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Immunotherapies on the horizon

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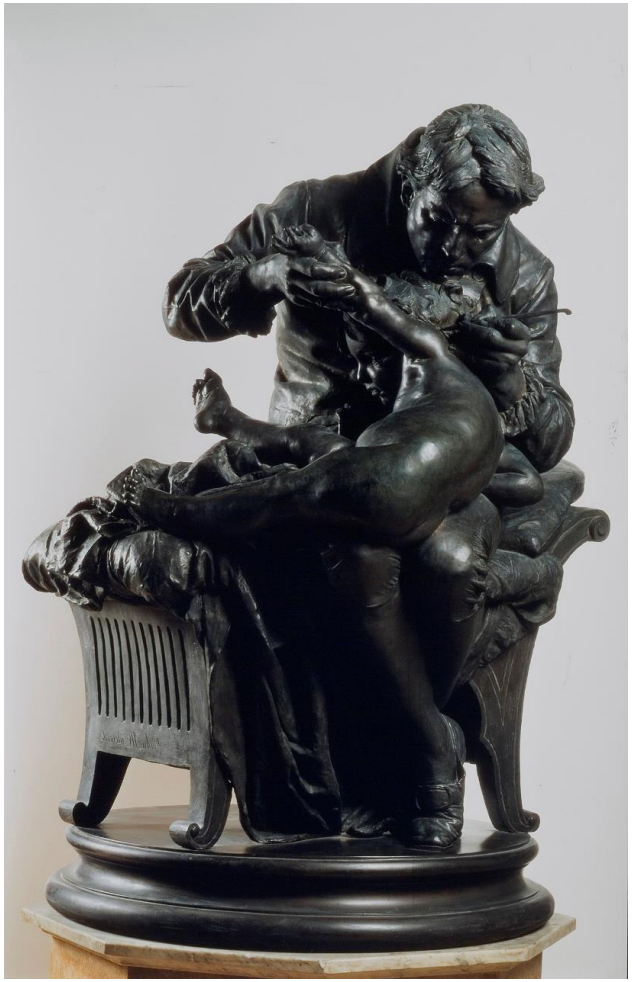

"Jenner". Giulio Monteverde, 1873

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Disclosures

Merck

-Research support

Biomed Valley Discoveries

-Consulting

Takeda

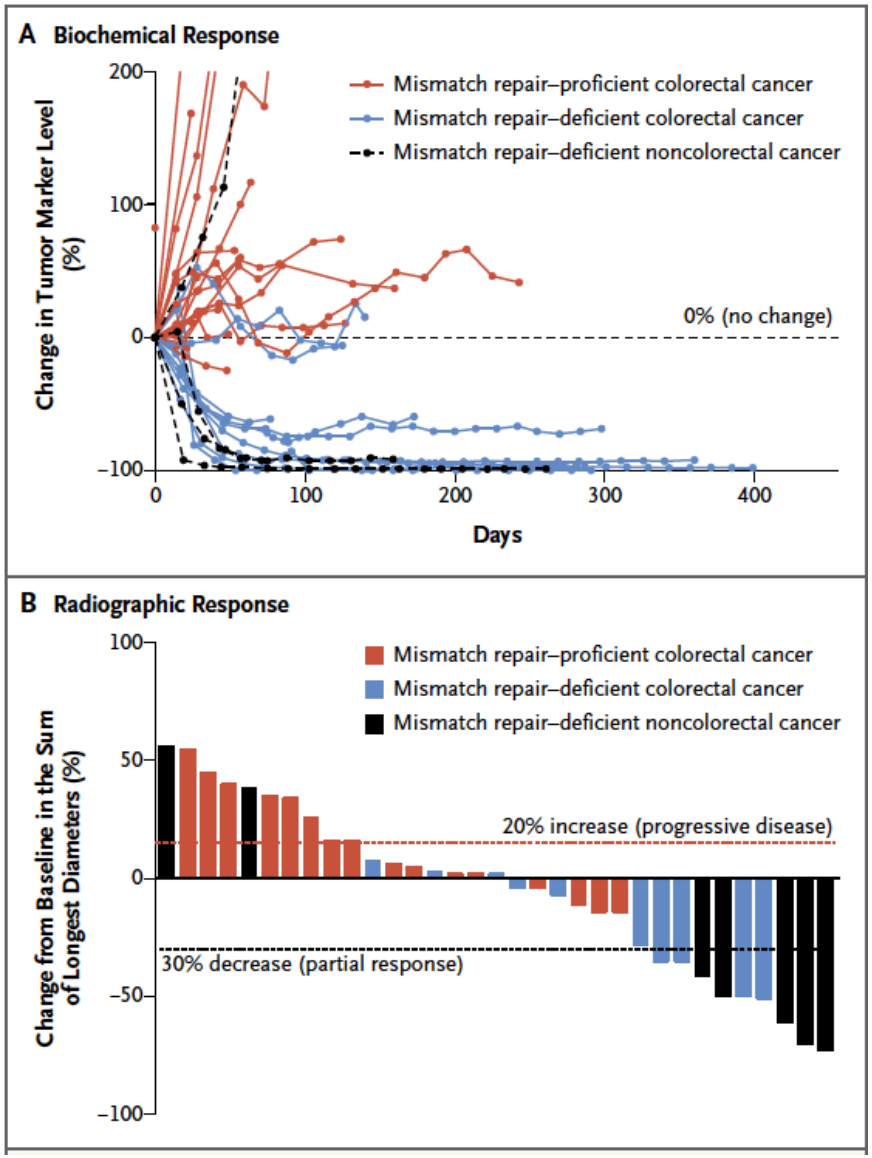
-Consulting

Sanofi

-Consulting

This presentation will include discussion of non-FDA-approved treatments

Immune checkpoint blockade can be effective against other cancers



Pembrolizumab (anti-PD-1) in mismatch repair-deficient cancers

Le D. et al., NEJM 2015

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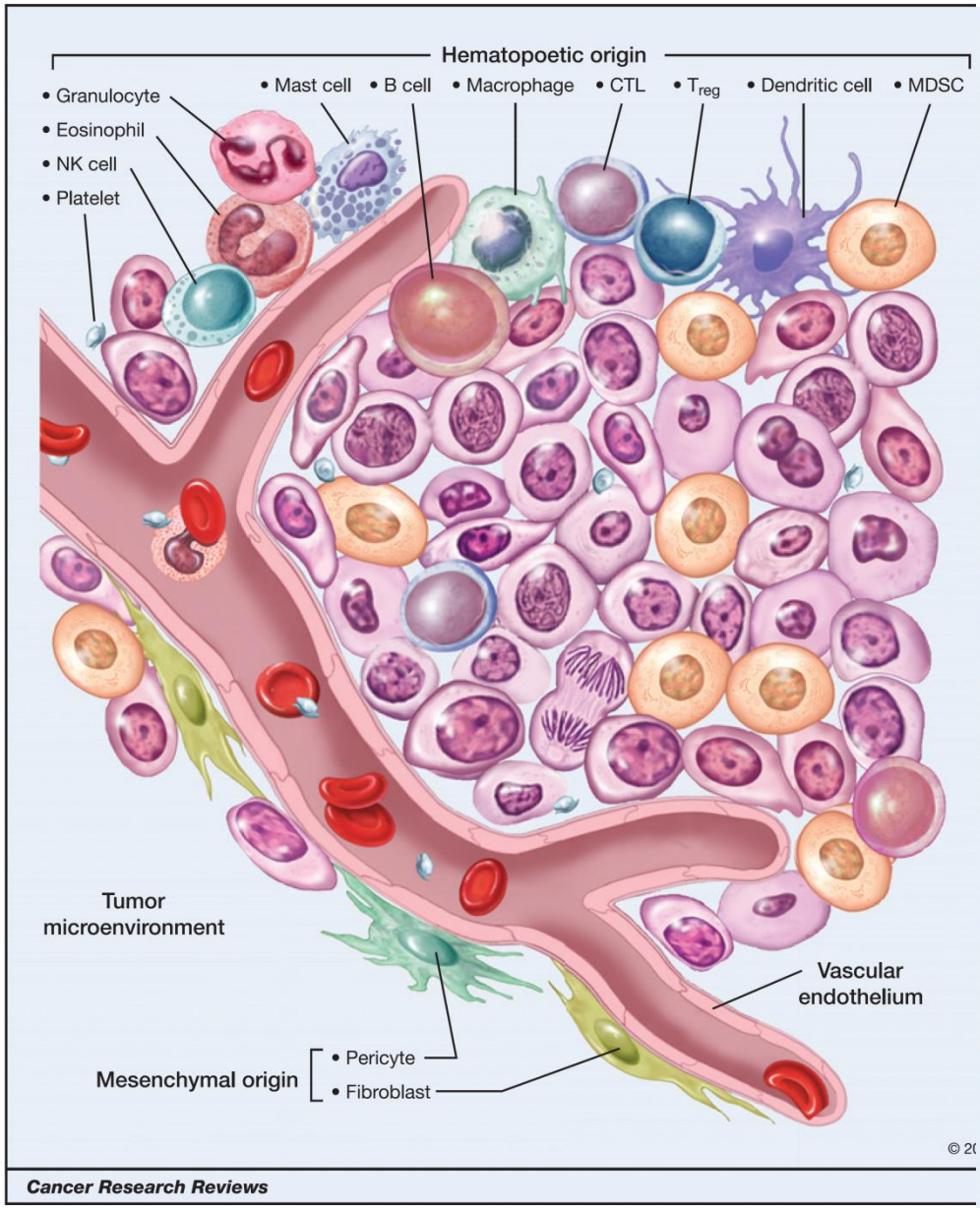
PD-1/PD-L1 blockade works in some cancers, but not all

- **Mismatch repair deficient cancers**
  - Pembrolizumab: 40% ORR, 90% DCR (NEJM 2015); *0% ORR in non-MSI CRC
- **Head and Neck Cancer**
  - Pembrolizumab: 18% ORR, 17% SD (ASCO 2016)
  - Nivolumab: improvement in OS compared to chemotherapy in phase III CheckMate 141 trial; most benefit seen in PD-L1+ and HPV+ patients (AACR 2016)
- **Gastric Cancer**
  - Pembrolizumab: ORR 22% in PD-L1+ patients (ASCO 2015), now FDA-approved
  - Nivolumab: ORR 14%, SD19% (2016 GI cancers symposium)
- **Triple negative breast cancer**
  - Pembrolizumab: ORR 18.5%, SD 26% in PD-L1+ patients (SABCS 2014)
- **Cervical Cancer**
  - Pembrolizumab: ORR 12.5%, SD 12.5% in PD-L1+ patients (ASCO 2016)
- **Ovarian Cancer**
  - Nivolumab: ORR 15%, SD 30% (JCO 2015)
  - Avelumab: ORR 17%, SD 48% (ASCO 2015)
  - Pembrolizumab: ORR 12%, SD 23% (ASCO 2015)
- **Soft tissue sarcomas**
  - Pembrolizumab: Limited activity (ASCO 2016)
  - Nivolumab: Limited activity (ASCO 2016)
- **Hematologic malignancies**
  - Hodgkin disease
    - Nivolumab (FDA - approved): ORR 87%, SD 13% (NEJM 2015)
    - Pembrolizumab: ORR 66%, SD 21% (ASH 2014)
  - Non-Hodgkin lymphoma
    - Nivolumab (ORR): DLBCL 36%, FL 40% (ASH 2014)
  - Multiple myeloma
    - Nivolumab: ORR 0%, SD 67%

New immune therapeutic strategies and combinations are needed

Various components of the tumor microenvironment inhibit the immune system and may prevent response to anti-PD-1/PD-L1 therapy



Suppressive mechanisms

MDSC cell

- Secretion of NO, arginase and ROS
- Sequestration of cysteine
- Impaired differentiation
- Defective antigen presentation

T_{reg} cell

- Secretion of suppressive cytokines (TGF-β, IL-10)
- Sink for IL-2, IL-7, IL-12, and IL-15
- Impaired activation of CTLs

Macrophage

- M2 differentiation/cytokine profile
- Defective antigen presentation
- Lack of costimulation for T cells
- Impaired tumorocidal activity

Dendritic cell

- IDO expression; induction of Tregs
- Impaired maturation
- Defective antigen presentation
- Lack of costimulation for T cells

Cancer cell

- Loss of MHC class I and antigen processing machinery
- Antigen loss variants
- Secretion of VEGF, GM-CSF, G-CSF and gangliosides

Kerkar SP, Restifo NP Cancer Res 2012;72:3125-3130

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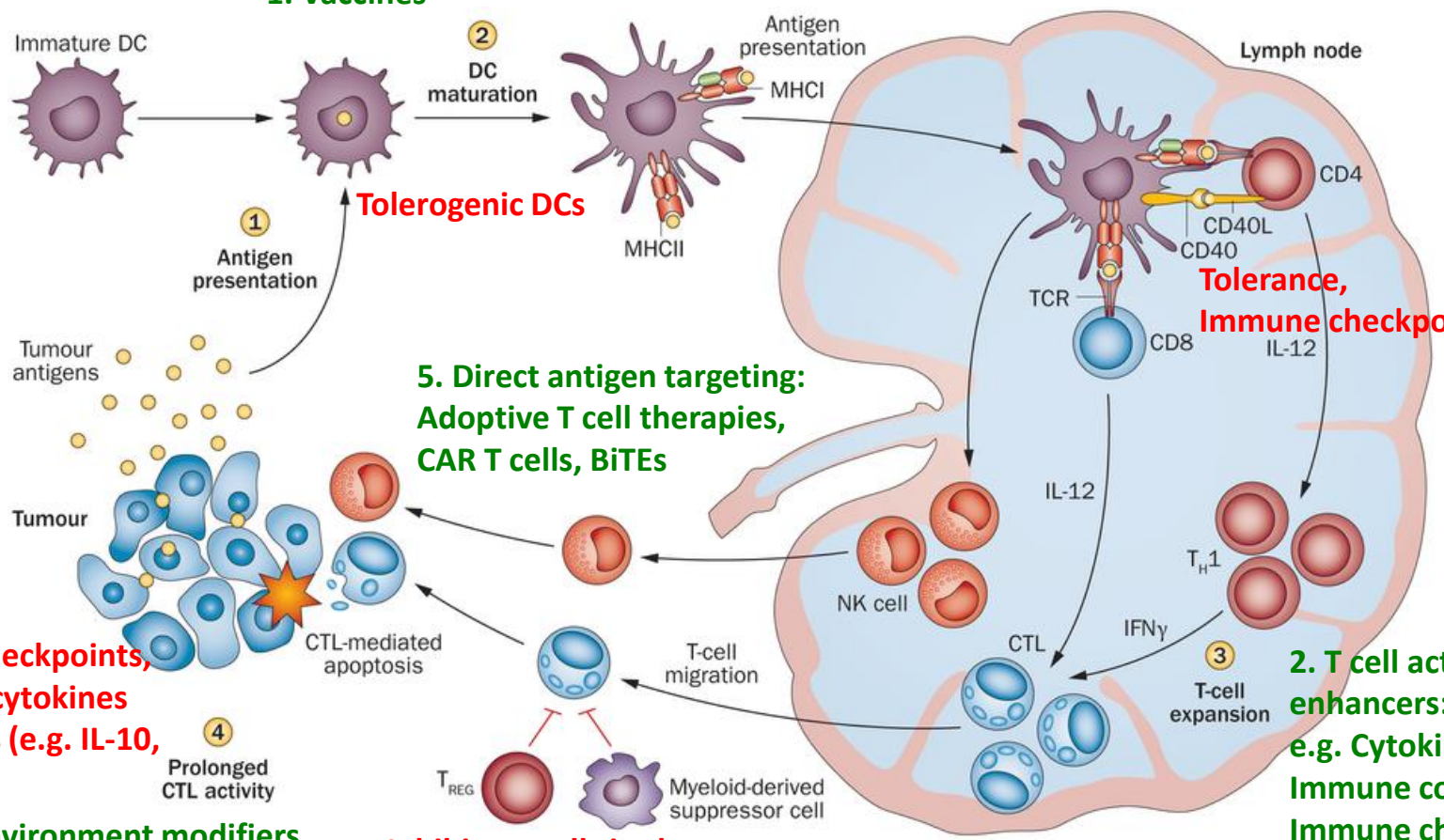
Each step in the anti-tumor immune response presents a barrier to successful immunotherapy



Adapted from Melero et. al, Nature Reviews Clinical Oncology, 2014

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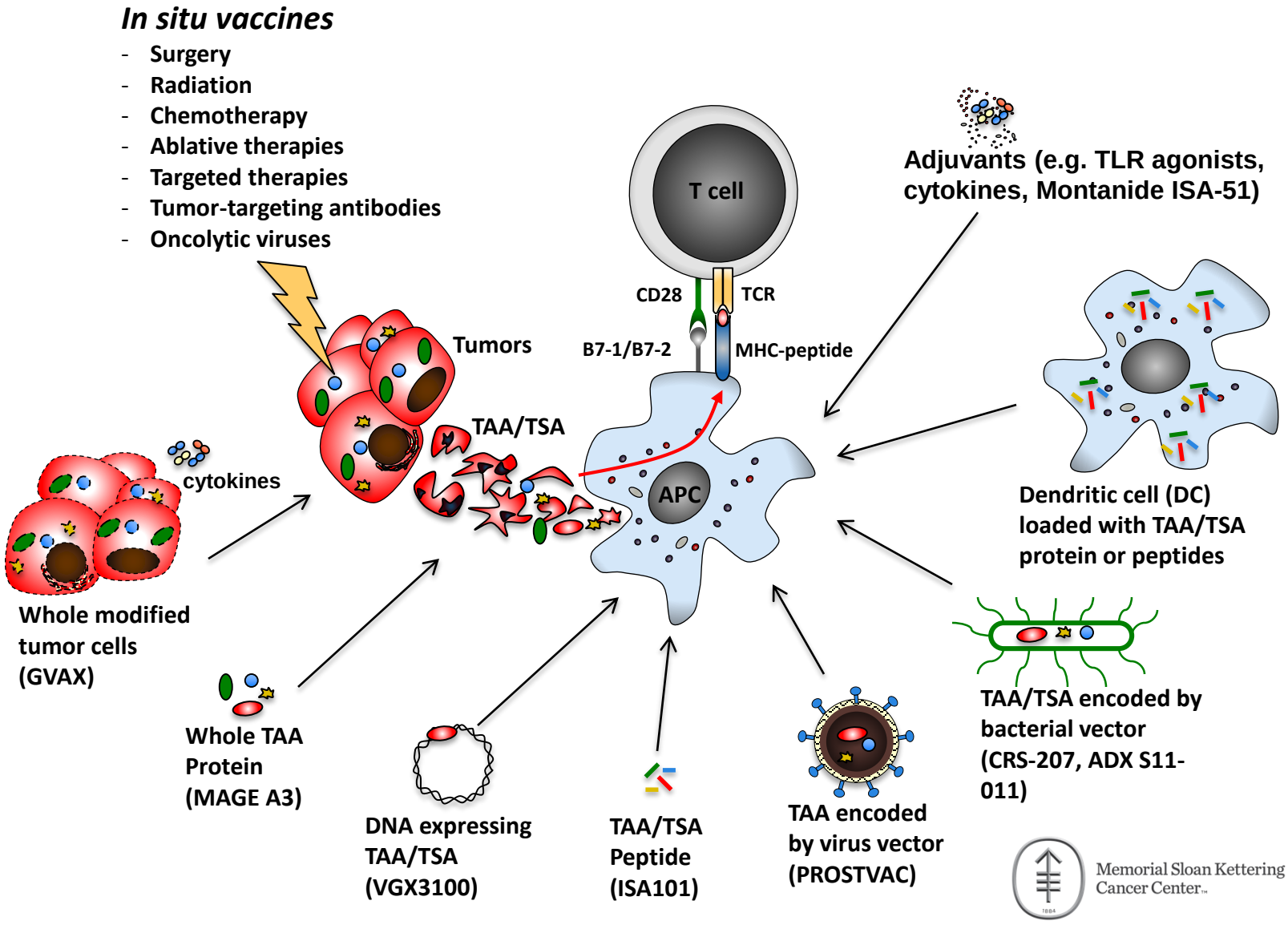
1. Cancer Vaccines

Cancer vaccines aim to enhance recognition of tumor antigens by the immune system



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DNA-encoded vaccines

Strategy

- Tumor antigen encoded by a DNA plasmid vector

Advantages:

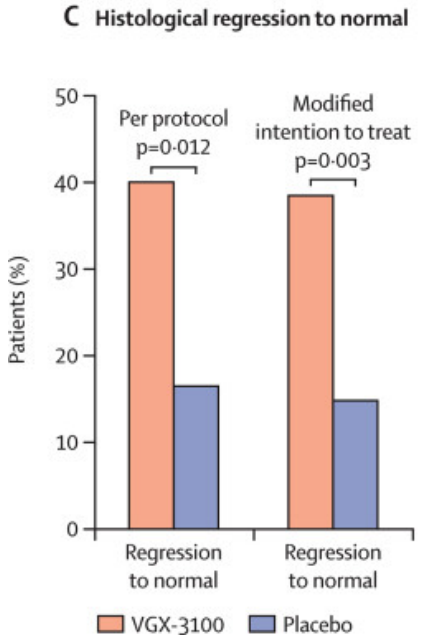
- DNA acts as an adjuvant
- Endogenous antigen processing, no HLA restriction

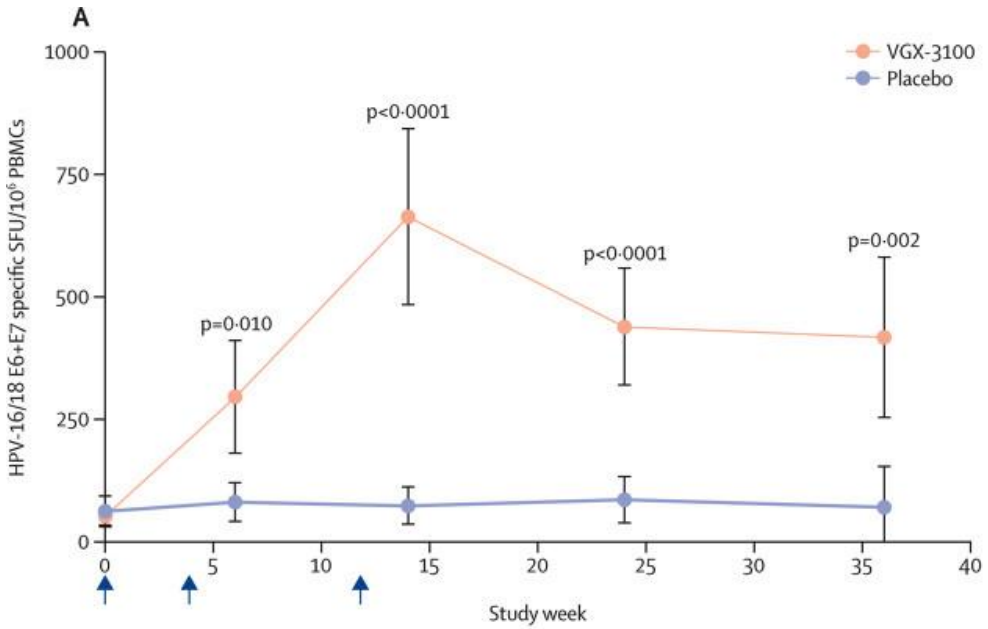
Disadvantages:

- Delivery may be cumbersome (e.g. electroporation)

Example:

- VGX3100: DNA vaccine against HPV16, 18 E6/E8 proteins in CIN2/3 patients





Trimble et. al, Lancet 2015

Virus-vectored vaccines

Strategy:

- Tumor antigen encoded by a replicating or non-replicating virus vector

Advantages:

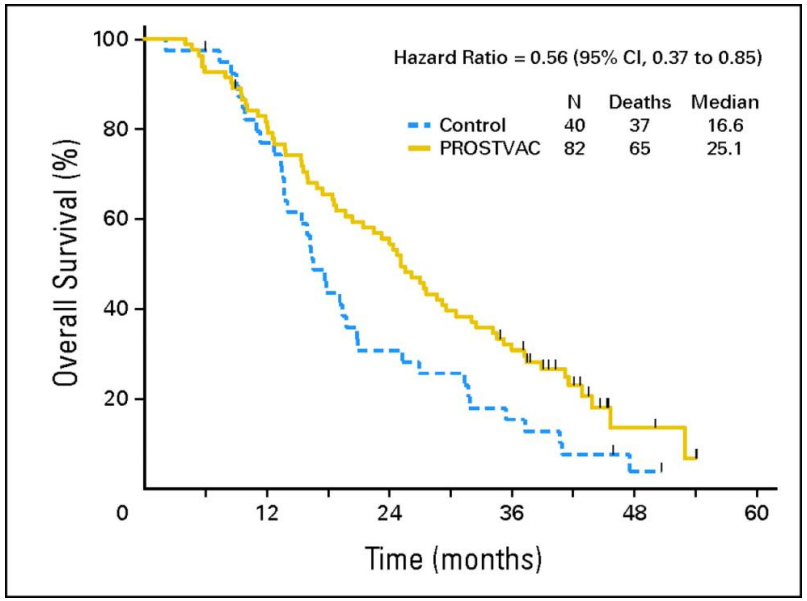
- Virus-induced activation of immune response acts as an adjuvant
- Sustained tumor antigen expression

Disadvantages

- Potential safety concerns, challenges with administration

Example:

- PROSTVAC (vaccine composed of two poxvirus vectors, vaccinia and fowlpox, encoding PSA, B7.1, ICAM-1, and LFA-3)



Kantoff et al., JCO 29:1099 (2010)

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Bacteria-vectored vaccines

Strategy

- TAA encoded by recombinant bacteria

Advantages:

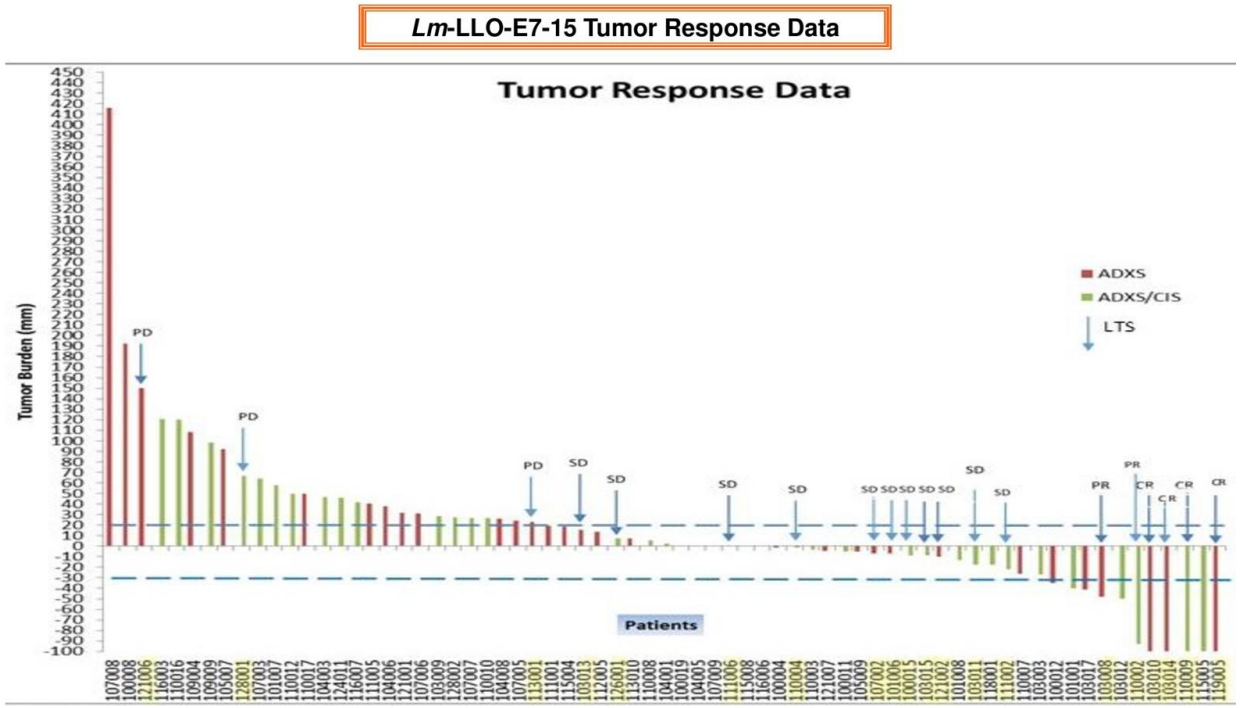
- Bacteria act as an adjuvant
- Sustained TAA production

Disadvantages

- Potential safety concerns, challenges with administration

Example

- ADX-S11-001 – engineered Listeria monocytogenes expressing HPV16 E7



Basu et. al ASCO 2014

Phase II GOG265 study is ongoing

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In situ vaccination

Strategy

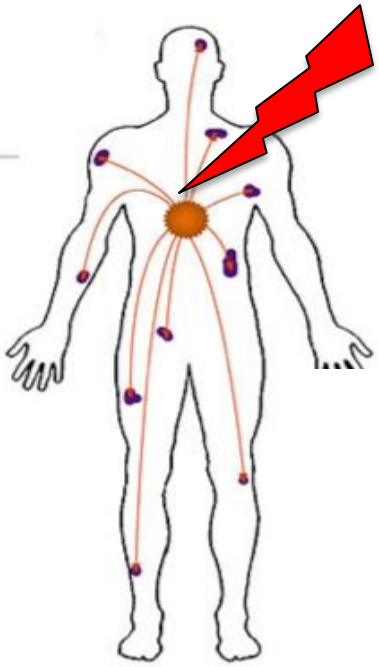
- Generate localized tumor lysis, antigen release and presentation, and activation of T cells that would be active systemically

Advantages

- Exploit broad tumor antigen repertoire available at the tumor site
- Low potential for systemic toxicity

Disadvantages

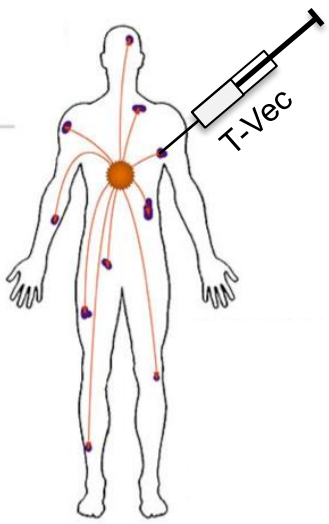
- Can be logistically challenging

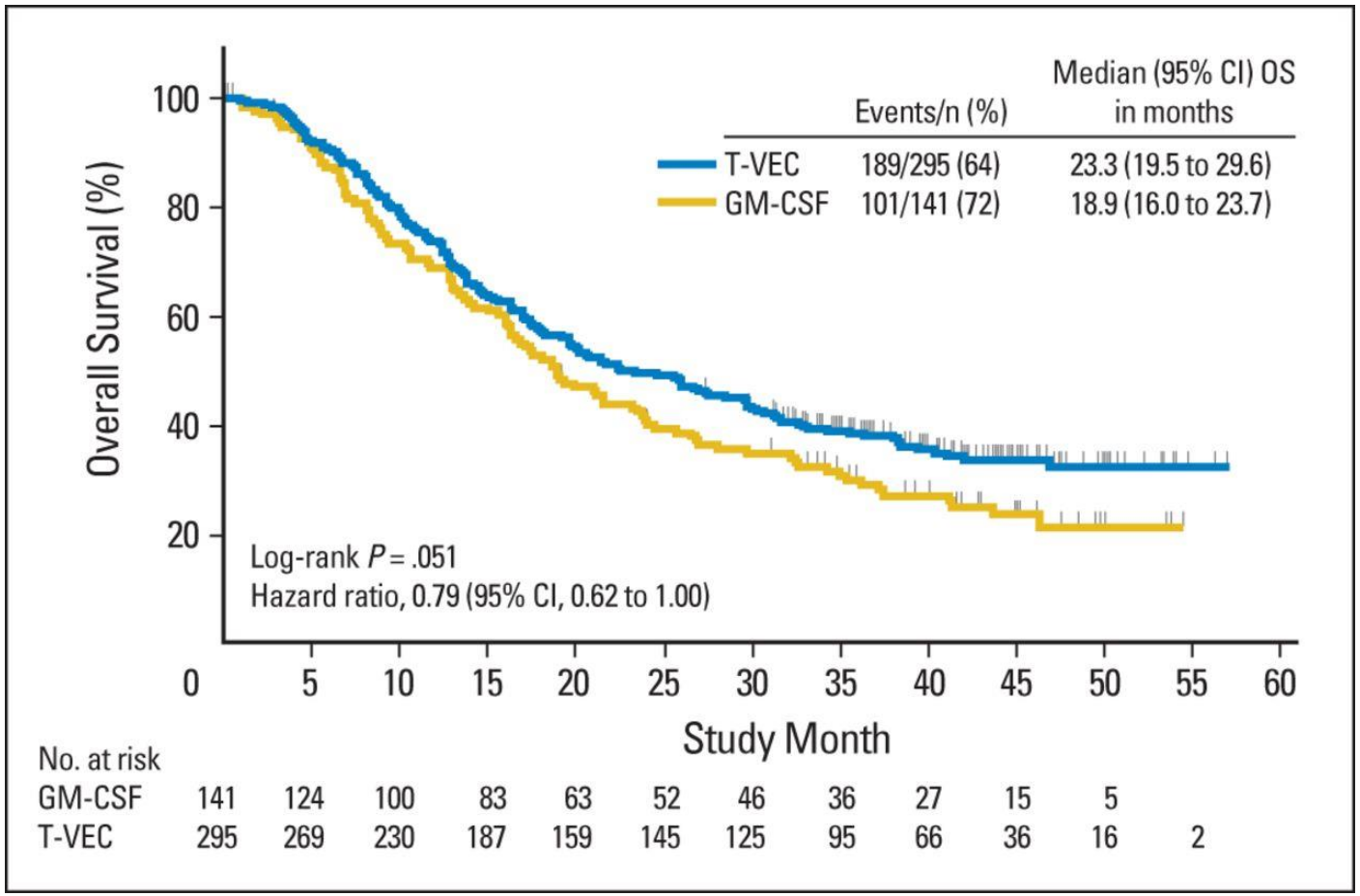


Examples

- **Local ablative therapies** (radiation, cryotherapy, microwave ablation, etc.)
- **Intratumoral cytokine injection** (e.g. IL-2)
- **Intratumoral TLR agonist injection** (e.g. CpG)
- **Intratumoral injection of bacteria** (e.g. Clostridium novyi)
- **Intratumoral injection of viruses** (e.g. Talimogene laherparepvec)

Talimogene laherparepvec in metastatic melanoma





Andtbacka et al., JCO 2015

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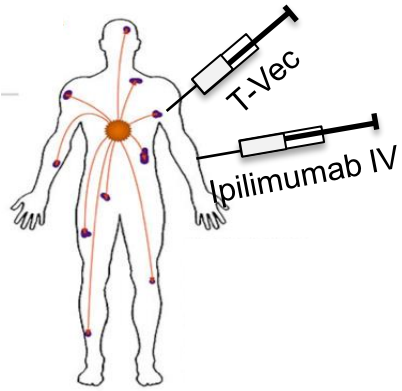
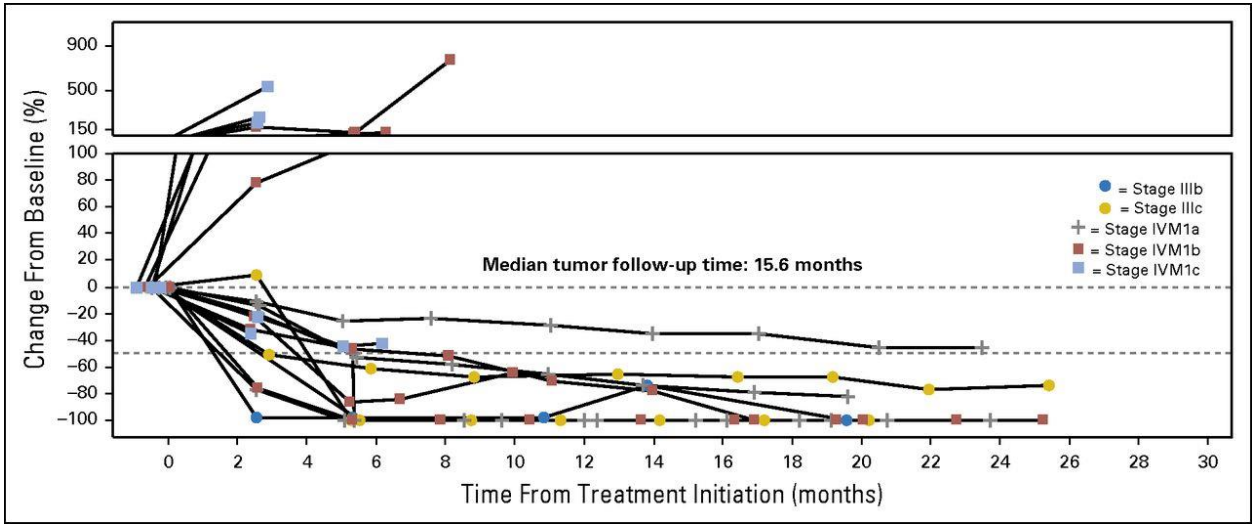
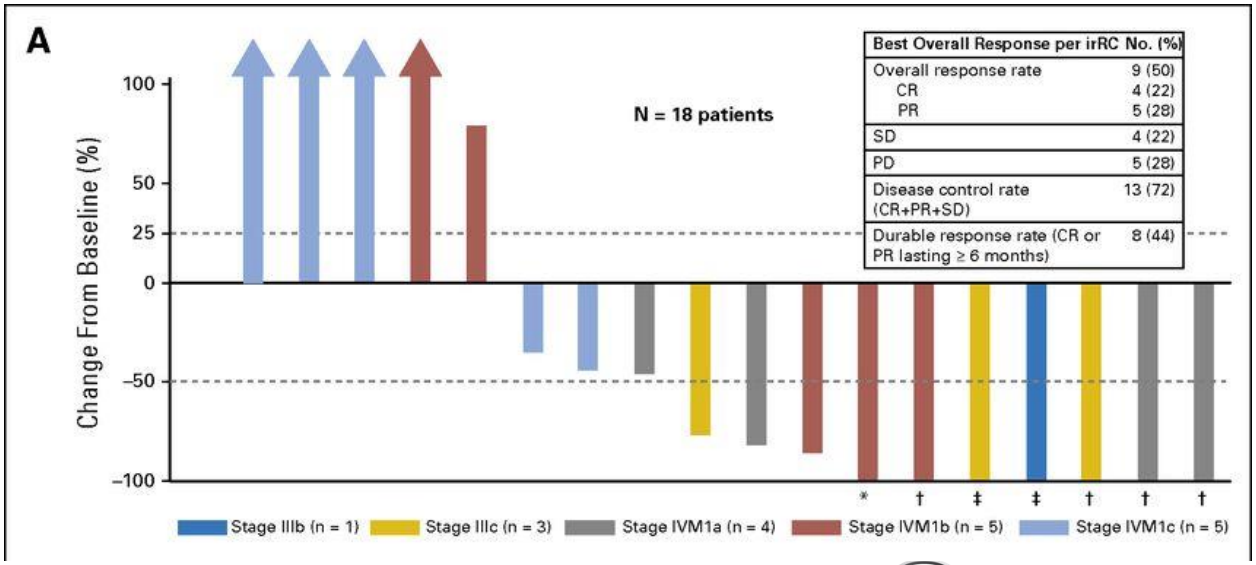
Intratumoral T-VEC in combination with ipilimumab (ipi) in previously untreated, unresected stage IIIB-IV melanoma







Puzanov I, et al., JCO 2016

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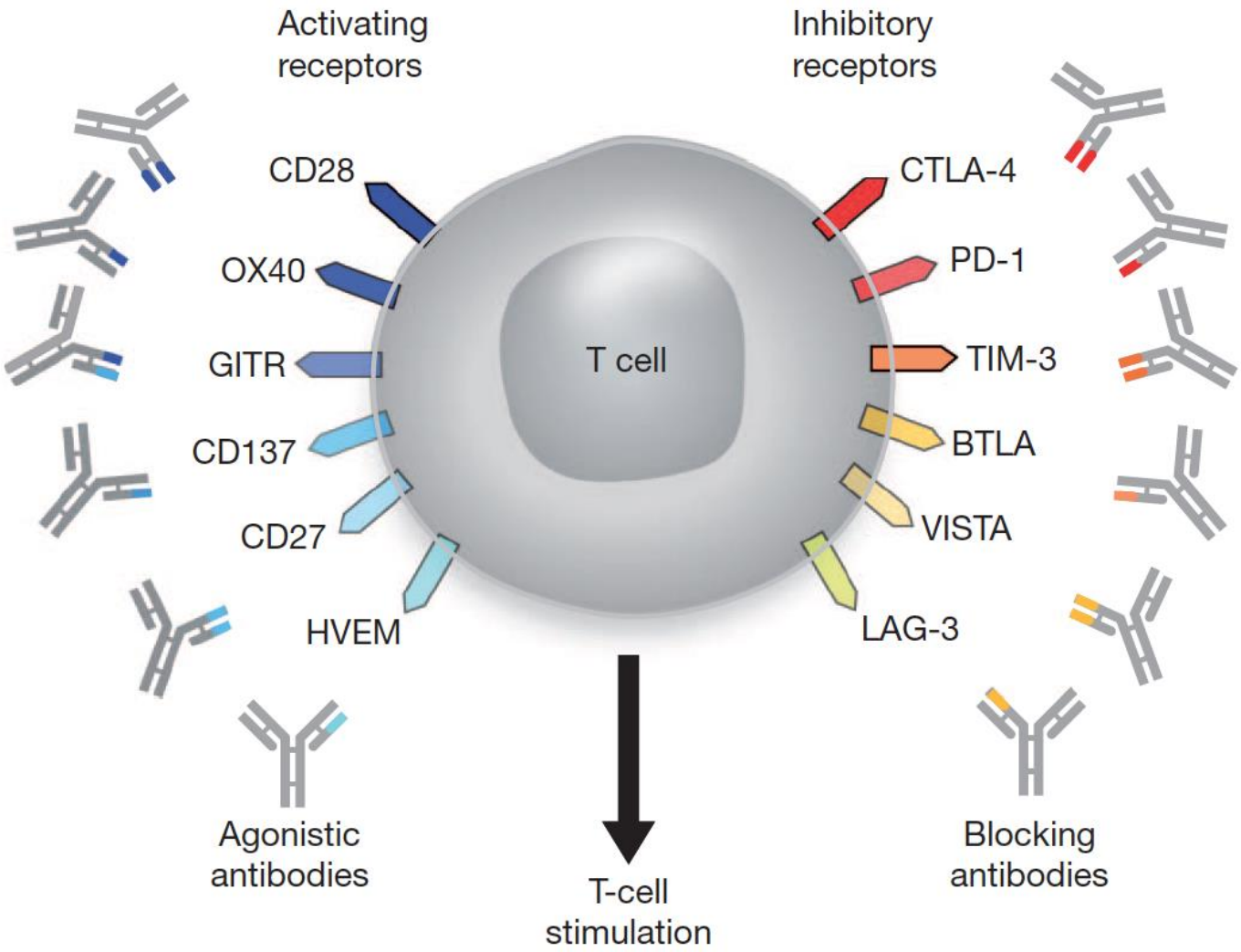
2. Immune strategies to enhance T cell activation

Multiple costimulatory/coinhibitory receptors and ligands control the activation state of T cells



Mellman I et al. *Nature* 480: 480 (2011)

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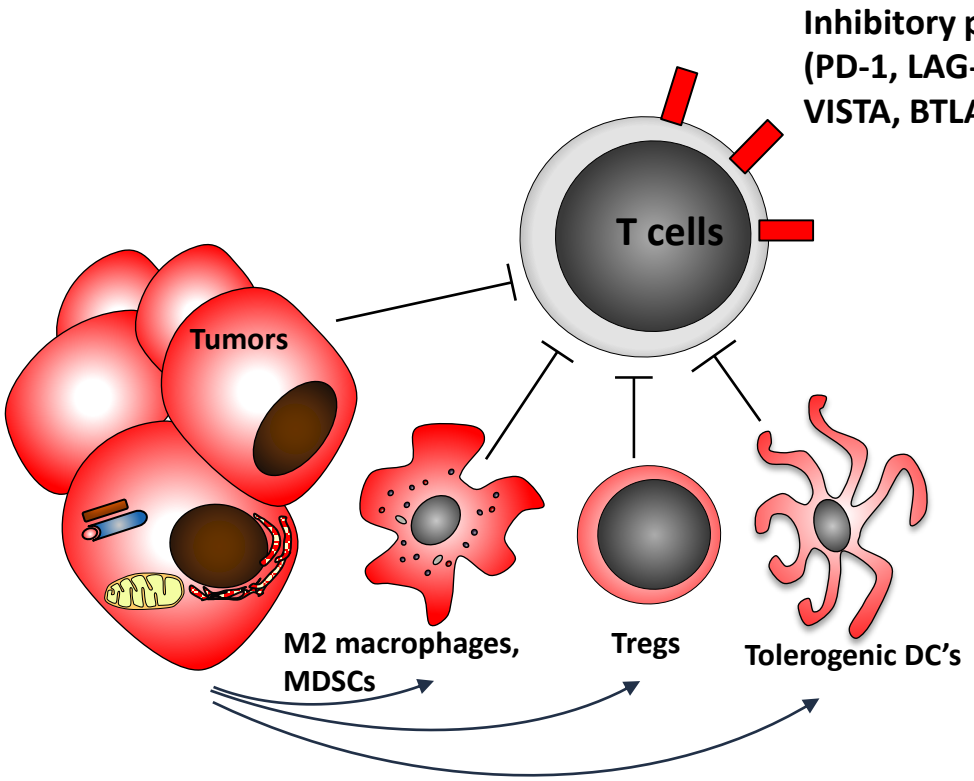
Targeting mechanisms of T cell inhibition in tumors

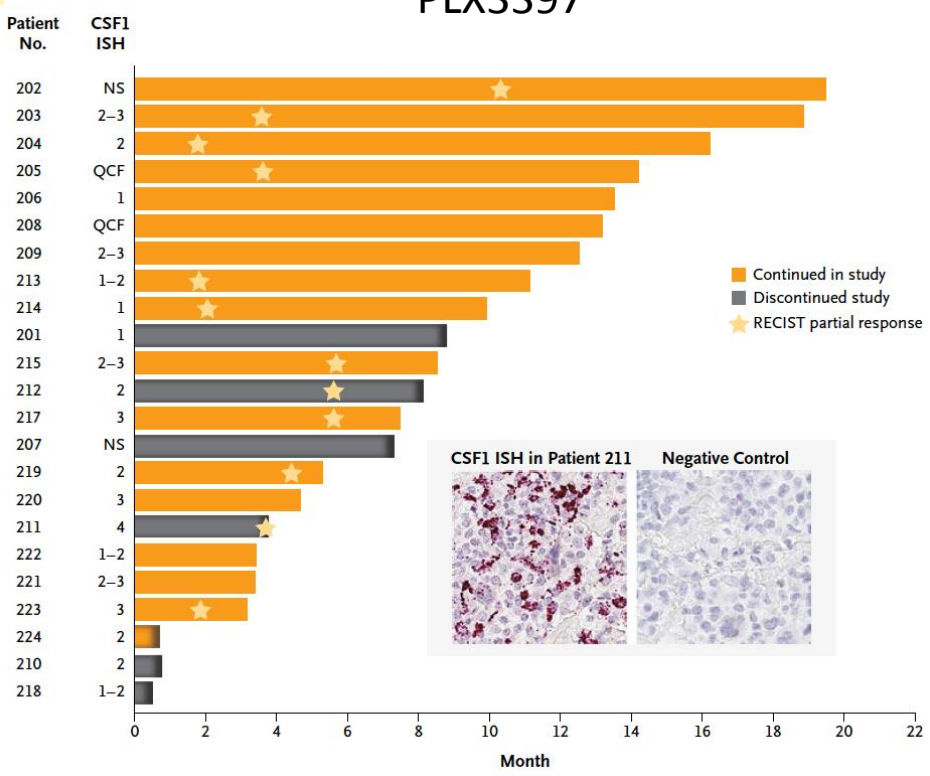


Immunotherapy examples:

1. Immune checkpoints:
Antibodies to LAG-3, TIM-3
2. Tregs:
Antibodies to CD25, CCR4
3. MDSC, M2 macrophages:
CSF1R antibodies/inhibitors
4. IDO: small molecule inhibitors
5. TGF-β: blocking antibodies

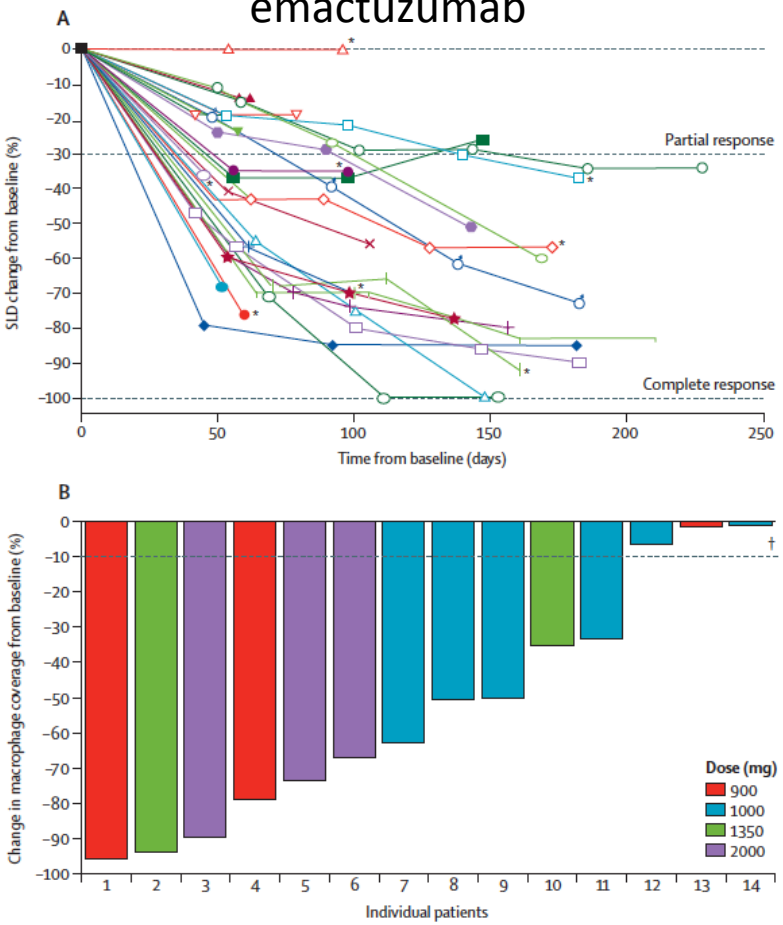
Targeting CSF1R to deplete tumor-associated macrophages in pigmented vilonodular tenosynovitis (PVNS)

PLX3397



Tap W., et al., NEJM 2015

emactuzumab



Cassier P.A., et al., Lancet Oncol 2015

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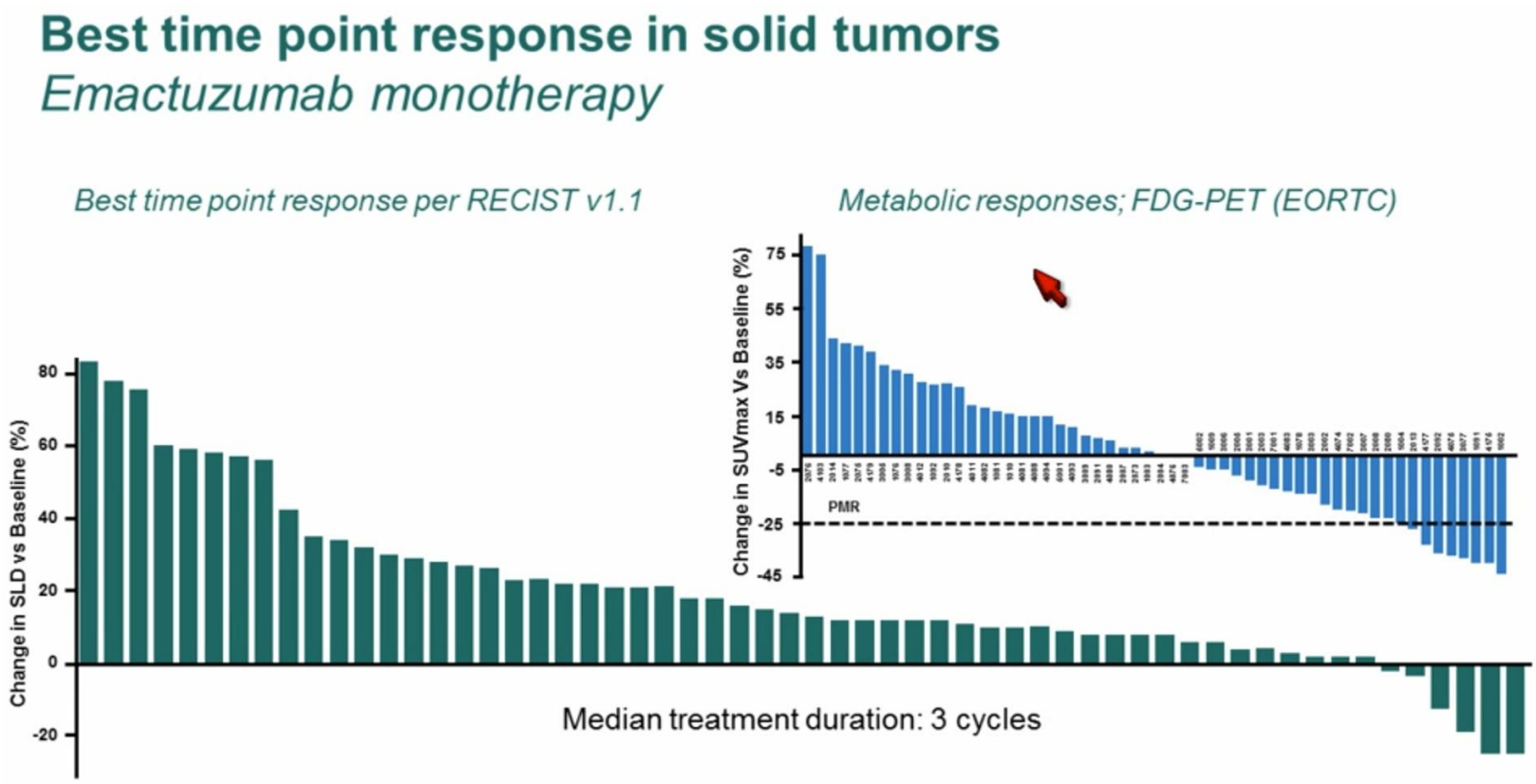
Emactuzumab as monotherapy in other cancers



Gomez-Roca et al., ASCO 2015

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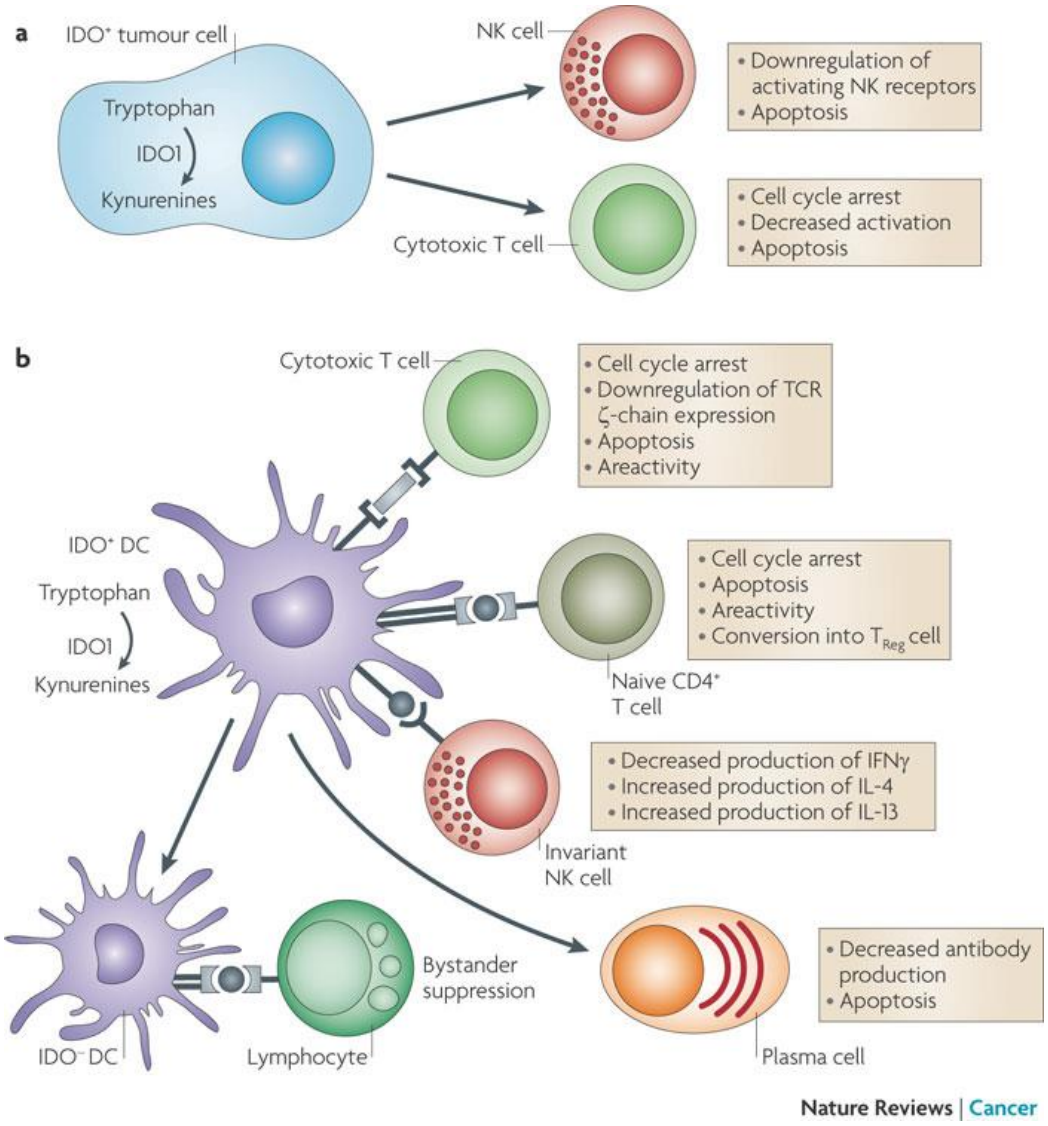
Targeting of indoleamine 2,3 dioxygenase (IDO)



Trials evaluating IDO inhibitors in combination with chemotherapy and with PD-1/PD-L1 blockade are ongoing.

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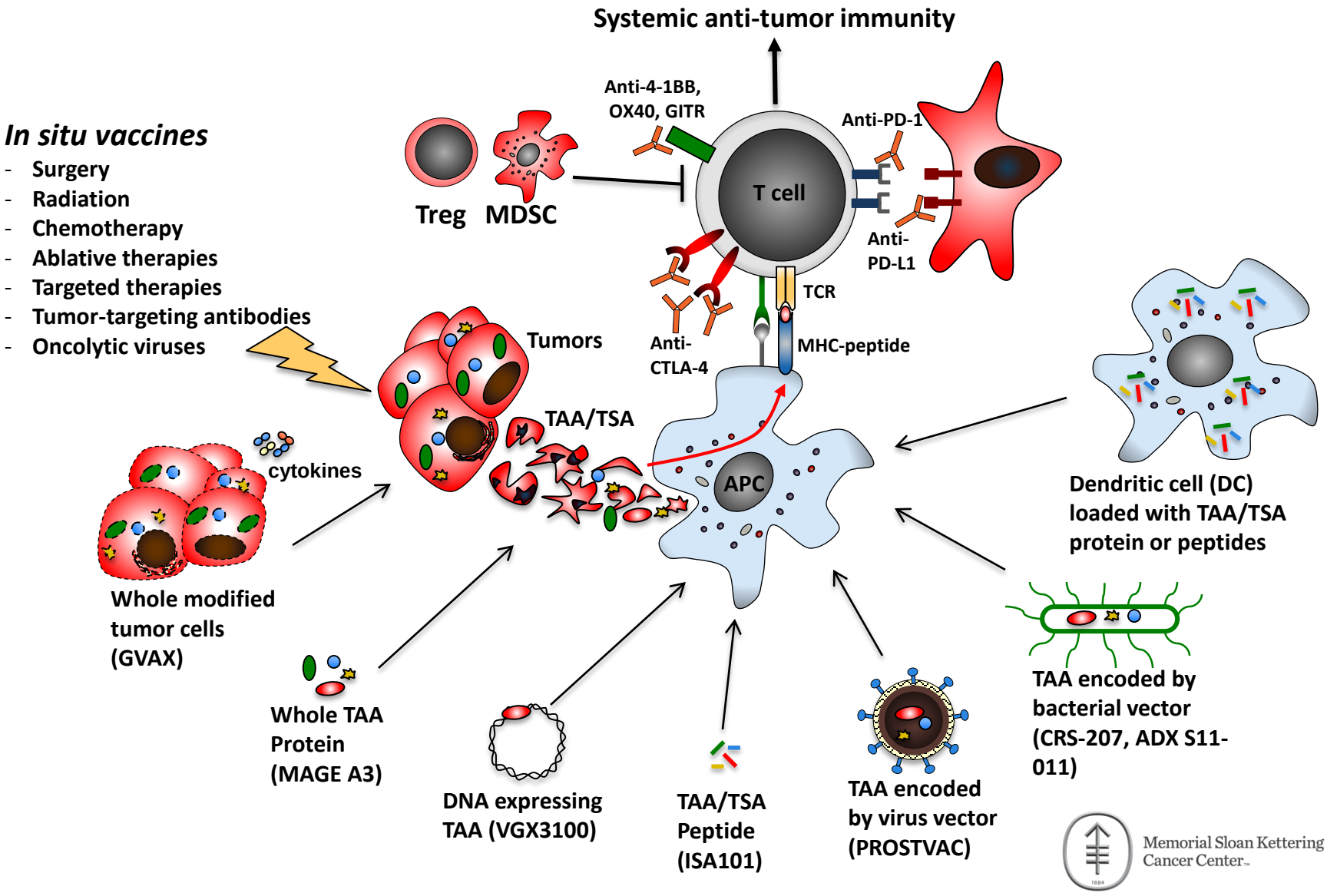
Management considerations

- New agents and their combinations may be associated with new and unique side effect profiles, some of which are not signs of toxicity, but pharmacodynamic markers of the specific drug
  - LFT and CPK elevations with CSF1R inhibitors
  - Non-clinically significant amylase/lipase elevations with PD-1/CTLA-4 inhibitors
  - Fever

- Distinguishing such side effects from actual toxicities may be challenging and require close involvement of multidisciplinary teams

Summary: optimal immunotherapies will require combinations



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