CSHP SEMINAR 2016
TRANSITIONS IN PHARMACY
DISNEYLAND® RESORT • OCTOBER 27th – 30th
New Drugs: Gotta Catch ‘Em All!
Part I

Timothy Chiu, PharmD, BCPS
Pharmacist Evidence Analyst & Strategist
Monica Yoshinaga, PharmD, BCPS
Pharmacist Evidence Analyst & Strategist
Doris Kao, PharmD, BCPS, FCSHP
Supervisor

Kaiser Permanente
Drug Information Services
Disclosure

Tim Chiu, Monica Yoshinaga, and Doris Kao work for Kaiser Permanente and have no potential conflicts of interest to disclose.
## Learning Objectives

<table>
<thead>
<tr>
<th>At the completion of this activity, the <strong>pharmacist</strong> will be able to:</th>
<th>At the completion of this activity, the <strong>pharmacy technician</strong> will be able to:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Describe selected new drug approvals and trends at the Food and Drug Administration (FDA) from October 2015 through July 2016.</td>
<td>1) List four or more new drug approvals by the FDA from October 2015 to July 2016.</td>
</tr>
<tr>
<td>2) Identify a novel therapy option that may address resistance to traditional therapies for EGFR mutation-positive non-small cell lung cancer</td>
<td>2) Name at least three new drugs approved for cancer indications.</td>
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<tr>
<td>3) Describe the indication and dosing for the first approved drug for the reversal of a target specific oral anticoagulant.</td>
<td>3) Name the first approved drug for reversal of a target specific oral anticoagulant.</td>
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</tbody>
</table>
New Drug Approvals: 2015

2015
- Approved 45 novel drugs
  - More than average number approved annually in the past decade
- Expedited pathways
  - 27 (60%) of novel drugs designated in one or more expedited categories
  - Fast Track: 14
  - Breakthrough Therapy: 10
  - Priority Review: 24
  - Accelerated Approval: 6

2016 (YTD)
- Approved 16 novel drugs
Total Drug Expenditures: 2015

- **New Therapies**: ↑$24.2B
- **Protected Brands**: ↑$28.3B
- **Generic Spending**: ↑$7.9B
- **Patent Expiries**: ↓$14.2B

*Total Drug Expenditures*: ↑ by $46.2B (Total: $425B)

*Based on invoice prices

R3. IMS Institute, Medicines Use and Spending in the US. April 2016
New Therapies: 2015

Major Drivers

- Specialty Medicines: spending ↑ by 21.5% in 2015 to $151B
  - Hepatitis C: 250,000 patients treated
  - Multiple sclerosis: new oral medicines $18B
  - HIV antivirals
  - Oncology $39B
    - 35% of all new drugs
    - Breakthrough targeted mechanisms
  - Autoimmune diseases $30B
- Diabetes: Insulin, DPP-IV inhibitors, SGLT2 inhibitors, GLP-1 agonists $44B

Total Spend $B
talimogene laherparepvec (Imlygic)

first approved oncolytic virus

FDA Approval: October 27, 2015

Indication: Local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery

Notes:
- Genetically modified, live, attenuated herpes simplex virus that replicates within tumors and produces the immunostimulatory protein GM-CSF
- Storage requires a special freezer and handling precautions should be considered

Dosing:
- Intralesional administration; dose depends on the size and number of lesions but total injection volume should not exceed 4 mL per cycle
talimogene laherparepvec (Imlygic)

first approved oncolytic virus

Efficacy:
- OPTiM (Phase 3, randomized, open-label, n=436) vs. GM-CSF
  - Durable responses (response maintained ≥6 months) observed in 16.3% of patients treated with talimogene laherparepvec vs. 2.1% with GM-CSF (p<0.0001)
  - No significant improvement in overall survival was observed (median overall survival of 22.9 months vs. 19 months, respectively; p=0.51)

Safety:
- Common adverse reactions include fatigue, chills, nausea, pyrexia, flu-like symptoms, and injection site pain
- Warnings include accidental exposure of talimogene laherparepvec, herpetic infection, injection site complications (i.e., impaired wound healing), immune-mediated events (i.e., glomerulonephritis, pneumonitis, vitiligo), and plasmacytoma at the injection site
- Contraindicated in immunocompromised patients and pregnant patients
ixekizumab (Taltz)
monoclonal antibody antagonist of interleukin-17A (IL-17A)

FDA Approval: March 22, 2016

Indication: For the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

Notes:
- Ixekizumab is the sixth biologic agent and second IL-17A inhibitor approved for plaque psoriasis.

Dosing:
- The recommended dose is 160 mg (two 80 mg injections) at Week 0, followed by 80 mg at Weeks 2, 4, 6, 8, 10, and 12, then 80 mg every 4 weeks, given by subcutaneous injection.

Efficacy:
- Efficacy was demonstrated in three pivotal phase 3 RCTs, UNCOVER-1, 2 and 3.
ixekizumab (Taltz)

monoclonal antibody antagonist of interleukin-17A (IL-17A)

<table>
<thead>
<tr>
<th>UNCOVER 3 @Week 12</th>
<th>Placebo</th>
<th>Etanercept</th>
<th>Ixekizumab Q2W</th>
<th>Ixekizumab Q4W</th>
</tr>
</thead>
<tbody>
<tr>
<td>PASI-75</td>
<td>7.3%</td>
<td>53.4%</td>
<td>87.3%</td>
<td>84.2%</td>
</tr>
<tr>
<td>sPGA 0/1</td>
<td>6.7%</td>
<td>41.6%</td>
<td>80.5%</td>
<td>75.4%</td>
</tr>
<tr>
<td>PASI-90</td>
<td>3.1%</td>
<td>25.7%</td>
<td>68.1%</td>
<td>65.3%</td>
</tr>
<tr>
<td>PASI-100</td>
<td>0</td>
<td>7.3%</td>
<td>37.7%</td>
<td>35%</td>
</tr>
<tr>
<td>sPGA 0</td>
<td>0</td>
<td>8.6%</td>
<td>40.3%</td>
<td>36%</td>
</tr>
</tbody>
</table>

Safety:

- **Warnings and Precautions:** ↑ risk of infections, active tuberculosis, hypersensitivity, inflammatory bowel disease, immunizations.
- **Adverse reactions:** injection site reactions (17%), upper resp tract infections (14%), nausea (2%), *Tinea* infections (2%).

Key: PASI - Psoriasis Area and Severity Index score; sPGA - static physician global assessment
cobimetinib (Cotellic)

MEK inhibitor

FDA Approval: November 10, 2015

Indication: In combination with vemurafenib, treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation

Notes:
- Provides a second FDA-approved BRAF/MEK inhibitor combination for the treatment of BRAF-mutation melanoma

Dosing:
- 60 mg PO once daily days 1-21 every 28-day cycle
  - May be taken with or without food
  - Vemurafenib taken twice daily days 1-28
cobimetinib (Cotellic)

MEK inhibitor

Efficacy:
- coBRIM (Phase 3, randomized, double-blind, n=493) vs. vemurafenib monotherapy

<table>
<thead>
<tr>
<th>Endpoint vs. vemurafenib</th>
<th>coBRIM (n=247)</th>
<th>COMBI-v (n=352)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Overall Survival, months</td>
<td>22.3 vs. 17.4*</td>
<td>25.6 vs. 18**</td>
</tr>
<tr>
<td>Median Progression Free Survival, months</td>
<td>12.3 vs. 7.2</td>
<td>12.6 vs. 7.3**</td>
</tr>
<tr>
<td>Overall Response Rate</td>
<td>70% vs. 50% (p&lt;0.001)</td>
<td>64% vs. 51% (p&lt;0.001)</td>
</tr>
<tr>
<td>Median Duration of Response, months</td>
<td>13 vs. 9.2</td>
<td>13.8 vs. 8.5**</td>
</tr>
</tbody>
</table>

*Updated OS analysis with median F/U 18.5 months, **Results presented at 2015 European Cancer Congress

Safety:
- Common adverse reactions include diarrhea, photosensitivity reaction, nausea, and pyrexia
- Warnings include new primary malignancies, hemorrhage, cardiomyopathy, severe dermatologic reactions, serious retinopathy and retinal vein occlusion, hepatotoxicity, rhabdomyolysis, and severe photosensitivity
idarucizumab (Praxbind)

humanized monoclonal antibody fragment; dabigatran reversal agent

FDA Approval: October 16, 2015 (Accelerated Approval)

Indication: in patients treated with dabigatran when reversal of the anticoagulant effects of dabigatran is needed for emergency surgery/urgent procedures or in life-threatening or uncontrolled bleeding

Notes:
- First agent approved for the reversal of dabigatran
- Binds specifically to dabigatran and its acylglucuronide metabolites with an affinity for dabigatran that is ~350 times greater than that of thrombin
- Neutralizes the anticoagulant effect within minutes.

Dosing:
- 5 g IV, provided as two separate vials each containing 2.5 g/50 mL idarucizumab
- Limited data to support administration of an additional 5 g
idarucizumab (Praxbind)

humanized monoclonal antibody fragment; dabigatran reversal agent

**Efficacy:**
- 3 dose-response trials in healthy volunteers (n=283, ages 45-64): immediate reduction of plasma concentrations of unbound dabigatran to below limit of quantification; dTT, ECT aPTT, TT and ACT parameters returned to baseline levels
- Ongoing single cohort case series trial (n=123) in dabigatran patients with life-threatening/uncontrolled bleeding due to dabigatran or required emergency surgery/urgent procedures
  - 60-70% of patients had been treated with dabigatran 110 mg twice daily
  - Subset of 90 patients showed all patients had median maximum reversal as measured by ECT or dTT in the first 4 hours, with >89% achieving complete reversal

**Safety:**
- Thromboembolic risk of underlying disease (resume anticoagulant therapy as soon as medically appropriate)
- ADEs ≥ 5%: hypokalemia, delirium, constipation, pyrexia, pneumonia
osimertinib (Tagrisso)

first approved 3rd-generation EGFR TKI

FDA Approval: November 13, 2015

Indication: Treatment of patients with metastatic EGFR T790M mutation-positive non-small cell lung cancer (NSCLC), as detected by an FDA-approved test, who have progressed on or after EGFR TKI therapy

Notes:
- Targets the T790M resistance mutation, which may be observed in approximately 50-60% of patients treated with a first- or second-generation EGFR TKI for EGFR mutation-positive NSCLC
- Less activity against EGFR wild-type, which contributes to adverse reactions commonly associated with EGFR TKIs
- Concern for new resistance mutation (C797S)

Dosing:
- 80 mg PO once daily
- May be taken with or without food
osimertinib (Tagrisso)

first approved 3rd-generation EGFR TKI

Efficacy:
- AURA (Phase 1/2, n=201) and AURA2 (Phase 2, n=210); both MC, single-arm, open-label
- Pooled analysis reveals that a majority (59%) of patients respond to treatment
- Responses appear to be durable, with 95% ongoing response (range 1.1+ to 5.6+ months)

Safety:
- Common adverse reactions include diarrhea, rash, dry skin, and nail toxicity
- Warnings include interstitial lung disease/pneumonitis, QTc interval prolongation, and cardiomyopathy
necitumumab (Portrazza)
anti-EGFR, recombinant human IgG1 monoclonal antibody

FDA Approval: November 24, 2015

Indication: In combination with gemcitabine and cisplatin, for first-line treatment of patients with metastatic squamous NSCLC

Notes:
- Another anti-EGFR monoclonal antibody, cetuximab, was recently removed from guidelines due to the slight benefit and poor tolerability issues when added to chemotherapy

Dosing:
- 800 mg IV (over 60 minutes) on Days 1 and 8 of each 3-week cycle
- Administered prior to gemcitabine (given Days 1 and 8) and cisplatin (given Day 1) for Cycles 1-6; necitumumab may be continued as monotherapy from Cycles 7 and on
- Premedications are not initially required, but should be considered for patients that experience Grade 1 or 2 infusion-related reactions with necitumumab
necitumumab (Portrazza)

anti-EGFR, recombinant human IgG1 monoclonal antibody

Efficacy:
- SQUIRE (Phase 3, open-label, randomized, n=1,093) vs. gemcitabine plus cisplatin alone
  - Improvement in median overall survival by 1.6 months by adding necitumumab to gemcitabine plus cisplatin (11.5 months vs. 9.9 months, respectively; p=0.01)
  - Modest improvements in median PFS (5.7 months vs. 5.5 months, respectively) and overall response rate (31% vs. 29%, respectively)

Safety:
- Boxed Warnings: cardiopulmonary arrest and/or sudden death, hypomagnesemia
- Common adverse reactions include rash and hypomagnesemia
- Warnings include cardiopulmonary arrest, hypomagnesemia, venous and arterial thromboembolic events, dermatology toxicities, infusion-related reactions, and increased toxicity and mortality (when combined with pemetrexed and cisplatin for non-squamous NSCLC)
alectinib (Alecensa)

ALK inhibitor

FDA Approval: December 11, 2015

Indication: Treatment of patients with ALK-positive, metastatic NSCLC who progressed on or are intolerant to crizotinib

Notes:
- Also targets RET
- CNS responses seen in patients treated with alectinib (brain metastases a concern with ALK-positive NSCLC)

Dosing:
- 600 mg PO twice daily
alectinib (Alecensa)

**ALK inhibitor**

**Efficacy:**
- NP28761 (n=87; North America) and NP28673 (n=138; global); both Phase 2, single-arm, open-label
- Approximately half of patients treated with alectinib responded to therapy (objective response rate ranged from 38% to 44% based on independent review committee assessment) and responses appeared to be durable (median durations of response ranged from 7.5 and 11.2 months) based on results from the two pivotal trials
- CNS objective response rate was 61% in 51 patients with measurable CNS lesions
- The Phase 3 J-ALEX trial data was recently presented at ASCO 2016, supporting potential standard first-line treatment with alectinib for ALK+ NSCLC

**Safety:**
- Common adverse reactions include fatigue, constipation, edema, and myalgia
- Warnings include hepatotoxicity, interstitial lung disease/pneumonitis, bradycardia, and severe myalgia and creatine phosphokinase elevation
## Coagulation Factors

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>FDA Approval</th>
<th>FDA Approved Indication</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coagulation Factor X (Human)</td>
<td>Coagadex</td>
<td>10/20/15</td>
<td>Treatment of patients with hereditary Factor X deficiency.</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; coagulation FX concentrate in US</td>
</tr>
<tr>
<td>Antihemophilic Factor (Recombinant) PEGylated</td>
<td>Adynovate</td>
<td>11/13/15</td>
<td>Adolescent and adult patients with hemophilia A (congenital factor VIII deficiency).</td>
<td>Long acting rFVIII</td>
</tr>
<tr>
<td>von Willebrand factor (Recombinant)</td>
<td>Vonvendi</td>
<td>12/08/15</td>
<td>On-demand treatment and control of bleeding episodes in adults with von Willebrand disease (VWD).</td>
<td>First rVWF in US</td>
</tr>
<tr>
<td>Coagulation Factor IX (Recombinant), albumin Fusion Protein</td>
<td>Idelvion</td>
<td>03/04/16</td>
<td>Adults and children with hemophilia B (congenital Factor IX deficiency).</td>
<td>Long acting rFIX</td>
</tr>
<tr>
<td>Antihemophilic Factor (Recombinant), full length</td>
<td>Kovaltry</td>
<td>03/16/16</td>
<td>Adults and children with hemophilia A (congenital Factor VIII deficiency).</td>
<td>3&lt;sup&gt;rd&lt;/sup&gt; generation rFVIII More concentrated, shorter infusion time</td>
</tr>
</tbody>
</table>
mepolizumab (Nucala)

anti-IL-5, recombinant human IgG1 monoclonal antibody

FDA Approval: November 4, 2015

Indication: Add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype

Notes:
- Estimated that 5-10% of all asthmatics have severe asthma, half of which have airway inflammation attributed to an eosinophilic phenotype
- Pipeline anti-IL5 monoclonal antibody, benralizumab, may have a BLA filed later this year for potential approval in 2017

Dosing:
- 100 mg subcutaneously every four weeks
- Mepolizumab should be reconstituted and administered by a healthcare professional
- Sites of administration include upper arm, thigh, or abdomen

R4. Prescribing Information: U.S. FDA. Drugs @ FDA.
mepolizumab (Nucala)

anti-IL-5, recombinant humanized IgG1 monoclonal antibody

Efficacy:
- Approval was based on data from 3 pivotal randomized, placebo-controlled studies in patients with severe asthma (DREAM, MENSA, SIRIUS)
- Across the trials, a statistically significant improvement in decreasing asthma exacerbations and/or ER visits and/or hospitalization
- Approximately half of the patients in the mepolizumab group achieved at least a 50% reduction in daily prednisone use (vs. one-third of patients in the placebo group)

Safety:
- Common adverse reactions include headache, injection site reaction, back pain, and fatigue
- Warnings include hypersensitivity reactions, Herpes zoster infections, not to be used to treat acute bronchospasm or status asthmaticus, not to discontinue systemic or inhaled corticosteroids abruptly upon starting mepolizumab, and to treat patients with pre-existing helminth infections prior to starting mepolizumab
reslizumab (Cinqair)

anti-IL-5, recombinant humanized IgG4 monoclonal antibody

FDA Approval: March 23, 2016

Indication: Add-on maintenance treatment of patients with severe asthma aged 18 years and older, and with an eosinophilic phenotype

Notes:
- Subcutaneous formulation being investigated
- Though patients aged 12 to <18 years of age were investigated in the pivotal trials the sample size was small, and there was a difference in the asthma exacerbation rate within this subgroup between treatment and placebo arms

Dosing:
- 3 mg/kg IV (over 20-50 minutes) every 4 weeks
- Administer in a healthcare setting prepared to manage anaphylaxis

R4. Prescribing Information: U.S. FDA. Drugs @ FDA.
reslizumab (Cinqair)

anti-IL-5, recombinant humanized IgG4 monoclonal antibody

**Efficacy:**
- Approval was based on data from 4 pivotal randomized, placebo-controlled studies in patients with severe asthma; 3 of these trials required patients to have high baseline eosinophil levels
- Across the trials, a statistically significant reduction in the frequency of asthma exacerbations was observed in patients treated with reslizumab vs. placebo
- Improvements in FEV\(_1\) were observed across trials; in 2 trials, improvements in FEV\(_1\) were observed at 4 weeks after the initial dose of reslizumab and maintained through week 52

**Safety:**
- Common adverse reactions include oropharyngeal pain
- Warnings include malignancy, not to be used to treat acute bronchospasm or status asthmaticus, not to discontinue systemic or inhaled corticosteroids abruptly upon starting reslizumab, and to treat patients with pre-existing helminth infections prior to starting reslizumab
Lesinurad (Zurampic)

Uric acid transporter 1 (URAT1) inhibitor

FDA Approval: December 12, 2015

Indication: In combination with a xanthine oxidase inhibitor (XOI) for the treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid levels with a XOI alone

Limitations: not recommended for the treatment of asymptomatic hyperuricemia; should not be used as monotherapy

Notes:

◦ URAT1 and organic anion transporter 4 (OAT4) are transporters responsible for renal reabsorption of uric acid

Dosing:

◦ 200 mg once daily in combination with an XOI, including allopurinol or febuxostat (max daily dose is 200 mg)
◦ Instruct patient to stay well-hydrated (i.e., at least two liters of liquid per day)
lesinurad (Zurampic)

uric acid transporter 1 (URAT1) inhibitor

Efficacy:

- 3 pivotal 12-month, phase 3 RCTs
  - Higher proportion of patients on lesinurad in combination with a XOI achieved target serum uric acid (sUA) goals (≤ 6 mg/dL or ≤ 5 mg/dL for patients with tophaceous gout) compared to XOI monotherapy
  - Mean reduction of 1 mg/dL considered by FDA to be clinically meaningful for patients unable to achieve target sUA level on monotherapy
  - No benefit seen in gout flare reduction or tophi resolution

Safety:

- Boxed Warning: Risk of acute renal failure, more common when used without an XOI
- Contraindications: severe renal impairment, ESRD, kidney transplant recipients, patients on dialysis; tumor lysis syndrome or Lesch-Nyhan syndrome
- Warnings include renal and cardiovascular events
- Adverse reactions ≥ 2% and more frequently than XOI alone: HA, influenza, blood creatinine increased, GERD
atezolizumab (Tecentriq)

first approved PD-L1 checkpoint inhibitor

FDA Approval: May 18, 2016

Indication: Treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy; or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy

Notes:
- Like the PD-1 checkpoint inhibitors, atezolizumab is being studied in a number of different cancer types, including NSCLC, renal cell carcinoma, colorectal cancer, and SCLC

Dosing:
- 1200 mg IV (over 60 minutes) every 3 weeks

R4. Prescribing Information: U.S. FDA. Drugs @ FDA.
atezolizumab (Tecentriq)

first approved PD-L1 checkpoint inhibitor

**Efficacy:**

- Imvigor210 (Phase 2, open-label); approval based on data from Cohort 2 (2\textsuperscript{nd}-line setting)
- Approximately 15% of patients had a response to therapy, with responses appearing to be durable (median duration of response was not reached, ranging from 2.1+ to 13.8+ months)

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atezolizumab (Tecentriq)

first approved PD-L1 checkpoint inhibitor

Safety:
- Common adverse reactions include fatigue, nausea, decreased appetite, urinary tract infection, pyrexia, and constipation
- Warnings include immune-related events (including pneumonitis, hepatitis, colitis, endocrinopathies, meningitis/encephalitis, motor and sensory neuropathy, and pancreatitis), ocular inflammatory toxicity, infection, and infusion reactions
lifitegrast (Xiidra)

lymphocyte function-associated antigen 1 (LFA-1) antagonist

FDA Approval: July 11, 2016

Indication: Treatment of the signs and symptoms of dry eye disease (DED).

Notes:
- Lifitegrast is a new molecular entity. It blocks the LFA-1 and the intercellular adhesion molecule (ICAM-1), important in the chronic dry eye inflammatory cycle.

Dosing:
- Instill one drop of lifitegrast twice daily (approximately 12 hours apart) into each eye.
lifitegrast (Xiidra)

lymphocyte function-associated antigen 1 (LFA-1) antagonist

Efficacy:
- Efficacy was assessed in three, 12-week, RCTs. The average baseline Eye Dryness Score (EDS) was between 40 and 70. A larger reduction in EDS favoring lifitegrast over placebo was observed at Day 42 and Day 84.

Safety:
- Warnings and Precautions: hypersensitivity reactions, infections, depression and suicide
- Adverse reactions (5-25%): instillation site irritation, dysgeusia, ↓ visual acuity.
  - (1% to 5%): blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus and sinusitis.

R4. Prescribing Information: U.S. FDA. Drugs @ FDA. R5. Biomedtracker Pharma Intelligence. Biomedtracker.com
selexipag (Uptravi)
oral prostacyclin IP receptor agonist

FDA Approval: December 21, 2015 (orphan drug designation)

Indication: Treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression and reduce the risk of hospitalization for PAH

Notes:
- Relaxation of vascular smooth muscle
- Selective IP receptor agonist, unlike prostacyclin epoprostenol and prostacyclin analogs iloprost and treprostinil

Dosing:
- Start at 200 mcg BID, increase by 200 mcg BID at weekly intervals to highest tolerated dose up to 1600 mcg BID
- **Once daily** for patients with moderate hepatic impairment

R4. Prescribing Information: U.S. FDA. Drugs @ FDA.
selexipag (Uptravi)

oral prostacyclin IP receptor agonist

Efficacy:

- MC, DB, PBO-controlled, parallel group event-driven study (GRIPHON) in patients with symptomatic PAH (n=1156)
  - WHO Functional Class I = 0.8%, II = 46%, III = 53%, IV = 1%
- Primary endpoint: time to first occurrence up to end-of-treatment of 1) death, 2) hospitalization for PAH, 3) PAH worsening resulting in need for lung transplantation, or balloon atrial septostomy, 4) initiation of parenteral prostanoid therapy or chronic oxygen therapy, or 5) other disease progression based on a 15% decrease from baseline in 6MWD plus worsening of Functional Class or need for additional PAH-specific therapy
- 40% reduction (99% CI: 22 to 54%; two-sided log-rank p-value < 0.0001) of the occurrence of primary endpoint events

Safety:

- Warnings and Precautions: pulmonary edema in patients with pulmonary veno-occlusive disease
- Adverse reactions >5% compared to placebo: headache, diarrhea, jaw pain, nausea, myalgia, vomiting, pain in extremity, flushing
trabectedin (Yondelis)
marine-derived anti-tumor/alkylating agent

FDA Approval: October 23, 2015

Indication: Treatment of patients with unresectable or metastatic liposarcoma or leiomyosarcoma who received a prior anthracycline-containing regimen

Notes:
- Approved in EU since 2007 for treatment of advanced soft tissue sarcoma and recurrent ovarian cancer

Dosing:
- 1.5 mg/m2 as a 24-hour IV infusion every 3 weeks via a central line
- Premedicate with dexamethasone 20 mg IV 30 minutes prior to each infusion (may reduce the risk of liver and bone marrow toxicity)
trabectedin (Yondelis)
marine-derived anti-tumor/alkylating agent

Efficacy:

- SAR-3007 (Phase 3, randomized, open-label, n=518) vs. dacarbazine in patients with L-sarcomas who previously received an anthracycline-based regimen followed by at least one additional line of chemotherapy
  - Significant reduction in the risk of disease progression with trabectedin (median progression-free survival [PFS] of 4.2 months) vs. dacarbazine (median PFS of 1.5 months)
  - No significant improvement in overall survival was observed (median overall survival of 13.7 months vs. 13.1 months, respectively; 95% CI: 0.75, 1.15; p=0.49)
trabectedin (Yondelis)

marine-derived anti-tumor/alkylating agent

Safety:
- Common adverse reactions include nausea, fatigue, constipation, diarrhea, decreased appetite, edema, dyspnea, and headache
- Warnings include neutropenic sepsis, rhabdomyolysis, hepatotoxicity, cardiomyopathy, and extravasation

Progression-Free Survival

Overall Survival

1. Which of the following statement(s) is false:
   a. Idarucizumab is the second agent approved for the reversal of dabigatran.
   b. Idarucizumab neutralizes the anticoagulant effect within hours.
   c. Idarucizumab is used in emergency surgery/urgent procedures or in life-threatening or uncontrolled bleeding.
   d. Idarucizumab is a humanized monoclonal antibody fragment.
   e. A and B.
2. Which of the following statement(s) is true:

a. Ixekizumab is the first IL-17 antagonist to be FDA approved for plaque psoriasis.

b. Ixekizumab showed greater efficacy for the treatment of psoriasis than secukinumab.

c. Maintenance dosing for ixekizumab is every four weeks after induction therapy is completed.

d. Ixekizumab is dosed by intravenous infusion.
3. Which of the following statement(s) is/are true:

a. Osimertinib is active against the T790M resistance mutation, frequently observed in patients treated with an EGFR TKI for EGFR mutation-positive NSCLC.

b. Treatment with osimertinib may lead to a new concern for another resistance mutation, C797S.

c. Osimertinib must be taken on an empty stomach.

d. Osimertinib is highly active against EGFR wild-type, similar to the activity observed with first- and second-generation EGFR TKIs (i.e., erlotinib, gefitinib, afatinib).

e. A and B.
R1. FDA Drug Approvals. Drugs@FDA.


R4. Prescribing Information: U.S. FDA. Drugs @ FDA.

