FORMULARY JEOPARDY: WHERE DO NOVEL DRUGS OF 2016 FIT IN?

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Program Objectives

By the end of the presentation, the pharmacist or pharmacy technician participant will be able to:

- Identify orphan drugs and first-in-class medications approved by the FDA in 2016.
- Describe the role of new agents approved for use in oncology patients.
- Identify and discuss the role of novel monoclonal antibodies.
- Discuss at least two new medications that address public health concerns.

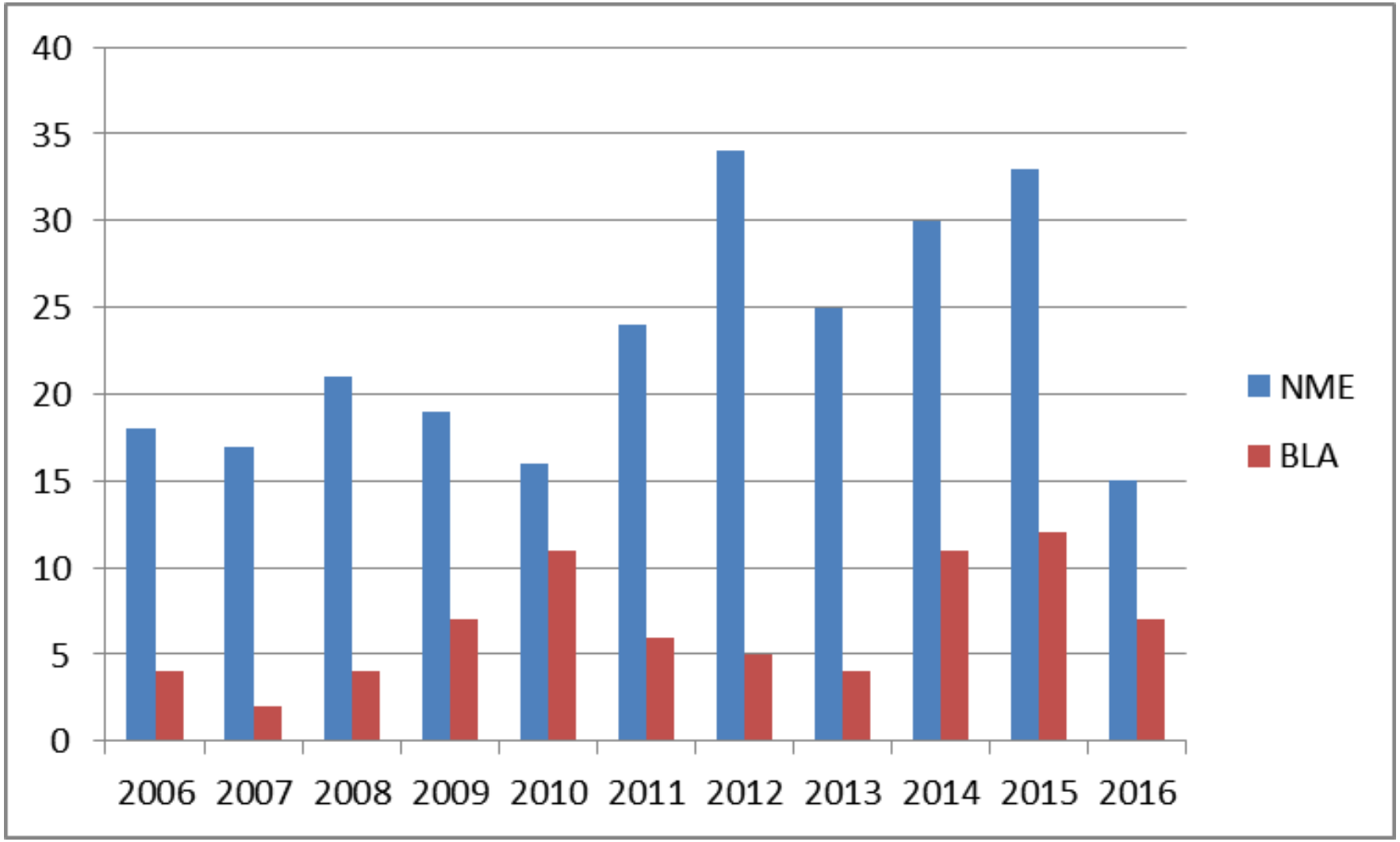
Neither Dr. Kludze nor Dr. Shlom have any conflicts of interest in regards to this presentation.

2016 NDA Approvals (NMEs/BLAs)

- Nuplazid (primavanserin) P
- Ocaliva (obeticholic acid) P, O
- Rubraca (rucaparib camsylate) P, O
- Spinraza (nusinersen sodium) P, O
- Taltz (ixekizumab)
- Tecentriq (atezolizumab) P
- Venclexta (venetoclax) P, O
- Xiidra (lifitigrast) P
- Zepatier (elbasvir and grazoprevir) P
- Zinbyrta (daclizumab)
- Zinplava (bezlotoxumab) P
- Adlyxin (lixisenatide)
- Anthim (obitoxaximab) O
- Axumin (fluciclovive F18) P
- Briviact (brivaracetam)
- Cinqair (reslizumab)
- Defitelio (defibrotide sodium) P, O
- Epclusa (sofosburvir and velpatasvir) P
- Eucrisa (crisaborole)
- Exondys 51 (eteplirsen) P, O
- Lartruvo (olaratumab) P, O
- NETSTPOT (gallium Ga 68 dotatate) P, O

O = Orphan; **P** = Priority Review; **Red** = BLA

History of FDA Approvals



Orphan Drugs

- FDA Office of Orphan Products Development
  - Orphan Drug Act (1983) – drugs and biologics
    - "intended for safe and effective treatment, diagnosis or prevention of rare diseases/disorders that affect fewer than 200,000 people in the U.S. or that affect more than 200,000 persons but are not expected to recover the costs of developing and marketing a treatment drug."
    - Incentives to pharmaceutical manufacturers:
      - Federal funding for clinical trials
      - Tax credit – 50% of clinical testing costs
      - 7 years market exclusivity from date of approval
      - FDA approval via priority status (6 vs 10 month approval; fee waived)
  - 7000 rare diseases affecting 25-30 million people in U.S.

www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/ucm2005525.htm

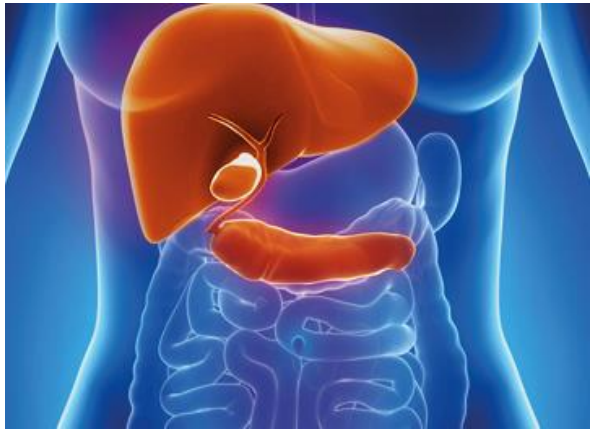
Orphan Drugs

- Orphan Drug Approvals
  - Average of 8 Orphan drugs approved per year
  - 349 Orphan drugs approved 1983-2009
    - Rising rate of approvals: 33% (1983-2005), 37% (2009-2015), 47% (2015)
    - 65% are NME vs. 35% are BLA
  - Drug categories
    - 28% oncology
    - 15% infectious diseases (including HIV)
    - 11% neurological/psychiatric
    - 10% enzyme deficiencies
  - Increasing Orphan drugs targeting biomarker-defined disease subsets (e.g. ALK+ NSCLC, BRAF V600E met melanoma)

Kesselheim AS. Innovation and the Orphan Drug Act, 1983-2009: Regulatory and Clinical Characteristics of Approved Orphan Drugs.
Kesselheim AS, Treasure CL, Joffe S. Biomarker-defined subsets of common diseases:: Policy and economic mplications of orphan drug act coverage. PLoS Med 2017;14(1):e1002190.

Hepatobiliary Diseases

- Defitelio® (defibrotide sodium)
- Epclusa® (sofosbuvir and velpatasvir)
- Zepatier® (elbasvir and grazoprevir)
- Ocaliva® (obeticholic acid)

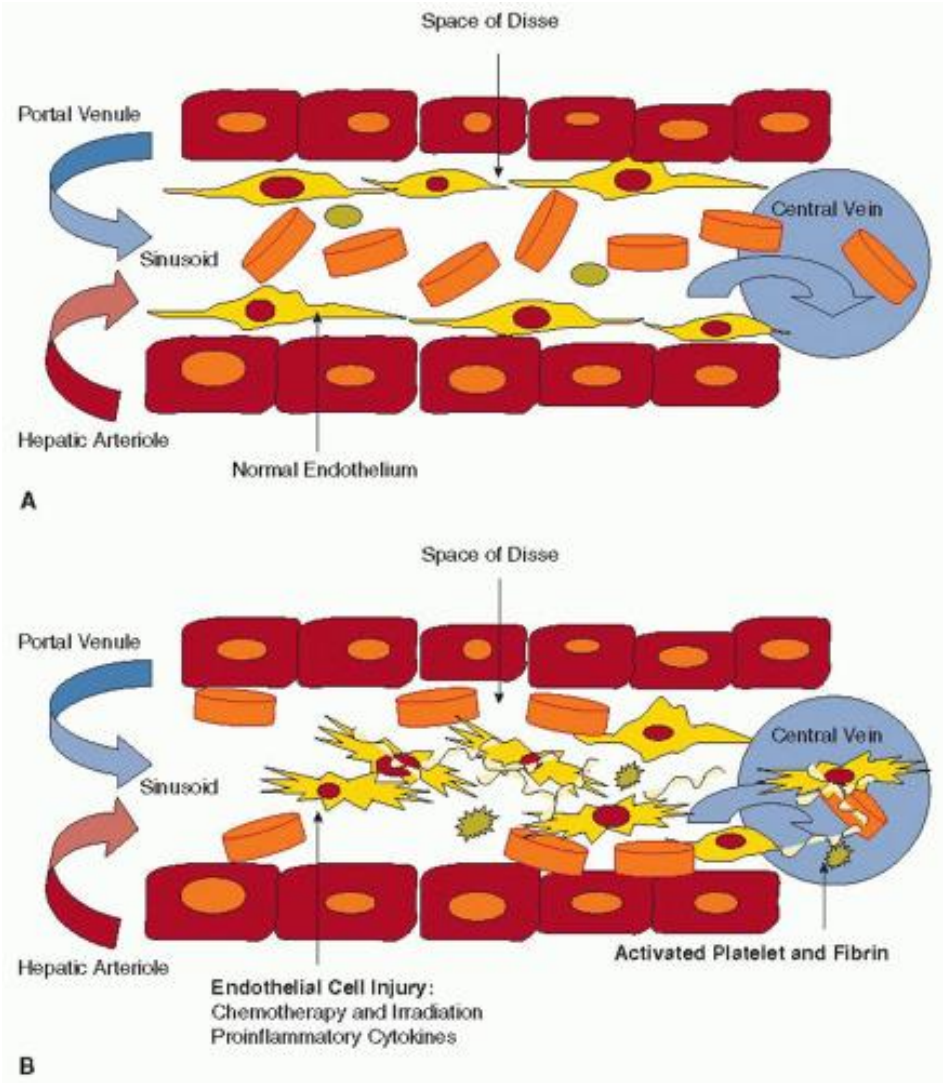


Defitelio® (defibrotide) by Jazz Pharmaceuticals

- Indication[1]: treatment of hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), with renal or pulmonary dysfunction after hematopoietic stem-cell transplantation (HSCT) in adults and pediatric patients

- **Veno-occlusive disease (VOD)/SOS[2]**
  - Occurs when damaged endothelial cells are torn away from the sinusoid leading to fibrin deposition and evenutally red blood cells entering the space are blocked in very small blood vessels within the liver
  - Incidence rate is estimated to be approximately 10–15% and occurs within 20–30 days of the transplant
  - Untreated hepatic VOD/SOS accompanied by multi-organ failure (MOF) is associated with >80% mortality

- Mechanism of action[2]
  - Oligonucleotide mixture with profibrinolytic properties
  - Promotes the breakdown of fibrin and protects endothelial cells from harmful effects of chemotherapy
  - Posseses anti-inflammatory, anti-ischemic, antithrombotic, and thrombolytic properties



1. Defitelio®[prescribing information]. Palo Alto, CA: Jazz Pharmaceuticals. March 2016
2. Stein C et a. *Mol Ther Nucleic Acids*. 2016 Aug; 5(8): e346. . 2016 Aug; 5(8): e346.

Defitelio® (defibrotide) by Jazz Pharmaceuticals

- Dose[1]
  - 6.25 mg/kg every 6 hours
  - Use weight prior to the preparative regimen for HSCT to calculate dose
- Administration[1]
  - Infuse over 2 hours using a 0.2 micron in-line filter
  - Administer for a minimum of 21 days and until the signs and symptoms of VOD have resolved or up to a maximum of 60 days
  - Must be used within 4 hours if stored at room temperature or within 24 hours if stored under refrigeration
- Safety
  - ADE's (incidence ≥10%): Hypotension, diarrhea, vomiting, nausea and epistaxis,
  - Serious ADRs: Hypotension (11%) and pulmonary alveolar hemorrhage (7%)
- Ordering[2]
  - Verify your institution has a contract with McKesson Plasma and Biologics before ordering
- Contraindications[1]
  - Antithrombotic agents

1.Defitelio®[prescribing information]. Palo Alto, CA: Jazz Pharmaceuticals. March 2016; 2. https://defitelio.com/

Defitelio® (defibrotide) by Jazz Pharmaceuticals

	Study Design	N	Dose & Administration	% Survived after 100 days of transplantation
Study 1	prospective study, patients had a diagnosis of VOD with an associated diagnosis of multi-organ dysfunction (pulmonary, renal, or both) by Day+28 post-HSCT	102	6.25 mg/kg every 6 hours for a minimum of 21 days until discharge from hospital	38% Day +100 survival after transplantation
Study 2	prospective study, diagnosis of hepatic VOD and multi-organ dysfunction following HSCT	75	6.25 mg/kg infused every 6 hours for a minimum of treatment duration of 14 days	44% Day +100 survival after transplantation
Study 3	expanded access program for defibrotide for the treatment of adult and pediatric patients who developed hepatic VOD after had received a HSCT and developed hepatic VOD with renal or pulmonary dysfunction.	351	6.25 mg/kg infused every 6 hours	45% Day +100 survival after transplantation

Epclusa® (sofosbuvir/velpatasvir) by Gilead Sciences

- First completely oral pan-genotypic single tablet regimen for the treatment hepatitis C virus (HCV) infection
- **Indication**
  - Treatment of adult patients with chronic HCV genotype 1, 2, 3, 4, 5, or 6 infection
  - Can be use in patients co-infected with HIV (expanded labeling August 2017)
- Potential to eliminate genotype testing
- Direct-acting antiviral agent
- **NS5B polymerase inhibitor (sofosbuvir) and NS5A inhibitor (velpatasvir)**
- **Dose/Administration**
  - Fixed-dose combination of sofosbuvir 400 mg/ velpatasvir 100 mg once daily for 12 weeks
  - Single tablet for patients without cirrhosis or with compensated cirrhosis
  - In combination with ribavirin for decompensated cirrhosis

Epclusa®[prescribing information]. Foster City, CA: Gilead Sciences. February 2017

Zepatier® (elbasvir/grazoprevir) by Merck Sharp & Dohme

- Indication
  - Treatment of hepatitis C genotypes 1 or 4 infection in adults with or without ribavirin
- Direct-acting antiviral agent
- Oral fixed-dose combination of a NS5A inhibitor (elbasvir) and a NS3/4A protease inhibitor (grazoprevir)
- Safety
  - Zepatier alone: fatigue, headache, nausea
  - Zepatier with ribavirin: anemia and headache
- Dosage
  - Elbasvir 50 mg /grazoprevir 100 mg once daily
  - Renal impairment
    - No dosage adjustments including dialysis
  - Hepatic Impairment
    - No adjustment in mild impairment
    - Contraindicated in moderate or severe impairment

Zepatier Dosage Regimens and Durations

Genotype	Patient Population	Therapy	Duration
1a	Treatment-naïve or PegIFN/RBV experienced* without baseline NS5A polymorphisms†	Zepatier alone	12 weeks
1a	Treatment-naïve or PegIFN/RBV-experienced* with baseline NS5A polymorphisms†	Zepatier plus ribavirin	16 weeks
1b	Treatment-naïve or PegIFN/RBV experienced*	Zepatier alone	12 weeks
1a or 1b	PegIFN/RBV/PI-experienced‡	Zepatier plus ribavirin	12 weeks
4	Treatment-naïve	Zepatier alone	12 weeks
4	PegIFN/RBV-experienced*	Zepatier plus ribavirin	16 weeks

*Peginterferon alfa (PegIFN) + ribavirin (RBV)
†Polymorphisms at amino acid positions 28, 30, 31, or 93.
‡Peginterferon alfa + ribavirin + HCV NS3/4A protease inhibitor.

Zepatier®[prescribing information]. Whitehouse, NJ: Merch Sh.arp & Dohme Corp. February 2017

Approval History of Direct-Acting Antiviral Agents for HCV

WARNING: Risk of hepatitis B reactivation in patients coinfected with HCV and HBV

Sovaldi®
(sofosbuvir)
Genotype: 1, 2, 3, 4
Approval: Dec 2013

Viekira Pak ®
Genotype: 1
Approval: Dec 2014

Daklinza®
(daclatasvir)
Genotype: 3
Approval: Jul 2015

Zepatier®
(elbasvirsvir/grazoprevir)
Genotype: 1, 4
Approval: Jan 2016

2013 2014 2015 2016

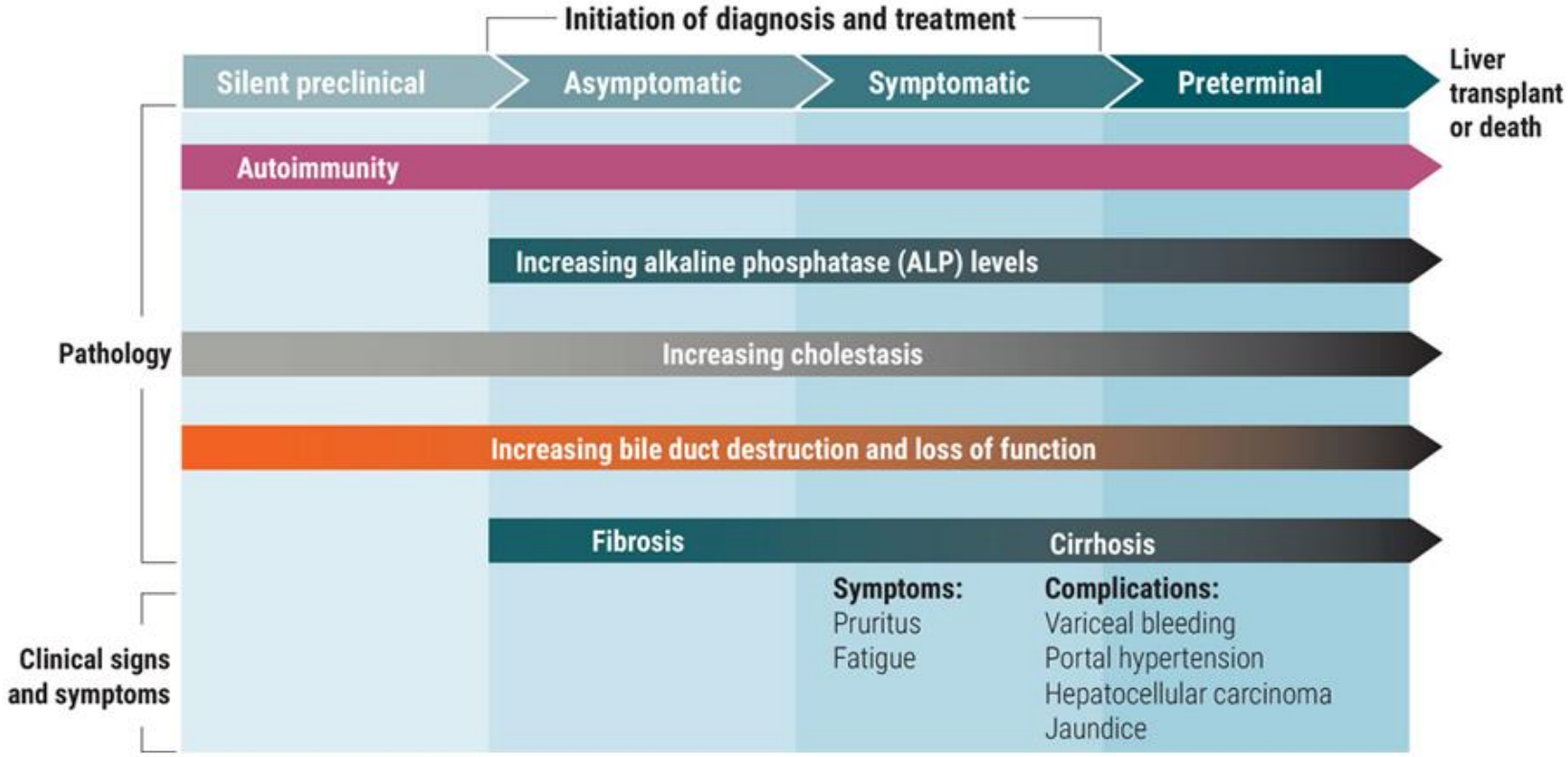
Olysio®
(simeprevir)
Genotype 1
Approval: Nov 2014

Harvoni®
(ledipasvir/sofosbuvir)
Genotype: 1, 4, 5, 6
Approval: Nov 2015

Eplcusa®
(sofosbuvir /velpatasvir)
Genotype: 1, 2, 3, 4, 5, or 6
Approval: June 2016

Ocaliva® (obeticholic acid) by Intercept Pharmaceuticals

- Indication
  - For the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in patients with poor response to UDCA for at least one year, or as monotherapy in adults unable to tolerate UDCA in adult patients
- Primary biliary cholangitis (PBC)
  - Rare autoimmune destruction of the bile ducts responsible for transporting bile acids (BAs) out of the liver resulting in cholestasis



Source: https://interceptpharma.com/research-development/therapeutic-areas/primary-biliary-cirrhosis/

Ocaliva® (obeticholic acid) by Intercept Pharmaceuticals

- Mechanism of Action
  - A farnesoid X receptor agonist that reduces ALP levels
- Approval/Efficacy
  - Granted accelerated approval based on reduction in ALP
  - No studies demonstrating improvement in survival or symptoms associated with PBC
- Dose
  - Starting dosage: 5 mg orally once daily
  - Dosage titration: increase dose to a maximum dose of 10 mg daily if there is insufficient reduction in ALP and/or total bilirubin levels after 3 months
- Side Effects
  - Pruritus, fatigue, abdominal pain and discomfort, rash, oropharyngeal pain, dizziness, constipation, arthralgia, thyroid function abnormality, and eczema

Dosage Adjustments	
Intolerable pruritus	• Add an antihistamine or bile acid binding resin
	• Reduce dosage to 5 mg every other day or 5 mg daily if patient is on 10 mg dose
	• Temporarily interrupt therapy for up to 2 weeks and reinitiate at a reduced dosage
Hepatic impairment (moderate and severe)	• 5 mg once weekly
	• Increase dosage to 5 mg twice weekly (minimum of 3 days apart) and then increase to 10 mg twice weekly (minimum of 3 days apart) based on response and tolerability

Ocaliva®[prescribing information]. New York, NY: Intercept Pharmaceuticals. May 2016

Oncology

- Lartruvo™ (olaratumab)
- Rubraca® (rucaparib camsylate)
- Tecentriq® (atezolizumab)
- Venclexta™ (venetoclax)

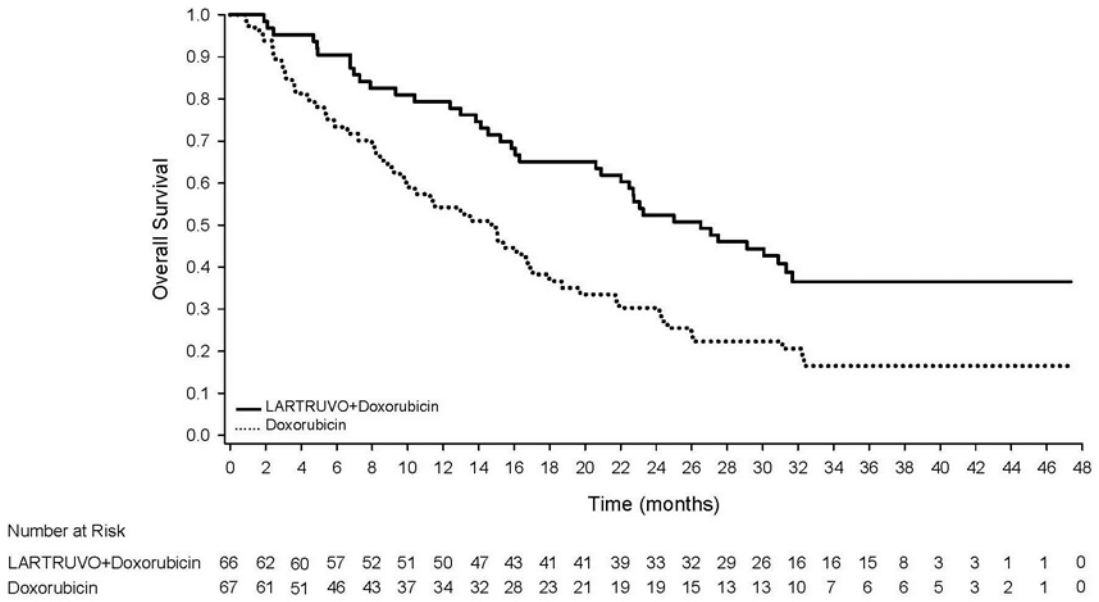
Lartruvo™ (olaratumab) by Eli Lilly and Co

- Indication: Soft tissue sarcoma
  - Platelet-derived growth factor receptor alpha (PDGFR-a) blocking antibody
  - Orphan, breakthrough drug – fast-track, accelerated approval
    - First new drug approved for STS in 40 years
    - First-line therapy (in combination with doxorubicin) for patients who have inoperable disease
- Dose: 15mg/kg IV infusion over 60 minutes on days 1 and 8 of 21-day cycles
  - Continue until disease progression or unacceptable toxicity
  - Premedicate with diphenhydramine and dexamethasone IV with first dose
- Adverse reactions
  - Most common: nausea (73%), fatigue (69%), musculoskeletal pain (64%), mucositis (53%), alopecia (52%), vomiting (45%), diarrhea (34%), etc.
  - Lab abnormalities: hyperglycemia (52%), increased PTT (33%), hypokalemia (21%), hypophosphatemia (21%), hypomagnesemia (16%)
  - 14% incidence of Infusion-related reactions
  - Most common reason for permanent d/c was infusion related reactions
  - Dose delays most often due to neutropenia, thrombocytopenia, anemia

Lartruvo® [prescribing information]. Indianapolis, IN: Eli Lilly and Company. February 2017.

Lartruvo™ (olaratumab) by Eli Lilly and Co

Phase 2 study: olaratumab + doxorubicin vs doxorubicin in 133 patients with metastatic or unresectable soft-tissue sarcoma



	Ola + Dox (N=66)	Dox (N=67)
Deaths	39	52
Med. Survival, months	26.5 (P=0.0003)	14.7
Med, Progression-free survival, months	6.6 (p=0.0615)	4.1

Lancet. 2016; 388(10043):488-497

Rubraca® (rucaparib camsylate) by Clovis Oncology

- Indication: Ovarian cancer with BRCA mutation
  - PARP (poly ADP-ribose polymerase) inhibitor
  - Orphan, breakthrough drug
  - Monotherapy for advanced disease previously treated with ≥ 2 chemo agents
- Dose: 600 mg orally twice daily
  - Dose reductions for adverse reactions to 300 mg twice daily
  - Continue until disease progression or unacceptable toxicity
- Adverse reactions
  - Most common: nausea (77%), fatigue (77%), vomiting (46%), anemia (44%), constipation (40%), dysgeusia (39%), diarrhea (34%), etc.
  - Lab abnormalities: increased creatinine (92%), increased ALT and AST (73%), anemia (67%), lymphopenia (45%), thrombocytopenia (39%) neutropenia (35%)
  - 0.5% incidence of Myelodysplastic sydrome/Acute Myeloid Leukemia
  - Median duration of treatment 5.5 months; 10% of d/c due to ADEs (fatigue/asthenia)

Rubraca® [prescribing information]. Boulder, CO: Clovis Oncology. December 2016.

Rubraca® (rucaparib camsylate) by Clovis Oncology

- Accelerated approval based on MC, single-arm, open-label trial

	Investigator assessed N=106
Objective Response Rate (95% CI)	54% (44,64)
Complete Response	9%
Partial Response	45%
Median Duration of Response (95% CI)	9.2 (6.6,11.6) months

- PARP inhibitors:
  - MOA: interrupt DNA repair and lead to apoptosis and cell death
  - Olaparib (Lynparza®) approved 12/19/14 for treatment of BRCA+ advanced ovarian cancer
  - Niraparib (Jejula®) approved 3/28/17 for maintenance treatment of ovarian, fallopian tube, or primary peritoneal cancer
  - Talazoparib approval expected in 2017
  - Veliparib approval expected in 2018

http://oncpracticemanagement.com/issue-archive/2017/january-2017-vol-7-no-1/plethora-of-targeted-agents-in-the-oncology-pipeline/

Tecentriq® (atezolizumab) by Genentech

- Programmed death-ligand 1 (PD-L1) blocking monoclonal antibody
- Indications: 2nd line agent after disease progression (salvage therapy) with platinum containing chemotherapy regimens
  - **Advanced/metastatic urothelial carcinoma (including bladder)**
  - **Metastatic non-small cell lung cancer (NSCLC**): also failed EGFR or ALK directed therapies if patient has these mutations
- Dose: 1200 mg by IV infusion over 60 minutes every 3 weeks
  - Continue until disease progression or unacceptable toxicity
- Adverse reactions
  - Most common: fatigue, decreased appetite, nausea, constipation, pyrexia
  - Infusion reactions in <2% of patients
  - Grades 3-4 lymphopenia (10%), hyponatremia (10%), anemia (8%), hyperglycemia (5%)
- Monitor patient for severe immune-related adverse reactions
  - Pneumonitis, hepatitis, colitis, endocrinopathies, myasthenia gravis, pancreatitis, infections, etc.

Tecentriq® [prescribing information]. South San Francisco, CA: Genentech, Inc. October 2016.

Venclexta™ (venetoclax) by Genentech

- BCL-2 inhibitor – first in class, breakthrough drug
  - BCL-2 is a pro-survival protein; venetoclax restores cell's apoptotic ability
- Indication: Chronic lymphocytic leukemia with 17p deletion
  - 2nd line agent for this orphan indication
  - 3-10% of CLL patients with 17p deletion at diagnosis
  - 30-50% of CLL relapsed or refractory patients have 17p deletion
- Dose:
  - Initial regimen: 20 mg PO once daily for 7 days
  - Ramp-up dosing phase over 5 weeks to 400 mg PO daily
  - Modify dose for Grade 3 or 4 ADEs, CYP3A or P-gp inhibitors; contraindicated with strong CYP3A inhibitors at initiation or during ramp-up
- Adverse reactions
  - Most common (>20%): neutropenia, diarrhea, nausea, anemia, upper respiratory track infection, thrombocytopenia, fatigue
  - 44% with serious ADES: pneumonia, febrile neutropenia, pyrexia, autoimmune hemolytic anemia, anemia and tumor

Venclexta® [prescribing information]. South San Francisco, CA: Genentech, Inc. April 2016.

Venclexta™ (venetoclax) by Genentech

- Tumor Lysis Syndrome (TLS)
  - Metabolic complications resulting from rapid tumor reduction
  - Risk factors: high tumor burden, renal impairment (<80 mL/min)
  - Occurs 6-8 hrs after first dose and increased doses
  - Sxs: nausea, vomiting, diarrhea, weakness, fatigue, electrolyte disturbances (increased potassium, phosphate, uric acid; decreased calcium)
  - Reduce incidence:
    - Administer prophylactic hydration and anti-hyperuricemic agents
    - Weekly dosing ramp-up to reduce the incidence of TLS
- Efficacy based on open-label, single-arm, multicenter trial (N=106)
  - Patient received median of 2.5 prior therapies
  - Objective response rate 80% (95% CI 71.3, 87.3)
  - Complete remission 6%
  - Partial remission 70%
  - Duration of response ranged 2.9 to 19+ months

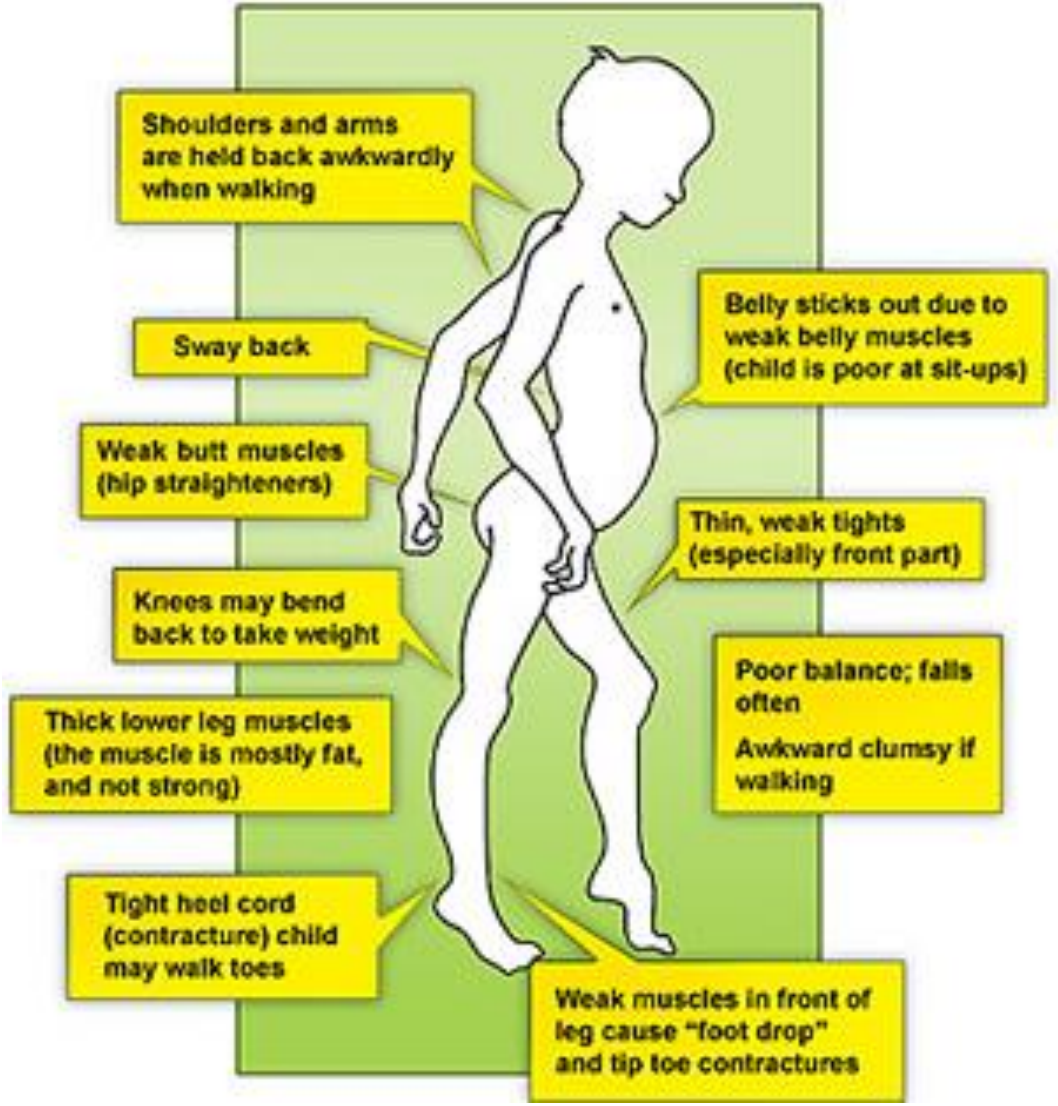
Neuromuscular Disorders

- Exondys 51™ (eteplirsen)
- Spinraza™ (nusinersen sodium)
- Zinbryta® (daclizumab)*

*This agent will not be discussed; however slides will be provided.

Exondys 51™ (eteplirsen) by Sarepta Therapeutics

- Duchenne Muscular Dystrophy
  - Recessive X-linked genetic disorder that effects predominantly males at very young age
  - Characterized by extreme muscle fatigue and rapid muscle degeneration due to lack of dystrophin in the body
  - Dystrophin is the necessary protein that keeps the muscles the body intact.
  - Symptoms generally present during preschool years and become progressively severe
    - As patients reach adulthood the disease has already affected heart and respiratory muscles



Exondys 51™ (eteplirsen) by Sarepta Therapeutics

- First and only treatment for Duchenne muscular dystrophy (DMD)
  - Approved under accelerated approval and heavily contested
    - FDA stated “A clinical benefit of Exondys 51, including improved motor function, has not been established”
    - Continued approval for this indication may be contingent upon verification of a clinical benefit in future trials
    - Significant support and public pressure (i.e. CureDuchenne)
    - Approval based on a surrogate marker of increase in dystrophin in skeletal muscle exhibited by some patients who were treated
- Indication
  - Treatment of DMD in patients with a confirmed mutation of the DMD gene that is to exon 51 skipping
  - Mechanism of Action
    - designed to bind to exon 51 of dystrophin pre-mRNA that causes exclusion of this exon during production of a truncated dystrophin protein

Exondys 51[prescribing information]. Cambridge, MA: Sarepta Therapeutics, Inc., September 2016

Exondys 51™ (eteplirsen) by Sarepta Therapeutics

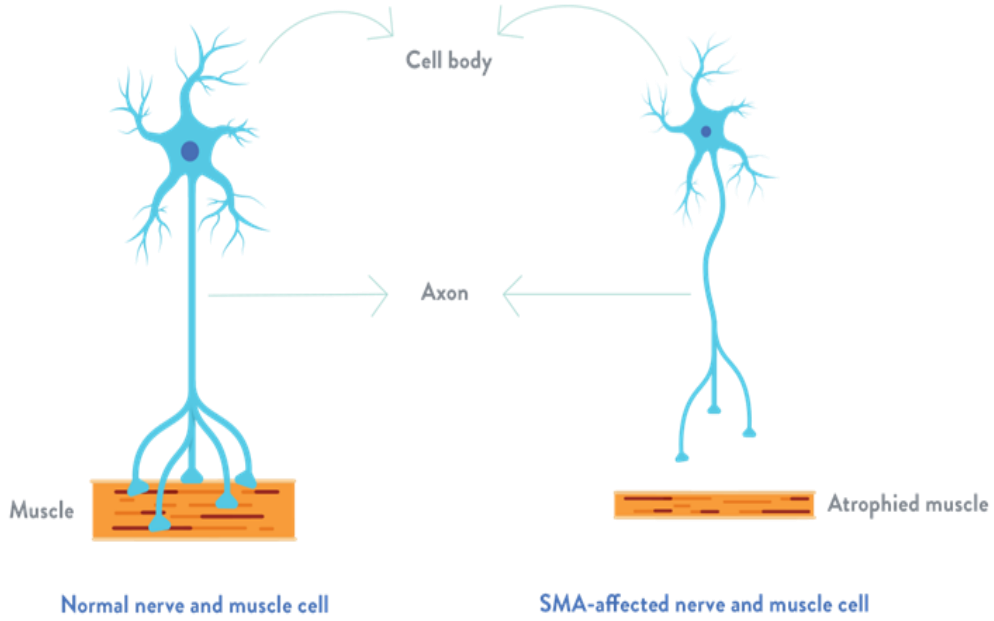
- Dosing and Administration
  - 30 mg/kg administered once weekly as a 35 to 60 minute intravenous infusion
  - Application of a topical anesthetic cream to the infusion site prior to administration may be considered
- Cost: $300,000 per patient per year
- Clinical trials
  - 48 week trials evaluating pre- and post-treatment percentage of normal dystrophin levels

	Study Endpoints	Study Conclusion
Study 1	Dystrophin production and the 6-minute walk test (6MWT)	No significant difference in change in 6MWD between treated and placebo patients
Study 2	6MWT	No evidence of a clinical benefit
Study 3	Dystrophin levels in muscle tissue	Dystrophin levels increased 0.28% from baseline (pre-treatment 0.16% vs. post-treatment 0.44%; p=0.008)

Exondys 51®[prescribing information]. Cambridge, MA: Sarepta Therapeutics, Inc., September 2016

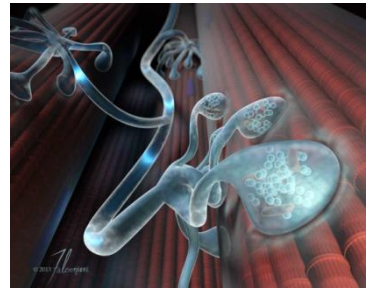
Spinraza™ (nusinersen) by Biogen Inc.

- Indication
  - First marketed treatment for spinal muscular atrophy (SMA) in pediatric and adult patients
- SMA
  - An autosomal recessive genetic disorder caused by a mutation in the survival motor neuron (SMN) gene 1
  - Normally the SMN1 gene produces a SMN protein in the spinal cord responsible for functioning nerves that control muscles
  - SMA patients produce minimal amounts of SMN protein causing improper nerve cell function and eventually muscle atrophy
  - Symptoms include difficulty breathing, swallowing that eventually leads to debilitating and oftentimes fatal muscle weakness



Spinraza™ [package insert]. Cambridge, MA. Biogen Inc., December 2016.
Image source: https://www.togetherinsma.com/en_us/home/introduction-to-sma/smn1-gene.html

Spinraza™ (nusinersen) by Biogen Inc



- Mechanism of Action [1]
  - Antisense oligonuceotide that modifies splicing of the SMN2 gene to a functional SMN1 gene
- Dosing[1]
  - 12 mg (5 mL) per administration
  - Initiate treatment with 4 loading doses
    - first three loading doses should be administered at 14-day intervals; the 4th loading dose should be administered 30 days after the 3rd dose
  - Maintenance doses should be administered once every 4 months thereafter
- Administration[1]
  - Administer as intrathecal bolus injection over 1 to 3 minutes
  - Must be administer within 4 hours of removal from vial
- Safety[1]
  - Common ADRs included upper and lower respiratory infection and constipation.
  - Warnings and precautions: coagulation abnormalities, low blood platelet and renal toxicity
- Clinical Studies[1]
  - 21 (40%) patients in the nusinersen-treated group (n=52) achieved improved motor milestones compared to 0 (0%) in the placebo-control group (n=30) ($p<0.0001$)
- Cost[2]
  - First year: $125,000 per injection x 6 injections = $750,000
  - $375,000 each subsequent year for the rest of the patient's life

1. Spinraza™ [package insert]. Cambridge, MA. Biogen Inc.,December 2016.
2. http://www.fiercepharma.com/pharma/biogen-s-375k-spinraza-price-puts-a-sovaldi-style-spotlight-rare-disease-meds

Dermatology

- Eucrisa™ (crisaborole)
- Taltz® (ixekizumab)

Infectious Diseases

- Anthim® (obiltoxaximab)
- Zinplava™ (bezlotoxumab)

Eucrisa™ (crisaborole) by Anacor

- Indication: Atopic Dermatitis (mild/moderate)
  - Phosphodiesterase-4 inhibitor
    - Increases intracellular cyclic adenosine monophosphate levels
  - Topical treatment: 2% ointment applied twice daily
    - Adults and children > 2 years old
- 4% of patients with burning or stinging at application site
- PK:
  - Absorption does occur – no drug interactions documented
  - Rapid systemic metabolism via hydrolysis; renal excretion of metabolites
- Studies
  - Two MC/R/DB/PG, vehicle-controlled trials – 1522 patients (2-79 yrs) with 5-95% treatable BSA

Table 2: Primary Efficacy Outcomes in Subjects with Mild to Moderate Atopic Dermatitis at Day 29

	Trial 1		Trial 2	
	EUCRISA (N=503)	Vehicle (N=256)	EUCRISA (N=513)	Vehicle (N=250)
Success in ISGA[a]	32.8%	25.4%	31.4%	18.0%

[a] Defined as an ISGA score of Clear (0) or Almost Clear (1) with a 2-grade or greater improvement from baseline.

Eucrisa® [prescribing information]. Palo Alto, CA: Anacor Pharmaceuticals. December 2016.

Taltz® (ixekizumab) by Eli Lilly and Co

- Indication: Plaque Psoriasis (moderate/severe)
  - Humanized interleukin-17A antagonist
  - Subcutaneous injection for adults only
    - 160 mg, then 80 mg at weeks 2, 4, 6, 8, 10 &12, then 80 mg every 4 weeks
    - 80 mg prefilled single-dose auto-injector or syringe
- Adverse reactions
  - Injection site reactions: 17% ixekizumab vs 3% with placebo
  - Neutropenia: 11% ixekizumab vs 3% with placebo; primarily in first 12 weeks
  - Serious adverse events: 2% ixekizumab vs 0.7% with etanercept
  - 22% developed antibodies to ixekizumab; 2% with neutralizing antibodies
- Pharmacokinetics
  - Peak serum level at 4 days
  - 60-81% bioavailability
  - 13 days t ½

Taltz® [prescribing information]. Indianapolis, IN: Eli Lilly and Company. January 2017.

Taltz® (ixekizumab) by Eli Lilly and Co

- Treatment of Plaque Psoriasis
  - Most common immune disease in U.S. @ 2-3% of population
  - Treatment based on severity, cost/convenience of products, efficacy, etc.
    - Topical treatment – with/without steroids
    - Phototherapy – UV light exposure
    - Systemic therapy for moderate/severe disease (PASI ≥12; sPGA ≥3)
      - Oral medications: oral retinoids, cyclosporine, methotrexate
      - Injectable biologic medications blocking actions of inflammatory cytokines: TNF-alpha (certolizumab, etanercept, etc); IL 12&23 (ustekinumab); IL 17-A (secukinumab, **ixekizumab**)
- UNCOVER 1, 2 and 3 P/DB/MC Phase-3 Trials (3736 total patients)
  - Initial mean PASI scores 24-28; sPGA scores ≥ 4 in 46-52% of patients
    - UNCOVER-1: 34-37% had PASI 100% improvement or sPGA 0 scores at week 12
    - UNCOVER-2 and 3: 87-90% PASI ≥75% improvement; 83% with sGPA 0/1 vs 36% with etanercept
    - UNCOVER-3: response maintained through week 60

PASI = Psoriasis area and severity index; sPGA = Static physician global assessment

Lancet. 2015; 386(9993):541-551; NEJM 2016;375(4):345-356

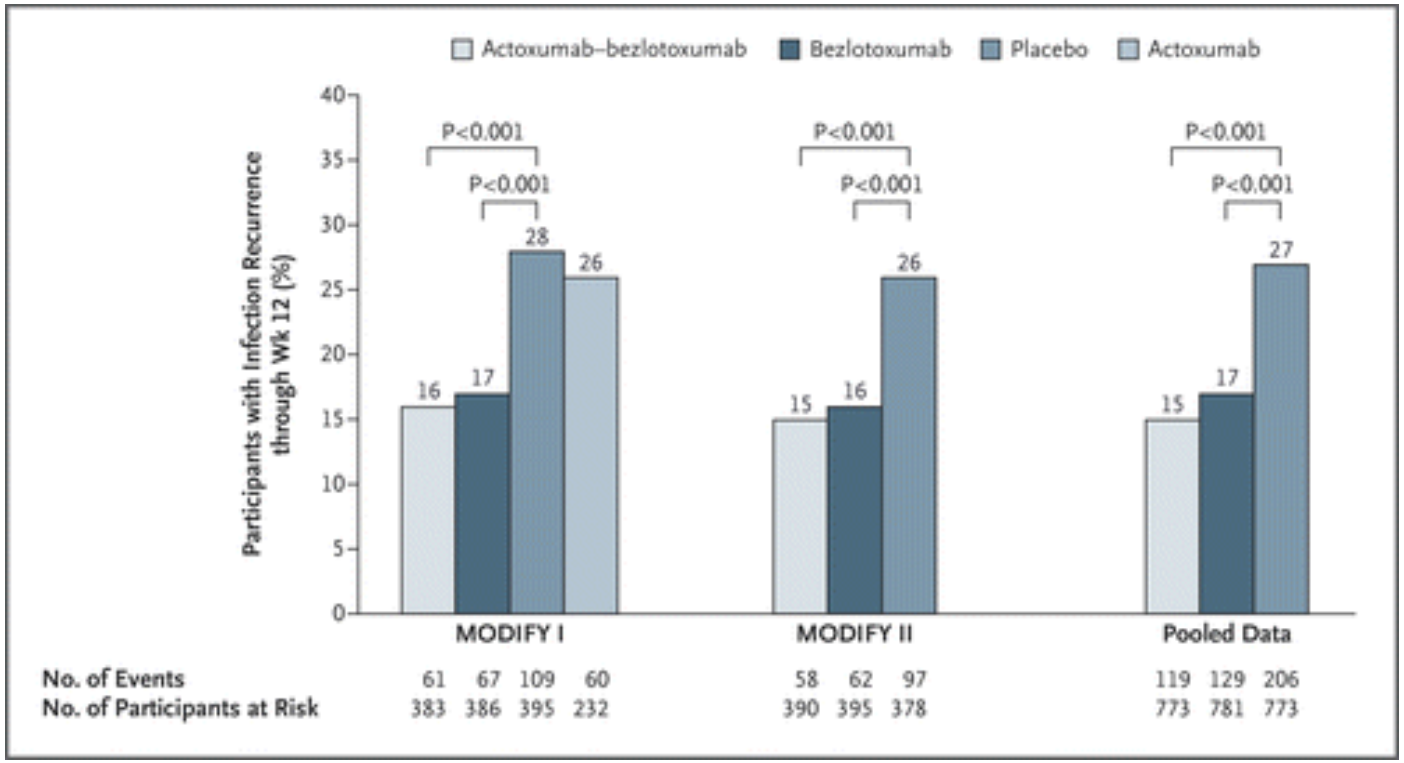
Zinplava™ (bezlotoxumab) by Merck

- Indication: *C. difficile* infection (CDI) – to reduce recurrence
  - Monoclonal antibody that neutralizes *C.difficile* toxin B
  - 10mg/kg IV infusion over 60 minutes – single dose
  - For adults on standard of care (SoC) antibiotics for *C.difficile* infection and at high risk for recurrence Of CDI
    - Age ≥ 65 years
    - ≥ 1 episodes of CDI prior to treatment episode
    - CDI in the past 6 months
    - Immunocompromised
    - Clinically severe CDI
- Adverse reactions
  - 10% have infusion-related reactions vs 8% with placebo
    - Nausea (7%), pyrexia (5%), headache (4%)
  - Serious adverse events: 2.3% with heart failure within 12 weeks of infusion
  - No patients with neutralizing antibodies in phase-3 trials
- Half-life 19 days

Zinplava® [prescribing information]. Whitehouse Station, NJ: Merck & Co, Inc. October 2016.

Zinplava™ (bezlotoxumab) by Merck

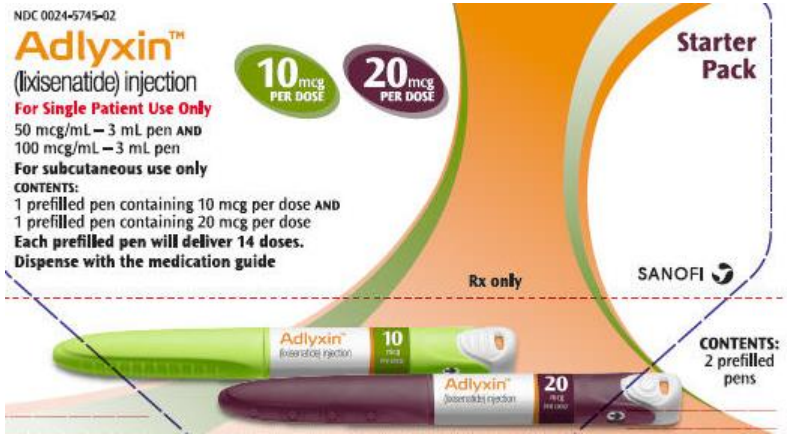
- Modify 1 and 2 trials - DB/R/PC Phase 3 studies in 30 countries
  - 2655 adults with primary or recurrent CDI on SoC antibiotics
  - Actoxumab (monoclonal antibody to neutralize CDI toxin A) included in Modify 1 trial
  - 12 week follow-up



NEJM. 2017 376(4):305-317

Metabolic Disorders

- Adlyxin® (lixisenatide)*



Neuropsychiatric Diseases

- Briviact® (brivaracetam)*
- Nuplazid® (pimavanserin)

Ophthalmology

- Xiidra® (lifitigrast)

*This agent will not be discussed; however slides will be provided.

Nuplazid® (pimavanserin) by Shire

- Indication[1]
  - First drug approved to treat hallucinations and delusions associated with psychosis in Parkinson's disease
  - Approval granted breakthrough therapy designation
  - Atypical antipsychotic that acts as an agonist and antagonist at serotonin 5-HT_{2A} receptors and to a lesser degree serotonin 5-HT_{2C} receptors
- **Parkinson's disease psychosis**[2]
  - Occurs in ≥50% of people with Parkinson's disease
  - Etiology
    - Natural progression of Parkinson's disease as a result of the pathological changes within the brain
    - Side effects associated with dopaminergic replacement therapies
- Dose[1]
  - 34 mg per day orally (two 17 mg tablets once daily); requires no titration
  - Not recommended in patients with severe renal impairment and hepatic impairment

- Safety[1]
  - Common side effects included: peripheral edema and state of confusion
  - Concentration-dependent QTc interval prolongation was observed in the therapeutic range but no reports of torsade de pointes
  - Boxed warning: increased mortality in elderly patients with dementia-related psychosis
- Clinical trial[1]: Pimavanserin demonstrated a statistically significantly decrease in the frequency and/or severity of hallucinations and delusions compared to placebo from baseline [-3.06 (-4.91, -1.20)]

1. Nuplazid®[prescribing information]. Lexington, MA: Shire US Inc., April 2016
2. https://www.nuplazid.com/hallucinations-delusion/

Xiidra® (lifitegrast 5% ophthalmic solution) by Shire Inc

- First in class[1]
  - lymphocyte function-associated antigen-1 (LFA-1) antagonist
- Mechanisms of Action[1]
  - Inhibits T cell-mediated inflammation by blocking the binding of two cell surface proteins LFA-1 and intercellular adhesion molecule resulting in less inflammation
- Indication[1]
  - Treatment of the signs and symptoms of dry eye disease
- Dosage/Administration[1]
  - Instill one drop twice a day into each eye approximately 12 hours apart

1. Xiidra®[prescribing information]. Lexington, MA: Shire US Inc., July 2016; 2. Source: http://www.toyosclinic.com/eye-news/restasis-vs-xiidra-3-big-differences; 3. www.goodrx.com; 4. Restasis®[prescribing informationIrvine, CA: Allergan, June 2013

Xiidra® (lifitegrast 5% ophthalmic solution) by Shire Inc

Dry Eye Treatment Market[2]		
	Xiidra (lifitegrast ophthalmic solution)[1]	Restasis (cyclosporine ophthalmic emulsion)[4]
Indication	Treatment of the signs and symptoms of dry eye disease	Increases tear production
Dosage	One drop in each eye 12 hours apart	One drop in each eye 12 hours apart
Efficacy	• All studies placebo controlled • Improvement noted as early as 2 weeks of therapy <u>Effect on symptoms of dry eye disease</u> • Larger reduction in eye dryness score in all studies at day 42 and 84 <u>Effect on signs of dry eye disease</u> • Larger reduction in ICSS with Xiidra in three of the four studies at day 84	<u>Significant increase in Schirmer wetting of 10 mm</u> • 15% in Restasis group versus 5% placebo • 6 months before improvements are observed
Side effects	• Instillation site irritation • Dysgeusia • Decreased visual acuity	• Most common: ocular burning (17%) • Other side effects (1-5%): Eye redness, discharge, watery eyes, eye pain, foreign body sensation, itching, stinging, and blurred vision
Launch date	2016	2003
Price	$444[3]	$483[3]
Spokesperson	Jennifer Aniston	Marissa Tomei

Respiratory Disorders

- Cinqair® (reslizumab)

Radiopharmaceuticals

- Axumin™ (fluciclovine F18)
- NETSPOT™ (gallium Ga 68 dotatate)

Cinqair® (reslizumab) by Teva

- Indication
  - Interleukin-5 (IL-5) antagonist monoclonal antibody
  - Add-on maintenance treatment of severe asthma in adults (≥18 years) with eosinophilic phenotype
  - Not for acute asthma exacerbations
- Dose
  - 3 mg/kg IV infusion over 20-50 minutes every 4 weeks
  - Available as 100mg/10mL single use vials
- Adverse reactions
  - Oropharyngeal pain (2.6%), elevated CPK (14%), myalgia (1%), musculoskeletal ADEs (2.2%)
  - Severe ADEs:
    - Anaphylaxis (0.3%) within 20 minutes after infusion of dose – administration by healthcare professional
    - Malignancies (0.6%) – diverse types
  - Neutralizing antibodies in 4.8% of patients over 36 months

Cinqair® [prescribing information]. Frazer, PA: Teva Respiratory, LLC. May 2016.

Cinqair® (reslizumab) by Teva

- Four Phase 3 studies included in FDA evaluation
  - 16 week and 52 week studies compared reslizumab 3.0 mg/kg q 4 weeks vs placebo
  - Patients with serum eosinophil level of ≥ 400/mcL (studies 1, 2 & 3) + at least one asthma exacerbation in past 12 months requiring systemic corticosteroids
  - Asthma exacerbations – primary efficacy outcome of Studies 1 and 2

    Statistically signif decrease in all exacerbations, exacerbations requiring systemic CS use, exacerbations resulting hospitalization and/or ED visit
  - Lung function – all studies and primary efficacy endpoint in Studies 3 and 4

Study	FEV_1 change in mL (95% CI)
Study 1	137 (76, 198)
Study 2	93 (30, 155)
Study 3	160 (60, 259)
Study 4 (patients not selected for eos ≥ 400/ mcL)	76 (-6, 158)

Cinqair® [prescribing information]. Frazer, PA: Teva Respiratory, LLC. May 2016.

Question 1

Spinraza (nusinersen) is the first marketed treatment for spinal muscular atrophy (SMA) in pediatric and adult patients who are deficient in this protein.

A. What is a survival motor neuron protein?
B. What is dystrophin?
C. What is an exon?
D. What is spinal musulary atrophy protein?

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Question 2

First approved agent to treat hallucinations and delusions associated with psychosis in Parkinson's disease.

A. What is Exondys 51 (eteplirsen)?
B. What is Nuplazid® (pimavanserin)?
C. What is Spinraza (nusinersen)?
D. What is Ocaliva (obeticholic acid)?

acurity

Question 3

A single dose of this drug is given to prevent recurrent *C. difficile* infection

A. What is venetoclax?
B. What is olaratumab?
C. What is belzotoxumab?
D. What is atezolizumab?

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Question 4

Orphan drugs are medications for diseases affecting this number of people in the U.S.

A. What is less than 200,000 people?
B. What is more than 200,000 people?
C. What is less than 200 people?
D. What is less than 2 million people?

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FORMULARY JEOPARDY: WHERE DO NOVEL DRUGS OF 2016 FIT IN?

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Zinbryta® (daclizumab) by AbbVie Inc.

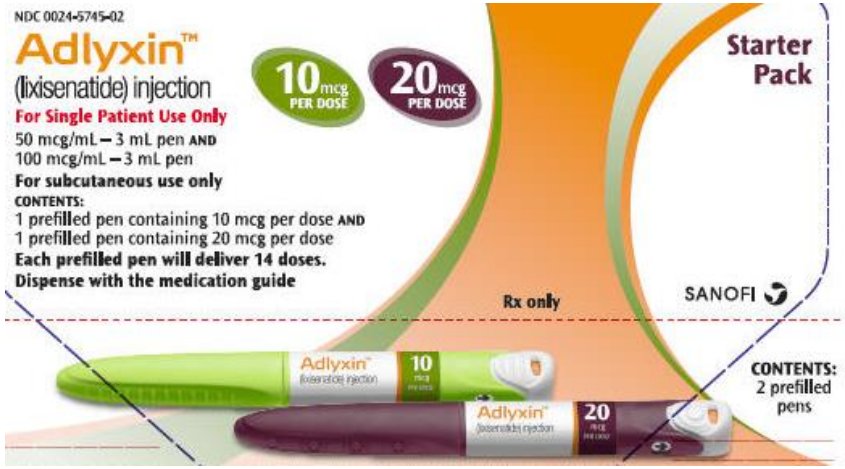
- Novel mechanism of action for relapsing multiple sclerosis (MS)
  - Humanized monoclonal antibody that selectively binds to the CD25 subunit of the interleukin-2 receptor
- Indication
  - Treatment of adult patients with relapsing forms of MS
  - Recommended to be reserved for patients who have had a poor response to two or more drugs for the treatment of MS due to safety profile
- Dosage/Administration
  - 150 mg self-administered subcutaneous injection once monthly
- Safety: Zinbryta Risk Evaluation and Mitigation Strategy (REMS) Program
  - Prescriber must be certified
  - Patients must enroll in the program and comply with ongoing monitoring requirements
  - Pharmacies must be certified and must only dispense to authorized patients
- Warnings/Precautions/Contraindications
  - Boxed warning for liver injury including autoimmune hepatitis and other immune-related conditions
  - Contraindicated in pre-existing liver impairment and history of autoimmune conditions of the liver
  - Live vaccines are not recommended during therapy and up to 4 months after discontinuation

Clinical Trials			
Primary Endpoints	**Zinbryta 150 mg SQ every 4 weeks**	**Avonex 30 mcg IM once weekly**	**p value**
Annualized relapse rate	0.216 45% (relative reduction)	0.393	<0.0001
Proportion of patients relapse free	67%	51%	<0.0001
MRI Results: mean number of new or newly enlarged lesions	4.31 54% (relative reduction)	9.44	<0.0001

Zinbryta®[prescribing information]. North Chicago, IL: AbbVie Inc., May 2016

Adlyxin® (lixisenatide) by Sanofi

- Glucagon-like peptide-1 (GLP-1) receptor agonist
  - Increases glucose-dependent insulin release, reduces glucagon secretion, and slows gastric emptying
- Indication
  - Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
- Dosage
  - Once daily injection administered within one hour prior to the first meal of the day
  - 10 mcg for first 14 days (starter pack) then increase to 20 mcg on day 15 (maintenance pack)
- Limitations of Use
  - Has not been studied in patients with chronic pancreatitis or a history of unexplained pancreatitis
- Efficacy and safety
  - Approval based on FDA review of:
    - GetGoal clinical program evaluated efficacy and tolerability
    - ELIXA trial – cardiovascular safety demonstrated in patients with high cardiovascular risk



Adlyxin®[prescribing information]. Bridgewater, NJ: Sanofi, July 2016

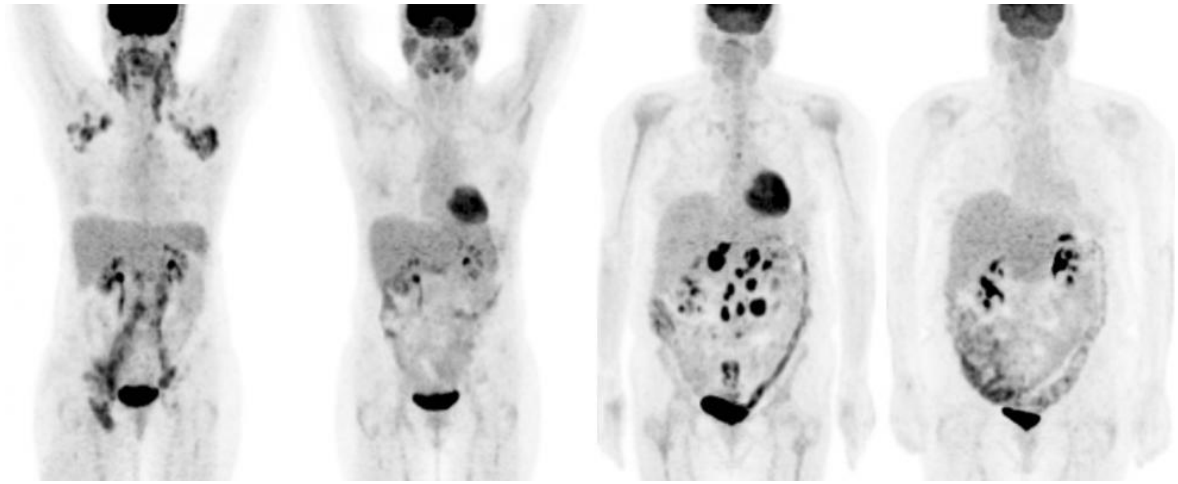
Briviact® (brivaracetam) by UCB Inc.

- Indication
  - Adjunct therapy in the management of partial-onset seizures in patients 16 years of age and older with epilepsy
  - Analog of levetiracetam with greater affinity towards the synaptic vesicle protein 2A in the brain
- Dose
  - Initial dosage is 50 mg twice daily
  - Maintenance doses may be adjusted based on patient's tolerability and therapeutic response
    - Adjust down to 25 mg twice daily (50 mg per day) or up to a maximum dosage of 100 mg twice daily (200 mg per day)
- Safety
  - Common side effects: drowsiness, dizziness, fatigue, nausea and vomiting
  - Brivaracetam is listed as a Schedule V controlled substance
- Advantages
  - No need for titration at onset of treatment
  - Several dosage forms: tablets (should not be chewed or crushed), oral solution, and injection

Briviact®[prescribing information]. Smyrna, GA: UCB Inc., March 2016

New Radiopharmaceuticals

- Axumin™ (fluciclovine F18)
  - **Indication:** Used with PET imaging in men with suspected prostrate CA recurrence and elevated PSA levels after treatment (positive scans increase as PSA levels increase)
  - **Dose:** 370 MBq (10 mCi) as bolus IV; scan 3-5 min after admin
  - **ADEs:** pain at injection site, erythema, dysgeusia
  - Fluciclovine F 18 is transported across cells by LAT-1 and ASCT2 which are more abundant in prostate cancer cells



Axumin® [prescribing information]. Oxford, UK: Blue Earth Diagnostics Ltd. May 2016.

New Radiopharmaceuticals

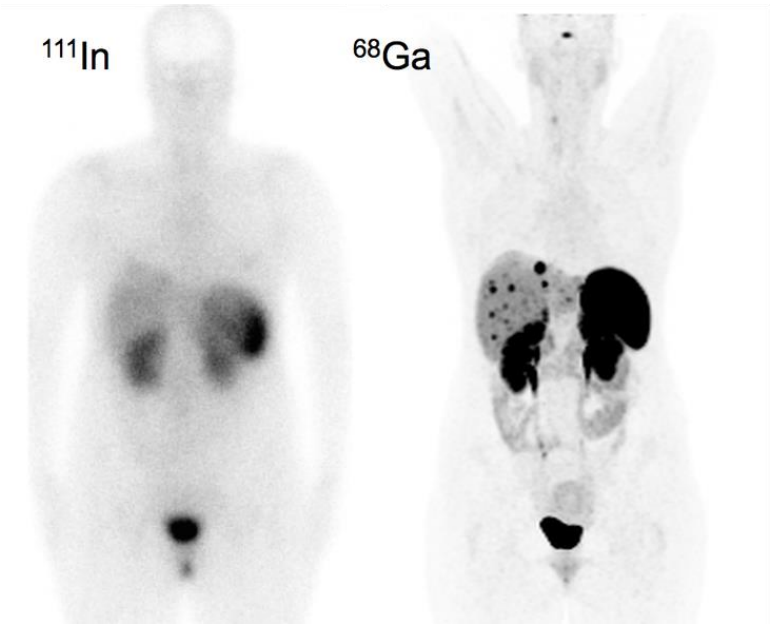
- NETSPOT™ (gallium Ga 68 dotatate)

Orphan Drug Indication: Used with PET imaging to identify somatostatin receptor positive neuroendocrine tumors (NET) in adults and children

Dose: 2 MBq/kg (0.054 mCi/kg) up to 200 MBq (5.4 mCi) by IV bolus

Drug Interaction: Somatostatin analogs may interfere with Ga 69 dotatate binding

Scanning with Ga 68 dotatate improves sensitivity and specificity



NETSPOT® [prescribing information]. New York, NY: Advanced Accelerator Applications USA, Inc. June 2016.

Anthim® (obiltoxaximab) by Elusys

- Orphan drug indication: Anthrax caused by *B. anthracis*
  - Antidote/antitoxin for treatment of inhalational anthrax with *B. anthracis;* administer with antibacterial agents
    - Monoclonal antibody binds and neutralizes anthrax toxin
    - Intended for patients with signs/symptoms of anthrax
  - Can use for prophylaxis when alternative therapies are not available or appropriate
- Administer in monitored setting - hypersensitivity (10.6%) and anaphylaxis (0.9%)
- Studies
  - Animal models used to demonstrate efficacy – survival improves with earlier administration and when co-administered with antibiotics
  - Safety and tolerability studied in adults – three trials with total of 320 adult healthy volunteers; single dose of 16 mg/kg IV over 90 minutes
  - Pediatric dosing based on PK extrapolation
- To be included in National Stockpile for biowarfare/bioterrorism preparedness

Anthim® [prescribing information]. Pine Brook, NJ: Elusys Therapeutics, Inc.. March 2016.

Other Agents for Anthrax

- Raxibacumab (raxibacumab) by GSK/Human Genome Sciences
  - First monoclonal anti-toxin FDA approved for inhalational anthrax
  - 40 mg/kg IV over 2.25 hours
  - Adverse events similar to obiltoxaximab
- Anthrasil® (anthrax immune globulin intravenous) by Cangene Corp/Emergent BioSolutions
  - Obtained from plasma of those vaccinated against anthrax
  - Passive immunizing agent neutralizes anthrax toxin
  - Adult dose: 420 units (7x 50 mL vials) administered as IV infusion
  - Adverse reactions: headache (20%), infusion site pain (9%), nausea (9%), infusion site swelling (7%)

Emerg Infect Dis. 2014 20(2):e130687