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New Drugs: Cyramza, Sylvant, Tanzeum, and Zykadia

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Dr. Thomas A. Gossel has no relevant financial relationships to disclose.

Goal. The goal of this lesson is to provide information on albiglutide (Tanzeum™), ceritinib (Zykadia™), ramucirumab (Cyramza™) and siltuximab (Sylvant™).

Objectives. At the completion of this activity, the participant will be able to:

1. recognize signs and symptoms and key features of targeted pathologies for the drug products included in this lesson;
2. select the indication(s), pharmacologic action(s) and clinical applications for each drug;
3. demonstrate an understanding of adverse effects and toxicity, significant drug-drug interactions, warnings, precautions, and contraindications for the drugs; and
4. list patient counseling information to convey to patients and/or their caregivers.

The new-molecular entity drugs discussed in this lesson are indicated to treat a variety of pathologies (Table 1). This lesson provides a brief introduction to the therapeutic agents, and its depth is not intended to extend beyond an overview of the topic. The reader is, therefore, urged to consult the products' full prescribing information leaflet (package insert), *Medication Guide* when available, and other published sources for detailed descriptions.

Albiglutide (Tanzeum)

Diabetes mellitus is a major global health threat with an estimated 246 million individuals affected worldwide in 2007, a number projected to exceed 380 million in 2030. In the United States, the number with type 2 diabetes mellitus (T2DM) is 24 million, with more than 1.5 million new cases diagnosed each year. Moreover, the number of people who have impaired glucose tolerance, often termed *prediabetes*, may be even greater than that of those with diagnosed diabetes. It is, therefore, clear that the availability of a broad spectrum of effective antidiabetic therapies is becoming increasingly important. Tanzeum is a new treatment option for people with T2DM.

Indications and Use. Tanzeum (TAN-zee-um) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. The drug is not recommended as first-line therapy for patients inadequately controlled by diet and exercise. It has not been studied in patients with a history of pancreatitis, or for treatment of type 1 diabetes mellitus or diabetic ketoacidosis. It is not recommended for patients with pre-existing severe gastrointestinal disease nor has it been studied in combination with prandial insulin.

Type 2 Diabetes Mellitus. T2DM is characterized by defects in insulin action in tissues (insulin resistance) and/or defects in pancreatic insulin secretion (beta-cell dysfunction), which eventually includes loss of pancreatic insulin-secreting cells. The associated complications of diabetes, such as cardiovascular disease, peripheral vascular disease, stroke, diabetic neuropathy, diabetic nephropathy, diabetic retinopathy (eventually blindness), result in increasing disability, reduced life expectancy, and enormous healthcare costs.

Results from numerous clinical trials have demonstrated repeatedly that treatment designed to meet the conventional goal of glycosylated hemoglobin A1c (HbA1c) <7 percent can significantly decrease the risk of long-term complications in patients with diabetes. A major challenge facing healthcare providers is maintaining the patient's balance between achieving HbA1c targets, while simultaneously minimizing adverse events, most notably hypoglycemia or weight gain, or both, that may negatively affect adherence to therapy and thus the treatment outcome.

The Incretin Effect. A significant advance in diabetes management followed identification of two naturally occurring gastrointestinal insulinotropic (insulin secretion inducing) hormones, the incretins: glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Blood levels of both hormones rise rapidly after nutrient intake, then fall precipitously thereafter as a result of rapid enzymatic degradation. In patients with T2DM, the incretin effect of both hormones is greatly

Table 1
Selected new drugs

Generic (Proprietary) Name	Distributor	Indication	Dose*/ Route	Dosage Form	Most Common Side Effects	Medication Guide±
Albiglutide (Tanzeum)	Glaxo-Smith-Kline	type 2 diabetes mellitus	30 mg SC once weekly, then 50 mg once weekly if needed	30 or 50 mg single-dose pen	(≥10%): upper respiratory tract infection, diarrhea, nausea, injection site reactions	Yes
Ceritinib (Zykadia)	Novartis	anaplastic lymphoma kinase-positive metastatic non-small cell lung cancer	750 mg orally, once daily	150 mg capsules	(≥25%): diarrhea, nausea, elevated transaminases, vomiting, abdominal pain, fatigue, decreased appetite, constipation	No
Ramucirumab (Cyramza)	Eli Lilly and Company	gastric cancer	8 mg/kg, IV infusion, every two weeks	100 mg/10 mL, 500 mg/50 mL single-dose vials	(≥10%): hypertension, diarrhea	No
Siltuximab (Sylvant)	Janssen Biotech	multicentric Castleman's disease	11 mg/kg IV infusion, over one hour every three weeks	100 or 400 mg lyophilized powder, single-dose vial	(>10%): pruritus, increased weight, rash, hyperuricemia, upper respiratory tract infection	No

*Recommended dose for most patients
±Availability at the time of publication of this lesson

diminished, as shown by decreased secretion of GLP-1 and impaired insulinotropic action of GIP. The incretin effect has been demonstrated to be responsible for up to 70 percent of the insulin response to a glucose load.

GLP-1 is a 30-amino acid peptide expressed in pancreatic alpha-cells and intestinal L cells, where it is stored in granules and released into the blood in response to a nutrient stimulus. It helps maintain glucose homeostasis through actions on both pancreatic alpha and beta cells. The L cells are located in the mucosa of the distal ileum and colon, and secrete regulatory peptide hormones including GLP-1. The primary physiological stimuli for secretion of GLP-1 are fat- and carbohydrate-rich meals. Mixed meals or individual nutrients, including glucose and other sugars, sweeteners, fatty acids, amino acids and dietary fiber, also can stimulate its secretion. GIP is secreted from duodenal cells of the terminal small bowel. Both hormones are released within minutes following food ingestion, implying that both endocrine and neural signals are acting in their release. Because early studies showed that individuals with T2DM have a reduced response to GIP, even at supraphysiologic (pharmacologic) plasma levels when compared with healthy individuals, GIP is a poor target of therapy in diabetic patients. On the other hand, GLP-1 significantly augments glucose-dependent insulin secretion and remains insulinotropic in T2DM. Its infusion is known to reduce glucose levels by increasing glucose-dependent insulin secretion in persons with T2DM. GLP-1 would, therefore, seem to be a logical means for treatment of T2DM. As with most antidiabetic therapy, the average decrease in HbA1c with GLP-1 is approximately 1 percentage point.

Mechanism of Action. Albiglutide (formerly known as albugon) is a GLP-1 receptor agonist, a hormone that helps normalize blood glucose levels.

Efficacy and Safety. Safety and effectiveness were evaluated as stand-alone therapy and in combination with other T2DM therapies in more than 2,000 patients with T2DM. Trial participants showed clinically relevant improvement in their HbA1c level compared to placebo.

The most common adverse effects (incidence ≥10 percent) in patients treated with Tanzeum were upper respiratory tract infection, diarrhea, nausea, and injection site reactions. The drug's labeling contains a *Boxed Warning* advising that although thyroid C-cell tumors

have been observed in rodents with some GLP-1 receptor agonists, it isn't known whether Tanzeum causes thyroid C-cell tumors in humans, including a type of thyroid cancer called medullary thyroid carcinoma (MTC). Tanzeum should not be used in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (patients have tumors in more than one gland, which predisposes them to MTC).

FDA is requiring the following post-marketing studies for Tanzeum:

- a clinical trial to evaluate dosing, efficacy, and safety in pediatric patients;
- a medullary thyroid carcinoma case registry of at least 15 years duration to identify any increase in MTC incidence related to Tanzeum; and
- a cardiovascular outcomes trial to evaluate the cardiovascular risk of Tanzeum in patients with high baseline risk of cardiovascular disease.

Warnings, Precautions, and Contraindications. The following **warnings** and **precautions** are listed:

- *Pancreatitis:* Discontinue drug promptly if suspected and do not restart if confirmed. Consider other antidiabetic therapies in patients with a history of pancreatitis.
- *Hypoglycemia:* This can occur when used in combination with insulin secretagogues (e.g., sulfonylureas) or insulin. Consider lowering sulfonylurea or insulin dosage when starting Tanzeum.
- *Hypersensitivity reactions:* Discontinue Tanzeum if suspected. Monitor and treat promptly per standard of care until signs and symptoms resolve.
- *Renal impairment:* Monitor renal function in patients with renal impairment who report severe adverse gastrointestinal reactions. Because these reactions may worsen renal function, use caution when initiating or escalating doses of Tanzeum in patients with renal impairment.
- *Macrovascular outcomes:* There have been no clinical trials establishing conclusive evidence of macrovascular risk reduction with Tanzeum or any other antidiabetic drug.

Contraindications include a personal or family history of medullary thyroid carcinoma or use in patients with Multiple Endocrine Neoplasia syndrome type 2, and use in persons with a history of serious hypersensitivity to albiglutide or any product components.

Drug Interactions. Albiglutide delays gastric emptying, and may impact absorption of concomitantly administered oral medications.

Administration, Dosing, and Availability. As a result of covalent binding of albumin, albiglutide has an advantage over earlier therapy – once-weekly dosing. Dosage should be initiated at 30 mg subcutaneously once a week, and increased to 50 mg once weekly in patients requiring additional glycemic control. The drug is injected in the abdomen, thigh or upper arm, on the same day each week, any time of day, without regard to meals. If a dose is missed, administer within three days of the missed dose. Tanzeum is available in single-dose pen injectors containing 30 mg or 50 mg albiglutide as a lyophilized powder with diluent for reconstitution.

Patient Counseling Information. An FDA-approved *Medication Guide* must be dispensed with each prescription and refill for Tanzeum. Specific points for counseling are summarized in Table 2.

Table 2
Patient counseling information for Tanzeum*

Advise patients:
- to read the FDA-approved *Medication Guide* prior to taking Tanzeum, to re-read it each time the prescription is refilled, and to take the drug exactly as prescribed;
- to understand the instructions for preparing the injector pen for use, storage, and disposal;
- about self-management practices, including the importance of proper storage of the drug, injection technique, timing of dosage and concomitant oral drugs, and recognition and management of hypoglycemia;
- about adverse effects, warnings and precautions, and what to do in response;
- that the risk of hypoglycemia is increased when Tanzeum is used in combination with another agent that induces hypoglycemia;
- that if you miss a dose, take the missed dose within three days after your usual scheduled day. If more than three days have passed since the missed dose, wait until your next regularly scheduled weekly dose;
- to tell their healthcare provider about all medicines they are taking.

*Summarized from the *Medication Guide* for Tanzeum

Ceritinib (Zykadia)

FDA granted Zykadia (zye-KAYE-dee-ah) breakthrough therapy designation, priority review, and orphan product designation because its sponsor demonstrated through preliminary clinical evidence that the drug may offer a substantial improvement over available therapies. The drug had the potential, at the time the application was submitted, to be a significant improvement in safety or effectiveness in the treatment of a serious condition, and the drug is intended to treat a rare disease, respectively. Thus, it was approved four months earlier than planned.

Indications and Use. Zykadia is indicated for treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib (Xalkori), the only other approved ALK tyrosine kinase inhibitor. Enzymatic assays have shown ceritinib to be 20 times as potent as crizotinib against ALK. Its indication was approved under the accelerated process, based on tumor response rate and duration of response. An improvement in survival or disease-related symptoms has not been established. Continued

approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Lung Cancer. Lung cancer is the leading cause of cancer-related deaths among men and women. According to the National Cancer Institute, an estimated 224,210 Americans will be diagnosed with lung cancer and 159,260 will die from the disease in 2014, accounting for about 13 percent of all cancer diagnoses. About 85 percent of lung cancers are NSCLC, making it the most common form of lung cancer; however, only 2 to 7 percent of patients with NSCLC are ALK-positive.

Mechanism of Action. Ceritinib is an ALK tyrosine kinase inhibitor that blocks proteins that promote development of cancerous cells.

Efficacy and Safety. Safety and efficacy were established in a clinical trial of 163 participants with metastatic ALK-positive NSCLC. All participants were treated with Zykadia. Results demonstrated that tumors shrunk in about half of the participants, and this effect lasted an average of about seven months. In one study, ceritinib induced response in almost 60 percent of patients with ALK-rearranged lung cancer. More striking is that responses were independent of whether patients had been treated with crizotinib previously. Thus, patients appear to have a second chance for response after relapse following crizotinib treatment.

The most common adverse reactions (incidence of at least 25 percent) were diarrhea, nausea, elevated transaminases, vomiting, abdominal pain, fatigue, decreased appetite, and constipation.

Warnings, Precautions, and Contraindications. The following **warnings** and **precautions** are listed:

• *Severe or persistent gastrointestinal toxicity:* Dose modification due to diarrhea, nausea, vomiting, or abdominal pain occurred in 38 percent of patients. Withhold if patient is not responsive to anti-emetics or anti-diarrheals, then reduce the Zykadia dose.

• *Hepatotoxicity:* Monitor liver laboratory tests at least monthly. Based on severity, withhold, then reduce the dose, or permanently discontinue Zykadia.

• *Interstitial lung disease (ILD)/Pneumonitis:* This occurred in 4 percent of patients. Permanently discontinue Zykadia in patients diagnosed with treatment-related ILD/pneumonitis.

• *QT interval prolongation:* Monitor electrocardiograms and electrolytes in patients with congestive heart failure, bradyarrhythmias, electrolyte abnormalities, or persons who are taking medications that are known to prolong the QTc interval. Withhold, then reduce the dose, or permanently discontinue Zykadia if indicated.

• *Hyperglycemia:* Monitor glucose and initiate or optimize anti-hyperglycemic medications as indicated. Based on severity, withhold, then reduce the dose, or permanently discontinue Zykadia.

• *Bradycardia:* Monitor heart rate and blood pressure regularly. Withhold, then reduce the dose, or permanently discontinue Zykadia.

• *Embryofetal toxicity:* Advise females of potential for fetal harm.

There are no **contraindications** reported.

Drug Interactions:

• *CYP3A Inhibitors and Inducers:* Avoid concurrent use of Zykadia with strong CYP3A inhibitors (e.g., ritonavir, telithromycin, ketoconazole, nefazodone) or inducers (e.g., carbamazepine, phenytoin, rifampin, St. John's Wort). If concurrent use of a strong CYP3A inhibitor is unavoidable, reduce the dose of Zykadia. Grapefruit and grapefruit juice should be avoided since they may inhibit CYP3A.

• *CYP3A and CYP2C9 Substrates:* Avoid concurrent use of Zykadia with CYP3A substrates with narrow therapeutic indices (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus), or CYP2C9 substrates with narrow therapeutic indices (e.g., phenytoin, warfarin).

Table 3
Patient counseling information for Zykadia*

Advise patients:
• to read the FDA-approved Patient Information sheet that is supplied with prescriptions for Zykadia;
• that diarrhea, nausea, vomiting, and abdominal pain are the most commonly reported adverse reactions. Inform them of supportive care options such as anti-emetic and anti-diarrhea medications. Tell them to contact their healthcare provider if experiencing severe or persistent gastrointestinal symptoms;
• to be aware of the signs and symptoms of hepatoxicity, ILD/pneumonitis, QTc interval prolongation and bradycardia, and hyperglycemia, and to contact their physician immediately if signs or symptoms persist;
• (females) that they should not breastfeed during treatment with Zykadia;
• not to consume grapefruit or grapefruit juice during treatment with Zykadia;
• to take the medication on an empty stomach (i.e., not to take it within two hours of a meal);
• that a missed dose can be taken, unless the next dose is due within 12 hours.

*Summarized from the FDA-approved Patient Information sheet.

Administration, Dosing, and Availability. Zykadia's recommended dosage is 750 mg orally once daily on an empty stomach (i.e., not within two hours of a meal). Missed doses should be taken, unless the next dose is due within 12 hours. In clinical trials, approximately 60 percent of patients initiating therapy at the recommended dose required at least one dose reduction, and the median time to the first reduction was seven weeks. Zykadia is available in 150 mg capsules.

Patient Counseling Information. Specific points for patient counseling are summarized in Table 3.

Ramucirumab (Cyramza)

Although the rate of gastric cancer in the United States has decreased over the past 40 years, patients require new treatment options, particularly when they no longer respond to other therapies. Cyramza (si-RAM-za)is a new treatment option that has been demonstrated to slow tumor growth and extend lives. Cyramza was submitted to FDA's priority review program, which provides an expedited review for drugs that have the potential, at the time the application was submitted, to offer a significant improvement in safety or effectiveness in the treatment of a serious condition. Cyramza was also granted orphan product designation because it is intended to treat a rare disease or condition.

Indications and Use. Cyramza is indicated for treatment of advanced gastric cancer or gastroesophageal junction adenocarcinoma as a single-agent, or in combination with paclitaxel, after prior fluoropyrimidine-containing (e.g., 5-FU, capecitabine) or platinum-containing (e.g., paclitaxel, cisplatin) chemotherapy.

Gastric Cancer. Gastric cancer forms in the tissues lining the stomach, mostly in older adults. According to the National Cancer Institute, an estimated 22,200 Americans will be diagnosed with gastric cancer and 10,990 will die from the disease in 2014. Gastric cancer is currently the fourth most common malignancy, and the second most common cause of cancer deaths worldwide. Survival has improved with validation and implementation of adjuvant therapy combined with surgery, including postoperative adjuvant chemotherapy, perioperative chemotherapy, and postoperative combined chemotherapy and radiotherapy. However, little progress has been made in either treatment of advanced gastric cancer or development of novel targeted treatments. Early diagnosis is crucial because of the possibility of metastases to the liver, pancreas, omentum (membrane in the abdominal cavity that connects and supports internal organs), esophagus, bile ducts, and regional and distant lymph nodes.

Vascular endothelial growth factor (VEGF) and VEGF receptor-2 (VEGFR2)-mediated signaling, and angiogenesis (new blood vessel formation) seem to have an important role in the pathogenesis of gastric cancer. In patients with gastric cancer, circulating and tumoral concentrations of VEGF are associated with increased tumor aggressiveness and reduced survival.

Mechanism of Action. Ramucirumab is a fully human monoclonal antibody that is a VEGFR2 antagonist. The drug specifically binds VEGFR2 and blocks binding of VEGFR2 ligands. As a result, ramucirumab inhibits ligand-stimulated activation of VEGFR2, thereby inhibiting ligand-induced proliferation, and migration of human endothelial cells. In other words, the drug is an angiogenesis inhibitor that blocks the blood supply to tumors.

Efficacy and Safety. Safety and effectiveness were evaluated in a clinical trial of 355 participants with unresectable or metastatic stomach or gastroesophageal junction cancer. Two-thirds of trial subjects received Cyramza, while the remaining individuals received placebo. The trial was designed to measure overall survival. Results showed that participants treated with Cyramza experienced a median overall survival of 5.2 months, compared to 3.8 months in subjects receiving placebo. Additionally, participants who took Cyramza experienced a delay in tumor growth (progression-free survival), compared to participants who were given placebo.

Common adverse effects experienced by Cyramza-treated participants (incidence ≥10 percent and ≥2 percent higher than placebo) were hypertension and diarrhea. A *Boxed Warning* advises that the drug increases the risk of fatal hemorrhagic events.

Warnings, Precautions, and Contraindications. The following **warnings** and **precautions** are listed:

• *Arterial thromboembolic events (ATEs):* Serious, sometimes fatal ATEs have been reported in clinical trials. Discontinue Cyramza for severe ATEs.

• *Hypertension:* Monitor blood pressure and treat hypertension. Temporarily suspend Cyramza for severe hypertension and discontinue the drug for hypertension that cannot be medically controlled.

• *Infusion-related reactions:* Monitor for signs and symptoms during infusion.

• *Gastrointestinal perforation:* Discontinue the drug.

• *Impaired wound healing:* Withhold the drug prior to surgery.

• *Clinical deterioration in*

Table 4
Patient counseling information for Cyramza*

Advise patients:
• that Cyramza can cause severe bleeding. Advise them to contact their healthcare provider for bleeding or symptoms of bleeding including lightheadedness;
• of increased risk of an arterial thromboembolic event;
• to undergo routine blood pressure monitoring and to contact their healthcare provider if blood pressure is elevated, or if symptoms from hypertension occur including severe headache, lightheadedness, or neurologic symptoms;
• to notify their healthcare provider for severe diarrhea, vomiting, or severe abdominal pain;
• that Cyramza has the potential to impair wound healing. Instruct patients not to undergo surgery without first discussing this potential risk with their healthcare provider;
• of the potential risk for maintaining pregnancy, risk to the fetus, or risk to postnatal development during and following treatment with Cyramza; and the need to avoid pregnancy, including use of adequate contraception, for at least three months following the last dose of Cyramza;
• to discontinue nursing during Cyramza treatment.

*Summarized from the FDA-approved package insert

patients with cirrhosis: New onset or worsening encephalopathy, ascites, or hepatorenal syndrome can occur in patients with Child-Pugh B or C cirrhosis.

•*Reversible posterior leukoencephalopathy syndrome:* Discontinue Cyramza.

No **contradictions** are listed and no formal **drug interaction** studies have been conducted.

Administration, Dosing, and Availability. Cyramza is administered at a dose of 8 mg/kg by intravenous infusion over 60 minutes every two weeks. It should not be administered by intravenous push or bolus injection. Before each infusion, patients should receive a histamine H_1-antagonist intravenously. Patients who have experienced a Grade 1 or Grade 2 infusion reaction should also be premedicated with dexamethasone (or equivalent) and acetaminophen. Cyramza is available in single-dose vials containing 100 mg/10 mL solution and 500 mg/50 mL solution.

Patient Counseling Information. Specific points for patient counseling are summarized in Table 4.

Siltuximab (Sylvant)

Sylvant's (SIL-vant) approval demonstrates FDA's commitment to approving drugs for rare diseases. The drug was submitted under FDA's priority review program, and also was granted orphan product designation because it is intended to treat a rare disease or condition.

Indications and Use. Sylvant is the first FDA-approved drug to treat patients with multicentric Castleman's disease (MCD) who are human immunodeficiency virus (HIV) negative and human herpesvirus-8 (HHV-8) negative. The drug has not been studied in patients with MCD who are HIV positive or HHV-8 positive because in a nonclinical study it did not bind to virally produced interleukin-6 (IL-6).

Multicentric Castleman's Disease. Castleman's disease (CD) is a rare, atypical disorder of lymph nodes and related tissues that was first described in 1956. Its prevalence is unknown. CD is also referred to as giant lymph node hyperplasia and angiofollicular lymph node hyperplasia. Although it is not officially a cancer, the multicentric form of the disease (i.e., MCD) acts very much like lymphoma (cancer of lymph nodes). In fact, many people with MCD eventually develop lymphoma. Instead of being classified as cancer, CD is often termed a lymphoproliferative disorder, indicating there is an abnormal overgrowth of immune cells of the lymph system that is similar in many respects to lymphomas. Like lymphoma, CD is often treated with chemotherapy or radiation.

Lymphoid (lymphatic) tissue constitutes the major part of the immune system. The main cells in lymphoid tissue are lymphocytes, a form of white blood cells. Lymphoid tissue is distributed throughout the body, including lymph nodes, thymus, spleen, tonsils and adenoids, bone marrow, and the digestive tract.

CD may be unicentric or multicentric. The two forms affect individuals differently. Unicentric (localized) CD presents in the vast majority of cases and affects only a single group of lymph nodes. Lymph nodes in the chest or abdomen are typically affected. These lymph nodes enlarge and may impinge on vital (e.g., neurovascular or vascular) structures within the chest or abdomen.

MCD involves more than a single group of lymph nodes. This form may occur in individuals infected with HIV and HHV-8. Because it involves multiple sites, MCD is much more serious than the localized type, particularly in persons with HIV infection.

CD can weaken the immune system severely, making it difficult to fight infection. Multicentric Castleman's disease can be life-threatening, and associated with other cell-proliferation disorders, incuding cancer of the lymphatic system (lymphoma) and Kaposi's sarcoma.

Mechanism of Action. High serum IL-6 levels correlate with worsening prognosis and survival in patients with lymphoma and multiple myeloma. Overproduction of IL-6 from affected lymph nodes is responsible for systemic manifestations. Siltuximab is a chimeric (murine human) monoclonal antibody with high binding affinity for human IL-6, and thus prevents IL-6 binding to both soluble and membrane-bound receptors. IL-6 has been shown to be involved in diverse normal physiologic functions such as induction of immunoglobulin secretion. Overproduction of IL-6 has been linked to systemic manifestations in patients with MCD. Considerable experimental and clinical evidence suggest a strong rationale for targeting IL-6 as a therapeutic strategy. In numerous preclinical models, binding of IL-6 resulted in tumor regression or prolonged survival.

Efficacy and Safety. Safety and effectiveness were evaluated in a clinical trial of 79 participants with MCD who were HIV and HHV-8 negative. Participants were randomly assigned to receive a combination of Sylvant and best supportive care, or placebo and best supportive care. Results showed 34 percent of participants treated with Sylvant plus best supportive care experienced tumor response, while no participants treated with placebo and best supportive care did.

Common adverse effects (incidence >10 percent compared to placebo) included pruritus, increased weight, rash, hyperuricemia, and upper respiratory tract infection. Hematology laboratory tests should be performed prior to each dose of siltuximab therapy for the first 12 months and every three dosing cycles thereafter, and results compared with criteria presented in the product's Prescribing Information.

Warnings, Precautions, and Contraindications. The following **warnings** and **precautions** are listed:

•*Concurrent active severe infections:* Do not administer Sylvant

Table 5
Patient counseling information for Sylvant*

Advise patients:
- to read the FDA-approved Patient Information sheet that is supplied with Sylvant;
- that Sylvant may lower resistance to infections. Instruct them of the importance of contacting their healthcare provider immediately when symptoms suggesting infection appear to assure rapid evaluation and treatment;
- that they should discuss recommended vaccinations prior to treatment with Sylvant;
- that serious allergic reactions may occur during the infusion. Symptoms include: difficulty breathing, chest tightness, wheezing, severe dizziness, or light-headedness, swelling of the lips, or skin rash;
- (females) to avoid pregnancy, which may include use of contraception during treatment and for three months after Sylvant therapy;
- to report any signs of new or worsening medical conditions to their healthcare provider.

*Summarized from the FDA-approved Patient Information sheet.

to patients with severe infections until the infection resolves. Monitor patients closely for infections. Institute prompt anti-infective therapy and do not administer Sylvant until the infection resolves.

- *Vaccinations:* Do not administer live vaccines because IL-6 inhibition may interfere with the normal immune response to new antigens.
- *Infusion related reactions:* Administer Sylvant in a setting that provides resuscitation equipment, medication, and personnel trained to provide resuscitation.
- *Gastrointestinal perforation:* Use with caution in patients who may be at increased risk. Promptly evaluate patients presenting with symptoms that may be associated or suggestive of GI perforation.

One **contraindication** is listed: Severe hypersensitivity reaction to siltuximab or any of the excipients in Sylvant.

Drug Interactions. No *in vitro* or *in vivo* drug-drug interaction studies have been conducted with Sylvant.

Administration, Dosing, and Availability. Sylvant is administered in a dose of 11 mg/kg given over one hour by intravenous infusion, every three weeks. The drug is available as a lyophilized powder in single-use vials containing 100 mg and 400 mg of siltuximab.

Patient Counseling Information. Specific points for patient counseling are summarized in Table 5.

Overview and Summary

Sylvant, Cyramza, and Zykadia have been recently approved by FDA through their priority review program. Tanzeum was recently approved as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Each of these new drugs offers additional therapeutic options for their respective diseases.

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The author, the Ohio Pharmacists Foundation and the Ohio Pharmacists Association disclaim any liability to you or your patients resulting from reliance solely upon the information contained herein. Bibliography for additional reading and inquiry is available upon request.

This lesson is a knowledge-based CE activity and is targeted to pharmacists in all practice settings.

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CE Hours: 1.5 (0.15 CEU)

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continuing education quiz

New Drugs: Cyramza, Sylvant, Tanzeum, and Zykadia

1. Which of the following is false concerning albiglutide?
   a. It is recommended as first-line therapy in patients inadequately controlled by diet and exercise.
   b. It is not recommended for persons with pre-existing severe gastrointestinal disease.
   c. It delays gastric emptying, and may impact absorption of concomitantly administered oral medications.

2. Treatment of type 2 diabetes mellitus (T2DM) should be designed to meet the conventional goal of glycosylated hemoglobin A1c which is:
   a. <3 percent.
   b. <5 percent.
   c. <7 percent.
   d. <9 percent.

3. The incretin effect has been demonstrated to be responsible for up to what percent of the insulin responses to a glucose load?
   a. 25 percent
   b. 50 percent
   c. 70 percent
   d. 90 percent

4. The primary physiological stimuli for secretion of GLP-1 are carbohydrate and:
   a. protein.
   b. fat.
   c. glucagon.
   d. gluten.

5. Tanzeum is contraindicated in persons with a history of:
   a. type 2 diabetes mellitus.
   b. QT interval prolongation.
   c. medullary thyroid carcinoma.
   d. arterial thrombotic events.

6. Enzymatic assays have shown that ceritinib is how many times as potent as crizotinib against anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer?
   a. 5 times
   b. 10 times
   c. 15 times
   d. 20 times

7. In clinical trials for Zykadia, all of the following were adverse effects, with an incidence of at least 25 percent, EXCEPT:
   a. nausea and vomiting.
   b. abdominal pain.
   c. elevated transaminases.
   d. injection site reactions.

Completely fill in the lettered box corresponding to your answer.

1.	[a]	[b]	[c]		6.	[a]	[b]	[c]	[d]	11.	[a]	[b]	[c]	
2.	[a]	[b]	[c]	[d]	7.	[a]	[b]	[c]	[d]	12.	[a]	[b]	[c]	[d]
3.	[a]	[b]	[c]	[d]	8.	[a]	[b]	[c]	[d]	13.	[a]	[b]	[c]	[d]
4.	[a]	[b]	[c]	[d]	9.	[a]	[b]	[c]	[d]	14.	[a]	[b]	[c]	
5.	[a]	[b]	[c]	[d]	10.	[a]	[b]	[c]		15.	[a]	[b]	[c]	[d]

❑ **I am enclosing $5 for this month's quiz made payable to: Ohio Pharmacists Association.**

1. Rate this lesson: (Excellent) 5 4 3 2 1 (Poor)
2. Did it meet each of its objectives? ❑ yes ❑ no
   If no, list any unmet_____
3. Was the content balanced and without commercial bias?
   ❑ yes ❑ no
4. Did the program meet your educational/practice needs?
   ❑ yes ❑ no
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8. The mechanism of action of ramucirumab to treat gastric cancer is through inhibition of:
   a. mitosis.
   b. angiogenesis.
   c. tyrosine kinase.
   d. interleukin-6.

9. A *Boxed Warning* in the label of Cyramza advises that it increases the risk of:
   a. gastrointestinal perforation.
   b. severe hypersensitivity reactions.
   c. fatal hemorrhagic events.
   d. QT interval prolongation.

10. One precaution for Sylvant therapy is:
   a. hematology lab tests should be preformed monthly.
   b. do not administer live vaccines.
   c. females should use contraception for six months after therapy.

11. Which of the following is false concerning Castleman's disease?
   a. It is prevalent is 1 percent of American men.
   b. The multicentric form is much more serious.
   c. It can weaken the immune system.

12. Targeting interleukin-6 is a therapeutic strategy for treatment of which of the following pathologies?
   a. Type 2 diabetes mellitus
   b. Non-small cell lung cancer
   c. Gastric cancer
   d. Castleman's disease

13. Which of the following is taken orally?
   a. Ramucirumab
   b. Siltuximab
   c. Albiglutide
   d. Ceritinib

14. Which of the following is not recommended in counseling patients taking Cyramza?
   a. Be aware of symptoms of hepatotoxicity.
   b. Females should avoid pregnancy.
   c. It may impair would healing.

15. An histamine H1-antagonist should be administered prior to dosing with which of the following drugs?
   a. Ramucirumab
   b. Siltuximab
   c. Albiglutide
   d. Ceritinib

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