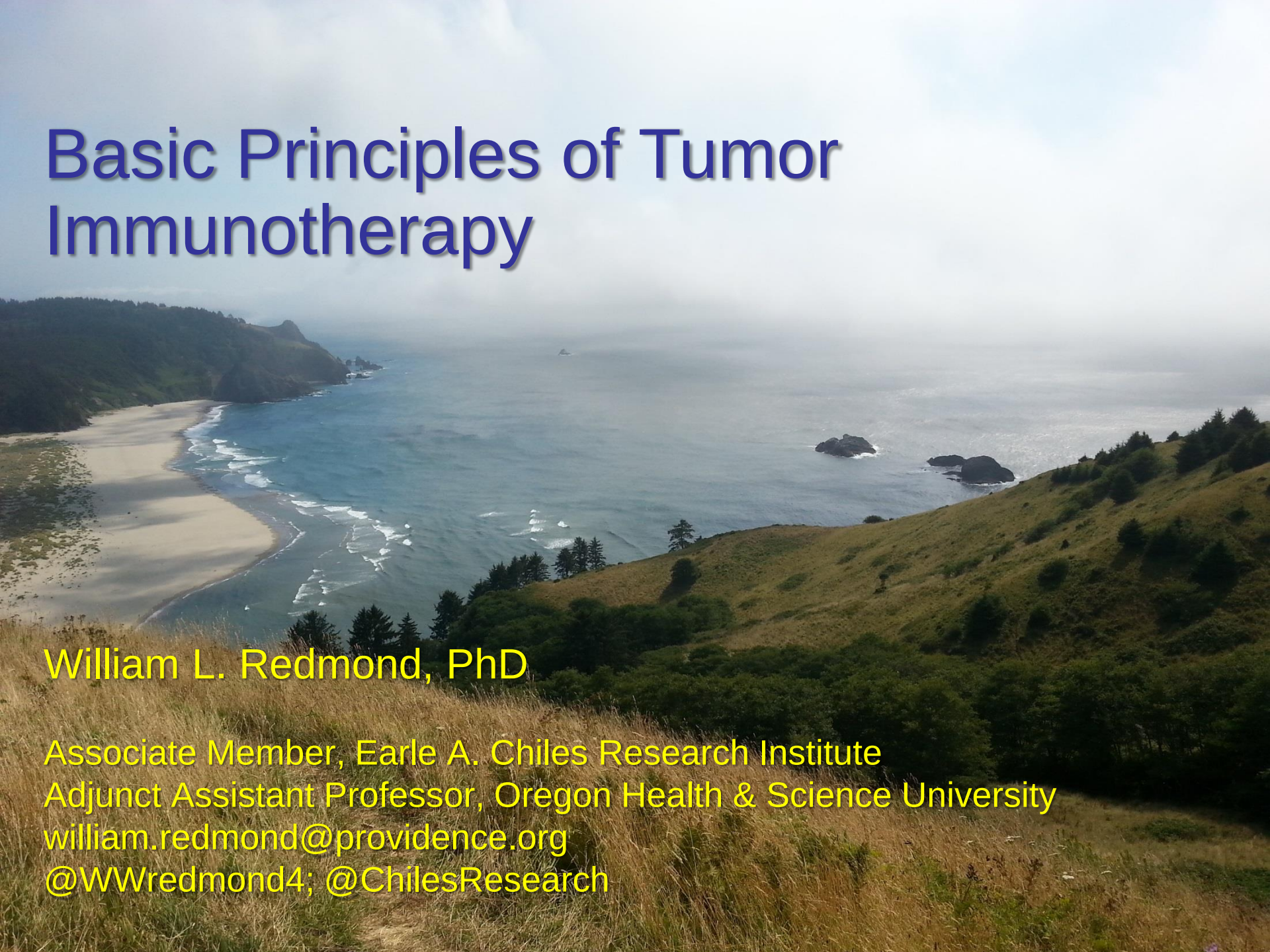
Basic Principles of Tumor Immunotherapy



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Adjunct Assistant Professor, Oregon Health & Science University
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@WWredmond4; @ChilesResearch

Disclosures

(Research grants, consulting, and/or royalties)

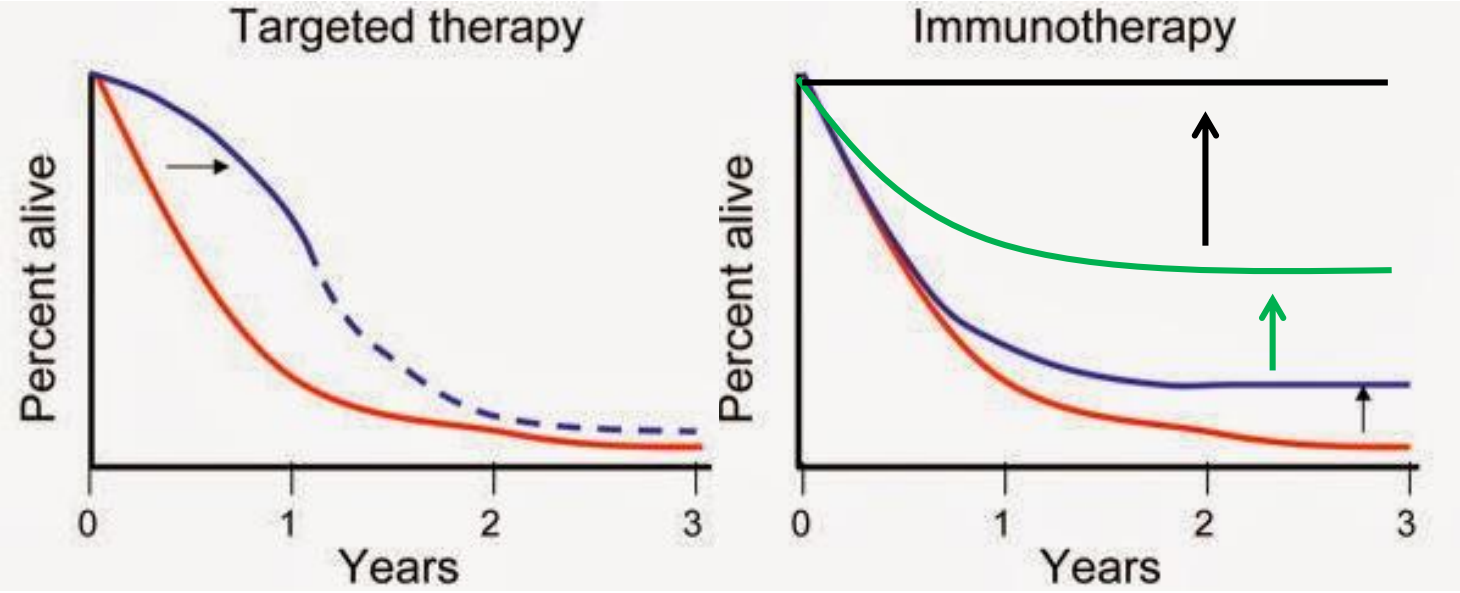
- Galectin Therapeutics, Merck, Nektar Therapeutics, Tesaro, IRX Therapeutics, CSRA Inc.
- *Some of the agents discussed are not FDA-approved cancer treatments*

Cancer immunotherapy

"Harnessing the power of the patient's own immune system to eradicate cancer"

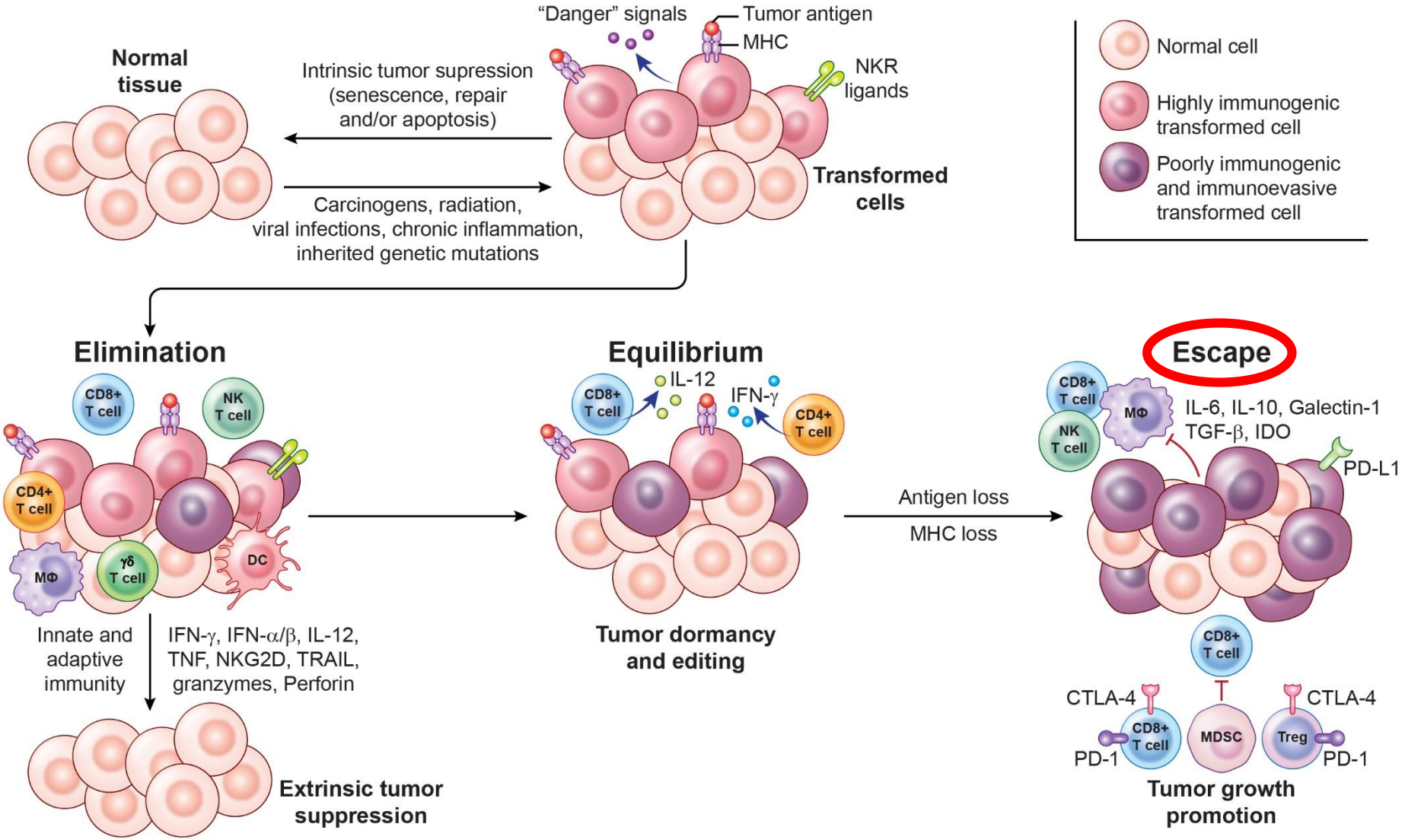
Benefits of immunotherapy

"shifting the curve"



Why does the immune system fail to eliminate cancer?

The 3 Es of cancer immunoediting



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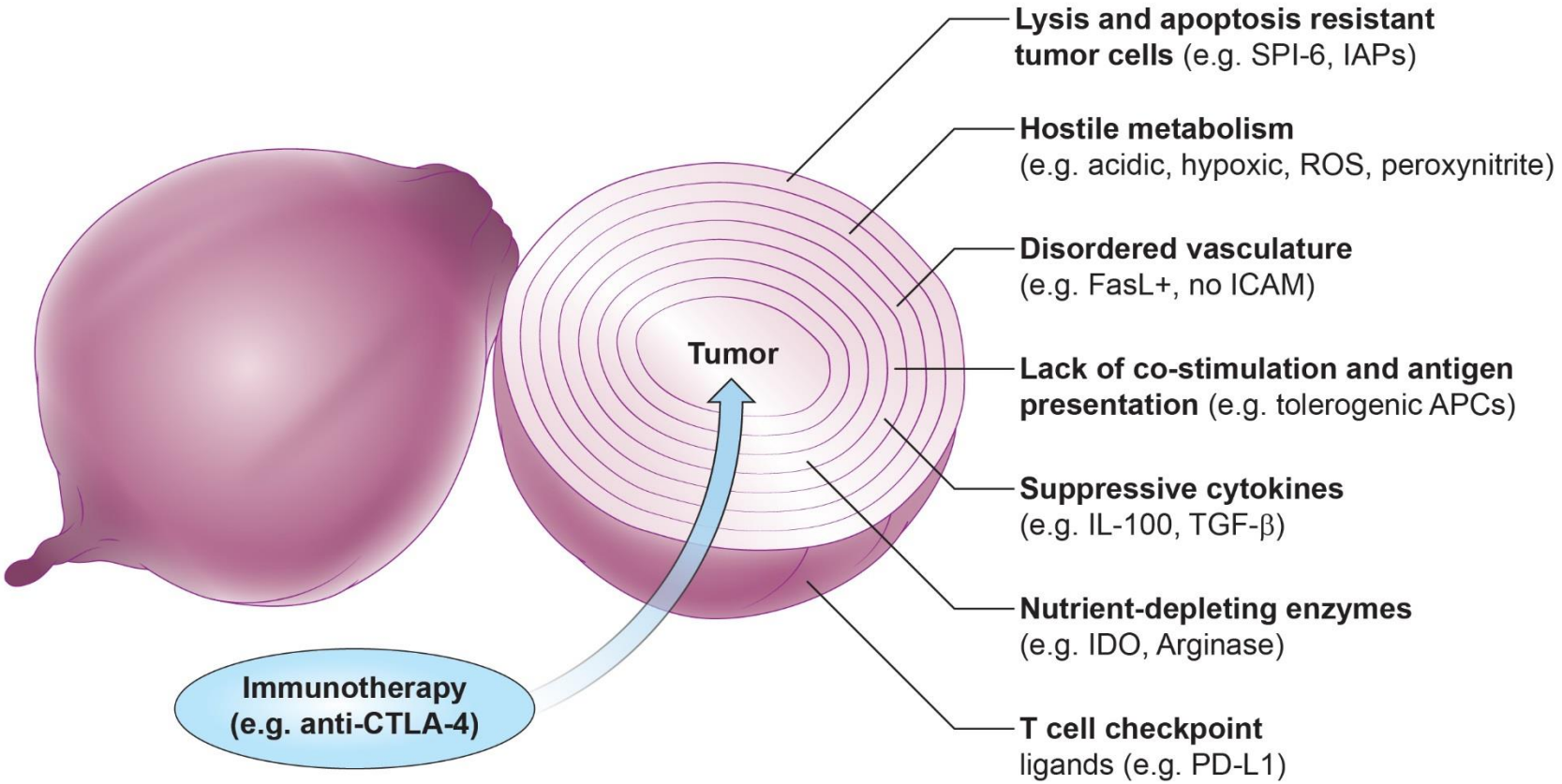
Multi-layered immunosuppression



- 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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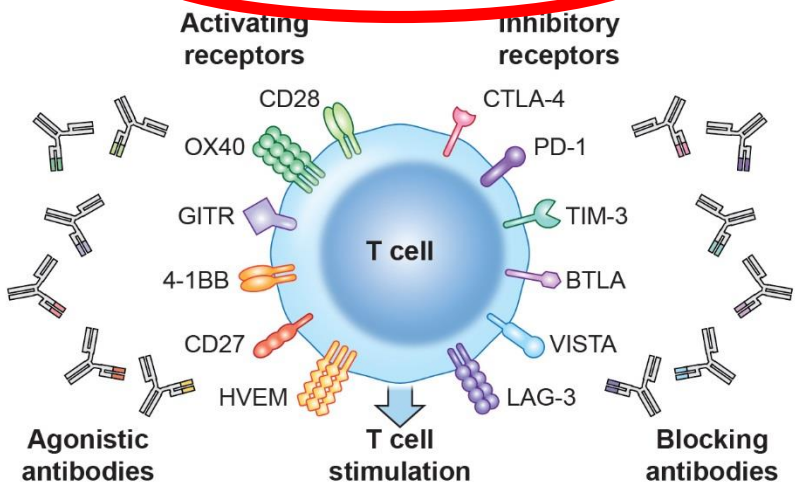
To exist, tumors must evolve mechanisms to locally disable and/or evade the immune system.

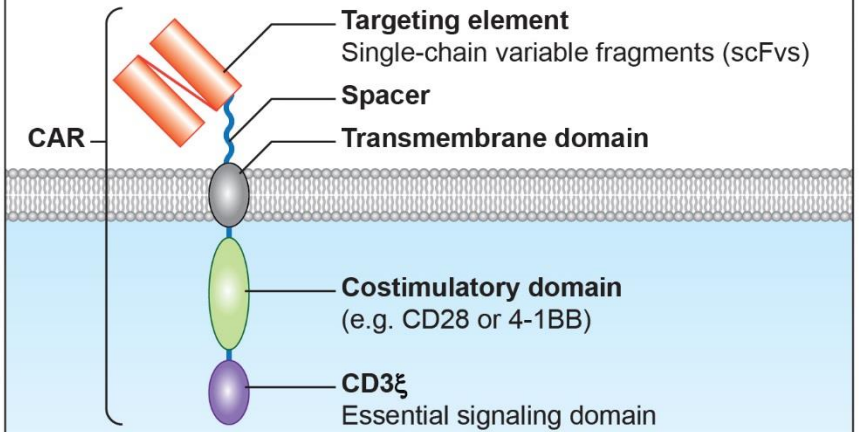
The goal of immunotherapy, then, is to restore the capacity of the immune system to recognize and reject cancer.

Types of immunotherapy

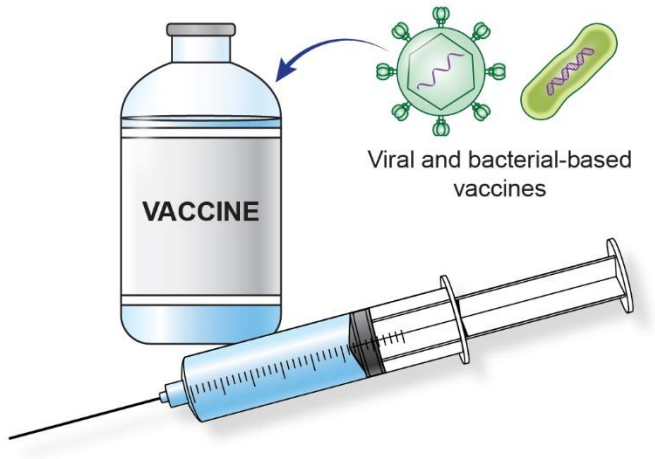
T cell checkpoint modulation



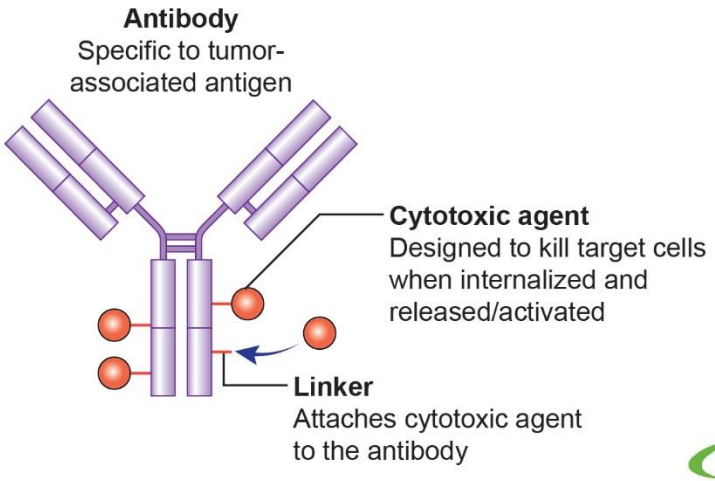
T cell adoptive transfer



Therapeutic cancer vaccines



Effector antibodies and antibody-drug conjugates



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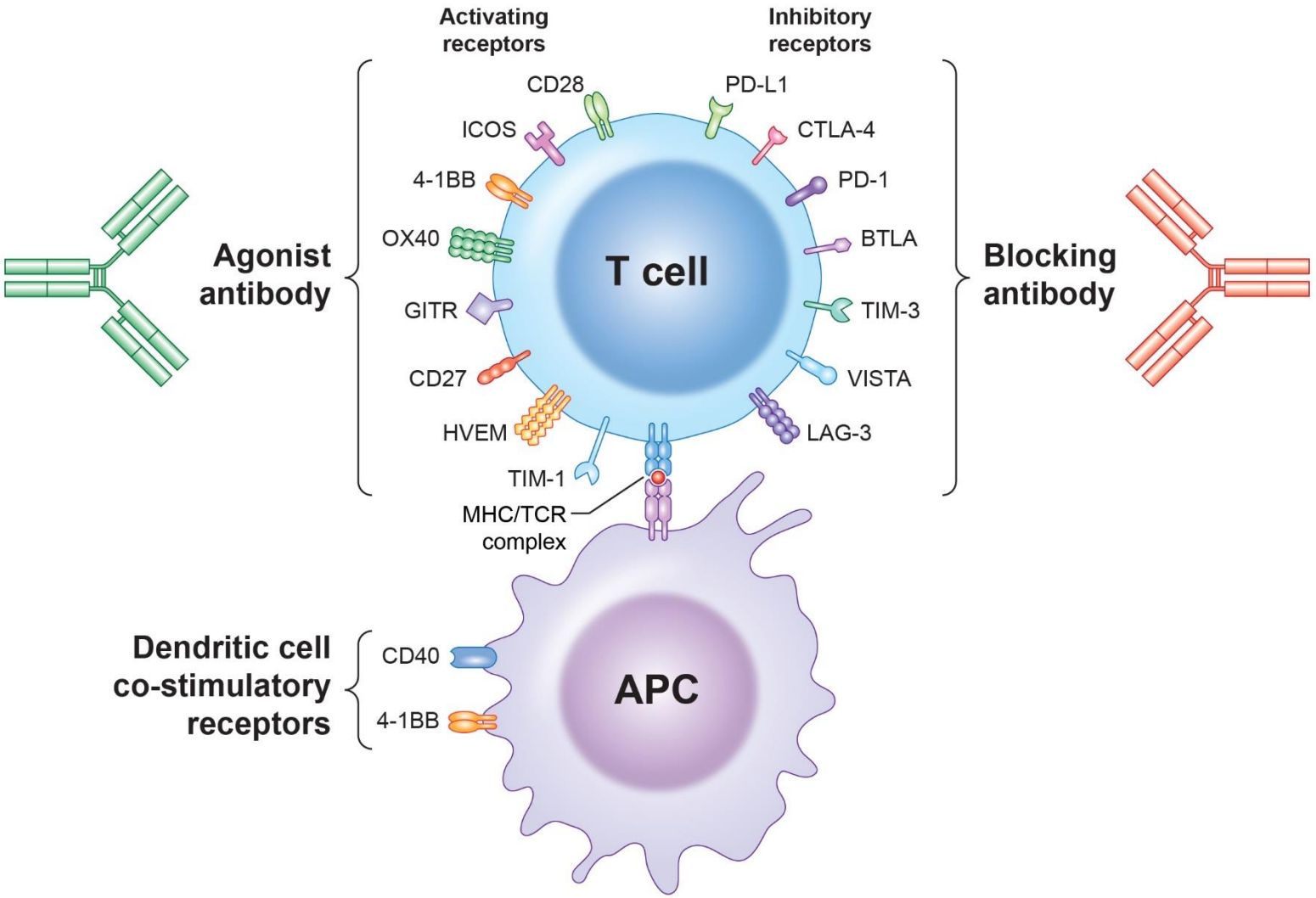
T cell checkpoint modulation



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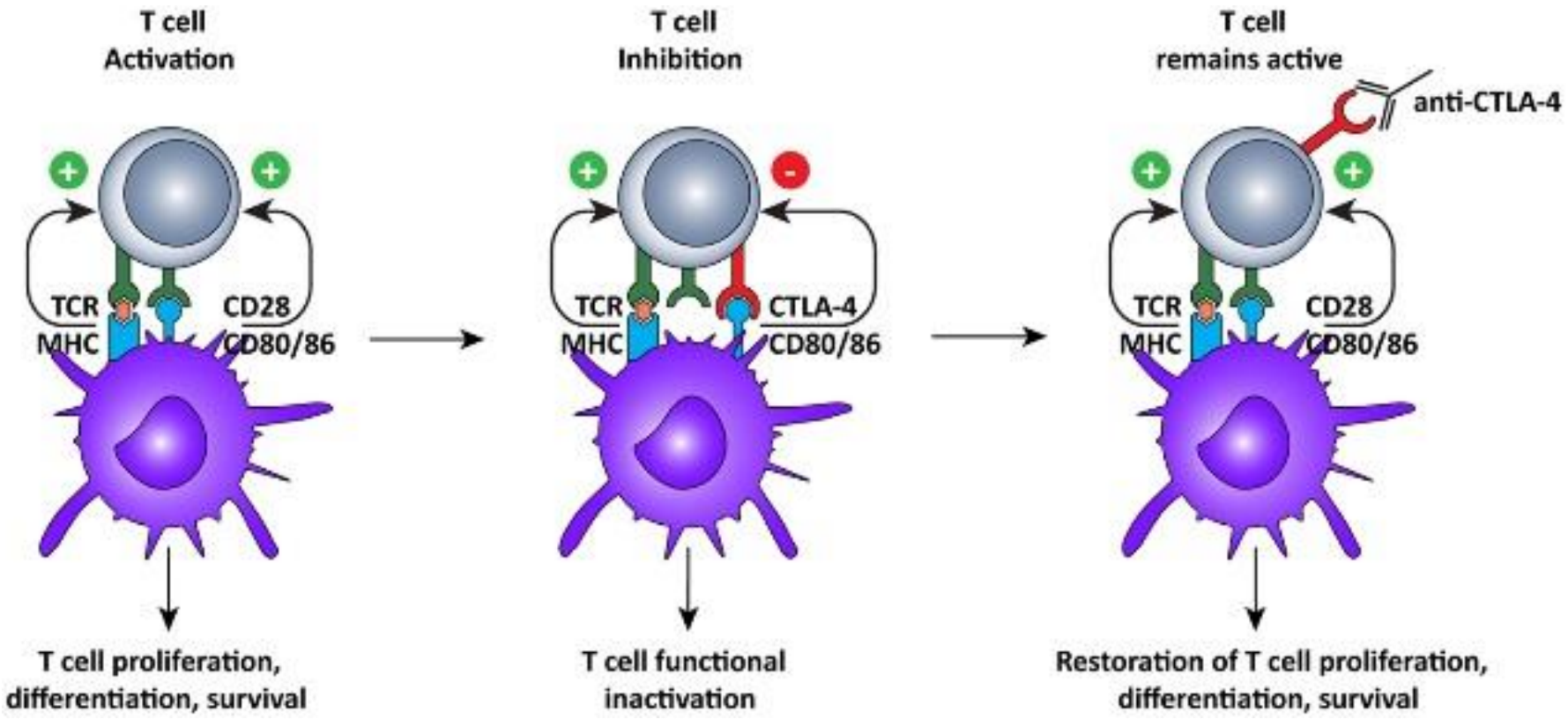
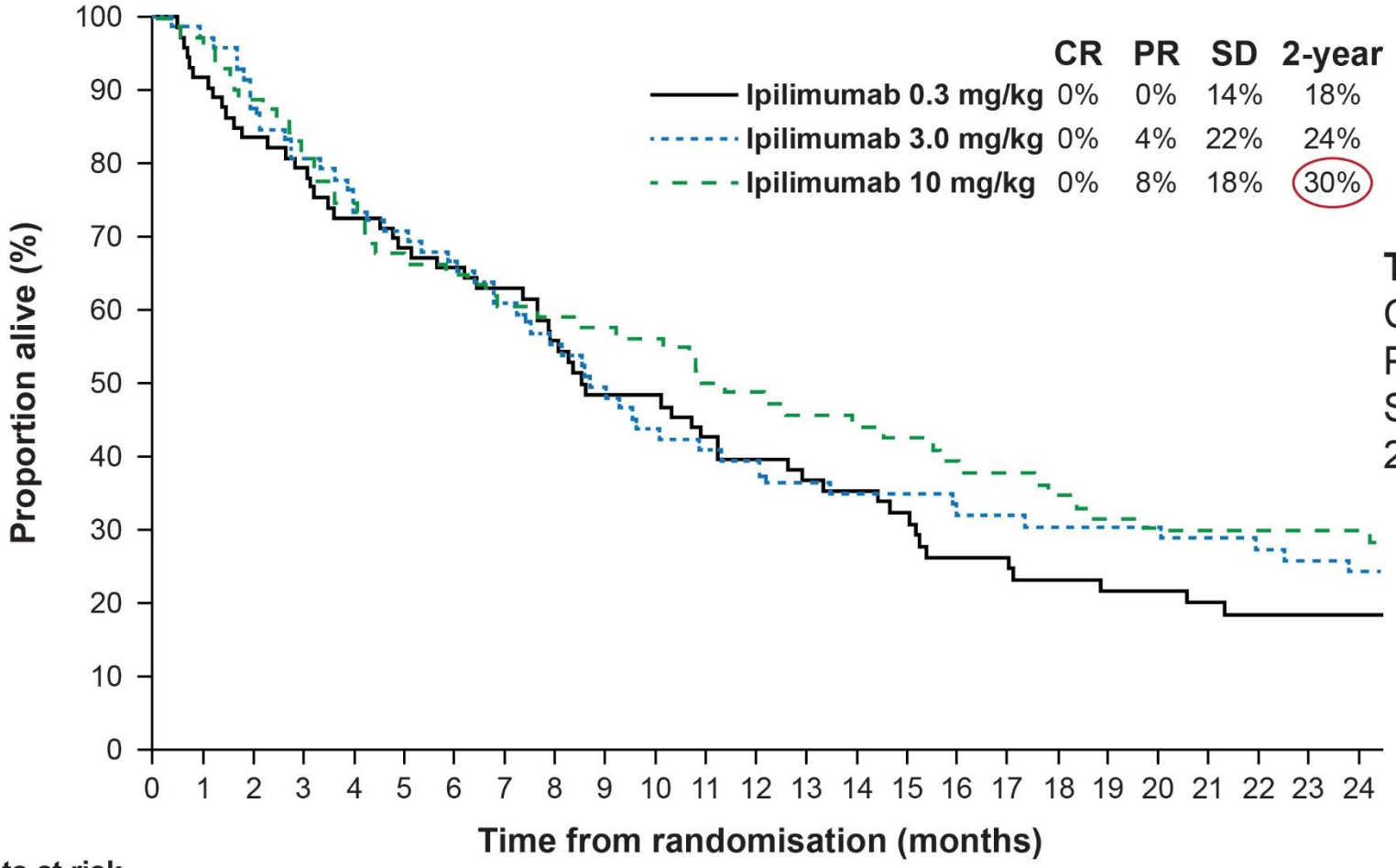
CTLA-4 blockade restores T cell function



Vasaturo A, *Front Immunol*, 2013

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



Temodar:
CR: 2.5%
PR: 11%
SD: 18%
2yr: 18%

Patients at risk

0.3 mg/kg	73	67	61	58	53	50	47	45	38	33	33	29	27	25	24	21	17	17	15	14	14	13	12	12	12
3.0 mg/kg	72	70	64	58	54	50	47	43	39	34	30	28	26	24	23	23	22	21	20	20	20	19	18	17	16
10 mg/kg	72	70	63	58	53	47	45	42	41	40	39	33	31	29	28	27	25	24	22	20	19	19	19	18	18

Wolchok et al. 2010. Lancet Oncol.

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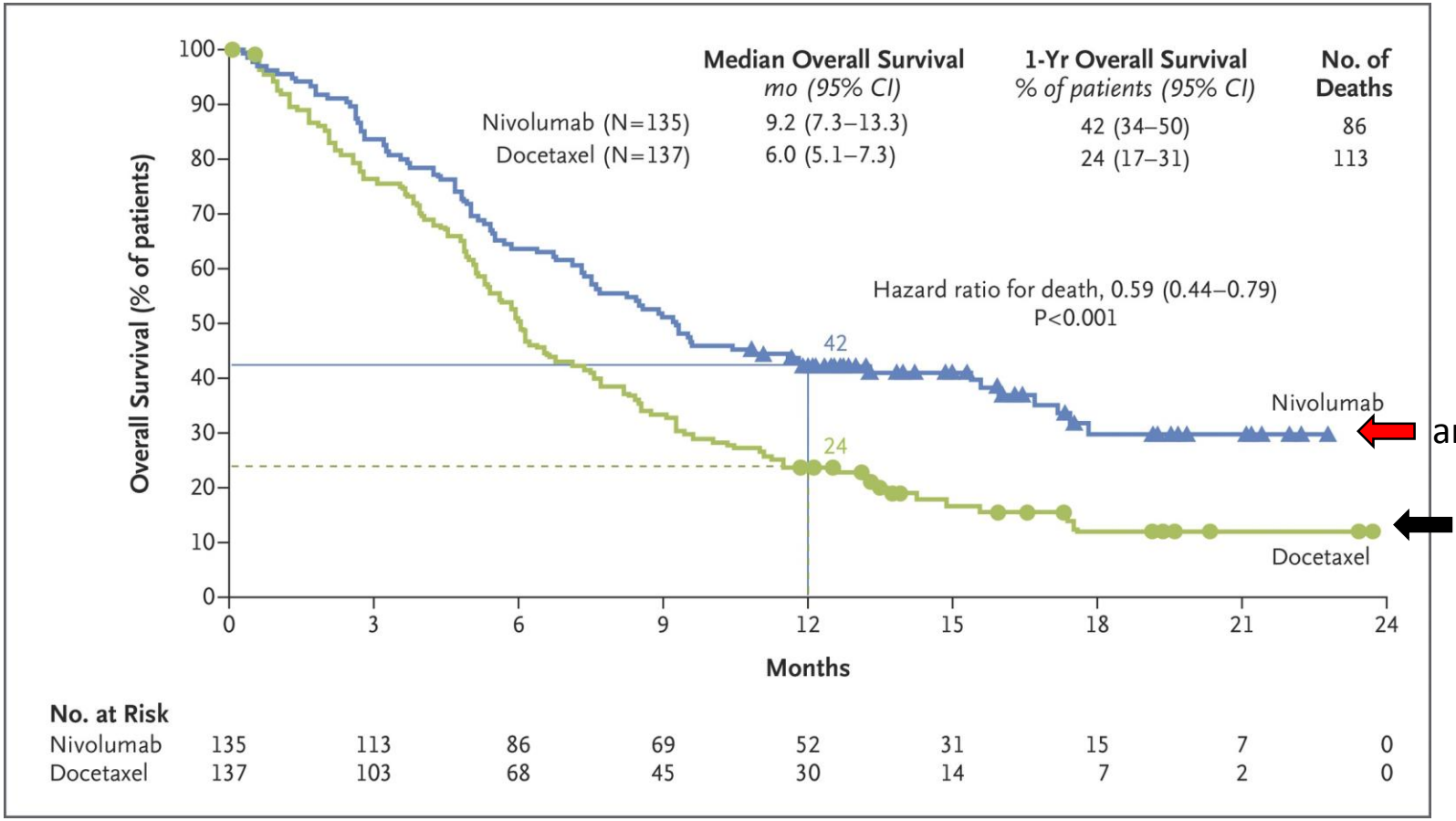
PD-1 blockade enhanced survival in patients with metastatic lung cancer (NSCLC)



anti-PD-1

chemo

Brahmer J, *New Eng J Med*, 2015

Immune-modulating antibodies in the clinic

Target molecule	Drug	Development stage
CTLA-4	Ipilimumab	FDA approved
	Tremelimumab	Phase III trial
PD-1	Pembrolizumab	FDA approved
	Nivolumab	FDA approved
	AMP-514/MEDI0680	Phase I trial
PD-L1	Atezolizumab	FDA approved
	Durvalumab	Phase III trial
	Avelumab	Phase III trial
	BMS-936559	Phase I trial
4-1BB	Urelumab	Phase I trial
	PF-05082566	Phase I trial
OX-40	MEDI6469	Phase I trial
	MEDI6383 (rOX40L)	Phase I trial
	MOXR0916	Phase I trial
GITR	TRX518	Phase I trial
CD27	CDX-1127	Phase I trial
CD40	CP-870, 893	Phase I trial
LAG3	BMS-986016	Phase I trial

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Types of immunotherapy

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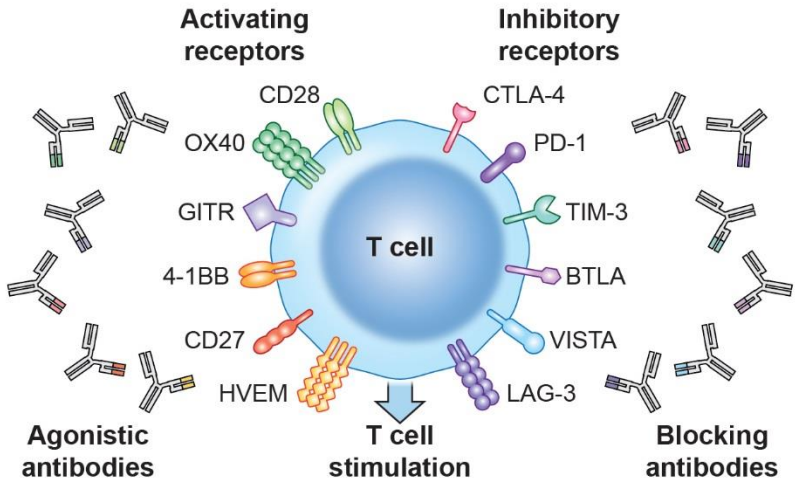

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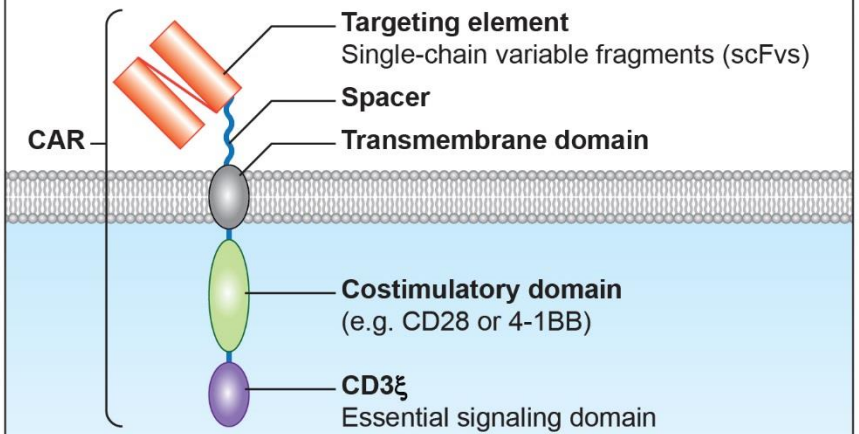
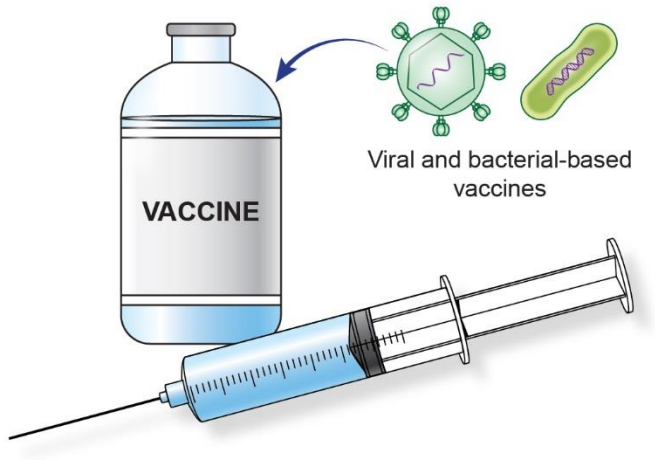


Therapeutic cancer vaccines



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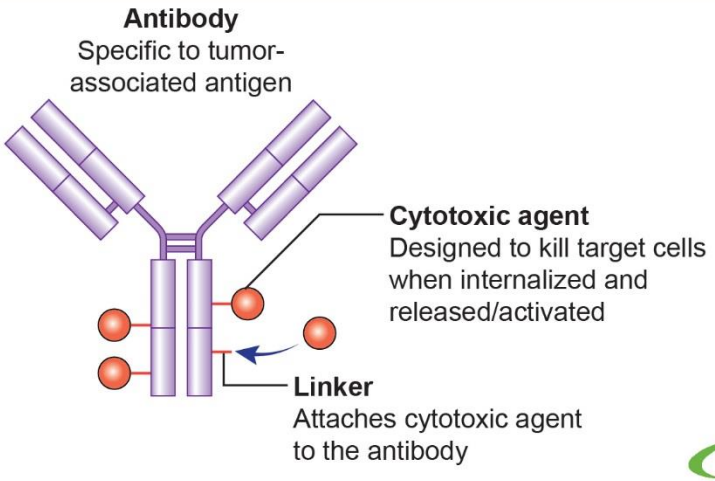

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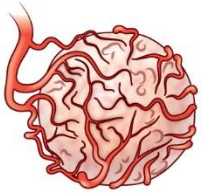
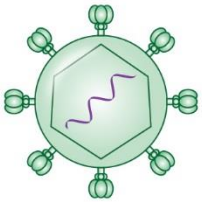
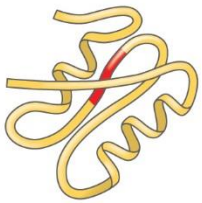
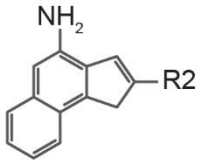
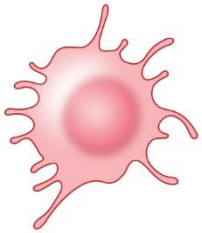
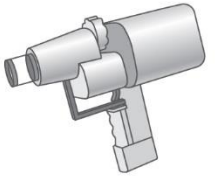
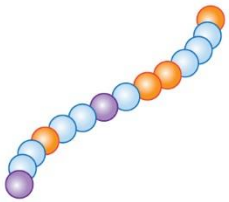
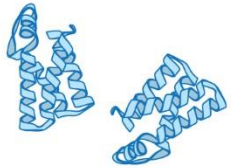
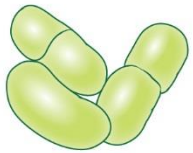
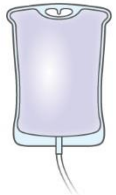
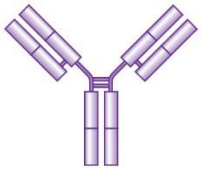
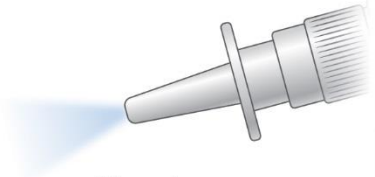
Components of a cancer vaccine

Antigen	Adjuvant	Vector	Vehicle
 Whole tumor	 Emulsifiers	 Viral vectors	 Injection
 Protein antigen	 Innate agonists	 Dendritic cells	 Gene gun
 Antigenic peptide(s)	 Cytokines	 Attenuated bacteria	 Systemic infusion
	 Antibodies		 Nasal spray

Active immunotherapies in phase III development

(a partial list…)

The first therapeutic cancer vaccine approved for human use was Sipuleucel-T for prostate cancer in 2010. Many others are in Phase III development as shown here and dozens more are currently in Phase I and Phase II. There is increasing interest in targeting the mutated antigens unique to each patient's cancer which are the targets for the most efficacious anti-tumor responses.

Immunotherapy	Targeted antigens	Adjuvants/ immune modulators	Study population	n	Outcomes
Prostate cancer					
Autologous cell vaccine: sipuleucel-T Provenge®	PAP	GM-CSF	Metastatic, castration-resistant prostate cancer	512	OS: 25.8 months vs 21.7 months (HR 0.78; *P*=0.03) PFS: 3.7 months vs 3.6 months (HR 0.95; *P*=0.63) T cell response in 74.0% vs 12.1% of patients
Allogeneic tumor cell vaccine: GVAX	Tumor cell	GM-CSF	Castration-resistant prostate cancer	626	OS: 20.7 months vs 21.7 months with docetaxel plus prednisone (HR 1.03; P=0.78)
Viral vector vaccine: Prostvac	PSA	GM-CSF	Castration-resistant prostate cancer	408	OS 25.1 months with Prostvac vs. 16.6 months with control vaccine (HR 0.56, P=0.0061)
Breast cancer					
Peptide vaccine: Theratope	Sialyl-Tn	KLH	Metastatic breast cancer, in remission after first-line chemotherapy	1,028	Median OS: 23.1 months vs 22.3 months (P=0.916) With concomitant endocrine therapy, OS: 39.6 months vs 25.4 months (P=0.005) Median TTP: 3.4 months vs 3.0 months (P=0.353) With concomitant endocrine therapy: 10.6 months vs 6.3 months (P=0.078)
Lung cancer					
Peptide vaccine: tecemotide (L-BLP25)	MUC1	Liposomal monophosphoryl lipid A plus cyclophosphamide	Unresectable stage II NSCLC; after chemo-radiotherapy	1,239	Median OS: 25.6 months vs 22.3 months (HR 0.88; P=0.123); OS with concurrent chemotherapy: 30.8 months vs 20.6 months (HR 0.78; P=0.016); OS with sequential chemotherapy: 19.4 months vs 24.6 months (HR 1.12; P=0.38)
Peptide vaccine: GSK1572932A	MAGE-A3	Liposomal AS15	Completely resected stage IB-II NSCLC	182	Trial terminated owing to failure to meet primary end points of extended DFS. Not possible to identify gene signature predicting benefit

Spectrum of current and potential therapeutic vaccine targets

Spectrum of current and potential therapeutic cancer vaccine targets

Target type	Examples	Selected references
Oncoprotein	Point mutated: ras, B-raf, frame shift mutations, undefined unique tumor mutations; HER2/neu, MUC-1 C-terminus, p53	(1, 7, 8, 48,4 9)
Oncofetal	CEA, MUC-1	(2-4, 19, 26)
Cancer-testes	MAGE-A3, BAGE, SEREX-defined, NY-ESO	(10, 50-52)
Tissue lineage	PAP, PSA, gp100, tyrosinase, glioma antigen	(5, 6, 24, 25, 27, 41, 44, 53)
Stem cell/EMT	Brachyury, SOX-2, OCT-4, TERT, $CD44^{high}/CD24^{10}$, $CD133^{+}$	(54-62)
Viral	HPV, HCV	(63, 64)
Glycopeptides	STn-KLH	(15, 16)
Antiangiogenic	VEGF-R	(65, 66, 67)
B-cell lymphoma	Anti-id	(11-14)

*BAGE = B melanoma antigen; CEA = carcinoembryonic antigen; EMT = epithelial-mesenchymal transition; gp100 = glycoprotein 100; HCV = hepatitis C virus; HPV = human papillomavirus; MAGE-A3 = melanoma-associated antigen-A3; MUC-1 = mucin 1; NY-ESO = New York esophageal carcinoma antigen 1; OCT-4 = octamer-binding transcription factor 4; PAP = prostatic acid phosphatase; PSA = prostate-specific antigen; SOX-2 = (sex determining region Y)-box-2; STn-KLH = sialyl-Tn-keyhole limpet hemocyanin; TERT = telomerase reverse transcriptase; VEGF-R = vascular endothelial growth factor receptor.

Published online 2012.
J Natl Cancer Inst. 104(8): 599-613.

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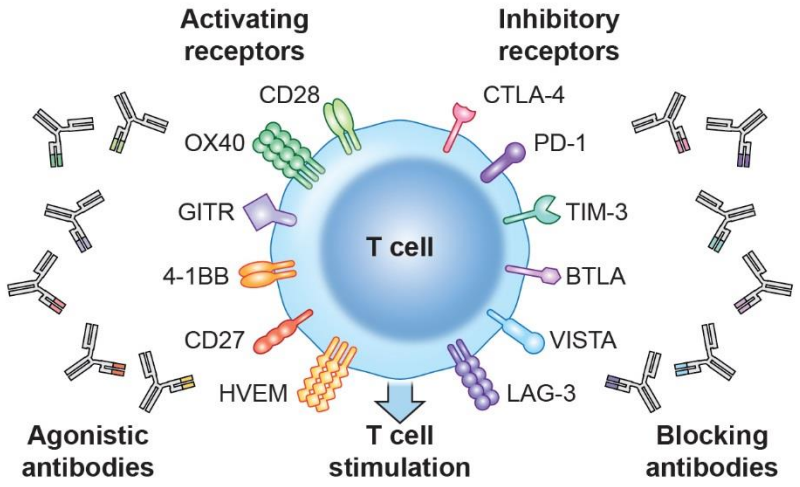
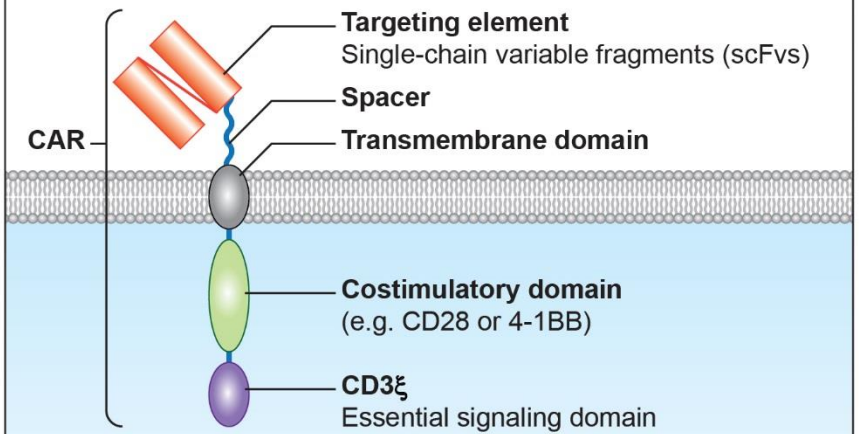
Types of immunotherapy

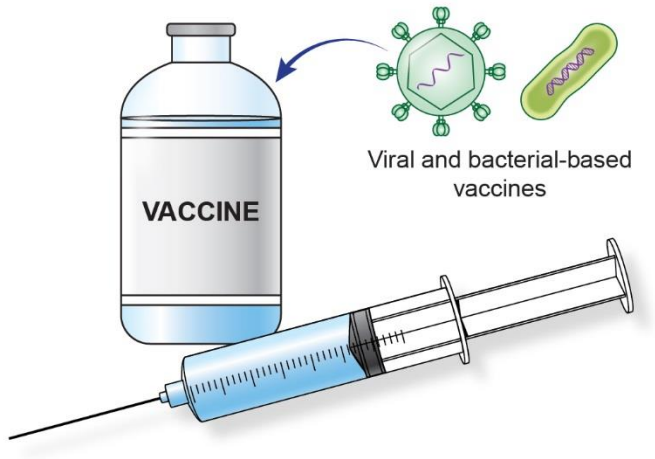
T cell checkpoint modulation



T cell adoptive transfer



Therapeutic cancer vaccines



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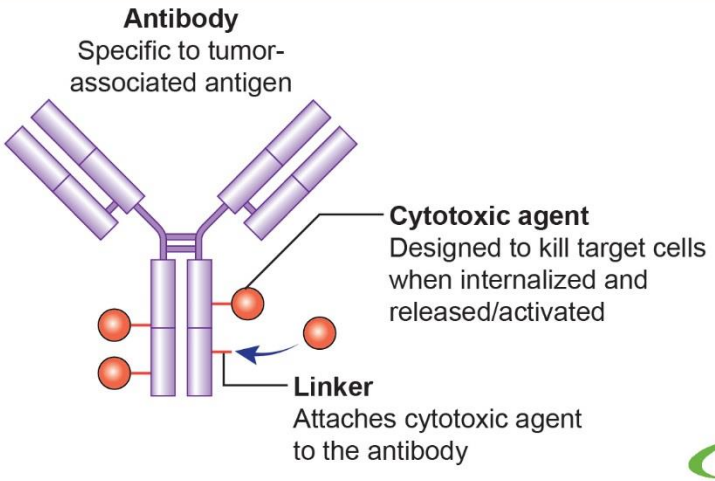

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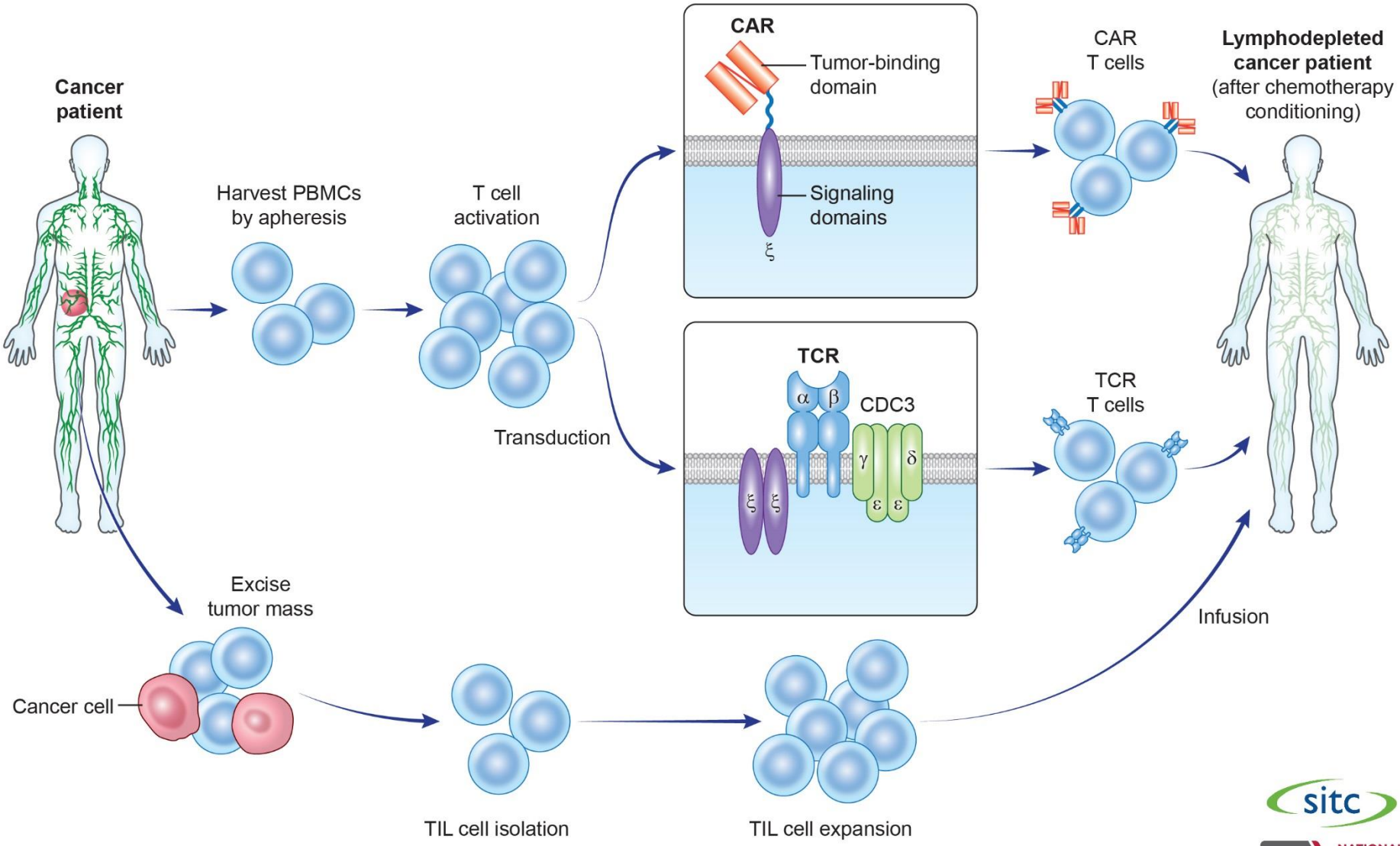
Adoptive T cell therapy can involve engineered (CAR, TCR) or patient-derived (TIL, PBMC) T cells



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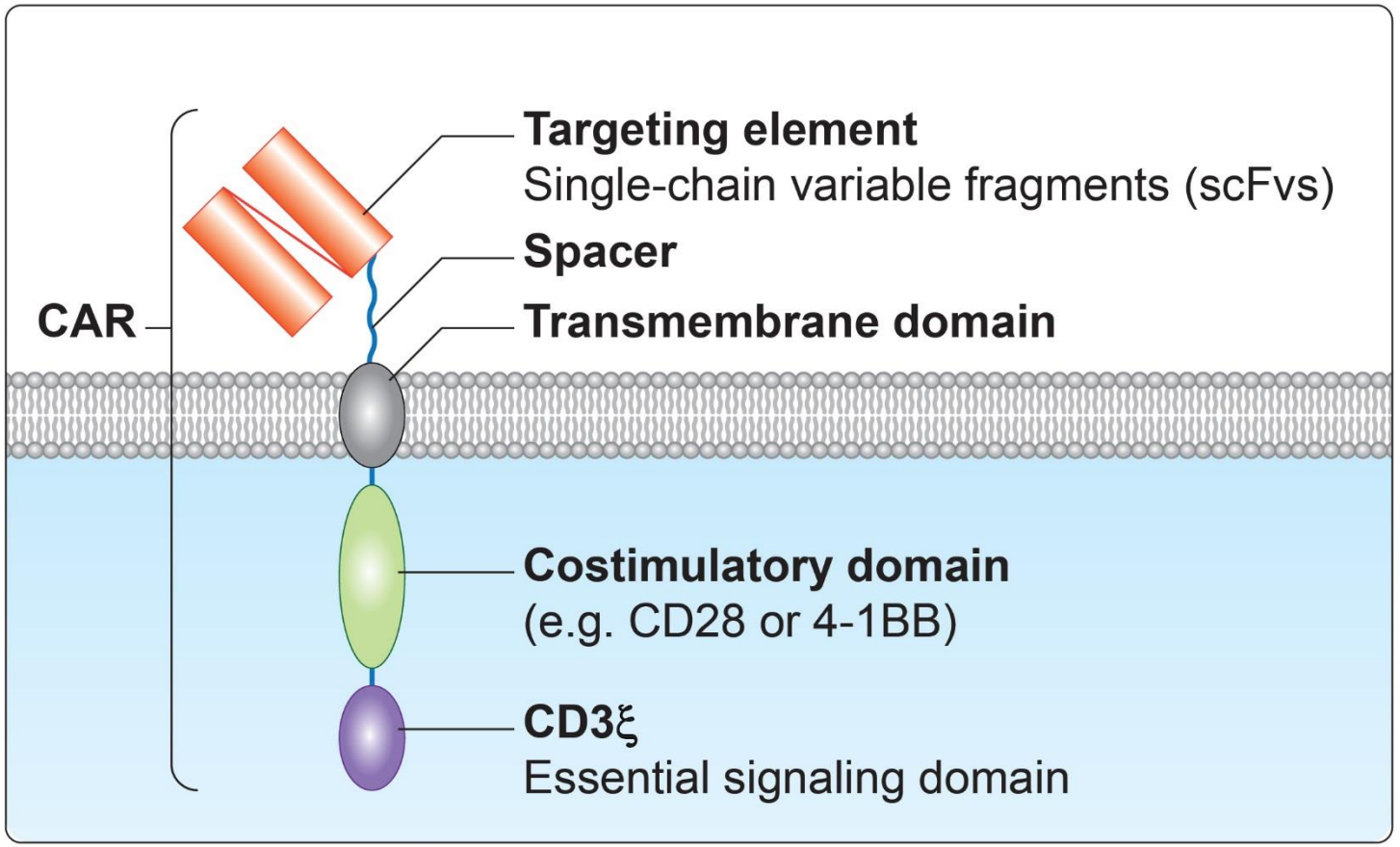

CARs, TIL, engineered PBMC, etc...

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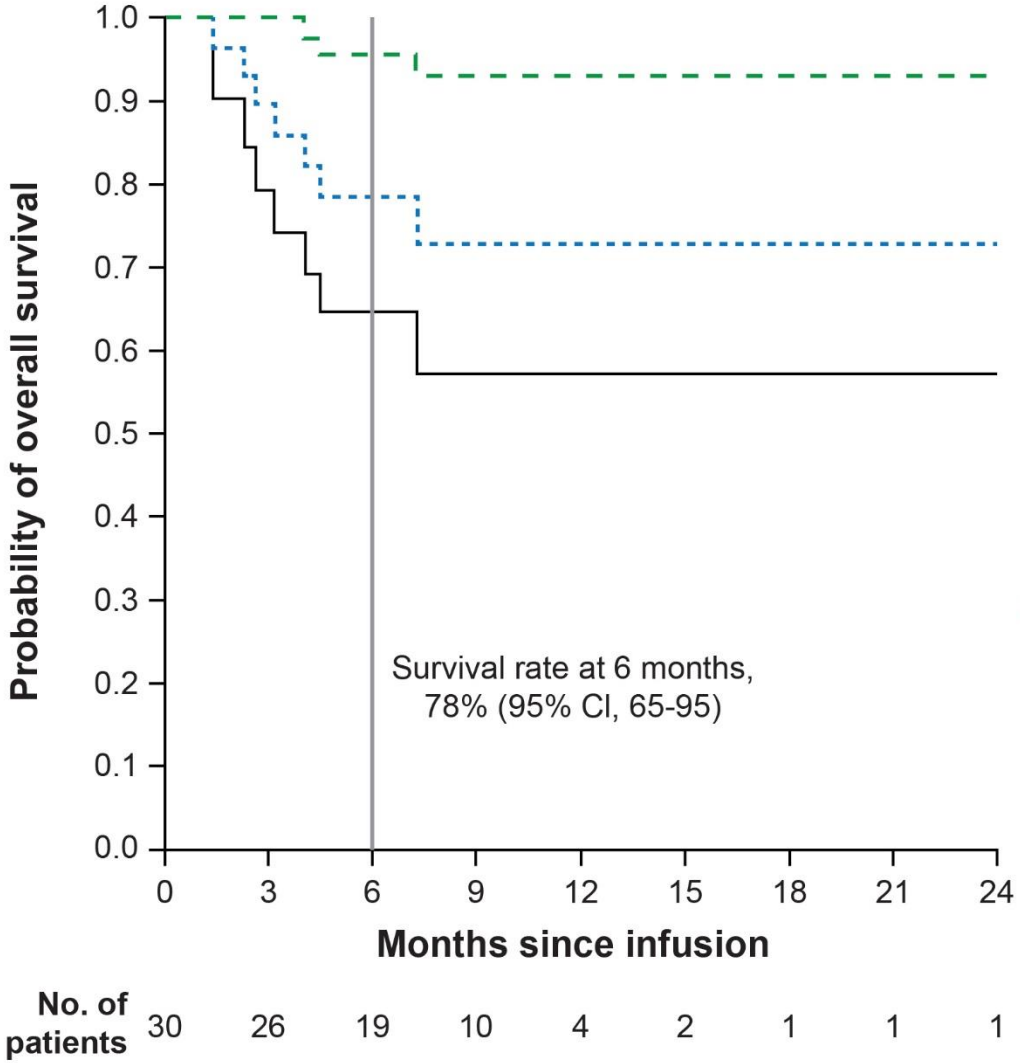
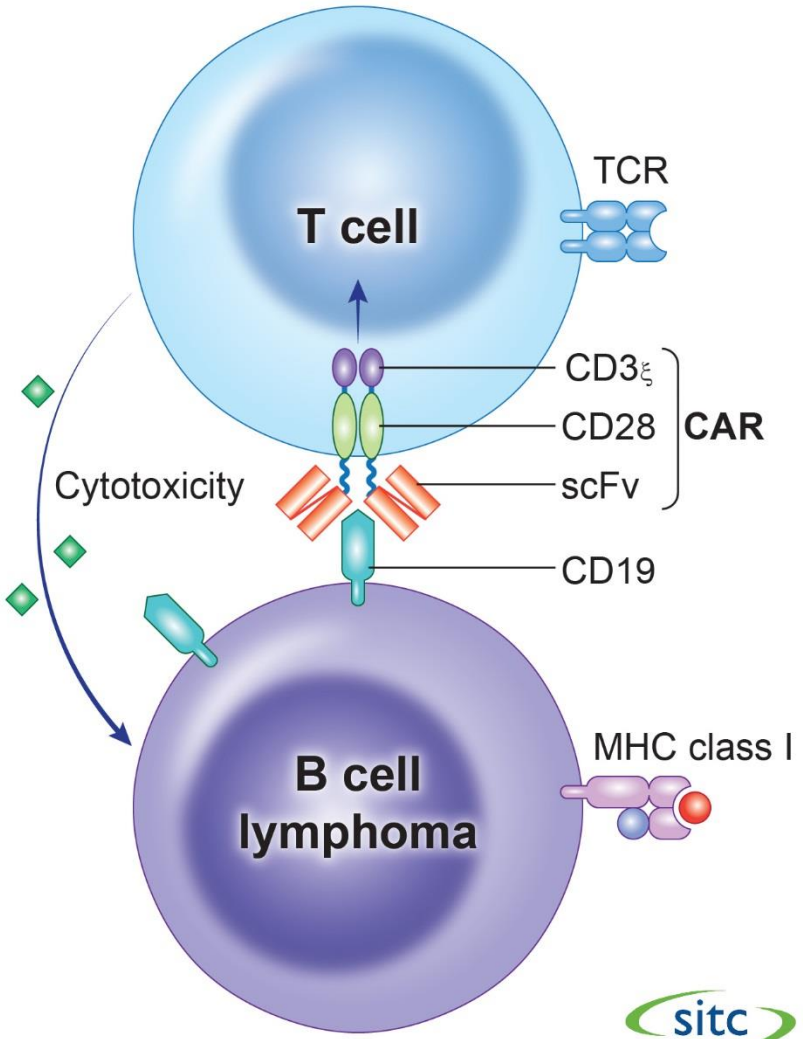
Effective treatment of relapsed B cell ALL with CD19 CAR T cell therapy





Maude S, Frey N, Shaw P, Aplenc R, Barrett D, Bunin N, Chew A, Gonzalez V, Zheng Z, Lacey S, et al. 2016.
Chimeric antigen receptor T cells for sustained remissions in leukemia.
The New England Journal of Medicine. 374(10): 998.

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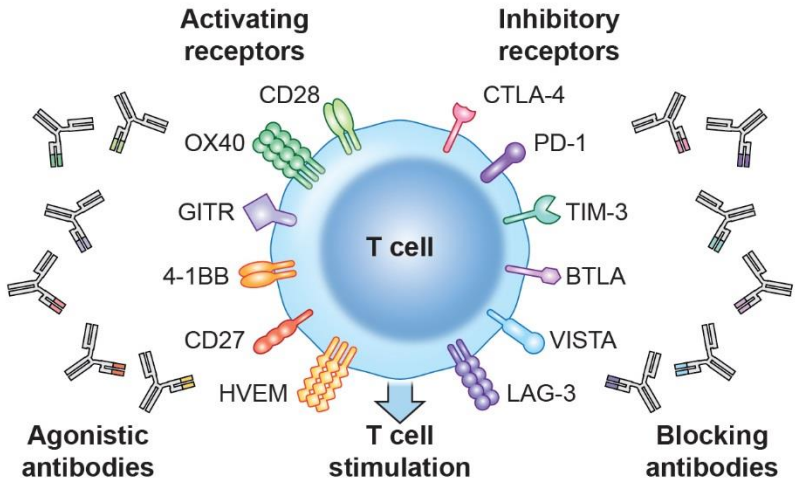

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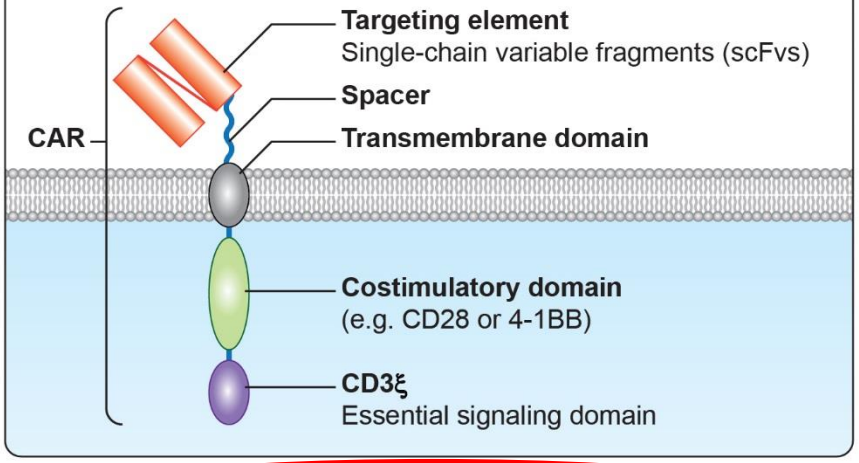

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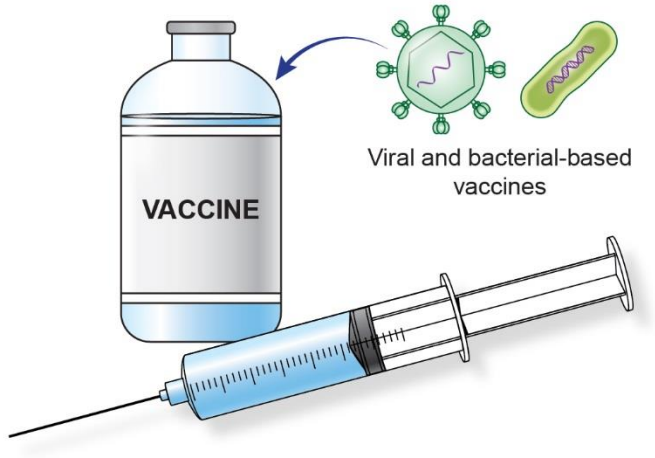
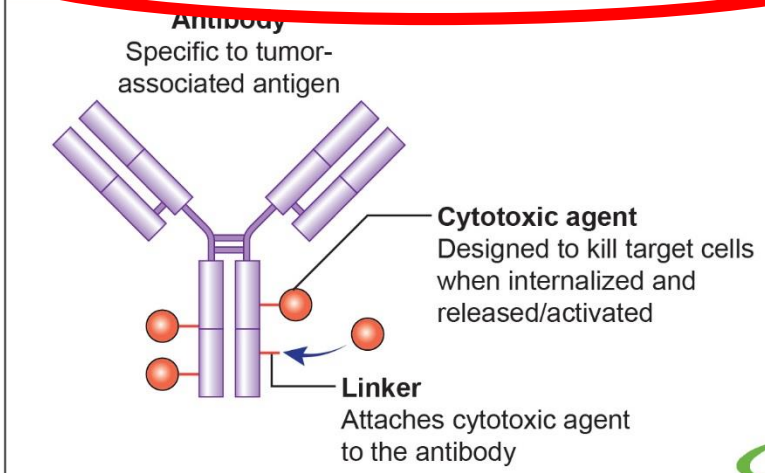


Effector antibodies and antibody-drug conjugates



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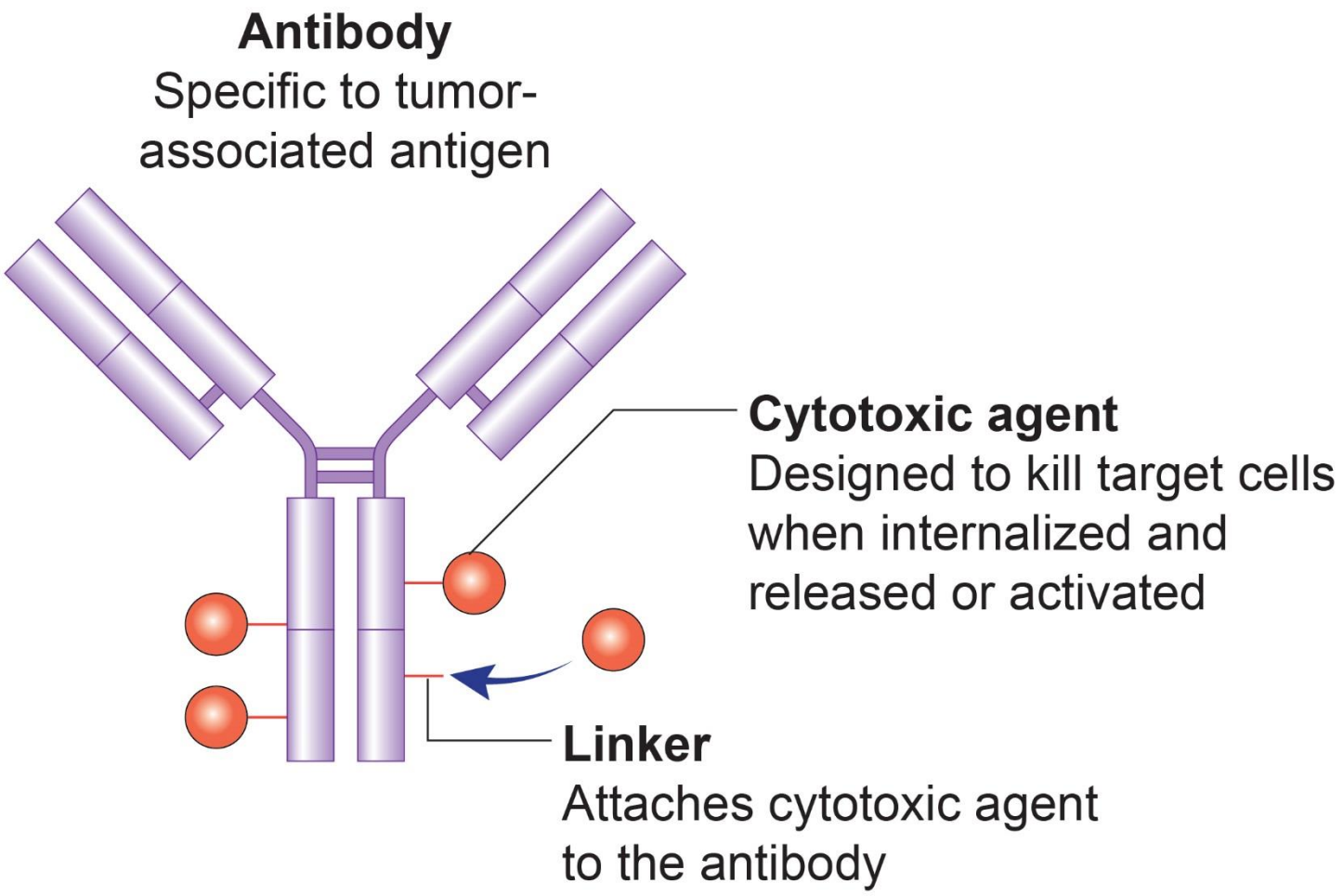
Effector antibodies and antibody-drug conjugates (ADCs)



Trastuzumab emtansine (T-DM1)

-Trastuzumab (anti-HER2 mAb) linked to cytotoxic agent (tubulin inhibitor; emtansine/DM1)

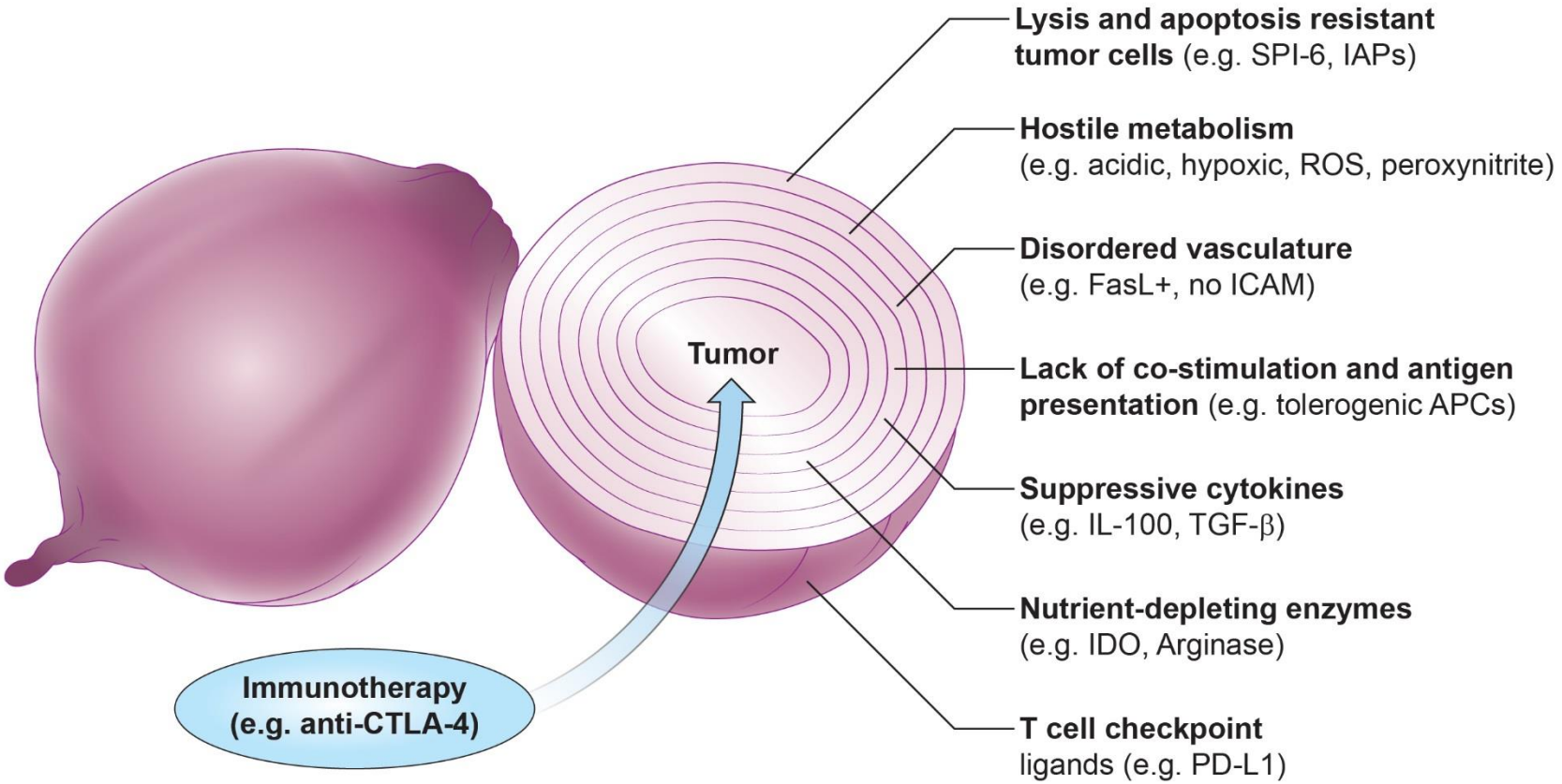
Key ADC/antibody principles

- **Specificity:** The more tumor specific the target antigen is, the higher the agent can be dosed without limiting toxicity

- **Internalization:** The target tumor surface protein must internalize to deliver the toxin - it should do so frequently and to a suitable endosomal compartment.

- **Stability:** The toxin must remain inert and tethered to the antibody until it is delivered to its target cell.

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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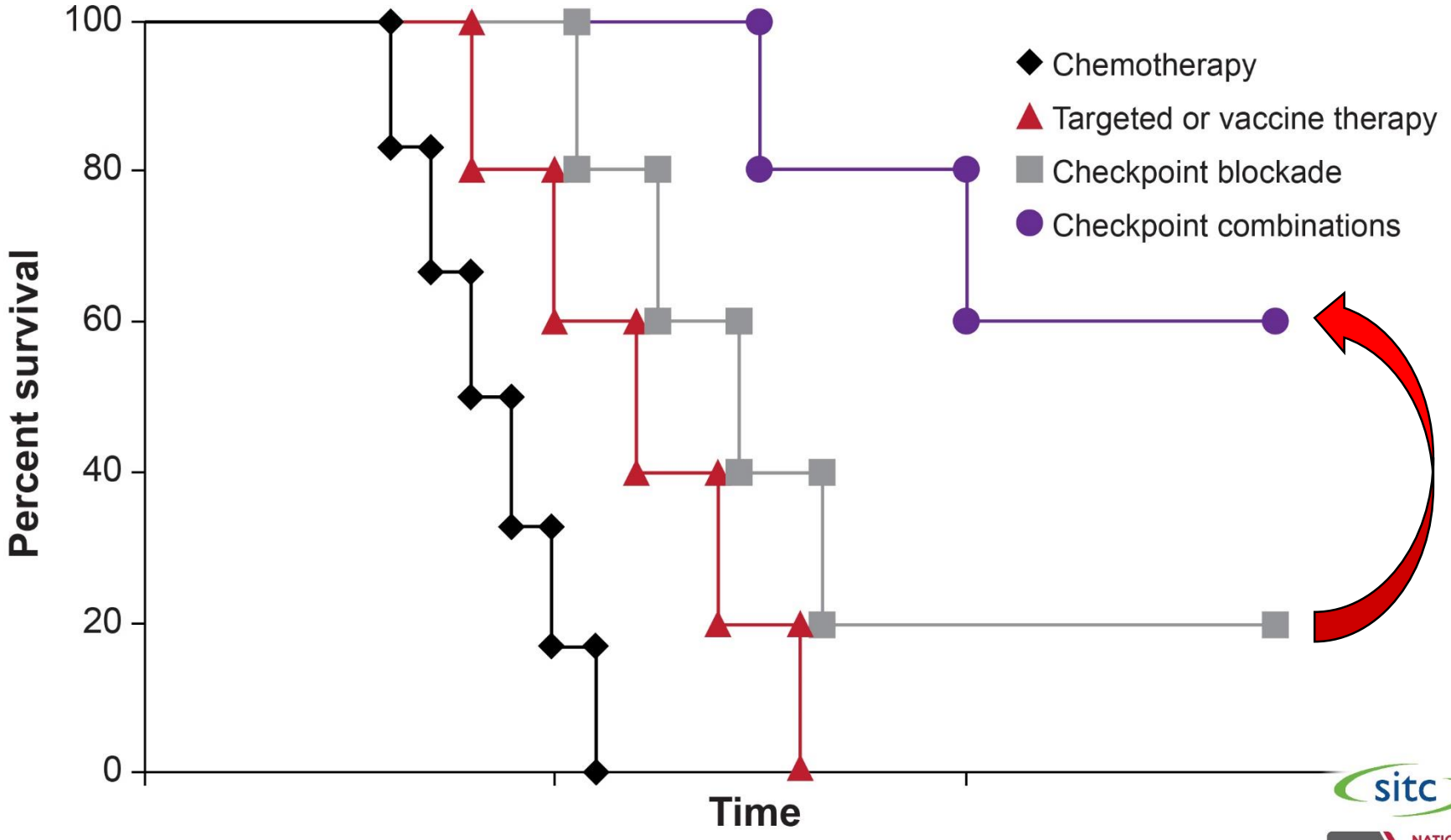
Combination immunotherapy



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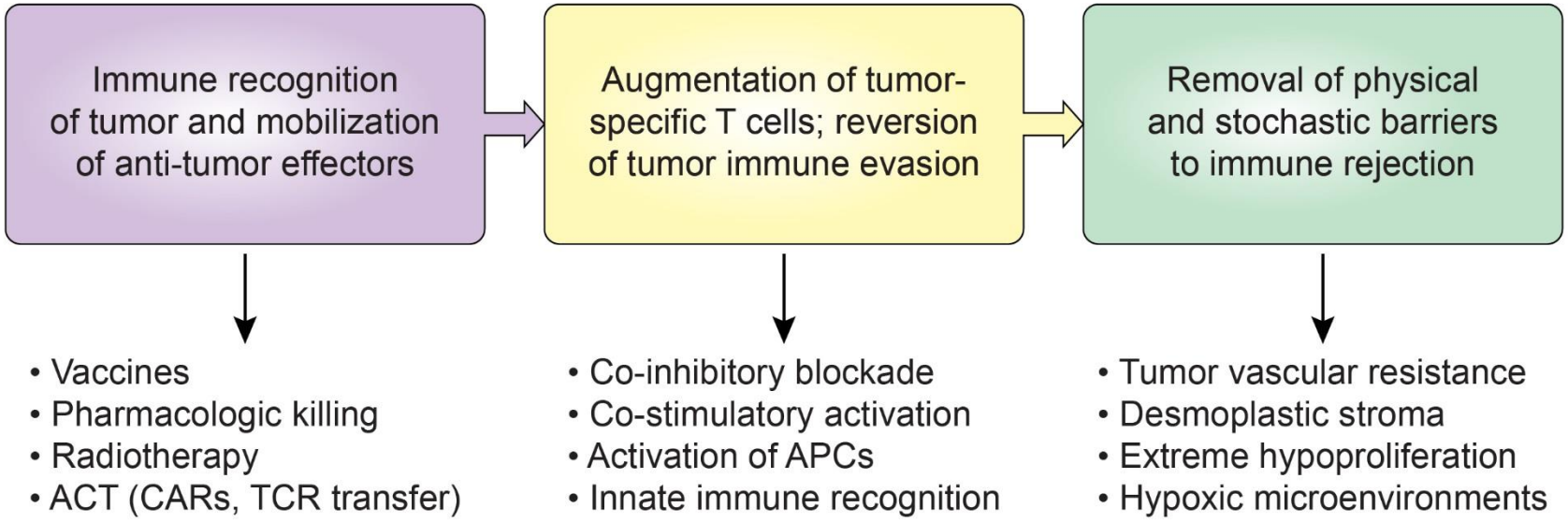
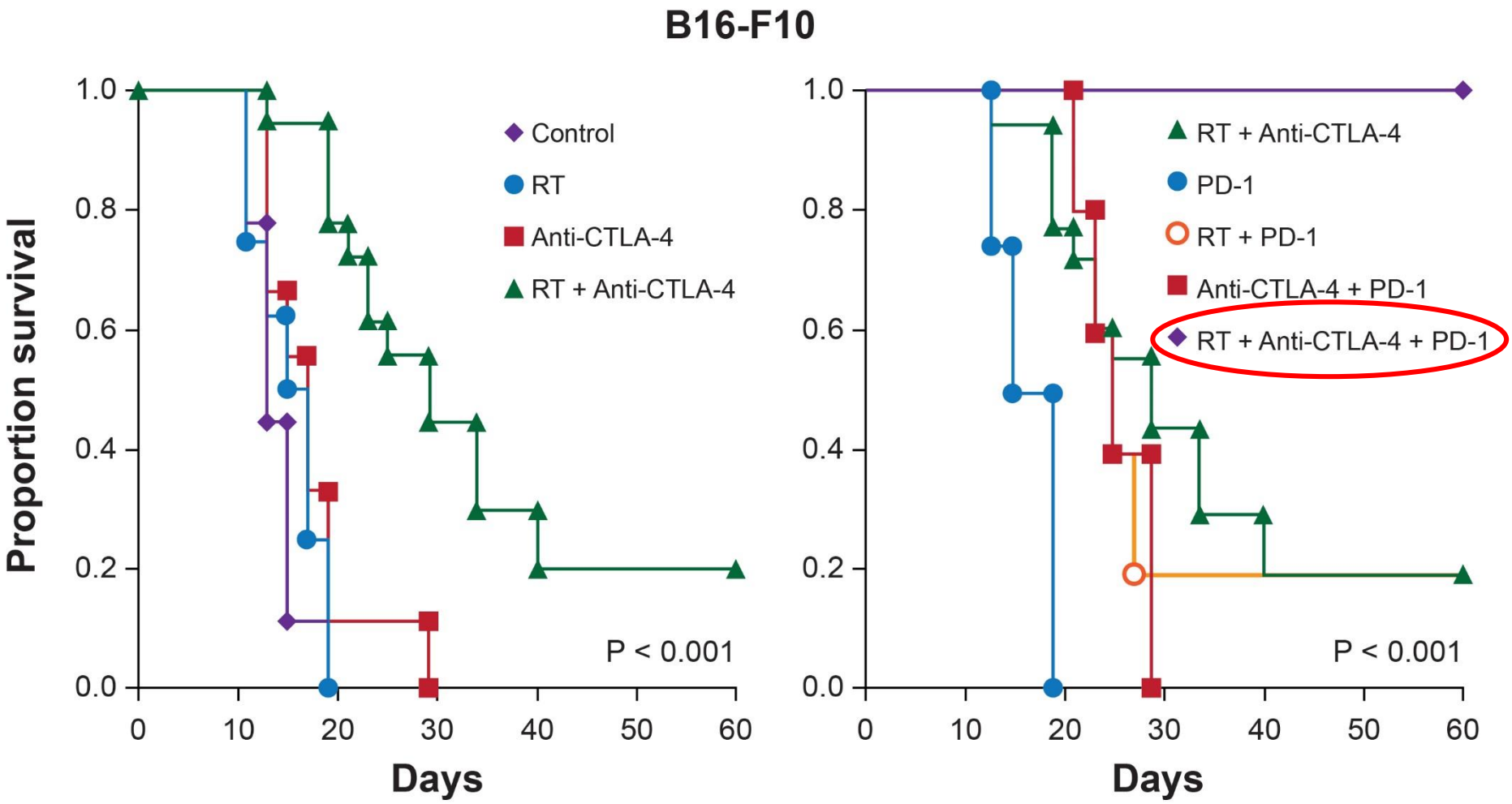
Seeking combinations outside of T cell checkpoint immunotherapy



Radiotherapy synergizes with blockade of CTLA-4 and PD-1 to cure melanoma lung metastases



Victor CT, Rech A, Maity A, Rengan R, Pauken K, Stelekati E, Benci J, Xu B, Dada H, Odorizzi P, et al. 2015. Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer. Nature. 520: 373-377.

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Summary

- Immunotherapy seeks to restore the capacity of the immune system to recognize and eliminate tumors
- 4 major types of immunotherapy
  - Immune-modulating antibodies (aPD-1, aCTLA-4, aOX40, etc.)
  - Adoptive immunotherapy (CAR, TIL)
  - ADC (antibody-drug conjugates)
  - Therapeutic vaccines
- Combinatorial strategies will be required for most patients
  - Checkpoint blockade(s) + therapy of choice (mAb, vaccines, adoptive therapy, ADC)
  - IT+conventional therapies (surgery/RT/chemo)