 expression (PD-L1 testing not required for enrollment), quality of life, and safety


Unresectable or metastatic squamous cell non–small cell carcinoma (n = 272)

R
1:1

Nivolumab 3 mg/kg IV q2wk (n = 135) until PD

Docetaxel 75 mg/m² q3wk (n = 137) until PD
## Nivolumab: CheckMate-017 Results

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Nivolumab</th>
<th>Docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>mOS, mo (95% CI)</td>
<td>9.2 (7.3, 13.3)</td>
<td>6 (5.1, 7.3)</td>
</tr>
<tr>
<td>1-year OS, (95% CI)</td>
<td>42 (34, 50)</td>
<td>24 (17, 31)</td>
</tr>
<tr>
<td>Median duration of response</td>
<td>Not reached</td>
<td>8.4 (1.4+, 15.2+)</td>
</tr>
<tr>
<td>mPFS, mo (95% CI)</td>
<td>3.5 (2.1, 4.9)</td>
<td>2.8 (2.1, 3.5)</td>
</tr>
<tr>
<td>1-yr PFS, % (95% CI)</td>
<td>21 (14, 28)</td>
<td>6 (3, 12)</td>
</tr>
</tbody>
</table>

Nivolumab: Dosing Details

- **Dosing**: 3 mg/kg IV over 60 minutes every 2 weeks
- **Premedications**: none
- **Dose adjustments**
  - Renal: No adjustment for mild-to-severe impairment
  - Hepatic: Not studied in moderate-to-severe impairment
  - Hold for moderate or severe immune-mediated adverse events and permanently discontinue for life-threatening*
- **Pharmacokinetics**: $t_{1/2} = 26.7$ days, steady state = 12 weeks
- **How supplied**: 40-mg and 100-mg single-use vial (SUV)

* See prescribing information for details.
# Nivolumab: Safety in Melanoma

<table>
<thead>
<tr>
<th>Immune-mediated adverse reactions</th>
<th>Nivolumab (n = 268)</th>
<th>ICC (n = 102)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Total % of patients with events</td>
<td>68</td>
<td>9</td>
</tr>
<tr>
<td>Fatigue</td>
<td>25</td>
<td>1</td>
</tr>
<tr>
<td>Anemia</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Constipation</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>11</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Pruritus</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>

A 46-year-old male presents today for cycle 4 pembrolizumab. He is complaining of diarrhea (7 stools above baseline) and headaches. Which of the following interventions is most appropriate?

A. Dose reduce pembrolizumab to 1 mg/kg  
B. Hold pembrolizumab  
C. Permanently discontinue pembrolizumab, obtain a CT to rule out brain mets, and educate on OTC loperamide  
D. Hold pembrolizumab, obtain a CT scan with pituitary cuts, and initiate steroids

Audience Response Question
Pembrolizumab

(MK-3475)

September 4, 2014
Pembrolizumab

- **Indication:** Unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600–mutation positive, a BRAF inhibitor

- **Mechanism of action:** Human programmed cell death protein 1 (PD-1)–blocking antibody

- **NCCN:** Preferred regimens (category 2A)

- **Cost:** $12,500/mo or $150,000/yr
  - Merck Access Program

Pembrolizumab: Keynote-001

Multicenter, open-label randomized phase Ib

Unresectable or metastatic melanoma (age > 18)
- PD within 24 wk after ipilimumab
- If BRAF V600 mutation (+) prior tx w/BRAF inhibitor

Exclusion criteria
- Autoimmune disease/concurrent immunosuppression/severe immune-mediated adverse reactions with ipilimumab

Primary endpoint: Overall response rate


Pembrolizumab 2 mg/kg IV q3wk until PD or toxicity (n = 89)

Pembrolizumab 10 mg/kg IV q3wk until PD or toxicity (n = 84)
Pembrolizumab: Keynote-001 (cont)

Primary endpoint: ORR = 24% (95% CI: 15, 34)
- 1 complete response, 20 partial responses
- Median duration of exposure, 6.2 months
- Median 9 doses (1–23 months)

Baseline characteristics from cohort from trial 1 (n = 89)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age</td>
<td>59 yr (18–88)</td>
</tr>
<tr>
<td>Age &gt; 65</td>
<td>33%</td>
</tr>
<tr>
<td>Male</td>
<td>53%</td>
</tr>
<tr>
<td>M1c disease</td>
<td>84%</td>
</tr>
<tr>
<td>Elevated LDH</td>
<td>44%</td>
</tr>
<tr>
<td>Brain metastases</td>
<td>8%</td>
</tr>
<tr>
<td>≥ 2 prior systemic therapies</td>
<td>70%</td>
</tr>
</tbody>
</table>

Pembrolizumab (cont)

- **Dosing:** 2 mg/kg IV over 30 minutes every 3 weeks
- **Premedications:** None
- **Dose adjustments**
  - Renal: No adjustment for mild-severe impairment
  - Hepatic: Not studied in moderate-to-severe impairment
  - Hold for moderate or severe immune-mediated adverse events and permanently discontinue for life-threatening events*
- **Pharmacokinetics:** $t_{1/2} = 26$ days, steady state $= 18$ wk
- **How supplied:** 50 mg (powder) and 100 mg/4 mL (liquid)

*See prescribing information for details.

Pembrolizumab: Safety

The most common adverse reactions (≥ 20%): Fatigue (47%), cough (30%), nausea (30%), pruritus (30%), rash (29%), decreased appetite (26%), constipation (21%), arthralgia (20%), and diarrhea (20%)

<table>
<thead>
<tr>
<th>Immune-mediated adverse reactions (n = 411)</th>
<th>Median onset</th>
<th>All grades n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis</td>
<td>22 days</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>Hypo/hyperthyroidism</td>
<td>1.5 mo</td>
<td>5 (1.2)</td>
</tr>
<tr>
<td>Hypophysitis</td>
<td>1.7 mo</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>5 mo</td>
<td>12 (2.9)</td>
</tr>
<tr>
<td>Colitis</td>
<td>6.5 mo</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Nephritis</td>
<td>11.6 mo</td>
<td>3 (0.7)</td>
</tr>
</tbody>
</table>
Anti–PD-1 Inhibitor: Tips

Counseling
- Diarrhea
- Shortness of breath, chest pain, cough
- Weight gain/loss, muscle aches, abdominal pain
- Headaches, weakness, vision changes
- Decreased urine output

Monitoring
- Liver function tests, serum creatinine, thyroid function
- Signs/symptoms of immune-mediated adverse reaction (pneumonitis, colitis, etc)

Treatment
- Corticosteroid until improvement to grade 1 or less and then taper over 1 month
New Agents in Hematology

- Blinatumomab
- Panobinostat

Blinatumomab

(MT103/AMG103)
December 3, 2014
Blinatumomab

- **Indication(s):** Philadelphia chromosome–negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL)
- **NCCN:** Relapsed refractory Ph-negative ALL (category 2A)
- **Cost:** $178,000

**WARNING:** CYTOKINE RELEASE SYNDROME and NEUROLOGIC TOXICITIES
Blinatumomab: Mechanism of Action

Blinatumomab: MT103-211
Open-label, multicenter, single-arm phase II study

Ph(-) relapsed or refractory B-precursor ALL
- Relapsed w/1st remission (≤ 12 months)
- Relapsed in first salvage or relapsed
- Refractory after salvage within 12 months of allo BMTx and ≥ 10% blasts

≥ 45 kg, in Cycle 1: CIVI
Days 1–7 dose: 9 μg/day
Days 8–28 dose: 28 μg/day
Subsequent cycles: 28 μg/day
Days 1–28 (n = 185)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Outcome</th>
<th>95% Confidence interval</th>
<th>Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>32%</td>
<td>26, 40</td>
<td>Cycle 2</td>
</tr>
<tr>
<td>CRh</td>
<td>9.2%</td>
<td>5, 14</td>
<td></td>
</tr>
</tbody>
</table>

CRh = complete remission with partial hematologic recovery.

Blinatumomab: Dosing Details

**Dosing:** A single cycle of treatment consists of 4 weeks of continuous IV infusion followed by a 2-week treatment-free interval

- If ≥ 45 kg, in cycle 1, administer blinatumomab at:
  - Days 1–7: 9 µg/day
  - Days 8–28: 28 µg/day
- For subsequent cycles, administer at 28 µg/day on days 1–28

**Premedications**

- Dexamethasone 20 mg IV 1 hour prior to the first dose of each cycle (such as cycle 1 day 8) or when restarting after an interruption of 4 or more hours

**How supplied:** 35-µg single-use vial along with an IV solution stabilizer (10 mL)
Blinatumomab: Safety

- The most common adverse reactions (≥ 20%) in relapsed/refractory ALL treated with blinatumomab (n = 212) were:
  - Pyrexia (62%), headache (36%), peripheral edema (25%), febrile neutropenia (25%), nausea (25%), hypokalemia (23%), rash (21%), tremor (20%), and constipation (20%)
  - A neurologic toxicity occurred in approximately 50% of patients and was a frequent reason for interruption of therapy.

Blinatumomab: Tips

**Counseling**
- Watch for yellowing of skin/eyes, dark urine
- Keep the area around IV catheter clean to prevent infections
- Do not change pump settings

**Monitoring**
- Signs/symptoms of infection
- Cytokine release syndrome
- Neurologic toxicities
- Tumor lysis syndrome
- Liver function tests
- Drug interactions

Panobinostat

(LBH-589)

February 23, 2015
Panobinostat

- **Indication(s):** In combination with bortezomib and dexamethasone, is indicated for the treatment of patients with multiple myeloma who have received at least two prior regimens, including bortezomib and an immunomodulatory agent
- **NCCN:** Preferred regimens (category 1)
- **Cost:** $7,000 per 3-week cycle
- **How supplied:** 10-, 15-, and 20-mg blister packs containing 6 capsules

Severe diarrhea occurred in 25% of patients. Monitor for symptoms, institute antidiarrheal treatment, interrupt panobinostat, and then reduce dose or discontinue.

Severe and fatal cardiac ischemic events, severe arrhythmia, and ECG changes have occurred. Arrhythmia may be exacerbated by electrolyte abnormalities.

Panobinostat: Mechanism of Action

## Panobinostat: Subgroup Interim Results (n = 193)

Randomized, international, two-arm, placebo-controlled

### Relapsed multiple myeloma who have received at least 2 prior regimens:
- including bortezomib and
- immunomodulatory agent

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Panobinostat-bortezomib-dexamethasone</th>
<th>Placebo-bortezomib-dexamethasone</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS, mo</td>
<td>10.6</td>
<td>5.8</td>
<td>HR 0.52 (95% CI: 0.36, 0.76)</td>
</tr>
<tr>
<td>ORR</td>
<td>58.5% (95% CI: 47.9, 68.6)</td>
<td>41.4% (95% CI: 31.6, 51.8)</td>
<td></td>
</tr>
</tbody>
</table>

Panobinostat: Dosing Details

- **Treatment phase 1**: Cycles 1–8, 3-week cycles (total time 24 wk)
  - Panobinostat 20 mg orally once daily 3 times a week for 2 weeks per 3-week cycle
  - Bortezomib 1.3 mg/m² IV twice weekly for 2 weeks per 3-week cycle
  - Dexamethasone 20 mg orally per day of bortezomib and the day after each dose

- **Dose adjustments**
  - Renal impairment (moderate/severe): No adjustment
  - Hepatic impairment: 15 mg (bilirubin 1x ULN), 10 mg (bilirubin 1.5–3x ULN)

ULN = upper limit of normal.

Panobinostat: Dosing Details (cont)

- Pharmacokinetics
  - CYP3A4 strong/moderate inhibitors: Avoid
    - If unavoidably strong: Reduce the starting dose 10 mg
  - CYP3A4 strong/moderate inducers: Avoid
  - CYP2D6 substrates: Avoid or monitor for toxicity
  - Avoid drugs that prolong QTc interval
  - Avoid star fruit, pomegranate, pomegranate juice, grapefruit juice, and grapefruit
Panobinostat: Safety

- The most common adverse reactions (> 20%) on the panobinostat-containing arm were:
  - Diarrhea, fatigue, nausea, peripheral edema, decreased appetite, pyrexia, and vomiting. Serious adverse reactions included pneumonia, diarrhea, thrombocytopenia, fatigue, and sepsis.
  - There was an increased incidence in deaths not due to progressive disease (7% vs. 3.2%) on the panobinostat-containing arm.

- The most common hematologic abnormalities included:
  - Thrombocytopenia and neutropenia

- The most common chemistry abnormalities were:
  - Hypophosphatemia and hypokalemia. ECG changes, including new T-wave changes and ST-segment depressions, occurred in 64% vs. 42% in controls. Arrhythmia occurred in 12% vs. 5% in controls.
Panobinostat: Tips

Counseling
- Diarrhea, vomiting, dehydration
- Bleeding or infection
- Symptoms of arrhythmia, angina, myocardial infarction
- Electrolytes
- Drug interactions

Monitoring
- ECG at baseline and periodically
- Electrolytes
- Liver function tests
- Drug interactions
- Diarrhea
- Hemogram (thrombocytopenia, neutropenia, anemia)
- Infection

New in Supportive Care

- **Pegfilgrastim on-body injector**
  - Approved in January 2015
  - Apply same day as chemotherapy and it delivers dose 27 hours after being placed
  - Patient must remain 4 inches away from electronic devices

- **Filgrastim-sndz**
  - First FDA-approved biosimilar March 6, 2015!

Posttest Question #1

Pembrolizumab was approved in September 2014 for treatment of unresectable metastatic melanoma. Which of the following adverse effects is a potential immune-mediated side effect that is related to this particular drug, which may require management with high-dose systemic corticosteroids followed by a taper dose should it occur?

A. Hyperthyroidism  JL454  
B. Reversible posterior leukoencephalopathy  JL455  
C. Thrombocytopenia  JL456  
D. Dysrhythmia  JL457
Posttest Question #2

Olaparib was initially approved for use in patients diagnosed with which of the following malignancies?

A. Advanced breast cancer  JL459
B. ALK-positive NSCLC  JL460
C. BRCA1 and BRCA2 advanced ovarian cancer  JL461
D. Non-Hodgkin lymphoma  JL462