CATALYST: The Immuno-oncology Revolution Continues: A 3D View

Chapter 4: Investigational Treatment

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Disclosures

- **Dr. Weber** has disclosed that he is a stockholder for Altor, Biond, and CytoMx. He is a consultant for AstraZeneca, Bristol-Myers Squibb, EMD Serono, Genentech, GlaxoSmithKline, Incyte, Merck, and Sellas Life Sciences.

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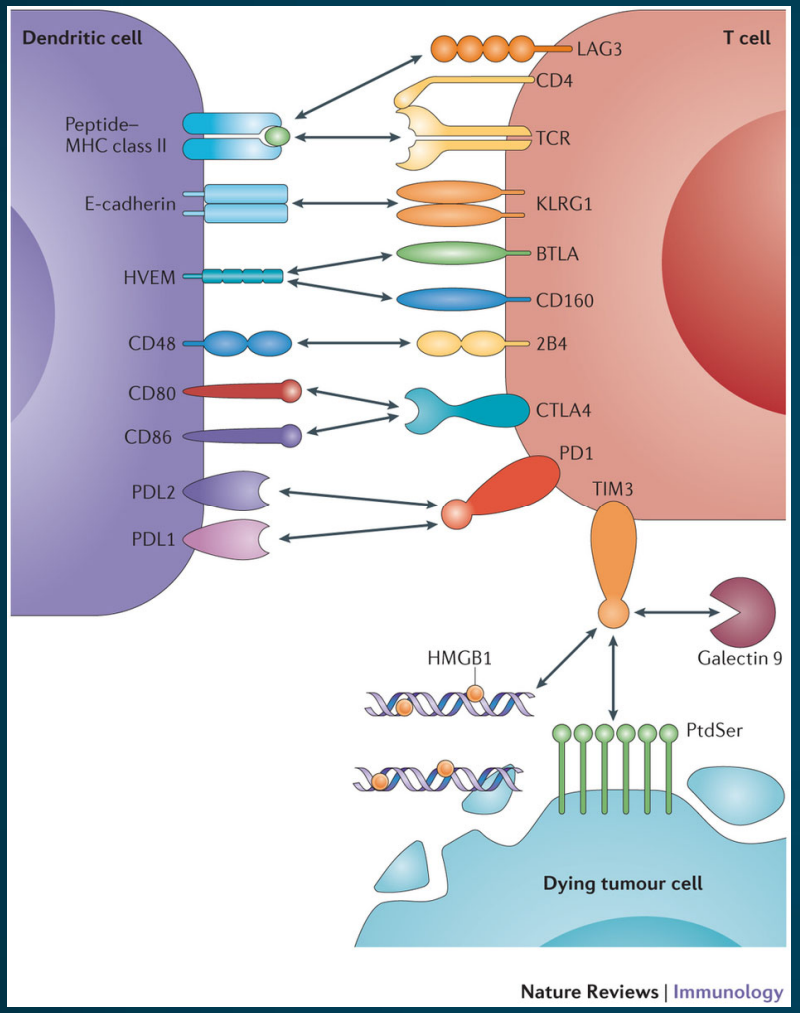
Learning Objectives

- Discuss the pathophysiology of adult malignancies with a focus on tumor immunosurveillance and immune evasion
- Review significant advances and unmet medical needs associated with currently available immuno-oncology therapies, including innate and adaptive resistance mechanisms (eg, T-cell exhaustion)
- Describe immune pathways that may be targeted to overcome immune-evasion mechanisms and emerging clinical data on novel immuno-oncology agents

T-cell Inhibitory Signals



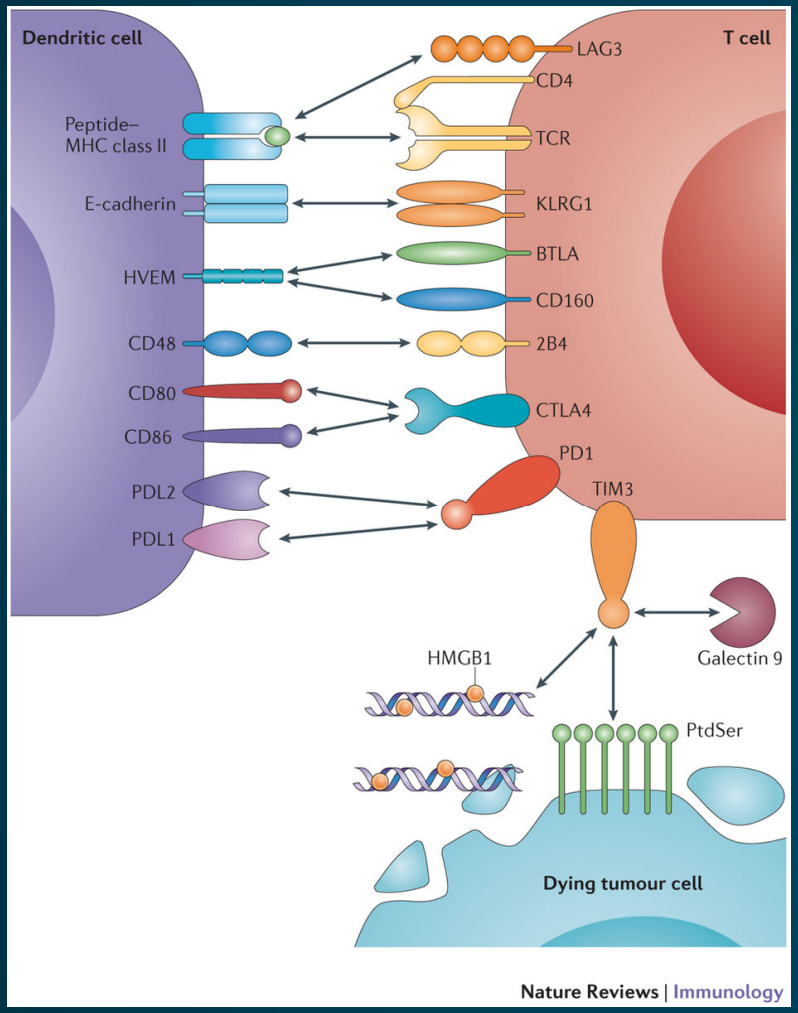
Key points

- Negative regulatory receptors, such as PD1 and LAG3, are expressed on 'exhausted' T cells
- The pre-therapeutic blockade of the PD1 pathway shows durable clinical responses in patients with melanoma and other types of cancer
- Assumed mechanism of action of PD1 blockade is prevention of the interaction between PD1 on tumor-infiltrating T cells and PDL1 expressed on tumor cells
- However, PDL1 expression by tumor cells is not an absolute biomarker of clinical response
- **Furthermore, 'reverse signaling' can occur through PDL1**

LAG-3 = lymphocyte-activation gene 3

Nguyen LT, et al. *Nature Rev Immunol. 2015;*15:45–56.

T-cell Inhibitory Signals (cont'd)

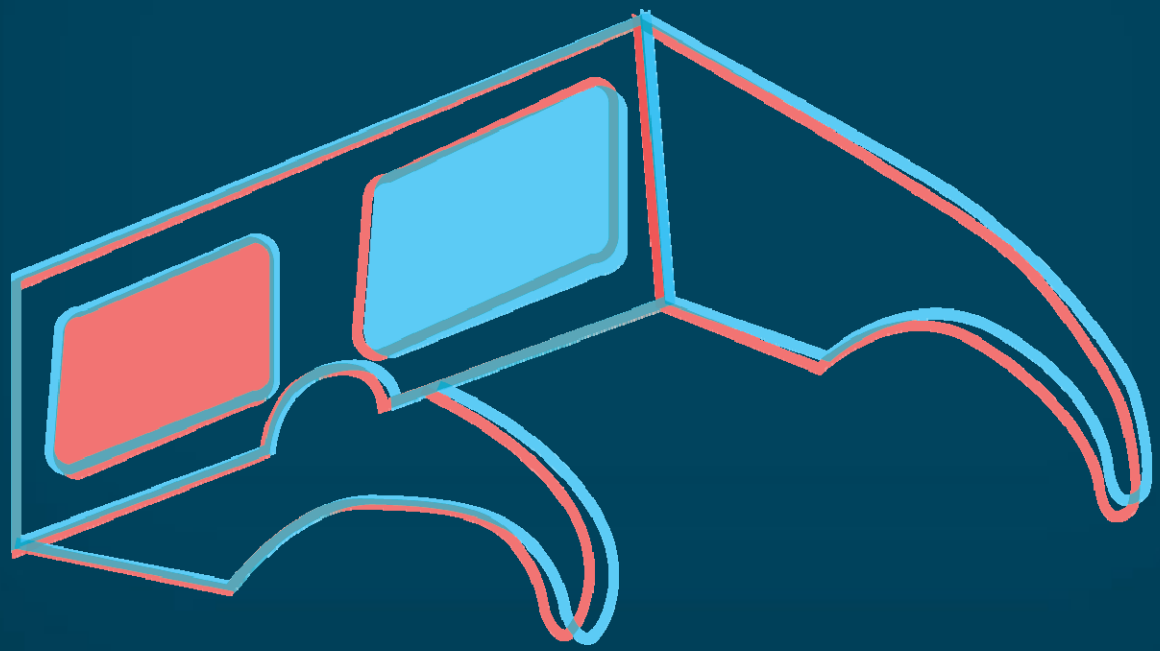


Key points

- The clinical activity of blocking LAG3 is not yet well defined, but has been shown to induce anti-tumor responses, especially with PD-1 blockade.
- Triggering of LAG3 on T cells by MHC class II ligands downregulates T cell function.
- It may also have other immunomodulatory roles.
- In addition, soluble LAG3 exhibits immune adjuvant activity.

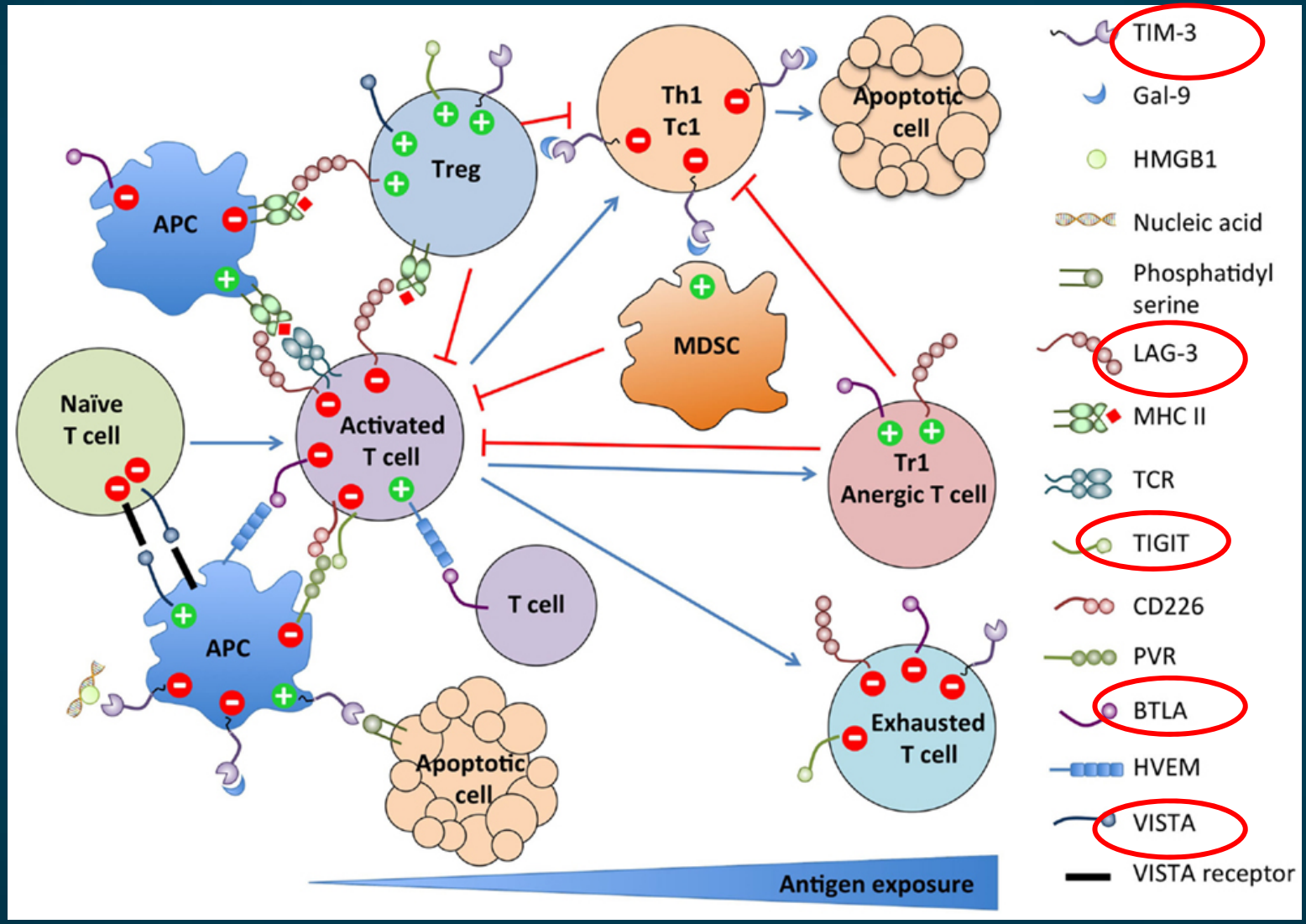
Nguyen LT, et al. *Nature Rev Immunol. 2015;*15:45–56.

Please put on your 3D glasses



We will now watch a short video animation: on New Checkpoint Pathways and Other Therapeutic Targets

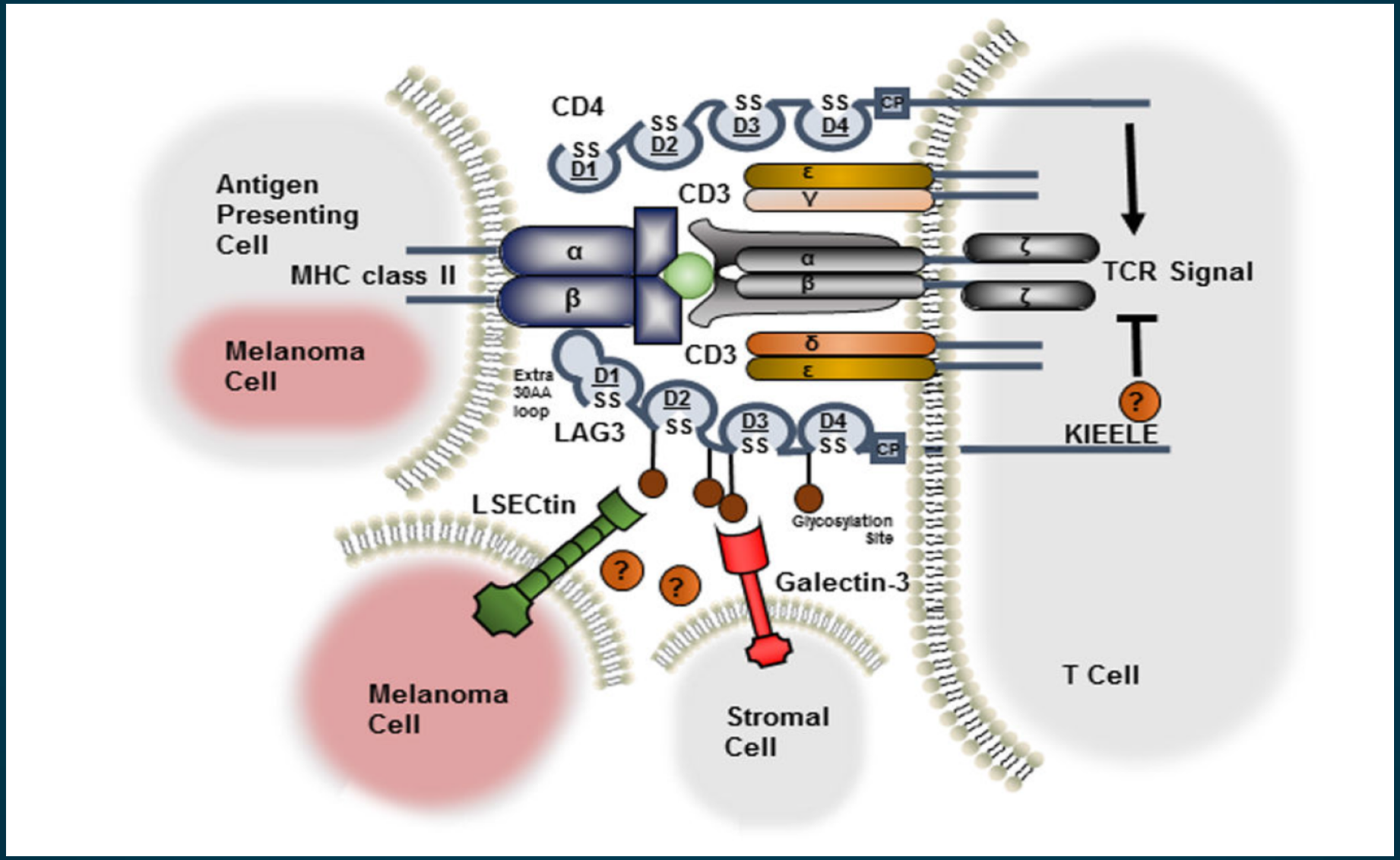
Beyond PD-1/PDL-1 And CTLA4: Other Negative Checkpoint Regulators



TIM-3 = T-cell immunoglobin mucin-3; T-cell immunoreceptor with Ig and ITIM domains; BTLA = B and T lymphocyte attenuator; VISTA = v-domain Ig suppressor of T cell activation

Anderson AC, et al. *Immunity Rev*. 2016;44:989-1004.

Mechanism of Action of LAG-3 Blockade



Andrews LA, et al. *Immunol Rev*. 2017;276: 80–96.

Beyond Checkpoints: Other Targets for Therapy

- Additional inhibitory molecules on T cells
  - TIGIT, a checkpoint expressed on cytotoxic and memory T cells, Tregs, and NK cells
  - TIM-3, involved in suppression of both innate and adaptive immune cells
  - VISTA and BTLA are other negative checkpoints

TIGIT = T cell immunoreceptor with Ig and ITIM domains.

Anderson AC, et al. *Immunity Rev*. 2016;44:989-1004.

Beyond Checkpoints: Other Targets for Therapy (cont'd)

– Agonistic or activating molecules on T cells

- CD137, a receptor on NK and T cells that enhances T-cell function
- GITR, a receptor on T cells and other immune cells that enhances cell division and promotes antitumor activity
- ICOS, a receptor expressed on activated cytotoxic T cells, regulatory T cells, NK cells, and other types of T cells that promote the activation, proliferation, and survival of cytotoxic T cells, as well as the survival of memory T cells
- OX40, an activating receptor on cytotoxic T cells and Tregs that activates and amplifies T-cell responses

GITR=glucocorticoid-induced TNFR-related protein; ICOS=inducible T-cell co-stimulator

Long L, et al. *Genes Cancer*. 2019; 9:176-1899; Jian-Feng L, et al. *Mol Oncol*. 2017;11:235-247; Omar HA, et al. *Crit Rev Oncol/Hematol*. 2019;135:21-20; Melero I et al. *Oncoimmunology*. 2017: 429-446; Peyraud F, et al. *Cur Onc Rep*. 2017;19:70; Zakharia Y, et al. 2017 AACR Annual Meeting; April 1-5, 2017, Washington, DC. Abstract CT117.

Beyond Checkpoints: Other Targets for Therapy (cont'd)

- NK mechanisms
  - KIR
- Non-effector cell mechanisms
  - Activating: NLRP3, STING to create an inflammatory microenvironment

NLRP3 = nucleotide-binding oligomerization domain-like receptor family, pyrin domain containing 3; STING = stimulator of interferon genes; KIR = killer cell immunoglobulin-like receptor

Corrales L, et al. *Clin Cancer Res*. 2015;21:4774-4779; Waldhauer I, et al. *Oncogene*. 2008; 27:5932-5943; Dupaul-Chiccione J, et al. *Immunity*. 2015;43:751-763.

Beyond Checkpoints: Other Targets for Therapy (cont'd)

- Inhibitory:
  - **CSF1R (TAMs) Describe MOA of blocking Ab**
  - CTLA-4 (Treg and activated effector cells)
  - IDO1 (enzymatic inhibition of tryptophan)
  - CCR2/5 (chemokine recruiting MDSCs, TAMs, and Tregs to the TME)
  - IL-8 (chemokine produced by macrophages, monocytes, and stromal cells that promotes the recruitment of immunosuppressive MDSCs and also activates the angiogenic response).
  - CD73 and CD39 (inhibitory ectonucleotidases on Tregs)
  - TGFbeta-R (suppression of immune activity an cellular migration, long-term effect on tumor cells)

MDSC = Myeloid-deprived suppressor cells; TAM = tumor-associated macrophages; Treg = regulatory T cells = tumor microenvironment.

Marshall HT, et al. *Front Oncol*. 2018;8:315; Huck BR, et al. *Angew Chem Int Ed Eng*. 2018;57L441204428; 33rd Ann Meeting * Pre-Conference Programs SITC 2018. *J Immunother Cancer*. 2018l 6(suppl 1):114; 2018 ASCO Annual Meeting New Highlights. https://myriadrbm.com/2018-asco-news-highlights/; Zhong Z et al. *Clin Cancer Res*. 2010;16:1191-1205.

Which molecules are in trials?

- LAG-3 ab has been added to nivolumab as front-line therapy
- Tim3 ab has been tested as a single agent
- ICOS ab is tested with pembrolizumab
- OX40 ab has been tested with pembrolizumab
- CD137 ab has been developed alone and with OX-40 ab
- GITR ab has been tested alone
- CSF-1R has been tested with pembrolizumab
- IDO inhibitor + pembrolizumab failed to show superiority to pembrolizumab alone

GITR = glucocorticoid-induced TNF receptor; ICOS = T-cell inducible co-stimulator; CSF-IR = colony-stimulating factor-1 receptor; IDO=indoleamine 2,3-dioxygenase

Long L, et al. *Genes Cancer*. 2019; 9:176-1899; Jian-Feng L et al. *Mol Oncol*. 2017;11:235-247; Omar HA, et al. *Crit Rev Oncol/Hematol*. 2019;135:21-20; Melero I, et al. *Oncoimmunology*. 2017: 429-446; Peyraud F et al. *Cur Onc Rep*. 2017;19:70; Zakharia Y et al. 2017 AACR Annual Meeting; April 1-5, 2017, Washington, DC. Abstract CT117.

Summary

- The adaptive immune system has many “brakes” and many “accelerators” whose expression may be altered in cancer
- Monoclonal antibodies have been developed that impact on, and block signaling through checkpoints like CTLA4 and PD1
- Those antibodies have activity in diverse cancers, and PD-1/PD-L1 blocking antibodies are now approved in a variety of malignancies and have changed the face of cancer therapy
- LAG3 and Tim3 are promising checkpoints whose blocking antibodies have entered phase I and II trials and shown early anti-tumor activity
- Numerous additional agents and antibodies that block checkpoints or promote activating molecules are in trials alone and in combination with PD-1 blockade

This has been chapter 4; the next chapter of CATALYST: The Immuno-oncology Revolution Continues, will be entitled "*Response to therapy and management of adverse events from targeted and immune-therapies*"

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