Carbone Cancer Center
UNIVERSITY OF WISCONSIN
SCHOOL OF MEDICINE AND PUBLIC HEALTH

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Direction of the Field: The Future of Cancer Immunotherapy

February 22, 2019
SITC Winter School

Christian Capitini, MD
University of Wisconsin—Madison

Disclosures

- Nektar Therapeutics – Advisory Board/Honorarium
- By virtue of discussing the future, I will be discussing non-FDA approved indications during my presentation.

Diagnostics

Therapeutics

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Improvements in Staging and Immunotherapy Biomarkers

- Immunoscore
  - CD3, CD8, T cell memory
  - PD-L1, TMB, GEP and others
- Next generation sequencing
  - MSI-high, MMR defects, etc.
- Gut microbiome
- Tumor microenvironment/metabolomics

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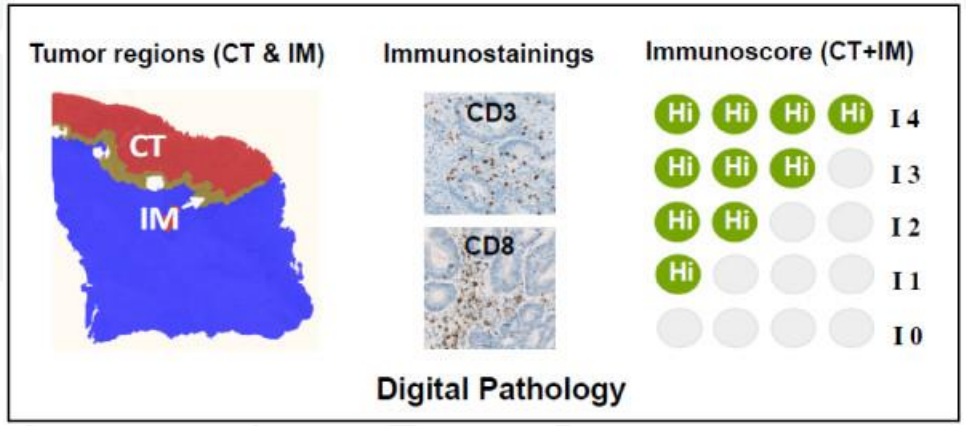
Current standard diagnostics

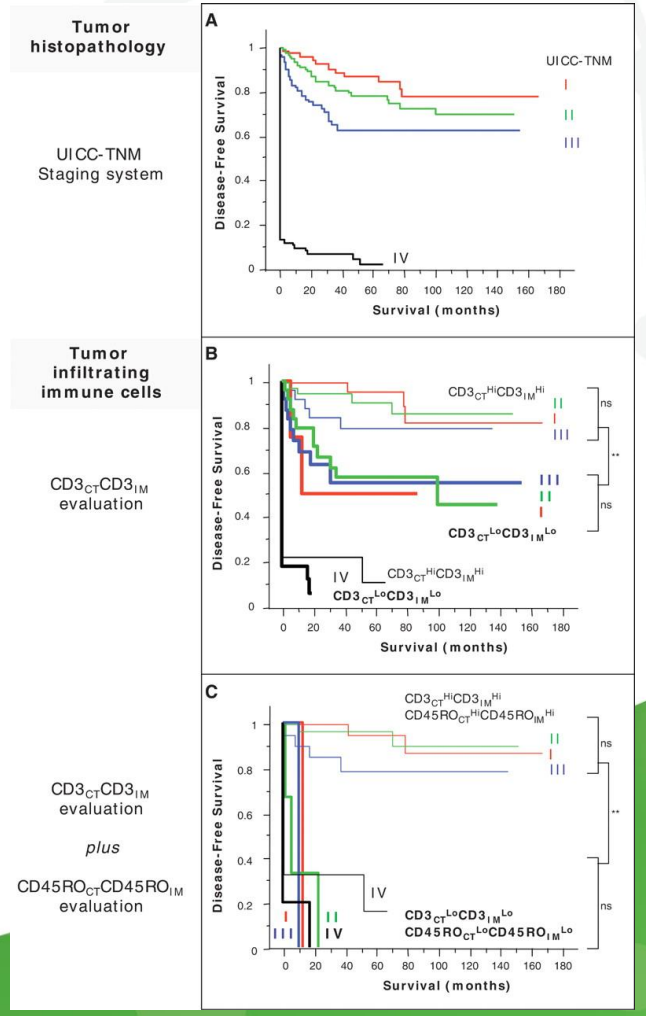
- Histopathology
- Flow cytometry
- Immunohistochemistry
- Cytogenetics
- Molecular studies: RT-PCR/FISH

Immunoscore will become part of standard pathologic reports for all tumors, used as a biomarker for responses and correlate with survival



CT = center of tumor; IM = invasive margin; Galon et al. 2012 J Transl Med

Cancers where immunoscore correlates with outcome	
Adult tumors	Hepatocellular carcinoma
Colorectal cancer	Breast cancer
Melanoma	Ovarian cancer
Renal cell carcinoma	Spinal chordoma
Non-small cell lung cancer	**Pediatric tumors**
Head and neck cancer	Neuroblastoma
Gastric cancer	Osteosarcoma



Galon et al. 2006 Science

Using assays together increases positive predictive value of responding to anti-PD(L)1 therapy

- Meta-analysis of 44 papers/abstracts examining the association between overall response rate to anti-PD(L)1 monotherapy and reported biomarkers including:
  - PD-L1 immunohistochemistry
  - Tumor mutation burden (TMB)
  - Gene expression profiling (GEP)
  - multiplex immunohistochemistry/immunofluorescence (mIHC/IF)

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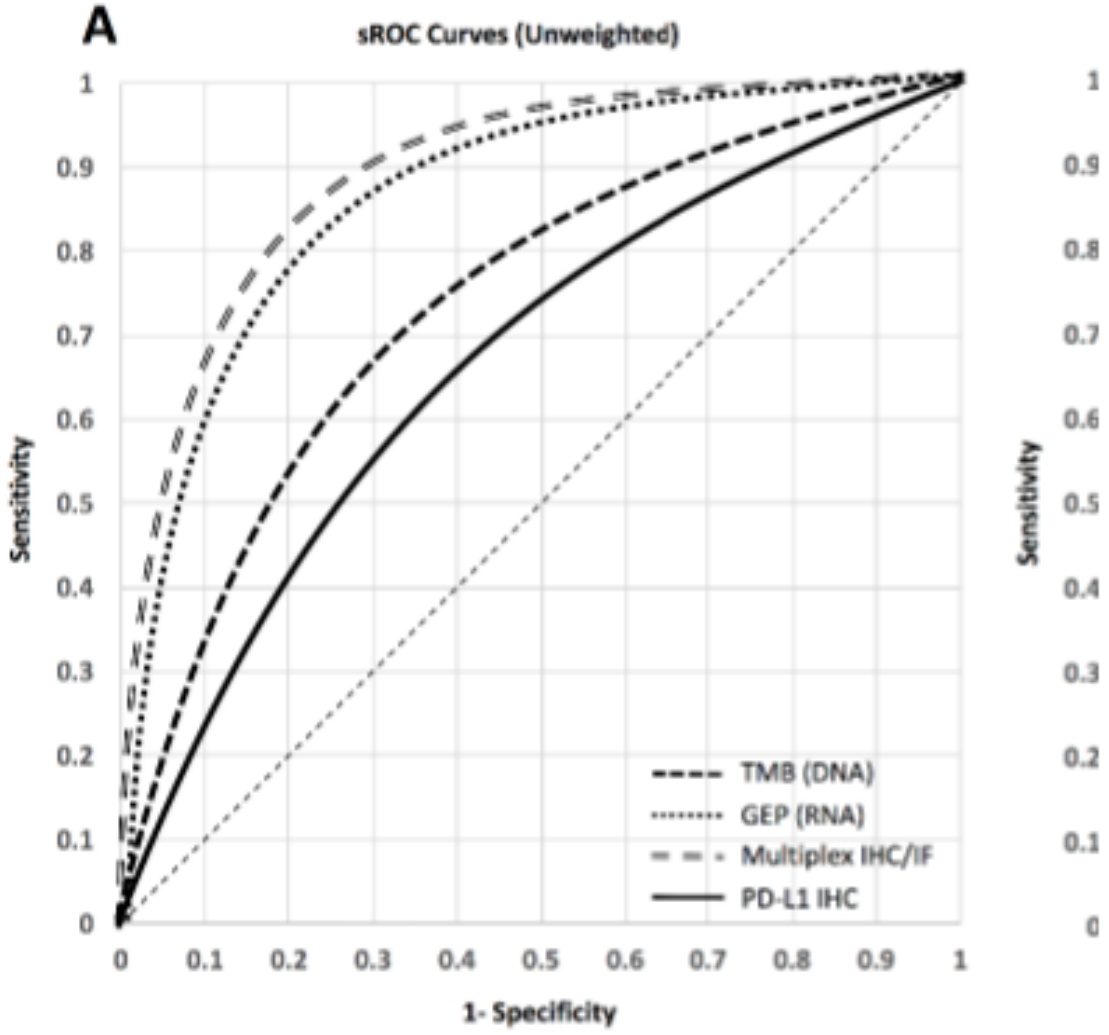
Abstract O6: Steve Lu et al. Comparison of biomarker assay modalities in anti-PD-(L)1 monotherapy: a meta-analysis

TMB has modestly better performance relative to PD-L1 IHC, and newer approaches may have improved sensitivity and specificity.



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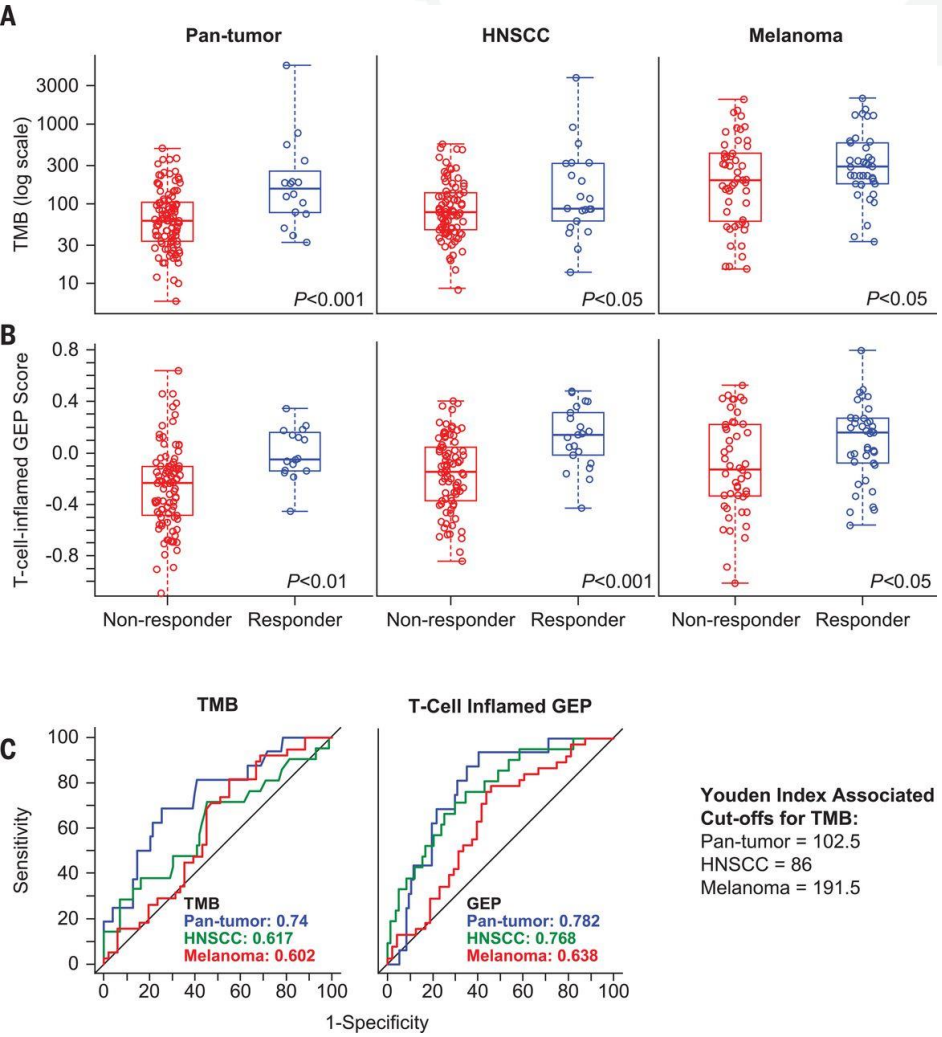
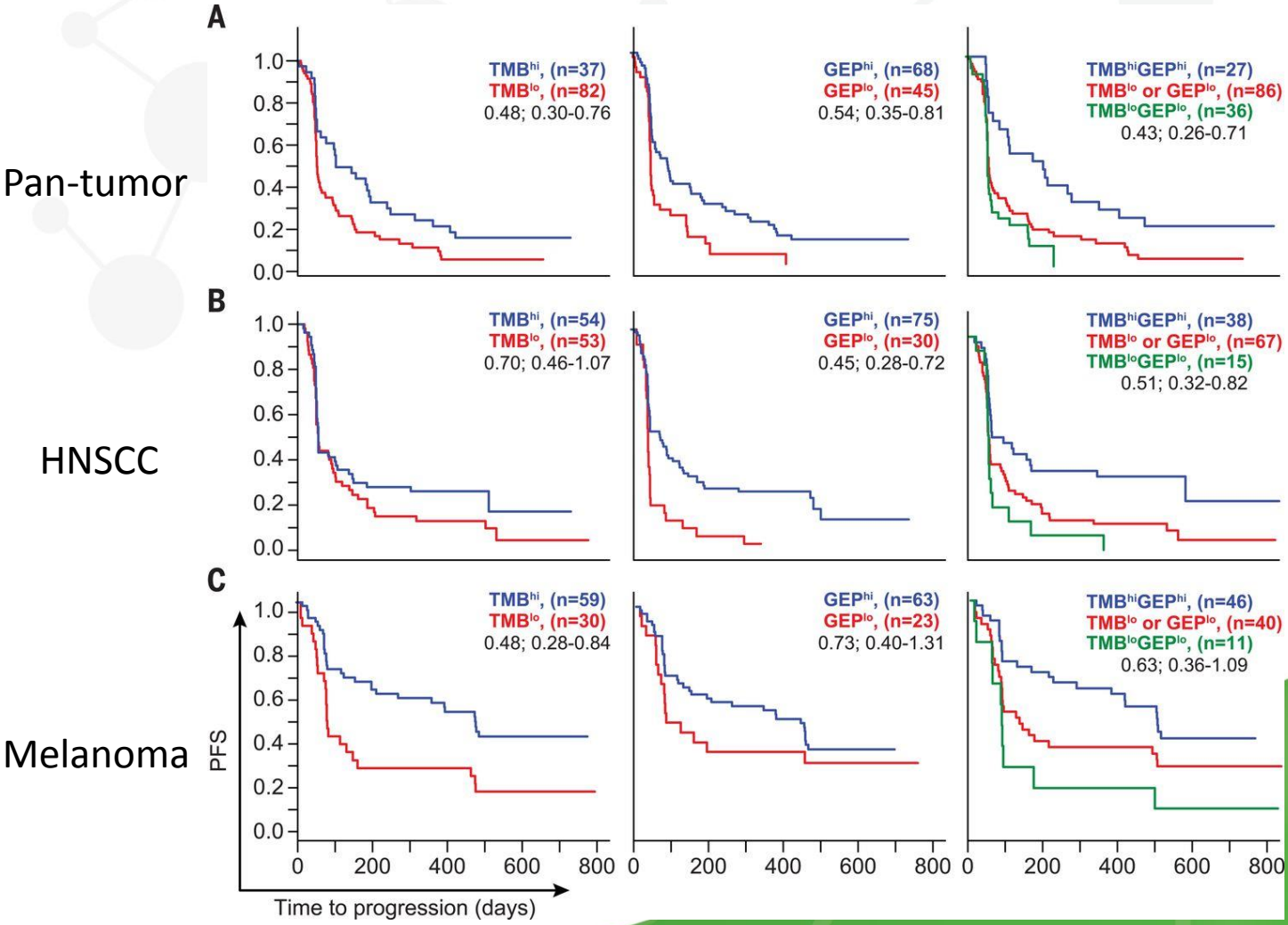
Abstract O6: Steve Lu et al. Comparison of biomarker assay modalities in anti-PD-(L)1 monotherapy: a meta-analysis

Individual association of TMB or T cell–inflamed GEP with anti–PD-1 response across multiple patient cohorts





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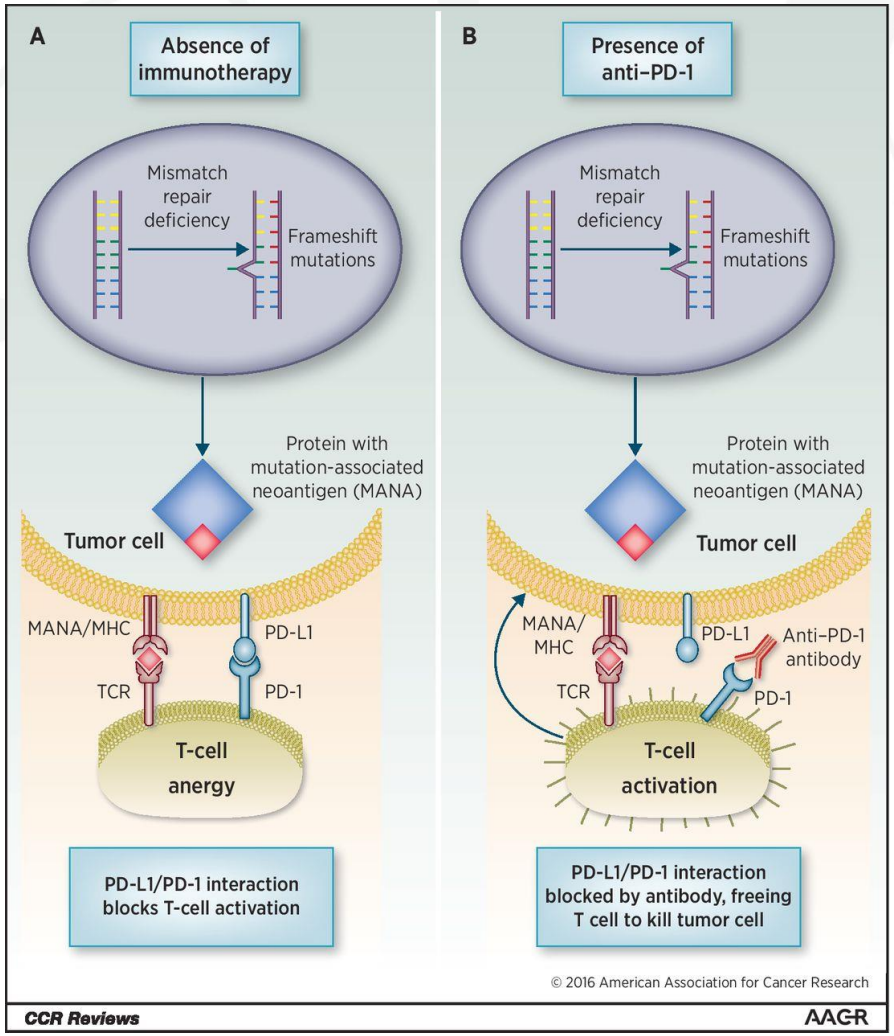
Razvan Cristescu et al. Science 2018;362:eaar3593

Science AAAS

Proposed relationship between MSI status and immunologic response.



Jonathan C. Dudley et al. Clin Cancer Res 2016;22:813-820

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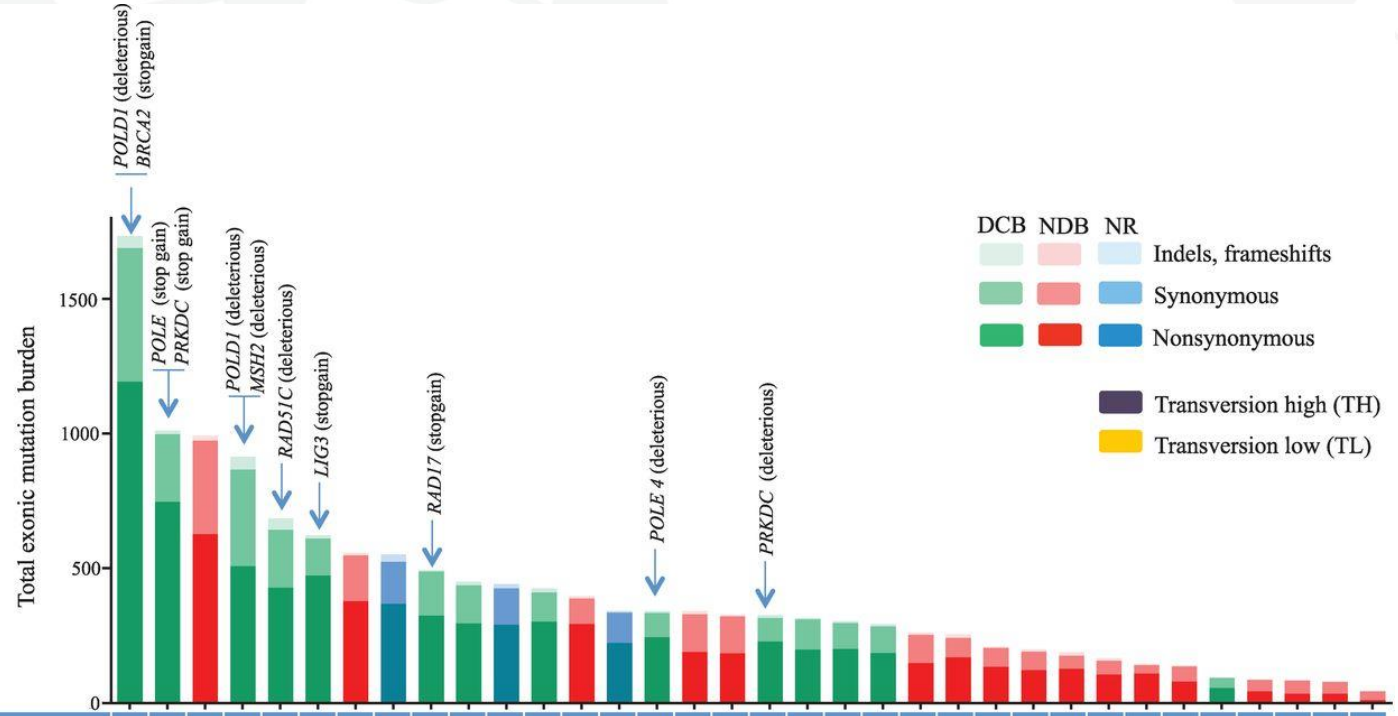
Clinical Cancer Research

Better intersection of next generation sequencing with predicting immunotherapy responses

Tumor mutational burden



Study ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34
Cohort	V	D	D	V	V	D	V	V	D	D	V	D	D	V	V	V	D	D	V	V	D	D	D	V	V	V	D	V	V	V	D	V	D	D
Objective Response	PR	PR	PD	SD	PR	PR	PD	SD	PR	PR	PR	SD	PD	PR	SD	PD	PD	PR	PR	PR	SD	SD	PD	PD	PD	PD	PD	SD	SD	PR	SD	PD	PD	SD
PFS (months)	8	14	2	8	14	16	2	4	15	13	4	8	2	4	8	3	3	10	27	10	8	7	2	2	1	2	2	4	6	8	4	2	2	6
Ongoing response	++	++			++	++		++		++	++			++	++			++	++	++														
Smoking signature	TH	TH	TH	TL	TH	TH	TL	TH	TH	TH	TH	TH	TH	TH	TH	TL	TL	TH	TL	TL	TH	TL	TH	TL	TL	TL	TL	TL	TL	TL	TL	TL	TL	TL

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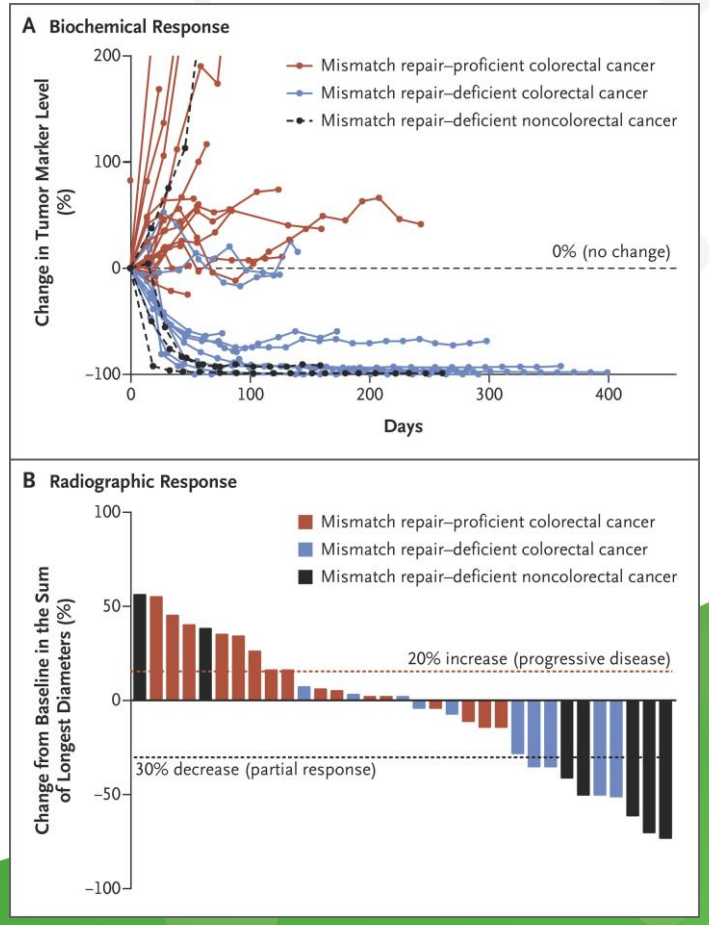
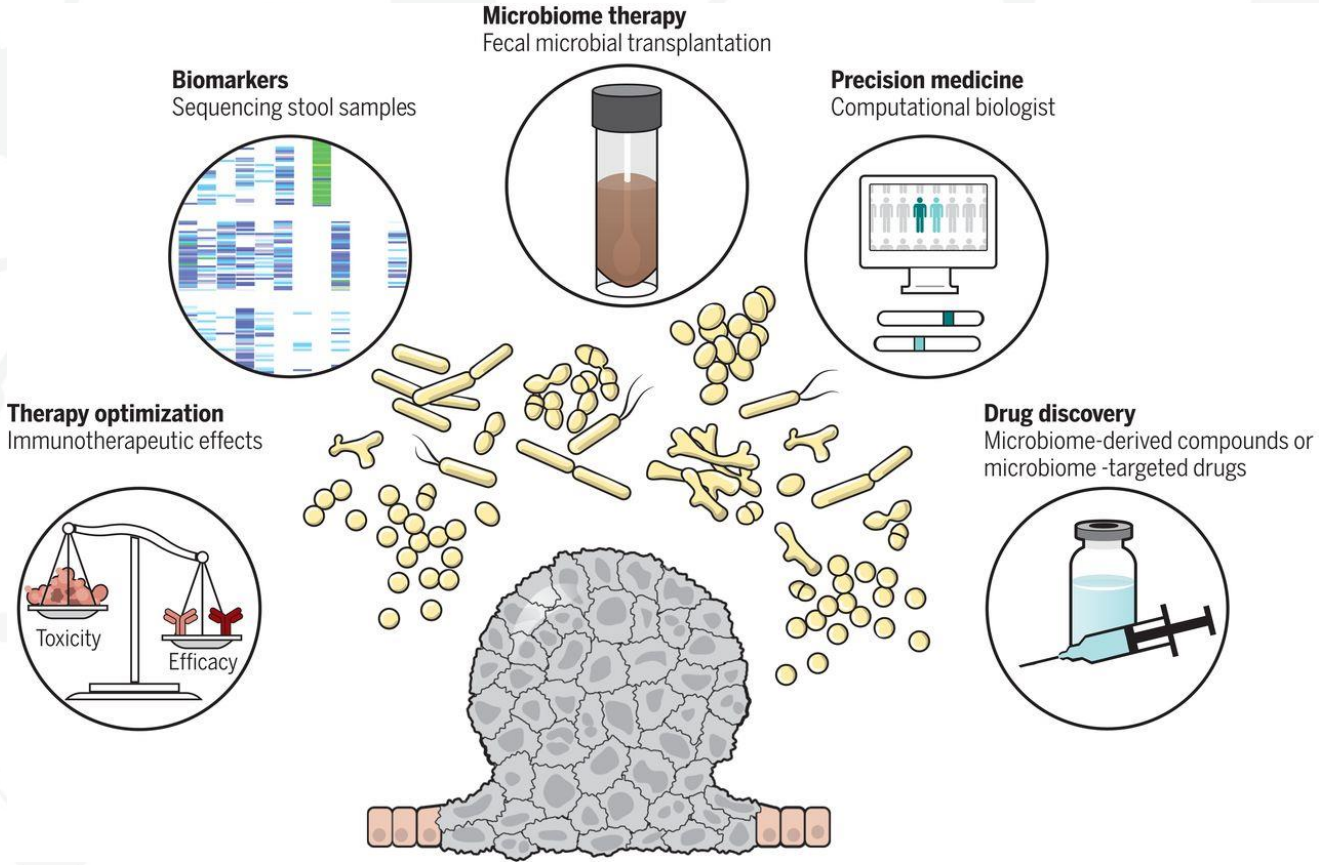
Rizvi et al. 2016 Science

Mismatch repair defects

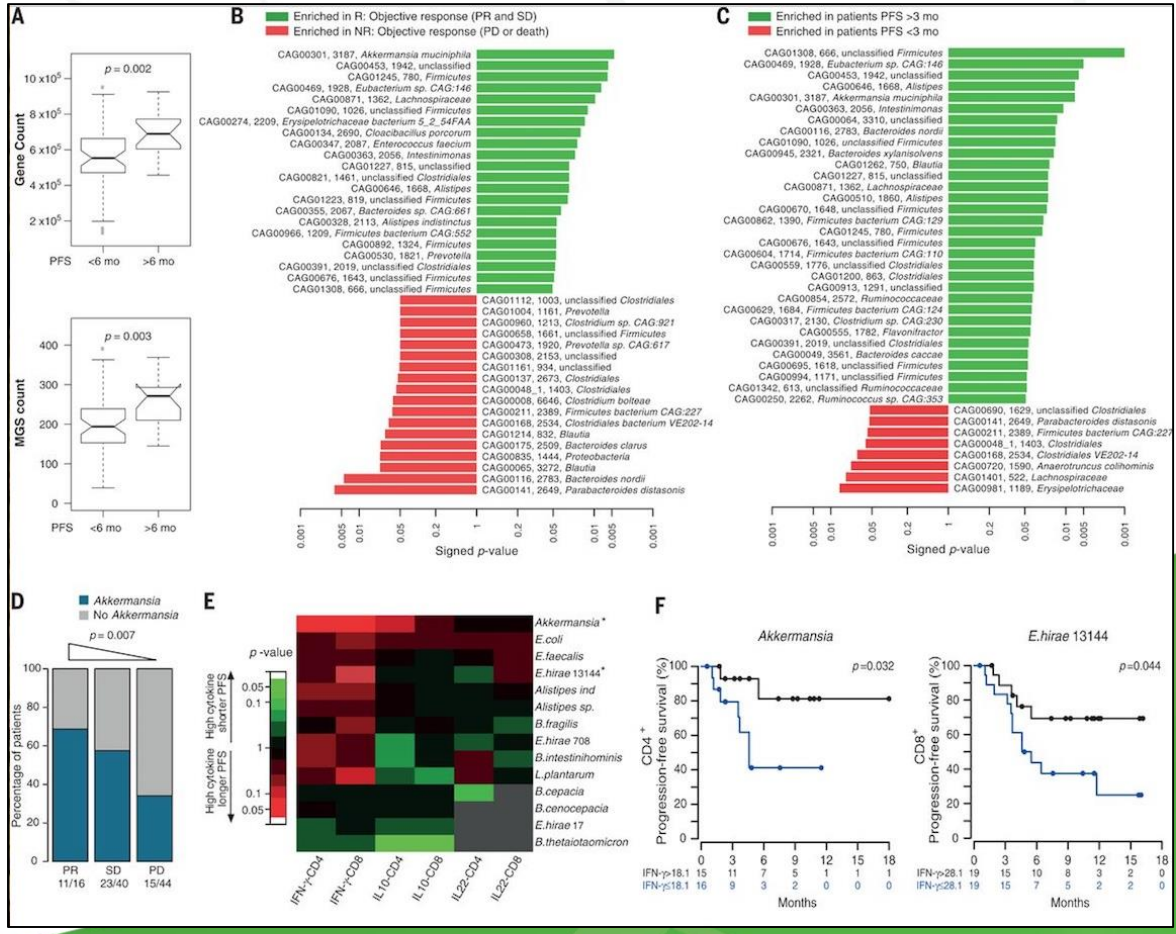


Le et al. 2015 New Engl J Med

Query and modulate the gut microbiome to improve responses to immunotherapy



Zitvogel et al. 2018 Science



Routy et al. 2018 Science

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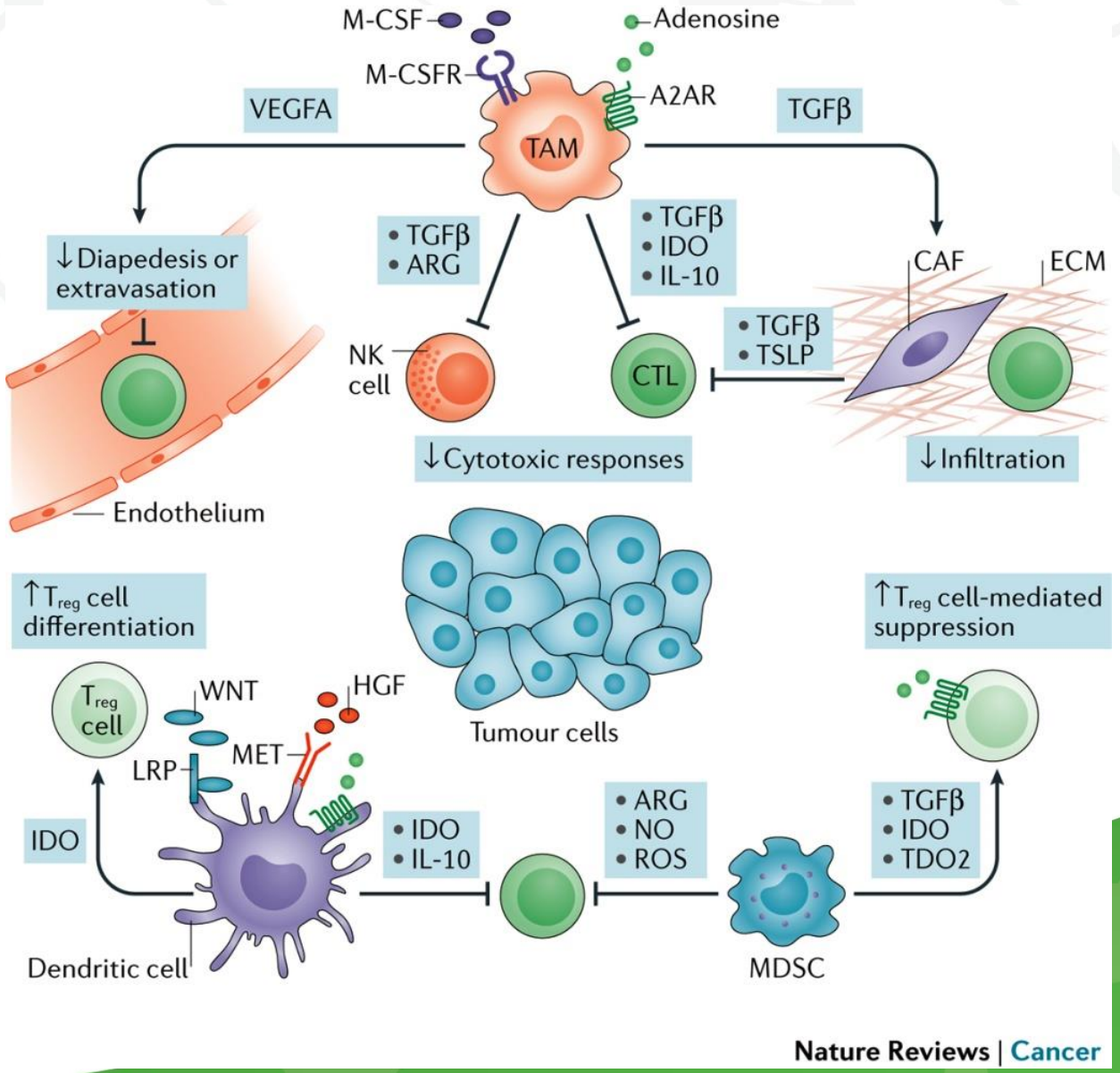
Tumor microenvironment is immuno-suppressive due to multiple cells and cytokines



Gotwals et al. 2017

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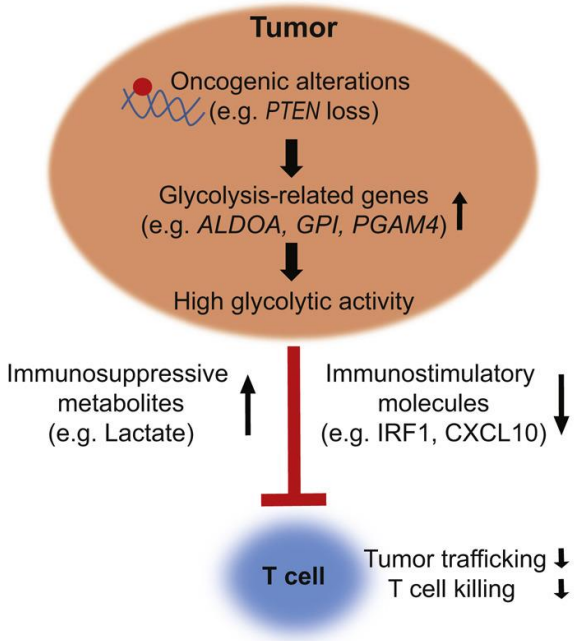
Manipulate the tumor metabolic environment to enhance immunotherapy responses



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GENE	FC (N/R)	P value
ALDOA	1.697746	0.136385
ALDOC	1.758665	0.186307
ENO2	1.257908	0.685237
ENO3	2.365525	0.205193
GAPDH	1.733471	0.143722
GPI	1.700951	0.015443
LDHA	1.429014	0.302088
LDHB	1.511258	0.152462
PFKM	1.152264	0.57808
PFKP	1.232823	0.463708
PGAM1	1.421356	0.108866
PGAM4	1.5305	0.033143
PGK1	1.636341	0.087465

Cascone et al. 2018 Cell Metab

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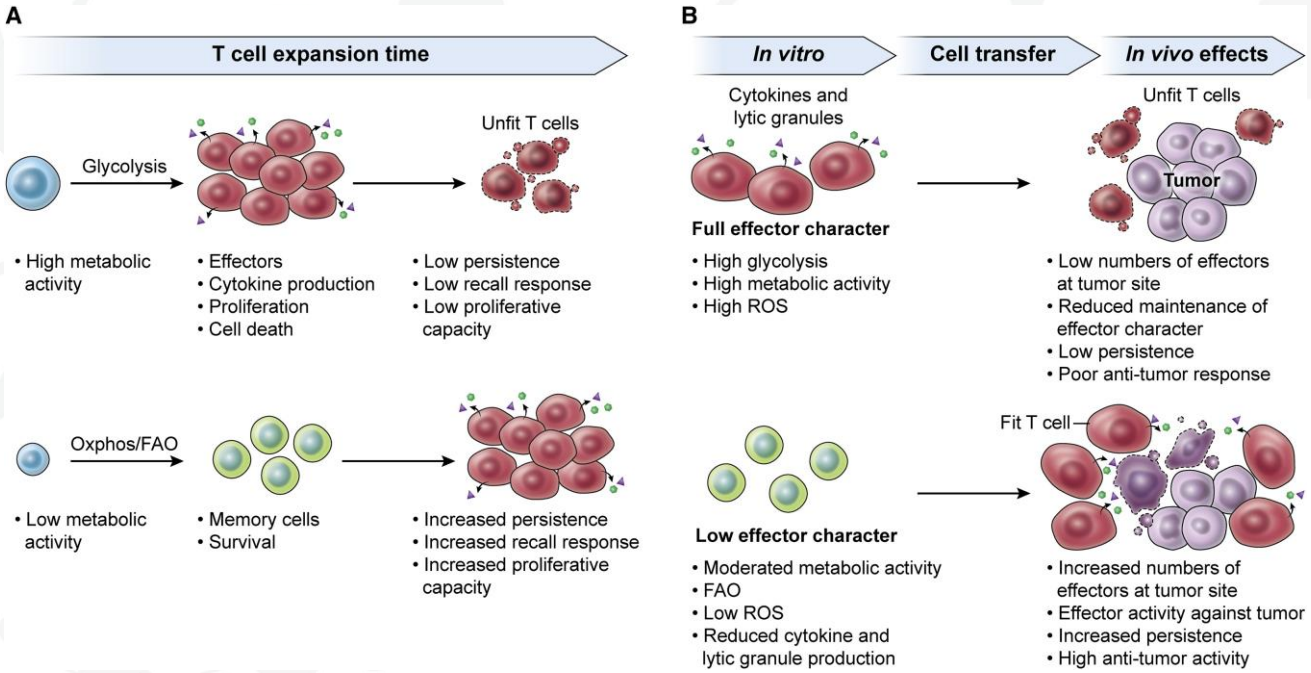
Will also change T cell metabolism to enhance immunotherapy responses



Kishton et al. 2017 Cell Metab

Molecule	Target	Metabolic outcome	Clinical (C), pre-clinical (P)
2-DG	Hexokinase	↓Glycolysis	P
Mdivi-1	Drp-1	↓Mitochondrial fission	P
JQ1	c-Myc	↓Glycolysis	P
STF-31	GLUT1	↓Glycolysis	P
WZB117	GLUT1	↓Glycolysis	P
Rapamycin	mTOR	↓Glutamine metabolism	C
Metformin	AMPK, ETC	↑FAO, others	C
Fenofibrate	PPARα	↑Fatty acid catabolism	P

Dugnani et al. 2017 Cancer Lett

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Diagnostics

Therapeutics

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Expansion of immunotherapy therapeutics

- Antibody therapy
  - Checkpoint agonists/inhibitors
  - Antibody-drug conjugates
  - Bispecifics
- Oncolytic viral therapy
- Radiotherapy/Immunotherapy
- Cellular therapy
  - Vaccines
    - +/- anti-PD1
  - CAR T, CAR NK,
    - CAR NKT, CAR CIK cells emerging
  - TCR transduced T cells
  - Gamma delta T cells

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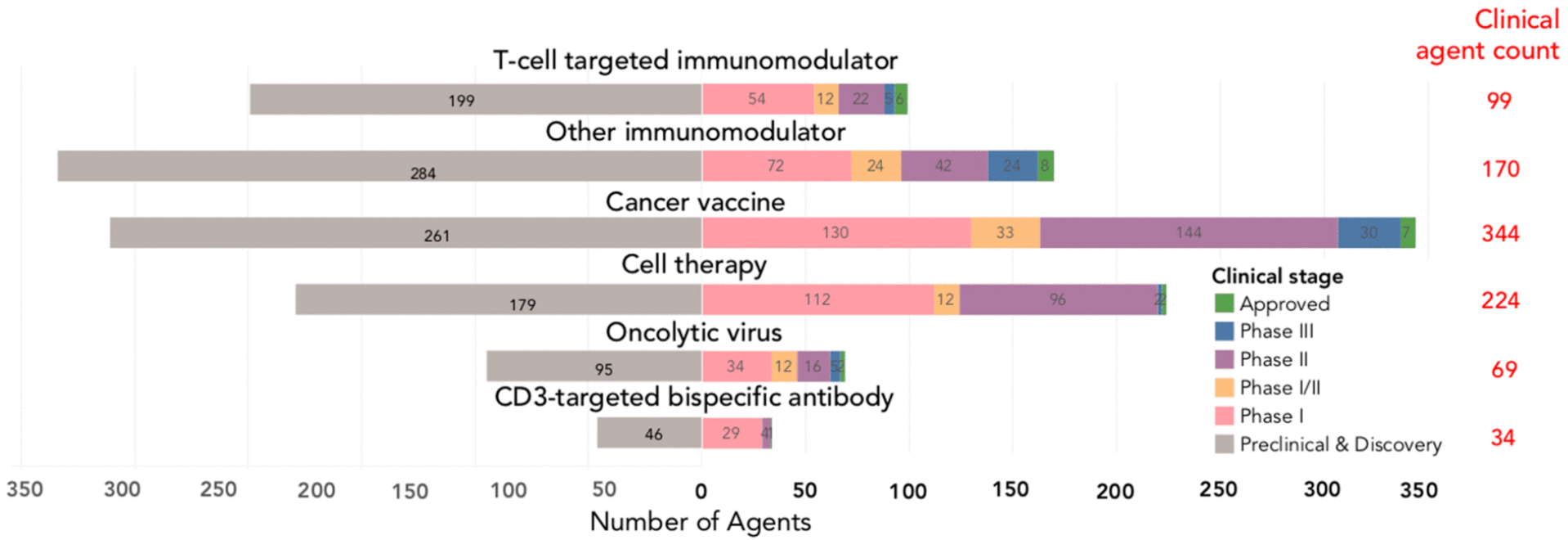
2,004 IO AGENTS IN DEVELOPMENT

940 Agents are in Clinical Stages, and 1,064 in Preclinical



ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

CANCER RESEARCH INSTITUTE The Anna-Maria Kellen Clinical Accelerator

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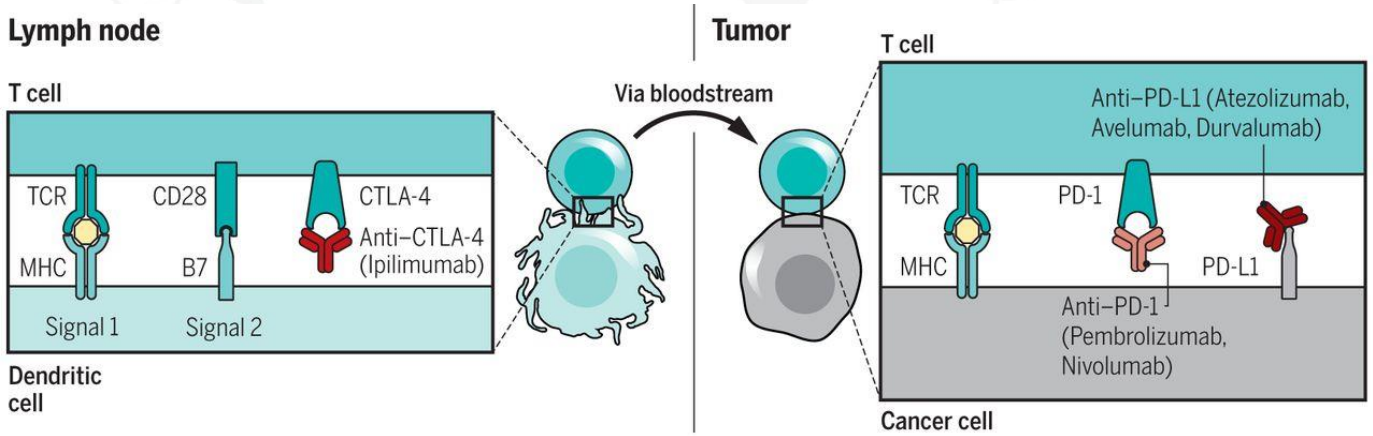

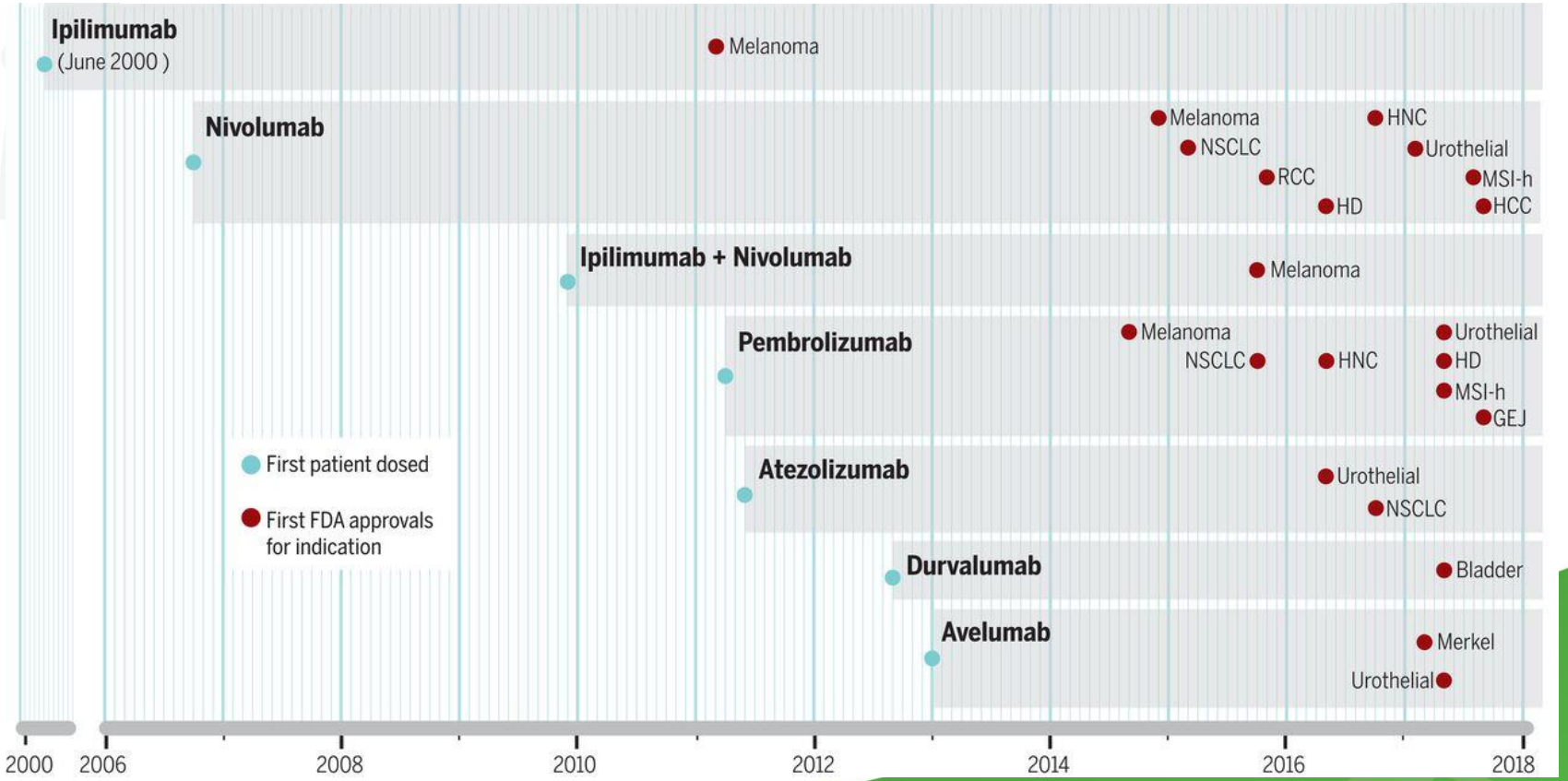

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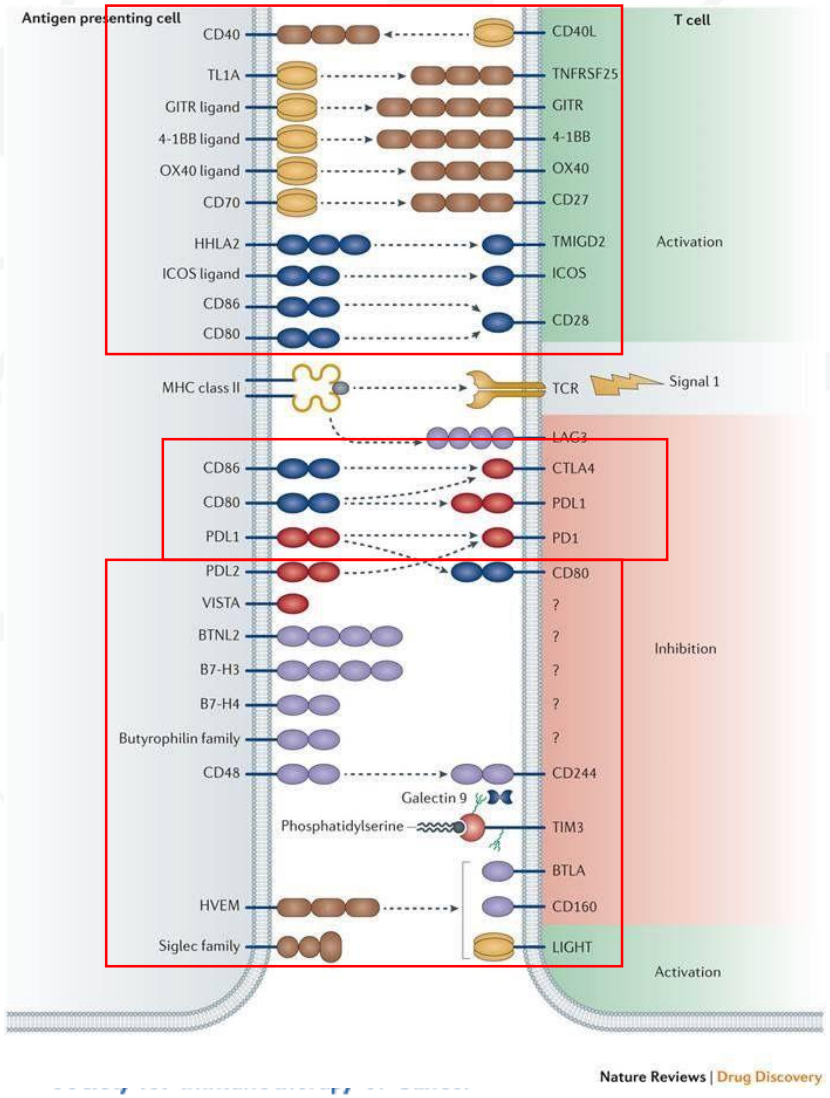
Ribas and Wolchok 2018 Science

The number of checkpoint agonists and antagonists will expand and be used in combination



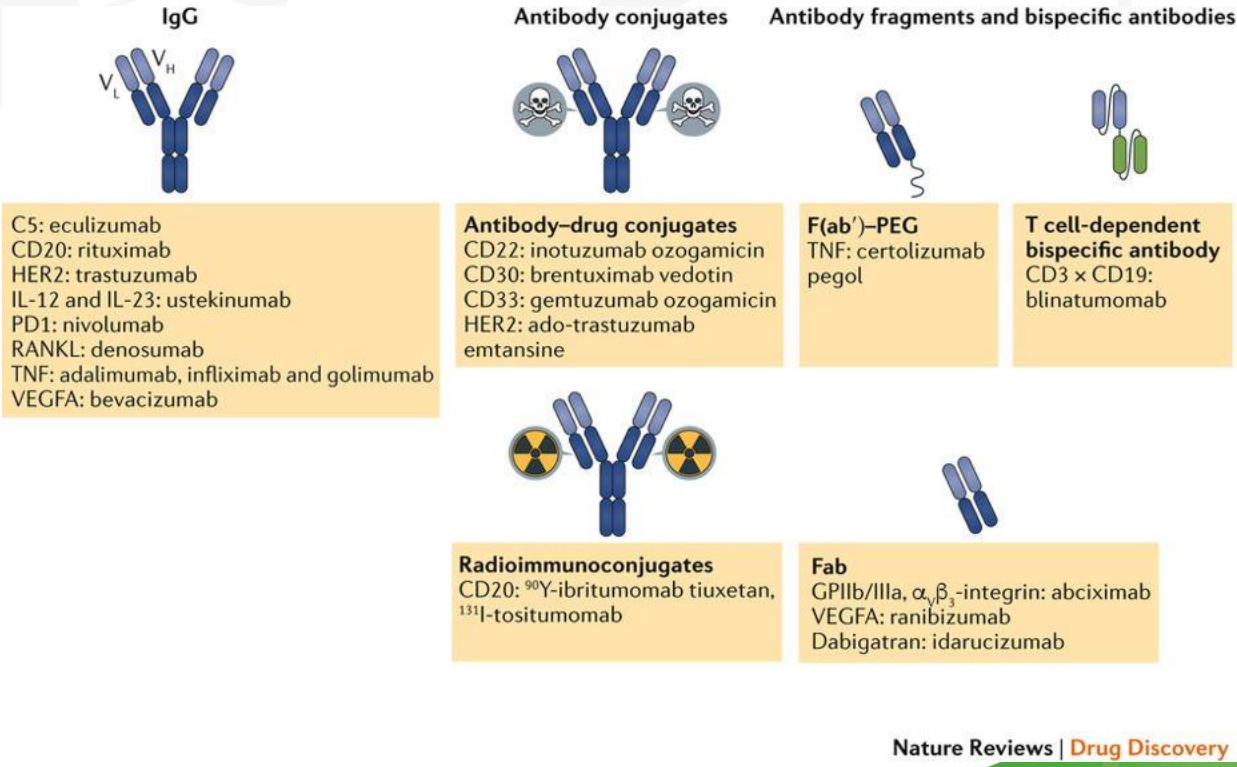
Mahoney KM et al. 2015 Nat Rev Drug Discovery

Appendix: Immune checkpoint modulators in combination clinical trials (August 2017)

Checkpoint modulator name	Target	Checkpoint modulator name	Target	Checkpoint modulator name	Target
PF-05082566 / Utomilumab	4-1BB	GWN323	GITR	MOXR0916	OX-40
Urelumab	4-1BB	INCAGN01876	GITR	PF-04518600	OX-40
AZD4635	ADORA2A	MK-1248	GITR	AMP-224	PD-1
CPI-444	ADORA2A	MK-4166	GITR	BGB-A317	PD-1
NIR178	ADORA2A	GSK3359609	ICOS	IBI308	PD-1
PBF-509	ADORA2A	JTX-2011	ICOS	JS001	PD-1
Preladenant / MK-3814 / SCH420814	ADORA2A	Epacadostat	IDO	MEDI0680	PD-1
		Indoximod	IDO	Nivolumab	PD-1
Enoblituzumab	B7-H3	KHK2455	IDO	PDR001	PD-1
Varlilumab	CD27	NLG919 / GDC-0919	IDO	Pembrolizumab	PD-1
APX005M	CD40	BMS-986205	IDO	PF-06801591	PD-1
CP-870,893 / RO7009789	CD40	Lirilumab	KIR	REGN2810	PD-1
Dacetuzumab	CD40	BMS-986016	LAG-3	SHR-1210	PD-1
Lucatumumab	CD40	LAG525	LAG-3	Atezolizumab	PD-L1
SEA-CD40	CD40	MK-4280	LAG-3	Avelumab	PD-L1
ISF35 / rAd-CD40L	CD40	REGN3767	LAG-3	Durvalumab	PD-L1
MEDI5083	CD-40L	IMP321	MHC II	FAZ053	PD-L1
ARGX-110	CD70	Monalizumab	NKG2A	LY3300054	PD-L1
Galiximab	CD80	ABBV-368	OX-40	CX-072	PD-L1
BMS-986218	CTLA-4	BMS-986178	OX-40	BMS-986207	TIGIT
Ipilimumab	CTLA-4	GSK3174998	OX-40	MTIG7192A	TIGIT
MK-1308	CTLA-4	MEDI0562	OX-40	LY3321367	TIM-3
Tremelimumab	CTLA-4	MEDI6383	OX-40	MBG453	TIM-3
BMS-986156	GITR	MEDI6469	OX-40	TSR-022	TIM-3

More development and potential approvals of antibody-drug conjugates

Emerging antibody-drug conjugates	Target cancer
Sacituzumab govitecan	Breast cancer
Mirvetuximab canavanine	Ovarian cancer
Rovalpituzumab tesirine	Lung cancer
Depatuxizumab mafodotin	Glioblastoma
Oportuzumab monatox	Bladder cancer
Denintuzumab mafodotin	B cell malignancies
Indatuximab ravtansine	Multiple myeloma
Lorvotuzumab mertansine	Small cell lung cancer
Moxetumomab pasudotox	B cell malignancies
Pinatuzumab vedotin	B cell malignancies
Polatuzumab vedotin	B cell malignancies



Nature Reviews | Drug Discovery

Carter and Lazar 2018 Nat Rev Drug Discovery

Oncolytic viral therapy will continue to expand viral agents, biologics, and target tumors

	Adenovirus [a]	Herpes simplex virus [b]	Pox virus	Coxsackie virus	Maraba virus	Poliovirus	Measles virus	Newcastle Disease virus
Genome	dsDNA	dsDNA	dsDNA	ssRNA	ss (–) RNA	ss (+) RNA	ss (–) RNA	ss (–) RNA
Genome size	Moderate (32 kb)	Large (152 kb)	Large (130–375 kb)	Small (~8 kb)	Small (11–15 kb)	Small (7.5 kb)	Small (~16 kb)	Small (~15 Kb)
Cell entry mechanism	Endocytosis	Endocytosis; penetration	Membrane penetration and fusion	Micropinocytosis via epithelial tight junctions	Endocytosis; pH-dependent fusion activation	Receptor-mediated endocytosis	Membrane fusion	Endocytosis; pH-independent direct fusion
Cell entry receptors	hCAR; VCAM1; CD46	HVEM; nectin 1; nectin 2	GAGs; EFC	CAR; DAF	Unknown	CD155	CD46; SLAM	Neuraminidase receptor; sialoglyco-conjugates

[a]E1B-55 K/E3B-deleted adenovirus in combination with chemotherapy was approved for the treatment of late-stage refractory nasopharyngeal cancer by the Chinese State Food and Drug Administration in 2005. [b]Herpes simplex virus type 1 (HSV-1) with ICP34.5 deletion and encoding granulocyte–macrophage colony-stimulating factor (GM-CSF) was approved for stage III–IV melanoma treatment by the US Food and Drug Administration in 2015 and by Australia and the European Medicines Agency (EMA) in 2016.

Adapted from Bommareddy et al. 2018 Nat Rev Immunol

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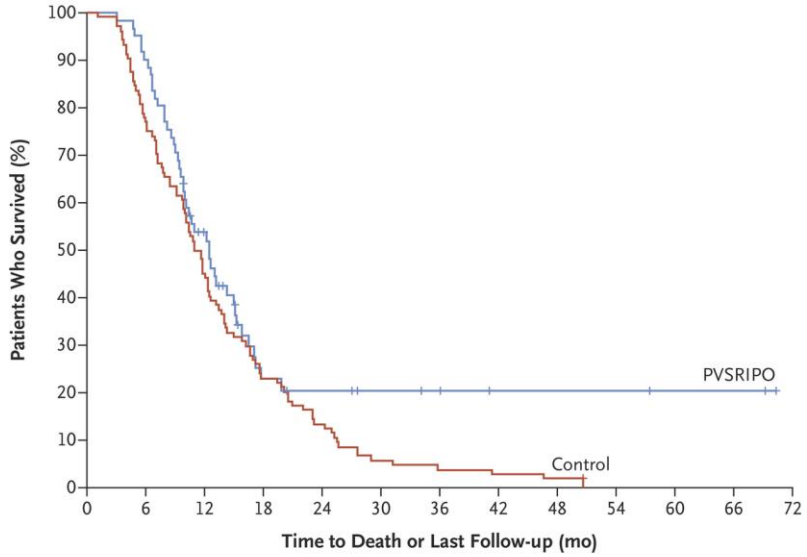
Oncolytic viral therapy will continue to expand viral agents, biologics, and target tumors

PVSRIPO for Glioblastoma multiforme



No. at Risk													
PVSRIPO	61	55	29	10	8	6	5	3	3	3	2	2	–
Control	104	80	47	24	14	6	4	3	2	–	–	–	–

Group	Total No. of Patients	No. of Deaths	Median Survival (95% CI)	Survival Rate (95% CI)						
				6 Mo	12 Mo	18 Mo	24 Mo	36 Mo	48 Mo	60 Mo
			mo				*percent*			
PVSRIPO	61	44	12.5 (9.9–15.2)	90 (79–96)	54 (40–65)	23 (12–35)	21 (11–33)	21 (11–33)	21 (11–33)	21 (11–33)
Control	104	103	11.3 (9.8–12.5)	77 (68–84)	45 (36–54)	23 (16–32)	14 (8–21)	4 (1–9)	2 (<1–6)	–

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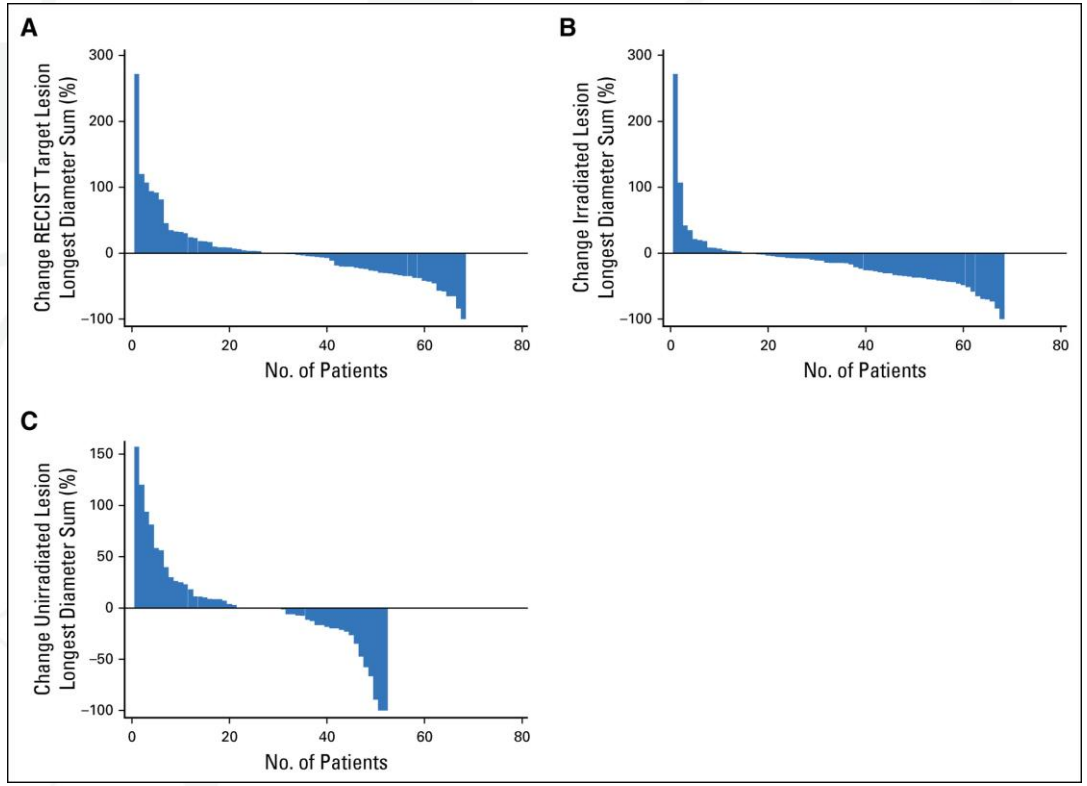
Desjardins et al. 2018 New Eng J Med

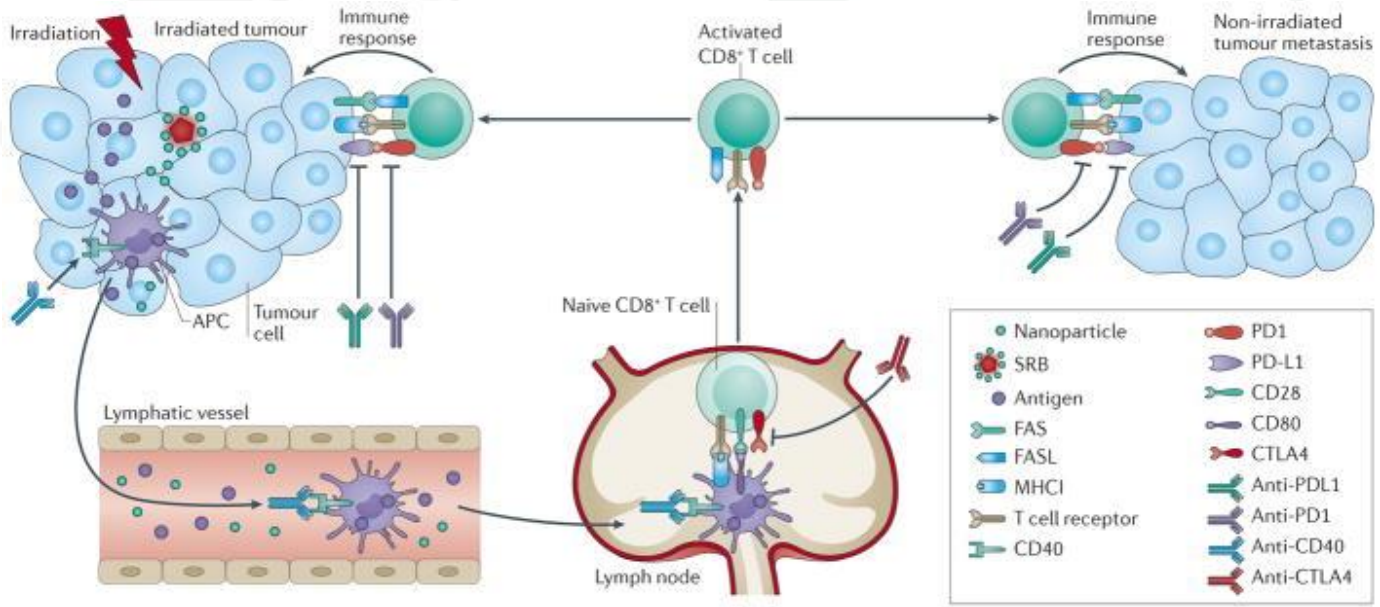
A Study of Intratumoral CAVATAK™ in Patients With Stage IIIc and Stage IV Malignant Melanoma (VLA-007 CALM)
Clinicaltrials.gov/NCT01227551

Outcome	Result
Percentage of Participants With Immune-related Progression-Free Survival (irPFS) at 6 Months	38.6 (26.0 to 52.4)
Percentage of Participants With Durable Response Rate of 6 months or more	21.1

Radiation therapy will be increasingly used as a means of enhancing immunotherapy



Luke et al. 2018 J Clin Oncol



Ngwa et al. 2018 Nat Rev Cancer

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Radiation therapy can be safely combined with immunotherapy

Institution (reference)	Primary site	*n*	Radiotherapy	Immunotherapy	Schedule	Nonirradiated lesions			Grade 3+ toxicities
						CR	PR	SD	
University of Pennsylvania	Melanoma	22	• 6 Gy × 2–3 or 8 Gy × 2–3 • 1 site	Ipilimumab 3 mg/kg every 3 weeks × 4	First ipilimumab 3–5 days after RT	0/22 (0%)	4/22 (18%)	4/22 (18%)	• Number of patients with any grade 3 toxicity not reported • Grade 3 anemia (4/22; 18%) most common • No grade 4–5 • No DLT
Stanford	Melanoma	22	• Multiple dose-fx regimens (BED10 range 28.0–112.5 Gy) • 1–2 sites	Ipilimumab 3 mg/kg every 3 weeks × 4	RT within 5 days of first ipilimumab	3/22 (14%)	3/22 (14%)	5/22 (23%)	• 2/22 (9%) grade 3 • 1/22 (5%) grade 4 • No grade 5
MD Anderson Cancer Center	NSCLC, CRC, sarcoma, RCC, and others	35	• 50 Gy/4 fx or 60 Gy/10 fx • 1 site	Ipilimumab 3 mg/kg every 3 weeks × 4	RT 1 day after first ipilimumab or 1 week after second ipilimumab	0/31 (0%)	3/31 (10%)	4/31 (13%)	• 12/35 (34%) grade 3 • No grade 4–5 • 2/35 (6%) with DLT

Ko and Formenti 2018 Ther Adv Med Oncl

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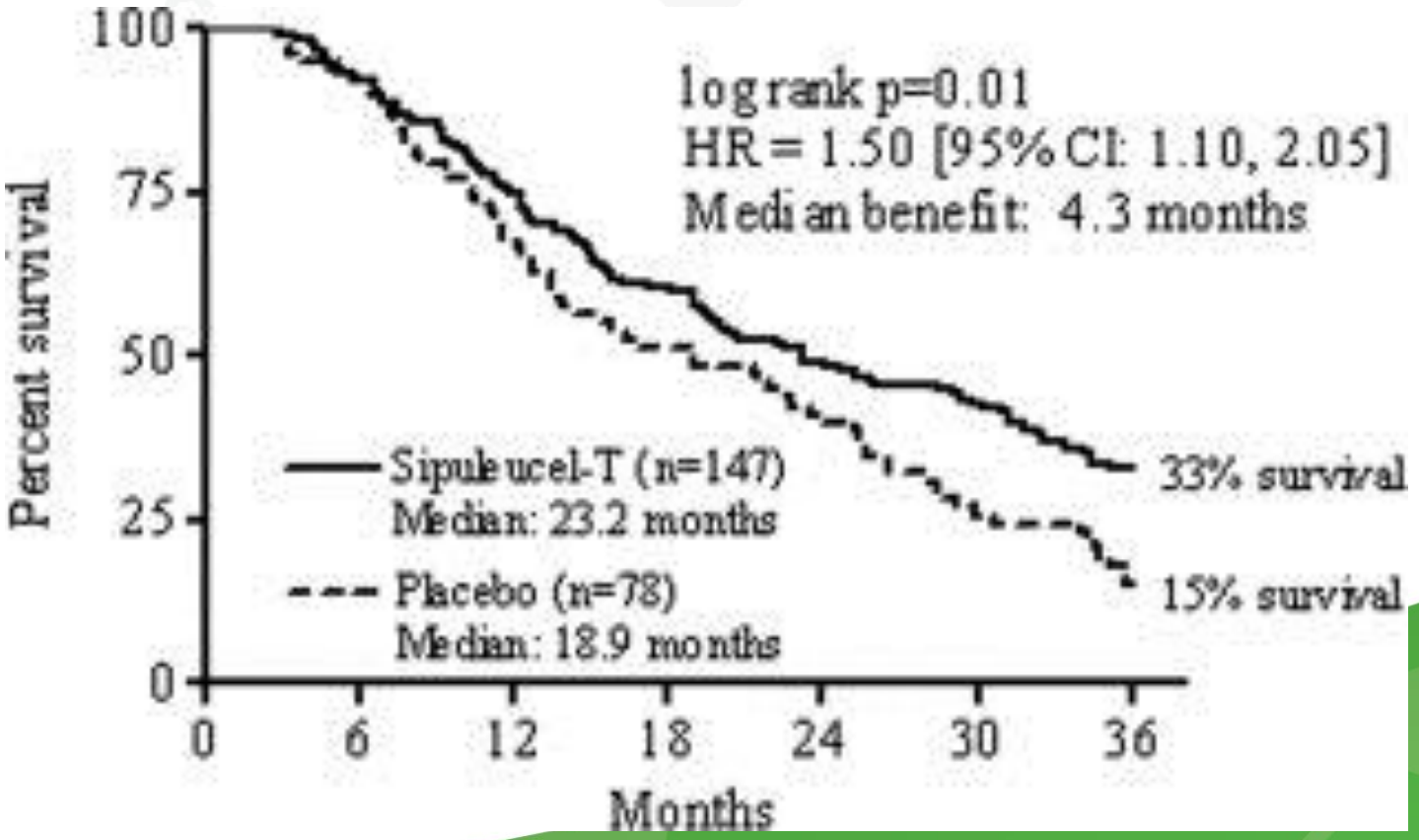
sipuleucel-T (Provenge)

- composed of autologous antigen presenting cells that express prostatic acid phosphatase and GM-CSF
- Patients demonstrated a 33% reduction in the risk of death for progression in asymptomatic, metastatic, hormone-refractory prostate cancer, extending overall survival 4.1 months
- FDA approved 2010



Higano et al. Cancer 2009

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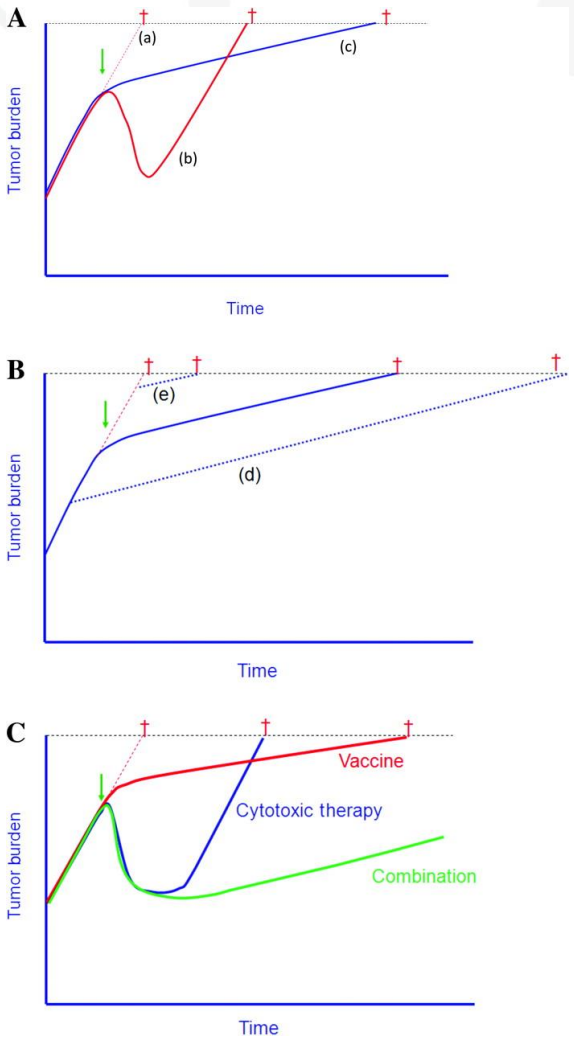
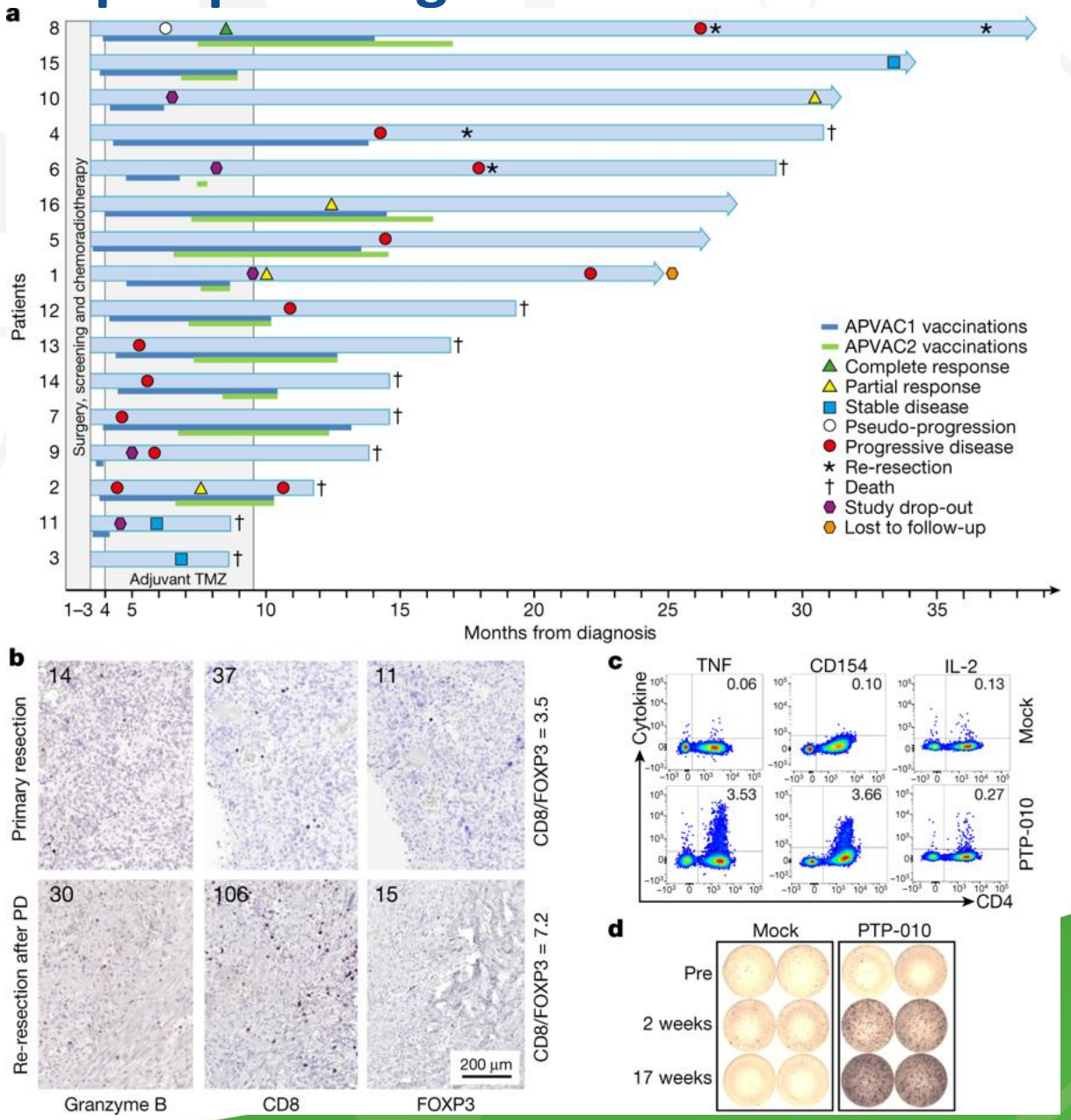
Tumor growth rates following chemotherapy vs vaccine therapy



Schlom J JNCI J Natl Cancer Inst 2012;104:599-613

Personalized vaccine of unmutated antigens and preferentially targeted neoepitopes for glioblastoma multiforme



Hilf et al. 2019 Nature

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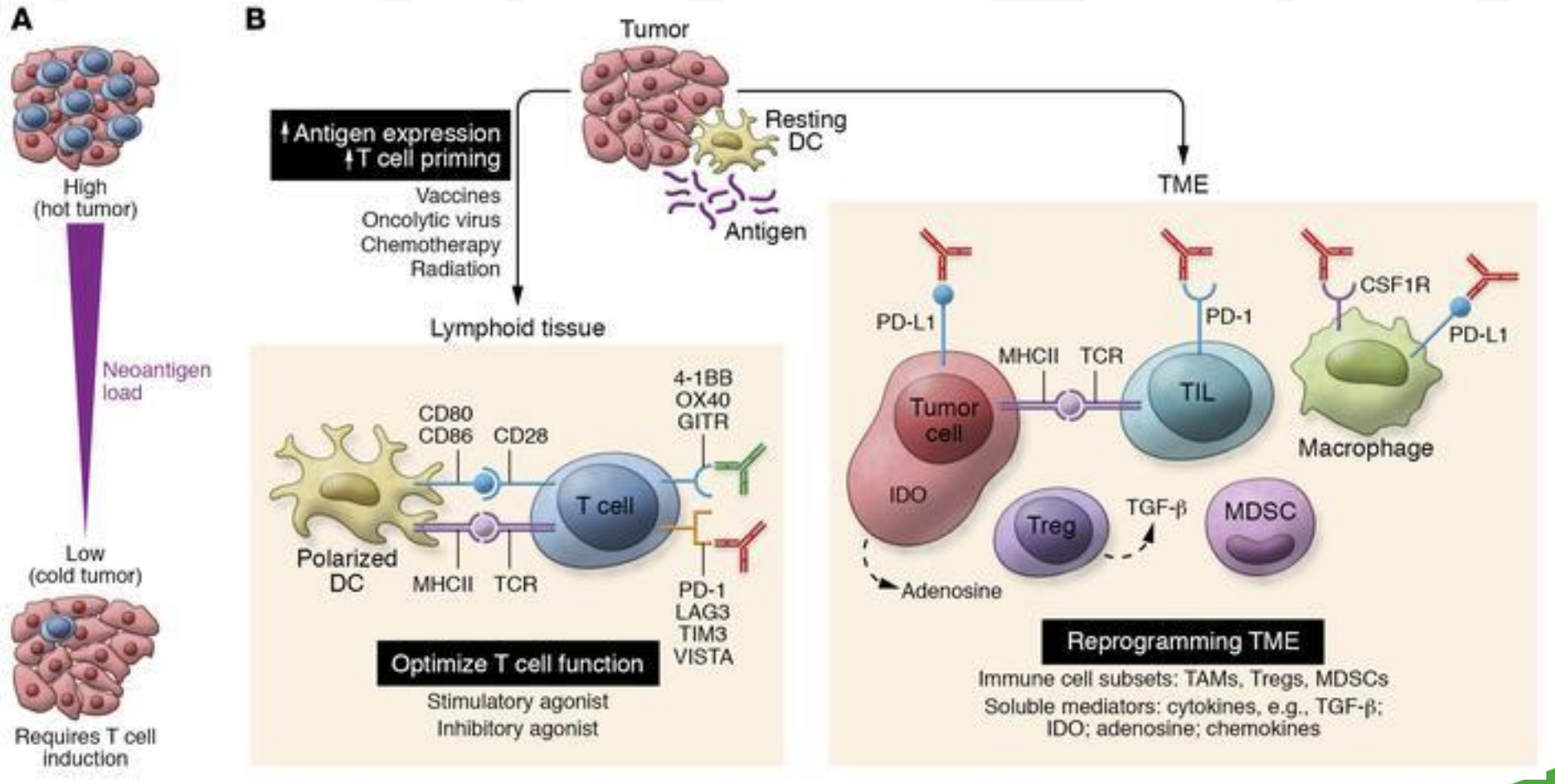
Emerging strategies for combination checkpoint modulators in cancer immunotherapy



Popovic et al. 2019 J Clin Invest

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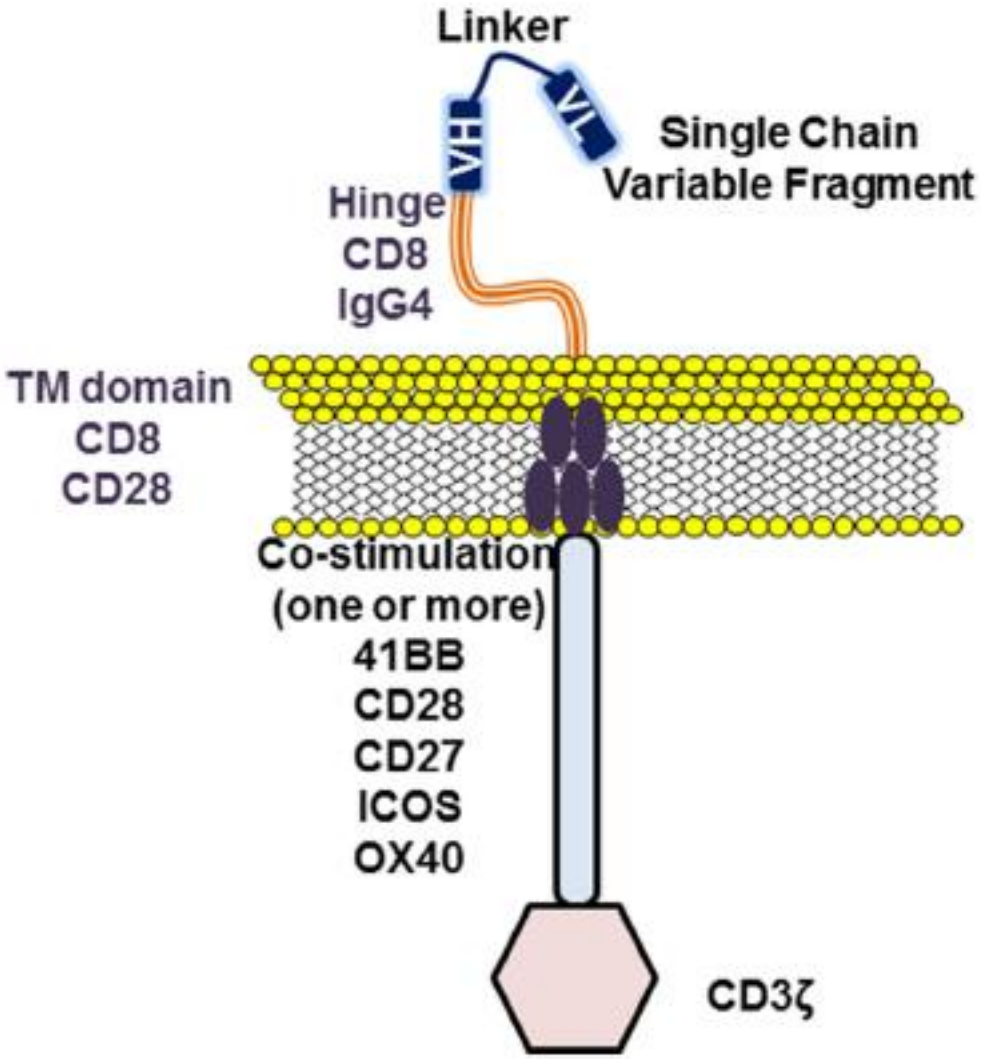
A variety of CAR constructs will be tested initially in hematologic malignancies, but then in solid tumors



Kenderian et al. 2017 Biol Blood Marrow Transplant

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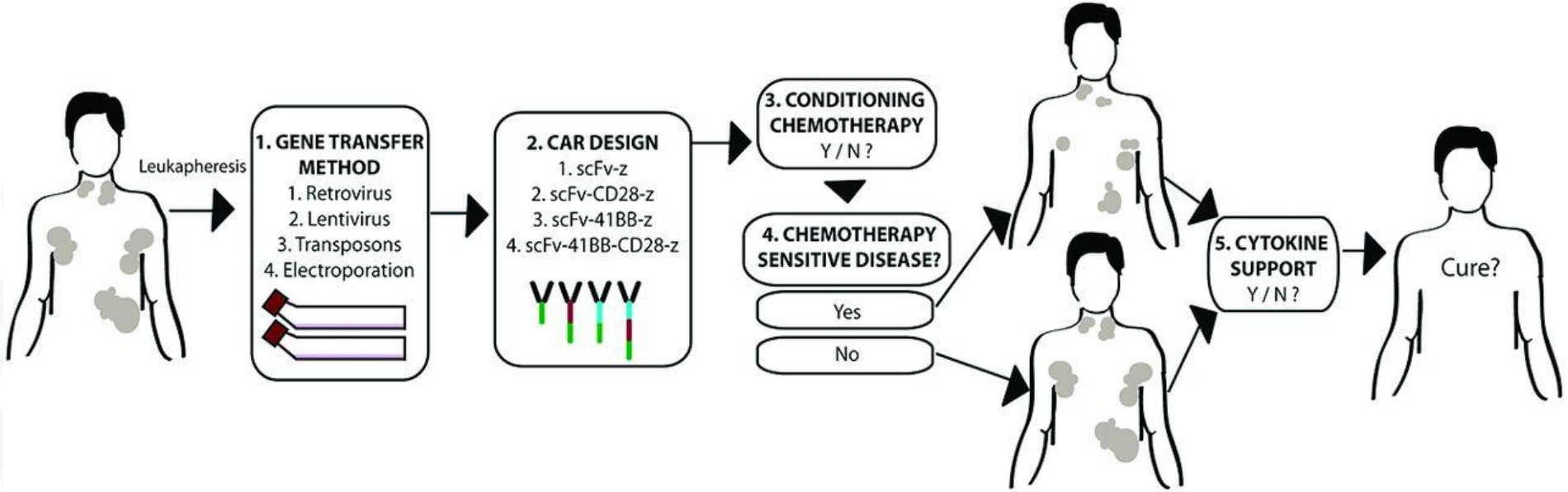
Test variables in clinical trial design.



Brentjens R J , and Curran K J Hematology 2012;2012:143-151

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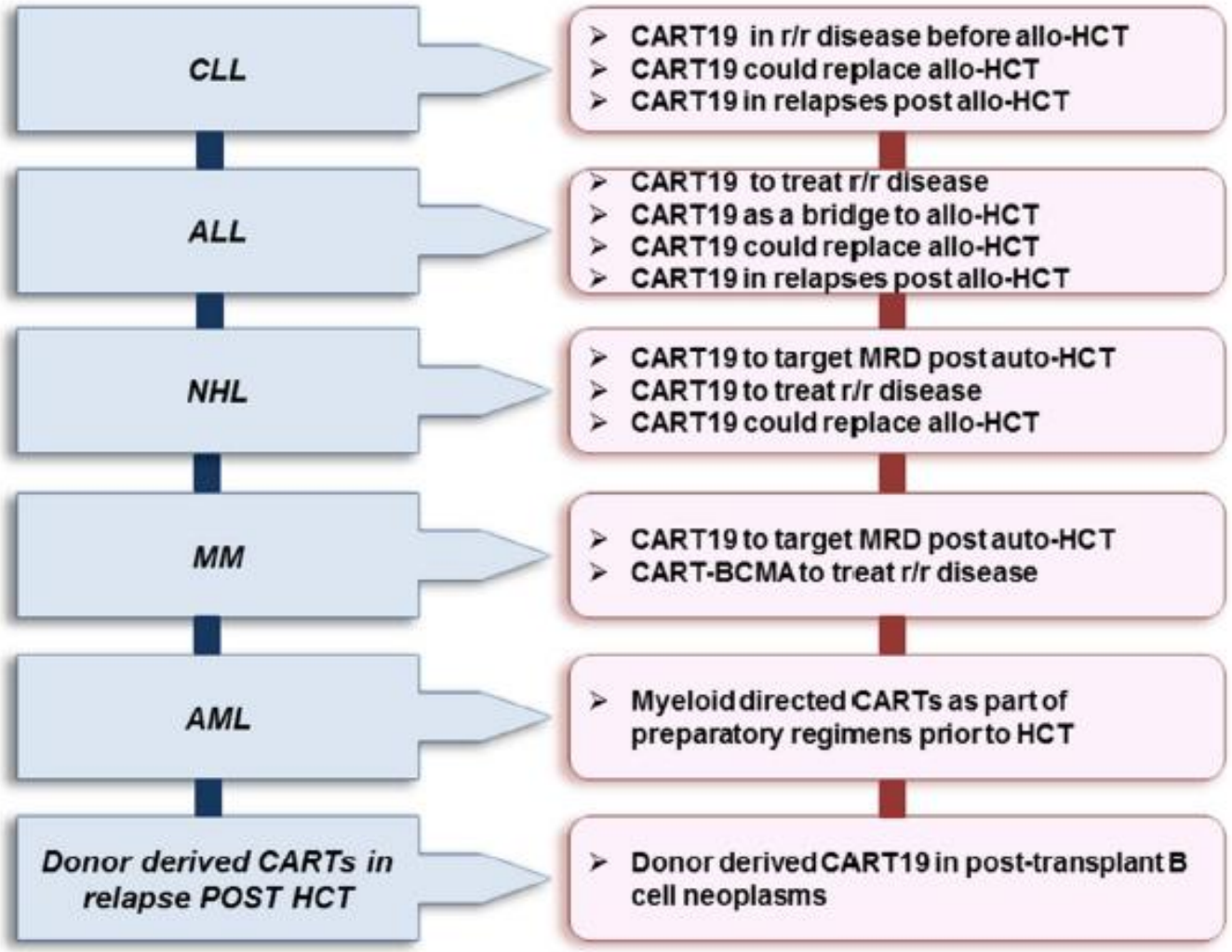
CAR T cells will be used as frontline therapy in lieu of, or as a bridge to, allogeneic hematopoietic stem cell transplant



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Kenderian et al. 2017 Biol Blood Marrow Transplant

CARs in development for hematologic malignancies

- **CD20** (B cell cancers)
- **CD22** (B cell cancers)
- **CD23** (B cell cancers)
- **CD30** (B cell cancers)
- **CD37** (B and T cell cancers)
- **ROR1** (lymphoid cancers)
- **CD133** (lymphoid and myeloid cancers)
- **TSLPR** (lymphoid cancers)

- **BCMA** (multiple myeloma)
- **CS1** (multiple myeloma)
- **CD138** (multiple myeloma)

- **CD5** (T cell cancers)
- **CCR4** (T cell cancers)
- **CD7** (T cell and myeloid cancers)

- **CD33** (myeloid cancers)
- **CD123** (myeloid cancers)
- **Lewis-Y** (myeloid cancers)
- **CD44v6** (myeloid cancers)
- **CLL-1** (myeloid cancers)
- **Folate receptor beta** (myeloid cancers)
- **FLT3** (myeloid cancers)
- **NKG2D** (myeloid cancers)

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CARs in development for solid tumors

- **AFP** (liver cancer)
- **ALK** (neuroblastoma)
- **Carbonic anhydrase IX** (kidney cancer)
- **CD24** (ovarian cancer)
- **CD70** (kidney cancer)
- **CD133** (liver, brain, breast cancer)
- **CD171** (neuroblastoma)
- **CD276** (multiple histologies)
- **CEA** (lung, colorectal, gastric, pancreatic cancers and liver metastases)
- **cMet** (breast cancer)
- **CSFR1** (tumor-associated macrophages)
- **EGFR** (lung, colorectal, ovary, pancreatic cancer)
- **EGFRvIII** (gliomas, glioblastoma)
- **EpCAM** (liver, stomach and colon cancer)
- **EphA2** (glioma)
- **Fibroblast activation protein** (mesotheiloma)
- **Folate receptor alpha** (breast, ovarian cancer)
- **GD2** (neuroblastoma, sarcomas and melanoma)
- **Glypican-3** (liver, lung cancer)
- **HER2** (breast cancer, glioblastoma, ovarian, lung, pancreatic, sarcoma and medulloblastoma)
- **IL-13Rα** (gliomas)
- **Lewis-Y** (breast cancer)
- **Mesothelin** (pancreatic, ovarian, mesothelioma, breast cancer)
- **MG7** (liver metastases)
- **MUC-1** (breast, liver, lung, pancreatic, glioma, colorectal, gastric cancer)
- **NKG2D** (multiple histologies)
- **PSCA** (pancreatic cancer)
- **PSMA** (prostate cancer)
- **TEM8/ANTRX1** (breast cancer)
- **VEGFR2** (multiple histologies)

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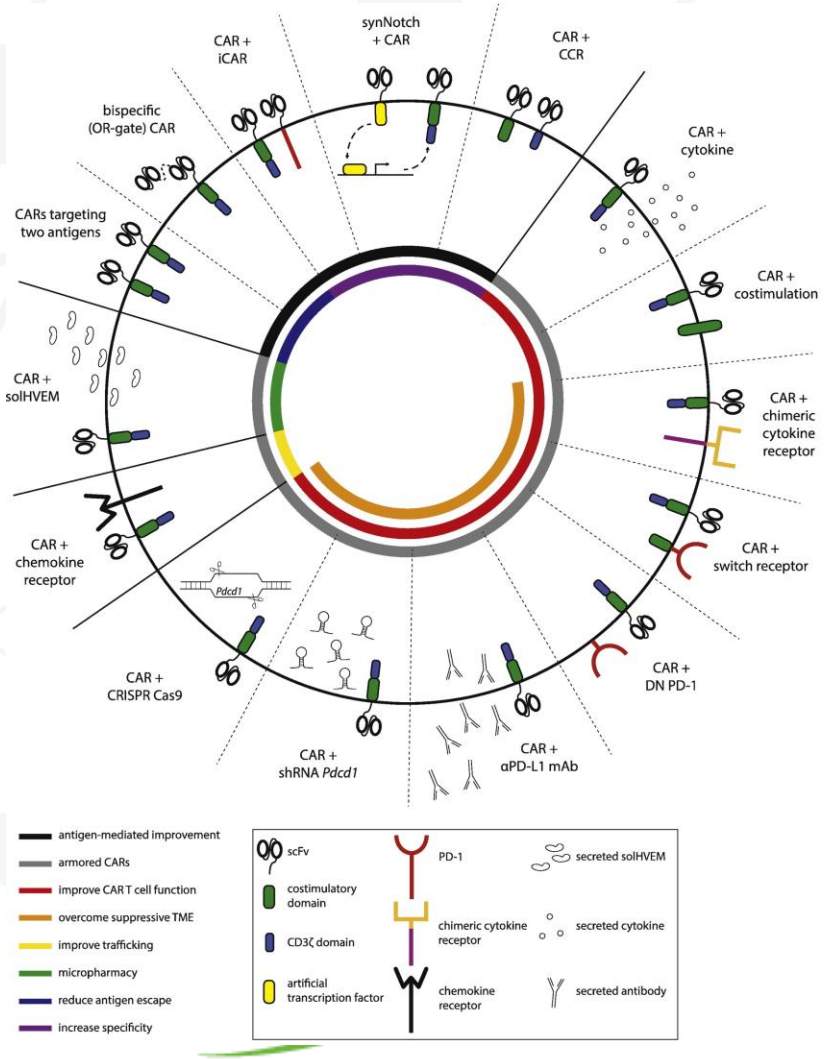
Enhanced engineering of CAR T, NK, NKT and CIK cells will help reduce side effects while improving efficacy



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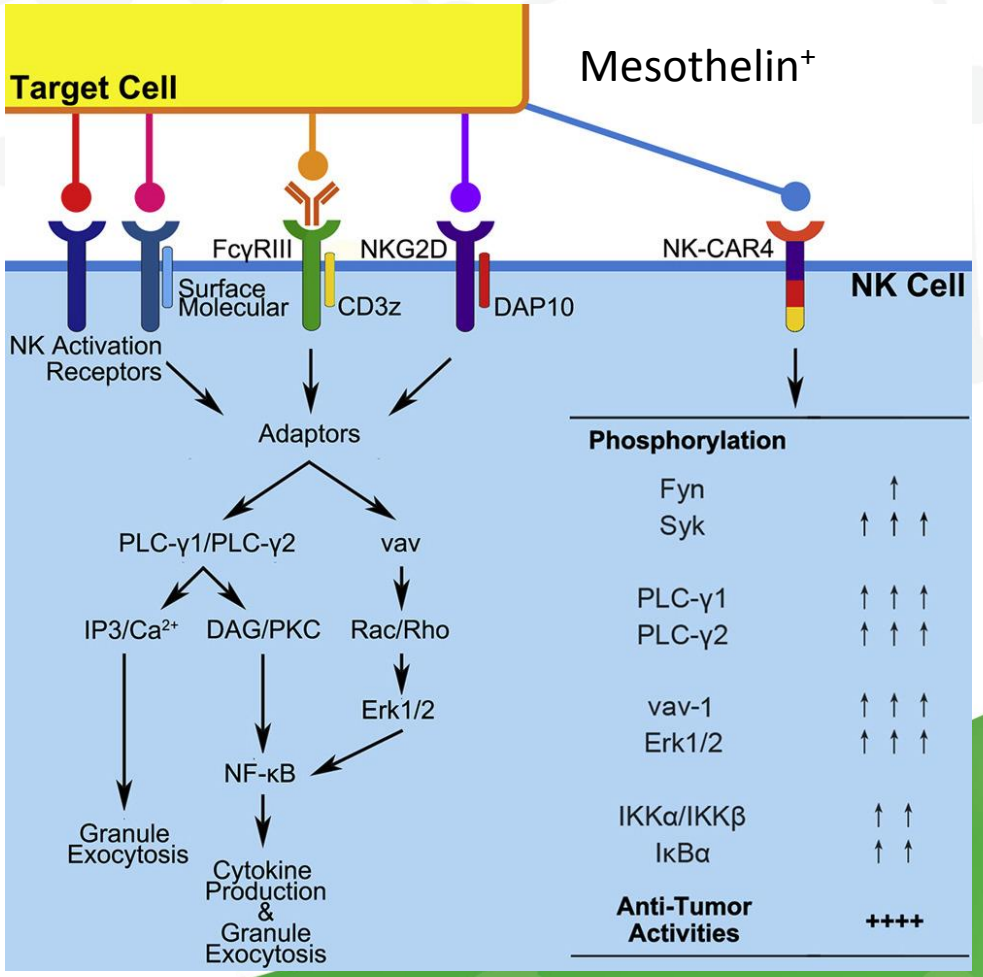
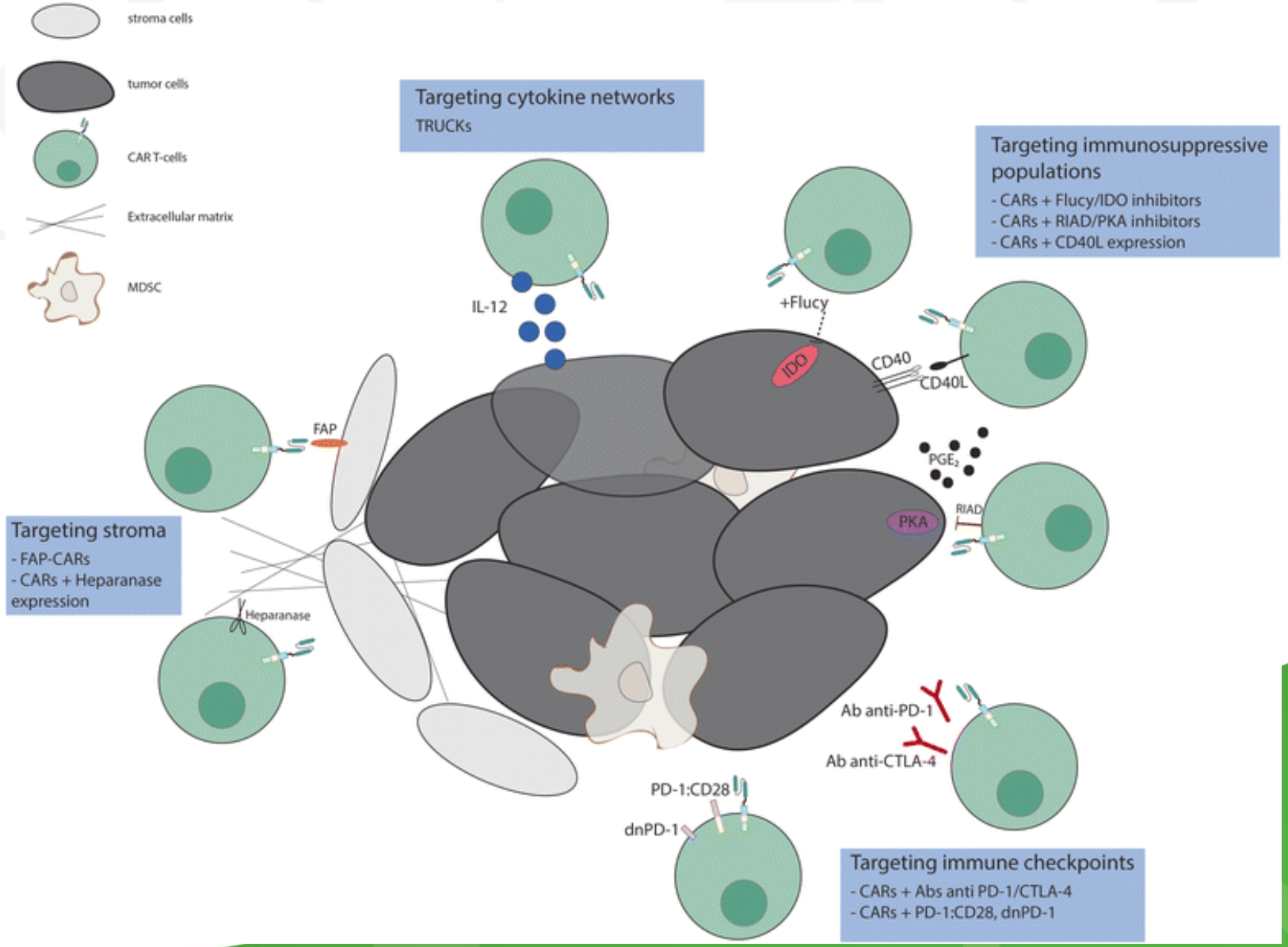
Jaspers and Brentjens 2017 Pharmacol Ther



Li et al. 2018 Cell Stem Cell

Combination strategies to improve CAR efficacy will be used for solid tumors



Scarfo and Maus 2017 J Immunother Cancer

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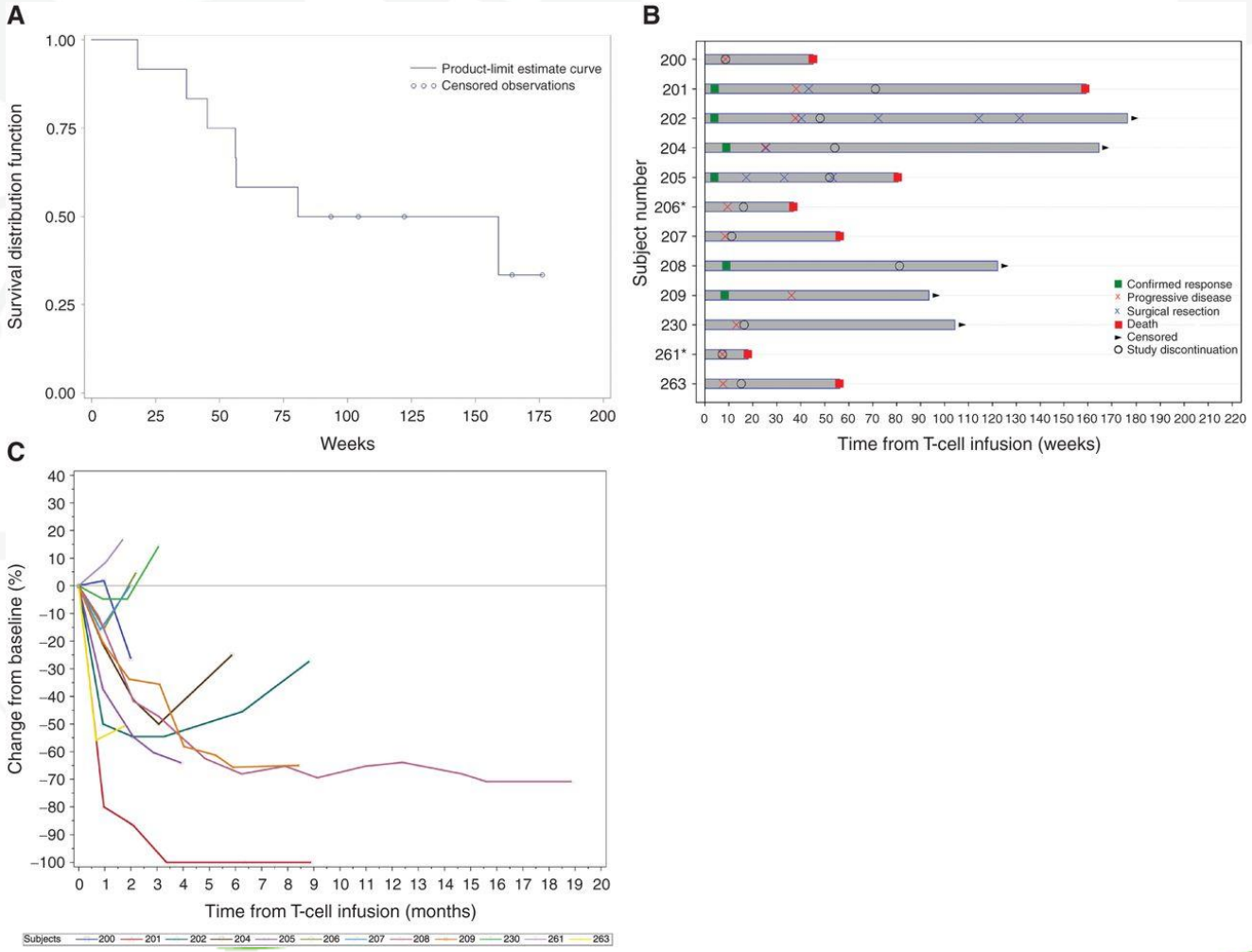
TCR transduced T cells will provide durable responses in solid tumors

NY-ESO-1 D'Angelo et al. 2018 Cancer Discov



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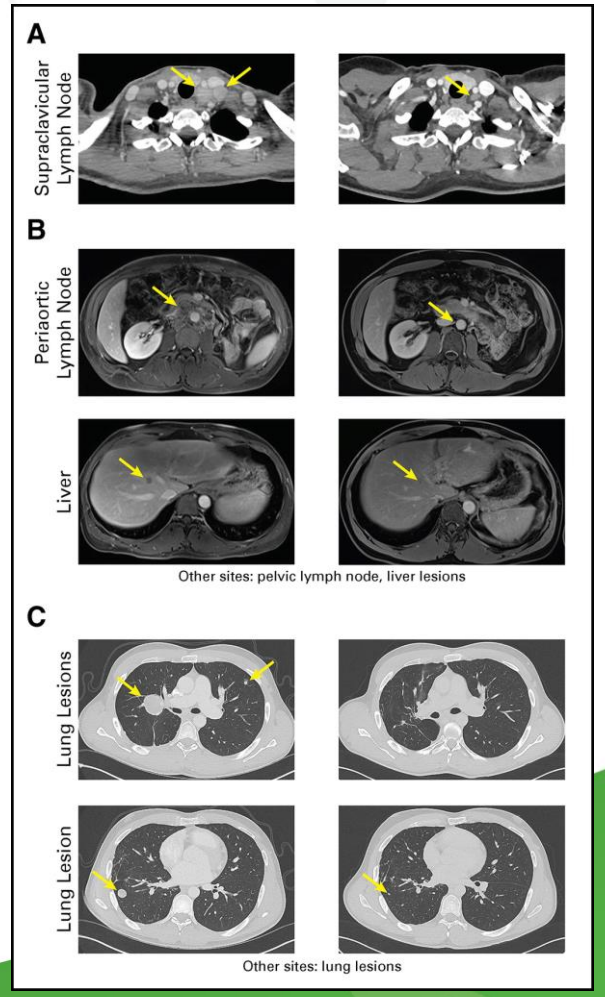
MAGE-A3 Lu et al. 2017 J Clin Oncol

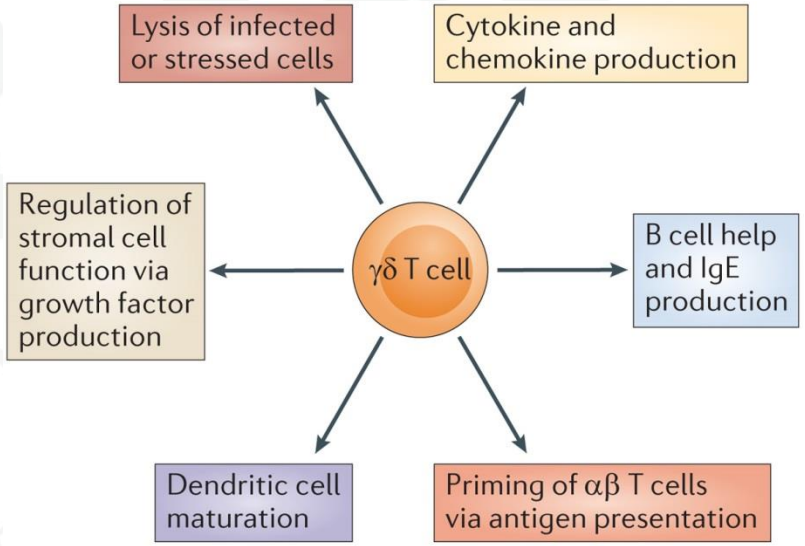


29 months

18 months

4 months

Gamma-delta (γδ) T cells will also be genetically engineered to serve as vaccines or express CAR or TCR



Nature Reviews | Immunology

Long term disease-free survival in acute leukemia patients recovering with increased γδ T cells after partially mismatched related donor bone marrow transplantation

KT Godder[1,2], PJ Henslee-Downey[1], J Mehta[1,3], BS Park[4], K-Y Chiang[1,5], S Abhyankar[1,6] and LS Lamb[1,7]

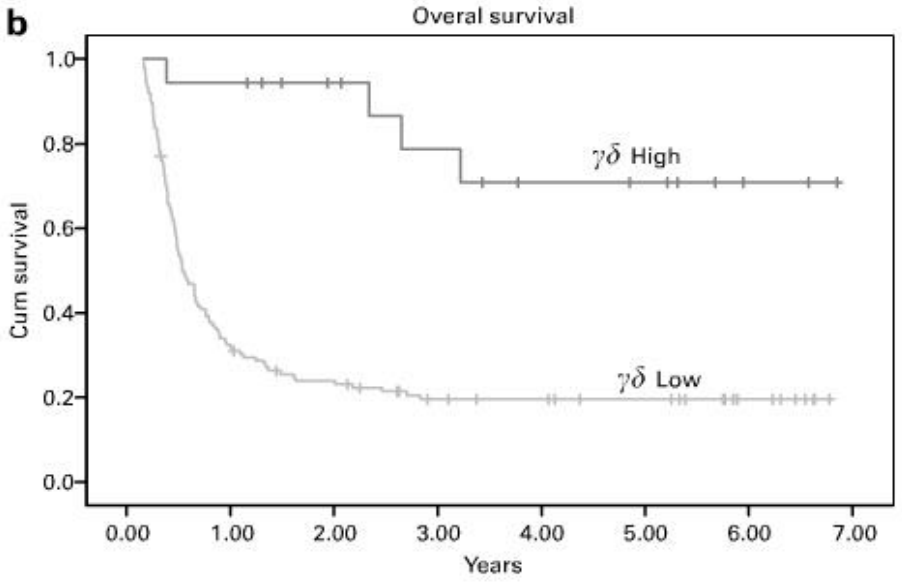


Figure 1 Kaplan Meier curves of event-free survival (**a**) and overall survival (**b**) of patients who recovered post PMRD-BMT with high vs low/normal γδ T-cells.

Bone Marrow Transplant. 2007 Jun;39(12):751-7

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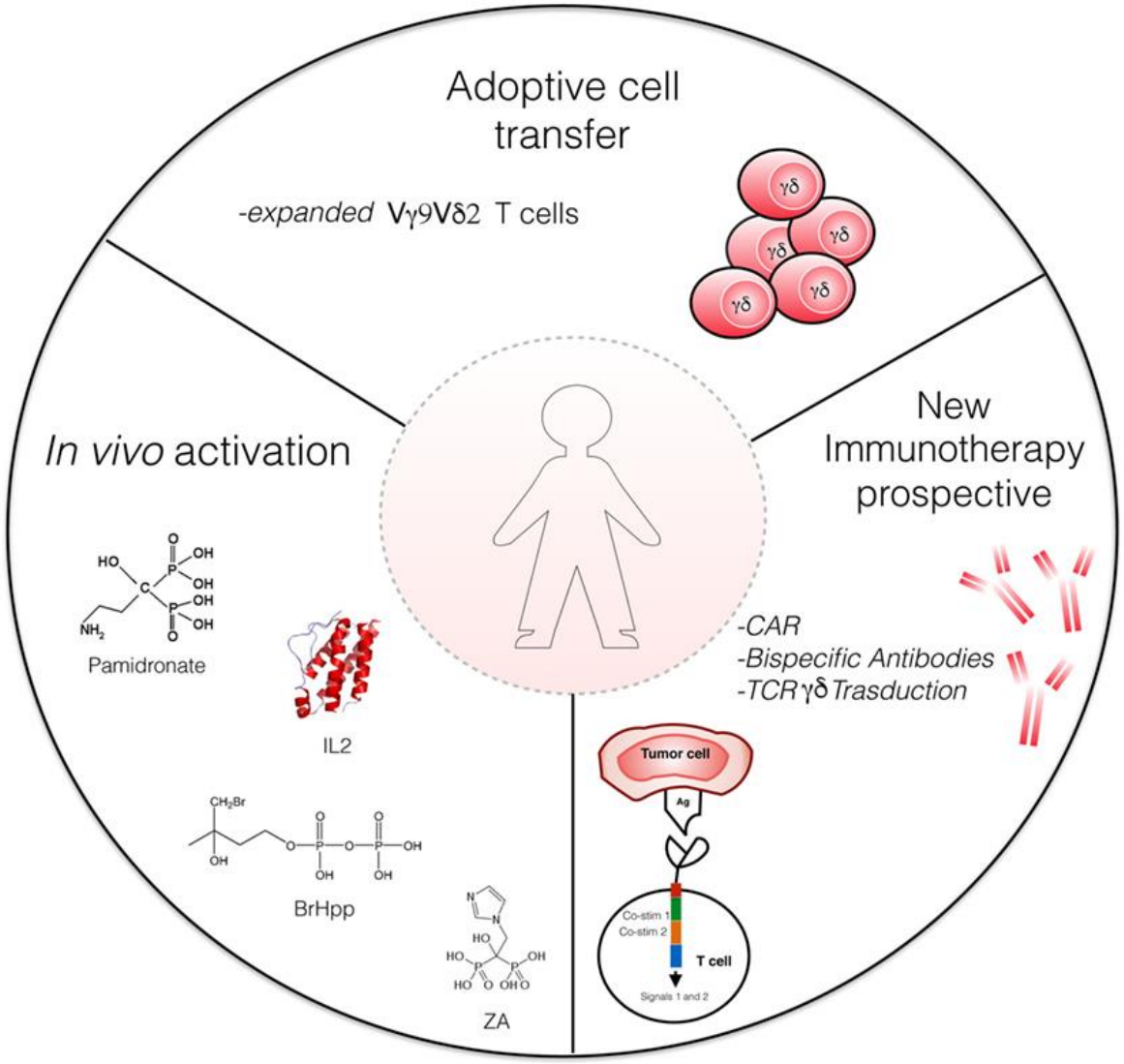
New and improved gamma-delta T cell therapy?



Lo Presti et al. 2018 Front Immunol

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Conclusions

- The future of cancer immunotherapy is bright, with advances occurring in both diagnostics and therapeutics at a rapid pace
- We will see improvements in our ability to distinguish immunologically “hot” vs. “cold” tumors, and potentially be able to convert “cold” into “hot” tumors
- Advances in genetic engineering and biomanufacturing will permit development of “next generation” antibodies, viruses, targeted radiotherapies and cellular therapies for cancer.

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