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MRx CLINICAL ALERT

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SPOTLIGHT: GENE THERAPY
FDA APPROVES FIRST CAR-T THERAPY

On August 30th, 2017 the Food and Drug Administration (FDA) granted priority approval for Novartis' first-in-class chimeric antigen receptor T cell (CAR-T) therapy, tisagenlecleucel (Kymriah™). This breakthrough gene therapy re-engineers a patient's own T cells (lymphocytes) to recognize and attack cancer cells. CAR-T therapy involves several steps, beginning with collection of the patient's blood, separating out T cells and attaching a specific chimeric antigen receptor to the cell surface, and then re-infusing the cells back into the patient.

Tisagenlecleucel is indicated for the treatment of patients up to 25 years of age with B cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse. With tisagenlecleucel, T cells are directed to kill cancerous B cells that express CD19. In clinical trials, complete response was reported in 83% of patients 3 months after a single dose of tisagenlecleucel; 75.4% of patients were relapse-free 6 months after treatment.

Prior to receiving tisagenlecleucel, patients will receive 1 course of fludarabine and cyclophosphamide lymphodepleting chemotherapy. Then, within 2 to 14 days, a single weight-based dose of tisagenlecleucel is infused intravenously (IV).

Serious adverse effects experienced with CAR-T therapy include cytokine release syndrome (CRS) that is seen within the first few weeks of infusion. CRS is due to a rapid release of cytokines and can lead to respiratory distress, coagulopathy, and end organ dysfunction. Severe or life-threatening cases are managed with the interleukin (IL)-6 blocker, tocilizumab (Actemra®), which received an expanded indication by the FDA to treat CRS associated with CAR-T therapy. Neurologic toxicities, including headache, encephalopathy, and delirium and serious infection can also occur. The FDA is requiring Novartis to conduct long-term studies to confirm safety and durability.

Tisagenlecleucel will only be available through a restricted program, at select sites. Those prescribing, dispensing, and administering tisagenlecleucel must be trained to recognize and manage CRS and neurological events.

ALL is the most common childhood cancer. An estimated 15% to 20% of patients do not respond to or relapse after conventional therapy. The approval of tisagenlecleucel is a significant step in individualized cancer therapy, offering a promising treatment to patients who have few options. Gilead/Kite is also seeking approval of their CAR-T therapy, axicabtagene ciloleucel, for treatment of aggressive non-Hodgkin's lymphoma; approval is expected in November, 2017.

HOT TOPIC: ABBVIE'S PANGENOTYPIC AGENT APPROVED FOR HEPATITIS C VIRUS (HCV)

On August 3rd, 2017, the FDA granted priority approval to Abbvie's HCV Breakthrough therapy, Mavyret™, a fixed-dose combination of the NS3/4A protease inhibitor, glecaprevir, and the NS5A inhibitor, pibrentasvir. Mavyret is indicated for the treatment of patients with chronic HCV genotype (GT) 1, 2, 3, 4, 5, or 6 infection, with or without compensated cirrhosis (Child-Pugh A), and for the treatment of adults with HCV GT 1, who have been previously treated with a regimen containing an HCV NS5A inhibitor or an NS3/4A protease inhibitor, but not both. It is dosed once daily with food as 3 tablets, each tablet containing glecaprevir 100 mg and pibrentasvir 40 mg.

In key clinical trials, Mavyret demonstrated sustained virologic response (SVR), ranging from 92% to 100%, in approximately 2,300 adults with GT 1–6, with and without compensated cirrhosis, who were treatment-naïve or treatment-experienced (including prior direct-acting antivirals [DAAs]).

Mavyret is the first pangenotypic agent that provides an 8-week regimen for select patients across all HCV genotypes. This shorter duration is approved for non-cirrhotic patients with GT 1–6 who are treatment-naïve or with GT 1, 2, 4, 5, or 6 who have received prior treatment with interferons, ribavirin, and/or sofosbuvir. Treatment lasting 12 weeks is required for treatment-naïve patients with compensated cirrhosis. Durations of 12 or 16 weeks are recommended in treatment-experienced patients based on genotype, prior treatment, and presence of compensated cirrhosis. No dosage adjustment is needed for patients with HCV/HIV co-infection or chronic kidney disease.

Mavyret, is the latest advancement in the HCV treatment landscape. It joins Gilead's sofosbuvir/velpatasvir (Epclusa®) and the recently approved salvage therapy, sofosbuvir/velpatasvir/voxilaprevir (Vosevi™), as fixed-dose, pangenotypic agents. While Epclusa and Vosevi require 12 weeks duration, Mavyret allows a shorter 8-week regimen for the majority of HCV patients. Notably, Mavyret and Vosevi are the only options in patients who have received prior DAA therapy.

In addition, on August 1st, 2017, Epclusa was granted an expanded indication to include HCV/HIV co-infected patients (at previously recommended dosing regimens). Although HCV therapy continues to evolve, there are no additional late-term HCV agents expected to enter the market in the next few years.

VICTOZA® APPROVED FOR REDUCTION OF CARDIOVASCULAR (CV) RISK

Novo Nordisk's glucagon-like peptide-1 (GLP-1) receptor agonist, liraglutide (Victoza), gained a new indication to reduce the risk of major adverse CV events (MACE) (e.g., nonfatal myocardial infarction, nonfatal stroke, and CV death), in adults with type 2 diabetes mellitus (T2DM) and established CV disease. The new indication is based on results from the LEADER trial that reported a 13% relative reduction in the first occurrence of MACE, primarily due to a reduction in death from CV or other causes.

Liraglutide is the second antidiabetic drug to be approved for CV risk reduction. Empagliflozin (Jardiance®), an oral sodium-glucose co-transporter 2 inhibitor, received this indication in December 2016, after demonstrating a 14% relative risk reduction of MACE in T2DM patients.

BEHAVIORAL HEALTH CORNER

ICER REPORT ON OPIOID ABUSE-DETERRENT FORMULATIONS (ADF)

The Institute for Clinical and Economic Review (ICER) issued a final report on opioid ADFs. Although ADFs are designed to discourage manipulation for abuse via routes such as chewing, intranasal inhalation, and IV injection, the most common form of abuse remains via the oral route. ICER reviewed data on 9 extended-release and 1 immediate-release formulations. While data suggest that abuse of OxyContin (particularly by non-oral routes) declined after release of its ADF reformulation, abuse may have shifted to other prescription opioids or heroin. ICER found moderate evidence of a comparable or better net health benefit with OxyContin for patients prescribed an opioid, but the evidence for all other ADFs was promising yet inconclusive. Evidence was not sufficient to show decreases in abuse in the broad population who use opioids.

ICER concluded that ADFs may be a safer option for individual patients, but advise against mandatory ADF substitution. A mandate may increase the use of other illicit drugs and rapid uptake may make the higher cost ADFs unaffordable. ICER suggests a change in terminology of ADF to "tamper-resistant formulation," along with public and patient education to avoid any misunderstanding that ADFs are devoid of any risks of abuse or addiction. Finally, ICER recommends the removal of barriers of access to non-pharmacologic treatments for pain.

DRUG INFORMATION **HIGHLIGHTS**

- Boehringer Ingelheim's adalimumab-adbm (Cylteoz™), the second biosimilar to Abbvie's Humira®, has received FDA approval. The tumor necrosis factor (TNF) inhibitor is approved for all eligible indications of the reference product, including rheumatoid arthritis (RA), juvenile idiopathic arthritis, ankylosing spondylitis, plaque psoriasis, psoriatic arthritis, Crohn's disease, and ulcerative colitis. Amgen's Amjevita™ (adalimumab-atto) was the first biosimilar to Humira, approved in September, 2016. Cylteoz is not interchangeable to the reference product, Humira. The final launch date is to be determined.
- The atypical antipsychotic aripiprazole extended-release (ER) injection (Abilify Maintena®) was granted a new indication as monotherapy for maintenance treatment of bipolar I disorder in adults. After establishing tolerability to oral aripiprazole, it is administered intramuscularly (IM) by a healthcare professional (HCP) at a dose of 400 mg once monthly (no sooner than every 26 days). An oral antipsychotic should be taken concurrently with the IM injection for the first 14 consecutive days. Abilify Maintena is also indicated in adults with schizophrenia.
- Accelerated approval was granted to nivolumab (Opdivo®), a programmed cell death receptor-1 (PD-1) blocker, for adult and pediatric (≥ 12 years) patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. The recommended dose is 240 mg IV over 60 minutes every 2 weeks, administered by an HCP, until disease progression or unacceptable toxicity occurs. Nivolumab is also indicated in select patients for several oncologic conditions.
- The vesicular monoamine transporter 2 (VMAT2) inhibitor deutetrabenazine (Austedo®) gained a new indication for the treatment of tardive dyskinesia (TD) in adults.The FDA granted Priority review and Breakthrough therapy status for TD. The starting dose for TD is 6 mg orally twice daily with food; it may be titrated to a maximum of 24 mg twice daily. Deutetrabenazine is also approved to treat chorea related to Huntington's disease.
- The FDA approved the kinase inhibitor, ibrutinib (Imbruvica®), as the first treatment of adult patients with chronic graft versus host disease (cGVHD) after failure of at least 1 treatment. Ibrutinib was granted Breakthrough therapy, Orphan drug, and Priority review for this indication. The dose for cGVHD is 420 mg (3 capsules) orally once daily. Ibrutinib is also approved for various hematological malignancies.
- The FDA approved the poly ADP ribose polymerase (PARP) inhibitor, olaparib tablets (Lynparza®; 100 mg and 150 mg), for the maintenance treatment of adults with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, who are in a complete or partial response to platinum-based chemotherapy and for the treatment of adults with deleterious germline BRCA-mutated advanced ovarian cancer (as based on an FDA-approved companion diagnostic for olaparib) after ≥ 3 prior lines of chemotherapy. The tablet dosage is 300 mg once daily until disease progression or unacceptable toxicity. Olaparib tablets and capsules are not interchangeable. Use of the capsules will be phased out in the U.S.
- The FDA extended the use of levonorgestrel-releasing intrauterine system (Liletta™; 52 mg) from 3 to 4 years for the prevention of pregnancy.

PIPELINE NEWS: UPCOMING PRESCRIPTION DRUG USER FEE ACT (PDUFA) DATES

- **September, 2017:** Rapivab®; peramivir; IM neuraminidase inhibitor; acute uncomplicated influenza; Biocryst.
- **September 13, 2017:** Aptiom®; eslicarbazepine; oral antiepileptic; partial seizure (4-17 years of age); Sumitomo Dainippon.
- **September 14, 2017:** ABP 215; bevacizumab (biosimilar to Genentech's Avastin®); IV vascular endothelial growth factor angiogenesis inhibitor; non-small cell lung cancer (NSCLC), cervical cancer, glioblastoma, colorectal cancer, hepatic cancer; Amgen.
- **September 15, 2017:** Solosec; secnidazole; oral nitrimidazole; bacterial vaginitis; Symbiomix.
- **September 21, 2017:** ITCA 650; exenatide continuous subcutenous (SC) infusion; T2DM; Intarcia.
- **September 22, 2017:** Opdivo; nivolumab; IV PD-1 inhibitor; hepatocellular carcinoma; Bristol-Myers Squibb/Ono.
- **September 22, 2017:** Keytruda®; pembrolizumab; IV PD-1 inhibitor; gastric/gastroesophageal junction cancers; Merck.
- **September 22, 2017:** Plivensia; sirukumab; SC IL-6 antagonist; RA; Janssen/GlaxoSmithKline.
- **October 3, 2017:** Soliris®; eculizumab; IV complement inhibitor; myasthenia gravis, neuromyelitis optica; Alexion.

RECENT FDA APPROVALS

GENERIC NAME	TRADE NAME	DESCRIPTION	APPLICANT	FDA STATUS
belimumab	Benlysta®	The SC injection of belimumab (Benlysta), a B-lymphocyte stimulator (BLyS)-specific inhibitor, was approved for the treatment of active, autoantibody-positive systemic lupus erythematosus in patients who are receiving standard therapy. It has not been evaluated to treat severe active forms of lupus nephritis or central nervous system (CNS) lupus. Benlysta is approved as 200 mg/mL single-dose prefilled autoinjector and syringe. The 200 mg once weekly SC dose may be self-administered. Benlysta is also available as an IV formulation dosed every 4 weeks in a hospital or clinic setting.	GlaxoSmithKline	FDA BLA approval 07/20/2017
nitisinone	Nityr™	The FDA has approved nitisinone (Nityr), a hydroxyphenyl-pyruvate dioxygenase inhibitor, for hereditary tyrosinemia type 1 (HT-1) in combination with dietary restriction of tyrosine and phenylalanine. The starting dose is 0.5 mg/kg orally twice daily; it may be titrated up to 1 mg/kg twice daily. No refrigeration is needed for the 2 mg, 5 mg, and 10 mg tablets.	Cycle	FDA NDA approval 07/26/2017
enasidenib	Idhifa®	Enasidenib (Idhifa), a first-in-class, oral, targeted inhibitor of mutant isocitrate dehydrogenase-2 (IDH2), is indicated for adults with relapsed or refractory AML with an IDH2 mutation as detected by an FDA-approved test. It is approved as 50 mg and 100 mg tablets. The recommended dose is 100 mg orally once daily for ≥ 6 months or until disease progression or unacceptable toxicity. Enasidenib was awarded an Orphan drug designation by the FDA.	Celgene	FDA NDA priority approval 08/01/2017
daunorubicin/ cytarabine	Vyxeos™	Liposomal daunorubicin/cytarabine (Vyxeos) is a combination of an anthracycline topoisomerase inhibitor and a nucleoside metabolic inhibitor, respectively. It is indicated for the treatment of newly-diagnosed therapy-related AML (t-AML) or AML with myelodysplasia-related changes (AML-MRC) in adults. The FDA granted Vyxeos Breakthrough therapy and Orphan drug designations. Vyxeos is approved as a daunorubicin 44 mg/cytarabine 100 mg lyophilized cake in a single-dose vial for reconstitution. During the induction phase, it is dosed as 44 mg/100 mg per m^2 administered IV by an HCP over 90 minutes on days 1, 3, and 5 and on days 1 and 3 for subsequent cycles of induction, if needed. During the consolidation phase, 29 mg/65 mg per m^2 is infused over 90 minutes on days 1 and 3. Vyxeos is not interchangeable with other daunorubicin and/or cytarabine liposome formulations. Launch is expected in the third quarter of 2017.	Jazz	FDA NDA priority approval 08/03/2017

ANDA=AbbreviatedNewDrugApplication;BLA=BiologicsLicenseApplication;NDA=NewDrugApplication;sBLA=SupplementalBiologicsLicenseApplication; sNDA = Supplemental New Drug Application

RECENT FDA APPROVALS continued

GENERIC NAME	TRADE NAME	DESCRIPTION	APPLICANT	FDA STATUS
spironolactone	CaroSpir®	Spironolactone oral suspension (CaroSpir), an aldosterone antagonist, was approved for the treatment of NYHA Class II-IV heart failure and reduced ejection fraction, management of edema, and as add-on therapy in the treatment of hypertension. Typically, the initial dose of the 25 mg/mL suspension is 20 mg daily and titrated upward, as needed, depending on disease state and co-morbid conditions. CaroSpir is not therapeutically equivalent to spironolactone tablets. Doses of CaroSpir > 100 mg may result in higher than expected concentrations. The FDA assigned CaroSpir an Orphan drug designation. CaroSpir is expected to launch during the fourth quarter of 2017.	CMP	FDA NDA approval 08/04/2017
inotuzumab ozogamicin	Besponsa™	The CD22-directed antibody-drug conjugate (ADC), inotuzumab ozogamicin (Besponsa), was FDA-approved to treat adults with relapsed or refractory B cell precursor ALL. It is approved as 0.9 mg lyophilized powder in a single-dose vial for reconstitution and further dilution. It is infused IV over 1 hour by an HCP. Dosing regimens for cycle 1 and subsequent cycles are dependent upon the response to treatment as outlined in the Besponsa labeling. The FDA granted the drug Breakthrough therapy and Orphan drug designations.	Pfizer	FDA BLA priority approval 08/17/2017
lesinurad/ allopurinol	Duzallo®	The fixed-dose combination of the URAT1 inhibitor, lesinurad, and the xanthine oxidase inhibitor, allopurinol, was approved for the treatment of gout-related hyperuricemia in patients who have not achieved target serum uric acid levels with allopurinol alone. Duzallo is not indicated to treat asymptomatic hyperuricemia. It was approved as tablets containing lesinurad/ allopurinol 200 mg/200 mg and 200 mg/300 mg. The recommended dose is 1 tablet once daily. Availability is expected in fourth quarter of 2017.	Ironwood	FDA NDA approval 08/21/2017
amantadine hydrochloride extended-release	Gocovri™	The FDA approved amantadine extended-release capsules (Gocovri) to treat dyskinesia in patients with Parkinson's disease receiving levodopa-based therapy, with or without concomitant dopaminergic medications. It is approved as 68.7 mg and 137 mg strengths. Initial dose is 137 mg administered once daily at bedtime; the dose may be increased to 274 mg daily after 1 week. Capsules should be swallowed whole; contents may be sprinkled on soft food. Gocovri received Orphan drug status. Availability is expected in fourth quarter of 2017, with full launch in January, 2018.	Adamas	FDA NDA approval 08/24/2017

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References:

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