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TREND ALERT
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YOUR QUARTERLY SOURCE FOR KEY TRENDS

INSIDE THIS ISSUE

THE PATH TO PRECISION MEDICINE: A NEW MILESTONE

In the world of chemotherapy, individual drugs are frequently utilized in more than 1 type of cancer. For example, the drug cisplatin was originally approved by the Food and Drug Administration (FDA) in 1978 for use in testicular and ovarian cancers. Since that time, cisplatin has also been approved for use in bladder and lung cancers. These individual approvals are for distinct types of cancer, which are defined by the location of the tumor origin (e.g., bladder, lung). A recent FDA approval has turned this long-standing paradigm on its head. In May 2017, pembrolizumab (Keytruda®) was approved for use in patients with advanced solid tumors shown to have a certain biomarker (MSI-H/dMMR). The approval is not based on the type or anatomical location of the cancer; rather the common thread is the presence of this distinct biomarker within the tumor cell, regardless of the site of origin of the tumor. The data presented to the FDA for approval of pembrolizumab for this indication represented 15 different types of cancer. This approval marks another trail blazing milestone on the journey towards personalized medicine.

Precision medicine involves testing for cancer cell mutations to identify patients most likely to respond to certain drugs. Many cancer drugs are now approved to target a variety of these mutations. However, all of these drug approvals to date had been for patients who demonstrated a distinct mutation and who had a specific type of cancer (e.g., lung cancer).

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Contemporary cancer treatment protocols now routinely recommend testing for genetic mutations in certain types of malignancies. What makes this approval for MSI-H/dMMR-positive solid tumors unique is that routine testing for this biomarker is unlikely to be part of the standard of practice (outside of colorectal cancer where there is a known higher frequency of this type of biomarker). How will physicians know when it might be worthwhile to test for MSI-H/dMMR in a patient with another type of solid tumor? For now, the FDA has limited the indication to patients with "no satisfactory alternative treatment options," so this may help to define the population of patients for whom testing would be appropriate.

Approval of further cancer treatments that are "tumor site-agnostic" appear to be on the horizon. There are currently large-scale "basket trials" underway that group patients together for treatment based on an identified genetic mutation in the cancer cell,

regardless of the site in the body where the cancer originated. As cancer research identifies more genetic mutations and more drugs are developed that target those mutations, the likelihood of treating cancer based on the underlying genetic abnormalities, as opposed to the site of the tumor, becomes more likely. ■

DID YOU KNOW? SCOTUS BIOSIMILAR CRESCENDO

The Supreme Court of the United States (SCOTUS) recently quickened the tempo by issuing a ruling on 2 specific provisions impacting biosimilars. The first measure dealt with the "Notice of Commercial Marketing," also known as the 180-day notice. SCOTUS voted that a biosimilar manufacturer does not have to wait until after FDA approval to give launch notice to the originator manufacturer. Rather, the notice can be provided before or after FDA approval of the biosimilar. On another score, the Supreme Court voted that there is not a federal mandate to provide the "Requirement for Disclosure" or "patent dance," which involves the exchange of application information between the biosimilar applicant and the originator manufacturer.

Biologics are already entitled to 12 years of market exclusivity. Because of this ruling, biologic exclusivity will not be extended to 12 ½ years and biosimilars will not have to wait 6 months to launch. Although the patent dance is not mandatory under federal law, it still may be under state law.

The practical impact of biosimilars can be substantial. Recently Renflexis™, Merck's biosimilar infliximab, launched at a 35% discount to brand Remicade®. Ensuing patent litigation seems intertwined with the biosimilar landscape. Nevertheless, given their potential for cost savings, more biosimilars on the market will accelerate competition. ■

KEEP ON YOUR RADAR: THE FALSE CLAIMS ACT VERSUS THE FIRST AMENDMENT

For more than 50 years, the FDA has strictly regulated prescription drug advertising in order to protect the public health. In the last decade, the FDA has successfully brought suit under the False Claims Act against several pharmaceutical companies for off-label promotion of their drug products. Recently, the pharmaceutical industry has begun to challenge these lawsuits by claiming the restriction of off-label promotion is a violation of the First Amendment right to free speech. This argument has found favor in several court cases and has weakened the FDA's governance over off-label promotion. Now, this argument has begun to produce legislative action. In March 2017, Arizona became the first state to pass a law that safeguards "Free Speech in Medicine" relating to manufacturer communications with providers. Also in March, the "Medical Product Communications Act," which seeks to expand a manufacturer's communications with providers regarding off-label use, was introduced in the U.S. House of Representatives.

Physicians can already legally prescribe medications for off-label use. Medical literature and compendia regarding unapproved uses are available for reference by physicians. Furthermore, providers may request off-label information from manufacturers so long as the inquiry is unsolicited. While some supporters contend that relaxing regulatory oversight will be beneficial for prescribers, others argue that such action primarily promotes drug companies' sales. An area of broad consensus among stakeholders is the lack of support for off-label promotion to consumers via direct-to-consumer advertisements.

While off-label promotion would be required to be "truthful and not misleading," the quality of the data presented and the scientific rigor behind the data may be of a lower standard than the study data currently required for FDA approval. There may also be a loss of incentive for manufacturers to conduct rigorous clinical trials to obtain approval for expanded indications. A situation could occur where a company pursues FDA approval for a very narrow indication but then promotes the drug for different uses with no incentive to seek further FDA approval. Future FDA guidance or court litigations may decide the fate of such off-label communications. ■

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MEDICAL PHARMACY CORNER

A NEW CLINICAL FRONTIER: CAR-T THERAPIES

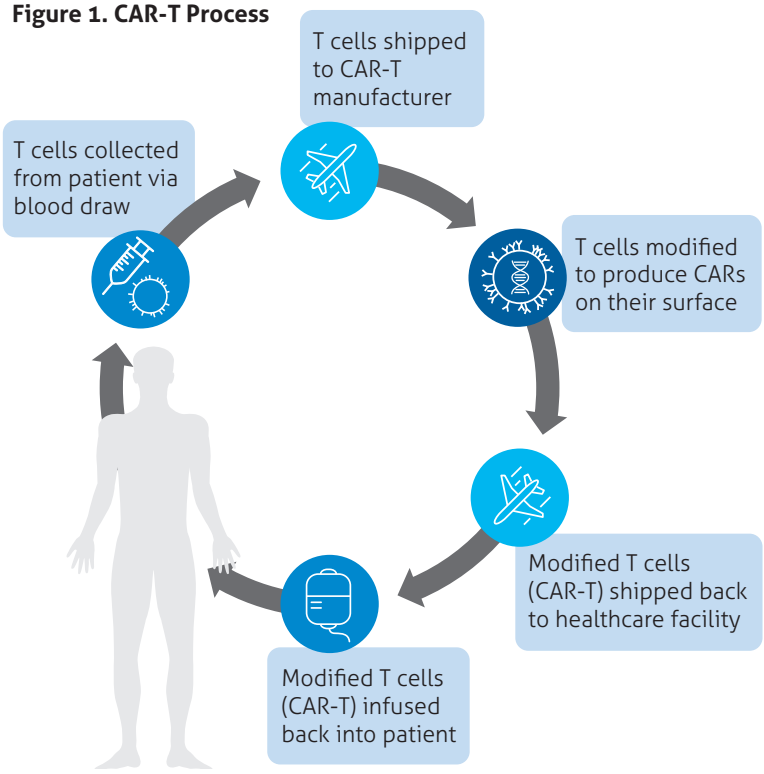
The era of immuno-oncology (IO) began nearly 3 decades ago with the approval of interferon alfa-2b and interleukin-2 (aldesleukin) to treat cancer. The concept behind IO is to harness the immune system to destroy malignant cells. The next generation of IO on the horizon is the impending arrival of chimeric antigen receptor (CAR)-T cell therapies. An FDA Advisory Committee has unanimously recommended approval of tisagenlecleucel-T for the treatment of pediatric and young adult patients with relapsed/refractory B cell acute lymphoblastic leukemia (ALL). A final FDA decision is expected in early October 2017. Approval for another CAR-T therapy, axicabtagene ciloleucel, is expected by late November 2017. Axicabtagene ciloleucel, if approved, will likely be indicated for the treatment of relapsed/refractory diffuse large B cell lymphoma (DLBCL). In addition to the novel nature of these drugs, CAR-T therapies are also designed to be a 1-time only treatment with the goal of curing the patient's cancer with just 1 infusion, an entirely new paradigm in cancer treatment.

It can be confusing to think of CAR-T therapy as "drug therapy" since the treatment is more of a procedure, somewhat analogous to bone marrow transplantation. CAR-T therapy involves several steps, beginning with the collection of a patient's blood, shipping it for processing, and then re-infusing it into the patient (see Figure 1). A patient's own T cells are genetically re-engineered by attaching a specific antigen receptor to the surface of the cell. These modified T cells are then re-infused into the patient to fight cancer cells. Due to the procedural nature of CAR-T therapy, it is unclear if reimbursement will be through a bundled payment or if each step in the process will be billed separately. A new ICD-10 code for CAR-T therapy is expected on October 1, 2017. Tisagenlecleucel-T will have a NDC code at launch and will eventually be assigned a specific J-code, paving the way for outpatient billing through standard drug reimbursement channels.

If approved, initial treatments with tisagenlecleucel-T will be limited to centers that participated in the clinical trials. This is related to the sophistication and expertise required both in handling the overall manufacturing process (cell collection, cryopreservation, and shipping to the manufacturing facility) as well as managing the drug toxicities frequently seen in patients receiving this therapy. While serious, potentially life-threatening toxicities may occur with CAR-T infusions, the decision of whether or not to treat the patient on an inpatient or an outpatient basis will likely be left to the discretion of the treating physician at the select sites. In the pivotal ELIANA registration trial of tisagenlecleucel-T, approximately 74% of patients received the treatment as an inpatient while the remaining 26% were administered tisagenlecleucel-T on an outpatient basis. However, 94% of the 68 patients in the trial who received the CAR-T infusion did require hospital admission at 1 or more time points. Of the patients who were hospitalized at any point, the median duration of hospitalization was 28.5 days with a range of 3 days to 161 days. Approximately half of the 68 patients required admittance to the ICU. The median duration of ICU stay was 7 days with a range of 1 to 51 days.

This next iteration of IO brings many promises and unanswered questions. The FDA plans to require 15 years of follow-up data to assess for any long-term toxicities. Based on the efficacy results seen to date, CAR-T therapy is being heralded as an astounding leap forward in curing refractory cancer patients who, until now, have had very few treatment options. ■

Figure 1. CAR-T Process



PIPELINE REPORT: 3RD/4TH QUARTER 2017

DRUG MANUFACTURER	CLINICAL USE	ANTICIPATED DATE	PROJECTED MARKET IMPACT
Select Branded Pipeline Agents: Potential New Emerging Expenses for Health Plans			
deutetrabenazine (Austedo™) Teva	Tardive dyskinesia (TD)	August 30, 2017	Oral vesicular monoamine 2 transporter (VMAT2) inhibitor; already approved for chorea associated with Huntington's disease; will join valbenazine (Ingrezza™) for TD; Breakthrough Therapy/Priority Review
tisagenlecleucel-T Novartis	Relapsed/refractory B cell acute lymphoblastic leukemia (ALL)	October 3, 2017	Intravenous (IV) chimeric antigen receptor T cell (CAR-T) therapy for pediatric patients and young adults; new treatment modality; Breakthrough Therapy/Priority Review/Orphan Drug
herpes zoster vaccine (Shingrix) GlaxoSmithKline	Herpes zoster (shingles) prevention	October 24, 2017	Non-live, varicella zoster virus (VZV) given as 2 intramuscular (IM) doses administered 2 months apart; recombinant sub-unit vaccine; may play a role for use in immunocompromised patients
axicabtagene ciloleucel Kite	Relapsed/refractory diffuse large B cell lymphoma (DLBCL)	November 29, 2017	IV CAR-T therapy for those ineligible for autologous stem cell transplant; new treatment modality; Breakthrough Therapy/Priority Review/ Orphan Drug
benralizumab AstraZeneca	Severe, uncontrolled asthma	4Q, 2017	Subcutaneous (SC) interleukin-5 (IL-5) antagonist; third IL-5 inhibitor for severe eosinophilic asthma; will compete with mepolizumab (Nucala®) and reslizumab (Cinqair®)
Select New Generics/Patent Expirations			
tadalafil oral tablets, generic for Eli Lilly's Adcirca®	Pulmonary arterial hypertension	November 21, 2017	Patent expiration; Mylan appears to be eligible for 180-day exclusivity; U.S. sales of $372 million in 2016
sildenafil citrate oral tablets, generic for Pfizer's Viagra®	Erectile dysfunction	December 11, 2017	Settlement agreement; U.S. sales of $1.41 billion in 2016
Select Biosimilars			
BI 695501 – biosimilar to Abbvie's Humira® Boehringer Ingelheim	All eligible indications	September 2017	SC tumor necrosis factor alpha blocker; product launch likely to be delayed due to regulatory hurdles; if approved, would be second FDA-approved biosimilar for Humira (adalimumab); Humira had U.S. sales of $14.09 billion in 2016
HERMyl 1401O – biosimilar to Genentech's Herceptin® Biocon/Mylan	Breast cancer (HER2+)	September 1, 2017	IV HER2/neu receptor antagonist; product launch likely to be delayed due to regulatory hurdles; Herceptin (trastuzumab) had U.S. sales of $2.73 billion in 2016
ABP215 – biosimilar to Genentech's Avastin® Allergan/Amgen	Oncology	September 14, 2017	IV vascular endothelial growth factor (VEGF)-specific angiogenesis inhibitor; product launch likely to be delayed due to regulatory hurdles; Avastin (bevacizumab) had U.S. sales of $3.09 billion in 2016

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