Advances in hematology and oncology for 2018

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The medical information doubling time is...

31 new approvals or uses in 10 months!

Table 1. FDA Approvals of Cancer Therapies From November 1, 2016, to October 31, 2017

Drug	Indication	Approval Date
New approval		
Rucaparib (Rubraca; Clovis Oncology, Boulder, CO)	For treatment of patients with deleterious BRCA mutation (germline and/or somatic)–associated advanced ovarian cancer who have been treated with two or more chemotherapies.	December 2016
Avelumab (Bavencio; EMD Serono, Darmstadt, Germany)	For the treatment of patients ≥ 12 years of age with metastatic Merkel cell carcinoma. Avelumab is a PD-L1–blocking human immunoglobulin G1λ monoclonal antibody. This is the first FDA-approved product to treat this type of cancer.	March 2017
Niraparib (Zejula; Tesaro, Waltham, MA)	Maintenance treatment for adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy.	March 2017
Ribociclib (Kisqali; Novartis, Basel, Switzerland)	In combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer.	March 2017
Brigatinib (Alunbrig; Takeda, Osaka, Japan)	For treatment of patients with metastatic anaplastic lymphoma kinase–positive NSCLC who experienced disease progression on or who are intolerant to crizotinib.	April 2017
Midostaurin (Rydapt; Novartis)	For treatment of adult patients with newly diagnosed AML who are FLT3 mutation–positive, as detected by an FDA-approved test, in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation.	April 2017
Durvalumab (Imfinzi; AstraZeneca, London, United Kingdom)	For treatment of patients with locally advanced or metastatic urothelial carcinoma who experience disease progression during or after platinum-containing chemotherapy or who experience disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.	May 2017
Rituximab and hyaluronidase human (Rituxan Hycela; Genentech, South San Francisco, CA)	For adult patients with follicular lymphoma, diffuse large B-cell lymphoma, and chronic lymphocytic leukemia.	June 2017
Neratinib (Nerlynx; Puma Biotechnology, Los Angeles, CA)	For extended adjuvant treatment of adult patients with early-stage HER2-overexpressed/amplified breast cancer, to follow adjuvant trastuzumab-based therapy.	July 2017
Daunorubicin and cytarabine (Vyxeos; Jazz Pharmaceuticals, Palo Alto, CA)	For treatment of adults with newly diagnosed therapy-related AML or AML with myelodysplasia-related changes, two types of AML that have a poor prognosis.	August 2017
Enasidenib (Idhifa; Celgene, San Francisco, CA)	For treatment of adult patients with relapsed or refractory AML with an isocitrate dehydrogenase-2 mutation as detected by an FDA-approved test.	August 2017
Inotuzumab ozogamicin (Besponsa; Wyeth, Madison, NJ)	For treatment of adults with relapsed or refractory B-cell precursor ALL.	August 2017
Tisagenlecleucel (Kymriah; Novartis)	For treatment of patients ≤ 25 years of age with B-cell precursor ALL that is refractory or in second or later relapse.	August 2017
Abemaciclib (Verzenio; Eli Lilly, Indianapolis, IN)	In combination with fulvestrant for women with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression after endocrine therapy.	September 2017
Bevacizumab-awwb (Mvasi; Amgen, South San Francisco, CA)	Approved as a biosimilar to bevacizumab (Avastin), bevacizumab-awwb is the first biosimilar approved in the United States for the treatment of cancer.	September 2017
Copanlisib (Aliqopa; Bayer HealthCare, Berlin, Germany)	For treatment of adult patients with relapsed follicular lymphoma who have received at least two prior systemic therapies.	September 2017
Gemtuzumab ozogamicin (Mylotarg; Pfizer, New York, NY)	Newly diagnosed CD33-positive AML in adults and for treatment of relapsed or refractory CD33-positive AML in adults and pediatric patients ≥ 2 years of age. May be used in combination with daunorubicin and cytarabine for adults with newly diagnosed AML or as a stand-alone treatment of certain adult and pediatric patients.	September 2017
Axicabtagene ciloleucel (Yescarta; Kite Pharma, Los Angeles, CA)	For treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy.	October 2017
New use		
Daratumumab (Darzalex; Janssen, Beerse, Belgium)	In combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy.	November 2016
Nivolumab (Opdivo; Bristol-Meyers Squibb, New York, NY)	Recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after a platinum-based therapy.	November 2016
Lenalidomide (Revlimid; Celgene)	Maintenance therapy for patients with multiple myeloma after autologous stem-cell transplantation.	February 2017
Nivolumab (Opdivo)	For treatment of patients with locally advanced or metastatic urothelial carcinoma who experience disease progression during or after platinum-containing chemotherapy or experience disease progression within 12 months of neoadjuvant or adjuvant treatment with a platinum-containing chemotherapy.	February 2017
Osimertinib (Tagrisso; AstraZeneca)	For treatment of patients with metastatic EGFR T790M mutation–positive NSCLC, as detected by an FDA-approved test, who experienced disease progression on or after EGFR tyrosine kinase inhibitor therapy.	March 2017
Palbociclib (Ibrance; Pfizer)	HR-positive, HER2-negative advanced or metastatic breast cancer in combination with an aromatase inhibitor as initial endocrine-based therapy in postmenopausal women.	March 2017
Pembrolizumab (Keytruda; Merck & Co, Kenilworth, NJ)	For treatment of adult and pediatric patients with refractory classic Hodgkin lymphoma or those who have experienced relapse after three or more prior lines of therapy.	March 2017
Regorafenib (Stivarga; Bayer HealthCare Pharmaceuticals)	For treatment of patients with HCC who have been previously treated with sorafenib.	April 2017
Avelumab (Bavencio)	For patients with locally advanced or metastatic urothelial carcinoma who experienced disease progression during or after platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy.	May 2017
Pembrolizumab (Keytruda)	In combination with pemetrexed and carboplatin for treatment of patients with previously untreated metastatic nonsquamous NSCLC.	May 2017
Pembrolizumab (Keytruda)	For patients with locally advanced or metastatic urothelial carcinoma who experience disease progression during or after platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.	May 2017
Nivolumab (Opdivo)	For treatment of HCC in patients who have been previously treated with sorafenib.	September 2017
Pembrolizumab (Keytruda)	For patients with recurrent locally advanced or metastatic, gastric, or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 as determined by an FDA-approved test.	September 2017

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; EGFR, epidermal growth factor receptor; FDA, US Food and Drug Administration; HCC, hepatocellular carcinoma; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; NSCLC, non–small-cell lung cancer; PD-L1, programmed death-ligand 1.

ASCO 2019 – Clinical Cancer Advances

Advance of the Year: Progress in Rare Cancers

This year, ASCO names Progress in Treating Rare Cancers as the Advance of the Year. In the United States, rare cancers account for about 20% of all cancers diagnosed each year, and incidence rates vary worldwide.[4] Progress has historically lagged behind the achievements made in more common cancers; however, five major studies this past year offer significant steps forward, making this a notable year for advances in rare cancers:

1. **A new combination of targeted therapies for a rare, hard-to-treat form of thyroid cancer** produced responses in over two thirds of patients

2. Sorafenib became the **first treatment to improve progression-free survival for desmoid tumors,** a rare type of sarcoma

3. Lutetium Lu 177 dotatate (^{177}Lu-Dotatate), a new therapy that delivers targeted radiation to tumor cells, **lowered the risk of disease progression or death by 79% for patients with advanced midgut neuroendocrine tumors,** compared to standard treatment

4. Trastuzumab, a standard treatment for HER2-positive breast cancer, **significantly slowed progression of HER2-positive uterine serous carcinoma**

5. **The first promising therapy**—the colony-stimulating factor-1 inhibitor pexidartinib—**for a rare cancer of the joints known as tenosynovial giant cell tumor, showed an overall response rate of 39.3%,** *v* 0% for those taking a placebo

ASCO 2019 – Clinical Cancer Advances

Additional Major Advances

Landmark advances in molecular diagnostics continue, with the most significant achievement made with the TAILORx breast cancer study. This study demonstrated that as many as 70% of women with hormone receptor-positive, node-negative breast cancer could safely forgo adjuvant chemotherapy, based on results from a 21 gene assay.

New successes are being achieved with targeted therapies, including the introduction of medicines that delay the progression of breast and lung cancers.

Growing microbiome research field identifies specific bacteria possibly associated with risk for certain head and neck cancers.

Immunotherapy advances continue to grow, expanding to cancers where there have been few immunotherapy treatment successes to date:

- A new combination immunotherapy regimen was proven to boost overall survival in patients with renal cell cancer, gaining Food and Drug Administration (FDA) approval and becoming the new standard of care.
- An investigational PD-1 inhibitor showed promise for advanced squamous cell cancer of the skin, which has few other treatment options.

2 main points

- Anti-coagulation in cancer patients
- Immunotherapy toxicity

The standard anticoagulation for a patient with stage IV, incurable pancreatic cancer with new PE (CAT, cancer-associated thrombosis) is:

Lovenox 1 mg/kg BID

Warfarin with goal INR 2.5-3

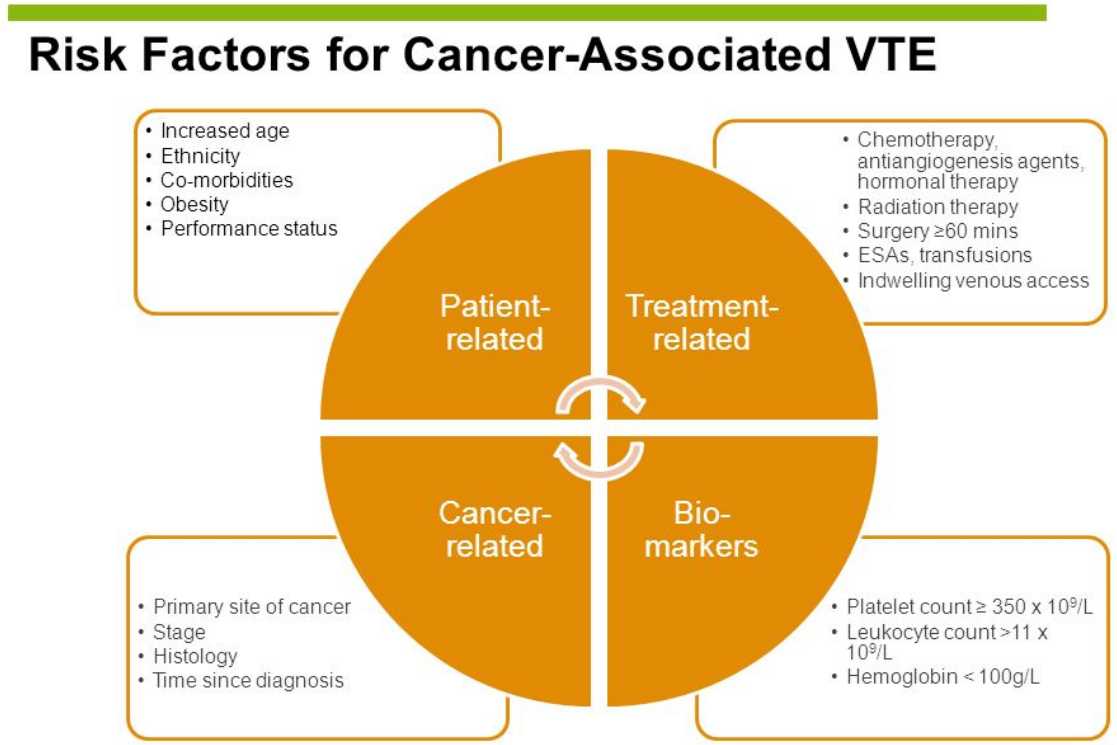
Rivaroxaban 15 mg po BID x 3 weeks followed by 20 mg/day

Aspirin 325 mg/day

None of the above

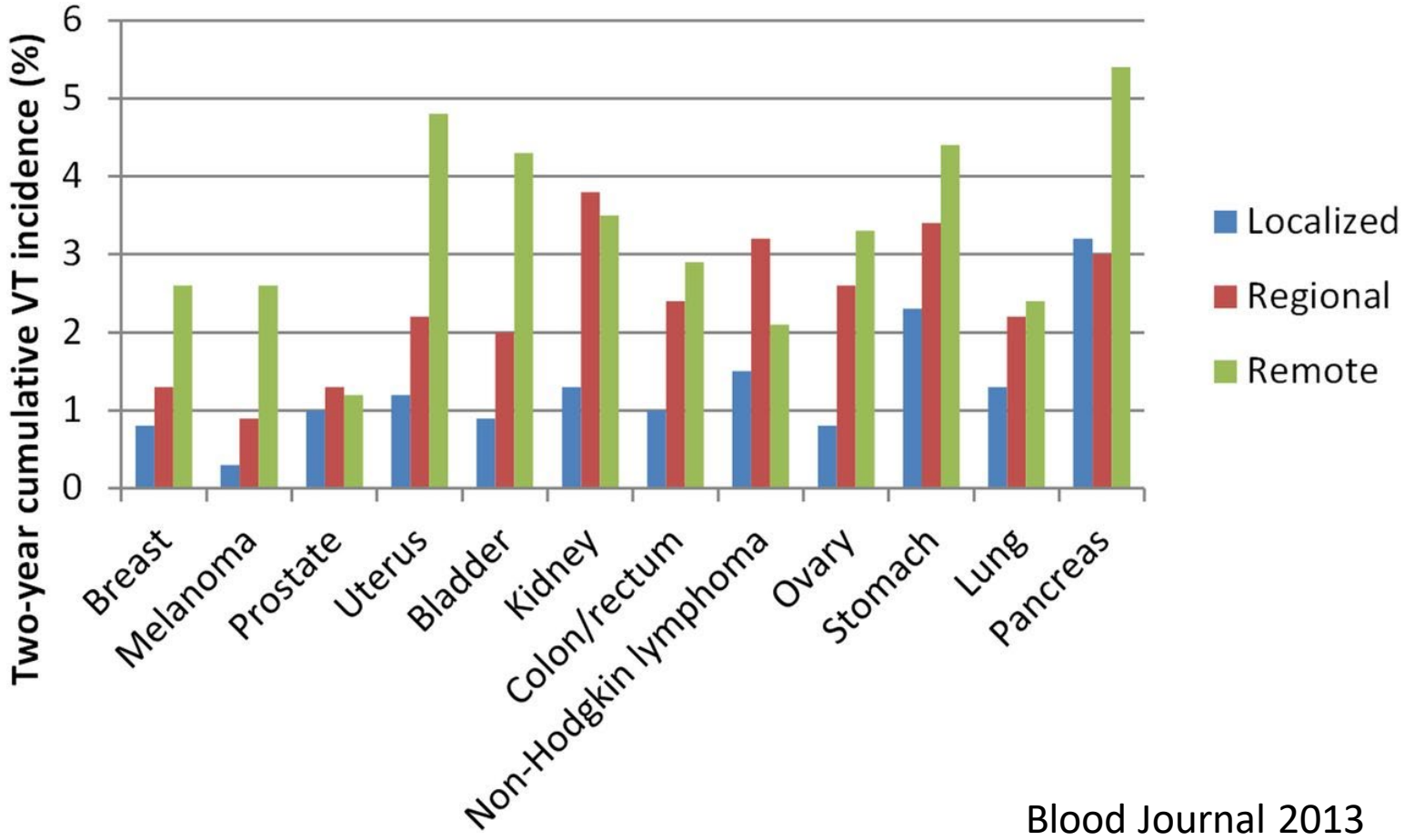
Cancer associated VTE

- Leading cause of cancer morbidity and mortality
- 2 previous RCTs showed superiority of LMWH to VKA
- Traditionally…
  - LMWHs were standard
  - Treat only after VTE (not prophylaxis)



Adapted from Lyman GH, *et al. ASCO Update. J Clin Oncol*. 2013;31:2189-204.

Cancer associated VTE



Blood Journal 2013

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JOURNAL OF CLINICAL ONCOLOGY

RAPID COMMUNICATION

Comparison of an Oral Factor Xa Inhibitor With Low Molecular Weight Heparin in Patients With Cancer With Venous Thromboembolism: Results of a Randomized Trial (SELECT-D)

Annie M. Young, Andrea Marshall, Jenny Thirlwall, Oliver Chapman, Anand Lokare, Catherine Hill, Danielle Hale, Janet A. Dunn, Gary H. Lyman, Charles Hutchinson, Peter MacCallum, Ajay Kakkar, F.D. Richard Hobbs, Stavros Petrou, Jeremy Dale, Christopher J. Poole, Anthony Maraveyas, and Mark Levine

JCO. July 2018

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Apixaban to Prevent Venous Thromboembolism in Patients with Cancer

Marc Carrier, M.D., Karim Abou-Nassar, M.D., Ranjeeta Mallick, Ph.D., Vicky Tagalakis, M.D., Sudeep Shivakumar, M.D., Ariah Schattner, M.D., Philip Kuruvilla, M.D., Danny Hill, M.D., Silvana Spadafora, M.D., Katerine Marquis, M.D., Mateya Trinkaus, M.D., Anna Tomiak, M.D., Agnes Y.Y. Lee, M.D., Peter L. Gross, M.D., Alejandro Lazo-Langner, M.D., Robert El-Maraghi, M.D., Glenwood Goss, M.D., Gregoire Le Gal, M.D., David Stewart, M.D., Timothy Ramsay, Ph.D., Marc Rodger, M.D., Debra Witham, B.Sc.N., and Philip S. Wells, M.D., for the AVERT Investigators*

NEJM. December 2018

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism

Gary E. Raskob, Ph.D., Nick van Es, M.D., Peter Verhamme, M.D., Marc Carrier, M.D., Marcello Di Nisio, M.D., David Garcia, M.D., Michael A. Grosso, M.D., Ajay K. Kakkar, M.B., B.S., Michael J. Kovacs, M.D., Michele F. Mercuri, M.D., Guy Meyer, M.D., Annelise Segers, M.D., Minggao Shi, Ph.D., Tzu-Fei Wang, M.D., Erik Yeo, M.D., George Zhang, Ph.D., Jeffrey I. Zwicker, M.D., Jeffrey I. Weitz, M.D., and Harry R. Büller, M.D., for the Hokusai VTE Cancer Investigators*

NEJM. February 2018

Table 2. Clinical Outcomes during the Overall Trial Period.*

Outcome	Edoxaban (N = 522)	Dalteparin (N = 524)	Hazard Ratio (95% CI)	P Value
Primary outcome				
Recurrent venous thromboembolism or major bleeding — no. (%)	67 (12.8)	71 (13.5)	0.97 (0.70–1.36)	0.006 for noninferiority; 0.87 for superiority
Secondary outcomes				
Recurrent venous thromboembolism — no. (%)	41 (7.9)	59 (11.3)	0.71 (0.48–1.06)	0.09
Recurrent deep-vein thrombosis — no. (%)	19 (3.6)	35 (6.7)	0.56 (0.32–0.97)	
Recurrent pulmonary embolism — no. (%)†	27 (5.2)	28 (5.3)	1.00 (0.59–1.69)	
Major bleeding — no. (%)	36 (6.9)	21 (4.0)	1.77 (1.03–3.04)	0.04
Severity of major bleeding among those with major bleeding — no./total no. (%)‡				
Category 1	0	0		
Category 2	24/36 (66.7)	8/21 (38.1)		
Category 3	12/36 (33.3)	12/21 (57.1)		
Category 4	0	1/21 (4.8)		
Clinically relevant nonmajor bleeding — no. (%)§	76 (14.6)	58 (11.1)	1.38 (0.98–1.94)	
Major or clinically relevant nonmajor bleeding — no. (%)§¶	97 (18.6)	73 (13.9)	1.40 (1.03–1.89)	
Death from any cause — no. (%)	206 (39.5)	192 (36.6)	1.12 (0.92–1.37)	
Event-free survival — no. (%)‖	287 (55.0)	296 (56.5)	0.93 (0.77–1.11)	

NEJM Feb 2018. Hokusai.

Take homes

- DOACS are standard for treatment of cancer associated VTE
  - Exception – Gastric/Esophageal cancer
  - Very insurance dependent which one
- Would not use as prophylaxis (unless other indication like Afib)
- In active cancer patients I continue indefinitely, otherwise I treat 6-12 months
- IVC filters are preserved for those with contraindication to anticoagulation

PD-1 and CTLA-4 are checkpoints in what process:

Humoral immunity (antibodies and complement)

G1 restriction point in the cell cycle

T cell adaptive immunity

Apoptosis

There is increasing use of the checkpoint inhibitors (immunotherapy) in hematology/oncology (e.g. nivolumab, pembrolizumab, atezolizumab, etc.). Which of the following is NOT true regarding this class of medications:

Immune mediated side effects are typically seen at least 4-6 weeks after exposure to the drug with the exception of rash

Exposure to this class of drugs causes immunosuppression and patients are at high risk for opportunistic infections such as PJP

Common immune-related adverse effects (irAEs) include colitis, pneumonitis, and thyroiditis; high-dose corticosteroids remain the cornerstone of management of irAEs

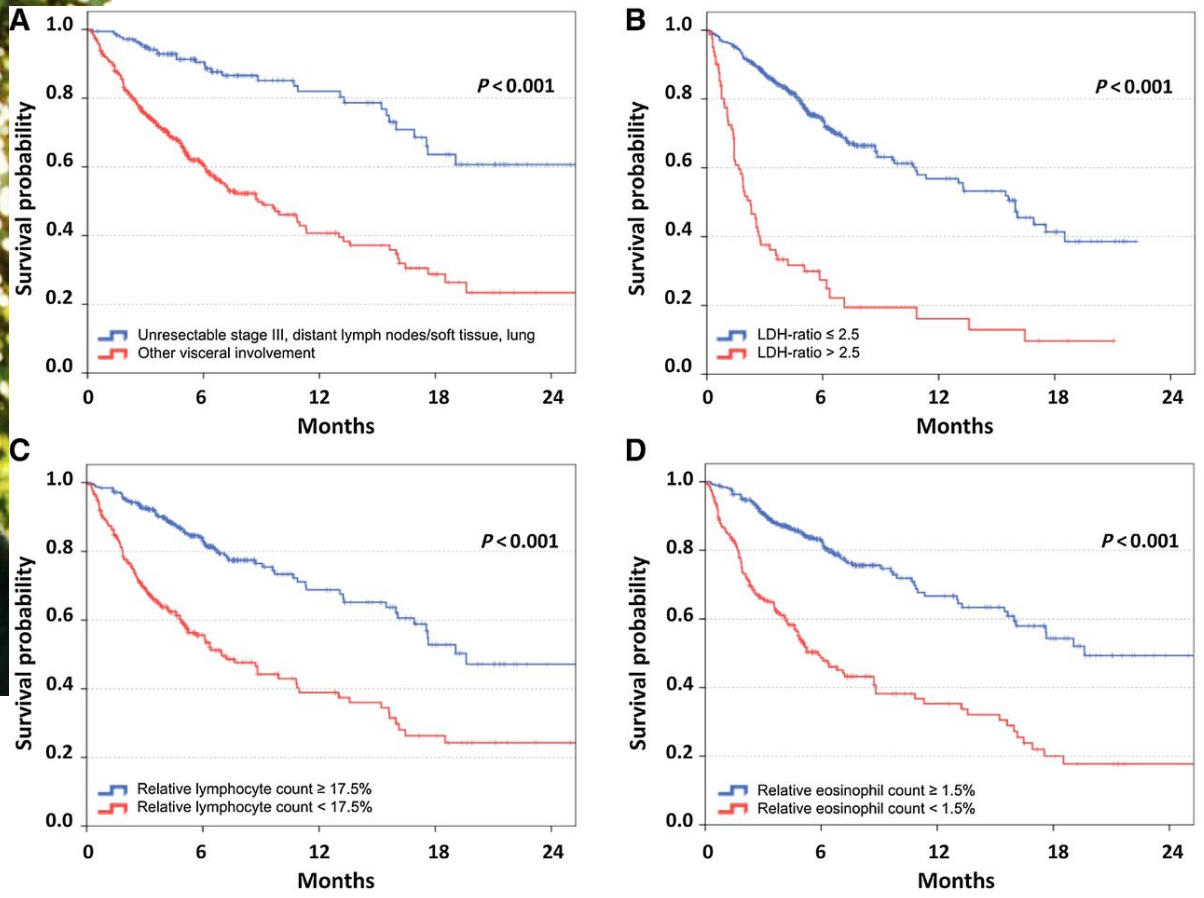
Immune hypophysitis can be difficult to pick up in the clinical setting and can be managed with physiologic doses of hydrocortisone

Combinations of more than one checkpoint inhibitor (e.g. nivolumab and ipilumumab) place patients at higher risk of AEs

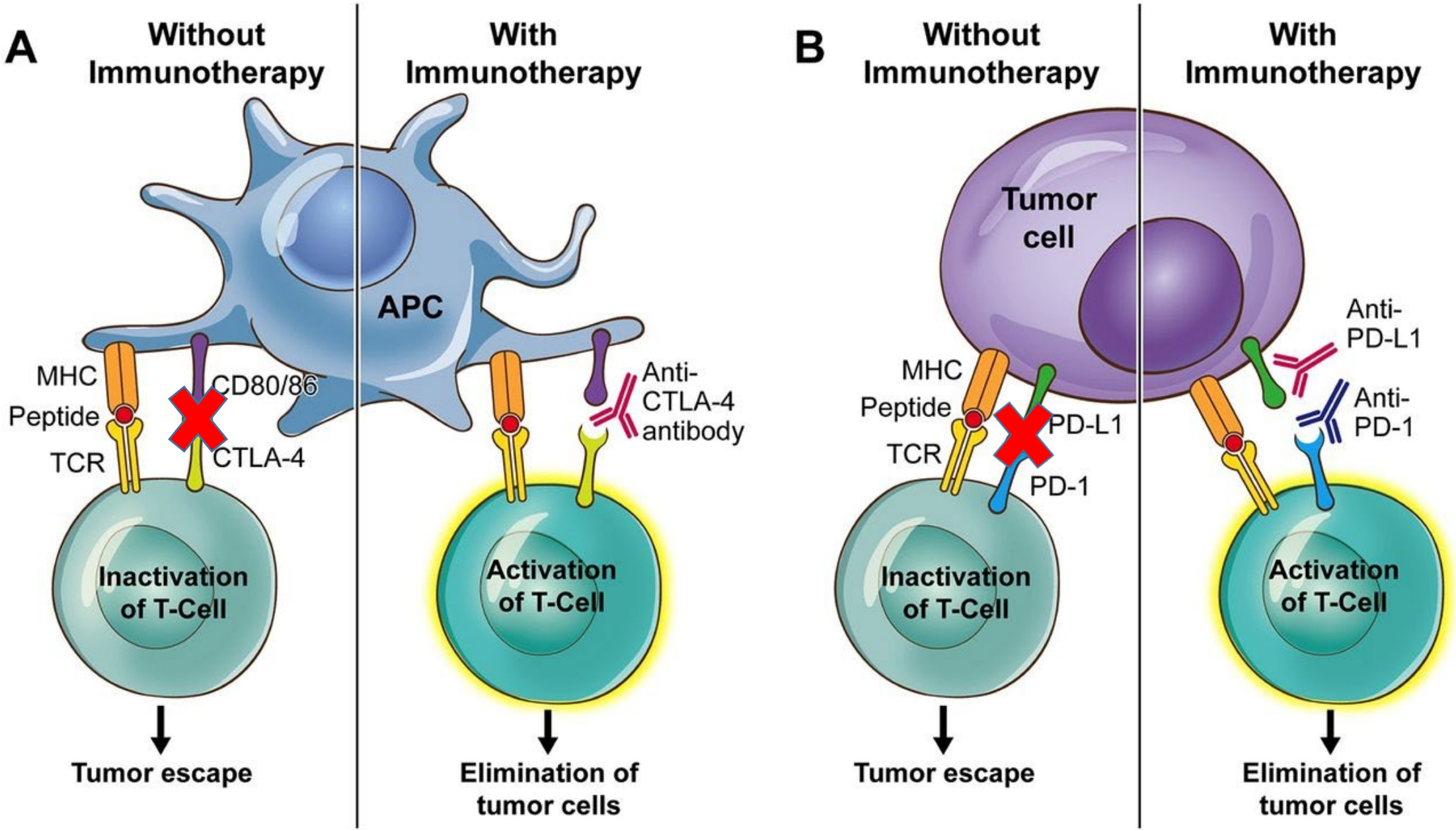
Advances in immunotherapy - checkpoint

- Pembrolizumab in first line advanced lung cancer
- Nivo/Ipi combination in renal cell carcinoma
- Nivo/Ipi decreases brain mets in melanoma
- Cemiplimab (PD-1 inhibitor) in cutaneous squamous cell carcinoma
- Pembrolizumab in head and neck
- Nivo/Ipi in subset of GI cancers (mostly colon)
- Ipilumumab in hepatocellular carcinoma

Immunotherapy - ToC



Clinical Cancer Research Nov 2016

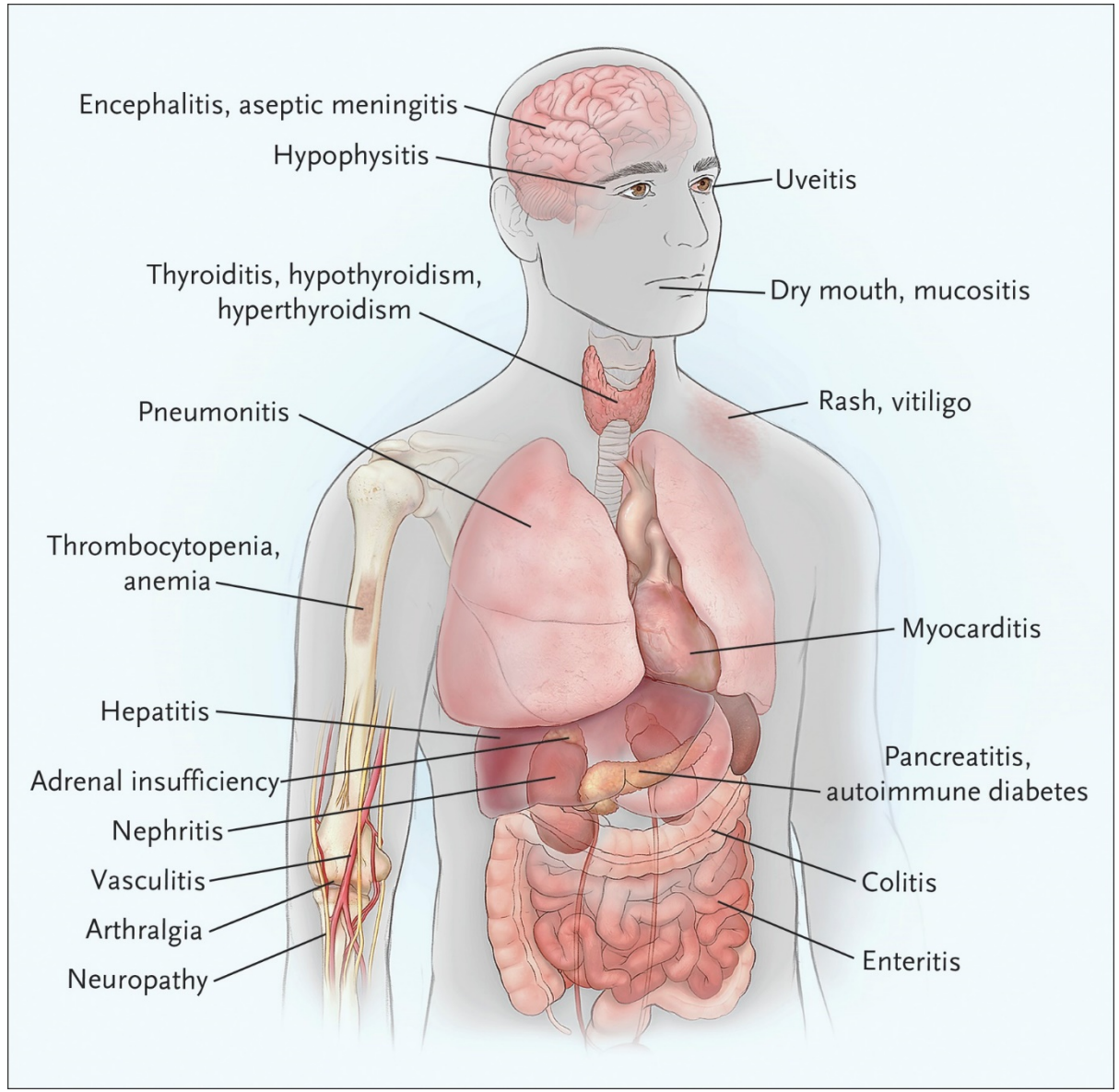

A
Without Immunotherapy
With Immunotherapy
APC
MHC
Peptide
TCR
CD80/86
CTLA-4
Anti-CTLA-4 antibody
Inactivation of T-Cell
Activation of T-Cell
Tumor escape
Elimination of tumor cells
B
Without Immunotherapy
With Immunotherapy
Tumor cell
MHC
Peptide
TCR
PD-L1
PD-1
Anti-PD-L1
Anti-PD-1
Inactivation of T-Cell
Activation of T-Cell
Tumor escape
Elimination of tumor cells

Gut 2018

Table 1. Immune Checkpoint–Blocking Antibodies Approved by the Food and Drug Administration.*

Drug	Target	Indication
Ipilimumab	CTLA-4	Melanoma
Nivolumab	PD-1	Melanoma, non–small-cell lung cancer, renal-cell carcinoma, hepatocellular carcinoma, classic Hodgkin's lymphoma, squamous-cell carcinoma of the head and neck, urothelial carcinoma, colorectal cancer with high microsatellite instability or mismatch-repair deficiency
Pembrolizumab	PD-1	Melanoma, non–small-cell lung cancer, classic Hodgkin's lymphoma, squamous-cell carcinoma of the head and neck, urothelial carcinoma, gastric cancer, solid tumors with high microsatellite instability or mismatch-repair deficiency
Atezolizumab	PD-L1	Non–small-cell lung cancer, urothelial carcinoma
Avelumab	PD-L1	Merkel-cell carcinoma, urothelial carcinoma
Durvalumab	PD-L1	Urothelial carcinoma

* CTLA-4 denotes cytotoxic T-lymphocyte antigen 4, PD-1 programmed cell death 1, and PD-L1 programmed cell death ligand 1.


Encephalitis, aseptic meningitis
Hypophysitis
Uveitis
Thyroiditis, hypothyroidism, hyperthyroidism
Dry mouth, mucositis
Rash, vitiligo
Pneumonitis
Thrombocytopenia, anemia
Myocarditis
Hepatitis
Pancreatitis, autoimmune diabetes
Adrenal insufficiency
Nephritis
Vasculitis
Colitis
Arthralgia
Enteritis
Neuropathy

Immune checkpoint inhibitors - AEs

- AEs - T cell, antibody, and cytokine driven
- Treat – immunosuppression/glucocorticoids are cornerstone
- When – typically weeks after starting
- NOT immunosuppressive
- Some AEs (like vitiligo) may correspond to response
- Probably do not lose response with immunosuppression treatment

POST Question - The standard anticoagulation for a patient with stage IV, incurable pancreatic cancer with new PE (CAT, cancer-associated thrombosis) is:

Lovenox 1 mg/kg BID

Warfarin with goal INR 2.5-3

Rivaroxaban 15 mg po BID x 3 weeks followed by 20 mg/day

Aspirin 325 mg/day

None of the above

Question 2 - Post

- The standard anticoagulation for a patient with stage IV, incurable pancreatic cancer with new PE (CAT, cancer-associated thrombosis) is:
  - A) Lovenox 1 mg/kg BID
  - B) Warfarin with goal INR 2.5-3
  - C) Rivaroxaban 15 mg po BID X 3 weeks followed by 20 mg/day
  - D) Aspirin 325 mg/day
  - E) None of the above

POST Question - PD-1 and CTLA-4 are checkpoints in what process:

Humoral immunity (antibodies and complement)

G1 restriction point in the cell cycle

T cell adaptive immunity

Apoptosis

Question 3 - Post

- PD-1 and CTLA-4 are checkpoints in what process:
  - A) Humoral immunity (Antibodies and complement).
  - B) G1 restriction point in the cell cycle
  - C) T cell adaptive immunity
  - D) Apoptosis

POST Question - There is increasing use of the checkpoint inhibitors (immunotherapy) in hematology/oncology (e.g. nivolumab, pembrolizumab, atezolizumab, etc.). Which of the following is NOT true regarding this class of medications:

Immune mediated side effects are typically seen at least 4-6 weeks after exposure to the drug with the exception of rash

Exposure to this class of drugs causes immunosuppression and patients are at high risk for opportunistic infections such as PJP

Common immune-related adverse effects (irAEs) include colitis, pneumonitis, and thyroiditis; high-dose corticosteroids remain the cornerstone of management of irAEs

Immune hypophysitis can be difficult to pick up in the clinical setting and can be managed with physiologic doses of hydrocortisone

Combinations of more than one checkpoint inhibitor (e.g. nivolumab and ipilumumab) place patients at higher risk of AEs

Question 4 - Post

- There is increasing use of the checkpoint inhibitors (immunotherapy) in hematology/oncology (e.g. nivolumab, pembrolizumab, atezolizumab, etc.). Which of the following is NOT true regarding this class of medications:
  - A) Immune mediated side effects are typically seen at least 4-6 weeks after exposure to the drug with the exception of rash.
  - B) Exposure to this class of drugs causes immunosuppression and patients are at high risk for opportunistic infections such as PJP.
  - C) Common immune-related adverse effects (irAEs) include colitis, pneumonitis, and thyroiditis; high-dose corticosteroids remain the cornerstone of management of irAEs.
  - D) Immune hypophysitis can be difficult to pick up in the clinical setting and can be managed with physiologic doses of hydrocortisone.
  - E) Combinations of more than one checkpoint inhibitor (e.g. nivolumab and ipilumumab) place patients at higher risk of AEs.