Cancer Immunotherapy

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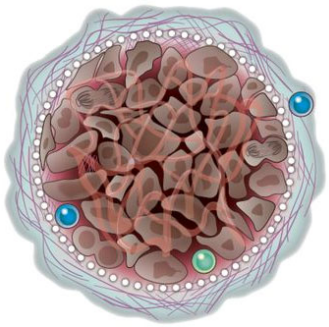

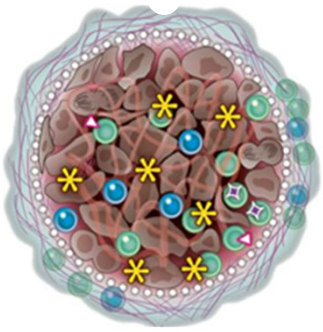

Virus associated cancer
Mutation associated neoantigens

Adapted from Padmanee Sharma, and James P. Allison Science 2015;348:56-61

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Available online at www.sciencedirect.com
ScienceDirect
Current Opinion in Immunology

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

2017

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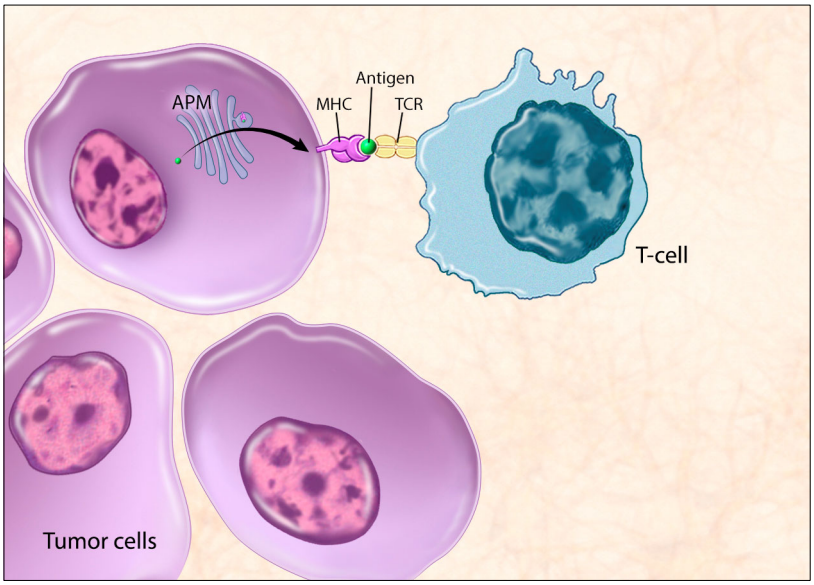
T cell recognition of tumor cell



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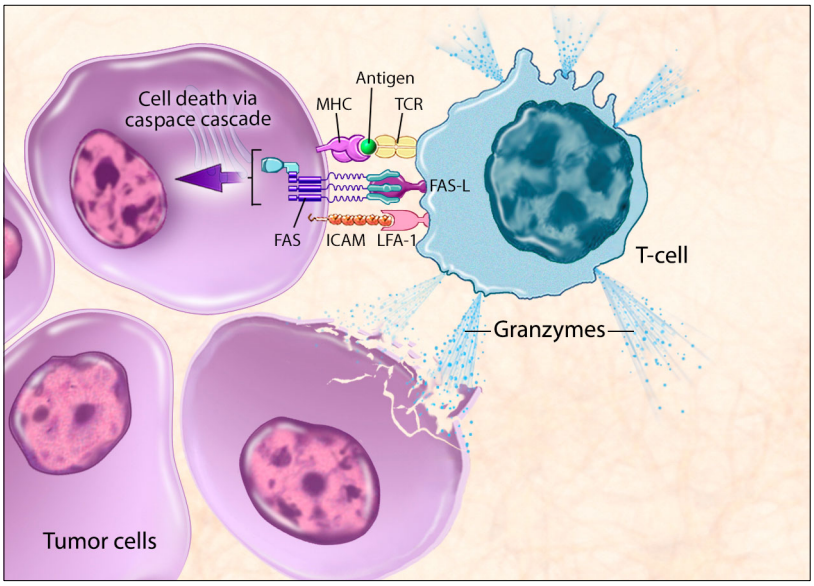
T cell function at tumor cell: to kill



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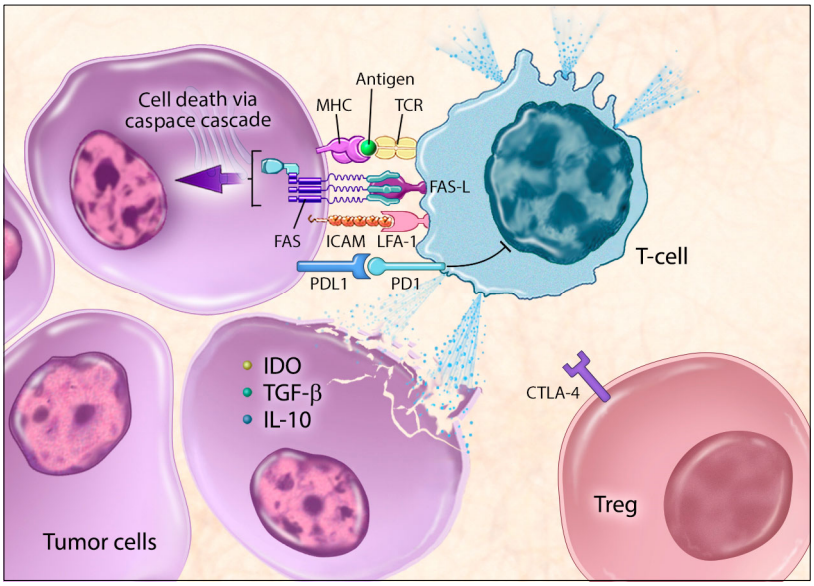
T cell function at tumor cell: or not to kill



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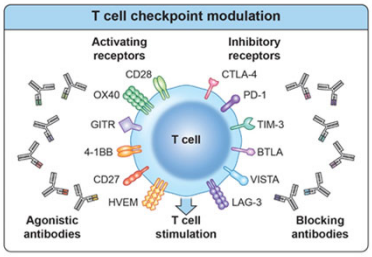
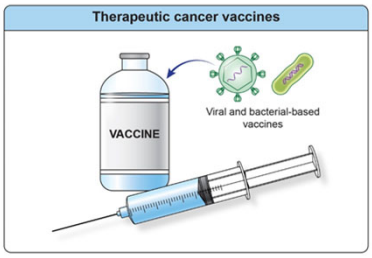
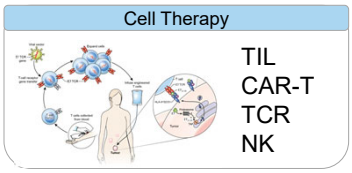
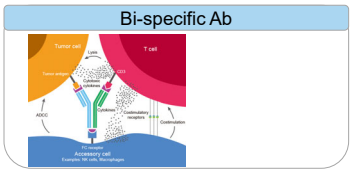
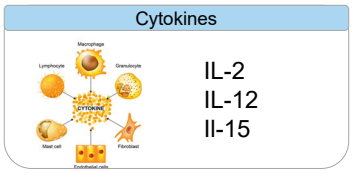
Types of immunotherapy











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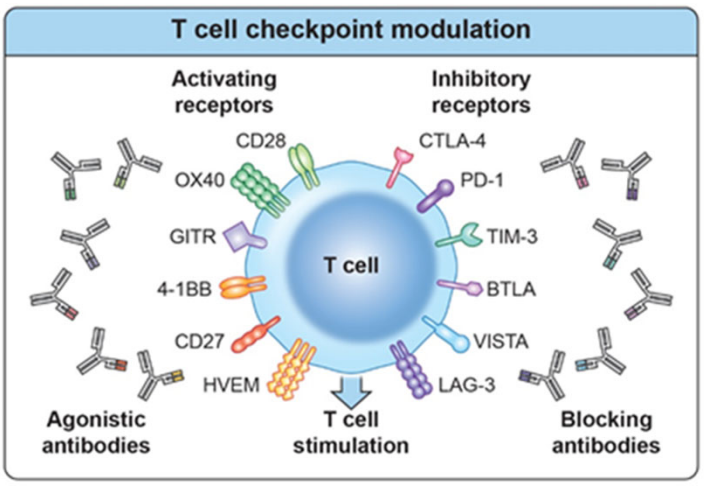

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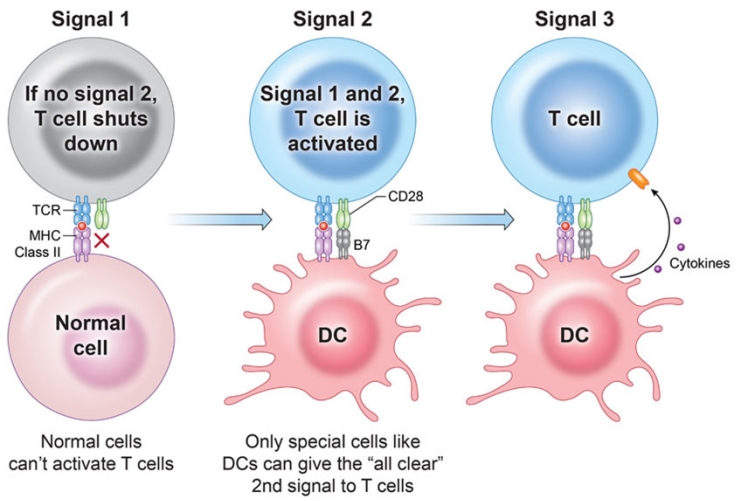
Three signals for antigen-specific T cell activation



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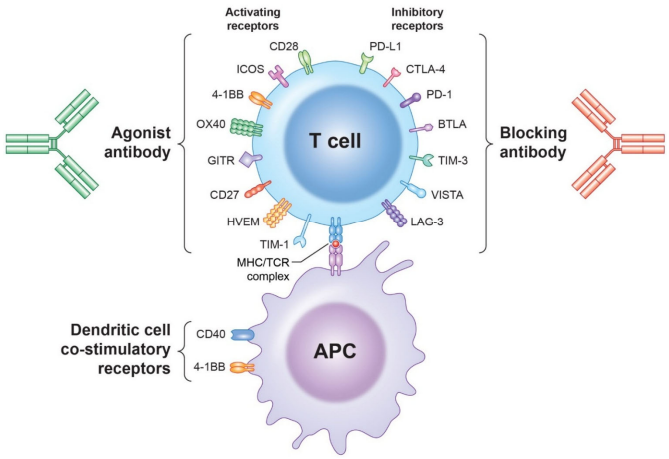
T cell checkpoint modulation



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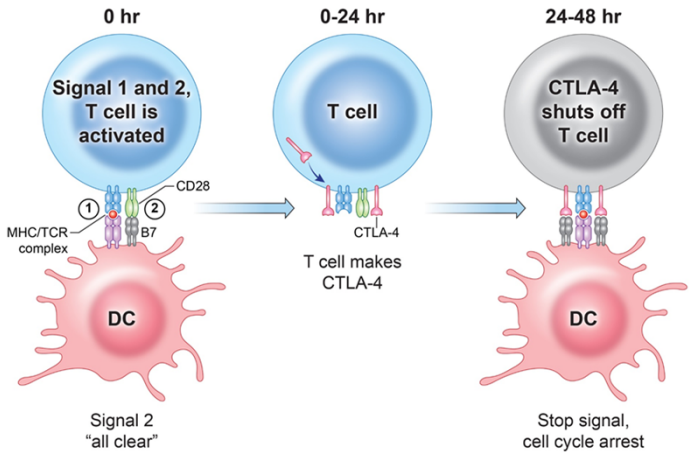
CTLA-4, a negative regulator of T cell activity limits the responsiveness of activated T cells



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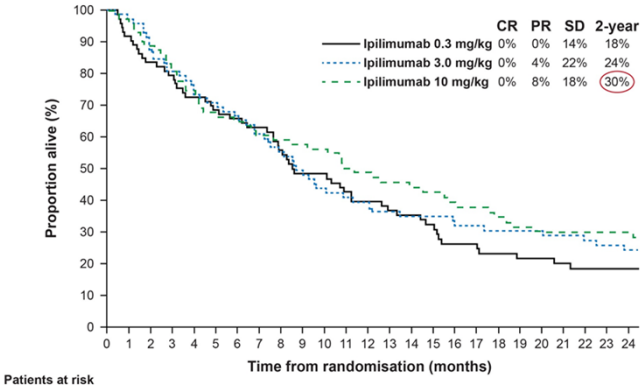
Ipilimumab (human anti-CTLA-4) was approved for the treatment of metastatic melanoma by FDA in 2010



Wolchok et al. 2010. Lancet Oncol.

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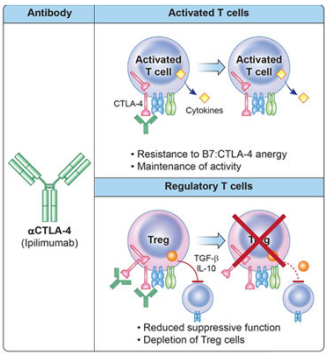
Which T cells are affected by ipilimumab (αCTLA-4)?



The efficacy of anti-CTLA-4 therapy increase in patients who have higher percentages of activated tumor-specific T cells at the time of treatment

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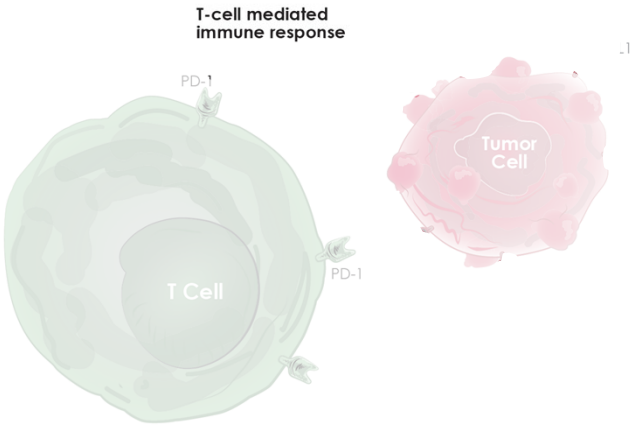
Importance of PD1 / PDL1 blockade



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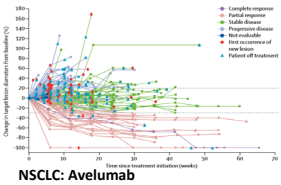
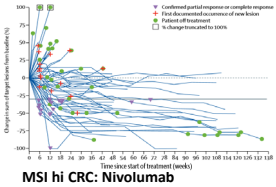
PD1/PDL1 inhibition

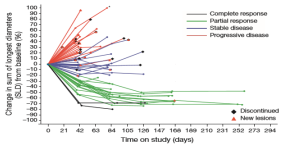
Rapid, deep durable responses
Across a wide range of tumors
Seen in a subset of patients



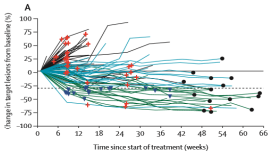
NSCLC: Avelumab
Gulley JL et al. *Lancet Oncol* 2017



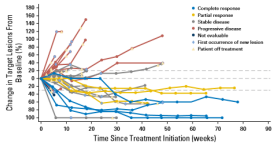
MSI hi CRC: Nivolumab
Overman MJ et al. *Lancet Oncol* 2017



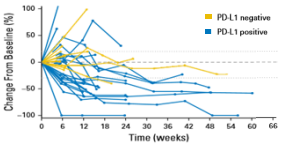
Urothelial: Atezolizumab
Powles T et al. *Nature* 2014



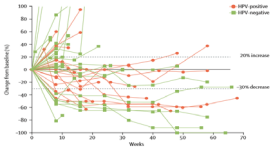
NSCLC (squamous only): Nivolumab
Rizvi NA et al. *Lancet Oncol* 2015



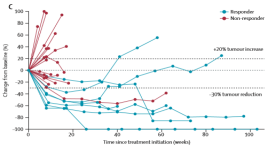
Urothelial Ca: Avelumab
Apolo AB et al. *JCO* 2017



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

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FDA Approved Anti PD-1 Antibodies*

	Nivolumab	Pembrolizumab
Melanoma	2014	2014
NSCLC	2015	2015
RCC	2015	
HD	2016	2016
SCCHN	2016	2016
Bladder	2017	2017
MSI-hi / dMMR		2017

*Dates represent year of first approval in that disease. Subsequent approvals within disease have occurred for some cancers.

Similar side effect profile
Similar level of clinical activity (no head-to-head studies)

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FDA Approved Anti PD-L1 Antibodies

	Indication	Date Approved	IgG	ADCC
Atezolizumab	Bladder NSCLC	5/18/2016 10/18/2016	IgG_1	No
Avelumab	MCC Bladder	3/23/2017 5/29/2017	IgG_1	Yes
Durvalumab	Bladder	5/1/2017	IgG_1	No

Similar side effect profile
Similar level of clinical activity

ADCC
--Con: PD-L1 can also be on activated T-cells
(Avelumab ADCC tumor >> PBMC, Boyerinas B et al., *Ca Imm Res* 2015;
No in ↓ PD-L1+ subsets, Heery C et al., *Lancet Oncology* 2017)
--Pros: 1) Another shot on goal, 2) Combination therapy

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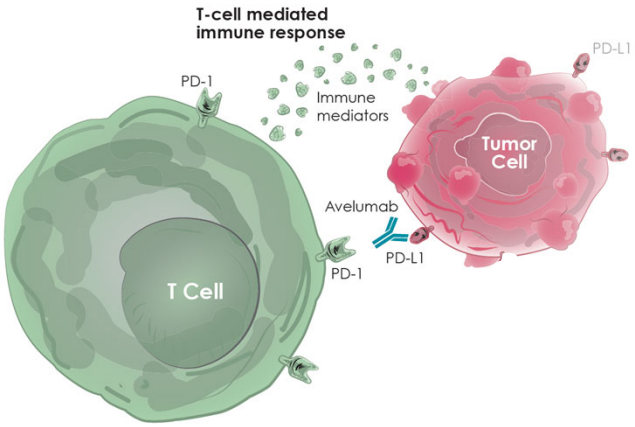
Importance of PD1 / PDL1 blockade



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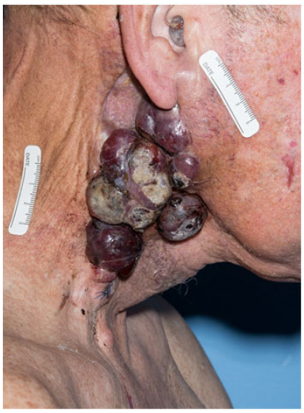
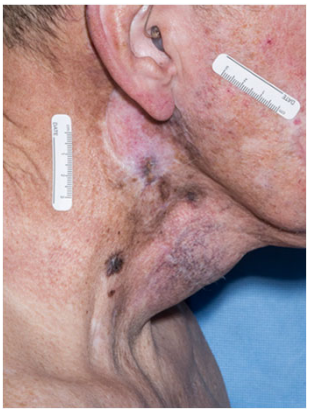
Avelumab: MCC patient 101-0003



baseline



4 months

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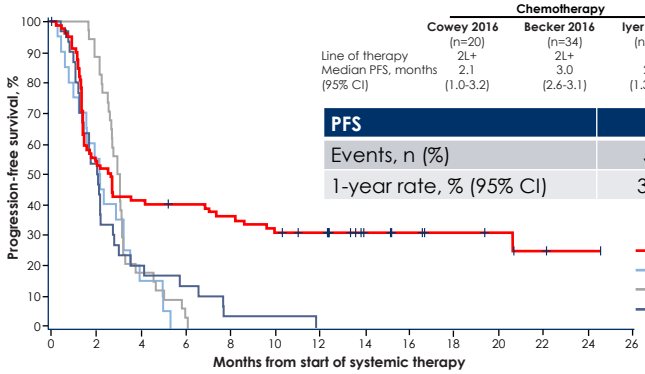
Avelumab: PFS at ≥1 year of follow-up*



PFS with 2L+ treatment in distant mMCC[1-3]

	Chemotherapy			Avelumab
	Cowey 2016 (n=20)	Becker 2016 (n=34)	Iyer 2016 (n=30)	(current study) (N=88)
Line of therapy	2L+	2L+	2L	2L+
Median PFS, months (95% CI)	2.1 (1.0-3.2)	3.0 (2.6-3.1)	2.0 (1.3-2.7)	2.7 (1.4-6.9)

PFS	N=88
Events, n (%)	55 (62.5)
1-year rate, % (95% CI)	30 (21-41)

Number at risk	88	43	32	30	27	24	21	11	8	6	5	2	1	0

2L+, second line or later
* This figure is for illustrative purposes only and is not a direct head-to-head comparison.
1. Cowey CL, et al. Value Health. 2016;19(7):Abstract A717. 2. Becker J, et al. Ann Oncol. 2016;27(Suppl):Abstract 1154P. 3. Iyer JG, et al. Cancer Med. 2016;5(9):2294-301.

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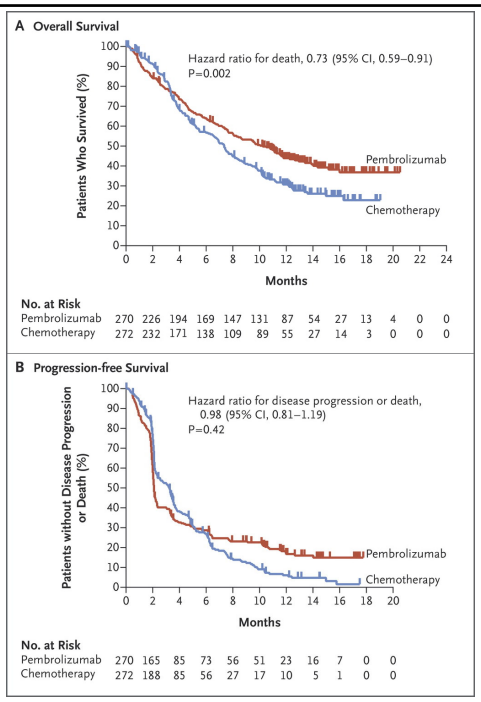
KEYNOTE-045 (Pembrolizumab in Urothelial Cancer)

OS: Median 10.3 months versus 7.4 months

PFS: Not significantly different

AE: Fewer TRAE of any grade in the pembrolizumab group (60.9% versus 90.2%)

Bellmunt, et al., NEJM, 376: 1015-1026, 2017



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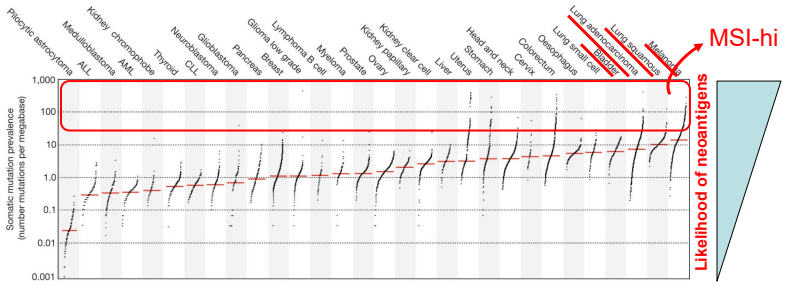
The prevalence of somatic mutations across human cancer types.



T-cell Poor?
Target Self Ag → vaccine

T -cell inflamed?
Target neoantigens

LB Alexandrov *et al. Nature* **000**, 1-7 (2013) doi:10.1038/nature12477

nature

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FDA Approved Therapeutic Vaccines for Cancer

	Indication	Date Approved
Sipuleucel-T	Prostate	2010
Talimogene laherparepvec	Melanoma	2015

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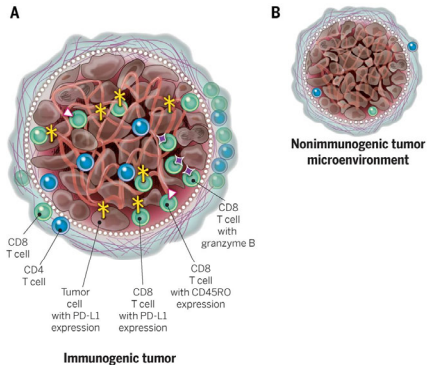
Potential characteristics of immunogenic and nonimmunogenic tumors.



Padmanee Sharma, and James P. Allison Science 2015;348:56-61

Science AAAS

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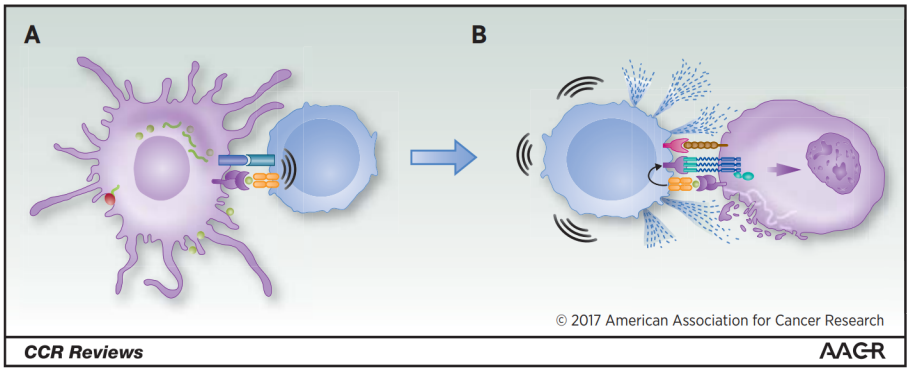
Requirements for Effective Immunotherapy

Generation of Immune Response | Functional Effector Cells within the Tumor



Bilusic M, Madan RA, Gulley JL *Clin Ca Res* 2017

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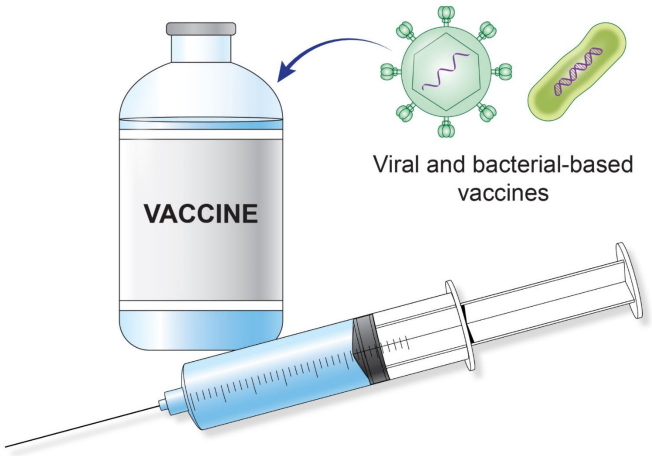
Therapeutic cancer vaccines



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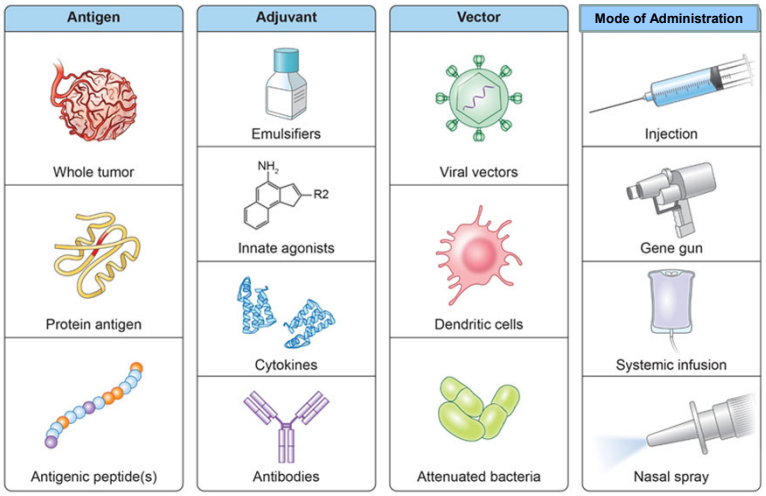
Components of a cancer vaccine



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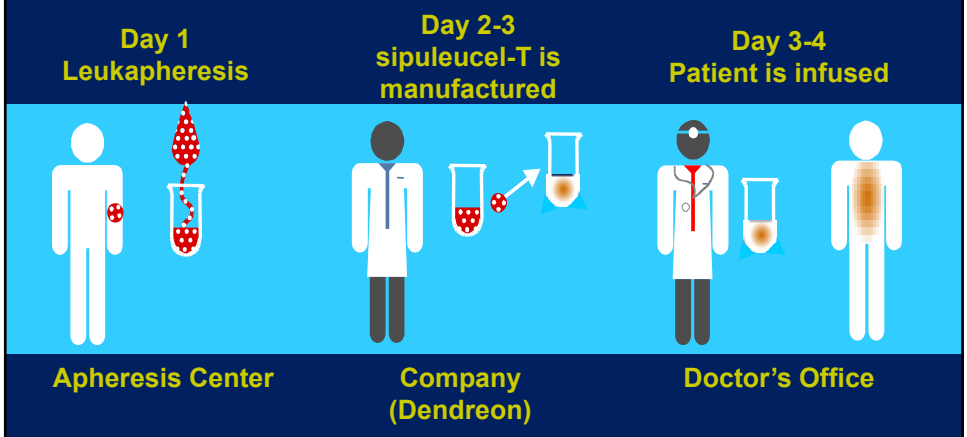
APC Vaccine: Sipuleucel-T (Provenge)



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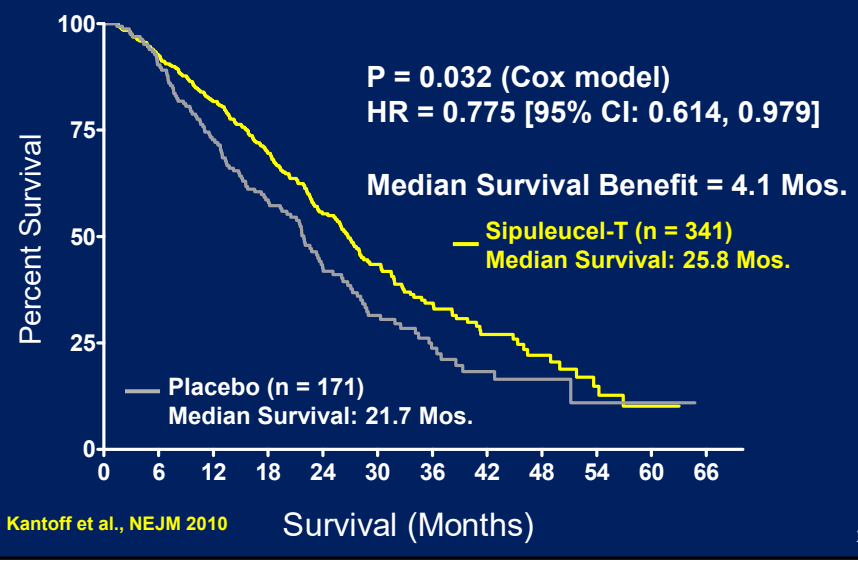
Sipuleucel-T: IMPACT trial



Kantoff et al., NEJM 2010

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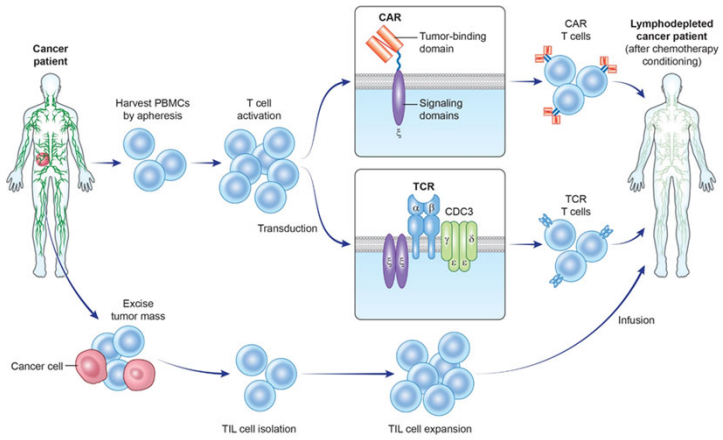
Adoptive T cell therapy can involve engineered (CAR, TCR) or patient-derived (TIL, PBMC) T cells



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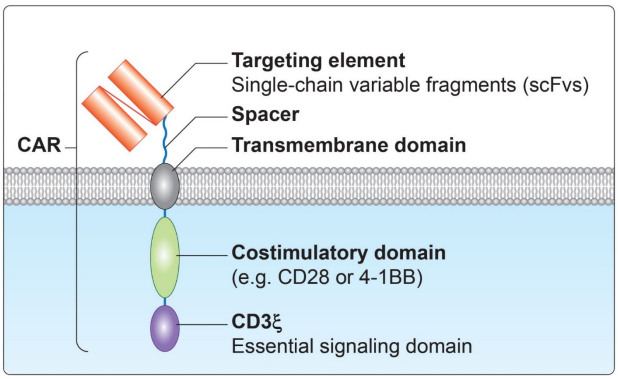
T cell adoptive transfer



CARs, TIL, TCR, PBMCs

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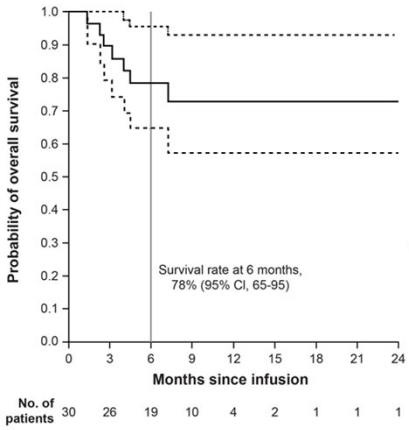
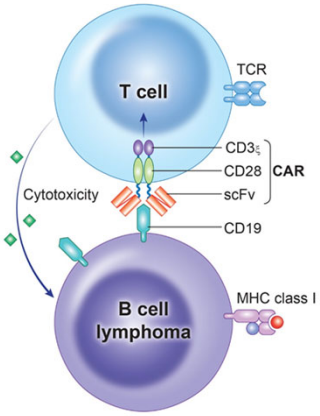
Effective treatment of relapsed B cell ALL with CD19 CAR T cell therapy



Maude S, Frey N, Shaw P, Aplenc R, Barrett D, Bunin N, Chew A, Gonzalez V, Zheng Z, Lacey S, et al. 2014. Chimeric antigen receptor T cells for sustained remissions in leukemia. The New England Journal of Medicine. 374(10): 998.



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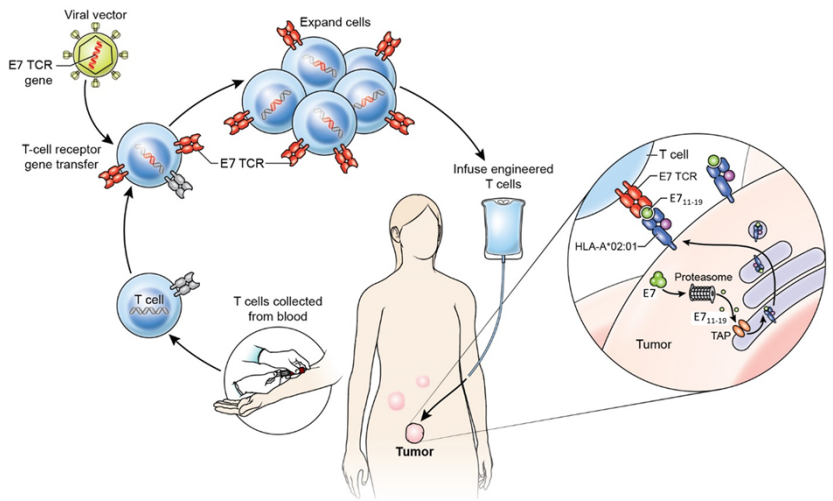
E7 TCR-T cell Treatment



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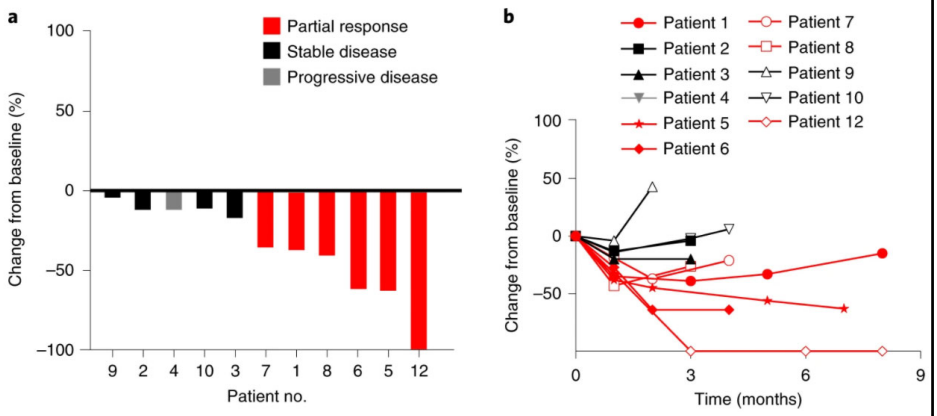
E7 TCR-T cell Treatment



Nagarsheth et al, Nature Medicine, 2021

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Immunotherapy at NIH CC

	FIH	Phase 2	Phase 3	Approved
Vaccine	✓	✓	✓	
Immune Checkpoint Inhibitor	✓	✓		✓
Bi-specific Ab	✓			
Cytokine	✓	✓		
Cell Therapy	✓	✓		

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Key Immunotherapy Concepts

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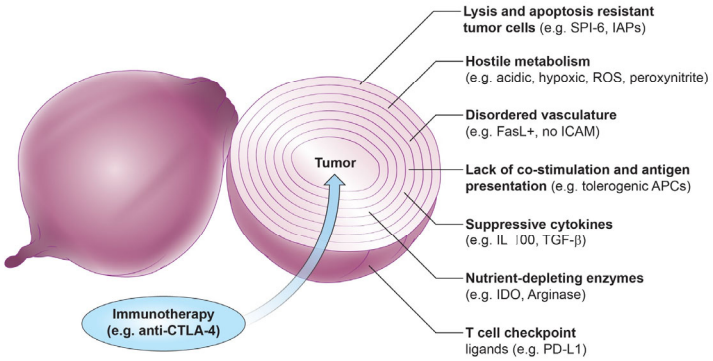
Multi-layered immunosuppression



- 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

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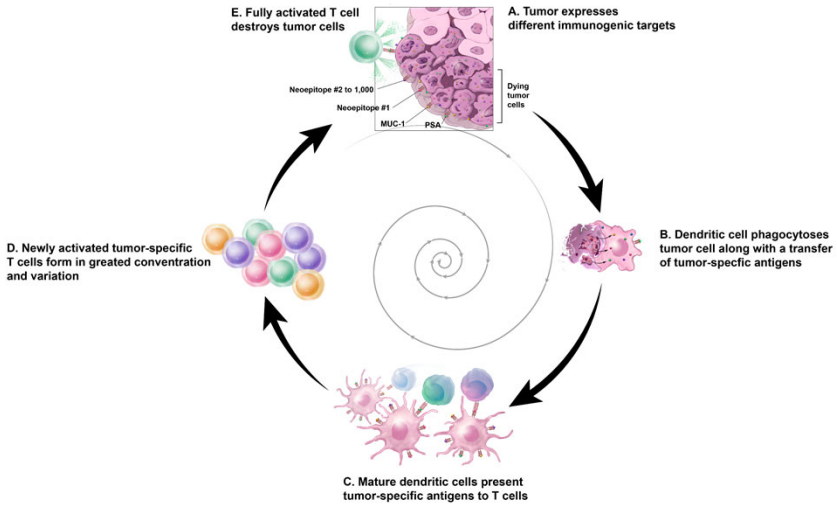
Antigen Spreading and the Tumor Immunity Cycle



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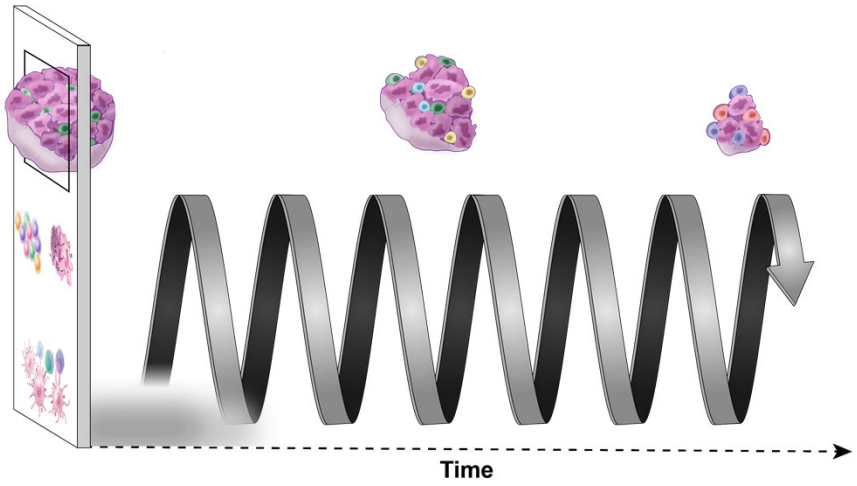
Antigen Spreading and the Tumor Immunity Cycle



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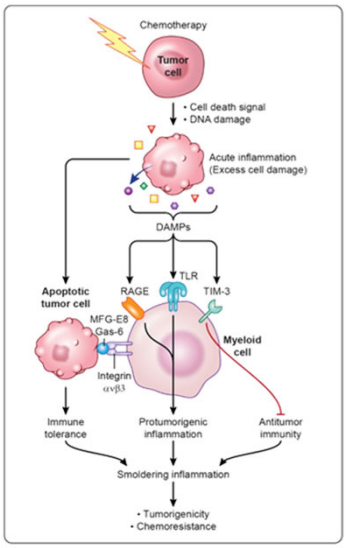
A different perspective on chemotherapy

Immunogenic versus non-immunogenic cell death



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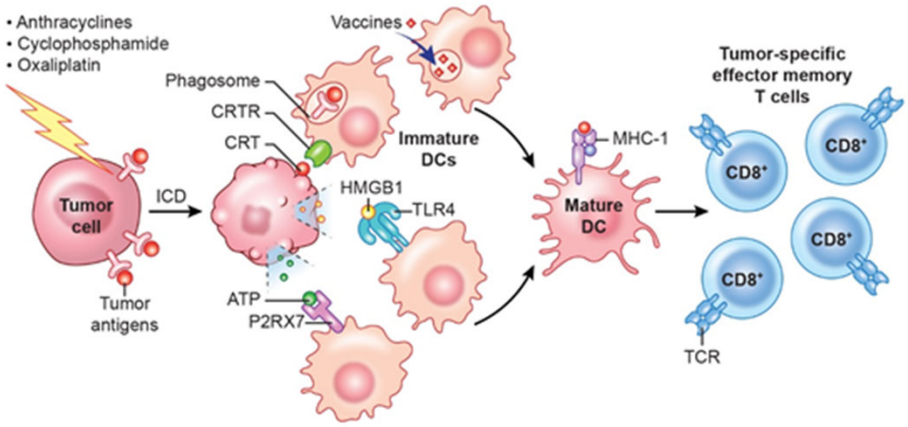
A different perspective on chemotherapy

Immunogenic versus non-immunogenic cell death



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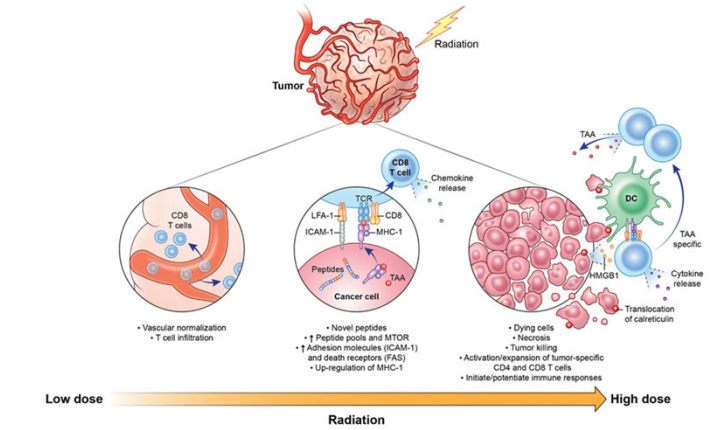
Immunogenic Modulation:

A potent adjuvant for tumor immunity (e.g., radiation)



Exploiting the untapped potential of immunogenic modulation by radiation in combination with immunotherapy for the treatment of cancer

http://www.ncbi.nlm.nih.gov/pubmed/18777956

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side effects

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Mechanism CTLA-4 &PD-1

- Involved in maintaining appropriate immune response
- Downregulates & prevents inappropriate activity
- Autoimmune type response
- Thinking “Chemo” will lead down wrong path
- Think Graft versus Host disease

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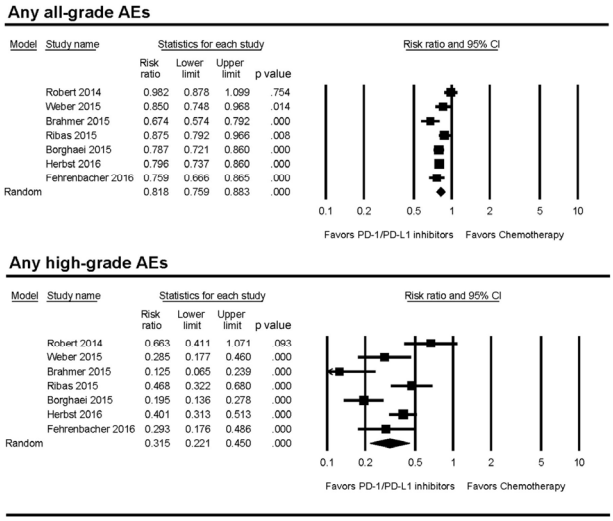
Forest plots of relative risk of any all- and high-grade AEs associated with PD-1/PD-L1 inhibitors versus chemotherapy.



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Incidence and RR of summary toxicity endpoints, including 95% CI and number of trials in each analysis

Summary AE endpoints	No. of trials	PD-1/PD-L1 inhibitor incidence % (95% CI)	Chemotherapy incidence % (95% CI)	RR (95% CI)	*p* value
Any all-grade AEs	7	67.6 (64.2–70.8)	82.9 (78.9–86.2)	0.82 (0.76–0.88)	<.001
Any high-grade AEs	7	11.4 (9.9–13.1)	35.7 (26.0–46.8)	0.32 (0.22–0.45)	<.001
Treatment discontinuation	7	4.5 (3.5–5.7)	11.1 (8.5–14.3)	0.44 (0.33–0.57)	<.001
Treatment-related deaths	3	0.6 (0.3–1.1)	1.4 (0.7–2.5)	0.42 (0.16–1.13)	.09

Abbreviations: AE, adverse event; CI, confidence interval; PD-1, programmed death receptor-1; PD-L1, programmed death-ligand 1; RR, relative risk.

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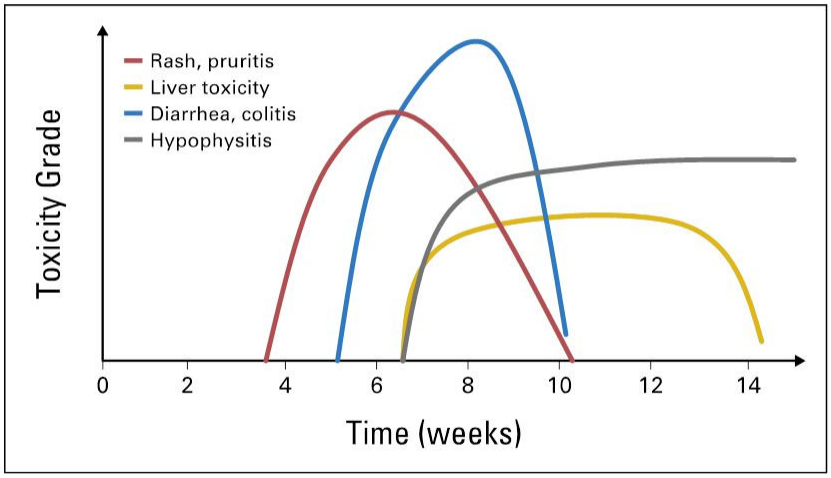
Kinetics of Immune Related Adverse Effects



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

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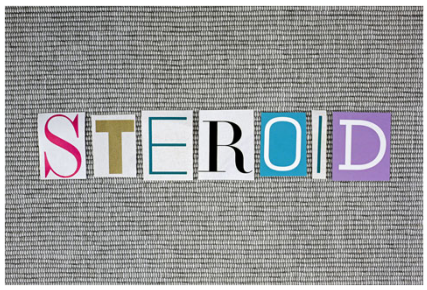
Common Medications

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



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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

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