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ADVANCES IN Cancer IMMUNOTHERAPY™

What's Next for Cancer Immunotherapy?

Jeremy Whalen, PharmD, BCOP

Specialty Clinical Program Director – Oncology

Prime Therapeutics

AAEM AMERICAN ACADEMY OF EMERGENCY MEDICINE CHAMPION OF THE EMERGENCY PHYSICIAN

ACCC Association of Community Cancer Centers

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Disclosures

- I have received compensation for non-CE presentations for the following companies:
  - TEVA
- I will be discussing non-FDA approved medications and indications during my presentation.

Outline

Important trends

New developments

- Check Point Inhibitors
- CAR-T
- Vaccines
- New Targets
- Combinations

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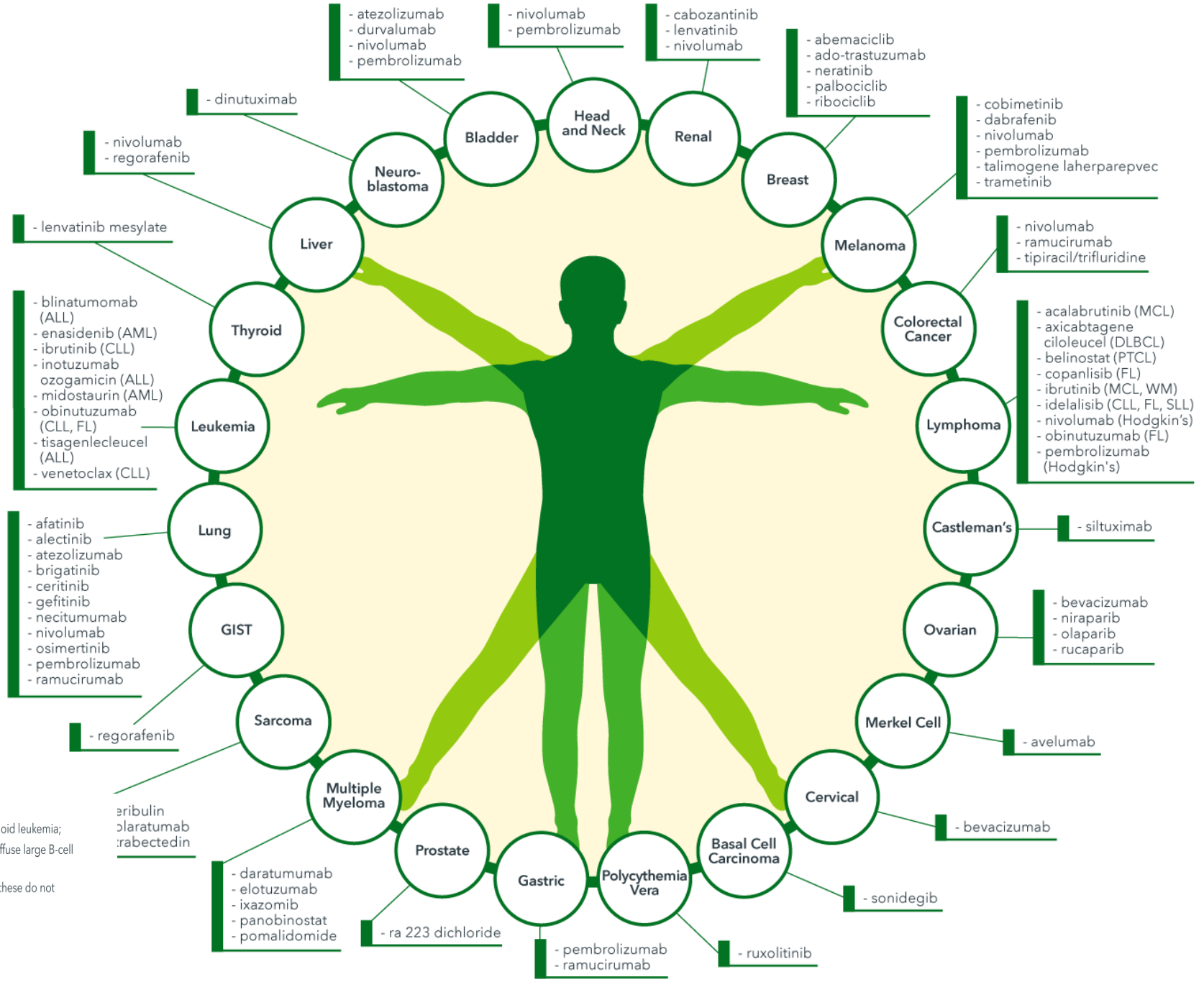
New Active Substance Approvals in Oncology by Indication, 2013-2017



Source: IQVIA, ARK R&D Intelligence, Apr 2018; IQVIA Institute, Apr 2018

Chart notes: Includes initial and subsequent indications. Excludes supportive care. GIST = gastrointestinal stromal tumor. ALL = acute myeloid leukemia; AML = acute myeloid leukemia; CLL = chronic lymphocytic leukemia; FL = follicular lymphoma; MCL = mantle cell lymphoma; DLBCL = Diffuse large B-cell lymphoma; PTCL = peripheral T-cell lymphoma; WM = Waldenstrom macroglobulinemia; SLL = small lymphocytic lymphoma.

*Irinontecan liposome (pancreatic cancer) and daunorubicin + cytarabine (AML), approved during this period, have not been included as these do not fulfil the criteria to be considered as New Active Substance..

Report: Global Oncology Trends 2018: Innovation, Expansion and Disruption. IQVIA Institute for Human Data Science, May 2018

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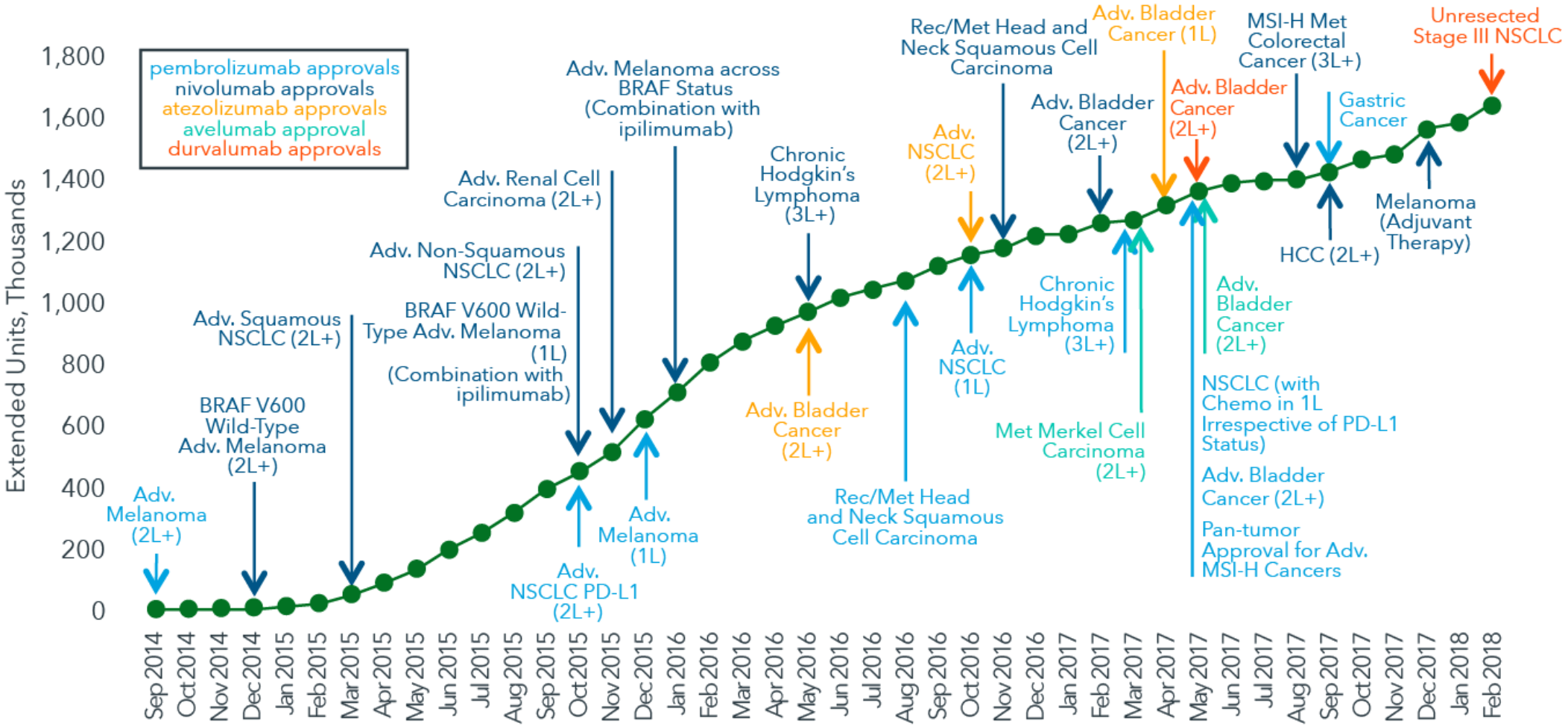
Immuno-Oncology PD-1 and PD-L1 Inhibitor Uptake in the United States



Source: U.S. FDA, IQVIA, National Sales Perspectives, Feb 2018; IQVIA Institute, Apr 2018

Notes: Met = metastatic; rec/met = recurrent/metastatic; 1L+ = 1st line; 2L+ = 2nd line; HCC = hepatocellular carcinoma.

Report: Global Oncology Trends 2018: Innovation, Expansion and Disruption. IQVIA Institute for Human Data Science, May 2018

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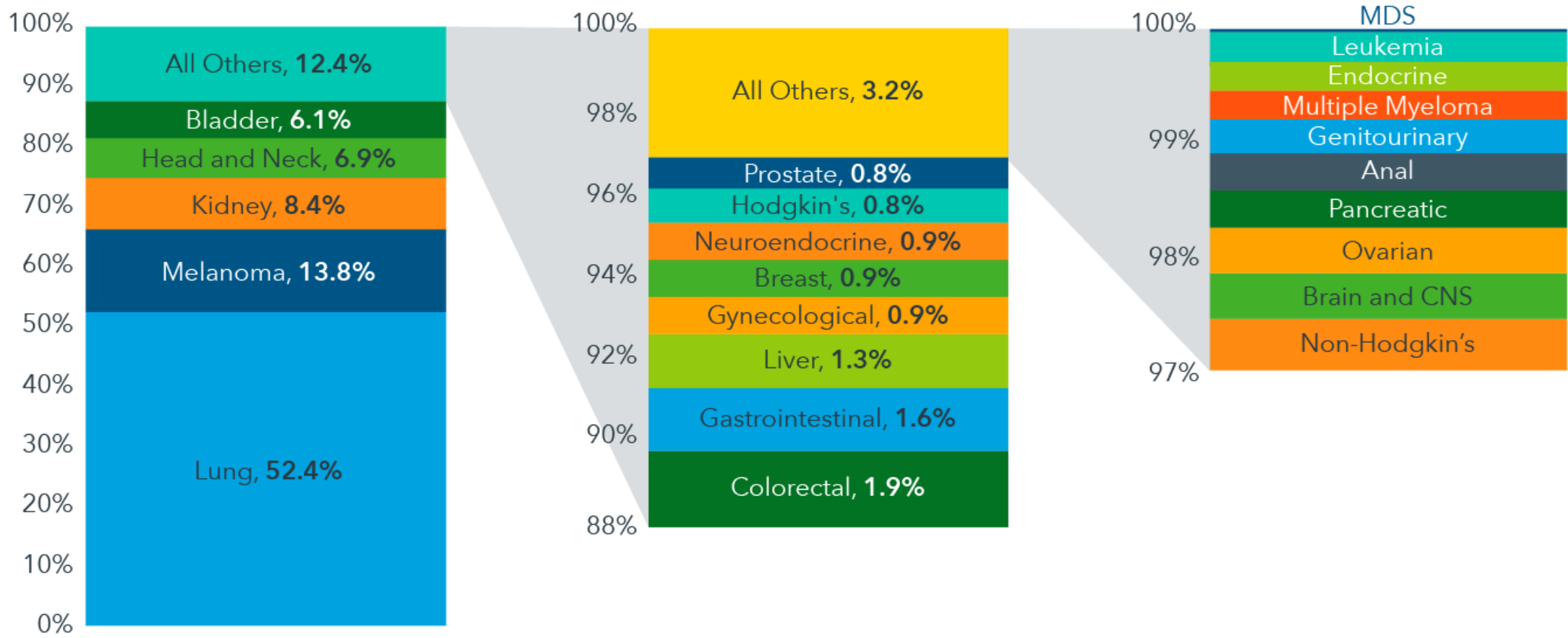
PD-1 and PD-L1 Inhibitor Treated Patients by Tumor Type in the United States

Patients treated in 2017 with PD-1 and PD-L1 medicines; total = 147,699



Source: IQVIA Oncology Anonymized Patient Level Data (APLD) sourced from longitudinally linked medical and pharmacy healthcare claims, Feb 2018; IQVIA Institute, Apr 2018

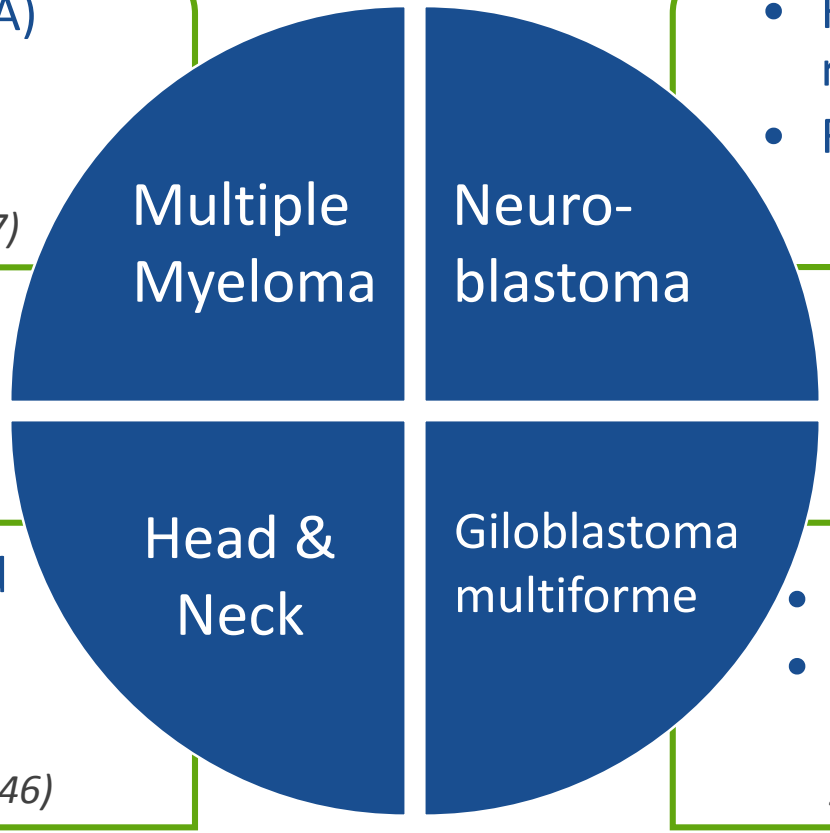
Notes: Chart totals may not sum due to rounding.

Report: Global Oncology Trends 2018: Innovation, Expansion and Disruption. IQVIA Institute for Human Data Science, May 2018

Adoptive T cell Transfer | Chimeric Antigen Receptors (CARs)

- B-cell maturation antigen (BCMA)
- Bb121

J Clin Oncol. 2018;36 (suppl; abstr 8007)



- Receptor tyrosine kinase-like orphan receptor-1 (ROR1) ROR1R*CD28 CAR
- ROR1R*CD28 CAR

J Clin Oncol. 2018;36 (suppl; abstr 10523)

- T1E28ζ (an ErbB ligand) coupled to a CD28+CD3ζ
- T4-Immunotherapy

J Clin Oncol. 2018;36 (suppl; abstr 3046)

- NKG2D CAR
- KD-025

J Clin Oncol. 2018;36 (suppl; abstr 2034)

CAR-T Future | Allogenic

GENE EDITED

- Universal Chimeric Antigen Receptors (UCART) – "Off-the-Shelf" CAR-Ts
  - UCART19 → CD19 expressing hematologic malignancies
  - UCART123 → CD123 on leukemic cells in AML
  - UCART22 → CD22 expressing B-cell ALL
  - UCARTCS1 → CS1 expressing hematologic malignancies (Multiple myeloma)
  - UCART38 → CD38 expressing hematologic malignancies (MM, T-cell ALL, NHL, MCL)

NON-GENE EDITED

- CYAD-101 → targets NKG2D ligand with co-stimulatory molecule DAP10
- Allo—SHRINK trial
  - Unresectable colorectal cancer in combination with standard chemotherapy
  - CYAD-101 (+ TCR inhibiting molecule [TIM])

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www.celyad.com

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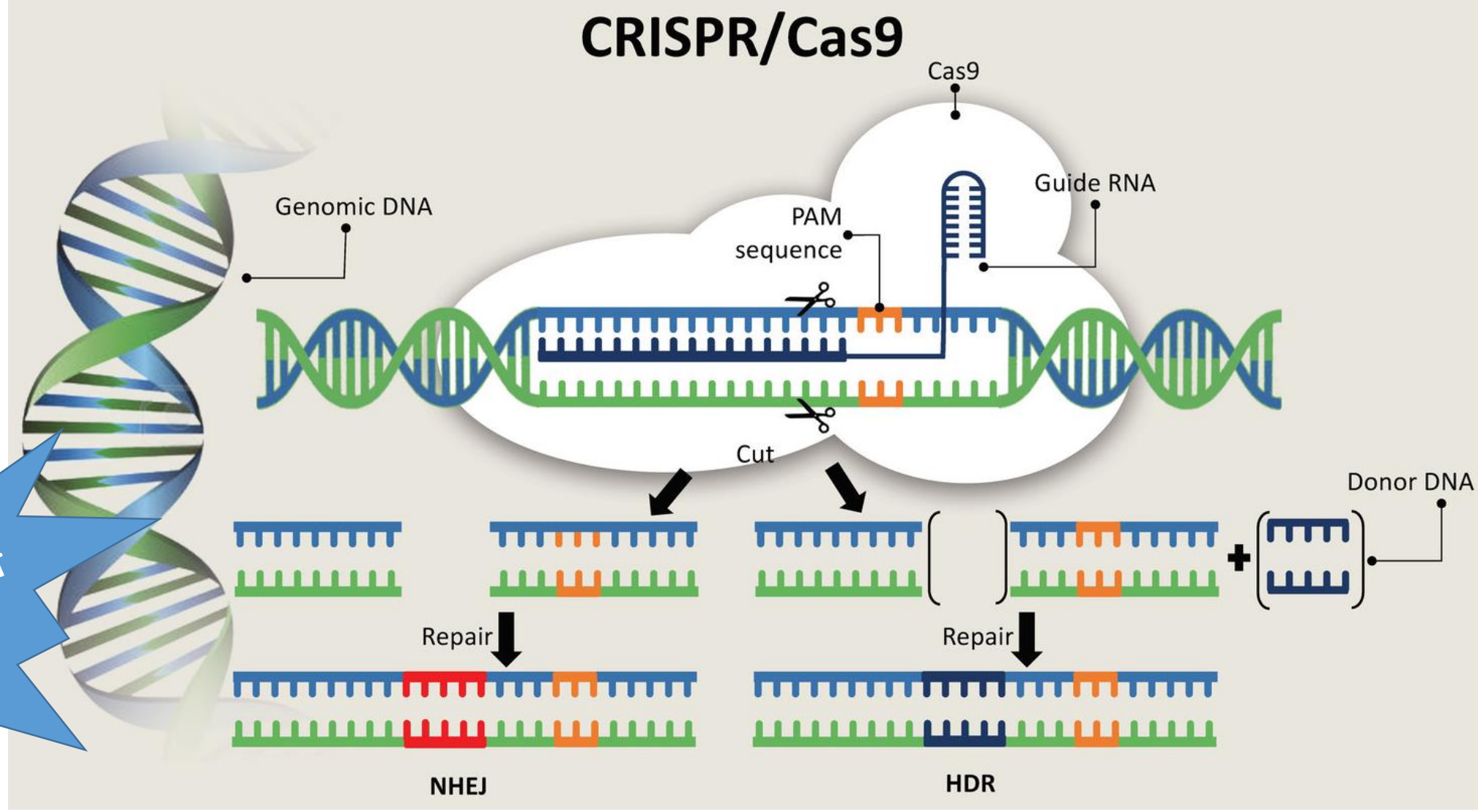
Genetic inactivation of CD33 to enable CAR-T targeting in AML



PAM: protospacer adjacent motif
NHEJ: non-homologous end joining
HDR: homology directed repair

Image: http://www.genedit.com/crisprcas9-1/
Cell. 2018 May 31;173(6):1439-1453.e19

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Vaccines

Oncolytic Virus

- Viruses that directly kill cancer cells and can also activate cells of the immune system to target and eliminate cancer throughout the body
- Talimogene laherparepvec

Therapeutic Cancer Vaccines

- Trigger the immune system to recognize and attack certain markers, or antigens, present on or in cancer cells
- There are many different types of therapeutic cancer vaccines.
  - Individual proteins
  - Whole cells
  - Antigen-presenting cells
- Sipuleucel-T

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Vaccines in Research

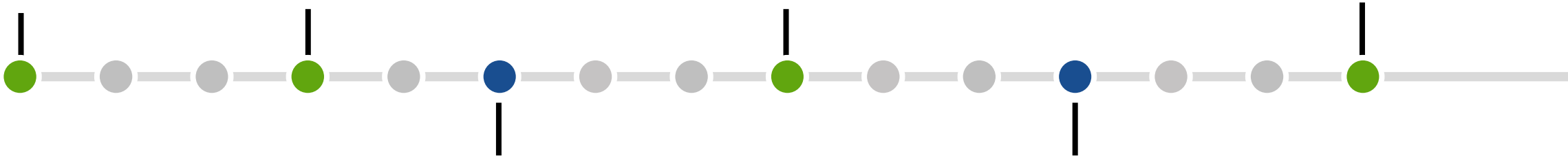
Oncolytic Virus

CG0070
- Adenovirus for GM-CSF
- BCG-unresponsive NMIBC

Pelareorep
- Reovirus targeting Ras pathway
- prostate, colorectal, ovarian, lung, and breast

CVA21
- Coxsackievirus type A21 (common cold)

Pexastimogene devacirepvec
- GM-CSF virus
- RCC failing at least 1 therapy, solid tumors



Therapeutic Cancer Vaccines

Nelipepimut-S
- Adjuvant TNBC

Dendritic cell-based immunotherapy
- Autologous tumor dendritic cell
- GBM, resectable tumors

Urol Oncol. 2017;36:440-447
J Clin Oncol. 2018;36:6_suppl, 671-671
J Clin Oncol 2018;36 (suppl; abstr 3092)
J Transl Med. 2018;16(1):142

GM-CSF = granulocyte-macrophage colony stimulating factor
NMIBC = non-muscle invasive bladder cancer
Reovirus = respiratory enteric orphan virus
TNBC = triple negative breast cancer
GBM = glioblastoma

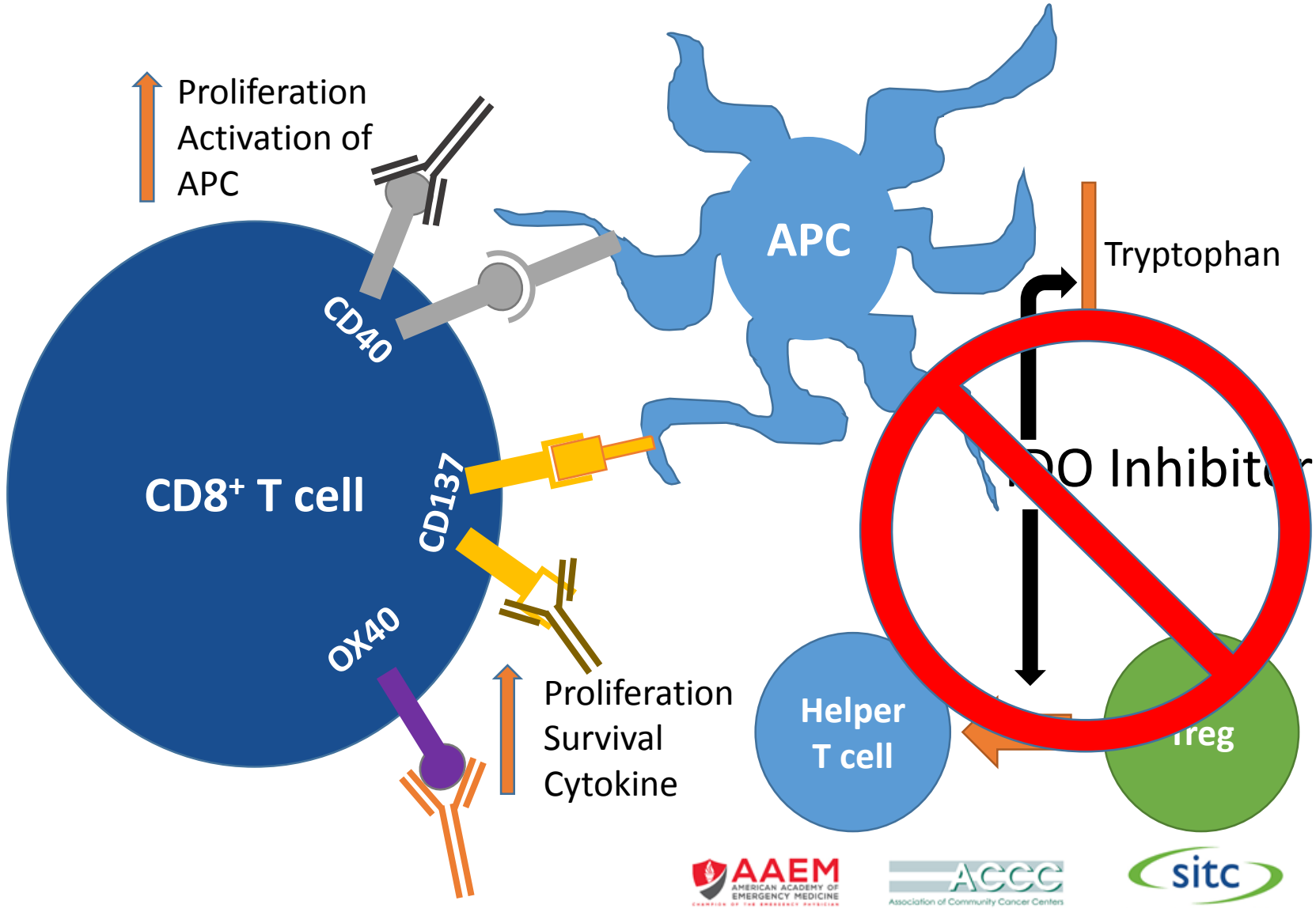
New Targets, New Drugs

Co-stimulatory Agents

- CD134/OX40 receptor agonist
  - 7 agents in research
- CD137/4-1BB
  - Utomilumab; Urelumab
- CD40
  - SEA-CD40; CDX-1140

Immunomodulatory (small molecules)

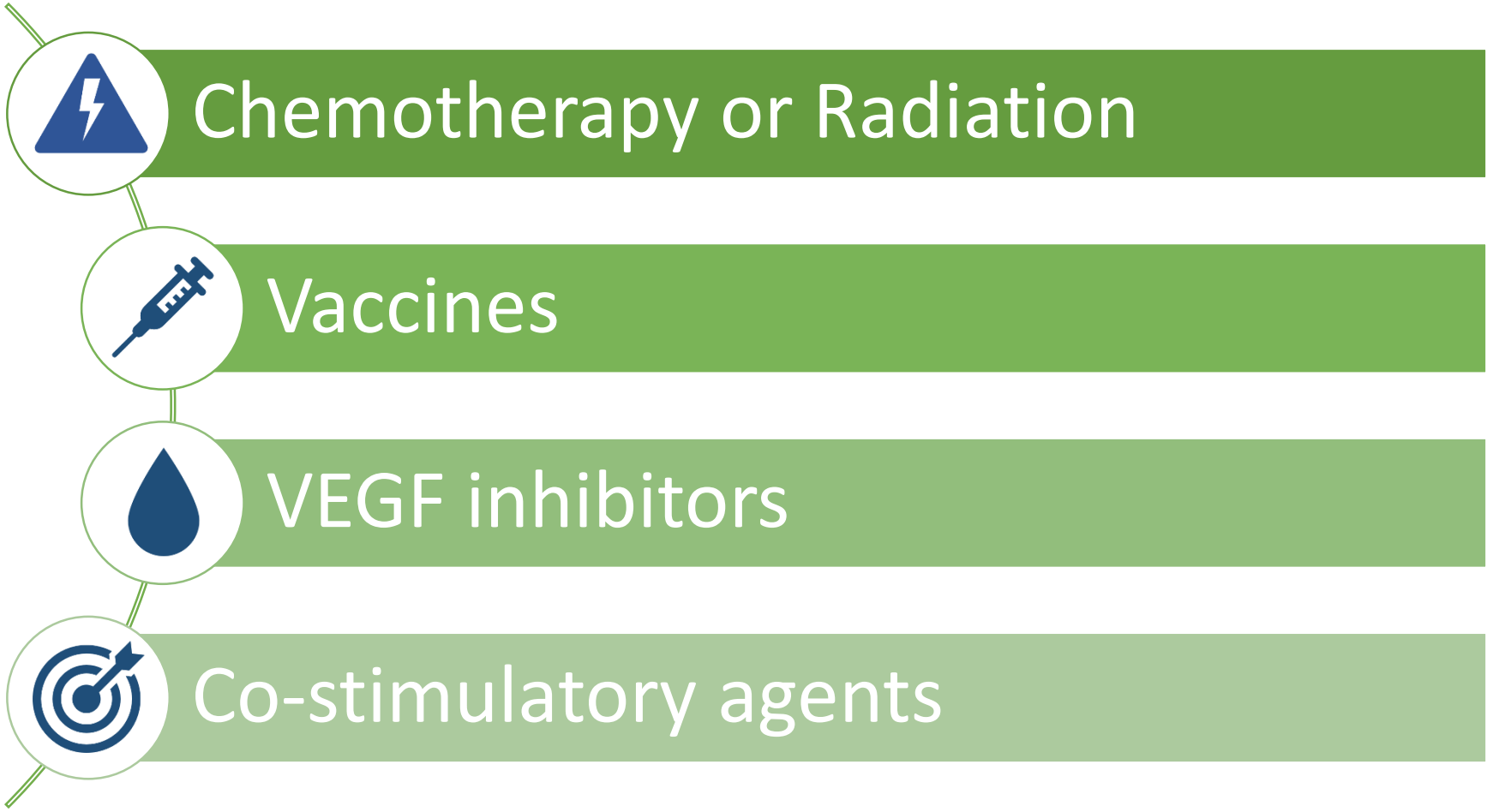
- IDO inhibitors
  - Epacadostat (Failure)



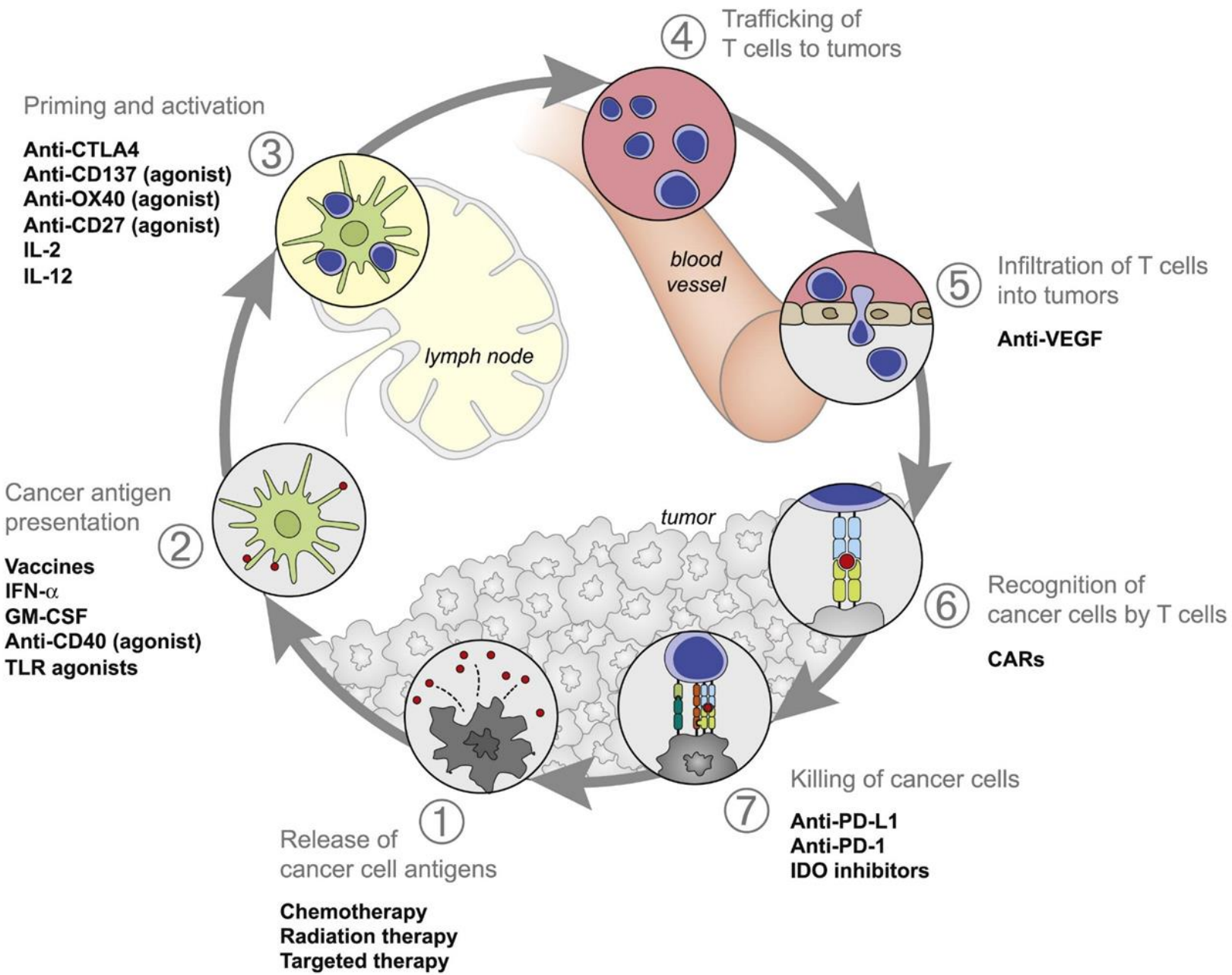
Blood 2017 :blood-2017-06-741041
Clin Cancer Res. 2017 Sep 15;23(18):5349-5357
J Clin Oncol. 2018;36:15_suppl, 108-108
J Clin Oncol. 2018;36 (suppl; abstr 3093)

Combinations

PD-1 / PDL-1



Ann Oncol. 2016;27:1492-1504
EMBO Mol Med. 2017;9:167-180
Clin Cancer Res. 2013;19:1035-1043



Immunity 2013;39:1-20

Immunotherapy Pipeline by Phase and Mechanisms of Action

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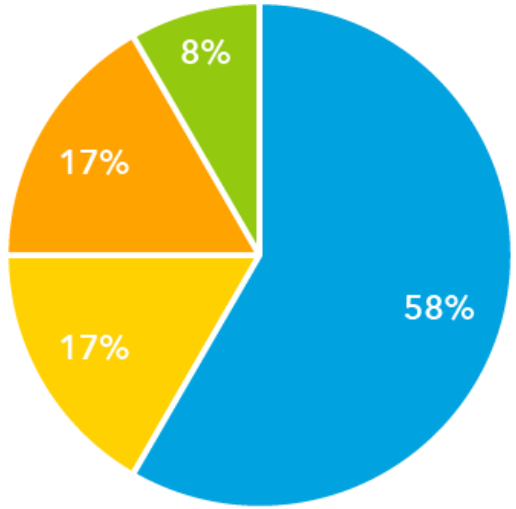
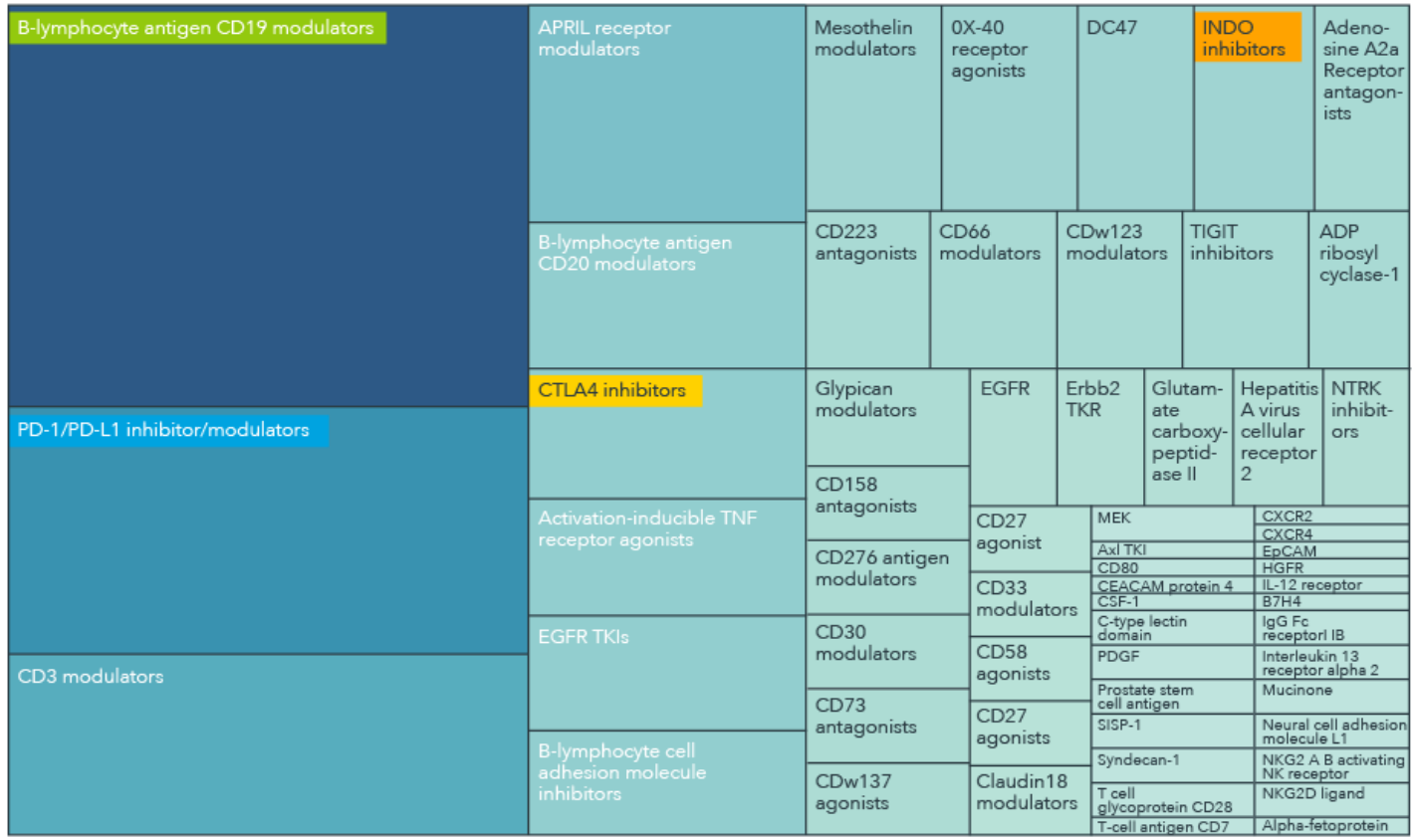
4 Mechanisms ⋯▶ **60 Mechanisms**

52 Number of molecules 1



Phase III and Pre-Reg; Molecules = 12
Phase I and II; Molecules = 289

- PD-1/PD-L1 inhibitor/modulators
- CTLA4 inhibitors
- INDO inhibitors
- B-lymphocyte antigen CD19 modulators



Source: Clarivate Analytics Cortellis, Apr 2018; IQVIA Institute, Apr 2018

Notes: Data query included immuno-oncology therapies sorted by highest status. Diagnostic molecules were not included. Sponsors include industry and non-industry. For molecules with multiple mechanisms, the first listed mechanism was chosen. PD-1 = Programmed cell death protein 1; PD-L1 = Programmed deathligand 1; INDO = Indoleamine-pyrrole-2,3-dioxygenase inhibitor; CTLA4 = cytotoxic T-lymphocyte-associated protein 4; APRIL = A proliferation-inducing ligand; TKIs = tyrosine kinase inhibitors; EGFR = Epidermal growth factor receptor; TIGIT = T-cell immunoreceptor with Ig and ITIM domains.

Report: Global Oncology Trends 2018: Innovation, Expansion and Disruption. IQVIA Institute for Human Data Science, May 2018

Predicting a Response

IMmuno-PREdictive Score (IMPRES)

- Predictor of immune checkpoint blockade in melanoma
- 15 pairwise transcriptomics relations between immune checkpoint genes
  - Immune mechanisms underlying spontaneous regression can predict response
  - Key immune interactions can be captured via specific pairwise relations of the expression of immune checkpoint genes
- Overall accuracy of AUC = 0.83

Nat Med. 2018 Aug 20. doi: 10.1038/s41591-018-0157-9. [Epub ahead of print]

Conclusions

Immunotherapy has become a mainstay,
but the frontier is **still out there.**