OPTUMRx®

RxOutlook®

3rd Quarter 2018

Pending drug approvals

Drug Name	Manufacturer	Indication/Use	Expected FDA Decision Date
amifampridine (Firdapse)	Catalyst/BioMarin/Jazz	Lambert-Eaton myasthenic syndrome	11/28/2018
amisulpride (Barhemsys)	Acacia	Post-operative nausea and vomiting	10/5/2018
baloxavir marboxil	Shionogi/Roche	Influenza	12/24/2018
brexanolone	SAGE/Ligand	Postpartum depression	12/19/2018
canakinumab	Novartis	Reduction in cardiovascular events	4Q2018
cemiplimab	Regeneron/Sanofi	Cutaneous squamous cell carcinoma	10/28/2018
dacomitinib	Pfizer	Non-small cell lung cancer	9/2018
doravirine	Merck	Human immunodeficiency virus infection	10/23/2018
doravirine/lamivudine/ tenofovir disoproxil fumarate	Merck	Human immunodeficiency virus infection	10/23/2018
duvelisib	Verastem/Infinity/ Yakult Honsha	Chronic lymphocytic leukemia, follicular lymphoma	10/5/2018
gilteritinib	Astellas	Acute myeloid leukemia	11/29/2018
glasdegib maleate	Pfizer	Acute myeloid leukemia	12/2018
larotrectinib	Loxo Oncology/Array BioPharma	Solid tumors	11/26/2018
prucalopride (Resolor)	Shire/Johnson & Johnson	Constipation	12/21/2018
solriamfetol	Jazz	Narcolepsy, obstructive sleep apnea	12/20/2018
talazoparib	Pfizer/BioMarin	Breast cancer	12/2018

amifampridine (Firdapse)

Manufacturers: Catalyst/BioMarin/Jazz

Therapeutic use

Amifampridine is in development for the treatment of Lambert-Eaton myasthenic syndrome (LEMS).

LEMS is a rare autosomal disorder characterized by muscle weakness in the limbs. The immune system attacks the nerve endings, thereby, adversely impacting muscle contraction and strength. In the U.S., the estimated prevalence of LEMS is 3,000.

- Treatment of LEMS

Clinical profile

Amifampridine is a potassium channel blocker, which prolongs the action potential of nerves and potentiates the release of acetylcholine. Acetylcholine is necessary for proper muscle function.

Amifampridine was compared to placebo in two trials. The primary endpoint was the change from baseline in Quantitative Myasthenia Gravis (QMG) score, a physician-rated test to evaluate muscle strength. In both trials, amifampridine showed slower rates of decline in QMG vs. placebo ($p = 0.0452$, $p = 0.0004$).

Amifampridine is approved in Europe for LEMS. Based on data from Europe, safety concerns with amifampridine include dose-dependent risk for seizures; risk of schwannomas, a type of tumor affecting the nerve sheath; QT prolongation; and potential for drug interactions in slow acetylators.

Amifampridine is administered orally three to four times daily.

- Potassium channel blocker
- Oral formulation
- Slower decline in QMG score vs. placebo
- Safety: seizures, schwannoma risk, QT prolongation, drug interactions
- Dose: three to four times daily

Continued…

amifampridine (Firdapse) (continued...)

Competitive environment

LEMS patients have limited treatments options available. If approved, amifampridine may offer a useful oral drug that may be added to a cholinesterase inhibitor.

However, amifampridine requires frequent dosing. Furthermore, there are serious safety concerns associated with this medication, including risk of seizures and tumor development.

The projected price for amifampridine varies widely from $37,000 to $200,000 per year. Most analysts project the price range to be $60,000 to $100,000 per year.

- Advantages: limited treatment options in LEMS, oral
- Disadvantage: frequent dosing, seizure risk, potential tumor risk
- Projected annual cost ~$37,000 – $200,000

Expected FDA decision date

The FDA granted breakthrough and orphan drug designations to amifampridine.

An FDA decision regarding the approval of amifampridine is expected by November 28, 2018.

- Orphan drug status
- Breakthrough status
- PDUFA: 11/28/2018

amisulpride (Barhemsys)

Manufacturer: Acacia

Therapeutic use

Amisulpride is in development for the management of post-operative nausea and vomiting (PONV), including patients who have received prior prophylaxis with standard antiemetics and in combination with prophylaxis with standard antiemetics in higher risk patients.

- Management of PONV, including patients who have received prior prophylaxis with standard antiemetics and in combination with prophylaxis with standard antiemetics in higher risk patients

Clinical profile

Amisulpride is a dopamine antagonist.

In adult surgery patients undergoing anesthesia at high risk of PONV, more patients achieved a complete response (CR) with amisulpride vs. placebo (57.7% vs. 46.6%, $p < 0.001$). CR was defined as no further PONV in a 24-hour period after surgery. In addition, more patients at low-to-moderate risk of PONV, with or without prior PONV prophylaxis, achieved a CR vs. placebo ($p = 0.003$, $p < 0.025$).

In the trials, the adverse event rates were comparable to placebo, including the overall adverse event rates, rates of laboratory abnormalities, and rates of electrocardiogram abnormalities.

Amisulpride was given as a single intravenous (IV) injection.

- Dopamine antagonist
- IV formulation
- Greater proportion of complete responders vs. placebo
- Safety: similar adverse event rates to placebo
- Dose: single injection

Competitive environment

The manufacturer is pursuing amisulpride as the standard of care in PONV.

If approved, amisulpride may benefit patients who are prophylaxis failures.

However, amisulpride will require IV administration. There is the potential for off-label use in chemotherapy-induced nausea and vomiting (CINV).

Alternative products are available, including the 5HT3 antagonists and generic products such as metoclopramide and promethazine.

- Advantages: potential standard of care in PONV, may benefit prophylaxis failures
- Disadvantage: IV administration, potential off-label use in CINV, alternatives are available (5HT3 antagonists, metoclopramide, promethazine)

Expected FDA decision date

An FDA decision regarding the approval of amisulpride is expected by October 5, 2018.

- PDUFA: 10/5/2018

baloxavir marboxil

Manufacturers: Shionogi/Roche

Therapeutic use

Baloxavir is in development for the treatment of acute, uncomplicated influenza in patients 12 years of age and older.

- Treatment of acute, uncomplicated influenza in patients ≥ 12 years old

Clinical profile

Baloxavir is an endonuclease inhibitor. It works by inhibiting the initiation of viral messenger RNA synthesis after entry into the host cell.

Data are available from one pivotal trial, which compared baloxavir to placebo and to Tamiflu® (oseltamivir). The primary endpoint was the time to symptom improvement from baseline, defined as improvement for at least 24 hours. Baloxavir demonstrated a greater reduction in the duration of influenza symptoms vs. placebo (53.7% hours vs. 80.2 hours, $p < 0.0001$), and a greater reduction in the duration of fever vs. placebo (24.5 hours vs. 42.0 hours, $p < 0.0001$). However, the improvement in the duration of symptoms or fever was not statistically different from Tamiflu.

In addition, the overall adverse event rates were comparable across the treatment arms (20.7% for baloxavir, 24.6% for placebo, and 24.8% for Tamiflu). The most common adverse events reported in the trial included diarrhea, bronchitis, nausea, and sinusitis. All of these common adverse events occurred at a lower frequency than placebo.

In the trial, baloxavir was administered as a single oral dose.

- Endonuclease inhibitor
- Oral formulation
- Greater reduction in duration of influenza symptoms and fever vs. placebo
- No difference in duration of influenza symptoms or fever vs. Tamiflu
- Common adverse events: diarrhea, bronchitis, nausea, sinusitis
- Dose: single dose

Competitive environment

Baloxavir offers a novel mechanism of action (MOA) and may be useful in patients who are resistant to Tamiflu or certain avian strains of influenza. It also offers an oral, single-dose treatment regimen.

However, baloxavir requires 2 to 4 pills per dose. In a pivotal trial, baloxavir failed to demonstrate superiority to Tamiflu. In addition, unlike Tamiflu, baloxavir is not intended for influenza prophylaxis or for use in patients < 12 years of age.

For reference, the wholesale acquisition cost (WAC) for Tamiflu is approximately $221 per prescription.

- Advantages: novel MOA, may benefit Tamiflu-resistant and certain avian strains, oral, single-dose regimen
- Disadvantage: requires 2 – 4 pills per dose, not superior to Tamiflu, not for prophylaxis, not for patients < 12 years of age
- WAC for Tamiflu ~$221 per prescription

Expected FDA decision date

An FDA decision regarding the approval of baloxavir is expected by December 24, 2018.

- PDUFA: 12/24/2018

brexanolone

Manufacturers: SAGE/Ligand

Therapeutic use

Brexanolone is in development for the treatment of postpartum depression (PPD).

- Treatment of PPD

Clinical profile

Brexanolone is a proprietary form of a progesterone metabolite and acts as a synaptic and extra-synaptic gamma aminobutyric acid A (GABA-A) receptor modulator.

In two pivotal studies, brexanolone was compared to placebo. The primary endpoint was the change in the Hamilton Depression Rating (HAM-D) scale score from baseline to day 3. In both trials, greater improvement in HAM-D scores from baseline was achieved vs. placebo.

The common adverse events reported in the trials included headache, dizziness, and somnolence.

In the trials, brexanolone was administered as a weight-based 60 hour IV infusion.

- GABA-A receptor modulator
- IV formulation
- Greater improvement in HAM-D scores from baseline vs. placebo
- Common adverse events: headache, dizziness, and somnolence
- Dose: weight-based 60-hour infusion

Competitive environment

Brexanolone works by a novel MOA. If approved, brexanolone will be the first FDA-approved drug for PPD.

However, it requires a prolonged IV infusion. Moreover, it is unclear if brexanolone is safe to administer to breastfeeding women. There is also some suggestion that the antidepressant effect may not be sustained beyond 30 days.

The projected cost of brexanolone is $15,000 to $20,000 per treatment and is anticipated to be a medical benefit medication.

- Advantages: novel MOA, potential first FDA-approved option for PPD
- Disadvantage: IV administration, long infusion time, unclear if safe in breastfeeding patients, possible loss of effect beyond 30 days
- Projected cost ~$15,000 – $20,000 per treatment

Expected FDA decision date

The FDA granted a breakthrough designation to brexanolone.

An FDA decision regarding the approval of brexanolone is expected by December 19, 2018.

- Breakthrough status
- PDUFA: 12/19/2018

canakinumab

Manufacturer: Novartis

Therapeutic use

Canakinumab is in development to reduce the risk of recurrent cardiovascular (CV) events in stable post-myocardial infarction (MI) patients with elevated high-sensitivity C-reactive protein (hsCRP).

Currently, canakinumab is available under the brand name, Ilaris®, for the treatment of periodic fever syndromes and systemic juvenile idiopathic arthritis. However, this new formulation of canakinumab will be marketed under its own brand name.

- To reduce the risk of recurrent CV events in stable post-MI patients with elevated hsCRP

Clinical profile

Canakinumab is a human monoclonal interleukin-1-beta (IL-1-beta) antagonist. In CV disease, canakinumab is believed to work by reducing inflammation without affecting patient lipid levels.

The main study was the CANTOS trial, which examined adult patients with a past history of an MI and elevated hsCRP despite aggressive treatment. Compared to placebo, canakinumab achieved a 15% reduction in CV risk (hazard ratio [HR] = 0.85 [95% CI: 0.74, 0.98]; p = 0.021), defined as the first occurrence of non-fatal MI, non-fatal stroke, or CV death. However, CV death and all-cause mortality rates alone were not statistically different from placebo.

The major safety concerns are expected to be similar to Ilaris including serious infection, potential risk of malignancy, and possible liver injury based on elevations in transaminase levels.

In the trial, canakinumab was administered subcutaneously (SC) every 3 months.

- IL-1-beta antagonist
- SC formulation
- 15% reduction in CV risk vs. placbo
- No difference in CV death or all-cause mortality vs. placebo
- Safety: serious infection, malignancy, liver injury
- Dose: every 3 months

Competitive environment

By acting on the inflammatory pathway, canakinumab reduces CV risk without impacting patient lipid levels. Furthermore, canakinumab is dosed infrequently and has shown positive CV outcomes in the CANTOS trial.

However, canakinumab will require SC injections and has not shown improvements in mortality rates over placebo.

Canakinumab is being formulated for self-administration.

The projected WAC for canakinumab is $64,000 per year.

- Advantages: novel MOA in this population, infrequent dosing, positive CV outcomes, self-administration
- Disadvantage: SC injection, no difference in mortality vs. placebo
- Projected WAC is $64,000 per year

Expected FDA decision date

An FDA decision regarding the approval of canakinumab is expected in the fourth quarter of 2018.

- PDUFA: 4Q2018

cemiplimab

Manufacturers: Regeneron/Sanofi

Therapeutic use

Cemiplimab is in development for the treatment of patients with metastatic cutaneous squamous cell carcinoma (cSCC) or patients with locally advanced cSCC who are not candidates for surgery.

cSCC is the second most common form of skin cancer after basal cell carcinoma and accounts for approximately 20% of non-melanoma skin cancers.

- Treatment of patients with metastatic cSCC or patients with locally advanced cSCC who are not candidates for surgery

Clinical profile

Cemiplimab is a programmed death-1 (PD-1) antagonist.

Data are available from one open-label, non-randomized, phase 2 trial. The primary endpoint was the overall response rate (ORR) at 96 weeks. The ORR was 47.5%. At the time of analysis, the duration of response, the progression-free survival (PFS) and overall survival (OS) had not been reached.

The most common treatment-emergent adverse events in the trial included diarrhea, fatigue, nausea, constipation, and rash. Similar to other PD-1 antagonists, the most significant safety concern is the risk of immune-mediated organ injury and inflammation. Approximately 10% of patients experienced an immune-related adverse event in the trial.

In the trial, cemiplimab was given IV every 2 or 3 weeks.

- PD-1 antagonist
- IV formulation
- ORR = 47.5%
- Safety: immune-mediated organ injury and inflammation
- Common adverse events: diarrhea, fatigue, nausea, constipation, and rash
- Dose: every 2 or 3 weeks

Competitive environment

If approved, cemiplimab would become the first PD-1 antagonist for the treatment of cSCC. Furthermore, cemiplimab may benefit elderly patients, who are often unable to tolerate traditional therapies.

However, cemiplimab requires IV administration. Keytruda® (pembrolizumab) is also being studied for use in the cSCC population and has shown some benefits, but no head-to-head studies have been conducted against cemiplimab.

The projected WAC for cemiplimab is approximately $158,000 per year.

- Advantages: potentially the first PD-1 antagonist for cSCC, may benefit elderly patients
- Disadvantage: IV administration, Keytruda is also being studied in cSCC
- Projected WAC is ~$158,000 per year

Expected FDA decision date

The FDA granted a breakthrough designation to cemiplimab.

An FDA decision regarding the approval of cemiplimab is expected by October 28, 2018.

- Breakthrough status
- PDUFA: 10/28/2018

dacomitinib

Manufacturer: Pfizer

Therapeutic use

Dacomitinib is in development for the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR)-activating mutations.

- First-line treatment of patients with locally advanced or metastatic NSCLC with EGFR-activating mutations

Clinical profile

Dacomitinib is a pan-EGFR tyrosine kinase inhibitor and blocks the signaling in both wild type and mutant EGFR NSCLC.

Dacomitinib was studied in two trials. In the first trial, dacomitinib was compared against Iressa® (gefitinib). Subjects were adult patients with advanced NSCLC and an EGFR mutation (ie, exon 19 deletion or L858R mutation in exon 21). The PFS was greater with dacomitinib vs. Iressa (14.2 months vs. 9.2 months; HR = 0.59, $p < 0.0001$). In the second trial, dacomitinib was compared against Tarceva® (erlotinib) in patients with prior treatment on 1 or 2 systemic therapies. Dacomitinib failed to beat Tarceva (2.9 months vs. 2.9 months, $p = 0.229$).

Common adverse events reported in the trials included dermatitis acneiform, diarrhea, elevated liver test, stomatitis, paronychia, and mucositis.

In the trials, dacomitinib was administered orally once daily.

- EGFR tyrosine kinase inhibitor
- Oral formulation
- Greater PFS vs. Iressa
- Failed to beat Tarceva
- Common adverse events: dermatitis acneiform, diarrhea, elevated liver test, stomatitis, paronychia, mucositis
- Dose: once daily

Continued…

dacomitinib (continued...)

Competitive environment

Dacomitinib is an oral drug given once daily and has demonstrated superior PFS to Iressa.

However, only 10% – 35% of NSCLC have EGFR mutations. Based on the history of existing EGFR tyrosine kinase inhibitors, most patients are expected to progress within 1 year after treatment. Potential competitors to dacomitinib include Tarceva, Iressa, Gilotrif® (afatinib), and Tagrisso® (osimertinib).

For reference, the WAC for existing EGFR tyrosine kinase inhibitors is $7800 to $8500 per month.

- Advantages: oral, once daily dosing, superior to Iressa
- Disadvantage: only 10% – 35% of NSCLC patients have EGFR mutations, patients often progress within 1 year, competitors are available (Tarceva, Iressa, Gilotrif, Tagrisso)
- WAC for EGFR inhibitors is $7800 – $8500 per month

Expected FDA decision date

The FDA granted an orphan drug designation to dacomitinib.

An FDA decision regarding the approval of dacomitinib is expected by September 2018.

- Orphan drug status
- PDUFA: 9/2018

doravirine

doravirine/lamivudine/tenofovir disoproxil fumarate

Manufacturer: Merck

Therapeutic use

Doravirine is in development for use in combination with other antiretroviral agents for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adult patients.

Doravirine is also in development as a fixed-dose combination with lamivudine (3TC) and tenofovir disoproxil fumarate (TDF), for the treatment of HIV-1 infection in adult patients.

- In combination with other antiretroviral agents for the treatment of HIV-1 infection in adult patients

Clinical profile

Doravirine is a novel non-nucleoside reverse transcriptase inhibitor (NNRTI). In contrast, 3TC is a nucleoside reverse transcriptase inhibitor, and TDF is a nucleotide analog reverse transcriptase inhibitor. These agents work by slightly different mechanisms to interfere with the HIV-1 lifecycle.

Doravirine was studied in two trials. The first trial compared doravirine/3TC/TDF to Atripla (efavirenz/emtricitabine/TDF). Doravirine/3TC/TDF was shown to be non-inferior to Atripla at achieving viral loads < 50 copies/mL up to 48 weeks (84.3% vs. 80.8%). The second trial compared doravirine against darunavir plus ritonavir. All patients were given either Truvada® (emtricitabine/TDF) or Epzicom® (abacavir/lamivudine). In both groups, comparable proportion of patients achieved viral loads < 50 copies/mL up to 48 weeks, which met the non-inferiority endpoint for doravirine.

Across the trials, the most common adverse events with the doravirine regimens included headache, diarrhea, nasopharyngitis, dizziness, abnormal dreams, and rash.

In the trials, both doravirine and doravirine/3TC/TDF were administered orally once daily.

- NNRTI
- As part of a combination regimen, doravirine was non-inferior to active comparators
- Common adverse events: headache, diarrhea, nasopharyngitis, dizziness, abnormal dreams, rash
- Dose: once daily

Continued…

doravirine

doravirine/lamivudine/tenofovir disoproxil fumarate (continued...)

Competitive environment

Doravirine is a novel NNRTI and is being studied as a fixed-dose combination, which will offer a complete therapeutic regimen for HIV-1 infection. Doravirine is dosed once daily.

However, doravirine has not shown superiority to available combination regimens. In addition, it is not intended for use in pediatric patients with HIV-1 infection. Thus, pediatric patients will still require other options.

Alternative NNRTIs are available – ie, Intelence® (etravirine), Rescriptor® (delavirdine), Sustiva® (efavirenz), Viramune® (nevirapine), Viramune XR® (nevirapine extended-release), Edurant® (rilpivirine). Sustiva, Viramune, and Viramune XR are generically available.

For reference, the WAC for Symfi™ (efavirenz/3TC/TDF) is $19,885 per year.

- Advantages: novel NNRTI, the combination offers a complete therapy regimen, once daily dosing
- Disadvantage: not superior to existing options, other NNRTI are available including generics
- WAC for Symfi is $19,885 per year

Expected FDA decision date

An FDA decision regarding the approval of doravirine and doravirine/3TC/TDF are expected by October 23, 2018.

- PDUFA: 10/23/2018

duvelisib

Manufacturers: Verastem/Infinity/Yakult Honsha

Therapeutic use

Duvelisib is in development for the treatment of relapsed or refractory chronic lymphocytic leukemia (CLL)/small lymphocytic leukemia (SLL), and for the treatment of relapsed or refractory follicular lymphoma (FL).

- Treatment of relapsed or refractory CLL/SLL
- Treatment of relapsed or refractory FL

Clinical profile

Duvelisib is a dual phosophoinositide-3-kinase (PI3K) inhibitor, which acts on the delta and gamma isoforms.

In the CLL/SLL trial, duvelisib was compared against Arzerra® (ofatumumab) in patients who had progressed after ≥ 1 previous CLL/SLL treatment. The primary endpoint was overall PFS. The PFS was 13.3 months with duvelisib vs. 9.9 months for Arzerra (HR = 0.52, $p < 0.0001$). However, the OS was similar ($p = 0.4807$).

The FL trial was a single-arm study and examined adults who had failed to achieve a complete or partial response or progressed within 6 months after the last dose of chemotherapy or radiation therapy. The overall ORR was 46%.

The common adverse events in the trials were neutropenia, anemia, thrombocytopenia, infection, diarrhea, and pneumonia.

In the trials, duvelisib was administered orally twice daily.

- PI3K inhibitor
- Oral formulation
- Greater PFS vs. Arzerra in the CLL/SLL trial but OS was not statistically significant
- In the FL trial, ORR = 46%
- Common adverse events: neutropenia, anemia, thrombocytopenia, infection, diarrhea, pneumonia
- Dose: twice daily

Competitive environment

Duvelisib is an oral drug that offers another treatment option for patients with CLL/SLL or FL.

However, duvelisib requires twice daily dosing and related products are available – ie, Aliqopa™ (copanlisib), Zydelig® (idelalisib).

For reference, the WAC for Zydelig is $10,216 per month.

- Advantages: offers another treatment option, oral
- Disadvantage: requires twice daily dosing, related products are available (ie, Aliqopa, Zydelig)
- WAC for Zydelig is $10,216 per month

Expected FDA decision date

The FDA granted fast track and orphan drug designations to duvelisib.

An FDA approval regarding the approval of duvelisib is expected by October 5, 2018.

- Fast track status
- Orphan drug status
- PDUFA: 10/5/2018

gilteritinib fumarate

Manufacturer: Astellas

Therapeutic use

Gilteritinib is in development for the treatment of adult patients who have relapsed or refractory acute myeloid leukemia (AML) with a FLT3 mutation as detected by an FDA-approved test.

- Treatment of adult patients who have relapsed or refractory AML with a FLT3 mutation

Clinical profile

Gilteritinib is a multikinase inhibitor with activity against the FLT3 and AXL receptor tyrosine kinases.

Data are only available from early phase trials. In the trials, the ORR was 53% – 60% in AML patients with a FLT3 mutation. There is also an ongoing trial investigating gilteritinib vs. salvage chemotherapy regimens.

The treatment-related adverse events reported in the trials included diarrhea, anemia, fatigue, and elevated hepatic aminotransferase levels.

In the trials, gilteritinib was administered orally once daily.

- Multikinase inhibitor
- Oral formulation
- ORR = 53% – 60%
- Treatment-related adverse events: diarrhea, anemia, fatigue, elevated hepatic aminotransferase levels
- Dose: once daily

Competitive environment

Currently, Rydapt® (midostaurin) is the only FDA-approved targeted therapy for AML patients with a FLT3 mutation; however, Rydapt is intended for newly diagnosed AML patients for use in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation. Thus, if approved, gilteritinib will offer an oral, once daily option for relapsed or refractory AML patients with a FLT3 mutation.

Data supporting gilteritinib is only available from early phase trials. In the trials, deaths were reported. It is not known if gilteritinib was the direct cause of these deaths.

For reference, the WAC for Rydapt is $17,024 per month.

- Advantages: oral, once daily dosing, possible benefit in treatment-experienced AML patients with a FLT3 mutation
- Disadvantage: data only from early phase trials, deaths reported in trials
- WAC for Rydapt is $17,024 per month

Expected FDA decision date

The FDA granted fast track and orphan drug designations to gilteritinib.

An FDA decision regarding the approval of gilteritinib is expected by November 29, 2018.

- Fast track status
- Orphan drug status
- PDUFA: 11/29/2018

glasdegib maleate

Manufacturer: Pfizer

Therapeutic use

Glasdegib is in development for the treatment of adult patients with previously untreated AML in combination with low-dose cytarabine (LDAC).

- Treatment of adult patients with previously untreated AML in combination with LDAC

Clinical profile

Glasdegib is a selective hedgehog inhibitor that binds to smoothened, a membrane that regulates the hedgehog pathway.

In a phase 2 trial, glasdegib plus LDAC was compared to LDAC alone. While the median OS was higher in the glasdegib arm vs. LDAC (8.8 months vs. 4.9 months; HR = 0.501 [80% CI: 0.384, 0.654; one-sided log rank p-value = 0.0003]), the difference in OS was small. Moreover, the study employed an 80% confidence interval, rather than the standard 95% confidence interval.

Currently, a phase 3 trial is in progress, comparing glasdegib as intensive and non-intensive regimens vs. placebo. The primary endpoint is OS but the results are not expected until in 2023.

The details of the safety concerns were not reported in the trials; however, there were cases of low blood counts, gastrointestinal (GI) toxicities, muscle spasms, thinning or loss of hair, taste distortion, and febrile neutropenia. Blood infections were less common among patients in the glasdegib arm vs. the LDAC arm.

In the trials, glasdegib was administered orally for once daily use.

- Hedgehog inhibitor
- Oral formulation
- Greater OS vs. LDAC (8.8 months vs. 4.9 months)
- Safety: low blood counts, GI toxicities, muscle spasms, thinning or loss of hair, taste distortion, and febrile neutropenia
- Dose: once daily

Competitive environment

Glasdegib offers a novel MOA for treating AML patients. It is given orally and only requires once daily dosing.

However, the reported data are limited at this time.

While other hedgehog inhibitors are available – ie, Erivedge® (vismodegib), Odomzo® (sonidegib) – these drugs are not approved for use in AML. Both Erivedge and Odomzo are indicated for use in basal cell carcinoma.

For reference, the WAC for Rydapt is $17,024 per month.

- Advantages: novel MOA in AML, oral, once daily dosing
- Disadvantage: limited data are available
- WAC for Rydapt is $17,024 per month

Expected FDA decision date

The FDA granted an orphan drug designation to glasdegib.

An FDA decision regarding the approval of glasdegib is expected by December 2018.

- Orphan drug status
- PDUFA: 12/2018

larotrectinib

Manufacturers: Loxo Oncology/Array BioPharma

Therapeutic use

Larotrectinib is in development for the treatment of adult and pediatric patients with locally advanced or metastatic solid tumors harboring a neurotrophic tropomyosin receptor kinase (NTRK) gene fusion.

NTRK is a family of genes that encodes for tropomyosin receptor kinases (Trk). These kinases belong to a larger group of receptor tyrosine kinases.

The NTRK genes are subject to oncogenic activating rearrangements (fusions), which can cause overexpression of the Trk proteins. While these fusion cancers are rare, they occur in a wide range of tumor types.

- Treatment of adult and pediatric patients with locally advanced or metastatic solid tumors harboring an NTRK gene fusion

Clinical profile

Larotrectinib is a selective inhibitor of Trk.

At this time, data are only available from early and mid-stage trials. In an uncontrolled trial in patients with solid tumors and an NTRK gene fusion who had progressed on prior therapy, the ORR was 75% (95% CI: 61, 85). At year 1, 71% of responses were still ongoing, and over half (55%) of patients remained progression-free.

In another early phase trial consisting of 15 patients with solid tumors and the NTRK gene fusion, the ORR was 93%.

The main safety concerns reported in the trials included elevated liver function test, increased weight, neutropenia, leukopenia, and decreased ejection fraction.

In the trials, larotrectinib was administered orally twice daily.

- Trk inhibitor
- Oral formulation
- ORR = 75% – 93% in early to mid-stage trials
- Safety: elevated liver function test, increased weight, neutropenia, leukopenia, decreased ejection fraction
- Dose: twice daily

Competitive environment

Larotrectinib is an oral pan-cancer drug that may potentially benefit a wide variety of solid tumor types with NTRK gene fusion.

However, larotrectinib will require twice daily dosing. Currently, data are only available from early to mid-stage trials.

- Advantages: pan-cancer drug, oral
- Disadvantage: twice daily dosing, data only from early to mid-stage trials

Expected FDA decision date

The FDA granted breakthrough and orphan drug designations to larotrectinib.

An FDA decision regarding the approval of larotrectinib is expected by November 26, 2018.

- Breakthrough status
- Orphan drug status
- PDUFA: 11/26/2018

prucalopride (Resolor)

Manufacturers: Shire/Johnson & Johnson

Therapeutic use

Prucalopride is in development for the treatment of chronic idiopathic constipation in adult patients.

- Treatment of chronic idiopathic constipation in adult patients

Clinical profile

Prucalopride is a selective 5HT4 receptor agonist.

The clinical program for prucalopride consisted of 6 controlled trials and evaluated 2,484 adult patients with chronic constipation in the integrated efficacy analysis and 2,552 adult patients in the integrated safety analysis. Over 12 weeks, more patients achieved ≥ 3 spontaneous and complete bowel movements per week with prucalopride vs. placebo (27.8% vs. 13.2%, $p < 0.001$).

There was also one trial that evaluated prucalopride against polyethylene glycol (PEG) plus electrolytes and concluded that PEG plus electrolytes was non-inferior and better tolerated than prucalopride.

The primary concern with 5HT4 receptor agonists is the risk for CV events. A related product, Zelnorm® (tegaserod), was withdrawn in 2007 due to increased risk of heart attack, stroke, and unstable angina. To evaluate this risk with prucalopride, Shire conducted a trial involving over 35,000 patients. No difference in CV risk was found compared to PEG.

In the trials, prucalopride was administered orally one daily.

- 5HT4 receptor agonist
- Oral formulation
- Greater response rate vs. placebo (27.8% vs. 13.2%)
- PEG plus electrolytes was non-inferior to prucalopride
- No difference in CV risk vs. PEG
- Dose: once daily

Competitive environment

Prucalopride offers another treatment option for patients with chronic idiopathic constipation. It is dosed orally once daily and has no greater risk for CV events than PEG.

However, PEG plus electrolytes was shown to be non-inferior to prucalopride. Moreover, several alternatives are currently available. These include over-the-counter and prescription products, such as Amitiza® (lubiprostone), Trulance® (plecanatide), and Linzess® (linaclotide).

For reference, the WAC for Amitiza, Trulance, and Linzess is approximately $345 to $390 per month

- Advantages: another treatment option for patients, oral, no greater risk for CV events vs. PEG
- Disadvantage: PEG plus electrolytes was non-inferior, alternatives are available (Amitiza, Trulance, Linzess)
- WAC for Amitiza, Trulance, Linzess is ~$345 – $390 per month

Expected FDA decision date

An FDA decision regarding the approval of prucalopride is expected by December 21, 2018.

- PDUFA: 12/21/2018

solriamfetol

Manufacturer: Jazz

Therapeutic use

Solriamfetol is in development for the treatment of excessive sleepiness in adult patients with narcolepsy or obstructive sleep apnea (OSA).

- Treatment of excessive sleepiness in adult patients with narcolepsy or OSA

Clinical profile

Solriamfetol is an optically pure derivative of phenylalanine and thought to work as a dopamine and norepinephrine reuptake inhibitor.

In the narcolepsy trial, solriamfetol was compared to placebo. Patients were measured for how long they could remain awake. Compared to baseline, patients showed an improvement of 7.7 – 10.2 minutes over placebo. Subjective reports of sleepiness also showed improvement. Similar results were reported in OSA patients in a dose-dependent manner ranging from 4.5 minutes to 12.8 minutes.

The most common adverse events reported in the trials were headache, nausea, decreased appetite, dry mouth, anxiety, dizziness, nasopharyngitis, and palpitations.

Because of solriamfetol's MOA, the risk of abuse is expected to be minimal. One study found less peak Drug Liking with solriamfetol vs. phentermine, a Schedule IV drug used for weight loss. However, the study has been criticized because the phentermine dose of 90 mg exceeded the recommended dose of 15 mg – 37.5 mg in the drug label. Furthermore, Next Day Drug Liking scores with solriamfetol 300 mg were not found to be statistically different from phentermine 45 mg.

In the trials, solriamfetol was administered orally once daily.

- Dopamine/norepinephrine reuptake inhibitor
- Oral formulation
- Greater improvement in ability to remain awake vs. placebo
- Common adverse events: headache, nausea, decreased appetite, dry mouth, anxiety, dizziness, nasopharyngitis, palpitations
- Dose: once daily

Competitive environment

Solriamfetol is an oral once daily option for patients with excessive sleepiness due to narcolepsy or OSA. Because of its MOA, solriamfetol is expected to have a lower risk of abuse or misuse than alternatives such as Provigil® (modafinil), Nuvigil® (armodafinil), or the CNS stimulants. In addition, rebound hypersomnia is unlikely with solriamfetol.

However, solriamfetol does not address the underlying cause of the narcolepsy or OSA. Moreover, the clinical benefit seen with solriamfetol was small.

Potential competitors include Provigil and Nuvigil.

For reference, the WAC for Provigil and Nuvigil are approximately $1,466 and $655 per month, respectively.

- Advantages: oral, once daily dosing, potential lower risk of abuse, less risk of rebound hypersomnia
- Disadvantage: does not address underlying cause, small clinical improvement, alternatives are available (eg, Provigil, Nuvigil)
- WAC for Provigil is ~ $1,466 per month
- WAC for Nuvigil is ~$655 per month

Expected FDA decision date

The FDA granted an orphan drug designation to solriamfetol.

An FDA decision regarding the approval of solriamfetol is expected by December 20, 2018.

- Orphan drug status
- PDUFA: 12/20/2018

talazoparib

Manufacturers: Pfizer/BioMarin

Therapeutic use

Talazoparib is in development for the treatment of patients with germline BRCA-mutated (gBRCAm), human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer.

- Treatment of patients with gBRCAm, HER2-negative locally advanced or metastatic breast cancer

Clinical profile

Talazoparib is poly ADP-ribose polymerase (PARP) inhibitor.

There is one pivotal, open-label phase 3 trial that evaluated adult females with BRCA mutated, HER2-negative breast cancer not amenable to curative radiation or surgical cure and/or metastatic disease. Patients were randomized to talazoparib or physician's choice of chemotherapy. Greater PFS was achieved with talazoparib vs. chemotherapy (8.6 months vs. 5.6 months; HR = 0.542, $p < 0.0001$).

While the median OS was greater with talazoparib vs. chemotherapy, the difference was not statistically significant (22.3 months vs. 19.5 months; HR = 0.761, p = 0.105).

Limited safety information is available from the trial, but cases of anemia and neutropenia were reported. Grade 3 or 4 adverse events were comparable between the arms, but non-hematological adverse events, GI disorders, and skin/subcutaneous tissue disorders were less frequent in the talazoparib arm than with chemotherapy.

In the trial, talazoparib was administered orally once daily.

- PARP inhibitor
- Oral formulation
- Greater PFS vs. chemotherapy
- Difference in OS vs. chemotherapy was not statistically significant
- Dose: once daily

Competitive environment

Talazoparib is an oral drug for once daily use that offers another treatment option for patients with gBRCAm, HER2-negative breast cancer.

However, this class of medication is not novel. Currently, Lynparza® (olaparib) tablets are available for a similar indication. In addition, the improvement in PFS and OS were not clinically impressive in the phase 3 trial.

For reference, the WAC for Lynparza tablets is $13,886 per month.

- Advantages: oral, once daily dosing, offers another treatment option to patients
- Disadvantage: not novel, alternative (Lynparza tablets), unimpressive PFS and OS data
- WAC for Lynparza tablets is $13,866 per month

Expected FDA decision date

An FDA decision regarding the approval of talazoparib is expected by December 2018.

- PDUFA: 12/2018

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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