FDA-Approved Cancer Drugs in 2021

- 2021 (up through 7/1/2021): 15 new agents
- 2021 (up through 7/1/2021): 13 supplemental indications

GW ONCOLOGY UPDATE

Antibody Drug Conjugates (ADC)

Sacituzumab Govitecan (April 7, 2021)
Loncastuximab Tesirine (April 23, 2021)

GW ONCOLOGY UPDATE

Early - vs New-Generation Antibody – Drug Conjugates

Early generation

- Mouse antibodies; immunogenic
- Unstable in circulation
- Unable to release cytotoxic drug within tumor cell
- Cytotoxic payload: chemotherapy drugs such as doxorubicin, vinca alkaloids (eg, vinblastine), or methotrexate

New generation

- Chimeric or humanized antibodies; reduced immunogenicity
- Stable in circulation
- Efficient linker technology able to release cytotoxic drug within tumor cell (eg, disulfide, dipeptide, or hydrazone linkage)
- Cytotoxic payload: highly potent agents with subnanomolar IC50 such as calicheamicin, maytansine derivative (eg, DM1, DM4), or auristatin (eg, MMAE, MMAF)

GW ONCOLOGY UPDATE

Sacituzumab Govitecan: FDA Indication

- Treatment of unresectable locally advanced or metastatic triple-negative breast cancer following two or more prior systemic therapies, with at least one of them for metastatic disease (4/7/21)
- Accelerated approval for advanced urothelial cancer (4/13/21) based on overall response rate and duration of response

GW ONCOLOGY UPDATE

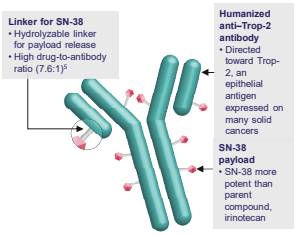
Sacituzumab Govitecan

- Trop-2-directed antibody-drug conjugate
- Humanized anti-Trop-2 IgG1 antibody that is covalently linked to SN-38 (govitecan), a topo I inhibitor
- SN-38 is the active metabolite of irinotecan
- Trop-2 is a cell surface glycoprotein and calcium signal transducer that is overexpressed in several solid tumors, including breast, colon, bladder, pancreatic, prostate, and lung, with only limited expression in normal tissues
- Trop-2 overexpression associated with more aggressive disease
- Trop-2 expression associated with lymph node metastasis and poorer survival in breast cancer

GW ONCOLOGY UPDATE

Sacituzumab Govitecan (SG) Is a First-In-Class Trop-2–Directed ADC

- Trop-2 is expressed in all subtypes of breast cancer and linked to poor prognosis
- Antibody highly specific for Trop-2
- High drug-to-antibody ratio (7.6:1)
- Internalization and linker cleaver by tumor cell not required for the liberation of SN-38 from the antibody
- Hydrolysis of the linker releases the SN-38 cytotoxic extracellularly in the tumor microenvironment, providing a bystander effect
- Granted accelerated approval by the FDA for metastatic TNBC and fast-track designation in metastatic urothelial cancer



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Sacituzumab Govitecan: Pharmacology

- SN-38 is metabolized in the liver by UGT1A1 and is eliminated via the hepatobiliary route
- Genetic variants of UGT1A1 gene, such as UGT1A1*28 lead to reduced UGT1A1 activity. About 20% of African-Americans, 10% of Caucasians, and 2% of East Asian are homozygous for UGT1A1*28 allele. These patients are at increased risk for neutropenia, febrile neutropenia, and anemia
- No change in exposure of sacituzumab govitecan in patients with mild hepatic dysfunction. Has not been studied in setting of moderate or severe hepatic impairment and has also not been studied in setting of moderate renal dysfunction or end-stage renal disease
- Avoid concomitant use of UGT1A1 inhibitors and inducers

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Sacituzumab Govitecan: Toxicity

- Myelosuppression with neutropenia and anemi (black-box warning)
- Diarrhea (black-box warning)
- Hypersensitivity and infusion-related reactions
- Nausea/vomiting
- Fatigue and anorexia
- Hypophosphatemia
- Embryo-fetal toxicity

GW ONCOLOGY UPDATE

Loncastuximab Tesirine: FDA Indication

- Treatment of relapsed or refractory large B-cell lymphoma after 2 or more lines of therapy, including DLBCL, DLBCL arising from low grade lymphoma, and high-grade B-cell lymphoma (April 23, 2021)
- Accelerated approval based on overall response rate

GW ONCOLOGY UPDATE

Loncastuximab Tesirine

- Antibody-drug conjugate targeting CD19
- Humanized anti-CD19 IgG1 antibody that is linked to SG3199, a novel pyrrolobenzodiazepine (PBD) dimer that is composed of 2 PBD monomers (antitumor antibiotics)
- CD19 is expressed on hematologic B-cell malignancies but not on normal hematopoietic cells
- Upon binding to CD19, the molecule is internalized followed by release of SG3199 via proteolytic cleavage. SG3199 then binds to the DNA minor groove forming DNA inter-strand crosslinks, leading to cell death

GW ONCOLOGY UPDATE

Loncastuximab Tesirine: Pharmacology

- Time to ready steady-state is about 210 days
- Mean half-life is on the order of 21 days
- Appears to be drug accumulation with multiple cycles of therapy
- Antibody part of the ADC is metabolized to small peptides and amino acids by catabolic pathways
- SG3199 is metabolized by liver CYP3A4/5 microsomal enzymes
- Major elimination pathway of SG3199 has not been well-studied but is presumably cleared via the hepatobiliary route. Expected to be minimal renal elimination
- No evidence for anti-drug antibodies (ADA)

GW ONCOLOGY UPDATE

Loncastuximab Tesirine: Toxicity

- Myelosuppression with neutropenia, thrombocytopenia, and anemia
- Fatigue and anorexia
- Nausea/vomiting
- Peripheral edema, pleural effusion, pericardial effusion, ascites, and generalized edema
- Skin toxicities with rash, erythema, maculopapular rash, pruritus, including photosensitivity reactions
- Hepatotoxicity with elevation in LFTs
- Infections with URI and pneumonia

GW ONCOLOGY UPDATE

Anti-HER2 Inhibitors

Trastuzumab (1998)
Pertuzumab (2012)
Ado-trastuzumab emtansine (T-DM1) (2017)
Fam-trastuzumab deruxtecan (Dec. 20, 2019)
Margetuximab (Dec. 16, 2020)
Lapatinib (2007)
Neratinib (Feb. 25, 2020)
Tucatinib (April 17, 2020)

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Margetuximab: FDA Indication

- Treatment of adult patients with metastatic HER2-positive breast cancer who have received 2 or more prior anti-HER regimens, at least one of which was for metastatic disease (Dec. 16, 2020)
- Clinical efficacy was evaluated in the SOPHIA clinical trial, which compared margetuximab plus chemotherapy versus trastuzumab plus chemotherapy

GW ONCOLOGY UPDATE

Margituximab

- Chimeric Fc-engineered IgG1 monoclonal antibody directed against the extracellular domain (IV) of the HER-2/neu human epidermal growth factor receptor
- Modified Fc region to increase affinity for activating Fcγ receptor CD16A (FCγRIIIa) and to decrease affinity for inhibitory FCγR CD32B (FCγRIIIb)
- These effects on Fc receptors are expected to increase activation of innate and adaptive immune responses
- HER-2/neu overexpressed in several human cancers including 25%-30% of breast cancers and up to 15%-20% of gastric cancers

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Margituximab: Mechanism of Action

- Precise mechanism(s) of action remains unknown
- Downregulates expression of HER-2/neu receptors
- Inhibits HER-2/neu intracellular signaling pathways
- Induction of apoptosis through as yet undetermined mechanisms
- Increased activation of immunological mechanisms when compared to trastuzumab, which include enhanced antibody-dependent cellular cytotoxicity (ADCC) and/or complement-mediated cell lysis
- Inhibition of inhibitory immune responses mediated by CD32B, which inhibits dendritic cell function and B-cell activation

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Margituximab: Mechanism of Resistance

- Mutations in HER-2/neu receptor leading to decreased binding affinity to trastuzumab
- Decreased expression of HER-2/neu receptors
- Expression of p95HER2, a constitutively active, truncated form of HER2 receptor
- Activation of alternative cellular signaling pathways, e.g. IGF-1R, PI3K/Akt, c-Met receptor

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Margituximab: Dosing Schedule

- Loading dose of 15 mg/kg IV over 120 min
- Maintenance dose of 15 mg/kg IV over 30 min every 3 weeks
- On days when margituximab and chemotherapy are to be administered, can give margituximab immediately after completion of chemotherapy

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Margituximab Special Considerations

- Evaluate LVEF in all patients prior to and during treatment with trastuzumab
- Should be withheld for >16% absolute decrease from baseline in LVEF or LVEF value below institutional limits of normal
- Closely monitor patients for infusion reactions. Discontinuation should be considered in patients who experience severe infusion reactions, including anaphylaxis, angioedema, interstitial pneumonitis, and/or ARDS

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Margituximab: Toxicity

- Infusion-related reactions – fever, chills, urticaria, flushing, fatigue, headache, bronchospasm, dyspnea, angioedema, hypotension. Occurs in up to 13% of patients. Usually mild to moderate in severity, and observed most often with administration of the first infusion. Benadryl and acetaminophen can be used as premeds
- Cardiac toxicity (black-box warning) – sub-clinical and clinical decreases in LVEF and CHF with greatest risk when given together with anthracyclines. Arrythmias and hypertension also can occur

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Margituximab: Toxicity

- Embryo-fetal toxicity (black-box warning) – exposure during pregnancy can result in oligohydramnios, pulmonary hypoplasia, and neonatal death
- GI toxicity: Nausea and vomiting, diarrhea. Generally mild
- Pulmonary toxicity – increased cough, dyspnea, rhinitis, and sinusitis

GW ONCOLOGY UPDATE

Anti-MET Inhibitors

Capmatinib (May 6, 2020)
Tepotinib (Feb. 3, 2021)
Amivantamab (May 21, 2021)

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Tepotinib

- Selective small molecule inhibitor of the MET-associated tyrosine kinase and inhibits MET receptor signaling caused by *MET* gene alterations, including *MET* exon 14 skipping alterations, and MET protein overexpression
- MET is overexpressed or mutated in several tumors and plays a key role in tumor cell proliferation, survival, invasion, and metastasis
- *MET* exon 14 skipping mutations seen in 3%-4% of NSCLC
- FDA accelerated approval for NSCLC with *MET* exon 14 skipping alterations (Feb. 3, 2021)

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Tepotinib: Mechanism of Resistance

- Activation of receptor tyrosine kinase pathways, including EGFR, ErbB2, ErbB3, FGFR3, AXL, and RET
- Activation of downstream cellular signaling pathways, e.g. RAS/RAF, MAPK, and PI3K/AKT
- Secondary *MET* mutations

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Tepotinib: Clinical Pharmacology

- Oral bioavailability of 72%. Food with high fat content increases AUC and C_{max}.
- Metabolized mainly by liver CYP3A4 and CYP2C8 microsomal enzymes. Elimination of drug metabolites is mainly in feces (85%), and 45% is in parent form
- Renal clearance of parent drug and metabolites account for only about 14% of an administered dose
- No need for dose reduction in setting of mild to moderate hepatic impairment and renal impairment. Effect of severe hepatic and renal impairment has not been studied

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Tepotinib: Drug-Drug Interactions

- Avoid concomitant use with strong CYP3A inducers
- Avoid concomitant use with strong CYP3A inhibitors and P-gp inhibitors
- Avoid concomitant use with P-gp substrates as tepotinib is a P-gp inhibitor

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Tepotinib: Toxicity

- Interstitial lung disease and pneumonitis, which in rare cases, can be fatal
- Hepatotoxicity with elevations in SGOT/SGPT and serum bilirubin
- Peripheral edema
- Nausea/vomiting
- Fatigue and anorexia
- Myalgias
- Embryo-fetal toxicity

GW ONCOLOGY UPDATE

Anti-EGFR Inhibitors

Erlotinib
Gefitinib
Afatinib
Osimertinib
Cetuximab
Panitumumab
Necitumumab
Amivantamab (May 21, 2021)

GW ONCOLOGY UPDATE

Amivantamab: FDA Indication

- FDA accelerated approval for locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutation following progression on or after platinum-based therapy (May 21, 2021)
- Accelerated approval based on overall response rate and duration of response

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Amivantamab

- Bispecific IgG1 antibody targeting the EGFR and MET pathways
- Activity in activating and resistant *EGFR* mutations and *MET* mutations and *MET* gene amplification
- First molecule to show activity in NSCLC with *EGFR* exon 20 insertion mutations
- Inhibits binding of ligands to EGFR and MET receptors

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Amivantamab: Mechanism of Action

- Leads to receptor downregulation through receptor internalization and lysosomal degradation
- Antitumor activity mediated by antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and antibody-dependent cellular phagocytosis (ADCP)
- Antibody-dependent cellular trogocytosis (ADCT), which is mediated by monocytes and macrophages, appears to be a dominant mechanism of action

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Amivantamab: Toxicity

- Infusion-related reactions. Usually occurs within 1 hour after start of infusion
- Acneiform skin rash, dry skin, pruritus
- Interstitial lung disease, pneumonitis
- Ocular toxicity with keratitis, dry eye, conjunctival redness, blurred vision, uveitis
- Paronychia
- Mild nausea/vomiting, diarrhea
- Fatigue

GW ONCOLOGY UPDATE

Anti-FGFR Inhibitors

Erdafitinib (April 12, 2019)
Pemigatinib (April 17, 2020)
Infigratinib (May 28, 2021)

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Infigratinib: FDA Indication

- Previously treated unresectable, locally advanced or metastatic cholangiocarcinoma with a FGFR2 fusion or other rearrangement (May 28, 2021)
- Accelerated approval based on overall response rate and duration of response

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Infigratinib

- Small molecule inhibitor of FGFR1, FGFR2, FGFR3, and FGFR4
- Inhibits FGFR signaling in tumors with activating FGFR amplification, mutations, or fusions
- FGFR plays a key role in tumor cell proliferation, survival, migration, invasion, and metastasis
- FGFR signaling pathway aberrantly activated in 15%-20% of intrahepatic cholangiocarcinoma and in other tumors types, including bladder cancer, breast cancer, NSLCL, endometrial cancer, and head and neck cancer

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Infigratinib: Mechanism of Resistance

- Activation of receptor tyrosine kinase pathways, including EGFR, ErbB2, ErbB3, and MET
- Activation of downstream cellular signaling pathways, e.g. PI3K/Akt, mTOR, MAPK, and STAT3
- Gatekeeper mutations in *FGFR2* gene, including V564F, that modify binding pocket with reduced binding to drug

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Infigratinib: Clinical Pharmacology

- Food with high fat / high calorie content increases oral bioavailability
- Metabolized mainly by liver CYP3A4 microsomal enzymes and to a lesser extent by flavin-containing monooxygenase 3 (FMO3)
- Two active metabolites, BHS697 and CQM157
- Elimination of drug is mainly in feces (77%) with only 3.5% in parent form
- Renal clearance of parent drug and metabolites account for only about 7% of an administered dose

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Infigratinib: Drug Dosing with Organ Dysfunction

- Mild hepatic impairment: reduce dose to 100 mg PO daily for 21 days with 1-week off in 28-day cycle
- Moderate hepatic impairment: reduce dose to 75 mg PO daily for 21 days with 1-week off in 28-day cycle
- Mild and moderate renal impairment (CrCl, 30-89 mL/min): reduce dose to 100 mg PO daily for 21 days with 1-week off in 28-day cycle
- Effect of severe hepatic and severe renal impairment has not been studied

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Infigratinib: Drug-Drug Interactions

- Strong or moderate CYP3A inducers
- Strong or moderate CYP3A inhibitors
- Gastric acid reducing agents, including proton pump inhibitors, H2 antagonists, and antacids
- Avoid drugs that alter serum phosphate levels, including potassium phosphate supplements, vit. D supplements, antacids, phosphate-containing laxatives or enemas

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Infigratinib: Toxicity

- Hyperphosphatemia
- Ocular disorders with retinal pigment detachment (RPED) leading to blurred vision, visual floaters, or photopsia. Dry eye symptoms are common
- Dysguesia, mucositis, dry mouth, and nausea/vomiting
- Fatigue and anorexia
- Dry skin, hand-foot syndrome, paronychia, and nail discoloration
- Arthralgias

GW ONCOLOGY UPDATE

KRAS G12C Inhibitors

Sotarasib (May 28, 2021)

GW ONCOLOGY UPDATE

Sotarasib

- Selective and irreversible small molecule inhibitor of *KRAS* G12C mutation
- Forms a covalent bond with the unique cysteine of *KRAS* G12C, which locks the protein in an inactive GDP-bound state that prevents downstream signaling without affecting wild-type KRAS
- *KRAS* G12C mutation present in 13% of NSCLC and 1%-3% of CRC and other solid cancers
- FDA accelerated approval for *KRAS* G12C-mutated locally advanced or metastatic NSCLC following at least one prior systemic therapy

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Sotarasib: Mechanism of Resistance

- Activation of receptor tyrosine kinase pathways, including EGFR, ErbB2, ErbB3, FGFR3, AXL, and RET
- Activation of downstream cellular signaling pathways, e.g. RAS/RAF, MAPK, and PI3K/AKT
- Increased expression of Aurora Kinase A

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Sotarasib: Clinical Pharmacology

- Food with high fat content increases AUC
- Metabolized mainly by non-enzymatic conjugation and oxidative metabolism by liver CYP3A microsomal enzymes
- Elimination of drug is mainly in feces (75%), and about 53% is in parent form
- Renal clearance of parent drug and metabolites account for only about 6% of an administered dose
- No need for dose reduction in setting of mild to moderate renal impairment and with mild hepatic dysfunction. Effect of severe renal impairment or moderate to severe hepatic impairment has not been studied

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Sotaranib: Drug-Drug Interactions

- Avoid acid-reducing agents, including proton pump inhibitors and H2-receptor antagonists
- Avoid concomitant use with strong CYP3A4 inducers
- Avoid concomitant use with CYP3A4 substrates
- Avoid concomitant use with P-gp substrates, such as digoxin

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Sotarasib: Toxicity

- GI side effects with diarrhea and nausea/vomiting
- Interstitial lung disease and pneumonitis with dyspnea and cough
- Hepatotoxicity with elevations in SGOT/SGPT and serum bilirubin
- Fatigue and anorexia
- Myalgias and arthralgias

GW ONCOLOGY UPDATE

Immune Checkpoint Inhibitors

Ipilimumab (2011)
Pembrolizumab (2014)
Nivolumab (2014)
Atezolizumab (2016)
Avelumab (2017)
Durvalumab (2017)
Cemiplimab (2018)
Dostarlimab (4/22/21)

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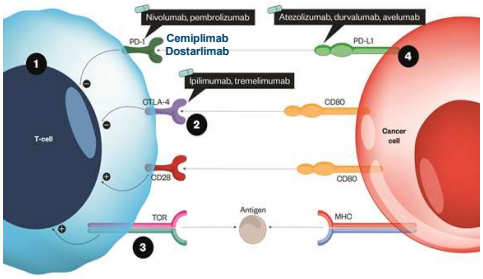
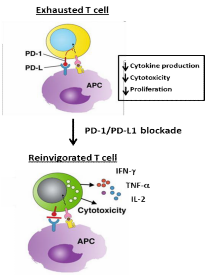
Immune Checkpoint Inhibitors



GW ONCOLOGY UPDATE

PD-1 Pathway Blockade Enhances Anti-Tumor Immunity

- Anti-PD-1/PD-L1 mAbs can reverse T cell exhaustion and stimulate T cell function
  - PD-1 pathway blockade can boost T cell immunity and demonstrate anti-tumor efficacy in preclinical models
  - Anti-PD-1 antibodies can increase T cell effector function in ex vivo clinical samples
- Anti-PD-1/PD-L1 antibodies have demonstrated clinical responses in multiple solid tumors:
  - Melanoma
  - NSCLC
  - SCLC
  - RCC
  - Bladder
  - MSI-H/dMMR mCRC
  - Gastric/GE junction
  - Hodgkins and non-Hodgkins lymphoma
  - Head and neck
  - Hepatocellular
  - Merkel cell



Adapted from Freeman et al 2008

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Immune Checkpoint Inhibitors: Targets

CTLA-4
- Ipilumumab

PD-1
- Nivolumab
- Pembrolizumab
- Cemiplimab
- Dostarlimab

PD-L1
- Atezolizumab
- Avelumab
- Durvalumab

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Dostarlimab: FDA-Approved Indication

- dMMR recurrent or advanced endometrial cancer (FDA-approved, 4/22/21)
- Approved under accelerated approval based on tumor response rate and duration of response
- Ventana MMR RxDx Panel approved by US FDA as a companion diagnostic for selecting patients with endometrial cancer for dostarlimab treatment

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Dostarlimab

- Humanized IgG4 antibody that binds to and inhibits PD-1 receptor
- Inhibits the interaction between PD-L1 and PD-L2 with the PD-1 receptor
- Blockade of PD-1 signaling restores T-cell immune function, including T-cell activation and proliferation

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Dostarlimab: Clinical Pharmacology

- Relatively long terminal half-life on order of 25 days
- Usually administered every 3 weeks for the first 4 doses and then every 6 weeks
- Metabolized to small peptides and amino acids by catabolic pathways
- PK and drug exposure not affected by hepatic or renal impairment

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Dostarlimab: Toxicity

- Infusion-related reactions
- Fatigue, anorexia, asthenia
- Nausea/vomiting
- Anemia
- Enterocolitis
- Hepatitis
- Pneumonitis
- Endocrinopathies with adrenal insufficiency, hypopituitarism, hypogonadism, and hypothyroidism
- Nephritis
- Skin rash, dermatitis, and pruritus
- Neurologic toxicity with neuropathy, myositis, and myasthenia gravis
- Musculoskeletal symptoms with myalgias, arthralgias, oligo or polyarthritis, polymyalgia rheumatica

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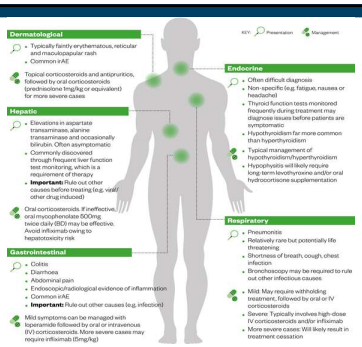

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Nivolumab: New FDA-Approved Indications

- Locally advanced unresectable or metastatic HER2-positive gastric or GEJ adenocarcinoma in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy (April 16, 2021)

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Pembrolizumab: New FDA-Approved Indications

- Locally advanced unresectable or metastatic HER2-positive gastric or GEJ adenocarcinoma in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy (May 5, 2021)
- Locally advanced unresectable or metastatic esophageal or GEJ cancer who are not candidates for surgical resection or definitive chemoradiation in combination with fluoropyrimidine- and platinum-based chemotherapy (March 22, 2021)

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Cemiplimab: New FDA-Approved Indications

- Locally advanced and metastatic basal cell cancer (Feb. 9, 2021)
- First-line treatment of advanced or metastatic NSCLC whose tumors have high PD-L1 expression (Tumor Proportion Score >50%) with no EGFR, ALK, or ROS1 alterations (Feb. 22, 2021)

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Immune Checkpoint Inhibitors: Management

- Early diagnosis of toxicities
- Increased awareness and heightened vigilance of health care team
- Patient – provider communication
- Rapid and aggressive use of steroids and other immune suppressive agents, such as infliximab
- CBC, metabolic panel, LFTs, and TFTs at each treatment visit and at frequent intervals for the first 6 months of completion of therapy
- ACTH, cortisol, and testosterone (men) should be checked in patients who develop fatigue and non-specific symptoms

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