Advances in hematology and oncology for 2018

G Weldon Gilcrease III, MD
University of Utah
March 1, 2019
The medical information doubling time is...

- 6 months
- 1-2 years
- 5 years
- 8-10 years
<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Indication</th>
<th>Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>MVA-287</td>
<td>Treatment of patients with severe recurrent BPAE due to familial (autosomal dominant) mutations in the BPAE2 gene (BPAE2A).</td>
<td>November 2023</td>
</tr>
<tr>
<td>Ataluren (Teslaspr)</td>
<td>For the treatment of patients with familial amyloid polyneuropathy due to mutations in the transthyretin (TTR) gene.</td>
<td>January 2024</td>
</tr>
</tbody>
</table>

**New approvals or uses in 10 months!**
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.¹ 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 (¹⁷⁷Lu-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%, vs 0% for those taking a placebo
**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)

Cancer associated VTE

Blood Journal 2013
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 Thrilwall, Oliver Chapman, Amand Lobur, Catherine Hill, Danielle Hale, Janet A. Owen, Gary H. Lyman, Charles Hutchinson, Peter MacCollum, Ajay Kakkar, K.D. Richard Hobbs, Starnes Peters, Jeremy Dale, Christopher J. Poole, Anthony Manoukian, and Mark Levine

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., Silvina 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 Whitham, B.Sc., and Philip S. Wells, M.D., for the AVERIT Investigators

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. Mercere, M.D., Guy Meyer, M.D., Annelise Segers, M.D., Mingqiao Shi, Ph.D., Tzu-Fei Wang, M.D., Erik Yeo, M.D., George Zhang, Ph.D., Jeffrey L. Zwicker, M.D., Jeffrey I. Weitz, M.D., and Harry R. Baller, M.D., for the Hokusa VTE Cancer Investigators

NEJM. February 2018

NEJM. December 2018
### Table 2. Clinical Outcomes during the Overall Trial Period.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Edoxaban (N = 522)</th>
<th>Dalteparin (N = 524)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent venous thromboembolism or major bleeding — no. (%)</td>
<td>67 (12.8)</td>
<td>71 (13.5)</td>
<td>0.97 (0.70–1.36)</td>
<td>0.006 for noninferiority; 0.87 for superiority</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent venous thromboembolism — no. (%)</td>
<td>41 (7.9)</td>
<td>59 (11.3)</td>
<td>0.71 (0.48–1.06)</td>
<td>0.09</td>
</tr>
<tr>
<td>Recurrent deep-vein thrombosis — no. (%)</td>
<td>19 (3.6)</td>
<td>35 (6.7)</td>
<td>0.56 (0.32–0.97)</td>
<td>0.09</td>
</tr>
<tr>
<td>Recurrent pulmonary embolism — no. (%)†</td>
<td>27 (5.2)</td>
<td>28 (5.3)</td>
<td>1.00 (0.59–1.69)</td>
<td>0.04</td>
</tr>
<tr>
<td>Major bleeding — no. (%)</td>
<td>36 (6.9)</td>
<td>21 (4.0)</td>
<td>1.77 (1.03–3.04)</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Severity of major bleeding among those with major bleeding — no./total no. (%)‡</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Category 1</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Category 2</td>
<td>24/36 (66.7)</td>
<td>8/21 (38.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Category 3</td>
<td>12/36 (33.3)</td>
<td>12/21 (57.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Category 4</td>
<td>0</td>
<td>1/21 (4.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinically relevant nonmajor bleeding — no. (%)§</td>
<td>76 (14.6)</td>
<td>58 (11.1)</td>
<td>1.38 (0.98–1.94)</td>
<td>0.09</td>
</tr>
<tr>
<td>Major or clinically relevant nonmajor bleeding — no. (%)¶</td>
<td>97 (18.6)</td>
<td>73 (13.9)</td>
<td>1.40 (1.03–1.89)</td>
<td>0.06</td>
</tr>
<tr>
<td>Death from any cause — no. (%)</td>
<td>206 (39.5)</td>
<td>192 (36.6)</td>
<td>1.12 (0.92–1.37)</td>
<td>0.09</td>
</tr>
<tr>
<td>Event-free survival — no. (%)</td>
<td>287 (55.0)</td>
<td>296 (56.5)</td>
<td>0.93 (0.77–1.11)</td>
<td>0.09</td>
</tr>
</tbody>
</table>
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 ipilimumab) 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)
• Ipilimumab in hepatocellular carcinoma
Immunotherapy - ToC
<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipiilimumab</td>
<td>CTLA-4</td>
<td>Melanoma</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>PD-1</td>
<td>Melanoma, non–small-cell lung cancer, renal-cell carcinoma, hepatocellular</td>
</tr>
<tr>
<td></td>
<td></td>
<td>carcinoma, classic Hodgkin’s lymphoma, squamous-cell carcinoma of the head</td>
</tr>
<tr>
<td></td>
<td></td>
<td>and neck, urothelial carcinoma, colorectal cancer with high microsatellite</td>
</tr>
<tr>
<td></td>
<td></td>
<td>instability or mismatch-repair deficiency</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>PD-1</td>
<td>Melanoma, non–small-cell lung cancer, classic Hodgkin’s lymphoma, squamous-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>cell carcinoma of the head and neck, urothelial carcinoma, gastric cancer,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>solid tumors with high microsatellite instability or mismatch-repair</td>
</tr>
<tr>
<td></td>
<td></td>
<td>deficiency</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>PD-L1</td>
<td>Non–small-cell lung cancer, urothelial carcinoma</td>
</tr>
<tr>
<td>Avelumab</td>
<td>PD-L1</td>
<td>Merkel-cell carcinoma, urothelial carcinoma</td>
</tr>
<tr>
<td>Durvalumab</td>
<td>PD-L1</td>
<td>Urothelial carcinoma</td>
</tr>
</tbody>
</table>

* CTLA-4 denotes cytotoxic T-lymphocyte antigen 4, PD-1 programmed cell death 1, and PD-L1 programmed cell death ligand 1.
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
<table>
<thead>
<tr>
<th>POST Question - PD-1 and CTLA-4 are checkpoints in what process:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humoral immunity (antibodies and complement)</td>
</tr>
<tr>
<td>G1 restriction point in the cell cycle</td>
</tr>
<tr>
<td>T cell adaptive immunity</td>
</tr>
<tr>
<td>Apoptosis</td>
</tr>
</tbody>
</table>
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 ipilimumab) place patients at higher risk of AEs
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 ipilimumab) place patients at higher risk of AEs.