Direction of the Field: The Future of Cancer Immunotherapy

January 28, 2022

Christian Capitini, MD
University of Wisconsin-Madison

Disclosures

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

Diagnostics

Therapeutics

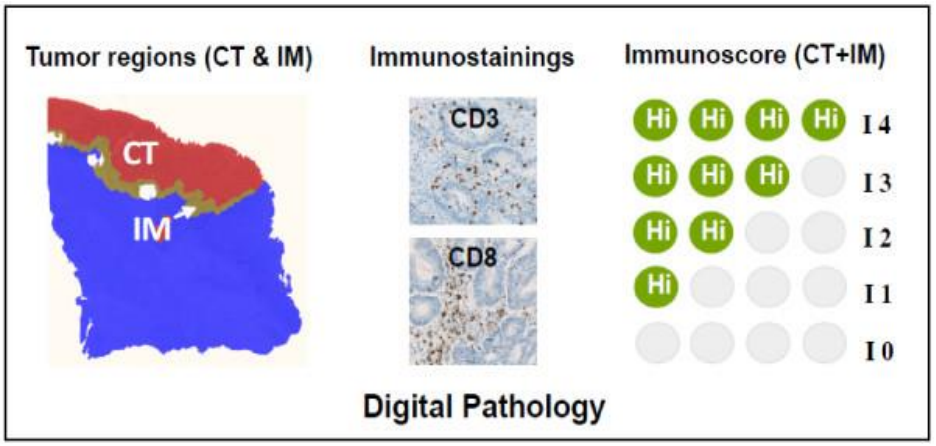
Improvements in Staging and Immunotherapy Biomarkers

- 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

Current standard diagnostics

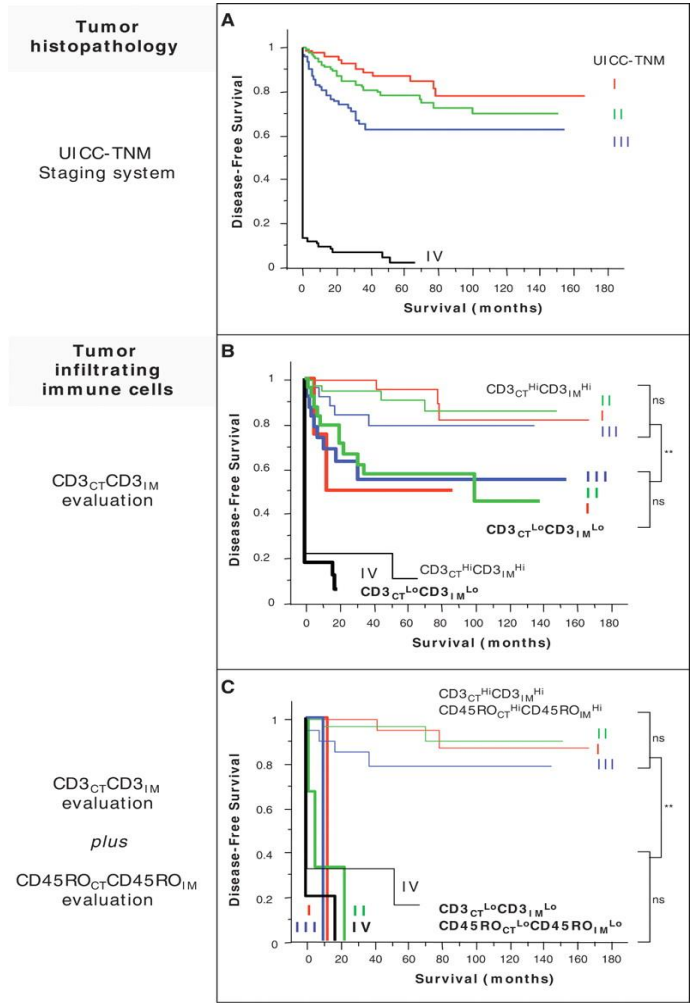
- Histopathology
- Flow cytometry
- Immunohistochemistry
- Cytogenetics
- Molecular studies: RT-PCR/FISH
- Next generation sequencing (NGS) panels
  - Identify fusions without having to know fusion partners
  - Identify pathways for targeting by FDA-approved drugs, on- or off-label

Immunoscore will become part of standard pathologic reports for all tumors



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	Cholangiocarcinoma
Head and neck cancer	**Pediatric tumors**
Esophageal/Gastric cancer	Neuroblastoma
Bladder cancer	Osteosarcoma`

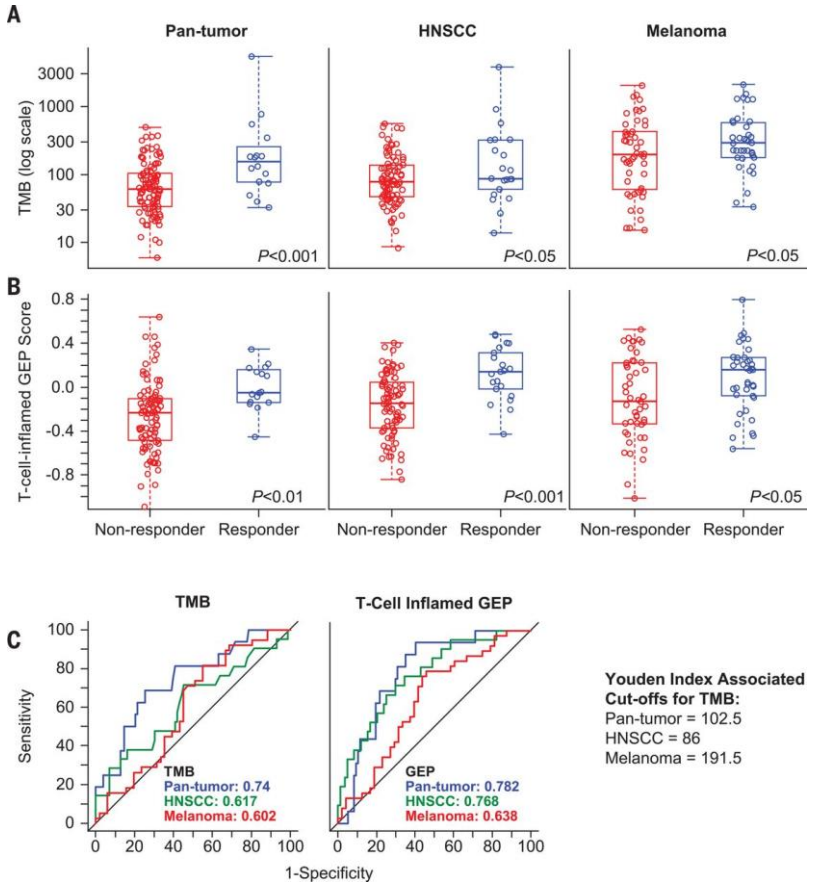


Galon et al. 2006 Science

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

- PD-L1 immunohistochemistry
- Tumor mutation burden (TMB)
- Gene expression profiling (GEP)
- Multiplex immunohistochemistry/immunofluorescence (mIHC/IF)

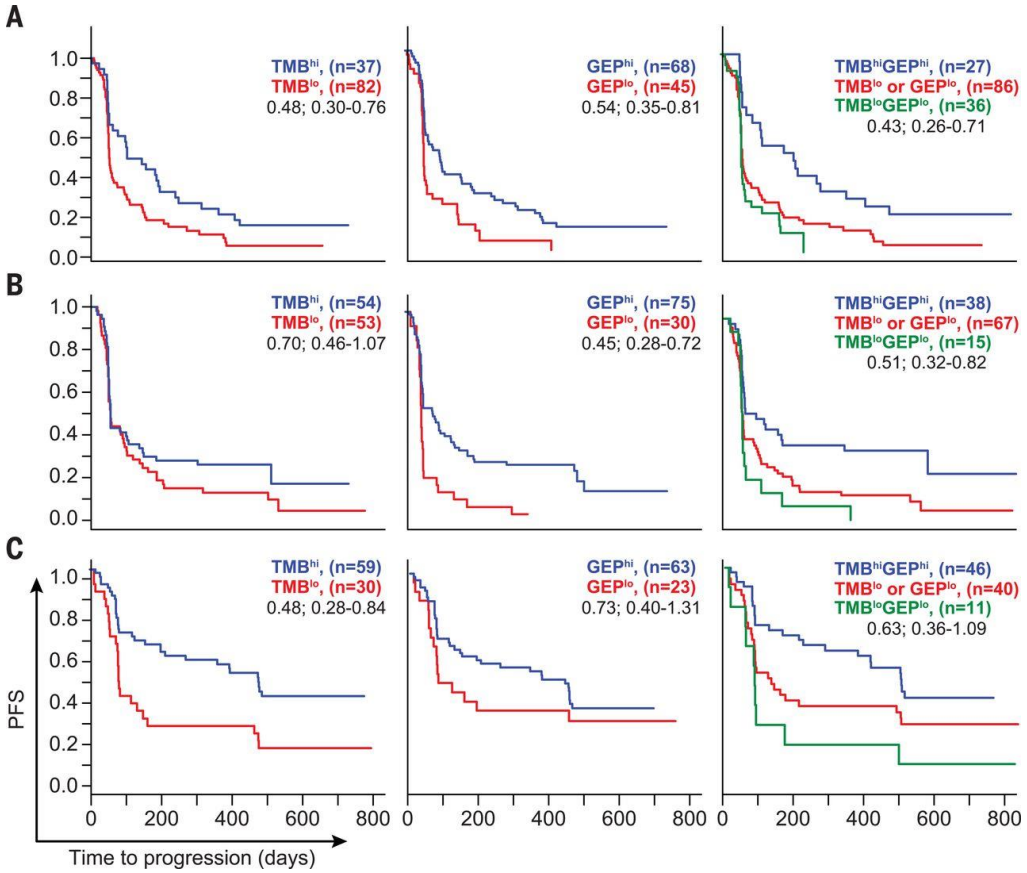
Individual association of TMB or T cell–inflamed GEP with anti–PD-1 response across multiple patient cohorts



Pan-tumor

HNSCC

Melanoma



Razvan Cristescu et al. Science 2018;362:eaar3593

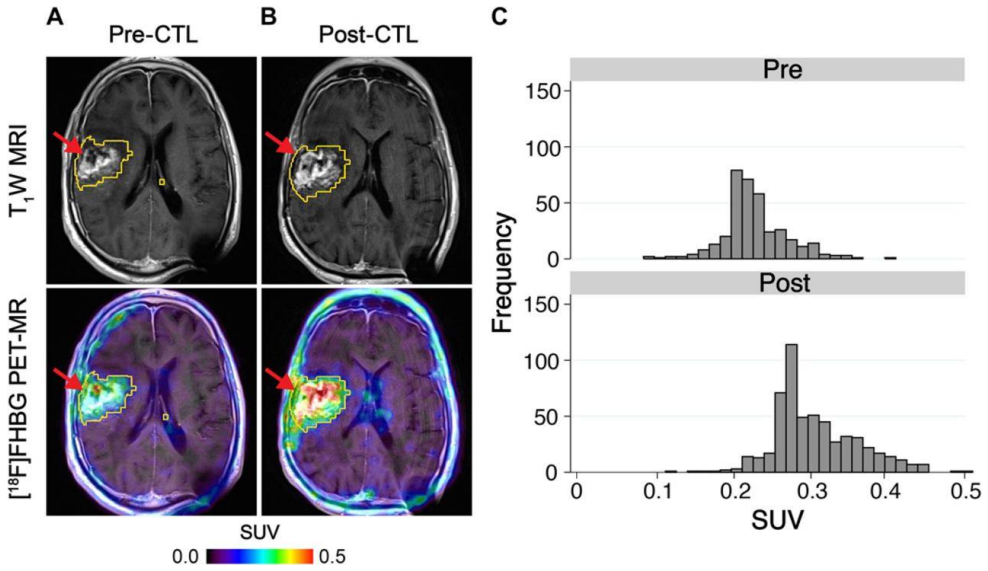
Science
AAAS

#SITCWinterSchool

Will see improvements in use of imaging modalities to track immune response

Ex vivo

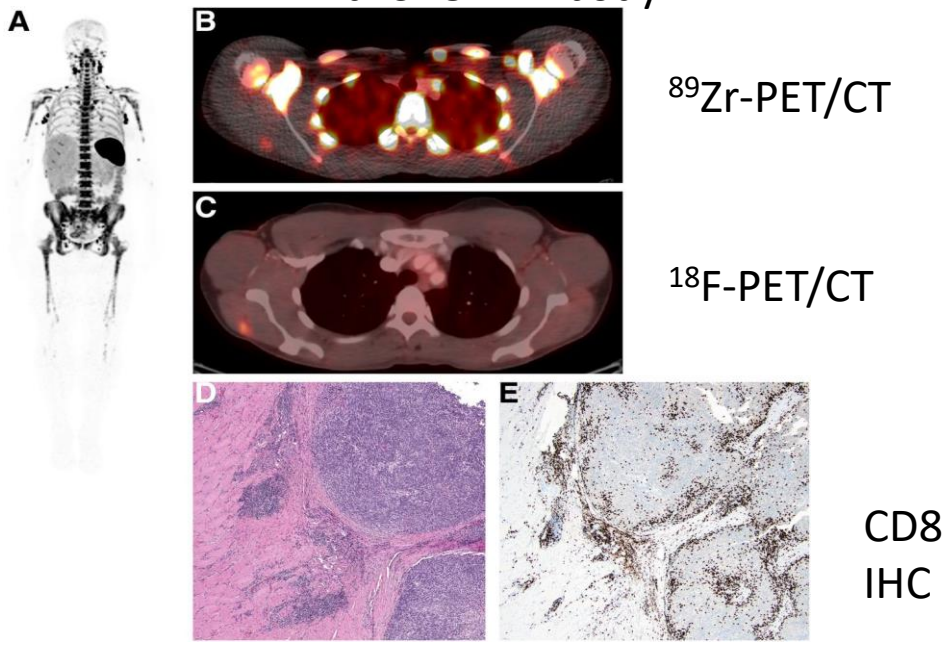
^{18}F-FHBG-IL13Rα CAR zetakine



Khun Visith Keu et al., Sci Transl Med 2017;9:eaag2196

In Vivo

^{89}Zr-Anti-CD8 minibody



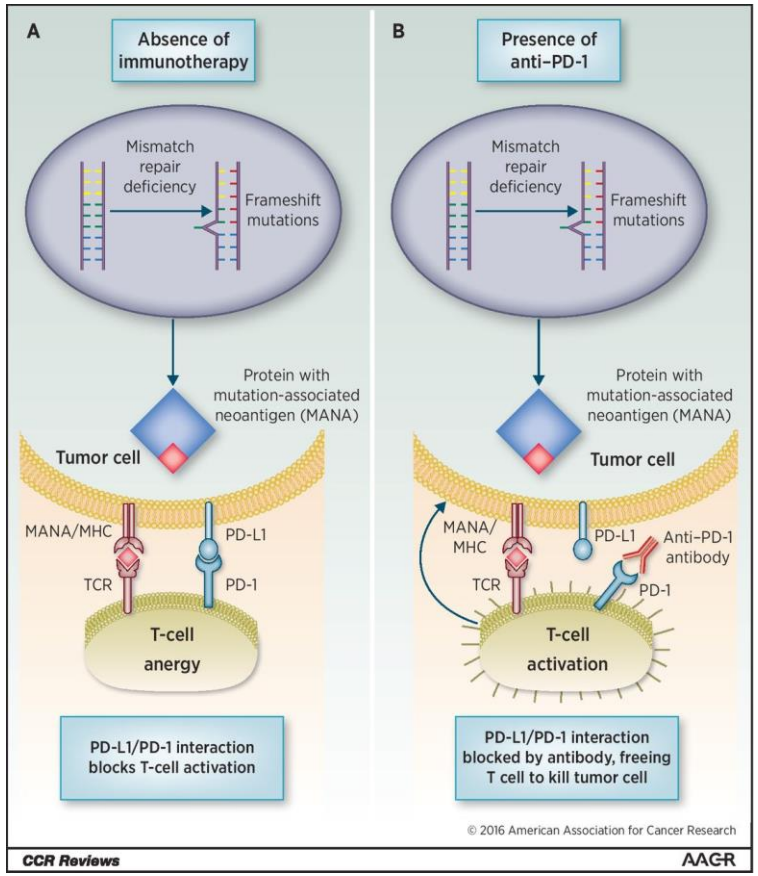
^{89}Zr-PET/CT

^{18}F-PET/CT

CD8 IHC

Neeta Pandit-Taskar et al. J Nucl Med 2020;61:512-519

Relationship between MSI status and immunologic response.

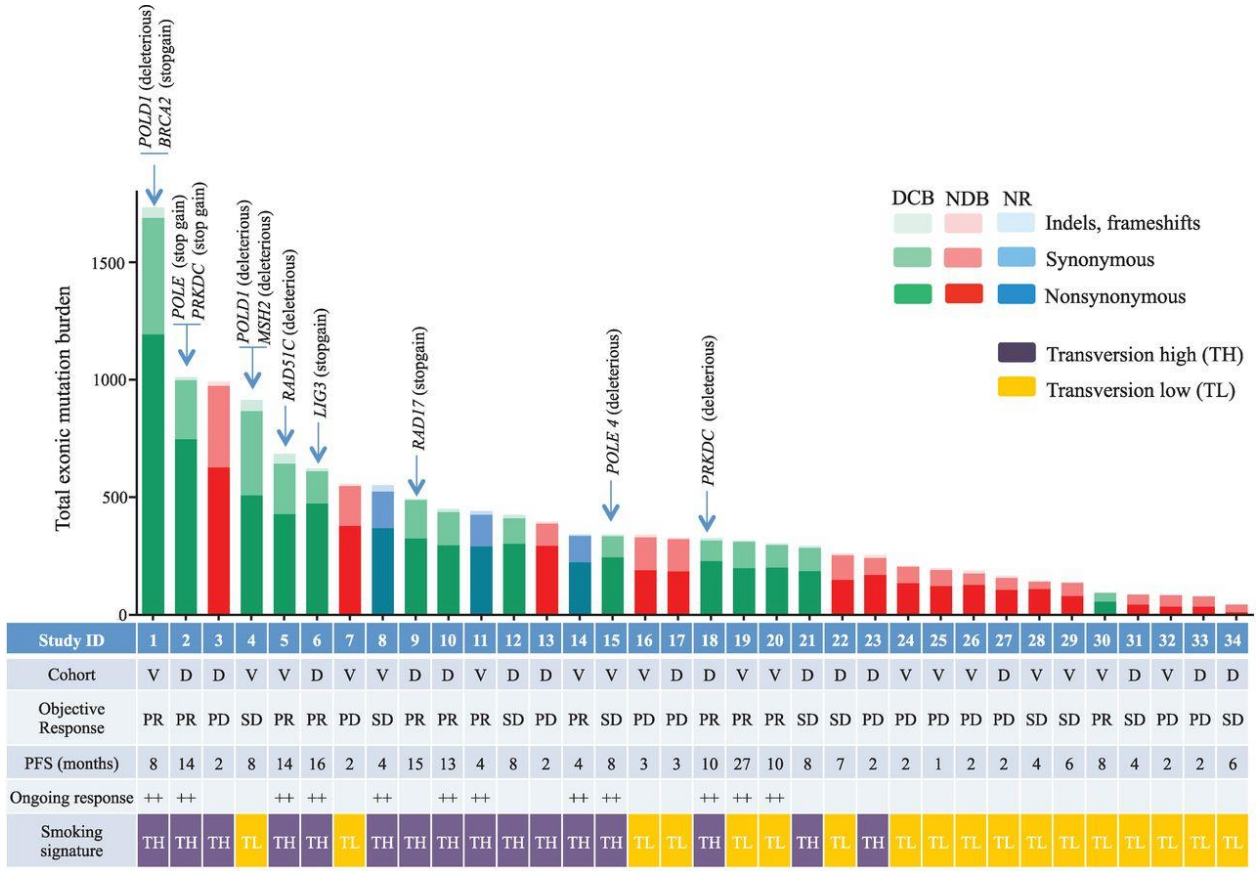


Jonathan C. Dudley et al. Clin Cancer Res 2016;22:813-820

Clinical Cancer Research

Better intersection of NGS with predicting immunotherapy responses

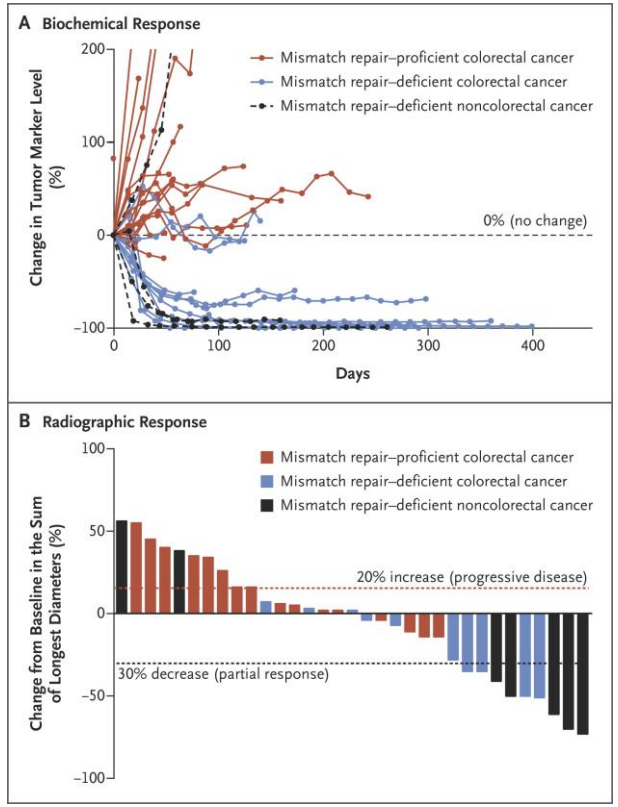
Tumor mutational burden



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

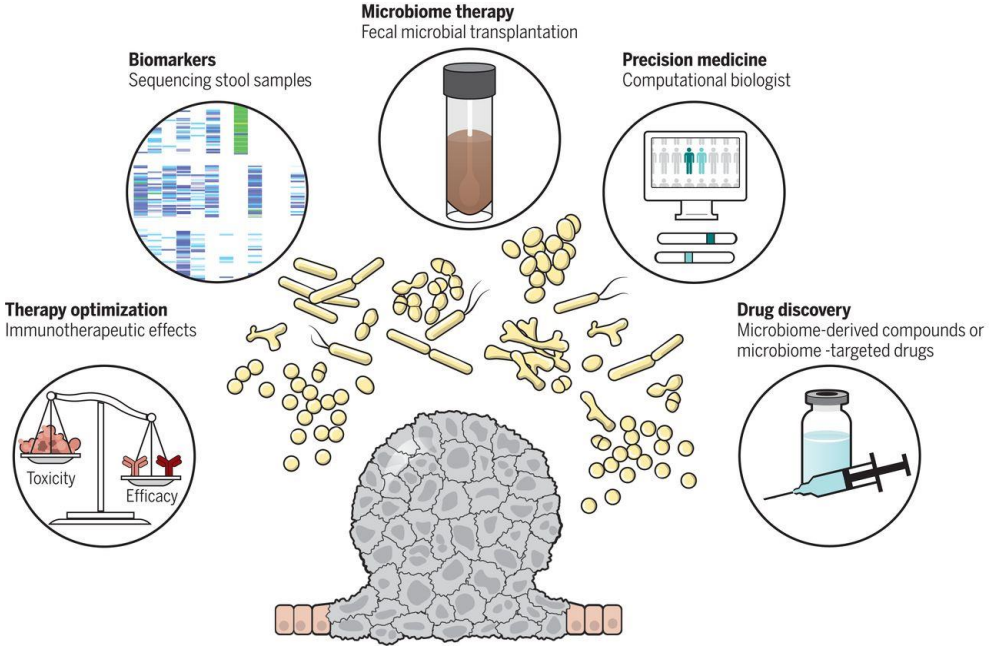
Rizvi et al. 2016 Science

Mismatch repair defects

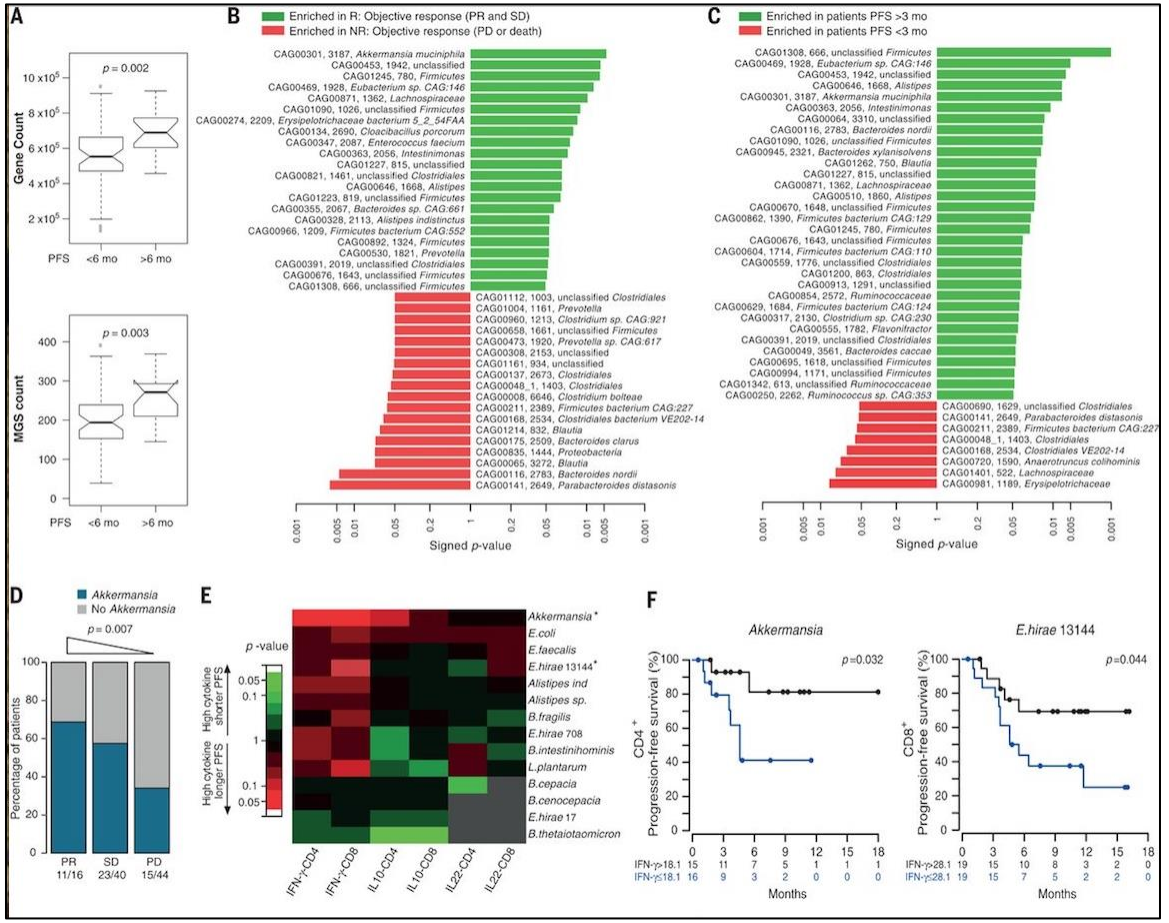


Le et al. 2015 New Engl J Med

Query and modulate the gut microbiome to improve responses to immunotherapy

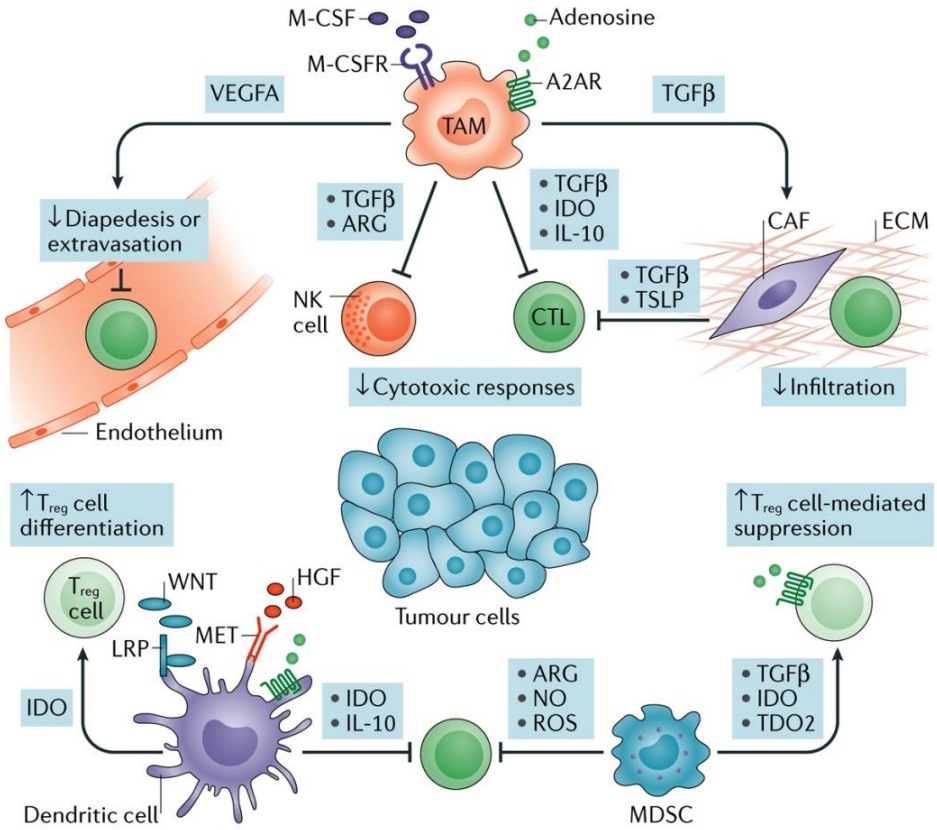


Zitvogel et al. 2018 Science



Routy et al. 2018 Science

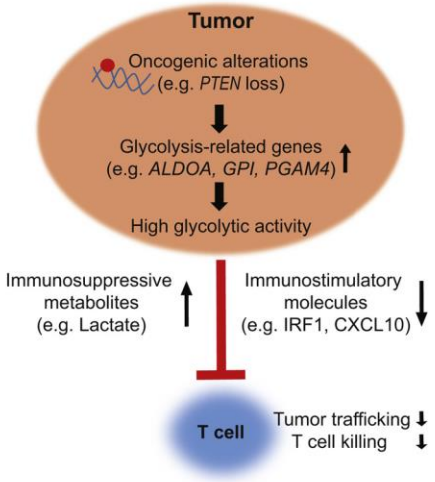
Tumor microenvironment is immuno-suppressive due to multiple cells and cytokines



Nature Reviews | Cancer

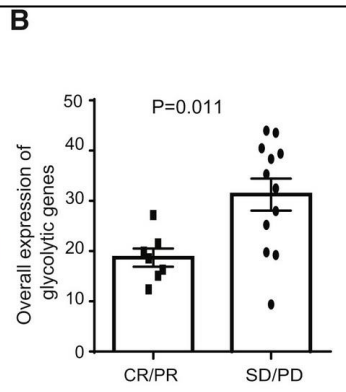
Gotwals et al. 2017

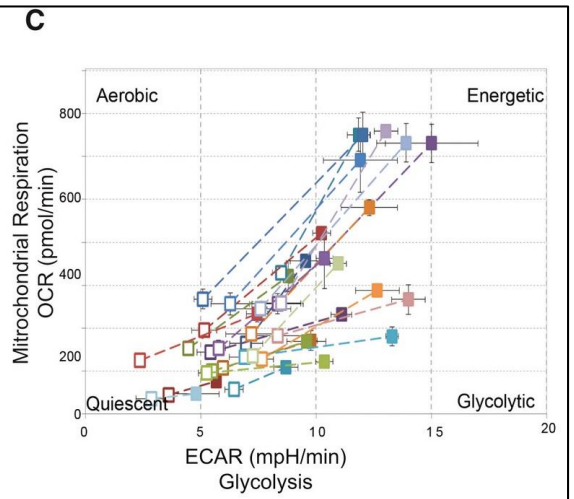
Manipulate the tumor metabolic environment to enhance immunotherapy responses



A

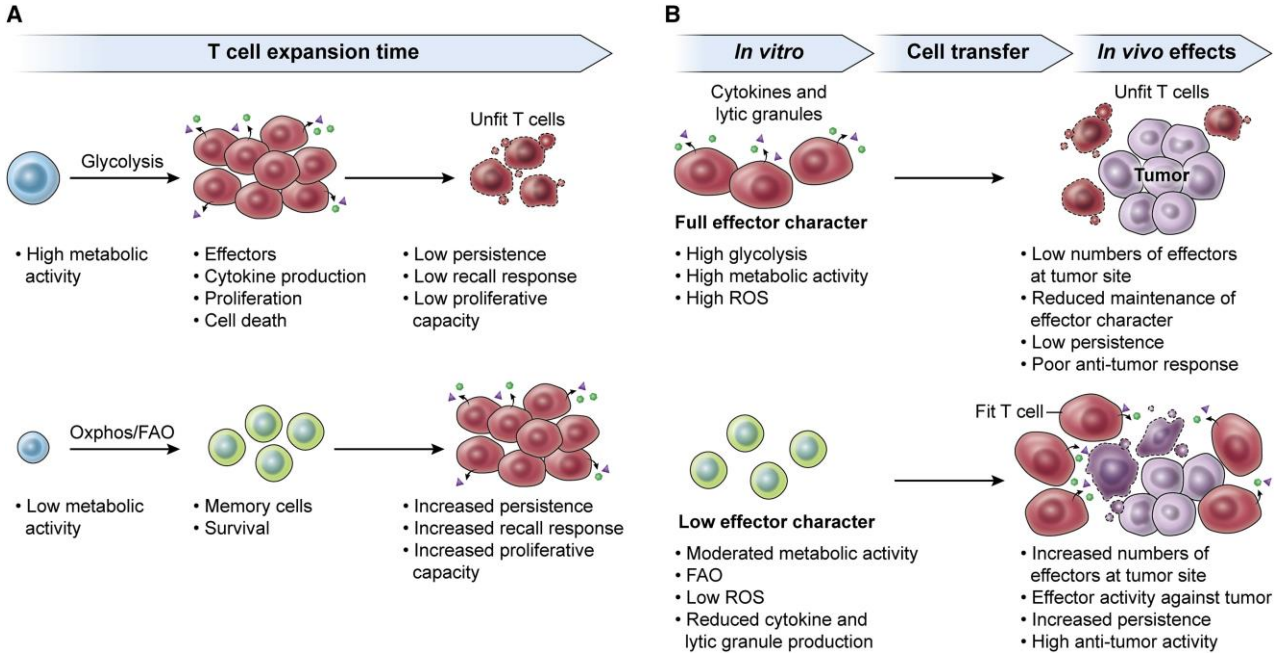
GENE	FC (N/R)	P value
ALDOA	1.697746	0.136385
ALDOC	1.758665	0.186307
ENO2	1.257908	0.685237
ENO3	2.365525	0.205193
GAPDH	1.733471	0.143722
GPI	1.700951	0.015443
LDHA	1.429014	0.302088
LDHB	1.511258	0.152462
PFKM	1.152264	0.57808
PFKP	1.232823	0.463708
PGAM1	1.421356	0.108866
PGAM4	1.5305	0.033143
PGK1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





Cascone et al. 2018 Cell Metab

Manipulate 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

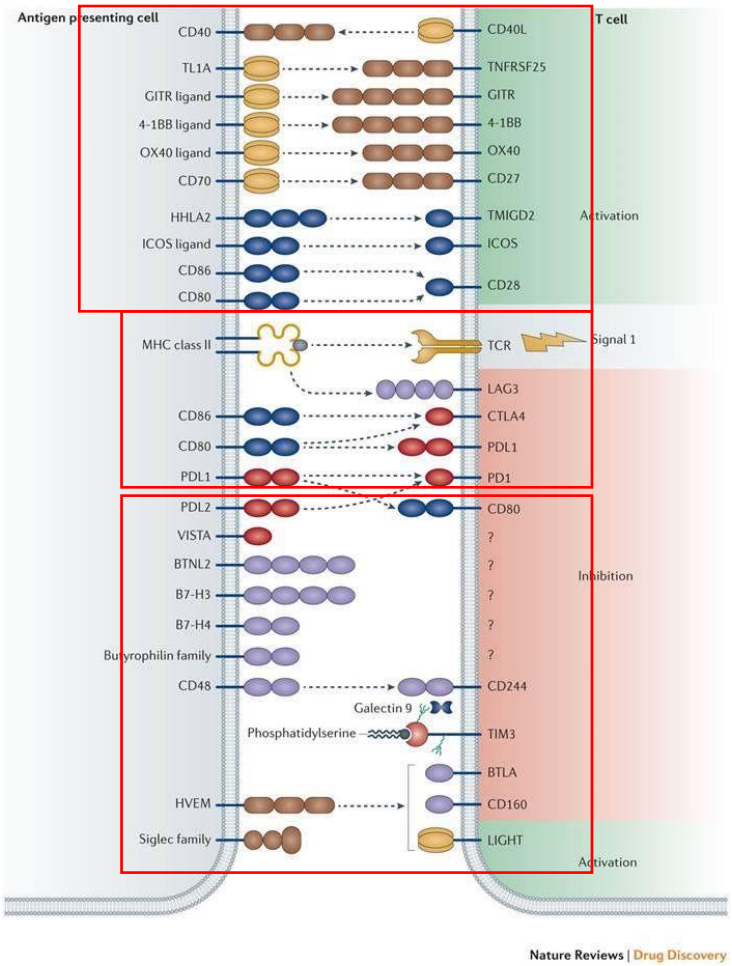
Diagnostics

Therapeutics

Expansion of immunotherapy therapeutics

- Antibody therapy
  - Checkpoint agonists/inhibitors
  - Antibody-drug conjugates
  - Bispecifics
- Oncolytic viral therapy
- Radiotherapy/Immunotherapy
- Cytokine therapy
  - Bempegaldesleukin
  - N-803
- Cellular therapy
  - Vaccines
    - +/- anti-PD1
  - CAR T, CAR NK
    - CAR NKT, CAR CIK cells emerging
  - TCR transduced T cells

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

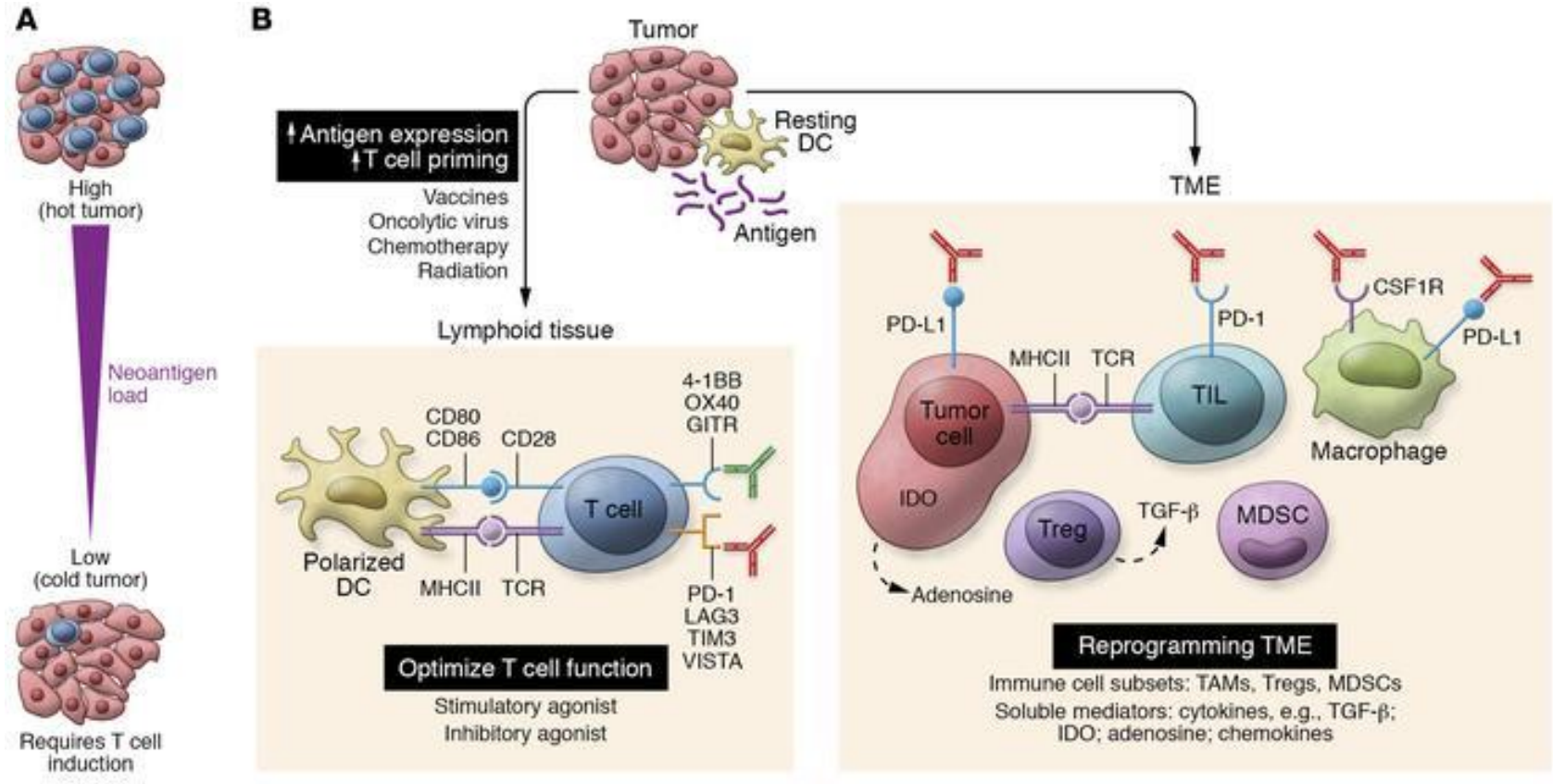


Mahoney KM et al. 2015 Nat Rev Drug Discovery

	Combination partner	Combination	Comparator	ORR comparison	HR for disease progression or death	HR for death	Trial
PD-1							
Melanoma	CTLA-4	Nivolumab and ipilimumab	Ipilimumab	OR 6·35 58% vs 19% (95% CI 4·38–9·22, p<0·001)	0·42 (95% CI 0·35–0·51, p<0·001)	0·52 (95% CI 0·42–0·64, p<0·001)	CheckMate 067[49,50] (NCT01844505)
Colorectal cancer (MSI-H or dMMR)	CTLA-4	Nivolumab and ipilimumab	–	55% (95% CI 45·2–63·8)	–	–	CheckMate 142[51] NCT02060188
Renal cell carcinoma	CTLA-4	Nivolumab and ipilimumab	Sunitinib	42% vs 27%, p<0·001	0·82 (99·1% CI 0·64 to 1·05), p=0·03**	0·63 (99·8 CI 0·44–0·89), p<0·001	CheckMate 214[37] (NCT02231749)
Non-small cell lung cancer (PD-L1 ≥ 1%, without EGFR or ALK alterations)	CTLA-4	Nivolumab and ipilimumab	Platinum-doublet chemotherapy	35·9% vs 30·0%	–	0·79 (0·65–0·96) in patients with PD-L1 ≥1%	CheckMate 227[33] (NCT02477826)
Malignant pleural mesothelioma	CTLA-4	Nivolumab and ipilimumab	Pemetrexed and cisplatin or carboplatin	40% vs 43%	1·0 (0·82–1·21)	0·74 (0·61–0·89), p=0·002	CheckMate 743[34] (NCT02899299)
Hepatocellular carcinoma	CTLA-4	Nivolumab and ipilimumab	–	32%	–	–	CheckMate 040[35] (NCT01658878)
Non-squamous non-small cell lung cancer (without EGFR or ALK alterations)	Chemotherapy	Pembrolizumab and pemetrexed and platinum	Pemetrexed and platinum	47·6% vs 18·9% (p<0·001)	0·48 (0·40–0·58)	0·56 (0·45–0·70)	KEYNOTE-189[36] (NCT02578680)
Squamous non-small cell lung cancer	Chemotherapy	Pembrolizumab and carboplatin and paclitaxel or nab-paclitaxel	Carboplatin and paclitaxel or nab-paclitaxel	57·9% vs 38·4%	0·56 (0·45–0·70), p<0·001	0·64 (0·49–0·85), p<0·001	KEYNOTE-407[37] (NCT02775435)
Triple negative breast cancer PD-L1 (CPS ≥10)	Chemotherapy	Pembrolizumab paclitaxel protein-bound, or paclitaxel, or gemcitabine plus carboplatin	Paclitaxel protein-bound, or paclitaxel, or gemcitabine plus carboplatin	–	0·65 (0·49–0·86), p=0·0012	–	KEYNOTE-355[38] (NCT02819518)
Renal cell carcinoma	Targeted	Pembrolizumab and axitinib	Sunitinib	59·3% vs 35·7% (p<0·001)	0·69 (0·57–0·84), p<0·001	0·53 (0·38–0·74), p<0·0001)	KEYNOTE-426[39] (NCT02853331)
Endometrial cancer (non-MSI-H or dMMR)	Targeted	Pembrolizumab and lenvatinib	–	39·6% (at 24 weeks)	–	–	KEYNOTE-146[40] (NCT02501096)
PD-L1							
Triple-negative breast cancer	Chemotherapy	Atezolizumab and nab-paclitaxel	Nab-paclitaxel	OR 1·52 (56·0% vs 45·9%), p=0·002	0·80 (0·69–0·92), p=0·002	0·86 (0·72–1·02), p=0·078), OS in PD-L1 positive patients exploratory stratified HR 0·71 months (range 0·54–0·94))	Mpassion13[41] (NCT03371017)
Non-squamous non-small cell lung cancer (without EGFR or ALK alterations)	Chemotherapy	Atezolizumab and nab-paclitaxel and carboplatin	Nab-paclitaxel and carboplatin	49·2% vs 31·9%, OR 2·07 (1·48–2·89)	0·64 (0·54–0·77), p<0·0001	0·79 (0·64–0·98), p=0·033	Mpower130[42] (NCT02367781)
Small cell lung carcinoma	Chemotherapy	Atezolizumab and carboplatin or etoposide	Carboplatin or etoposide	60·2% vs 64·4%	0·77 (0·62–0·96), p=0·02	0·70 (0·54–0·91), p=0·007	Mpower133[43] (NCT02763579)
Renal cell carcinoma	Targeted	Avelumab and axitinib	Sunitinib	51·4% vs 25·7%	0·69 (0·563–0·840), two-sided p=0·0002	–	JAVELIN Renal 101[44] (NCT02684006)
BRAF V600E mutant melanoma	Targeted	Atezolizumab and vemurafenib and cobimetinib	Vemurafenib and cobimetinib	66·3% vs 65%	0·78 (0·63–0·97), p=0·025	0·85 (0·64–1·11), p=0·23	Mspire150[45] (NCT02908672)

Meric-Bernstam et al. 2021 Lancet

Emerging strategies for combination checkpoint modulators in cancer immunotherapy



#SITCWinterSchool

Popovic et al. 2019 J Clin Invest

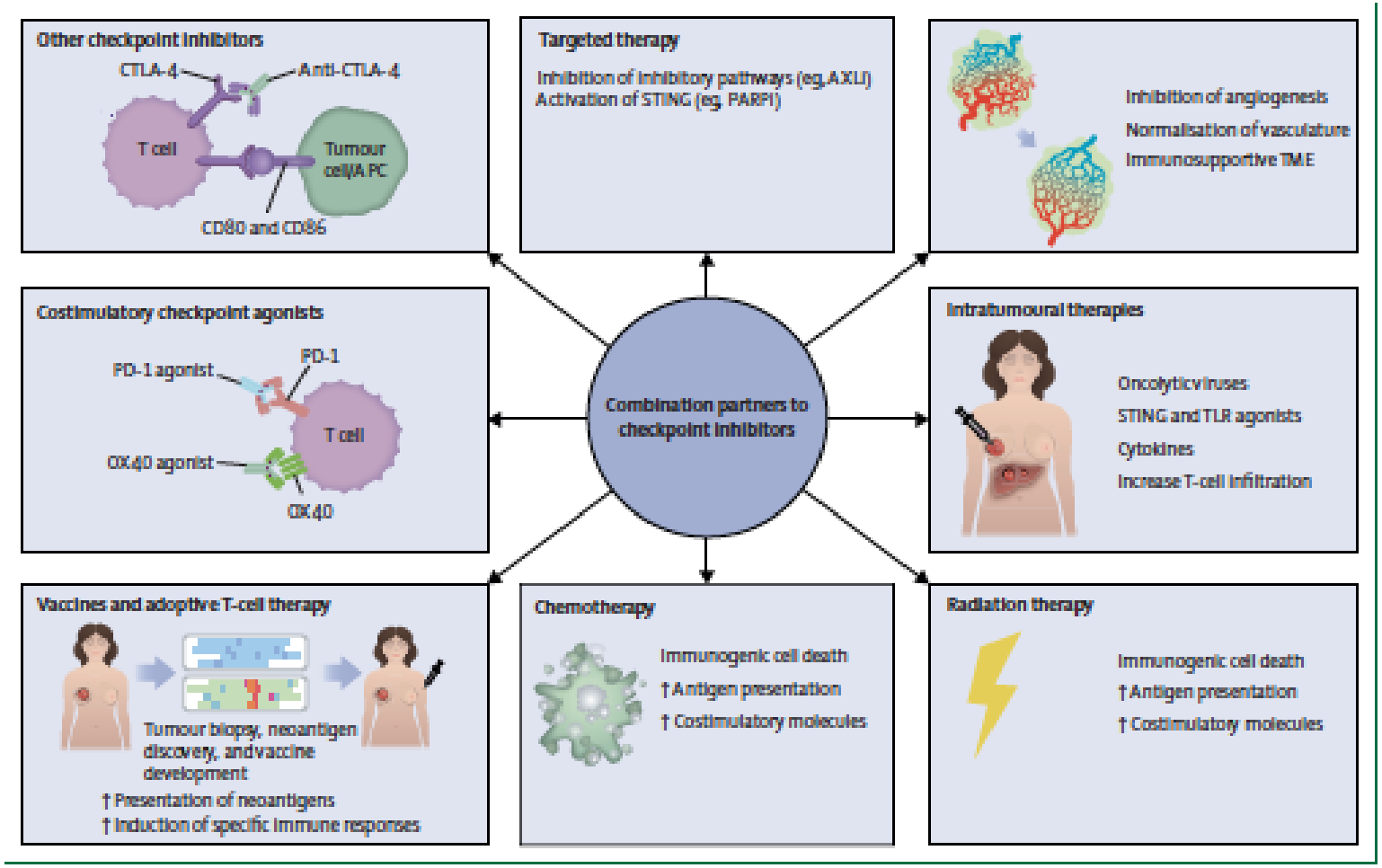
The number of checkpoint agonists and antagonists will expand and be used in combination

	Drug	Clinical trial
Checkpoint inhibitors		
Anti-CTLA-4	Ipilimumab	NCT03651271
Anti-TIM-3	LY3321367	NCT03099109
Anti-LAG-3	BMS-986016	NCT01968109
Anti-PVRIG	COM701	NCT03667716
Anti-TIGIT	Tiragolumab	NCT04294810
Checkpoint agonist		
Anti-4-1BB (CD137)	Utomilumab	NCT03217747
Anti-OX40	PF-04518600	NCT03971409
Anti-GITR	ASP1951	NCT03799003
Anti-ICOS	KY1044	NCT03829501
Anti-CD27	MK-5890	NCT03396445
Cytokine inhibitors		
Anti-IL-8	BMS986253	NCT03369223
Cytokines		
IL-2	IL-2	NCT03835533
IL2Rβγ-biased cytokine	NKTR-214	NCT03138889
IL-10	Pegilodecakin (pegylated IL-10)	NCT02009449
IL-15	NIZ985 (IL-15 or sIL-15Rα, heterodimeric IL-15)	NCT02452268
Tumour directed cytokines		
Tumour-directed IL-2	RO6874281	NCT03386721
Intratumoural agents		
Oncolytic viruses	Talimogene laherparepvec	NCT02509507
STING agonists	ADU-S100 (also known as MIW815)	NCT03937141
TLR agonists	NKTR-262 (TLR 7 and 8) IMO-2125 (TLR 9)	NCT03435640 NCT03445533
Cytokine mRNA	SAR441000	NCT03871348
Chemotherapy		
Systemic chemotherapy	Atezolizumab; paclitaxel with carboplatin and cyclophosphamide and doxorubin or epirubicin	NCT03036488
ADC	Trastuzumab deruxtecan (anti-HER2)	NCT04042701

	Drug	Clinical trial
(Continued from previous page)		
Targeted therapy		
VEGF	Bevacizumab	NCT03074513
Multikinase	Cabozantinib	NCT03170960
BRAF/MEK	Dabrafenib or trametinib	NCT02967692
BRAF/EGFR	Encorafenib or cetuximab	NCT04017650
ERK1/2	LY3214996	NCT02857270
PI3K	Copanlisib	NCT03502733
PI3Kβ	GSK2636771	NCT03131908
Akt	Ipatasertib	NCT03395899
FGFR	Pemigatinib; vofatamab	NCT02393248; NCT03123055
c-MET	Savolitinib	NCT02819596
AXL	Bemcentinib	NCT03184571
CDK4/6	Abemaciclib	NCT02779751
SHP2	TNO155	NCT04000529
PARP	Talazoparib; olaparib	NCT03565991; NCT03801369
PARP/Akt	Olaparib and capivasertib	NCT03772561
PARP/PI3K	Copanlisib and olaparib	NCT03842228
PARP/MEK	Talazoparib and binimetinib	NCT03565991
Androgen receptor	Enzalutamide	NCT03338790
KRAS G12C	AMG-510	NCT03600883
MDM2	APG-115	NCT03611868
Metabolic modulators		
A2AR inhibitor	NIR178	NCT03207867
Glutaminase inhibitor	IPN60090	NCT03894540
Other systemic strategies		
Bispecific antibodies	AMG 160 (anti-PSMA with anti-CD3 bispecific T-cell engager)	NCT03792841
Microbiome	SER-401	NCT03817125
Epigenetic agents	Entinostat (histone deacetylase 1 and 3 inhibitor)	NCT02437136
Intravenous STING agonists	GSK3745417	NCT03843359
Anti-TGFβ	SAR439459	NCT03192345
Anti-CD73	NZV930	NCT03549000
Anti-CD47	TTI-621	NCT03530683
Anti-CD40 (agonist)	ABBV-927	NCT02988960
XPO1 inhibitor	Selinexor	NCT02419495

Meric-Bernstam et al. 2021 Lancet

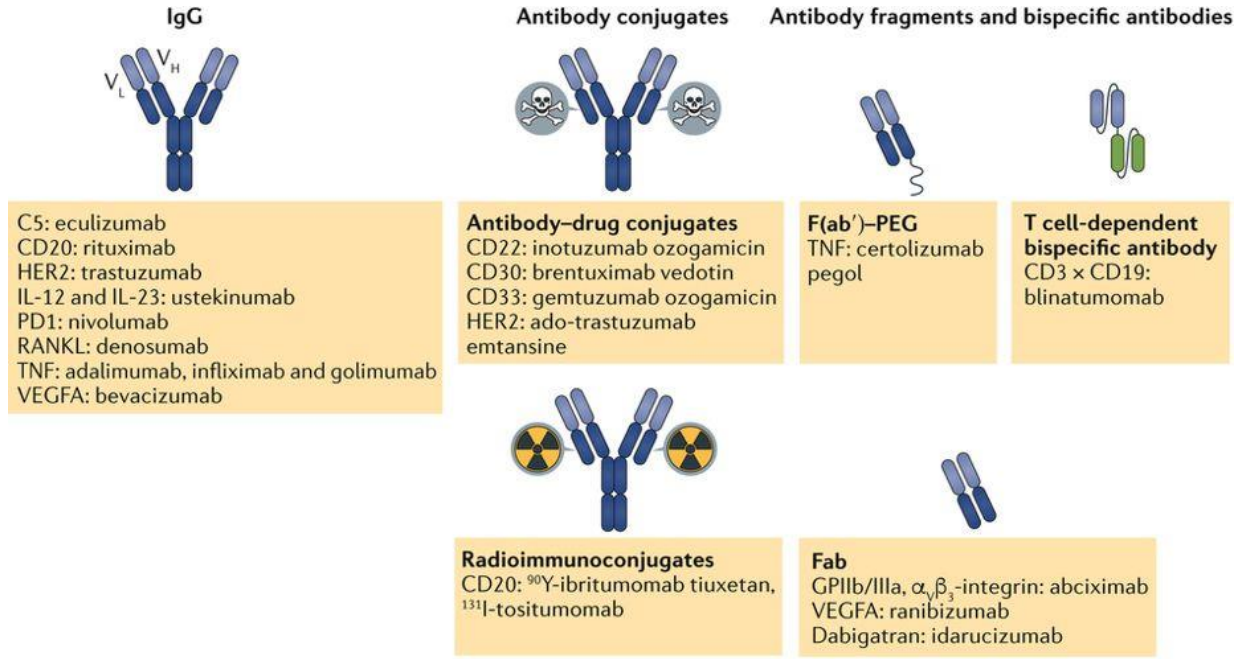
The number of checkpoint agonists and antagonists will expand and be used in combination



Meric-Bernstam et al. 2021 Lancet

More development and potential approvals of antibody-drug conjugates

Emerging antibody-drug conjugates	Target	Target cancer
Mirvetuximab soravtansine	Folate receptor	Ovarian cancer
Oportuzumab monatox/Vicineum	EpCAM	Bladder cancer
Indatuximab ravtansine	CD138	Multiple myeloma



Carter and Lazar 2018 Nat Rev Drug Discovery

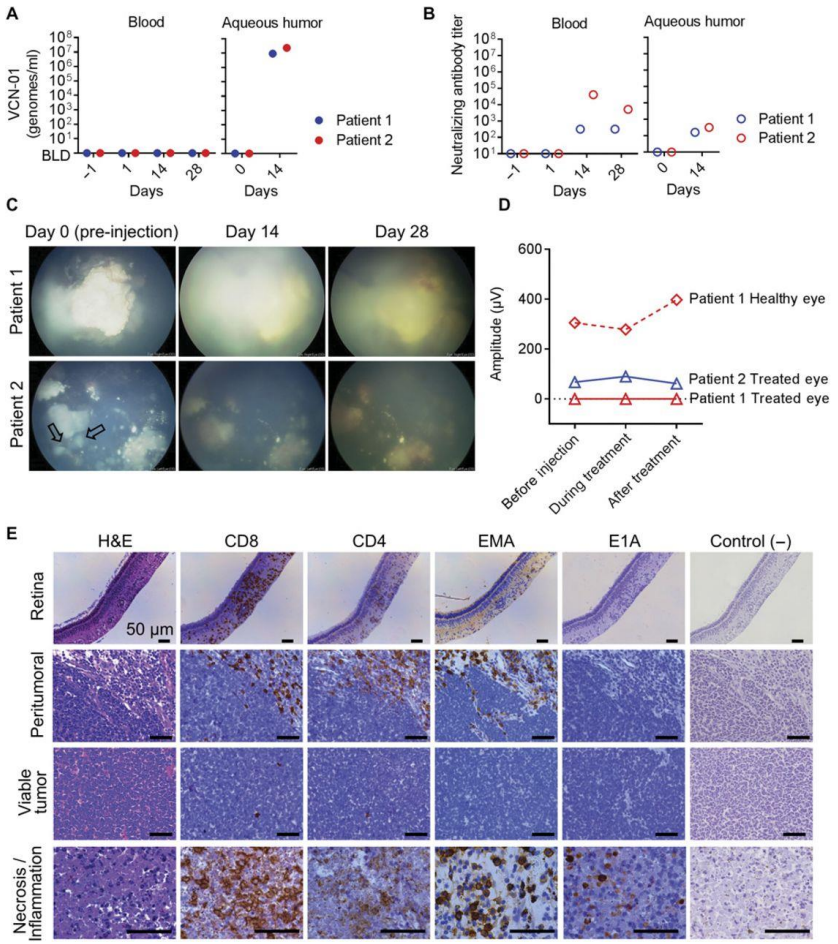
Oncolytic viral therapy will continue to expand viral agents, biologics, and target tumors

	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

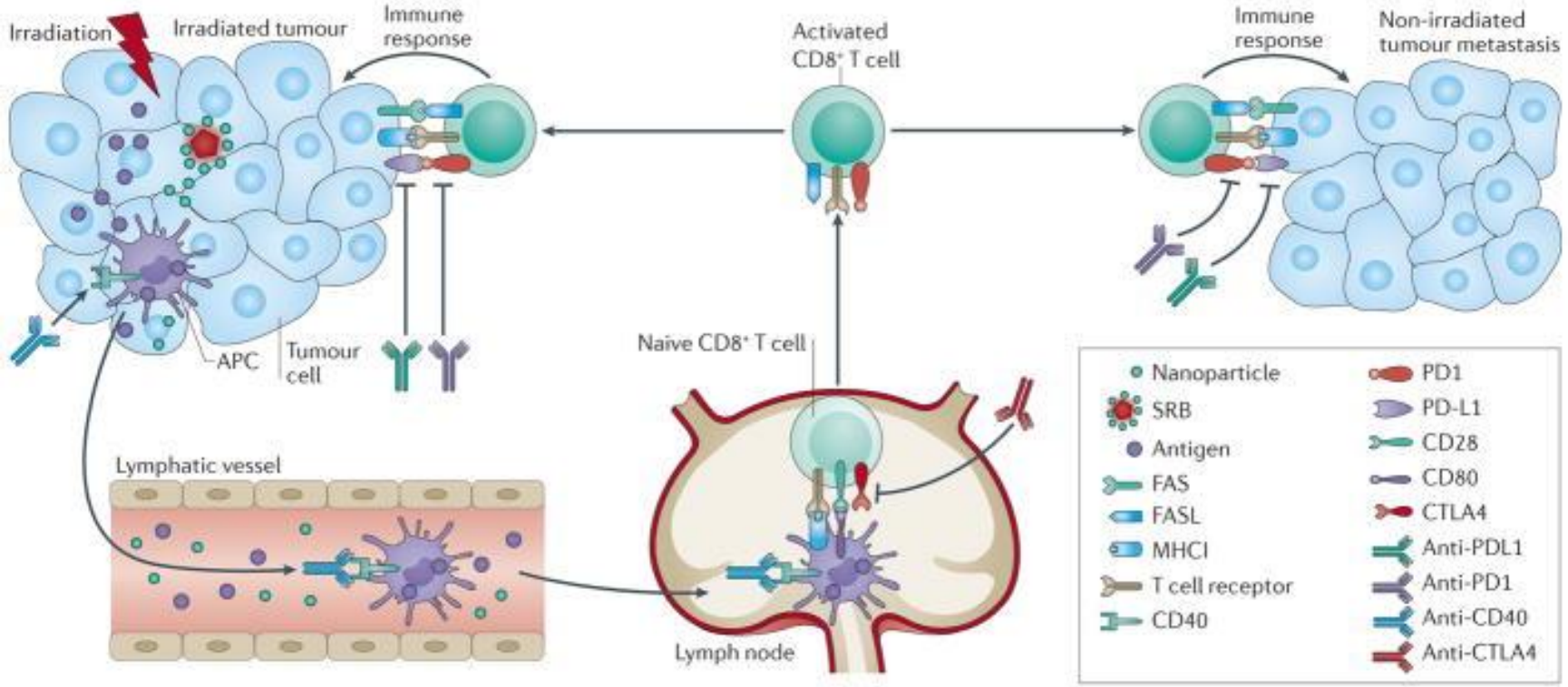
Oncolytic viral therapy will continue to expand viral agents, biologics, and target tumors



Guillem Pascual-Pasto et al., Sci Transl Med 2019;11:eaat9321

Science Translational Medicine
AAAS

Radiation therapy is immunogenic and can be safely combined with checkpoint inhibitor



Ngwa et al. 2018 Nat Rev Cancer

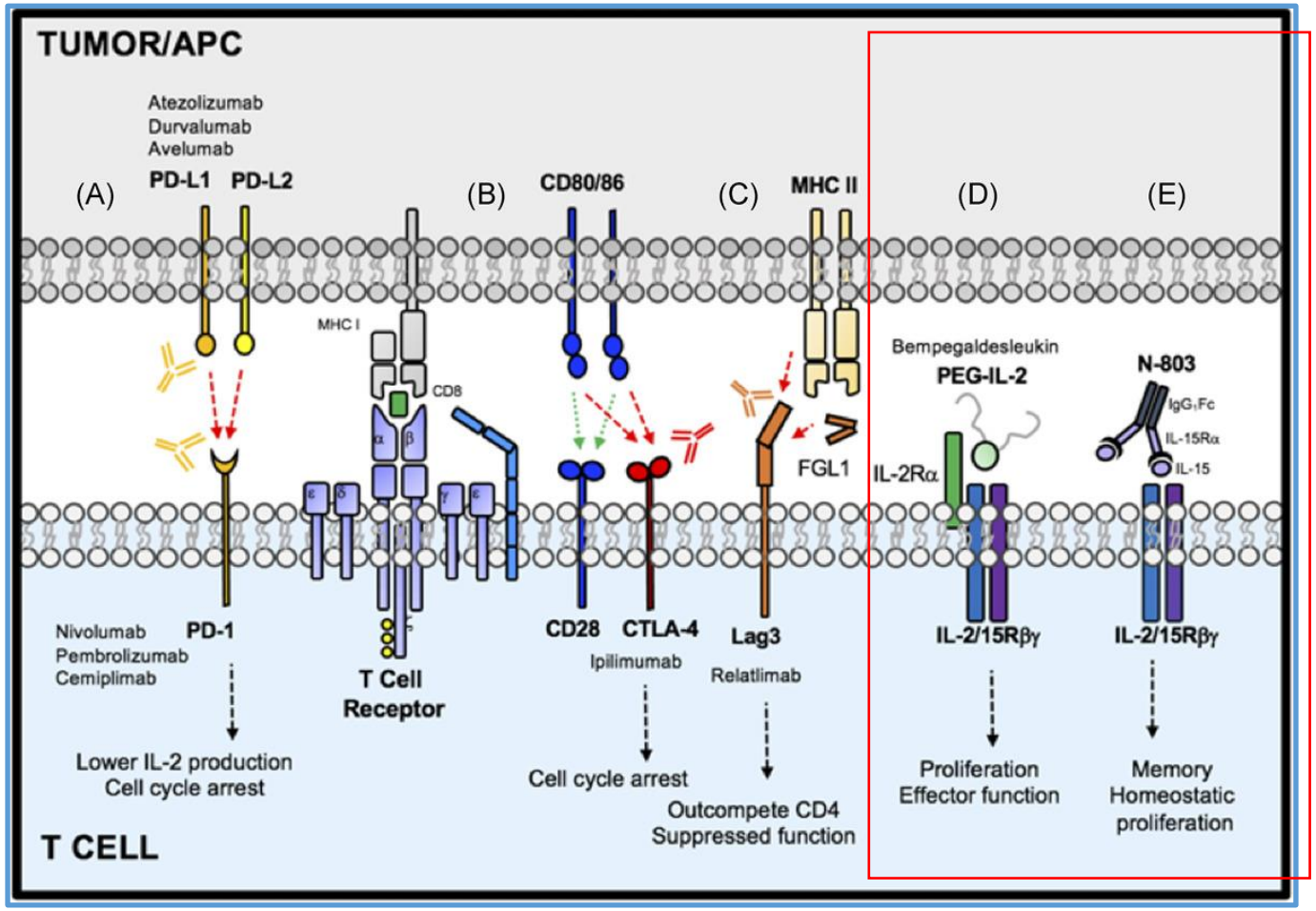
Radiation therapy will be increasingly used as a means of enhancing immunotherapy

Table 1. Summary of main prospective available data related to the efficacy of radiotherapy and ICI combination.

Population	Reference	Phase	Intervention	Results
Locally advanced NSCLC	[31]	I	Pembrolizumab + chemoradiotherapy	6-mo PFS rate = 81% 12-mo PFS rate = 69.7% Median PFS = 18.7 mo
Locally advanced NSCLC	PACIFIC [32–34]	III	Durvalumab (12 mo) as consolidation therapy vs. placebo (12 mo)	ORR = 28.4% vs. 16.0% ($p < 0.001$) Median PFS = 16.8 mo vs. 5.6 ($p < 0.001$) 36 months OS = 55.3% vs. 43.5%
Locally advanced NSCLC	[35]	II	Chemoradiation + pembrolizumab (12 mo) as consolidation therapy	Time to metastatic disease = 30.7 mo PFS = 18.7 mo OS = 35.8 mo
1–4 metastatic sites NSCLC	[36]	II	Pembrolizumab within 4–12 weeks after locally ablative therapy	Median PFS from the start of locally ablative therapy = 19.1 mo
Locally advanced HNSCC	[37]	I	Cisplatin-based chemoradiotherapy + pembrolizumab (concurrently + as maintenance)	CR (HPV+) = 85.3% CR (HPV−) = 78%
Locally advanced HNSCC	JAVELIN H&N 100 [38]	III	Avelumab + chemoradiotherapy + avelumab maintenance vs. Placebo + chemoradiotherapy + placebo maintenance	At the time of the interim analysis: no significant improvement in PFS or OS
Locally advanced HNSCC (cisplatin-unfit patients)	PembroRad [39]	II	Once-daily RT up to 69.9 Gy associated with: Cetuximab vs. pembrolizumab	Loco-regional-control at 15 mo = 59% vs. 50% ($p = 0.91$) 24-mo PFS = 40% vs. 42% ($p = 0.41$) 24-mo OS = 55% vs. 62% ($p = 0.5$)
Stage III/IV RCC	RADVAX RCC [40]	II	Nivolumab + ipilimumab + SBRT (40–50 Gy in 5 fractions)	PR = 56% SD = 24% PD = 16% 12-mo PFS rate = 36%
2nd or 3rd line RCC	NIVES [41]	II	Nivolumab + SBRT (10 Gy × 3 fractions 7 days after the 1st infusion of nivolumab)	ORR = 17.4% 12-mo median OS = 73.4%
Metastatic Melanoma	[42]	I	RT (6–8 Gy, 2–3 times) followed by ipilimumab injections	PR = 18% SD = 18%
Metastatic Melanoma	[43]	I	Ipilimumab + RT (between 18–50 Gy, in 1–15 fractions)	Clinical benefit = 50% PR = 15% CR = 15%
Metastatic Melanoma	[44]	I	Nivolumab + ipilimumab + extracranial RT (30 Gy in 10 fractions or 27 Gy in 3 fractions)	PR outside of the irradiated volume: 6/19 No progression of irradiated metastases

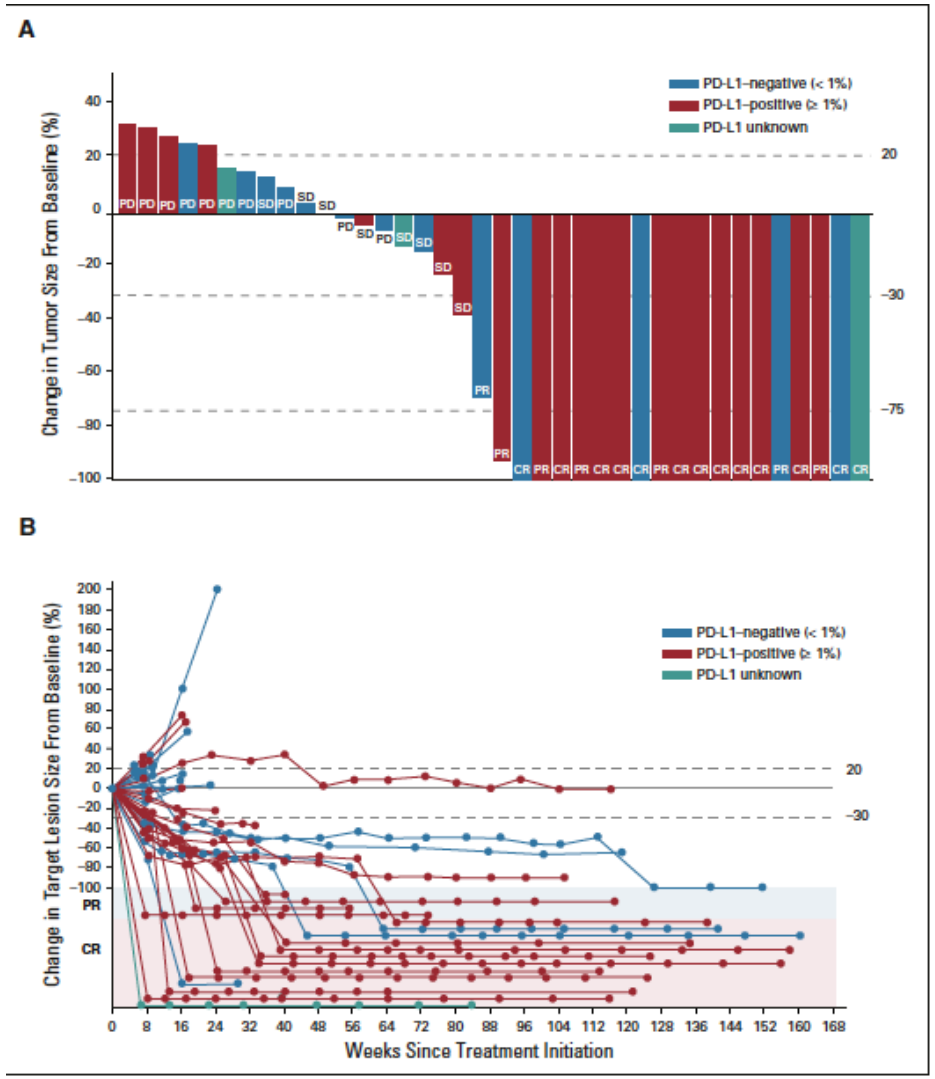
Procureur et al 2021 Cancers

Cytokine "superagonists" will emerge as adjuvants for combination immunotherapy



Keilson et al 2021 J Surgical Oncol

Bempegaldesleukin plus nivolumab for first-line metastatic melanoma



#SITCWinterSchool

Diab et al. 2021 J Clin Oncol

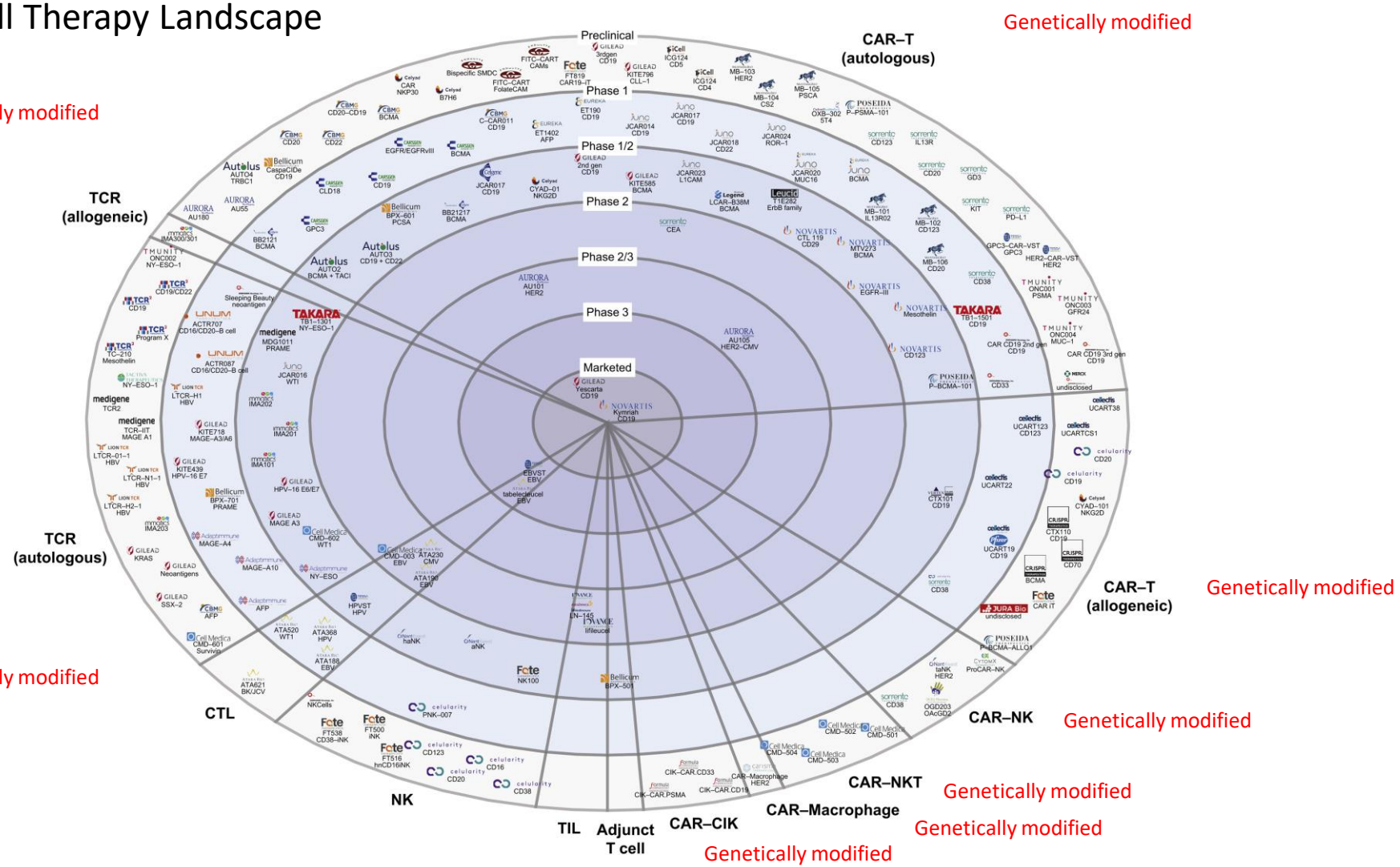
Tumor vaccines will re-emerge and become part of standard of care

Table 3 Select ongoing phase 3 studies evaluating cancer vaccines

Vaccine platform type	Product name	Antigen(s)	Identifier (phase, name)	Patient population	Enrollment	Regimens	Primary outcome measures
Cell-based (trivalent DC)	–	Autologous tumor stem cells, survivin, and hTERT	NCT03548571 (phase 2/3, DEN-STEM)	Glioblastoma IDH wild-type, with unmethylated MGMT-gene promotor	60	Trivalent DC immunization vs. radiotherapy with concomitant and adjuvant temozolomide	PFS
Peptide	GP96 heat shock protein-peptide complex	–	NCT04206254 (phase 2/3)	Liver cancer	80	GP96 vaccination after surgery vs. no treatment after surgery	2-year recurrence-free survival rate
Adenoviral vector containing the herpes simplex virus thymidine kinase gene	ProstAtak® (AdV-tk) + valacyclovir	–	NCT01436968 (phase 3)	Localized prostate cancer (intermediate risk or one NCCN high-risk feature) due to undergo standard prostate-only EBRT	711	ProstAtak® (AdV-tk) + valacyclovir + radiation therapy ± androgen deprivation therapy vs. placebo + valacyclovir + radiation therapy ± androgen deprivation therapy	DFS
Cell-based (bacterial)	BCG Tokyo-172 strain solution	–	NCT03091660 (phase 3)	Stage 0/0is/1 urothelial carcinoma	969	Tokyo-172 strain BCG (arm 2) vs. Tokyo-172 strain BCG solution with priming (arm 3) vs. TICE® BCG (arm 1)	Time to high-grade recurrence for arm 1 vs. arm 2, and arm 2 vs. arm 3
Cell-based (DCs)	DCs plus autologous tumor RNA	–	NCT01983748 (phase 3)	Stage T2, T3, or T4 melanoma of the uvea	200	Autologous DCs loaded with autologous tumor RNA vs. SOC	Prolongation of OS
Cell-based (tumor cell)	OncoVAX®	–	NCT02448173 (phase 3)	Stage II colon cancer	550	OncoVAX® and surgery vs. surgery	DFS
Oral vaccine (tablet) derived from pooled blood	Hepcortespenlisimut-L (Hepko-V5)	–	NCT02232490 (phase 3, Hepko-V5)	Advanced hepatocellular carcinoma	120	Hepcortespenlisimut-L vs. placebo	Changes in plasma AFP
Cell-based (bacterial)	BCG	–	NCT04165317 (phase 3)	High-risk non-muscle-invasive transitional cell carcinoma of the urothelium and complete resection of all Ta/T1 papillary disease	999	PF-06801591 + BCG induction and maintenance (arm A) vs. PF-06801591 + BCG induction only (arm B) vs. BCG induction and maintenance (arm C)	EFS (arm A vs. arm C and arm B vs. arm C)

Morse et al. 2021 Target Oncol

Immune Effector Cell Therapy Landscape

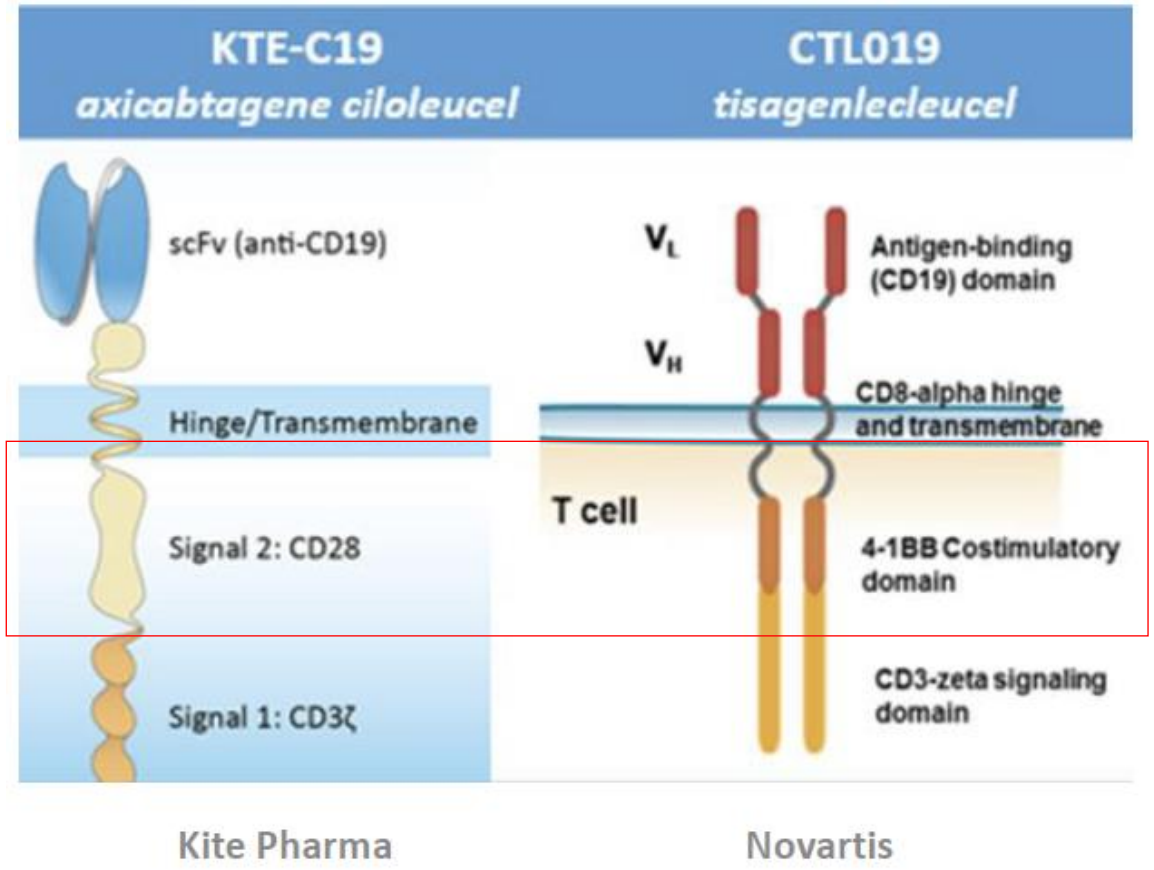


Cauchon et al. 2019 *J Pharm Sciences*

#SITCWinterSchool

Current FDA approved CAR T cells

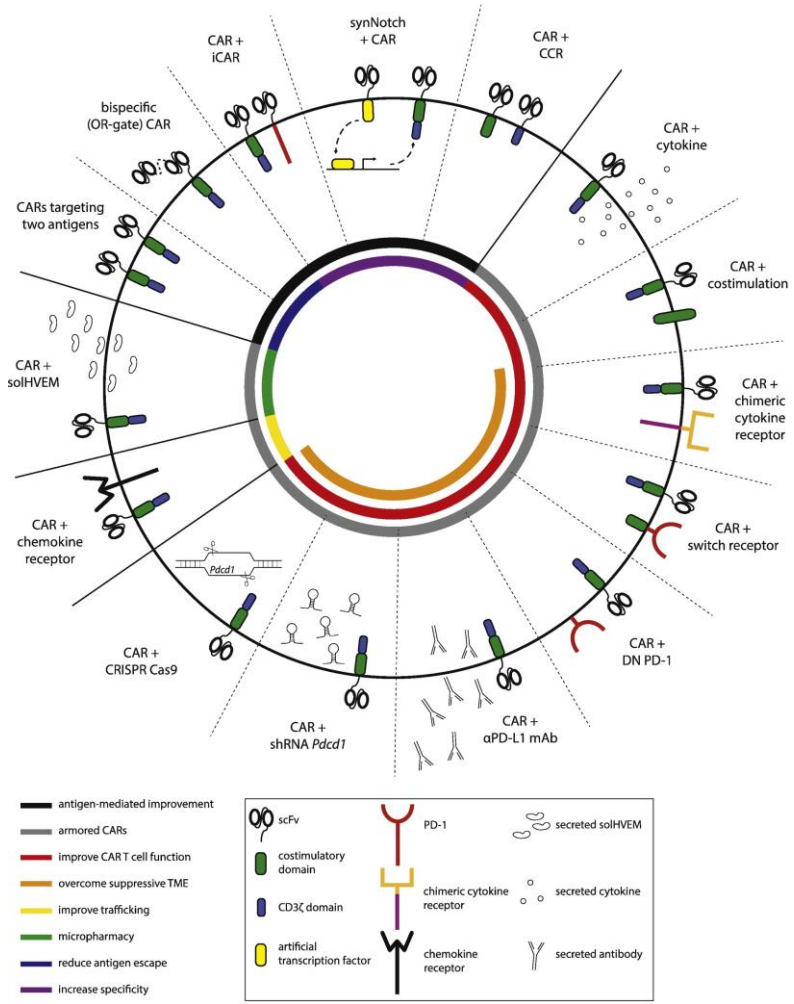
- Tisagenlecleucel (Kymriah)
  - Children with B cell leukemia
  - Adults with non-Hodgkin B cell lymphomas
- Axicabtagene clioleucel (Yescarta)
- Brexucabtagene autoleucel (Tecartus)
- Lisocabtagene maraleucel (Breyanzi)
  - Adults with non-Hodgkin B cell lymphomas
- Idecabtagene vicleucel (Abecma)
  - Multiple myeloma



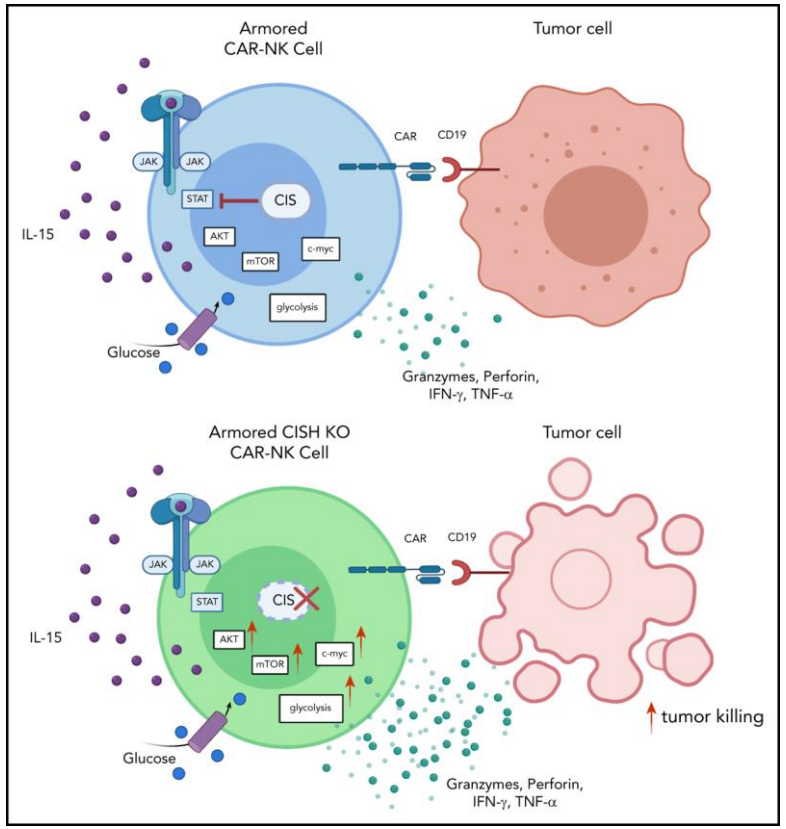
Yescarta
- CD28 costimulation
- More rapid killing
- Infused as inpatient
- Less persistence

Kymriah
- CD137 costimulation
- Gradual killing
- Infused as outpatient
- Better persistence

Enhanced engineering of CAR T and CAR NK will help reduce side effects while improving efficacy

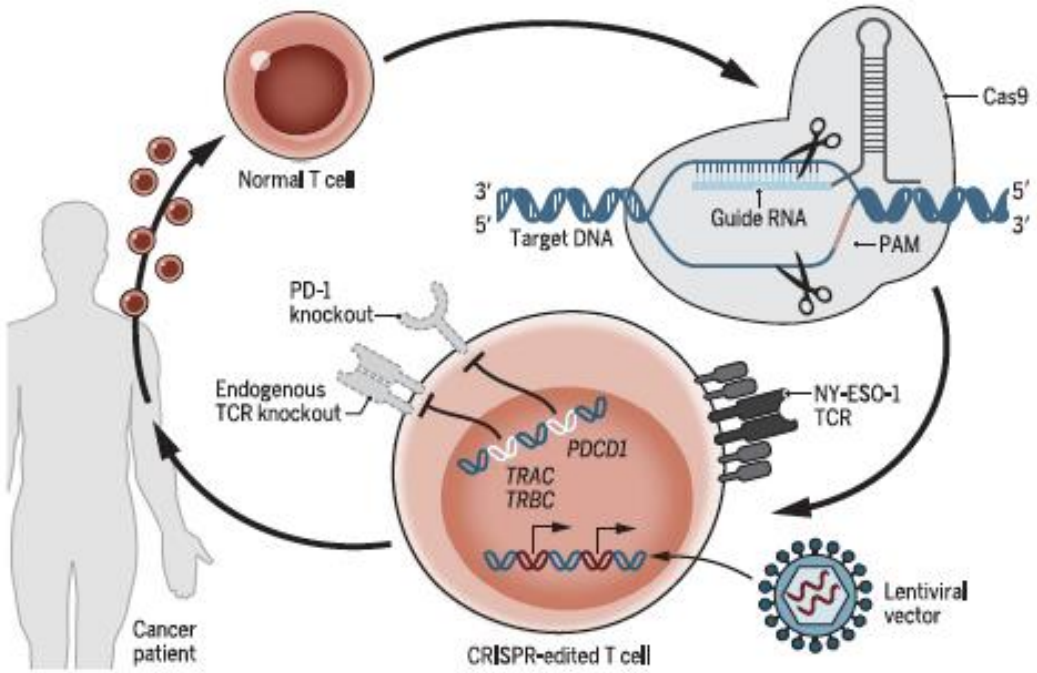


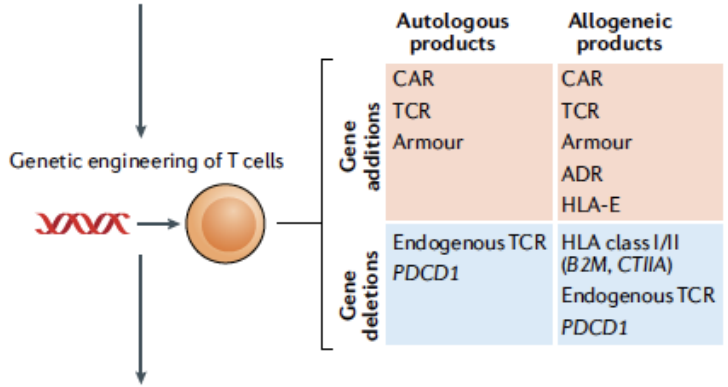
Jaspers and Brentjens 2017 Pharmacol Ther



Daher et al Blood 2021

CRISPR-based editing of immune effector cells





Science
AAAS

Edward A. Stadtmauer et al. Science 2020;367:eaba7365

Ellis et al. 2021 Nat Reviews Genetics

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)

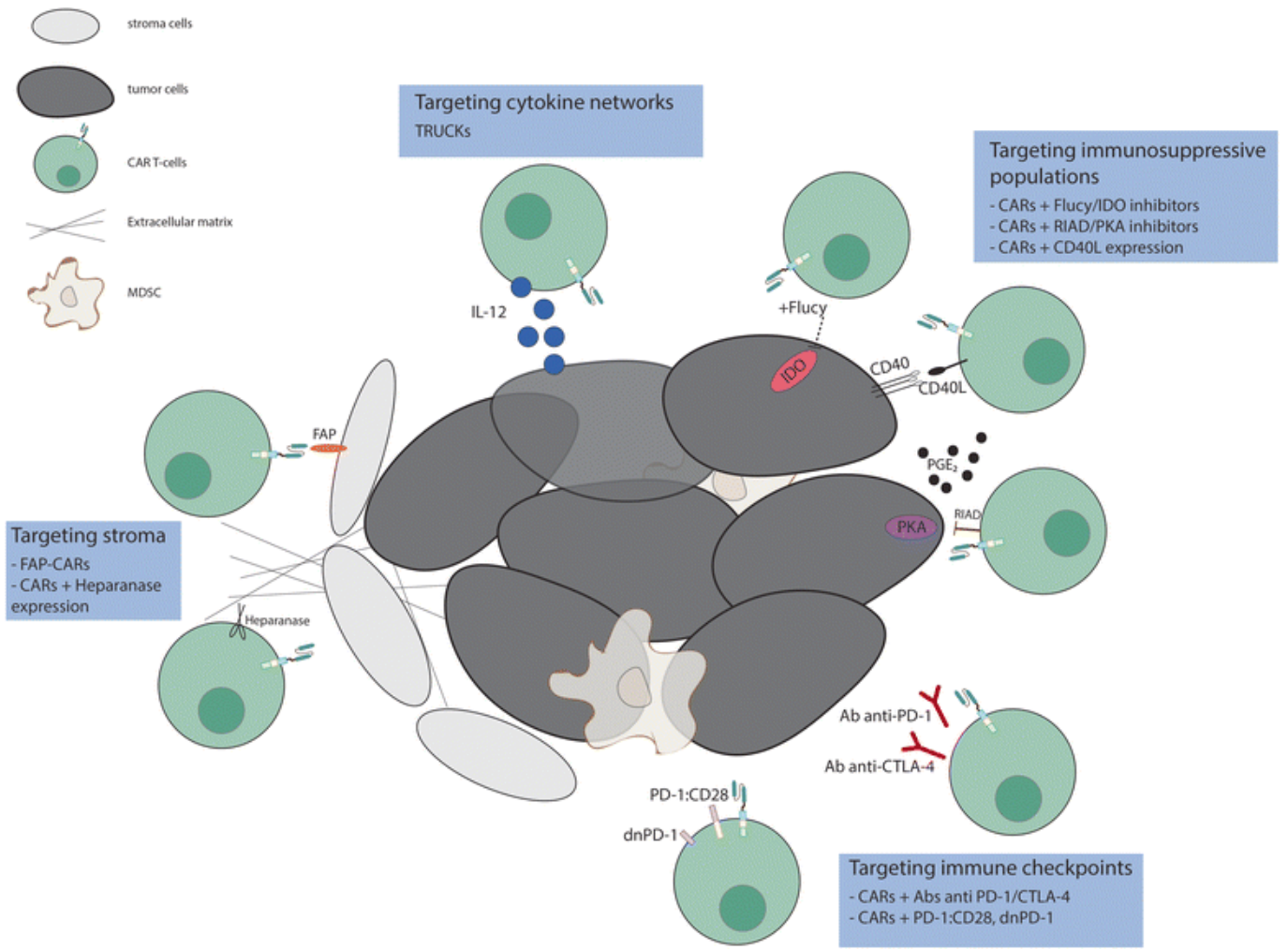
- **CD5** (T cell cancers)
- **CCR4** (T cell cancers)
- **CD7** (T cell and myeloid cancers)

- **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)

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)

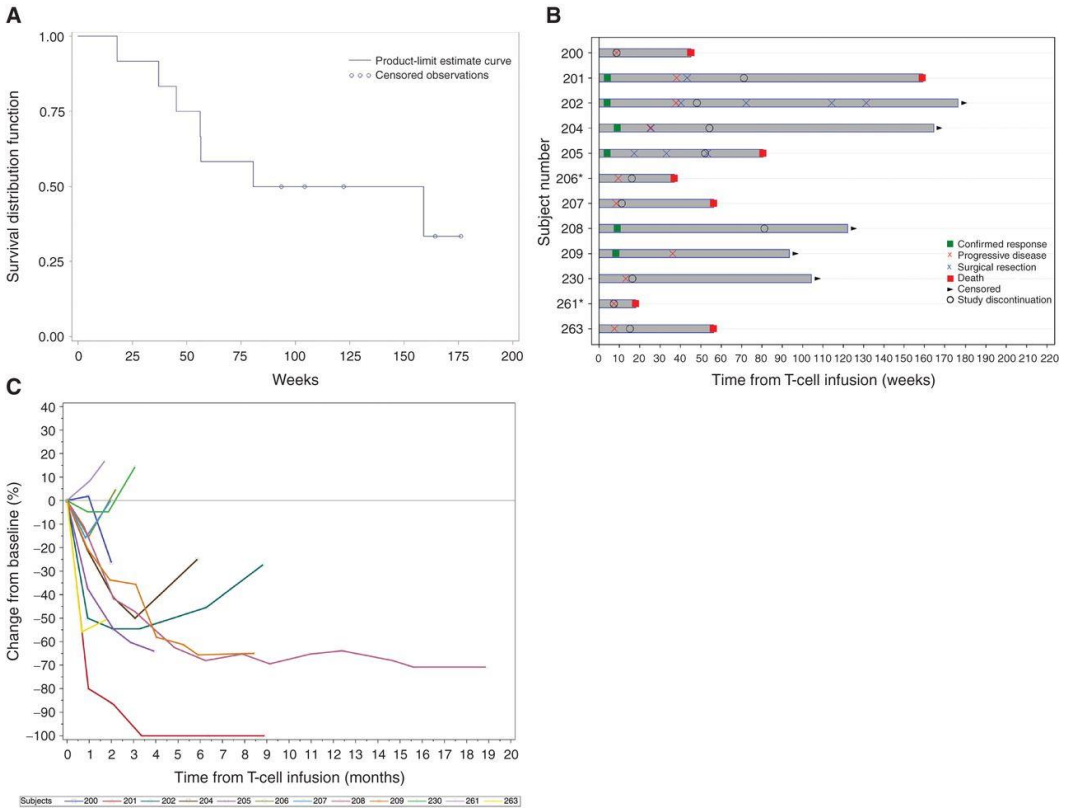
Combination strategies to improve CAR efficacy will be used for solid tumors



Scarfo and Maus 2017 J Immunother Cancer

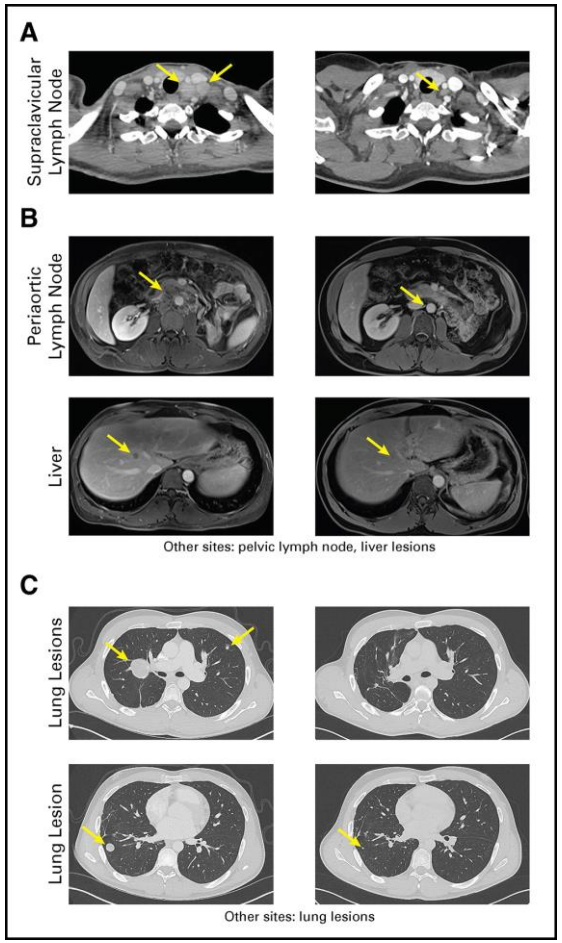
TCR transduced T cells will provide durable responses in solid tumors

NY-ESO-1



D'Angelo et al. 2018 Cancer Discov

MAGE-A3



29 months

18 months

4 months

Lu et al. 2017 J Clin Oncol

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.