OPTUMRx®

RxOutlook®

1st Quarter 2017

Pending drug approvals

Drug name	Manufacturer	Indication/use	Expected FDA decision date
axicabtagene ciloleucel (KTE-C19)	Kite Pharma	Non-Hodgkin lymphoma	2Q2017 – 4Q2017
avelumab	Merck/Pfizer	Merkel cell carcinoma	5/2017 – 6/2017
betrixaban	Portola/Lee Pharmaceutical	Venous thromboembolism	6/24/2017
binimetinib	Array BioPharma/Pierre Fabre Medicament	Melanoma	6/30/2017
brigatinib	ARIAD	Non-small cell lung cancer	4/29/2017
delafloxacin (Baxdela™)	Melinta/Eurofarma/ Ligand	Bacterial skin and skin structure infections	6/2017
durvalumab	AstraZeneca/Celgene/Eli Lilly/Juno	Urothelial carcinoma	2Q2017
edaravone (Radicava®)	Mitsubishi Tanabe Pharma	Amyotrophic lateral sclerosis	6/16/2017
L-glutamine	Emmaus Medical	Sickle cell disease	7/7/2017
midostaurin	Novartis	Acute myelogenous leukemia, Aggressive systemic mastocytosis	2Q2017
niraparib	Tesaro/Johnson & Johnson/Merck/ZAI Labs	Ovarian, fallopian tube, primary peritoneal cancers	6/30/2017
ribociclib	Novartis/Otsuka	Breast cancer	4/2017 – 5/2017
tisagenlecleucel-T (CTL019)	Novartis	Acute lymphoblastic leukemia	2Q2017
valbenazine (Ingrezza™)	Neurocrine Biosciences/ Mitsubishi Tanabe Pharma	Tardive dyskinesia	4/11/2017

axicabtagene ciloleucel (KTE-C19)

Manufacturers: Kite Pharma

Therapeutic use

KTE-C19 is in development for the treatment of relapsed or refractory aggressive B-cell non-Hodgkin lymphoma in patients who are ineligible for autologous stem cell transplantation (ASCT).

- Treatment of relapsed or refractory B-cell NHL in patients ineligible for ASCT

Clinical profile

KTE-C19 is a form of gene therapy and uses a chimeric antigen receptor T-cell (CAR-T) platform to target CD19, a specific antigen expressed in B-cell lymphomas and leukemias. KTE-C19 contains an antibody fragment, a co-stimulatory domain, and a signaling domain, which is needed to activate the T-cell.

In a single-arm trial, 79% of subjects with ≥ 3 months follow-up achieved an objective response (ORR) ($p < 0.0001$). Moreover, 52% of subjects achieved a complete response.

Grade ≥ 3 treatment-emergent adverse events included anemia, thrombocytopenia, febrile neutropenia, encephalopathy, cytokine release syndrome, and neurological events.

Prior to the administration of KTE-C19, patients must undergo leukapheresis to separate their white blood cells (WBCs) from other blood constituents. Afterwards, the patients' WBCs are taken to a facility where the T-cells are isolated and re-engineered to express CARs, which aid in targeting malignant B-cells. Then, the modified T-cells are grown and expanded in culture. Finally, chemotherapy is administered prior to reinfusion of the CAR-T cells into the respective patients.

KTE-C19 is administered by intravenous (IV) infusion as a single dose.

- CAR-T agent
- IV formulation
- ORR = 79%
- Serious adverse events: anemia, thrombocytopenia, febrile neutropenia, encephalopathy, cytokine release syndrome, and neurological events
- Requires leukapheresis and chemotherapy prior to CAR-T treatment
- Dose: single dose

Competitive environment

KTE-C19 offers a novel, patient-specific treatment that targets B-cell malignancies and only requires a single dose.

However, the entire treatment is a long process, which includes leukapheresis, chemotherapy prior to CAR-T infusion, and a period of post-treatment monitoring. Furthermore, KTE-C19 requires IV administration and is expected to carry a high cost.

The projected drug cost for the single treatment is $200,000.

- Advantages: novel mechanism, patient-specific therapy, single treatment
- Disadvantages: long treatment process, IV administration, high cost
- Projected cost is ~$200,000 for a single dose

Expected FDA decision date

KTE-C19 was granted breakthrough status.

A rolling submission was filed but has not been finalized. Completion of the KTE-C19 application is expected soon with an FDA decision between the 2nd quarter and 4th quarter of 2017.

- Breakthrough status
- Rolling submission
- Projected approval: 2Q2017 – 4Q2017

avelumab

Manufacturers: Merck/Pfizer

Therapeutic use

Avelumab is in development for use in patients with Merkel cell carcinoma (MCC).

MCC is a rare aggressive form of skin cancer. Merkel cells are found in the outer layer of the skin and are responsible for relaying touch information to the brain, including texture and pressure. MCC is most common in patients > 50 years of age, and appears as a flesh-colored or bluish-red nodule, often affecting the face, head, or neck.

The response rates with standard chemotherapy are often inadequate and not durable. Thus, patients with MCC are often advised to enter a clinical trial. However, immunotherapeutic agents, such as Keytruda® (pembrolizumab) and Opdivo™ (nivolumab), have been used off-label and are being studied in clinical trials for MCC.

- Treatment of MCC

Clinical profile

Avelumab is a fully human monoclonal antibody that targets programmed death ligand-1 (PD-L1).

Avelumab was evaluated in a phase 2, single-arm trial in adult patients with MCC. Patients were followed for a median duration of 10.4 months, and 31.8% (95% CI: 21.9, 43.1) achieved an objective response. Responses were still ongoing in 82% of subjects at the time of analysis. Moreover, the overall survival (OS) at 6 months was 69% (95% CI: 58, 78).

Serious treatment-related adverse events occurred in 6% of patients, including enterocolitis, infusion-related reactions, increased aminotransferases, chondrocalcinosis, synovitis, and interstitial nephritis. Other patients (5%) experienced grade 3 adverse events, such as lymphopenia, increased creatine phosphokinase (CPK) levels, and elevated blood cholesterol levels.

Based on trial protocol, avelumab is dosed by weight and given IV once every 2 weeks.

- PD-L1 antagonist
- IV formulation
- ORR = 31.8%
- OS at 6 months = 69%
- Serious adverse events: enterocolitis, infusion-related reactions, increase in aminotransferases, chondrocalcinosis, synovitis, and interstitial nephritis
- Dose: weight-based every 2 weeks

Continued…

avelumab (Continued…)

Manufacturers: Merck/Pfizer

Competitive environment
Effective treatment options for MCC are limited. If approved, avelumab would be the first FDA-approved immunotherapeutic agent for MCC.

Nonetheless, avelumab will require IV administration. Moreover, efficacy data is limited as only data from one phase 2 single-arm trial is available.

Serious safety concerns have also been reported in the trial. In addition, other immunotherapeutic agents have been used off-label and are being studied in clinical trials (ie, Keytruda, Opdivo).

The projected annual U.S. sales for avelumab are $37.5 million by 2020.

- Advantages: limited treatment options for MCC, possible first FDA-approved immunotherapeutic therapy for MCC
- Disadvantages: IV administration, data only available from one phase 2 trial, other immunotherapeutic agents are used off-label for MCC
- Projected annual U.S. sales are $37.5 million by 2020

Expected FDA decision date
Avelumab was granted orphan drug designation, fast track status, and breakthrough status. Avelumab was also granted priority review by the FDA.

An FDA decision regarding the approval of avelumab is expected between May and June 2017.

- Orphan drug designation
- Fast track status
- Breakthrough status
- Priority review
- PDUFA: 5/2017 – 6/2017

betrixaban

Manufacturer: Portola/Lee's Pharmaceutical

Therapeutic use

Betrixiban is in development for extended duration prophylaxis of venous thromboembolism (VTE) in acute medically ill patients with risk factors for VTE.

- For extended duration prophylaxis of VTE

Clinical profile

Betrixiban is an oral factor Xa inhibitor similar to Eliquis® (apixaban), Xarelto® (rivaroxaban), and Savaysa® (edoxaban).

In a phase 3 clinical trial, betrixaban was compared against Lovenox® (enoxaparin). While betrixaban showed a 19% relative risk reduction in the composite risk for VTE and VTE-related death, this reduction failed to reach statistical significance in the primary cohort ($p = 0.054$).

Moreover, a comparable incidence of major bleeding events was seen in the betrixaban group vs. the Lovenox group (0.6% vs. 0.7%, $p = 0.72$). However, in patients ≥ 75 years old, more non-major bleeding events were seen with betrixaban vs. Lovenox (3.1% vs. 1.9%, $p < 0.009$).

Based on trial protocol, betrixaban is administered orally once daily when given for prophylaxis of VTE.

- Factor Xa inhibitor
- Oral formulation
- Failed to demonstrate superiority to Lovenox
- Comparable incidence of major bleeding episodes vs. Lovenox
- Greater incidence of non-major bleeding events vs. Lovenox in elderly patients
- Dose: once daily

Competitive environment

Because of its long half-life and low peak-to-trough ratio, betrixaban may not require dose adjustments or patient monitoring. In addition, because it is not renally excreted, no dose adjustments are expected in renally impaired patients.

Betrixaban has no known cytochrome 3A4 interactions and has a comparable risk for major bleeding events compared to Lovenox.

Nonetheless, its key trial failed to show superiority to Lovenox in its primary population. Other related products are also available (ie, Eliquis, Xarelto, and Savaysa).

Based on the cost of other factor Xa inhibitors, the projected drug cost for betrixaban is estimated at $315 – $360 per month.

- Advantages: long half-life, not renally excreted, no CYP3A4 interactions, comparable risk for major bleeding events vs. Lovenox
- Disadvantages: failed to show clear superiority to Lovenox, other related products are available
- Projected drug cost is $315–$360 per month

Expected FDA decision date

Betrixaban was granted fast track status and priority review by the FDA.

An FDA decision regarding the approval of betrixaban is expected by June 24, 2017.

- Fast track status
- Priority review
- PDUFA: 6/24/2017

binimetinib

Manufacturer: Array BioPharma/Pierre Fabre Medicament

Therapeutic use

Binimetinib is in development for the treatment of patients with advanced NRAS mutation-positive melanoma.

- Treatment of advanced NRAS mutation-positive melanoma

Clinical profile

Binimetinib is a mitogen-activated extracellular kinase 1/2 (MEK 1/2) inhibitor.

In a clinical trial in patients with NRAS Q61 mutant melanomas, binimetinib was compared to dacarbazine. Overall, the progression-free survival (PFS) was 2.8 months with binimetinib vs. 1.5 months for dacarbazine (HR = 0.62 [95% CI 0.47-0.80], $p < 0.001$). However, in patients with prior immunotherapy, the PFS was 5.5 months for binimetinib vs. 1.6 months for dacarbazine (HR = 0.46 [95% CI: 0.26-0.81]).

Common adverse events reported in trials include rash, diarrhea, nausea, vomiting, stomatitis, and peripheral edema. However, ≥ 5% of NRAS mutation-positive melanoma patients receiving binimetinib experienced increases in CPK levels and hypertension.

Based on trial protocol, binimetinib is given orally twice daily.

- MEK 1/2 inhibitor
- Oral formulation
- PFS was greater with binimetinib vs. dacarbazine
- Adverse events: rash, diarrhea, nausea, vomiting, stomatitis, and peripheral edema, increased CPK levels and hypertension
- Dose: twice daily

Competitive environment

Current treatment options for NRAS mutation-positive melanoma are limited. Thus, if approved, binimetinib will offer another option for these patients.

Nonetheless, there are no OS data available at this time, and the PFS benefit was clinically small in its pivotal trial in NRAS mutation-positive melanoma.

The wholesale acquisition cost (WAC) for existing combination therapies involving MEK inhibitors range from approximately $17,500 to $20,000 per month.

- Advantages: limited treatment options in NRAS-mutant melanoma, offers another treatment option to patients
- Disadvantages: no OS data, small PFS benefit small

Expected FDA decision date

Binimetinib was granted an orphan drug designation by the FDA.

An FDA decision regarding the approval of binimetinib is expected by June 30, 2017.

- Orphan drug designation
- PDUFA: 6/30/2017

brigatinib

Manufacturers: ARIAD

Therapeutic use

Brigatinib is in development for the treatment of anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) in patients previously treated with Xalkori® (crizotinib).

- Treatment of ALK-positive NSCLC in patients previously treated with Xalkori

Clinical profile

Brigatinib is an ALK inhibitor designed to overcome resistant mutations in ALK, including ALK-L1196M.

In a phase 2 trial examining two different dosing regimens of brigatinib, the interim analysis revealed an ORR of 49%–54% with brigatinib use. The PFS ranged from 9.2–15.6 months; however, the median OS had not been reached at the time of the interim analysis and could not be reported.

In patients with intracranial brain metastases at baseline, the ORR was 46%–67% with median intracranial PFS of 15.6–18.4 months.

The most common treatment-emergent adverse events were nausea, diarrhea, cough, headache, and increased blood CPK levels.

Serious adverse events (≥ grade 3) included increased CPK levels, hypertension, pneumonia, and increased lipase levels. A subset of pulmonary adverse events with early onset occurred in 6% of all patients.

Based on trial protocol, brigatinib is expected to be dosed orally once daily.

- ALK inhibitor
- Oral formulation
- ORR = 49% - 54%
- PFS = 9.2 – 15.6 months
- Adverse events: nausea, diarrhea, cough, headache, increased CPK and lipase levels, hypertension, and pneumonia
- Dose: once daily

Competitive environment

Brigatinib is an oral, once daily drug that offers another treatment option for ALK-positive patients with NSCLC.

However, other related drug alternatives are available (ie, Zykadia® and Alecensa®). In addition, OS data are not available at this time.

The projected annual U.S. sales for brigatinib are $68 million by 2020.

- Advantages: oral, once daily dosing, another treatment option for ALK-positive NSCLC
- Disadvantages: other related drugs area available, no OS data
- Projected annual U.S. sales are $68 million by 2020

Expected FDA decision date

Brigatinib was granted breakthrough status and an orphan drug designation. Brigatinib is under priority review by the FDA.

An FDA decision regarding the approval of brigatinib is expected by April 29, 2017.

- Orphan drug designation
- Breakthrough status
- Priority review
- PDUFA: 4/29/2017

delafloxacin (Baxdela)

Manufacturer: Melinta Therapeutics/Eurofarma/Ligand

Therapeutic use
Delafloxacin is in development for the treatment of patients with acute bacterial skin and skin structure infections (ABSSSI).

- Treatment of ABSSSI

Clinical profile
Delafloxacin is a broad-spectrum fluoroquinolone antibiotic. It has shown greater potency than levofloxacin, ciprofloxacin, and moxifloxacin against quinolone-resistant methicillin resistant *Staphylococcus aureus* (MRSA).

In two randomized trials in adult patients with ABSSSI, delafloxacin was compared against vancomycin plus aztreonam. Both arms achieved similar responses (81.3% vs. 80.7%), defined as ≥ 20% change from baseline in lesion erythema area at 48–72 hours.

The most common treatment-related adverse events were nausea, pruritus, and diarrhea. With IV delafloxacin, infusion site extravasation, infections, and headaches were also reported in the trials.

Delafloxacin is being developed as oral and IV formulations with a dosing schedule every 12 hours.

- Fluoroquinolone antibiotic
- IV and oral formulations
- Similar response to vancomycin plus aztreonam at 48–72 hours
- Common adverse events: nausea, pruritus, and diarrhea
- Dose: every 12 hours

Competitive environment
Delafloxacin offers another treatment option for ABSSSI. It is in development as an oral pill and as an injection, and has much greater potency than existing fluoroquinolones against quinolone-resistant MRSA.

However, many other treatment options are available for ABSSSI, including other fluoroquinolones and various generic alternatives, such as vancomycin, aztreonam, linezolid, and daptomycin. Moreover, in trials, delafloxacin did not show superiority to vancomycin plus aztreonam.

- Advantages: offers another treatment option for patients with ABSSSI, oral and IV formulations, greater potency than existing fluoroquinolones
- Disadvantages: other treatment alternatives are available, did not show superiority to vancomycin plus aztreonam

Expected FDA decision date
Delafloxacin was granted fast track status and designated as a Qualified Infectious Disease Product (QIDP) by the FDA. A QIDP designation grants delafloxacin an additional 5 years of market exclusivity upon approval.

An FDA decision regarding the approval of delafloxacin is expected by June 2017.

- Fast track status
- QIDP
- PDUFA: 6/2017

durvalumab

Manufacturers: AstraZeneca/Celgene/Eli Lilly/Juno Therapeutics

Therapeutic use

Durvalumab is in development for the treatment of locally advanced or metastatic urothelial carcinoma in patients whose disease has progressed during or after one standard platinum-based regimen.

Urothelial carcinoma is a form of bladder cancer.

- Treatment of locally advanced or metastatic urothelial carcinoma in patients who have failed one platinum-based regimen

Clinical profile

Durvalumab is a human monoclonal antibody that targets PD-L1.

Data from mid-stage or late-stage trials are not available at this time. However, in an early phase trial, durvalumab was evaluated in 1,038 subjects with various solid tumors. Sixty-one patients had advanced bladder cancer. In those patients who were PD-L1 positive (≥ 5% expression), the ORR was 46%.

Notable safety concerns included acute kidney injury, infusion-related reactions, and tumor flare. Common adverse events included fatigue, diarrhea, nausea, decreased appetite, arthralgia, and fever.

Based on available information, durvalumab is being studied for IV administration every 2 weeks. Other trials are also investigating durvalumab for once monthly dosing.

- PD-L1 antagonist
- IV formulation
- ORR = 46% in PD-L1 positive patients
- Adverse events: fatigue, diarrhea, nausea, decreased appetite, arthralgia, fever, acute kidney injury, infusion-related reactions, and tumor flare
- Dose: once every 2 to 4 weeks

Competitive environment

If approved, durvalumab will be entering a market with limited treatment options for patients with advanced urothelial carcinoma.

However, durvalumab requires IV administration. Furthermore, a related product is currently available (ie, Tecentriq®) for the treatment of urothelial carcinoma.

The projected annual worldwide sales for durvalumab are $2.5 billion by 2020.

- Advantage: limited treatment options
- Disadvantages: IV administration, related product is available, high cost
- Projected annual worldwide sales are $2.5 billion by 2020

Expected FDA decision date

Durvalumab was granted breakthrough status and will be evaluated under priority review by the FDA.

An FDA decision regarding the approval of durvalumab is expected in the 2nd quarter of 2017.

- Breakthrough status
- Priority review
- PDUFA: 2Q2017

edaravone (Radicava)

Manufacturers: Mitsubishi Tanabe

Therapeutic use

Edaravone is in development for the treatment of amyotrophic lateral sclerosis (ALS).

ALS, also known as Lou Gehrig's disease, is a rapidly progressive neurological disease. ALS attacks the nerve cells responsible for voluntary muscle control. Most patients with ALS die within 3 to 5 years after diagnosis.

- Treatment of ALS

Clinical profile

Edaravone is a free radical scavenger, which is thought to block radicals that mediate both neuronal and vascular damage.

In a randomized trial, edaravone demonstrated less functional loss in ALS patients compared to placebo as measured by the revised ALS Functional Rating Scale (ALSFRS-R). Patients in the placebo arm were permitted to transition to the edaravone arm after 6 months.

The most common adverse events were contusion and dysphagia. Two patients died due to adverse events related to respiratory failure/disorder in the edaravone arm. In the open-label, active phase of the trial, of the patients who started on placebo and were transitioned to edaravone, four died due to respiratory failure/disorder, pneumonia aspiration, and stress cardiomyopathy.

Based on trial protocol, edaravone is administered IV once daily for 14 days, followed by 14 days of observation per treatment cycle. For subsequent cycles, patients were given edaravone for 10 days followed by 14 days of observation.

- Free radical scavenger
- IV formulation
- Less functional loss compared to placebo
- Common adverse events: contusion and dysphagia
- Dose: once daily for 10–14 days, followed by 14 days of observation per cycle

Competitive environment

Edaravone has demonstrated a reduced loss of function in ALS patients compared to placebo. Moreover, it is entering a market with very limited treatment alternatives. Currently, Rilutek® (riluzole) is the only FDA-approved drug for treating ALS and has been shown to extend survival and/or time to tracheostomy in these patients.

Edaravone requires IV administration and will likely require life-long therapy. Furthermore, in a trial evaluating edaravone in ischemic stroke, edaravone was associated with fatal renal failure, abnormal hepatic function, and exacerbations of brain infarction. Whether these risks also pertain to the ALS population is not known.

An estimated 2 in 100,000 people have ALS worldwide. The majority of ALS cases do not have a definite cause for their condition.

- Advantages: reduced loss of function compared to placebo, limited treatment alternatives
- Disadvantages: IV administration, likely requires life-long therapy, long-term risks are unknown
- Worldwide prevalence is 2 in 100,000 people

Expected FDA decision date

Edaravone was granted orphan drug designation by the FDA.

An FDA decision regarding the approval of edaravone is expected by June 2017.

- Orphan drug designation
- PDUFA: 6/2017

L-glutamine

Manufacturer: Emmaus Medical

Therapeutic use
L-glutamine is in development for the treatment of sickle cell disease.

Sickle cell disease is an inherited blood disorder. It is characterized by the production of an altered form of hemoglobin. This altered form causes a rigid, sickle shaped red blood cell (RBC), in turn, increasing the risk for sickle cell crises. Sickle cell crises occur when the altered RBCs occlude blood vessels. Eventually, this condition may lead to organ damage, stroke, pulmonary problems, skin ulceration, infection, and other complications.

- Treatment of sickle cell disease

Clinical profile
L-glutamine is a pharmaceutical grade amino acid.

The precise mechanism of how L-glutamine helps sickle cell disease is not clear; however, L-glutamine is believed to work by enhancing nicotinamide adenine dinucleotide, a necessary component of cellular respiration. In addition, L-glutamine has been associated with reduced adhesion to vascular endothelium and improved exercise tolerance.

In a phase 3 clinical trial, L-glutamine achieved a 25% reduction in the median frequency of sickle cell crises compared to placebo (3 events vs. 4 events, p = 0.008). In addition, there was a 33% reduction in the median frequency of hospitalizations (p = 0.018) over a 48 week period.

However, the overall p-value showed a statistically insignificant difference in reducing the frequency of painful sickle cell crises (p = 0.063).

Generally, L-glutamine was well-tolerated. Patients experiencing acute chest syndrome did occur but was less common with L-glutamine vs. placebo (11.9% vs. 26.9%).

Based on trial protocol, L-glutamine is expected to be dosed by weight and given orally twice daily.

- Amino acid
- Oral formulation
- Greater reduction in the frequency of sickle cell crises vs. placebo
- Well-tolerated by patients
- Dose: twice daily

Continued…

L-glutamine (Continued…)

Manufacturers: Emmaus Medical

Competitive environment

If approved, L-glutamine would be the first FDA-approved treatment for pediatric sickle cell disease and the first new treatment in two decades for adults with this condition. Moreover, data from its phase 3 trial demonstrate that the product is relatively safe.

While it is dosed orally, it still requires twice daily dosing. Moreover, L-glutamine is available over-the-counter (OTC) as a nutritional supplement. However, because sickle cell disease is an orphan condition, L-glutamine will likely exceed the cost of other related OTC products.

An estimated 100,000 patients are afflicted with sickle cell disease in the U.S.

- Advantages: possible first FDA-approved treatment for pediatric sickle cell disease, relatively safe and well-tolerated
- Disadvantages: twice daily dosing, L-glutamine is available OTC, high cost expectation
- Estimated 100,000 Americans have sickle cell disease

Expected FDA decision date

L-glutamine was granted orphan drug designation and fast track status by the FDA.

An FDA decision regarding the approval of L-glutamine is expected by July 7, 2017.

- Orphan drug designation
- Fast track status
- PDUFA: 7/7/2017

midostaurin

Manufacturers: Novartis

Therapeutic use
Midostaurin is in development for the treatment of newly diagnosed FMS-like tyrosine kinase-3 (FLT3) mutation-positive acute myelogenous leukemia (AML). It is also being pursued for the treatment of aggressive systemic mastocytosis (ASM).

AML is an aggressive cancer of the blood and bone marrow.

Systemic mastocytosis is a group of rare diseases in which uncontrolled growth and accumulation of mast cells occur in one or more organs.

- Treatment of newly diagnosed FLT3 mutation-positive AML
- Treatment of ASM

Clinical profile
Midostaurin is a multi-kinase inhibitor. It inhibits protein kinase C, cytokine receptor C-KIT, and FLT3. It may also impact vascular endothelial growth factor receptor-2 (VEGFR-2), platelet-derived growth factor receptor (PDGFR), and the P-glycoprotein (Pgp)-mediated multidrug resistance gene, MDR.

In a pivotal phase 3 trial in AML patients, midostaurin plus chemotherapy was compared to placebo plus chemotherapy. Up to 2 cycles of standard induction therapy and up to 4 cycles of consolidation treatment were administered. In patients who continued in complete remission after consolidation therapy, midostaurin or placebo was given as a single agent for up to 1 year. OS improved by 23% with midostaurin over placebo (hazard ratio = 0.77, p = 0.0074), corresponding to a median survival of 74.7 months with midostaurin vs. 25.6 months for placebo.

In a single-arm, phase 2 trial in ASM patients, midostaurin achieved an ORR of 60% (95% CI: 49%, 70%) with a median duration of response of 24.1 months. Moreover, the overall OS in the primary efficacy population was 28.7 months.

Across its trials, the most common adverse events reported with midostaurin use included nausea, vomiting, cough, and fatigue. However, pleural effusions, QT-prolongation, and new or worsening hematologic abnormalities, such as neutropenia, anemia, and thrombocytopenia, have also been reported.

Based on trial protocol, midostaurin is given orally twice daily.

- Multi-kinase inhibitor
- Oral formulation
- AML: 23% improvement in OS vs. placebo
- ASM: ORR = 60%
- Adverse events: nausea, vomiting, cough, and fatigue, pleural effusions, QT prolongation, and new or worsening hematologic abnormalities
- Dose: twice daily

Continued…

midostaurin (Continued…)

Manufacturers: Novartis

Competitive environment

Midostaurin is an oral drug that acts on multiple targets, including the FLT3 mutation. There are no FDA-approved drugs specifically targeted against FLT3 mutation-positive AML. In addition, positive OS has been reported in the AML and ASM trials.

However, midostaurin requires twice daily dosing, and serious safety concerns have been reported in trials, including pleural effusions, QT prolongation, and new or worsening hematologic abnormalities. Moreover, based on trials, AML patients will require chemotherapy during the induction and consolidation phases, which may expose these patients to a greater risk for adverse events.

Leukemia affects an estimated 350,000 people worldwide. Approximately 25% of these patients have AML and one-third of AML patients have an FLT3 gene mutation.

Systemic mastocytosis affects an estimated 1 in 20,000 to 40,000 people worldwide.

The projected annual U.S. sales for midostaurin are $165 million by 2020 for AML and ASM.

- Advantages: oral, targets multiple kinases, no FDA approved drugs for FLT3 mutation-positive AML, positive OS data
- Disadvantages: twice daily dosing, serious safety concerns, requires chemotherapy in the induction and consolidation treatment phases of AML
- Projected annual U.S. sales are $165 million by 2020

Expected FDA decision date

Midostaurin was granted orphan drug designations and priority reviews for AML and ASM by the FDA. It also has breakthrough status for AML.

An FDA decision regarding the approval of midostaurin is expected in June or July 2017.

- Orphan drug designation
- Breakthrough status
- Priority review
- PDUFA: 6/2017–7/2017

niraparib

Manufacturers: Tesaro/Johnson & Johnson/Merck/ZAI Laboratory

Therapeutic use

Niraparib is in development for the treatment of patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer following response to platinum-based chemotherapy.

- Treatment of recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer following response to platinum-based chemotherapy

Clinical profile

Niraparib is a poly ADP-ribose polymerase (PARP) inhibitor. PARP enzymes are involved with the normal cell cycle, including gene transcription and DNA repair. Inhibition of PARP is believed to limit or suppress tumor growth.

In a pivotal phase 3 trial, niraparib was compared to placebo in 533 platinum-sensitive, adult women who received at least 2 prior courses of platinum-based therapy for ovarian, fallopian tube, or primary peritoneal cancer. The PFS in germline BRCA (gBRCA) mutated patients was 21 months with niraparib vs. 5.5 months for placebo ($p < 0.001$). For non-gBRCA mutated patients, PFS was 9.3 months with niraparib vs. 3.9 months for placebo ($p < 0.001$).

The most common adverse events reported in trials were nausea, thrombocytopenia, fatigue, anemia, constipation, vomiting, and neutropenia. Serious (grade 3 or 4) adverse events included thrombocytopenia (33.8%), anemia (25.3%), and neutropenia (19.6%), which were managed with dose adjustments.

Based on trial protocol, niraparib is dosed orally once daily.

- PARP inhibitor
- Oral formulation
- Greater PFS vs. placebo for both gBRCA and non-gBRCA mutated patients
- Common adverse events: nausea, thrombocytopenia, fatigue, anemia, constipation, vomiting, and neutropenia
- Dose: once daily

Competitive environment

Niraparib will be an oral, once daily treatment option for patients with ovarian, fallopian tube, or primary peritoneal cancer. It has shown positive clinical efficacy (based on PFS) in a phase 3 trial in both gBRCA and non-gBRCA mutated patients.

However, PARP inhibitors are not novel. Related products are available (ie, Lynparza™ [olaparib] and Rubraca™ [rucaparib]). In fact, both Lynparza and Rubraca are indicated to treat advanced ovarian cancer following prior chemotherapy, and Rubraca also targets gBRCA and non-gBRCA mutations.

The projected annual U.S. sales for niraparib are $603 million by 2020.

- Advantages: oral, once daily dosing, targets both gBRCA and non-gBRCA mutations, positive clinical efficacy
- Disadvantages: not a novel mechanism, related products are available
- Projected annual U.S. sales are $603 million by 2020

Expected FDA decision date

Niraparib was granted orphan drug designation and fast track status by the FDA.

An FDA decision regarding the approval of niraparib is expected by June 30, 2017.

- Orphan drug designation
- Fast track status
- PDUFA: 6/30/2017

ribociclib

Manufacturers: Novartis/Otsuka

Therapeutic use

Ribociclib is in development for the first-line treatment of postmenopausal women with hormone-receptor positive (HR+), human epidermal growth factor receptor-2 (HER2) negative advanced or metastatic breast cancer in combination with Femara® (letrozole).

- First-line treatment of HR+, HER2-negative advanced or metastatic breast cancer in combination with letrozole

Clinical profile

Ribociclib is a cyclin dependent kinase (CDK) inhibitor and highly selective for CDK 4 and 6. CDK is involved in cell cycle regulation, and disturbances in these kinases have been associated with various cancers.

In one pivotal trial, ribociclib in combination with letrozole was compared to placebo plus letrozole in HR+, HER2-negative advanced breast cancer patients who received no prior treatment for advanced disease. Based on the positive results of a pre-planned interim analysis, the analysis of the primary endpoint (PFS) was stopped early. The PFS was greater in the ribociclib arm vs. placebo (PFS was not reached vs. 14.7 months, p = 0.00000329). OS was not mature at the time of the interim analysis, and follow-up to measure OS is ongoing.

The most common adverse events reported in the trial included neutropenia, nausea, infections, fatigue, and diarrhea. Nausea, infection, fatigue, and diarrhea were mostly grade 1 or 2. However, severe adverse events (grade 3 or 4) included neutropenia, leukopenia, elevated alanine aminotransferase, lymphopenia, and elevated aspartate aminotransferase.

Based on trial protocols, ribociclib is expected to be dosed orally once daily for 3 weeks of each 28 day treatment cycle.

- CDK 4/6 inhibitor
- Oral formulation
- Greater PFS vs. placebo (p = 0.00000329)
- Common adverse events: neutropenia, nausea, infections, fatigue, and diarrhea
- Dose: once daily for 3 weeks of each treatment cycle

Competitive environment

Ribociclib is a highly selective CDK 4/6 inhibitor. It is an oral once daily drug seeking approval as a first-line treatment option for advanced breast cancer patients.

However, several serious safety concerns have been noted, including neutropenia, leukopenia, increased liver enzymes, and infection. Moreover, because this drug requires use in combination with another agent, there may be other serious concerns that arise once the drug is widely available. Currently, Ibrance® (palbociclib), another CDK 4/6 inhibitor, is marketed to treat breast cancer as well.

The projected annual U.S. sales are $600 million by 2020.

- Advantages: highly selective CDK 4/6 inhibitor, oral, once daily dosing, potential first-line agent for advanced breast cancer
- Disadvantages: serious safety concerns, related product is available
- Projected U.S. sales are $600 million by 2020

Expected FDA decision date

The FDA has granted priority review to ribociclib.

An FDA decision regarding the approval ribociclib is expected by April or May 2017.

- Priority review
- PDUFA: 4/2017 – 5/2017

tisagenlecleucel-T (CTL019)

Manufacturer: Novartis

Therapeutic use

CTL019 is in development for the treatment of relapsed or refractory B-cell acute lymphoblastic leukemia (ALL) in pediatric and adult patients.

- Treatment of relapsed or refractory B-cell ALL

Clinical profile

CTL019 is a form of gene therapy and uses a chimeric antigen receptor T-cell (CAR-T) platform to target CD19, a specific antigen expressed in B-cell lymphomas and leukemias. CTL019 contains an antibody fragment, a co-stimulatory domain, and a signaling domain, which is needed to activate the T-cell.

In a single-arm trial, the ORR at 3 months post-infusion was 82%. Moreover, 60% of responders were relapse-free 6 months post-infusion.

Notable safety concerns witnessed in trials included cytokine release syndrome, infections, transient neuropsychiatric events, and tumor lysis syndrome.

Prior to administration of CTL019, patients must undergo leukapheresis to separate their WBCs from other blood constituents. The patients' WBCs are taken to a facility where the T-cells are isolated and re-engineered to express CARs, which aid in targeting malignant B-cells. Then, the modified T-cells are grown and expanded in culture. Finally, chemotherapy is administered prior to reinfusion of the CAR-T cells into the respective patients.

CTL019 is administered by IV infusion as a single treatment.

- CAR-T agent
- IV formulation
- Serious adverse events: cytokine release syndrome, infections, transient neuropsychiatric events, and tumor lysis syndrome
- Requires leukapheresis and chemotherapy prior to CAR-T treatment
- Dose: single dose

Competitive environment

CTL019 offers a novel, patient-specific treatment that targets B-cell malignancies and only requires a single dose.

However, the entire treatment is a long process, which includes leukapheresis, chemotherapy prior to CAR-T infusion, and a period of post-treatment monitoring. Furthermore, CTL019 requires IV administration and is expected to carry a high cost.

Based on analysts' projections for a related CAR-T product, the drug cost for a single treatment of CTL019 is expected to be approximately $200,000.

- Advantages: novel mechanism, patient-specific therapy, single treatment
- Disadvantages: long treatment process, IV administration, high cost
- Projected cost is ~$200,000 for a single dose

Expected FDA decision date

CTL019 was granted orphan drug designation and fast track status by the FDA.

At this time, Novartis has not filed an application with the FDA for CTL019. However, Novartis expects to file in the upcoming weeks and anticipates a rapid FDA review with a decision as early as the 2nd quarter of 2017.

- Orphan drug designation
- Fast track status
- Projected approval: 2Q2017

valbenazine (Ingrezza)

Manufacturer: Neurocrine Biosciences/Mitisubishi Tanabe Pharma

Therapeutic use

Valbenazine is in development for the treatment of tardive dyskinesia (TD).

TD is characterized by involuntary muscle movements affecting the tongue, lips, trunk, and extremities. It is often the result of long-term use of antipsychotic medications.

- Treatment of TD

Clinical profile

Valbenazine is a vesicular monoamine transporter 2 (VMAT2) inhibitor.

In a placebo-controlled trial, valbenazine significantly improved the symptoms of TD from baseline compared to placebo, as measured by the Abnormal Involuntary Movements Scale (AIMS) (score difference: -3.1 points, $p < 0.0001$).

Common adverse events reported in trials included fatigue, headache, decreased appetite, nausea, somnolence, and dry mouth. There were no clinically significant changes in vital signs, electrocardiogram (ECG), or lab parameters, including liver function test.

Based on trial protocols, valbenazine is dosed orally once daily.

- VMAT2 inhibitor
- Oral formulation
- Greater improvement in TD symptoms vs. placebo
- Common adverse events: fatigue, headache, decreased appetite, nausea, somnolence, and dry mouth
- Dose: once daily

Competitive environment

If approved, valbenazine will be the first FDA-approved treatment for TD.

In addition, because valbenazine is highly selective for VMAT2, it may pose a lower risk for certain adverse events compared to another marketed VMAT inhibitor, Xenazine® (tetrabenazine). However, there are no head-to-head trials comparing valbenazine against Xenazine.

Xenazine has been used off-label for TD and is generically available.

The projected annual U.S. sales for valbenazine are $750 million by 2021.

- Advantages: may be the first FDA-approved drug for TD, may pose lower risk for certain adverse events than Xenazine
- Disadvantages: Xenazine is used off-label for TD and is generically available
- Projected U.S. sales are $750 million by 2021

Expected FDA decision date

Valbenazine was granted fast track and breakthrough designations by the FDA.

Valbenazine was granted priority review by the FDA, and a decision is expected regarding the approval of valbenazine by April 11, 2017.

- Fast track status
- Breakthrough status
- Priority review
- PDUFA: 4/11/2017

OptumRx brand pipeline forecast

OptumRx closely monitors and evaluates the pipeline landscape for upcoming brand drug approvals, including both traditional and specialty medications. This report provides a summary of developmental drugs that may be approved in the upcoming two years.

Read more

OptumRx generic pipeline forecast

OptumRx closely monitors and evaluates the pipeline landscape for upcoming first-time generics and biosimilars. This report provides a summary of upcoming first-time generic drugs and biosimilars that may be approved in the upcoming two years.

Read more

Getting acquainted with pipeline forecast terms

Clinical trial phases

Phase I trials	Researchers test an experimental drug or treatment in a small group of people for the first time to evaluate its safety, determine a safe dosage range, and identify side effects.
Phase II trials	The experimental study drug or treatment is given to a larger group of people to see if it is effective and to further evaluate its safety.
Phase III trials	The experimental study drug or treatment is given to large groups of people to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the experimental drug or treatment to be used safely.
Phase IV trials	Post marketing studies delineate additional information including the drug's risks, benefits, and optimal use.

Pipeline acronyms

ANDA	Abbreviated New Drug Application
BLA	Biologic License Application
CRL	Complete Response Letter
FDA	Food and Drug Administration
NME	New Molecular Entity
NDA	New Drug Application
sBLA	Supplemental Biologic License Application
sNDA	Supplemental New Drug Application
OTC Drugs	Over-the-Counter Drugs
PDUFA	Prescription Drug User Fee Act
REMS	Risk Evaluation and Mitigation Strategy

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