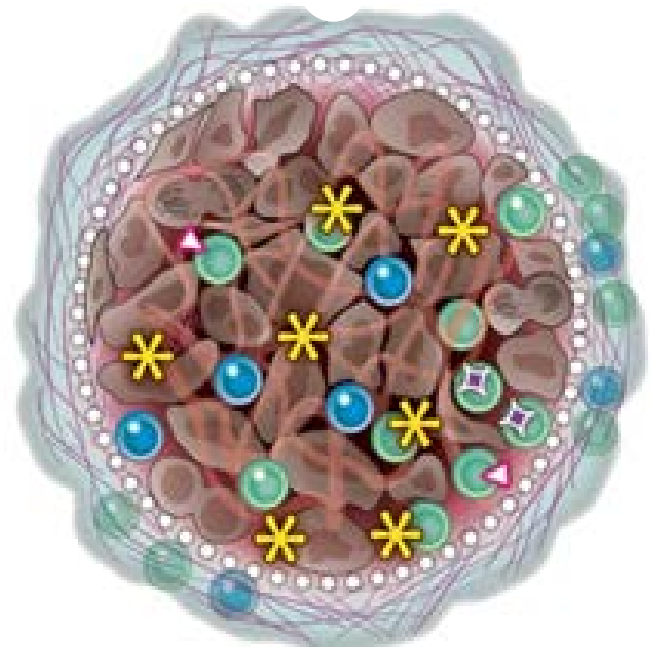
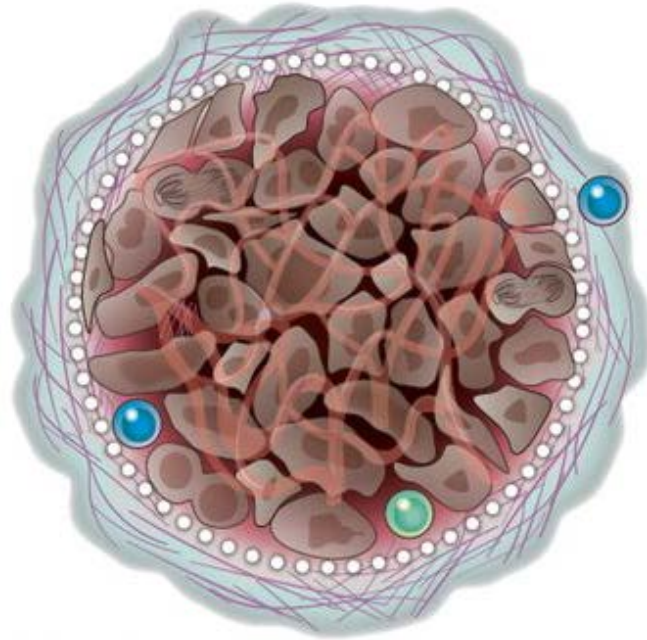




Introduction to Immunotherapy

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Virus associated cancer
Mutation associated neoantigens



Immunoprofiling as a predictor of patient’s response to cancer therapy—promises and challenges

Daniel Bethmann^{1,2}, Zipei Feng^{2,3} and Bernard A Fox^{2,4}



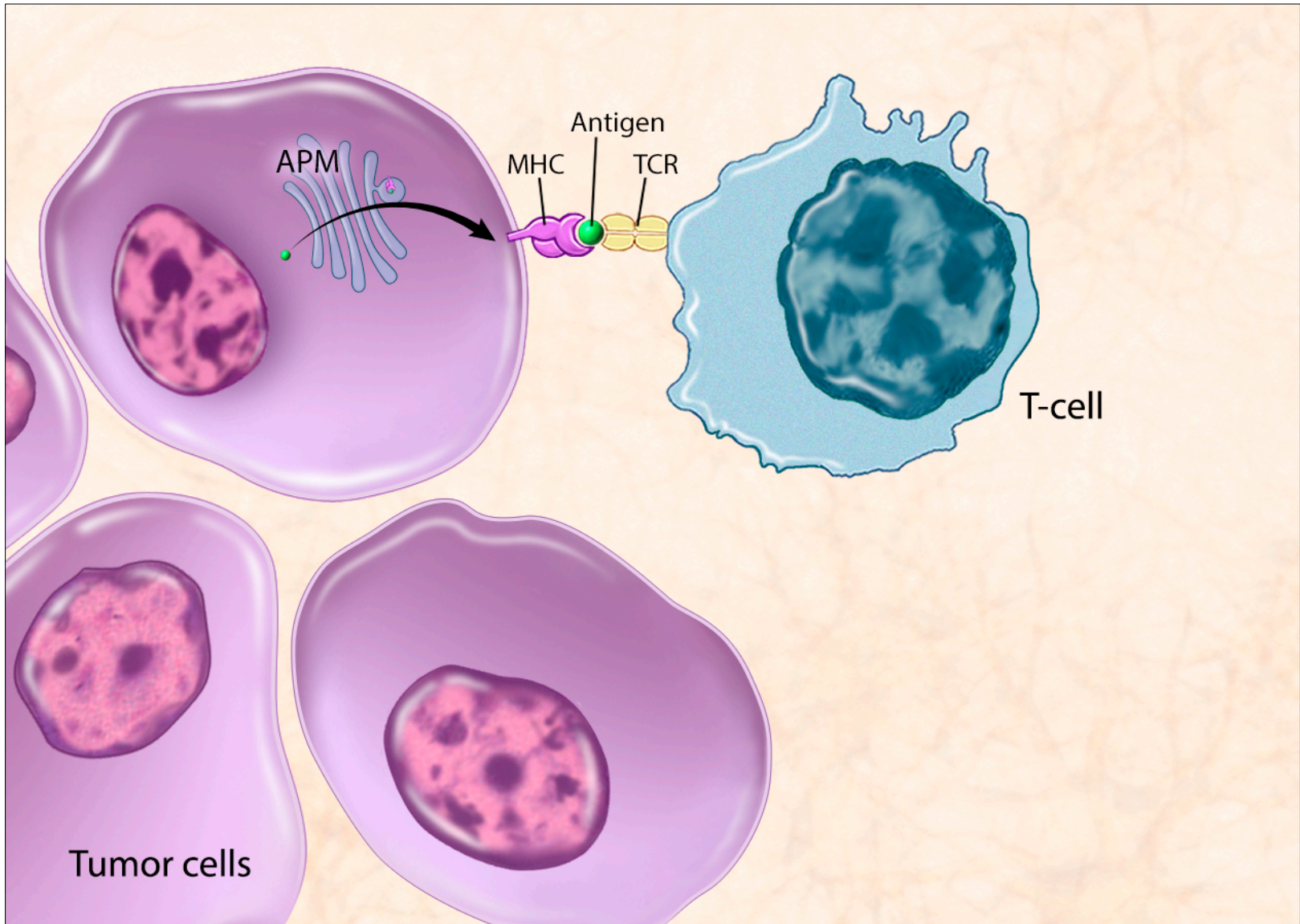
Table 1

Association of immune cell infiltrates with prognosis in cancer

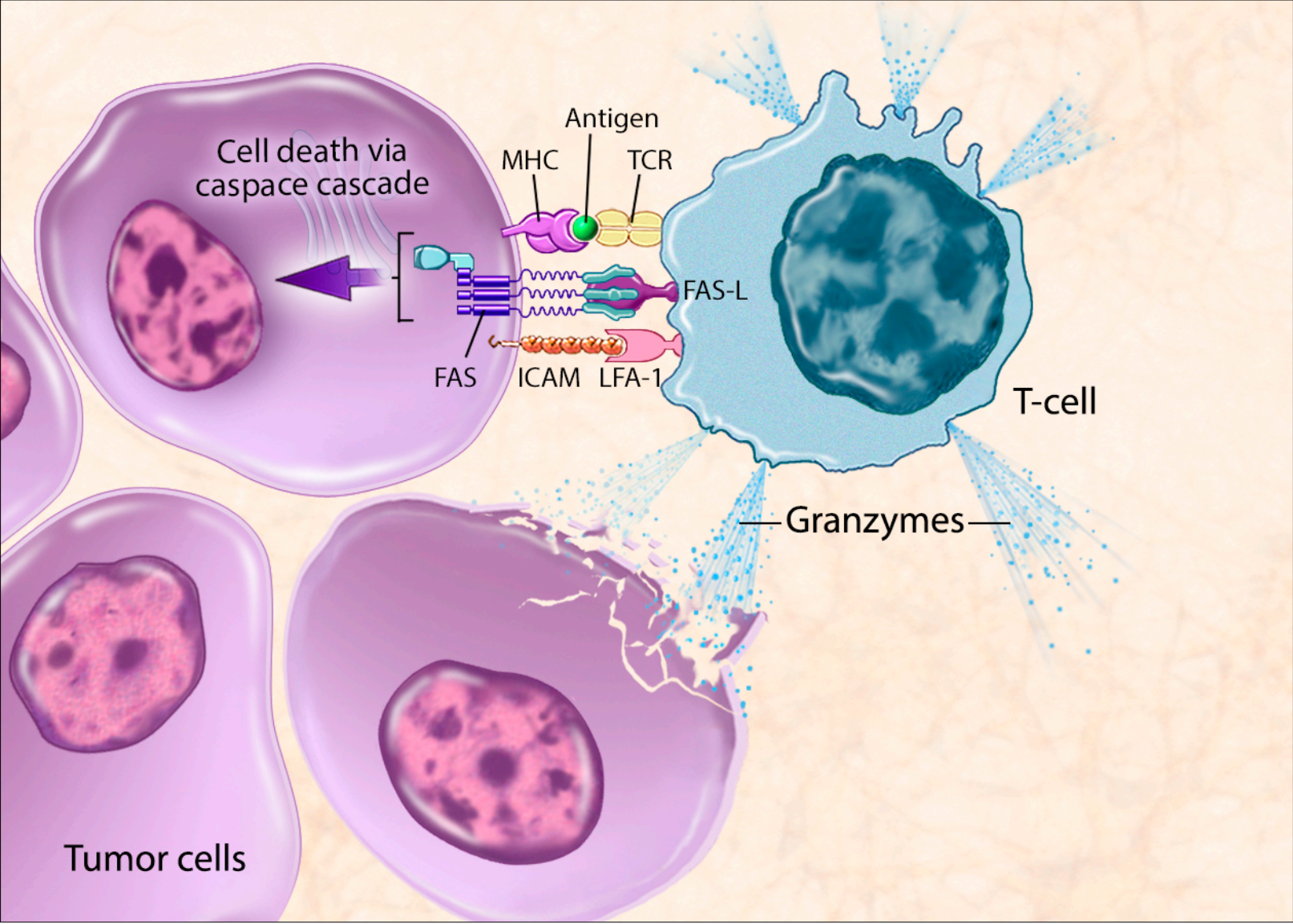
Histology	Markers tested*	Type of assessment	Effect on prognosis* and significance ##, #	First author	Year
Melanoma	CD3, CD4, CD8, FoxP3, PD-1	Pathologist	High intratumoral number of CD3, CD4 and CD8 is favorable. High peritumoral number of PD-1+ lymphocytes is unfavorable [52]. ##	Kakavand	2015
	CD8, CD20, CD45	Pathologist, Aperio Software	High intratumoral density of CD8, CD45 and CD20 is favorable [53]. ##	Erdag	2012
	CD4, CD8, CD68, HLA-DR	Pathologist	High intratumoral density of CD4 and CD8 as well as the presence of HLA-DR cells is favorable [54]. #	Piras	2005
	CD3, CD4, CD8	Pathologist	High intratumoral number of CD4 and CD8 is favorable [55]. ##	Al-Batran	2005

...87 references in 21 diseases correlating immune profiling with clinical outcome

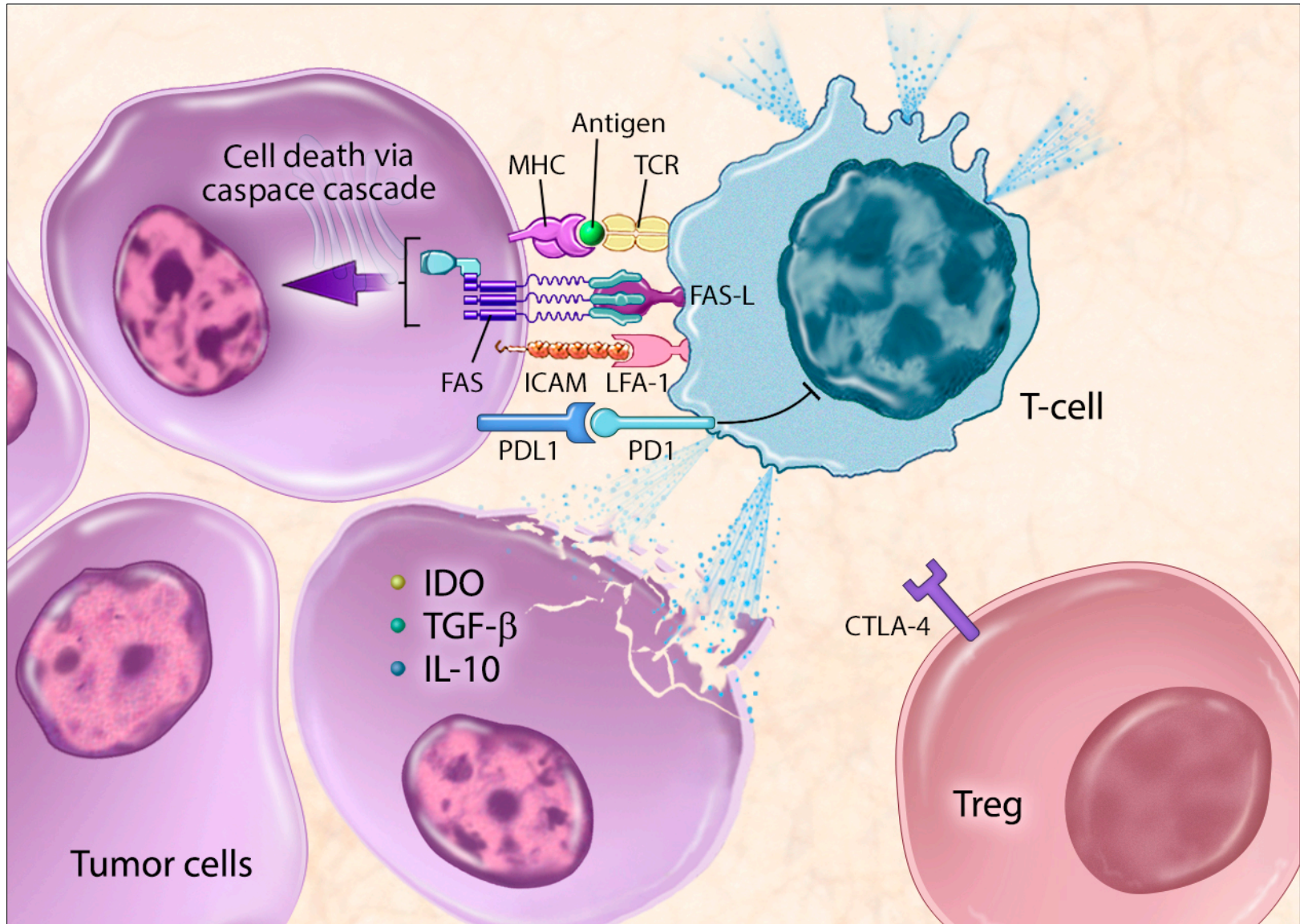
T cell recognition of tumor cell



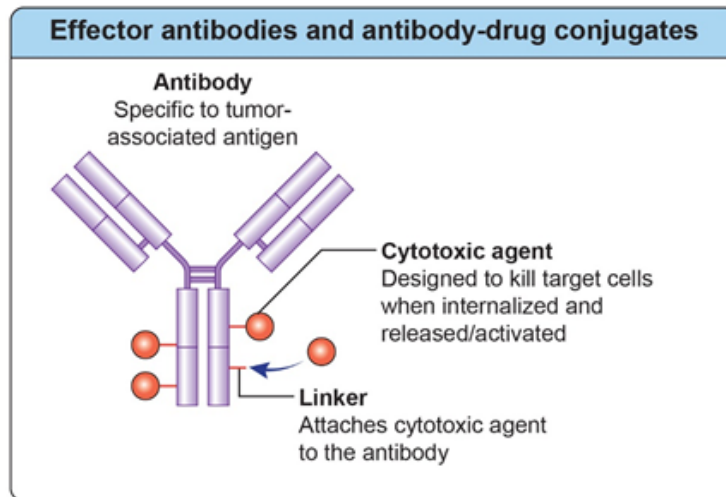
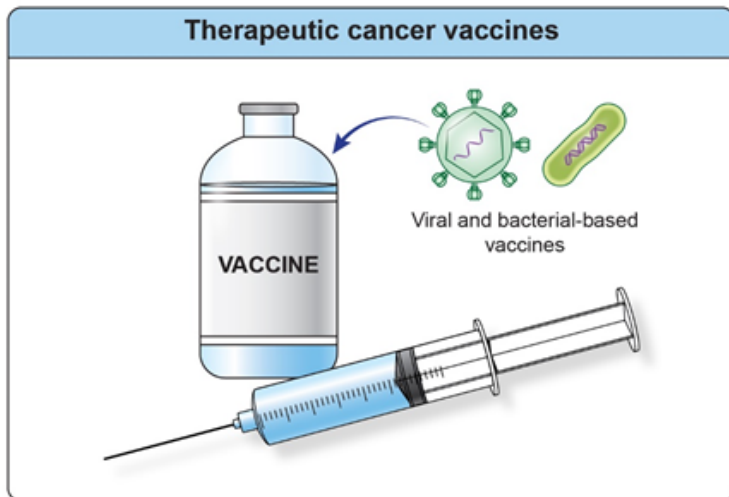
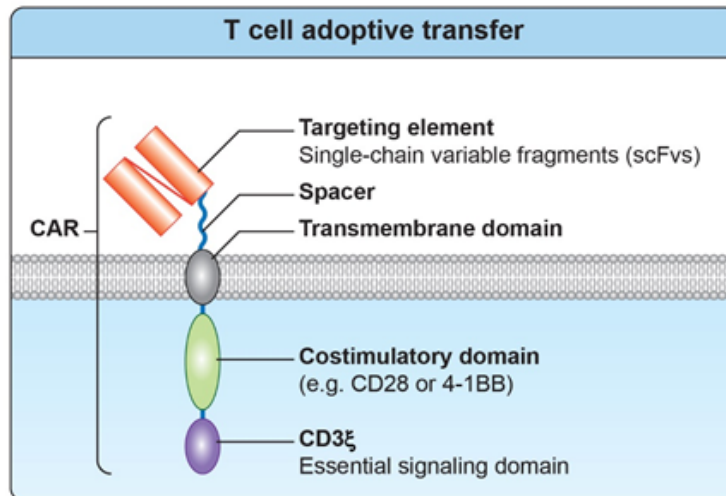
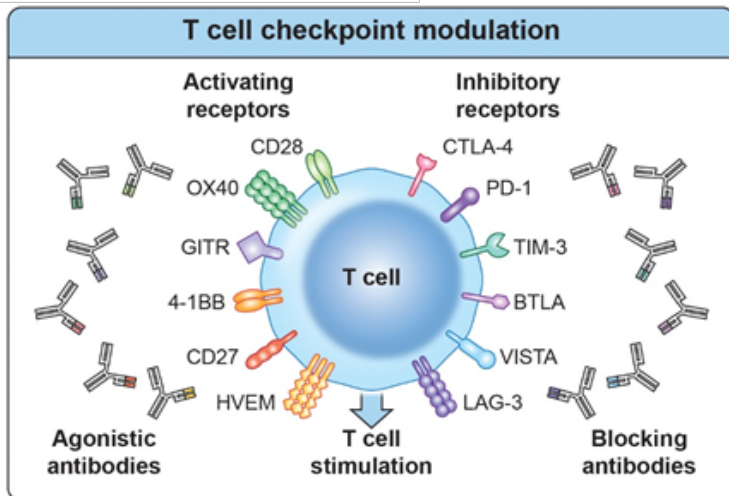
T cell function at tumor cell: to kill



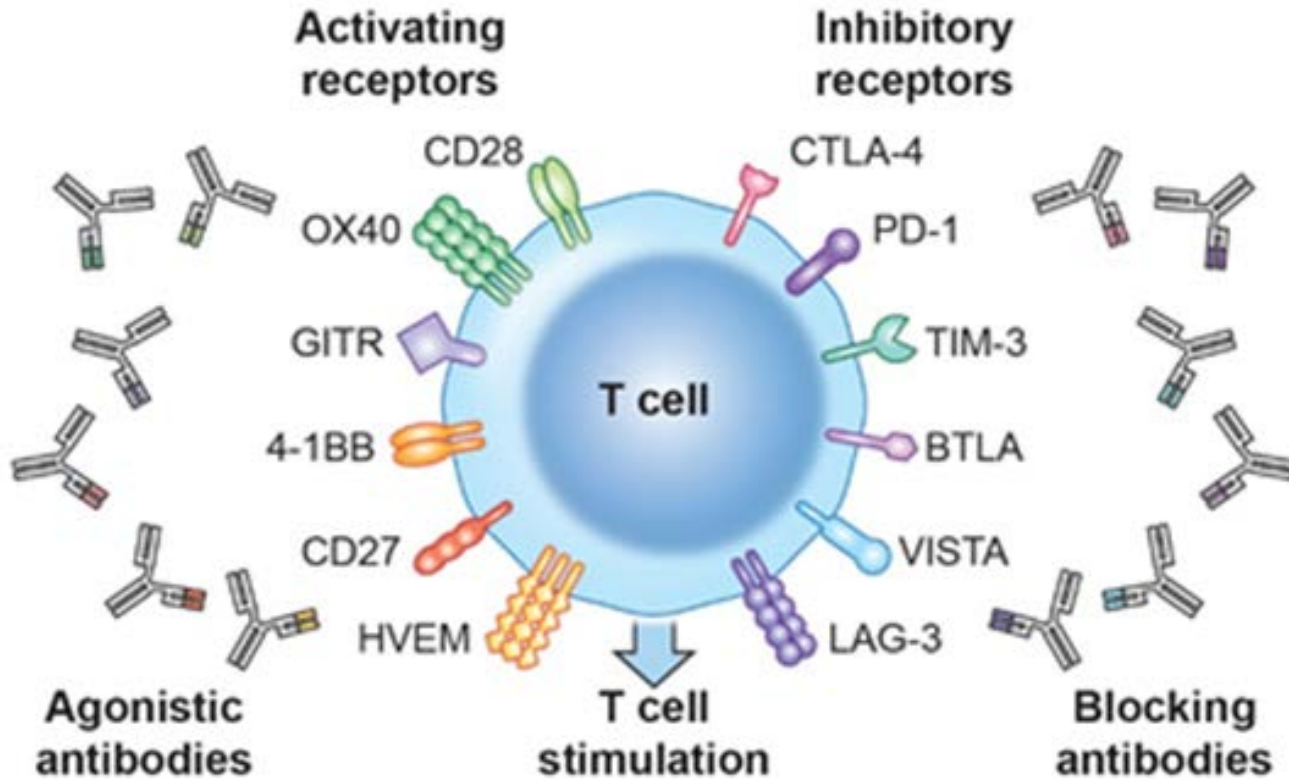
T cell function at tumor cell: **or not to kill**



Types of immunotherapy



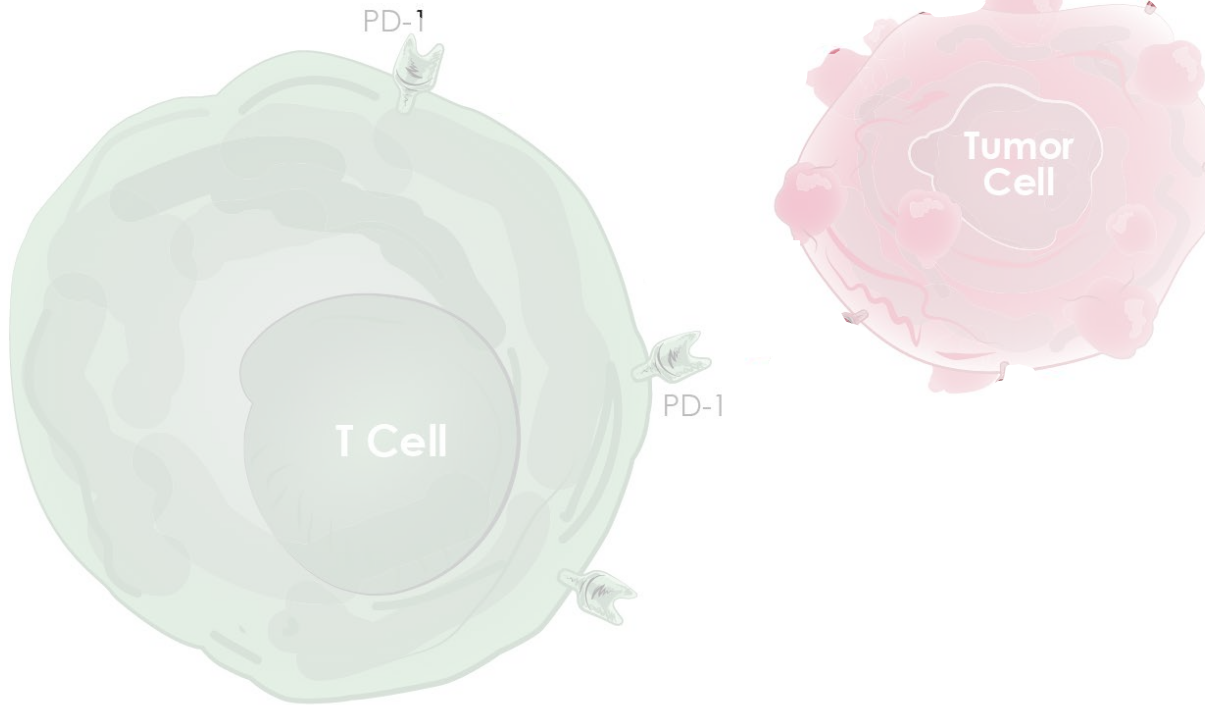
T cell checkpoint modulation



Importance of PD1 / PDL1 blockade

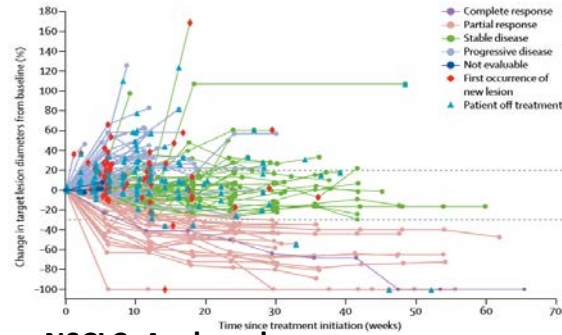
T-cell mediated
immune response

-1

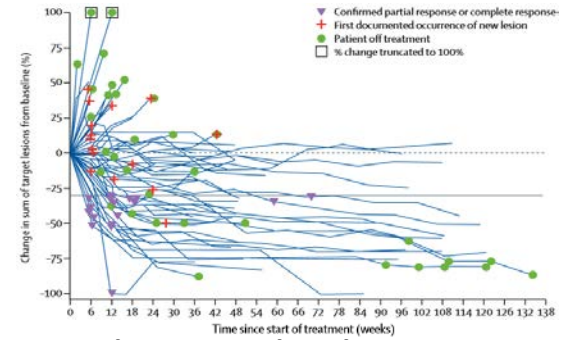


PD1/PDL1 inhibition

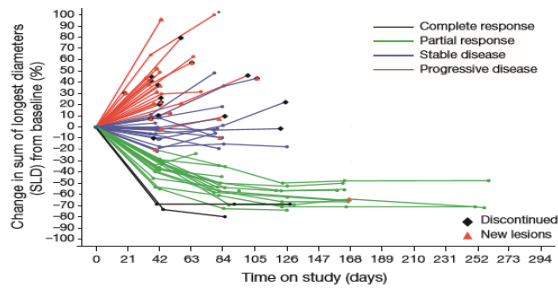
Rapid, deep durable responses
 Across a wide range of tumors
 Seen in a subset of patients



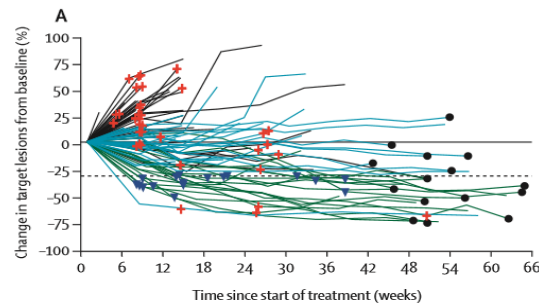
NSCLC: Avelumab
 Gulley JL et al. *Lancet Oncol* 2017



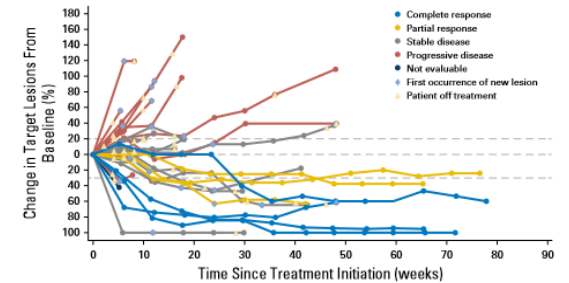
MSI hi CRC: Nivolumab
 Overman MJ et al. *Lancet Oncol* 2017



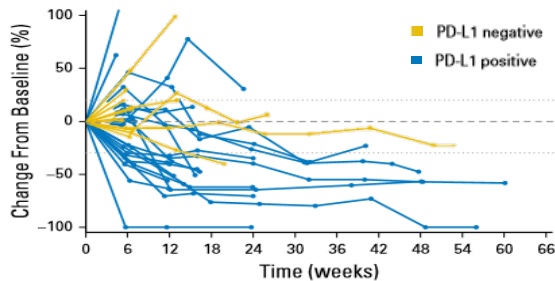
Urothelial: Atezolizumab
 Powles T et al. *Nature* 2014



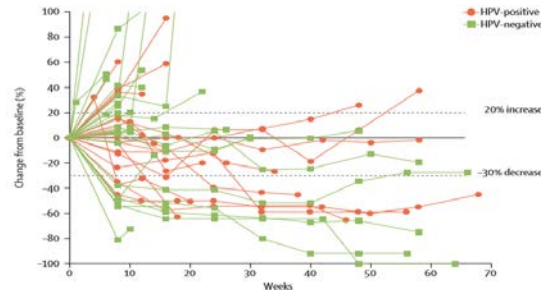
NSCLC (squamous only): Nivolumab
 Rizvi NA et al. *Lancet Oncol* 2015



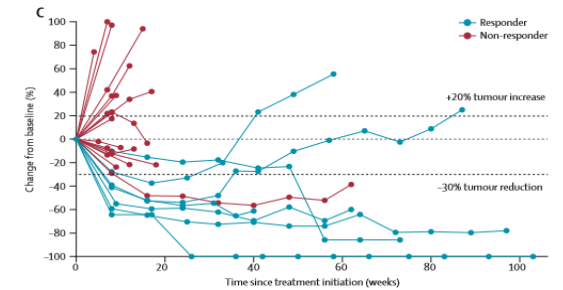
Urothelial Ca: Avelumab
 Apolo AB et al. *JCO* 2017



Urothelial: Durvalumab
 Massard C et al. *JCO* 2016



HNSCC: Pembrolizumab
 Seiwert TY et al. *Lancet Oncol* 2016

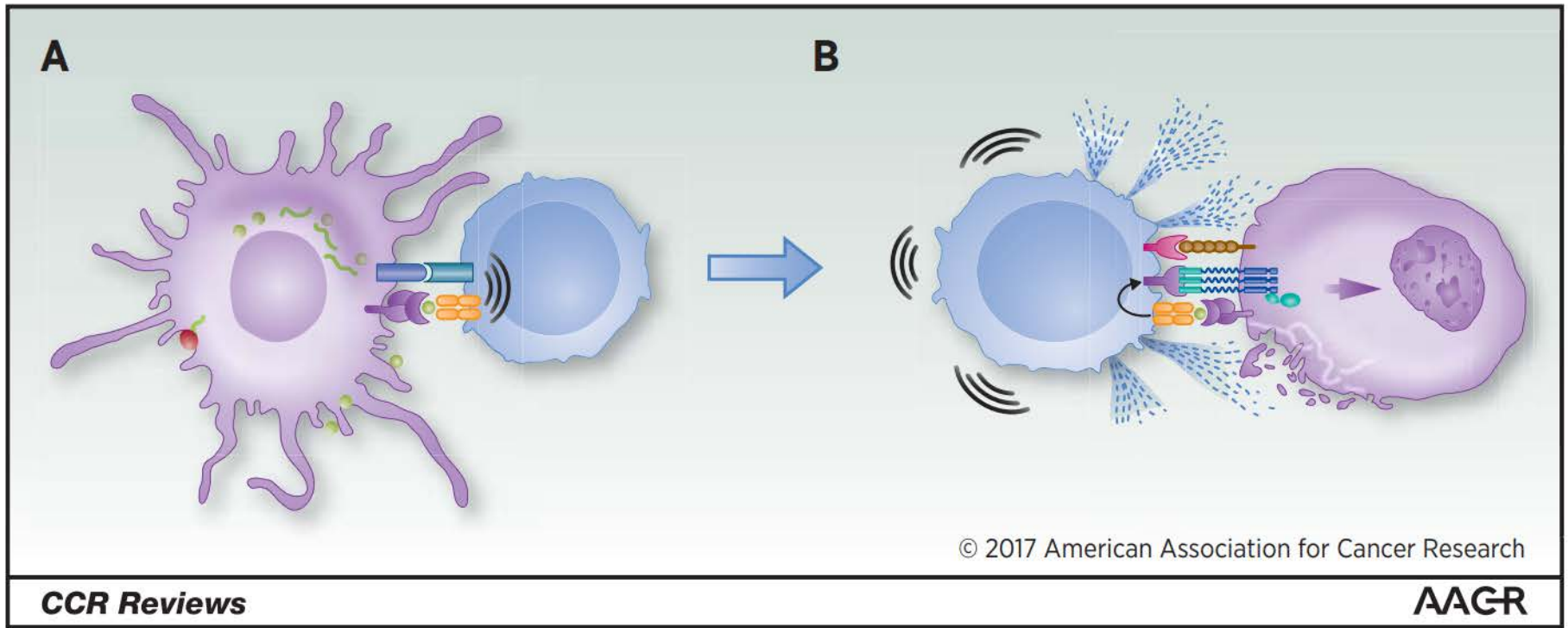


Urothelial Ca: Pembrolizumab
 Plimack ER P et al. *Lancet Oncol* 2017

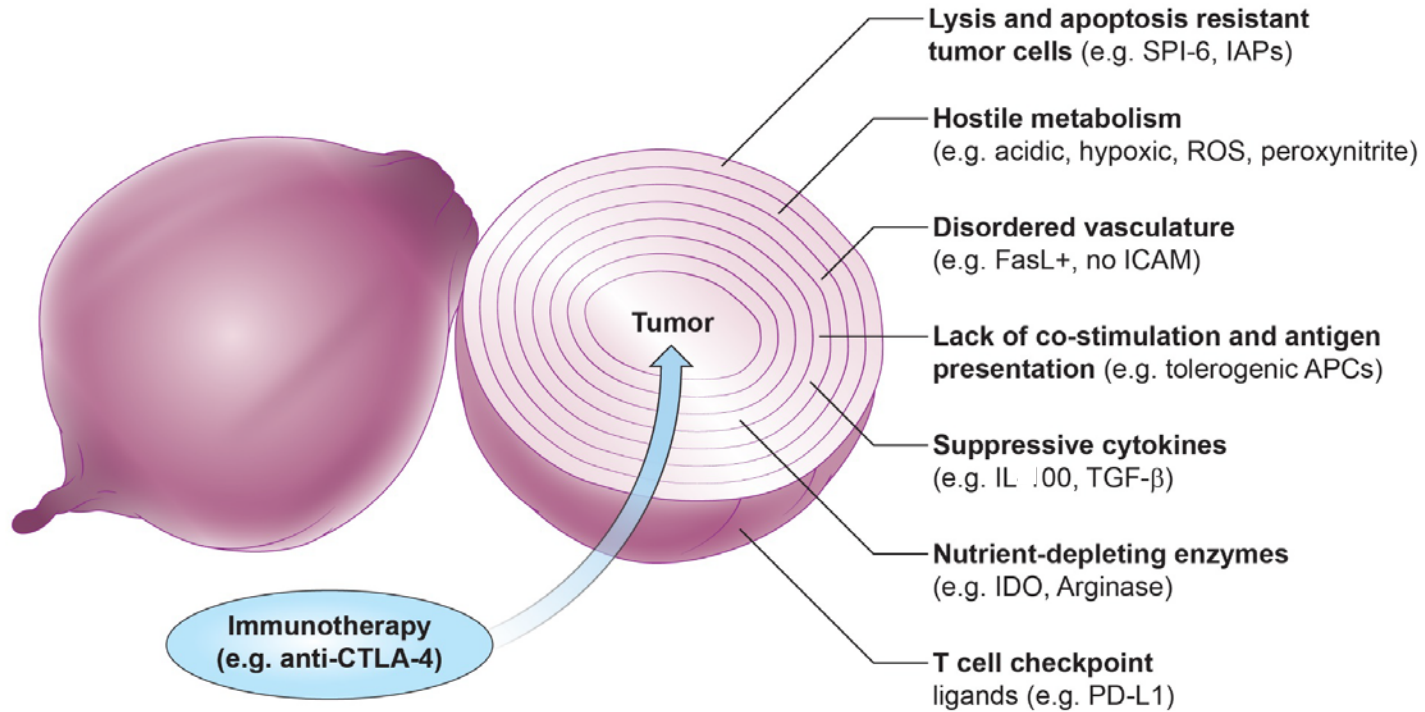
Requirements for Effective Immunotherapy

Generation of Immune Response

Functional Effector Cells within the Tumor



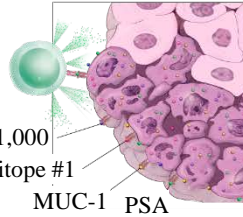
Multi-layered immunosuppression



- Tumors insulate themselves with dense layers of immunosuppressive stroma
- Overcoming the many layers of interconnected and often functionally redundant immune suppressive mechanisms represents a daunting challenge for tumor-specific T cells
- Immunotherapy can “peel back” the layers of local immune suppression, thereby restoring the capacity of T cells to eradicate the tumor

Antigen spreading and the tumour immunity cycle

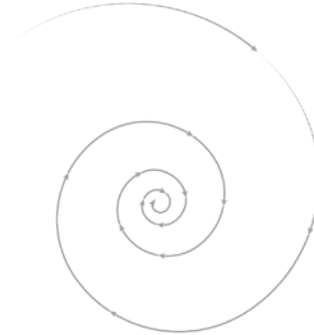
E. Fully activated T cell destroys tumour cells



A. Tumour expresses different immunogenic targets

Neopeptide #2 to 1,000
Neopeptide #1
MUC-1 PSA
Dying tumour cells

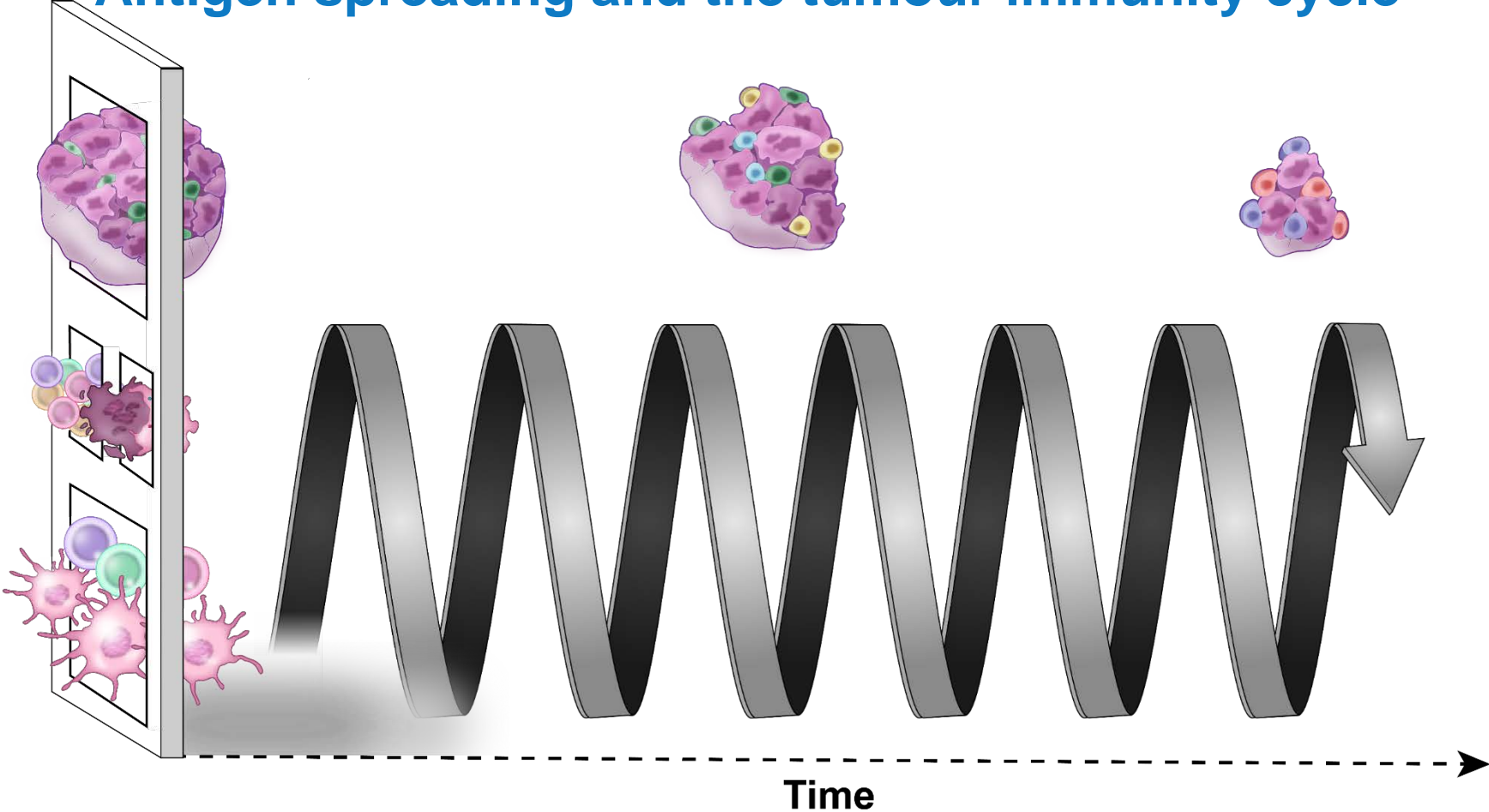
D. Newly activated tumour-specific T cells form in greater concentration and variation



B. Dendritic cell phagocytoses tumour cell along with a transfer of tumour-specific antigens

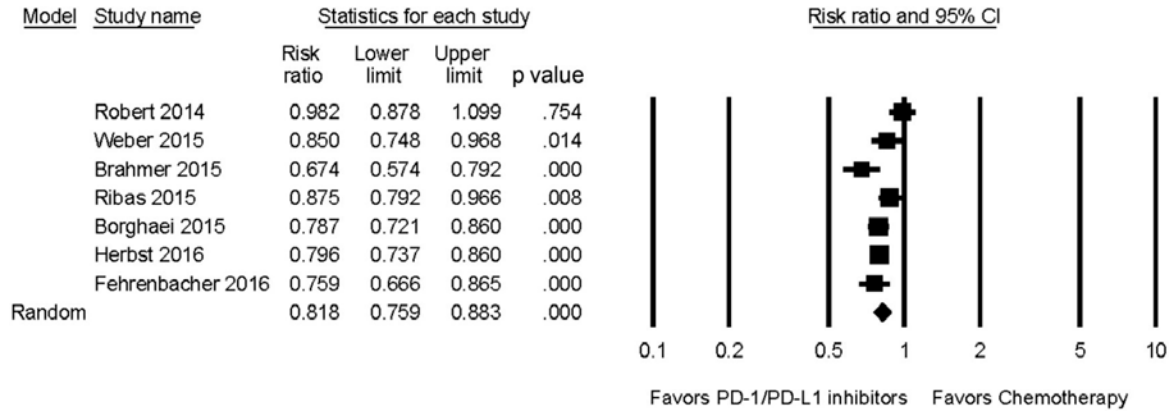
C. Mature dendritic cell presents tumour-specific antigens to T cells

Antigen spreading and the tumour immunity cycle

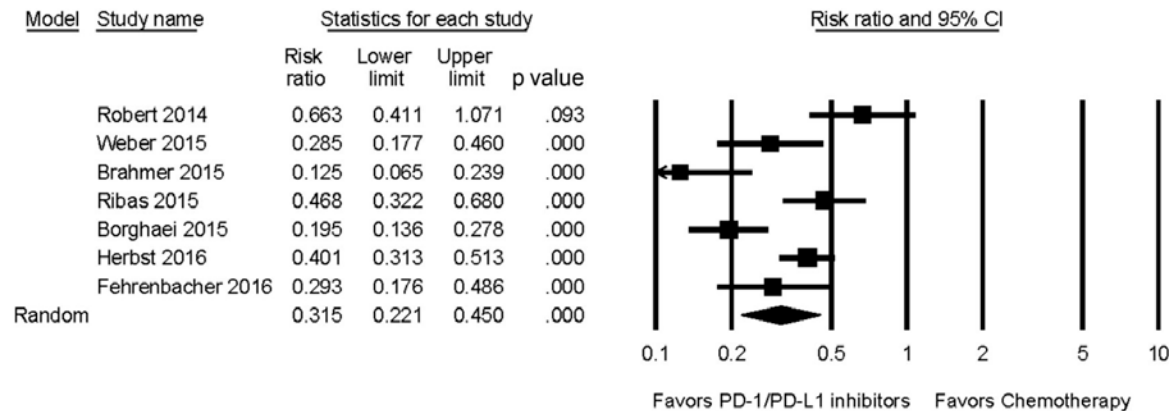


Forest plots of relative risk of any all- and high-grade AEs associated with PD-1/PD-L1 inhibitors versus chemotherapy.

Any all-grade AEs

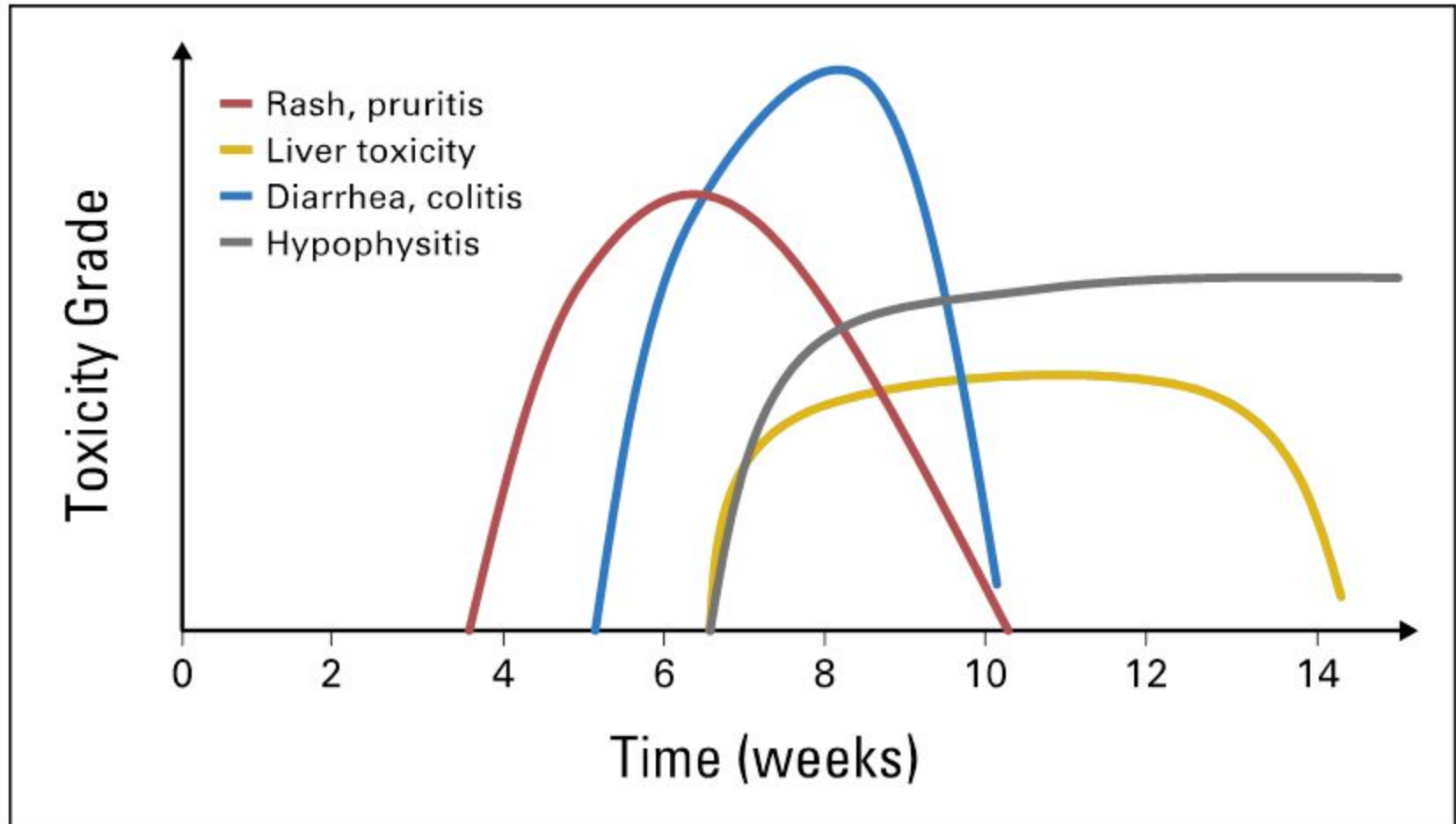


Any high-grade AEs



Tomohiro F. Nishijima et al. *The Oncologist* 2017;22:470-479

Kinetics of Immune Related Adverse Effects



Weber JS et al. Management of immune-related adverse events and kinetics of response with ipilimumab. *J Clin Oncol* 2012;30:2691-2697.

Common Medications

- Corticosteroids
 - Prednisone
 - Dexamethasone
 - Methylprednisolone
 - Hydrocortisone
 - Cortisone
- Mycophenolate mofetil (CellCept)
 - Standard BID
- TNF inhibitors
 - Infliximab
 - Adalimumab
 - Others





Conslusions

- Immunotherapy can lead to rapid, deep and durable responses
- Immunotherapy may be curative in some cases
- Future efforts in combination therapy are seeking to expand the proportion of patients with clear clinical benefit
- These should focus not only on generating anti-tumor immune response but making sure effector cells are functional within TME
- Immune related AEs are typically transient and manageable but should be identified and treated promptly
- Overall, immunotherapy is better tolerated than chemotherapy



National Cancer Institute
Center for Cancer Research