NASDC
NCI Awardee Skills Development Consortium

Bispecific Antibodies As Cancer Therapeutics

Sandra P. D'Angelo, MD
Associate Attending, Research Director • Sarcoma Medical Oncology
Memorial Sloan Kettering Cancer Center

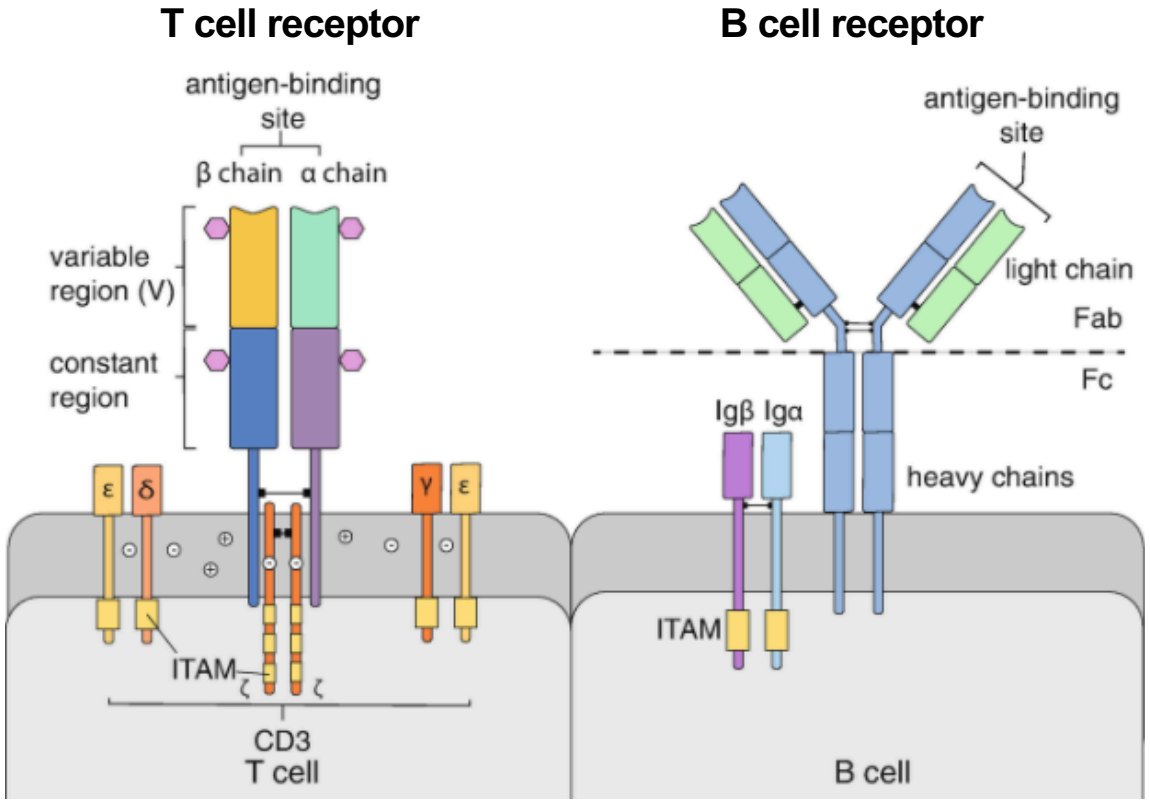
Outline

Background

Bispecific antibodies

- Developmental history
- What are they
- How do they work
- Types
- Targets
- Future directions

B cell receptors and T cell receptors provide specificity to the immune response

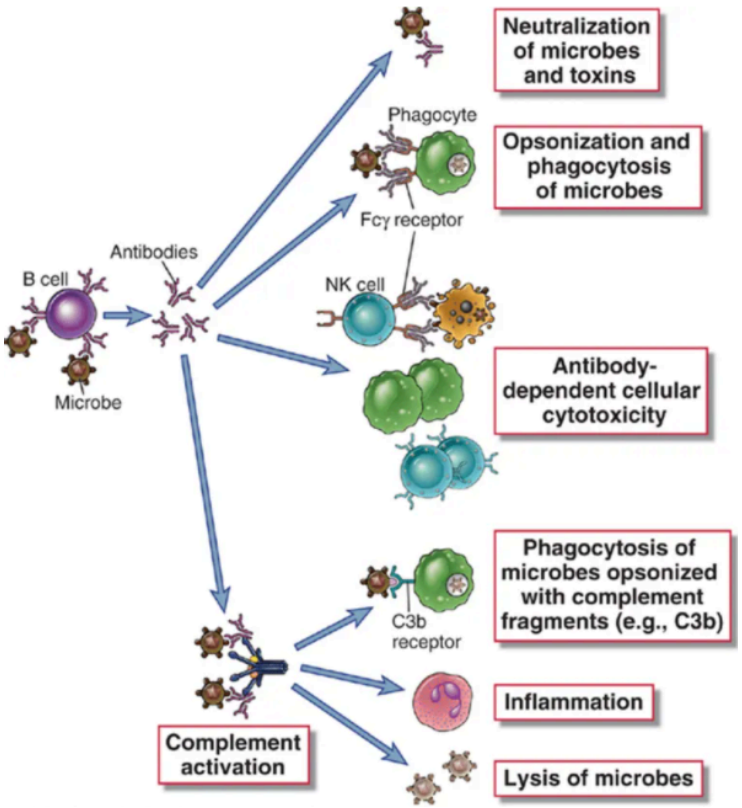


Kavathas et al. Adaptive Immunity, Immunoepidemiology 2019

How do antibodies work?

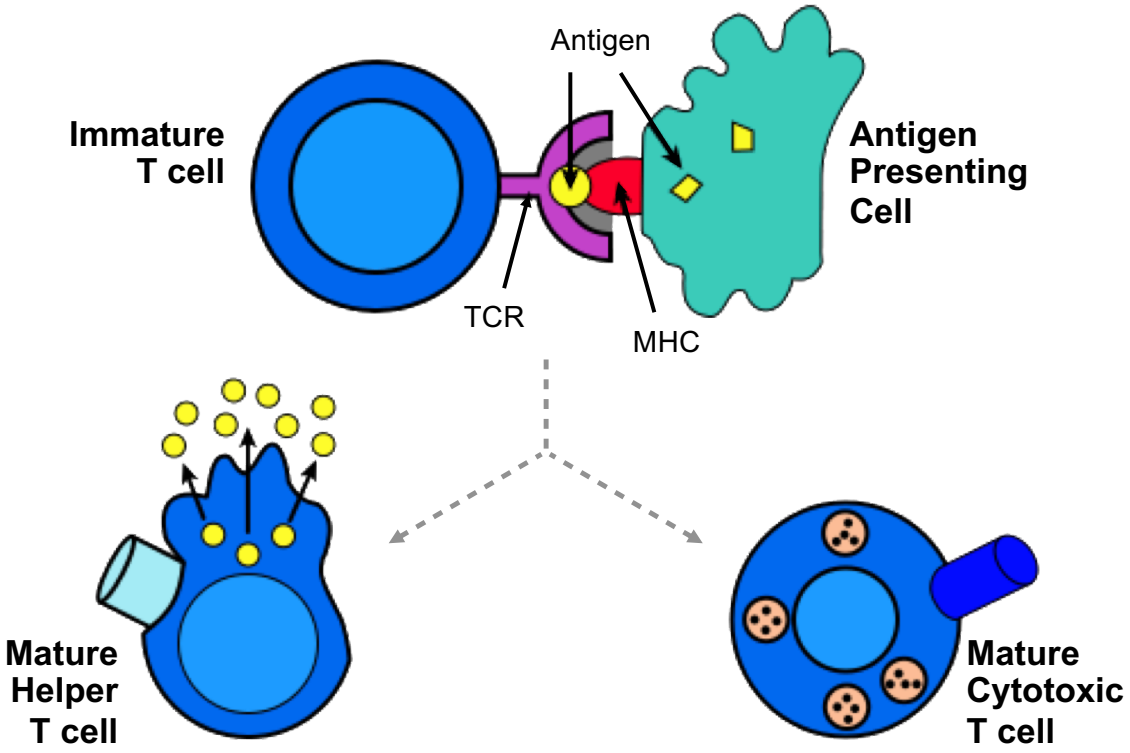
» Recognize and bind antigen

» Induce immune response after binding

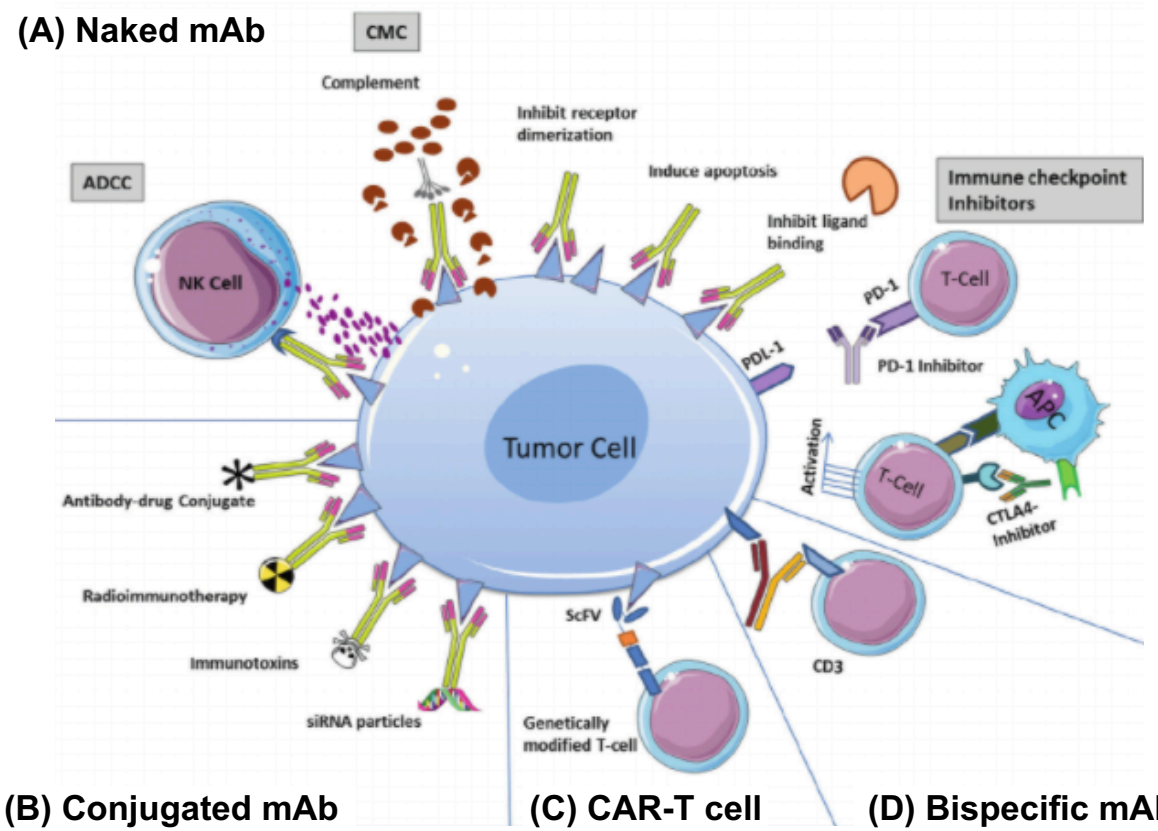


Abbas et al. Cellular and Molecular Immunology, 7e. 2012

How do cytotoxic T cell work?

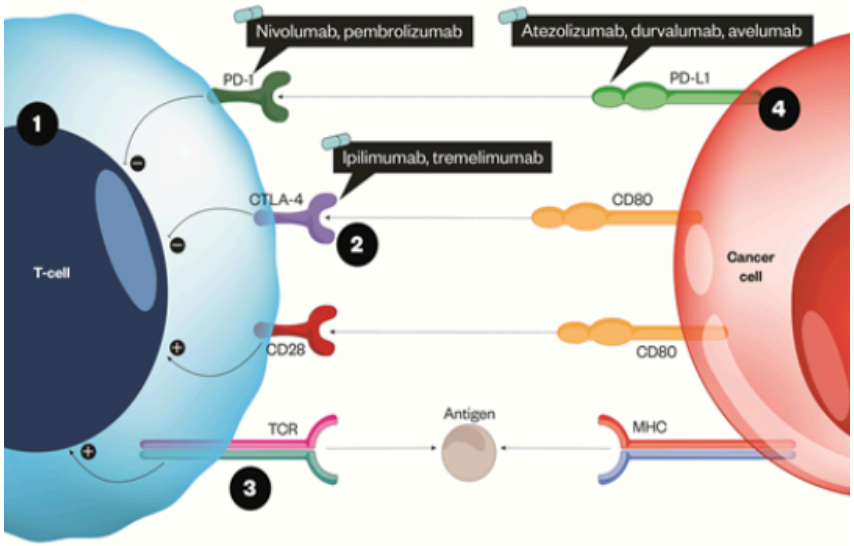


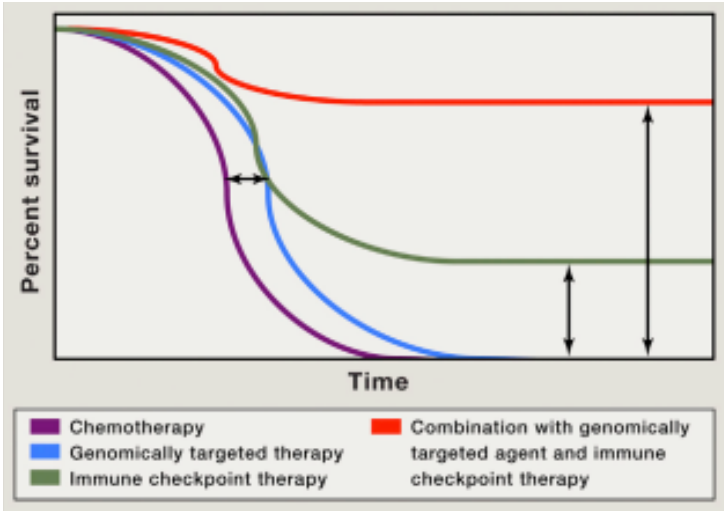
Antibody therapies for cancer targeting



Charmsaz et al. Experimental Hematology 2017

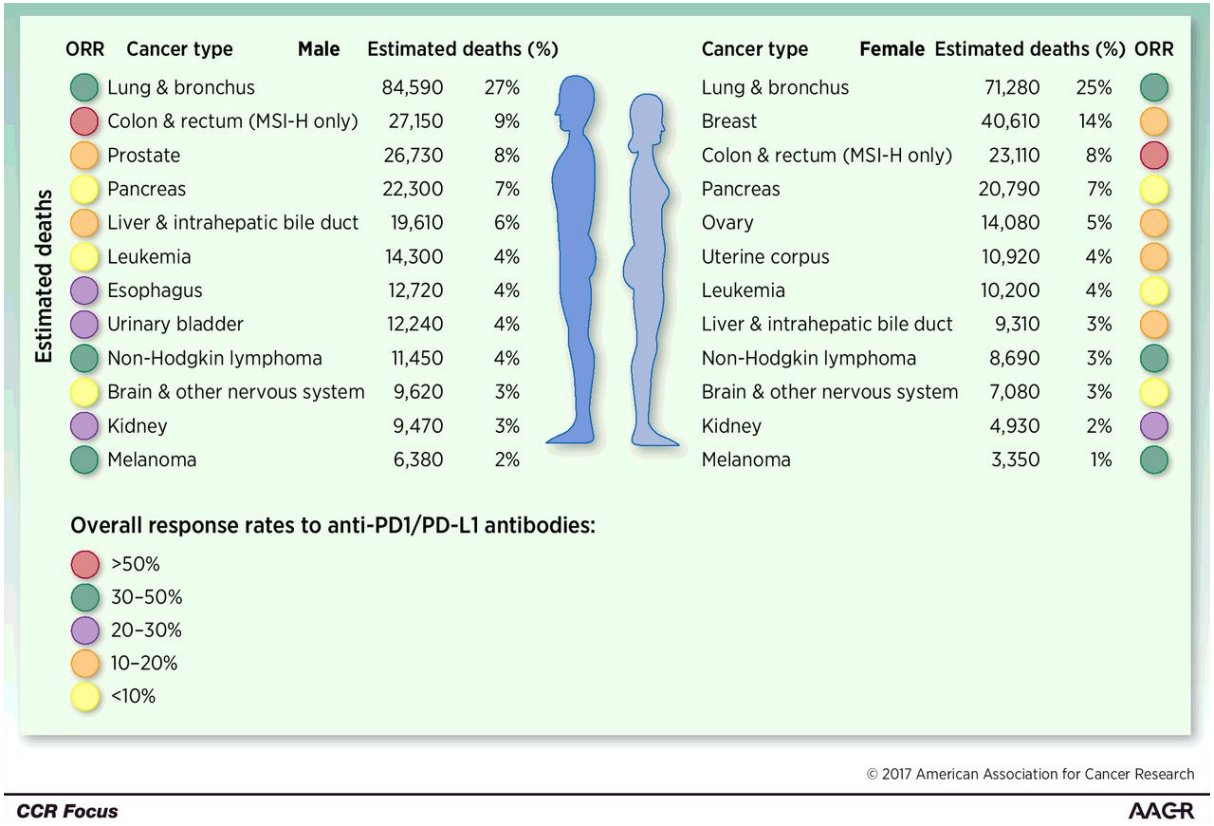
Immune checkpoint inhibitors





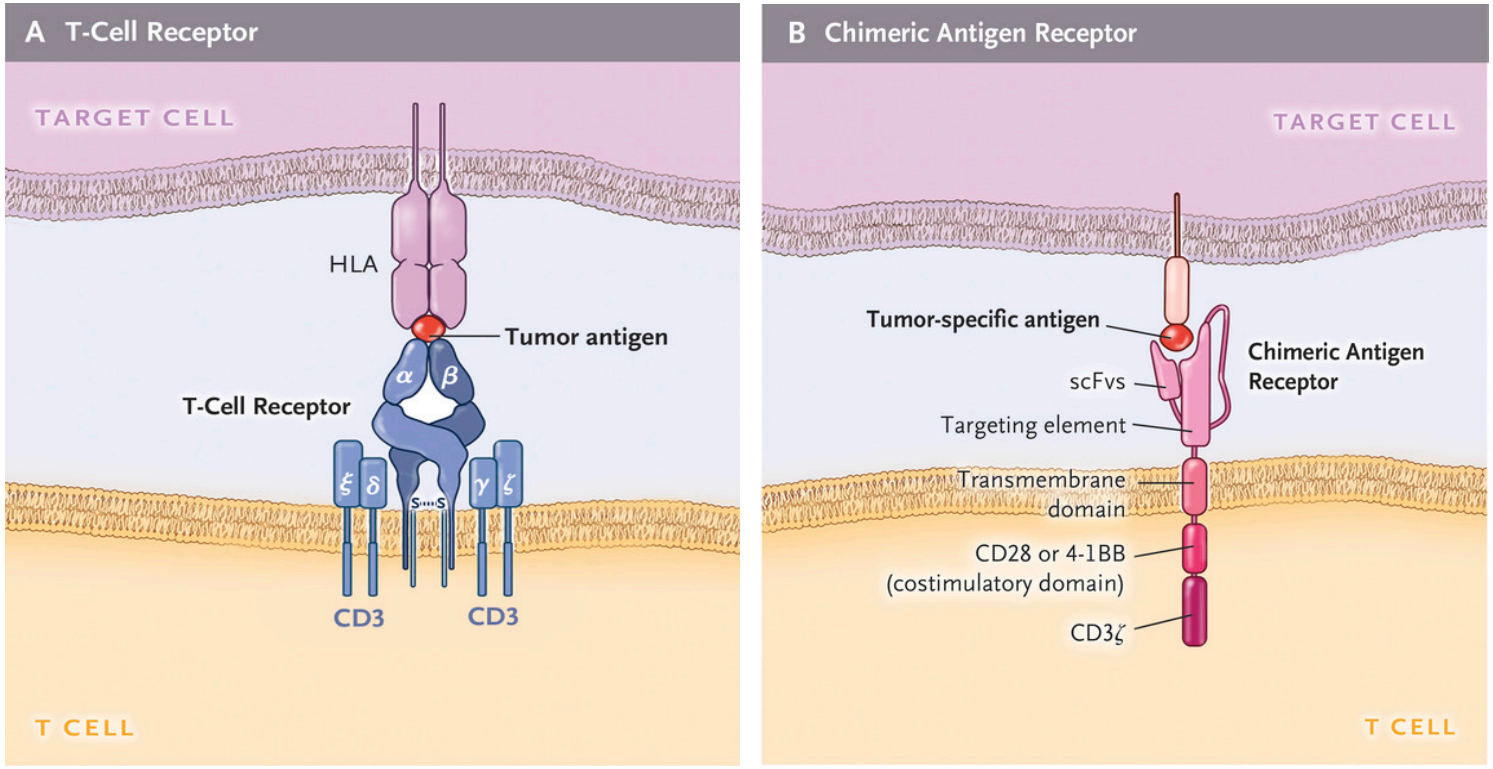
Evans et al. Pharmaceutical Journal 2018, Sharma et al. Cell 2015

Checkpoint inhibitors FDA approved for numerous malignancies but with 10-30% ORR



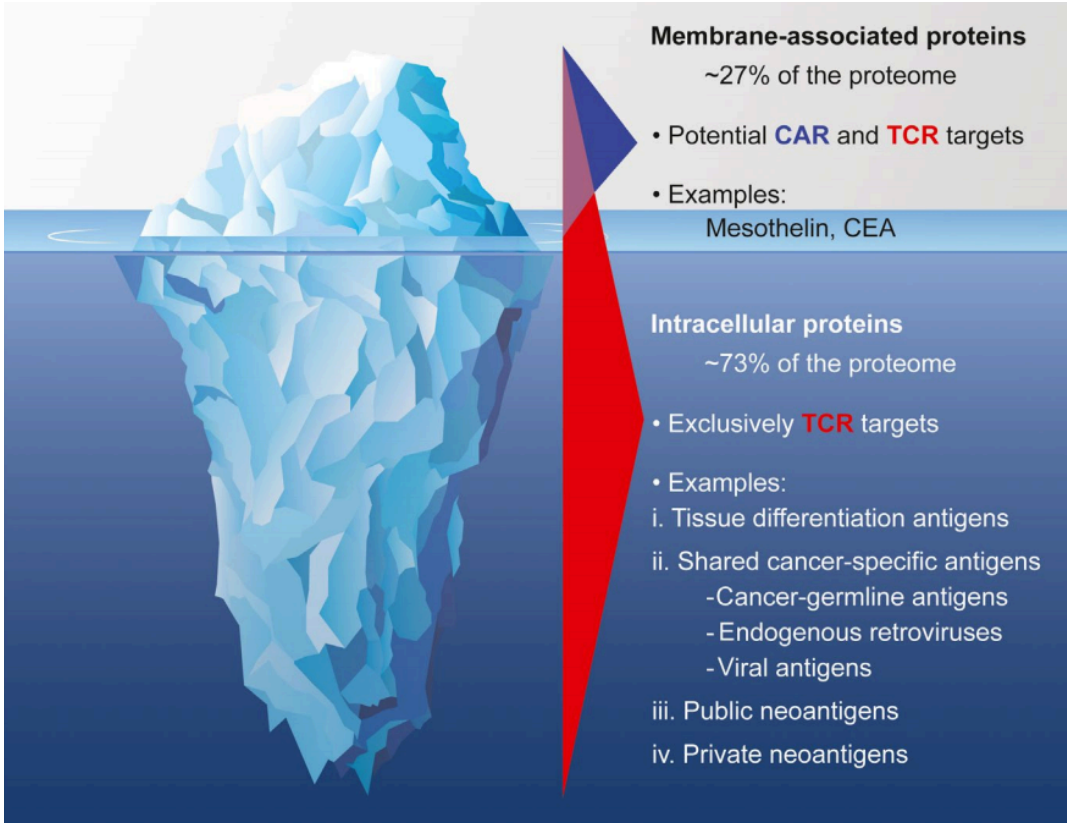
Lillian L. Siu et al. Clin Cancer Res 2017

T cell receptors and chimeric antigen receptors



June C et al. NEJM 2018

TCRs vs CARs



Memorial Sloan Kettering Cancer Center

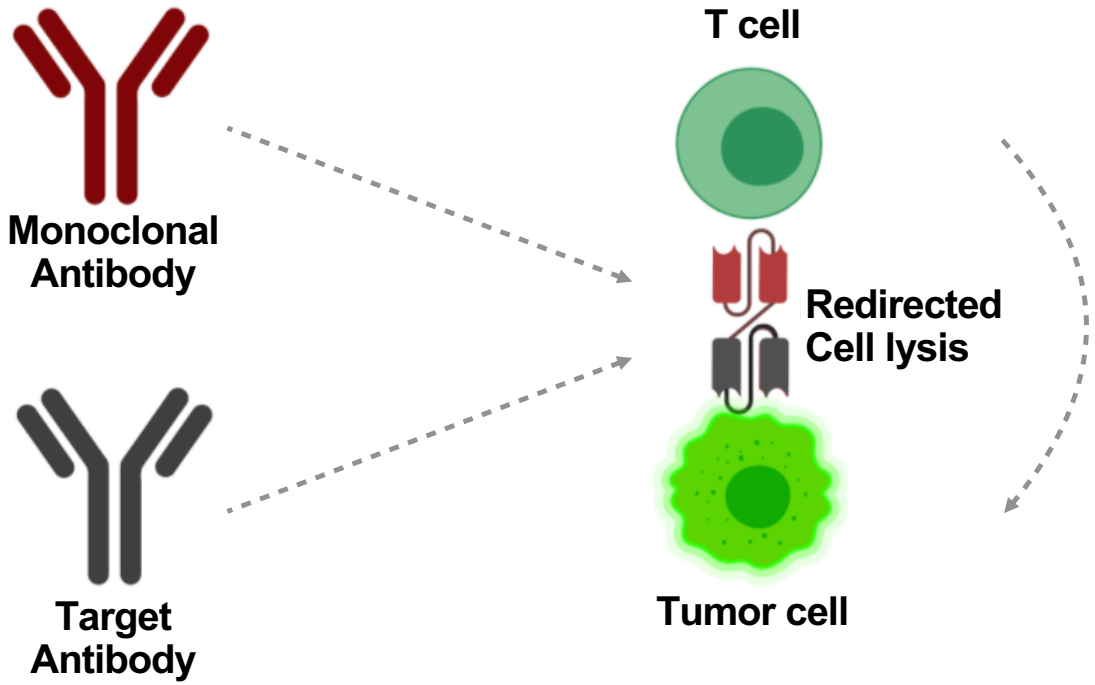
Klebanoff et al.
Immunological Reviews 2019

Barriers/Challenges in developing Adoptive T cell therapies in solid tumors

Adapted from Weber et al. Cell 2020

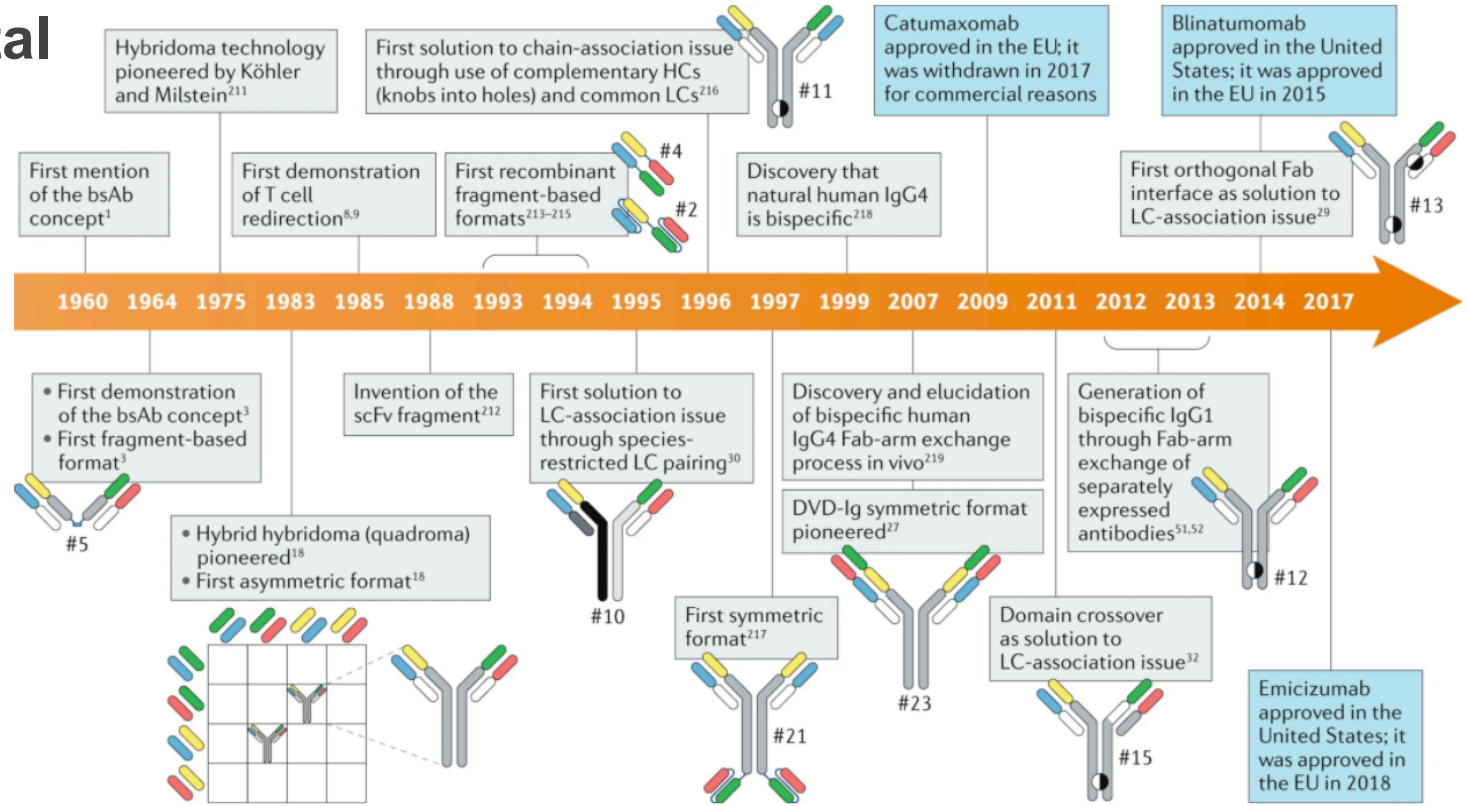
What is Bispecific Antibody?

Engineered protein composed of antigen binding fragments from 2 different monoclonal antibodies



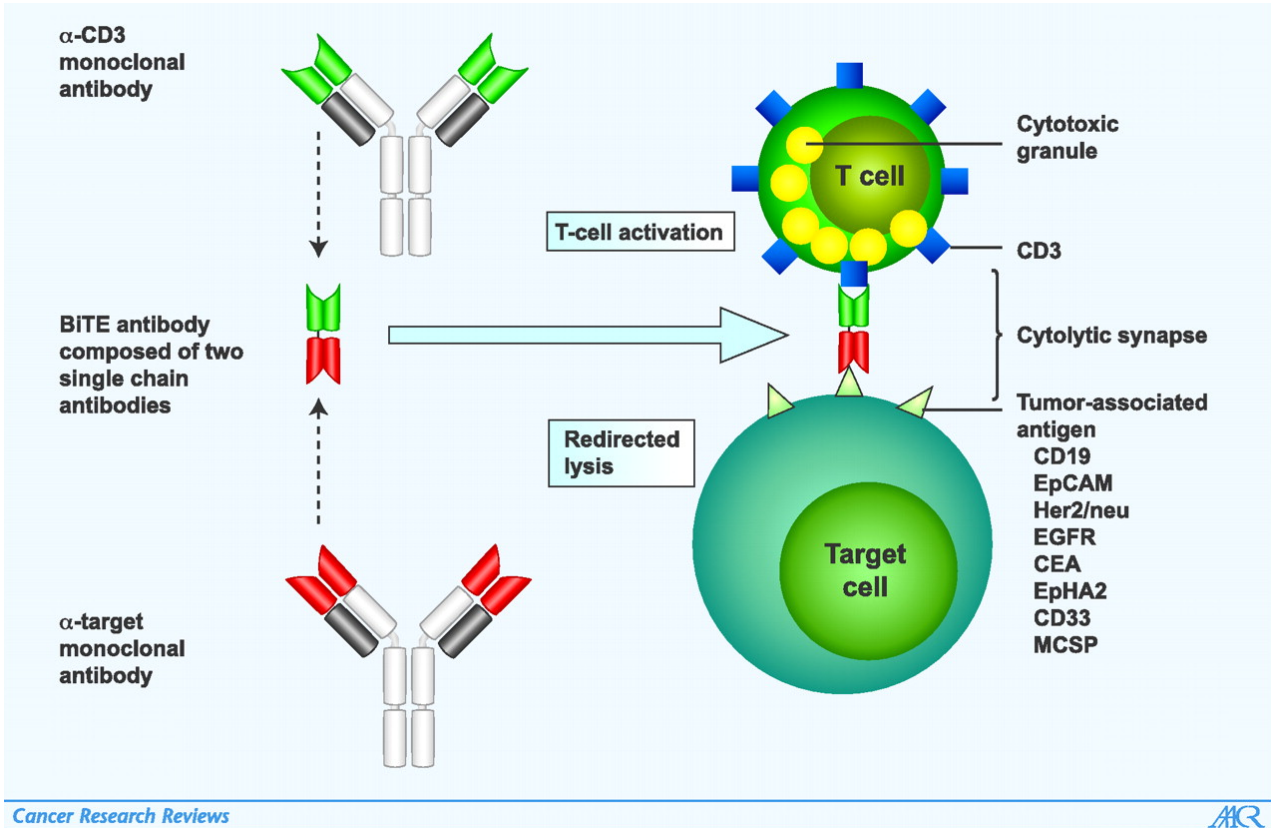
Patrick A et al. Cancer research 2009

Developmental history of bispecific antibody



Labrijn A et al. Nature Review 2019

How do they work?

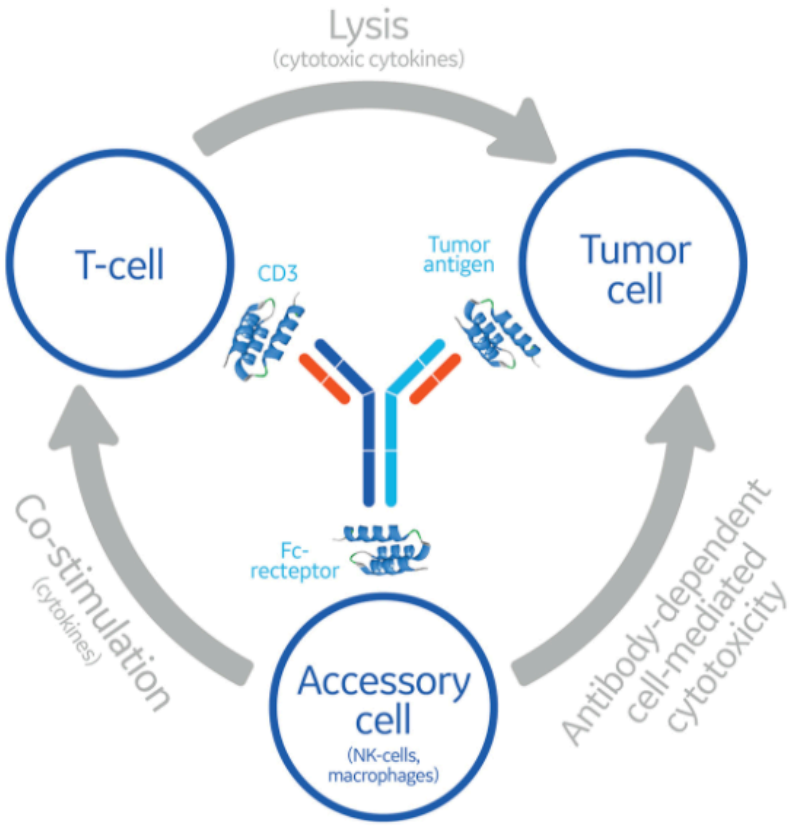


Patrick A et al. Cancer research 2009

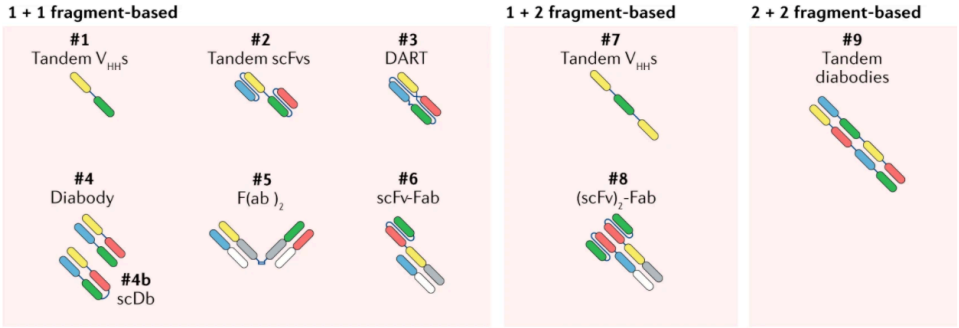
Advantages of bispecific antibodies

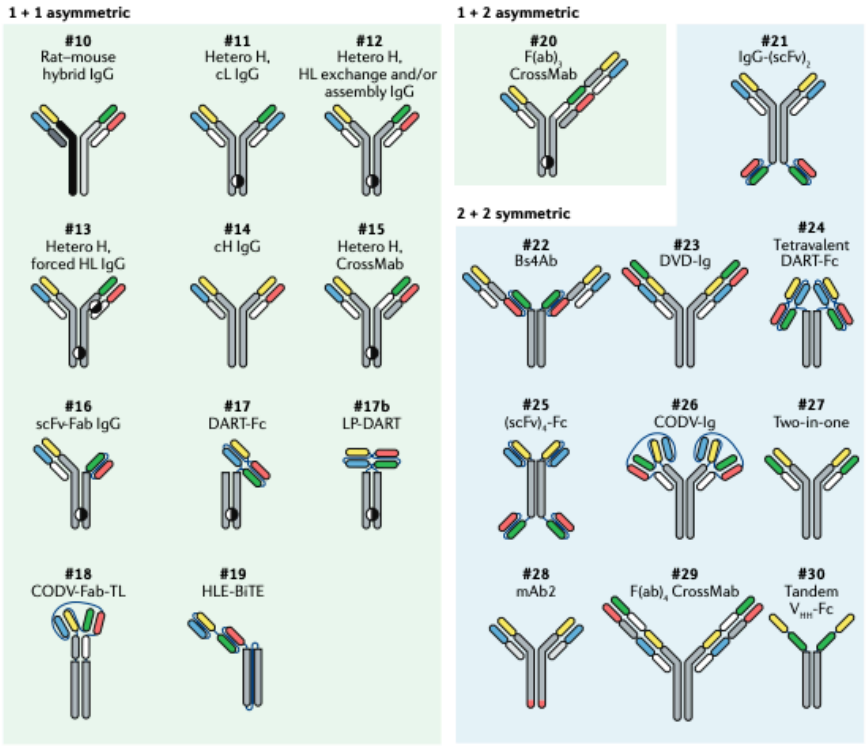
Attach to 2 different proteins at the same time

Brings the cancer cells and immune cells together which is thought to cause the immune system to attack cancer cells



Bispecific antibody formats

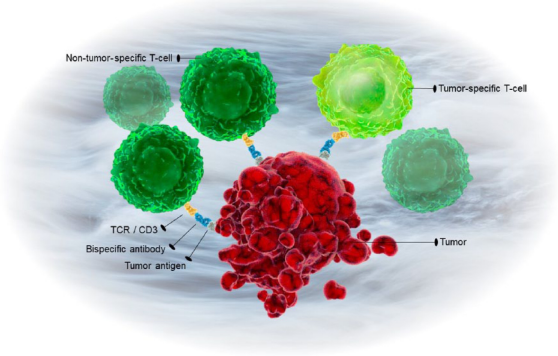




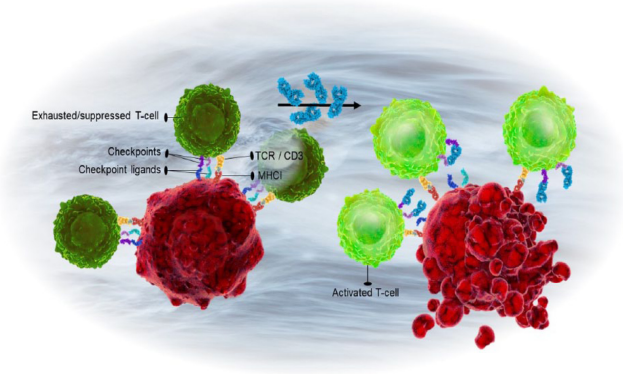
Patrick A et al. Cancer research 2009

Classes of Bispecifics

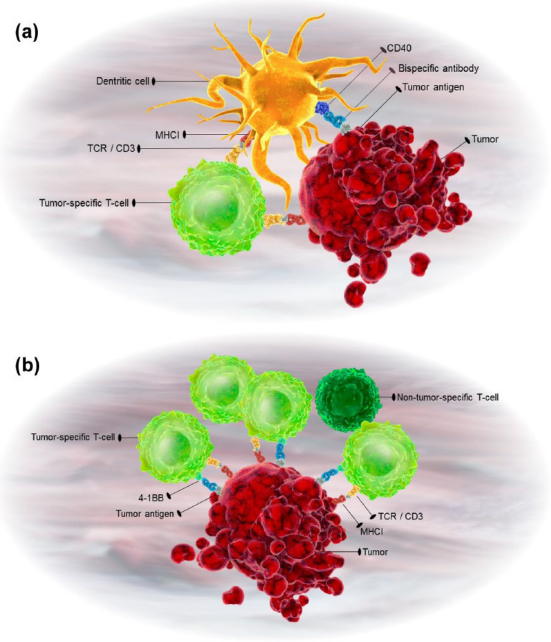
Cytotoxic effector cell redirectors (T and NK cells)



Dual immunomodulator



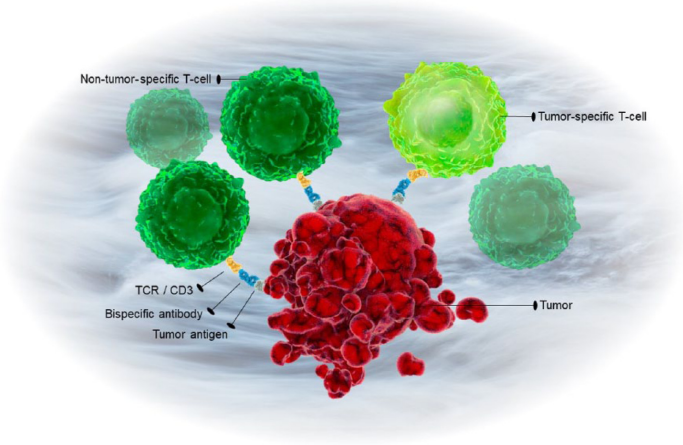
Tumor targeted immunomodulators



Dahlen E et al. Therapeutic Advances in Vaccines and immunotherapy. 2018

T cell Redirectors

Redirect T cells to malignant cells by targeting a tumor antigen and CD3

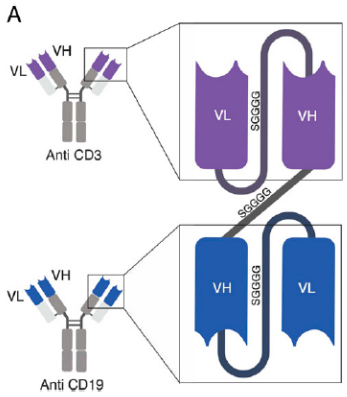


Dahlen E et al. Therapeutic Advances in Vaccines and immunotherapy. 2018

Target	Example	Stage
CD19 x CD3	Blinatumomab	Market
EpCAM x CD3	Catumaxomab	Market (withdrawn)
CD20 x CD3	XmAb13676, BTCT4465A, R07082859	I
CD123 x CD3	MGD006, JNJ-63709178, Xmab14045	I
BCMA x CD3	JNJ-64007957, BI836909	I
B7H3 x CD3	MGD009	I
CEA x CD3	R06958688, MT111	I
PSMA x CD3	Pasotuximab, ES414/MOR209	I

Blinatumomab

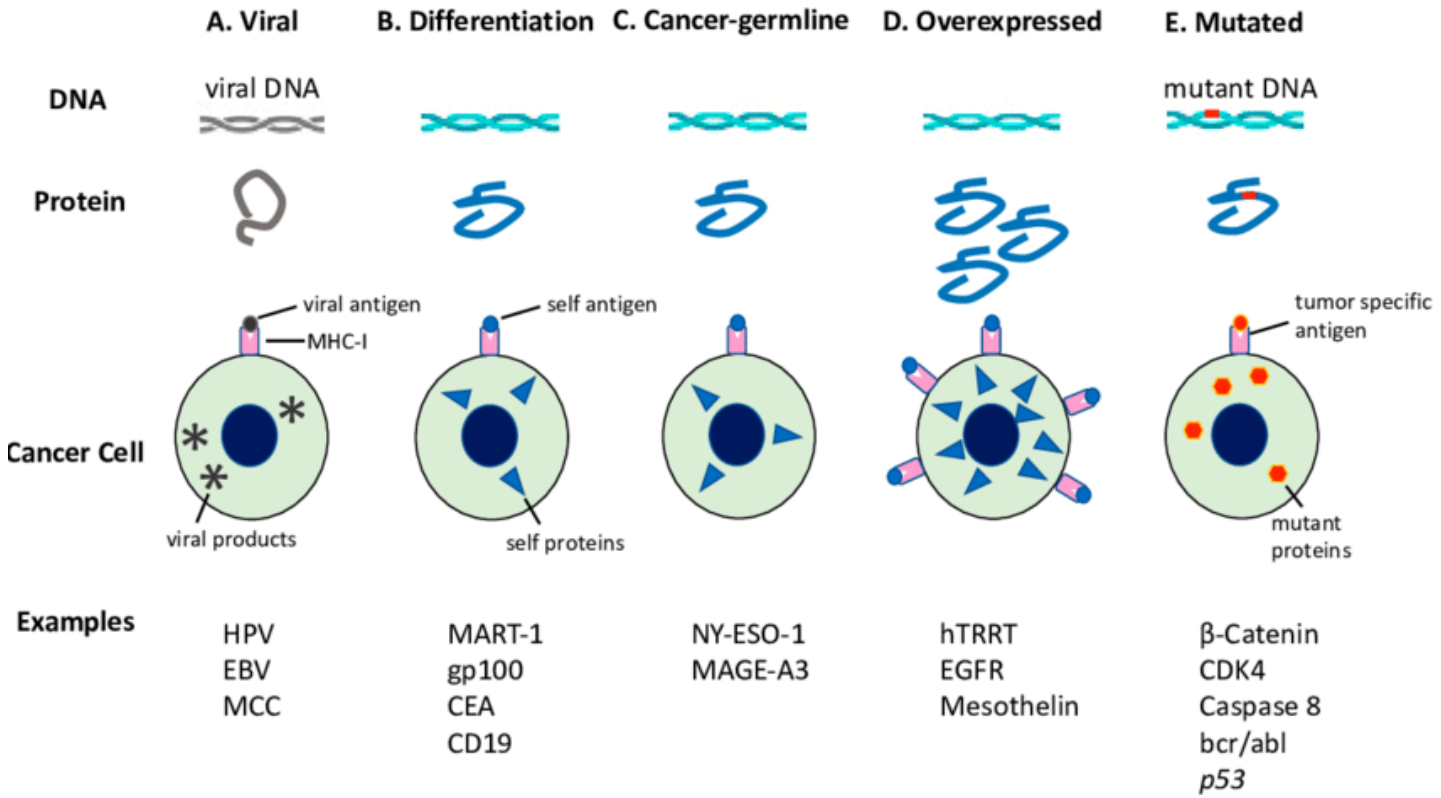
Bispecific T-Cell engager for precursor B-cell acute lymphoblastic leukemia



Population	N	Regimen	Prior HSCT	≥ 2nd Salvage	Response	MRD Response	Median Overall Survival	Grade 3+ CNS (%)	Grade 3+ CRS (%)
R/R Ph-	36	BLN	42%	21%	CR/CRh: 69%	88%	9.8	16%	6%
R/R Ph-	189	BLN	34%	39%	CR/CRh: 43%	82%	6.1	11%	2%
R/R Ph-	405	BLN vs CT	34%	45%	CR: 34% CR/CRh/CRi: 44%	76%	7.7	9%	5%
R/R Ph-	84	h-CVD, INO, ± BLN	23%	42%	CR/CRi/CRp: 80%	80%	11.0	–	–
R/R Ph+	45	BLN	44%	82%	CR: 31% CR/CRh: 36%	88%	7.1	7%	0%
MRD+	21	BLN	0%		–	80%	–	19%	0%
MRD+	116	BLN	0%	36%	–	78%	36.5	13%	2%
Frontline, Ph-, younger	27	H-CVAD + BLN	–		CR: 100%	96%	89% (1y OS)	17%	5%
Frontline, Ph-, older	64	h-CVD, INO, ± BLN	–		CR/CRi/CRp: 98%	94%	54% (3y OS)	–	–
Frontline, Ph+	63	BLN + TKI	–		CMR/PNQD: 80%	100%	94% (1y OS)	–	–

Franquiz M et al. Biologics 2020.

Tumor Antigens



Memorial Sloan Kettering Cancer Center

Yarchoan et al, Nature Reviews Cancer 2017
Goto et al. Vaccines 2019

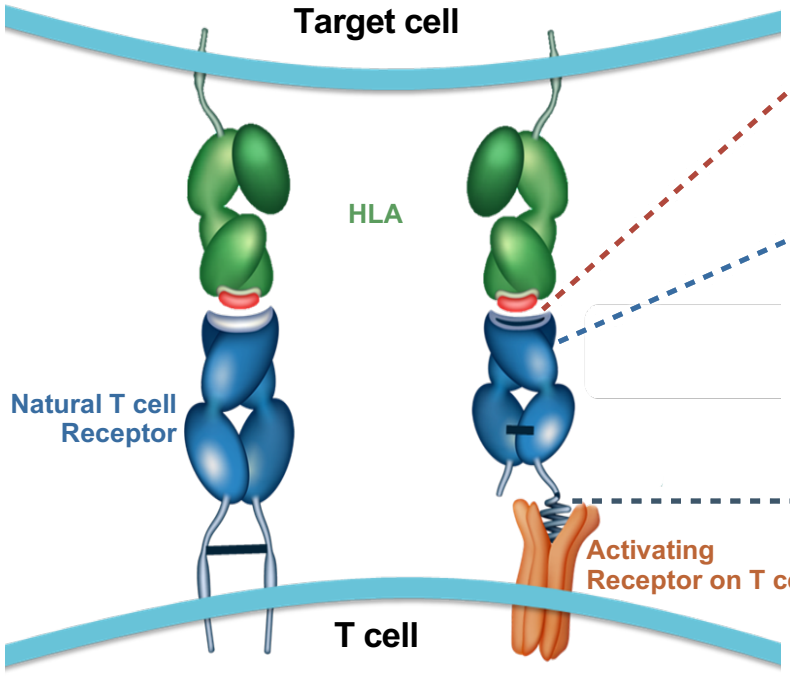
Categories of tumor antigens

Antigen type	Description	Examples of antigen type	Examples of approved immunotherapies for target antigen
Tumour-specific antigens[8,9]	• Completely absent from normal host cells • Arise in cancer cells from oncogenic viral proteins or nonsynonymous somatic mutations	• HPV oncoproteins E6 and E7 (HPV-associated cancers of the cervix, anus and oropharynx)[11,12] • Individual KRAS mutations (pancreatic, colon, lung and various other cancers)[18,19]	None approved, multiple in clinical development
Tumour-associated antigens[9]	• Low levels of expression on normal host cells • Disproportionately expressed on tumour cells • Often result from genetic amplification or post-translational modifications • Can be selectively expressed by the cell lineage from which the cancer evolved	• ERBB2 (some breast cancers and various other cancers)[158] • Mesothelin (pancreatic cancer and mesothelioma)[159–161] • CD19 on B cell malignancies[27,28]	• Sipuleucel-T (anti-PAP vaccine, prostate cancer)[135] • Blinatumomab (CD19–CD3 bispecific antibody, ALL)[130]
Cancer/testis antigens[13,14]	• Absent on normal adult cells, except in reproductive tissues (e.g. testes, fetal ovaries and trophoblasts) • Selectively expressed by various tumour types	• MAGE (various cancers)[162] • NY-ESO-1 antigen (various cancers)[163]	None approved, multiple in clinical development

Yarchoan et al, Nature Reviews Cancer 2017

ALL, acute lymphoblastic leukemia; HPV, human papilloma virus; MAGE, melanoma-associated antigen; PAP, prostatic acid phosphatase

Immunocore ImmTAC Platform: Combining TCR with anti-CD3 effector function



Peptide (the "address")

Engineered TCR (the "GPS")

- » High affinity for target peptide bound to HLA-A*0201
- » Highly specific for tumor

Plug-and-play Effector

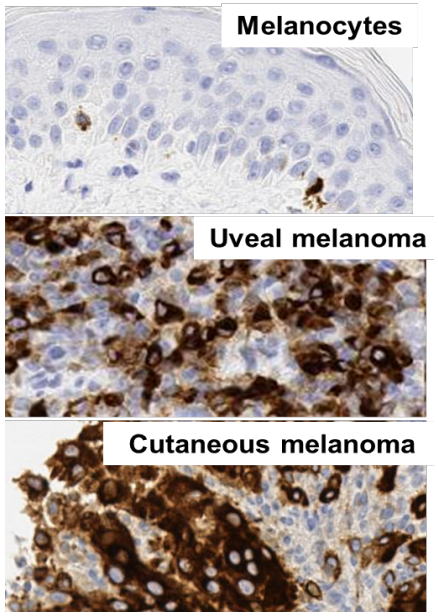
- » Single-chain antibody variable domain (scFv) targeting CD3 binds to and activates T cells

Oates J, et al. Mol Immunol 2015, Liddy N, et al. Nat Med 2021, Li Y, et al. Biotechnology 2005.

Gp100: TCR therapeutics can target gp100, an intra-cellular protein

Middleton MR, et al.
ASCO 2019

Melanocyte-specific protein



Melanoma - two stories

Cutaneous

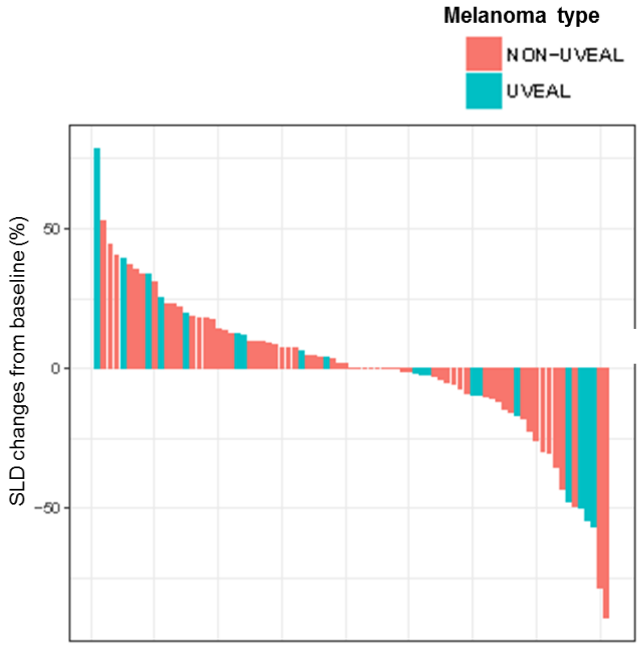
- UV damage - high tumor mutation burden
- Among most sensitive to anti-PDx
- Long term survival from checkpoints

Uveal

- Unrelated to UV-low mutation burden
- Insensitive to anti-PDx
- No SoC- clinical trials only
- Metastases to liver - highly immunosuppressive organ
- No change in survival for 50 years

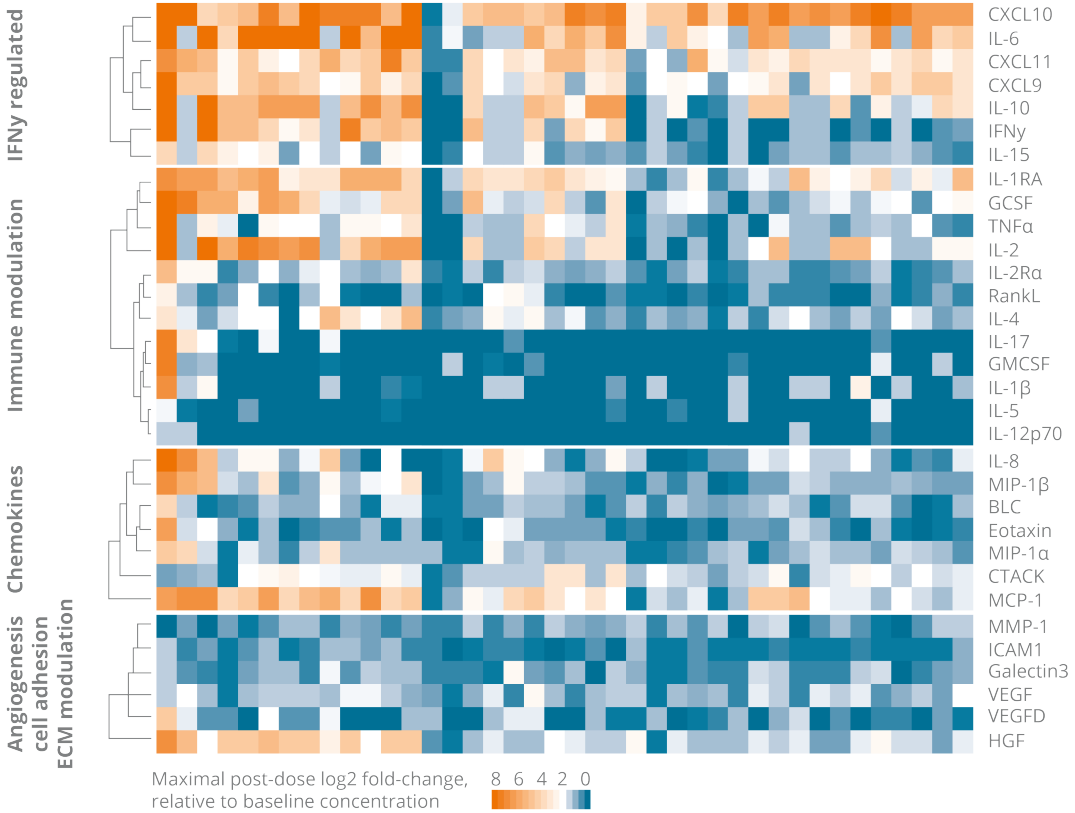
Tebentafusp showed activity in both uveal and cutaneous melanoma

Yarchoan et al. N Engl J Med 2017, Middleton MR, et al. ASCO 2016. Abstract 3016.



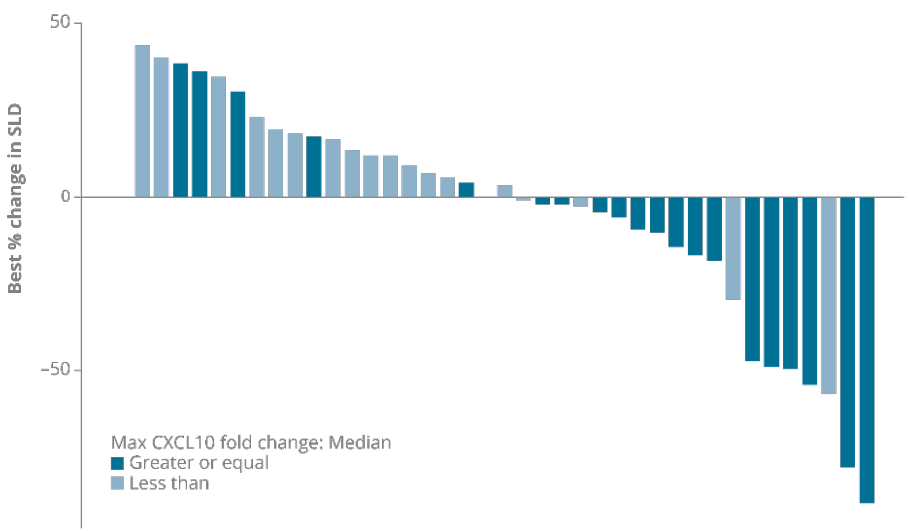
Tebentafusp induced increase IFNγ and other inflammatory pathways, most prominently CXCL10 (IP-10)

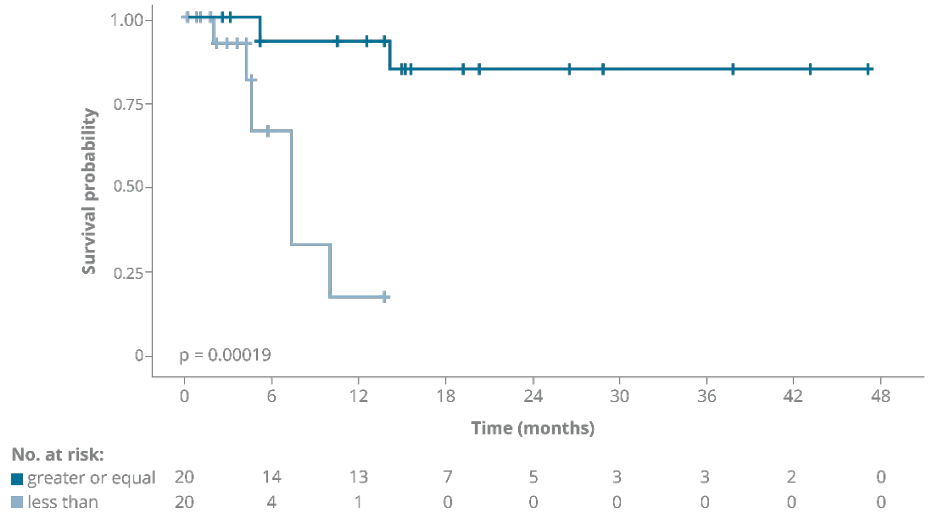
CXCL10, a chemoattractant, binds to CXCR3 receptor on T cells



Middleton MR, et al.
ASCO 2019

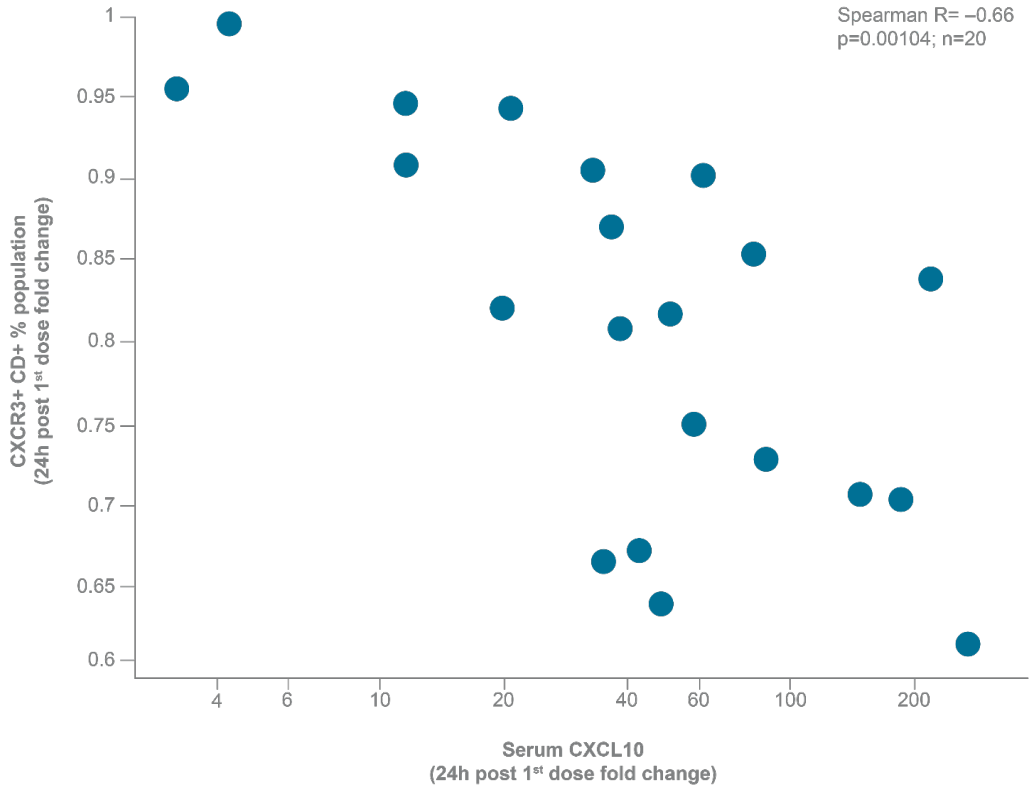
Greater increase in serum CXCL10 appear was associated with longer OS and tumor shrinkage





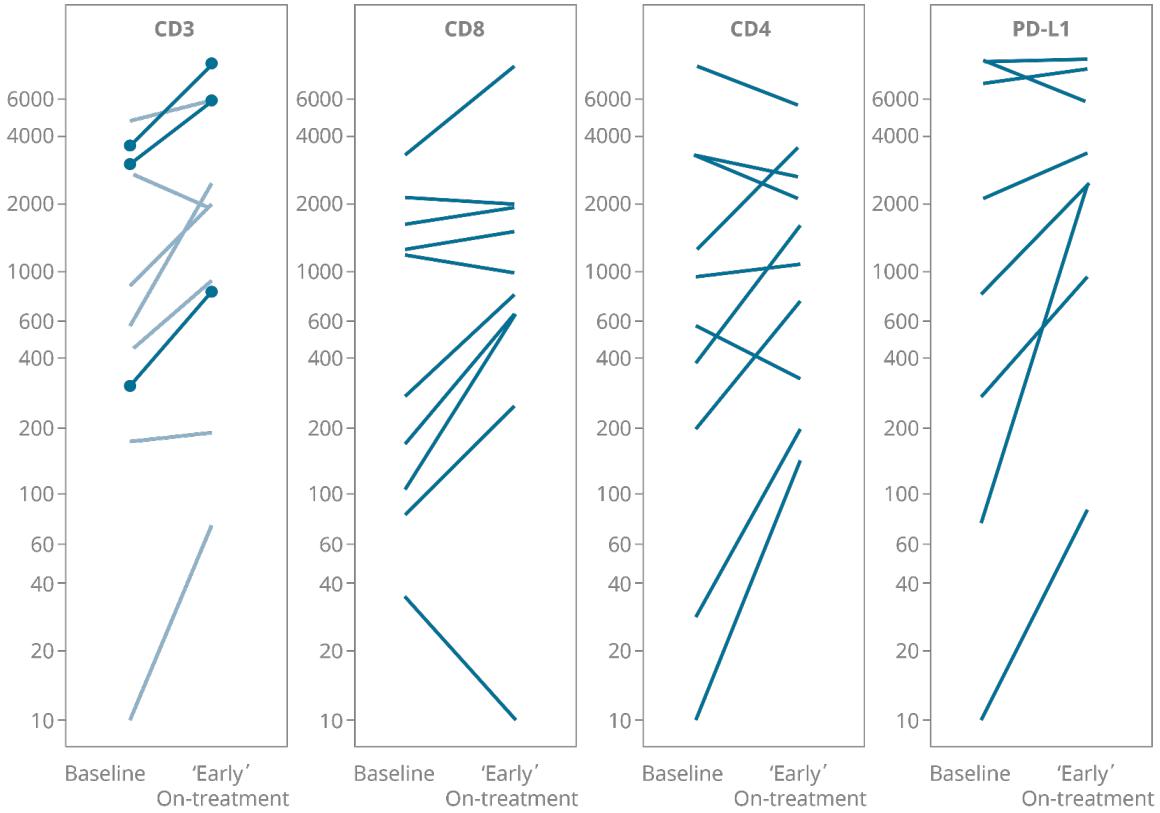
Middleton MR, et al.
ASCO 2019

Increase in serum CXCL10 correlated with reduction in CXCR3+ cells



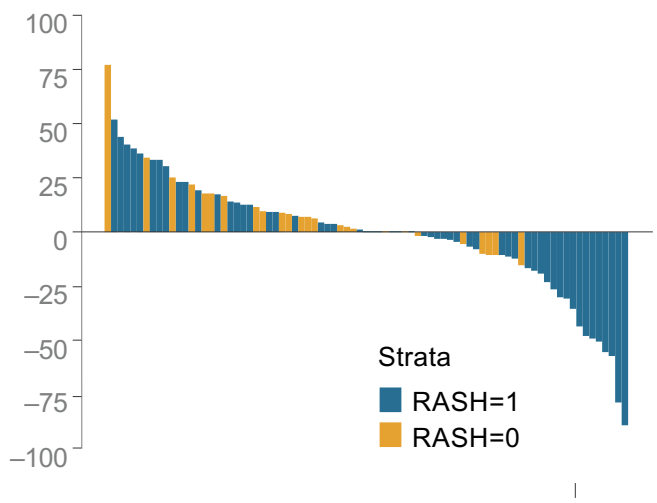
Middleton MR, et al.
ASCO 2019

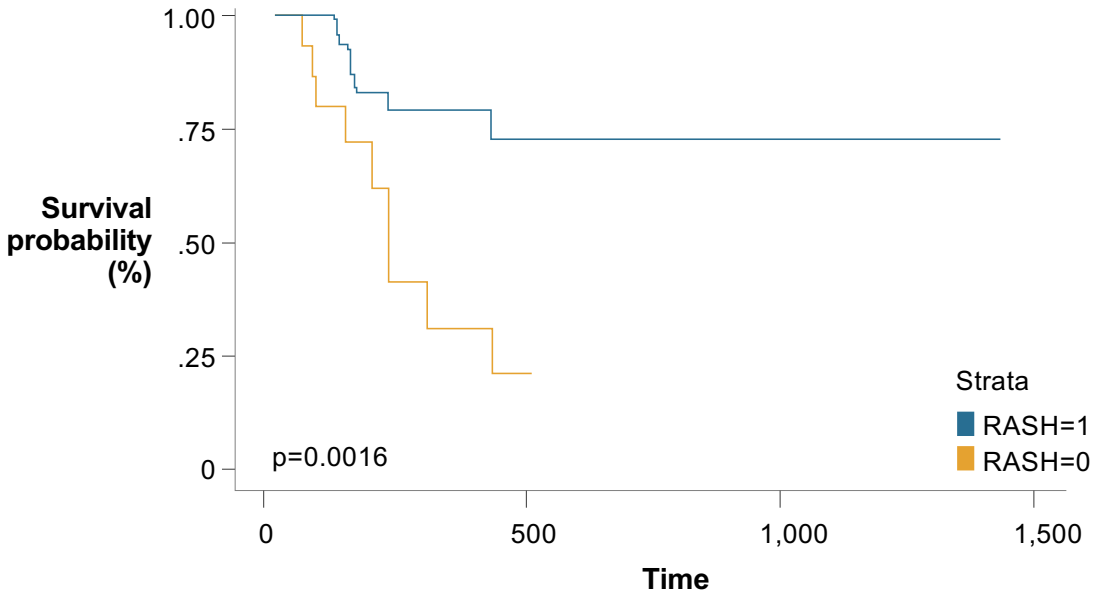
Increase in CD3+, CD4+, CD8+ and PD-L1+ cells in tumor on tebentafusp treatment



Middleton MR, et al.
ASCO 2019

Development of rash (on target/off tumor) was associated with better efficacy



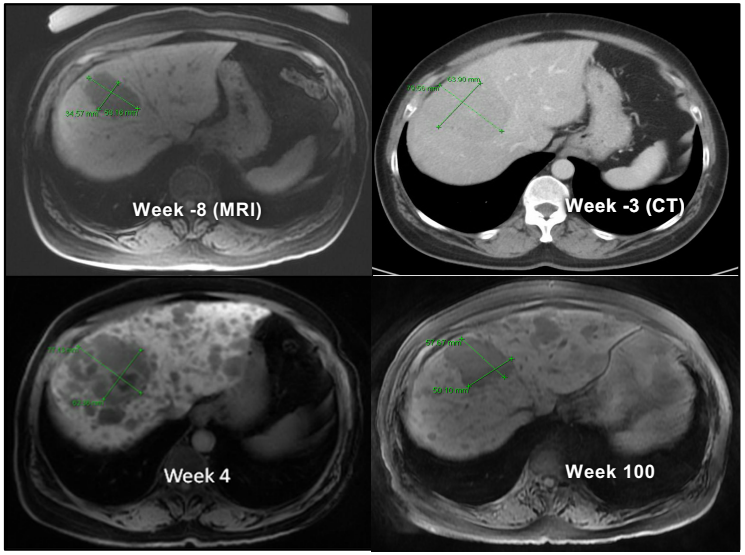


Middleton MR, et al.
ASCO 2019

In early phase studies, IMCgp100 active in liver metastases - highly immunosuppressive environment

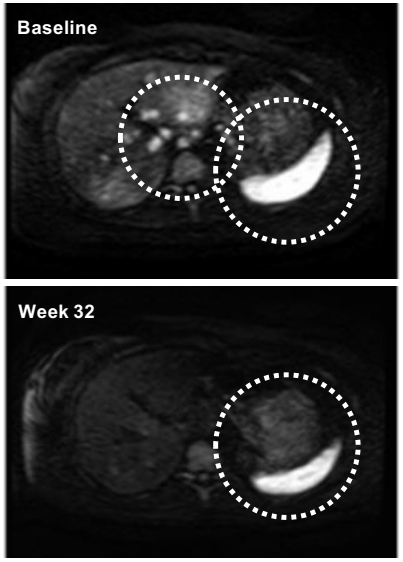
Patient 1

Pseudo-progression followed by response; patient remains on treatment after 25 months



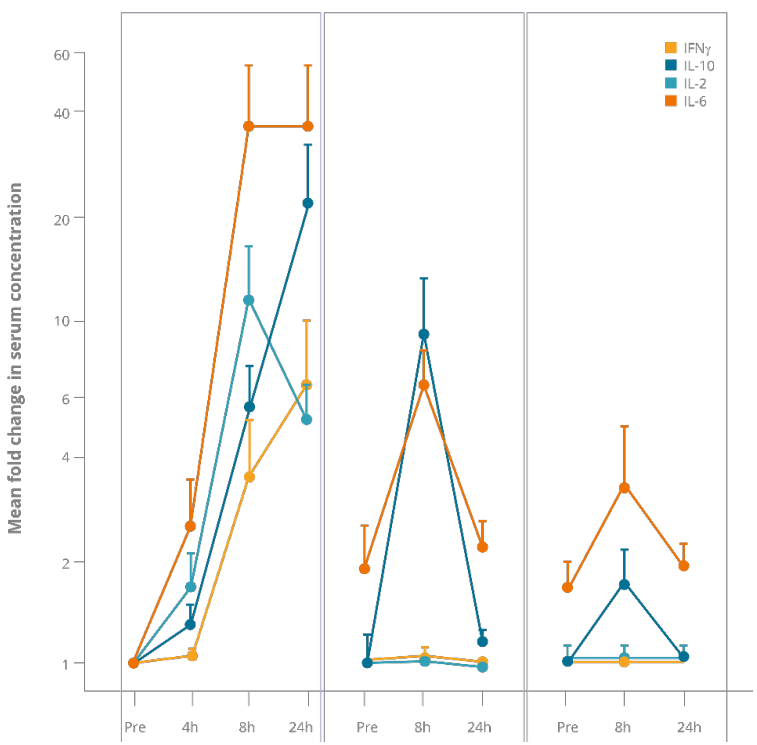
Patient 2

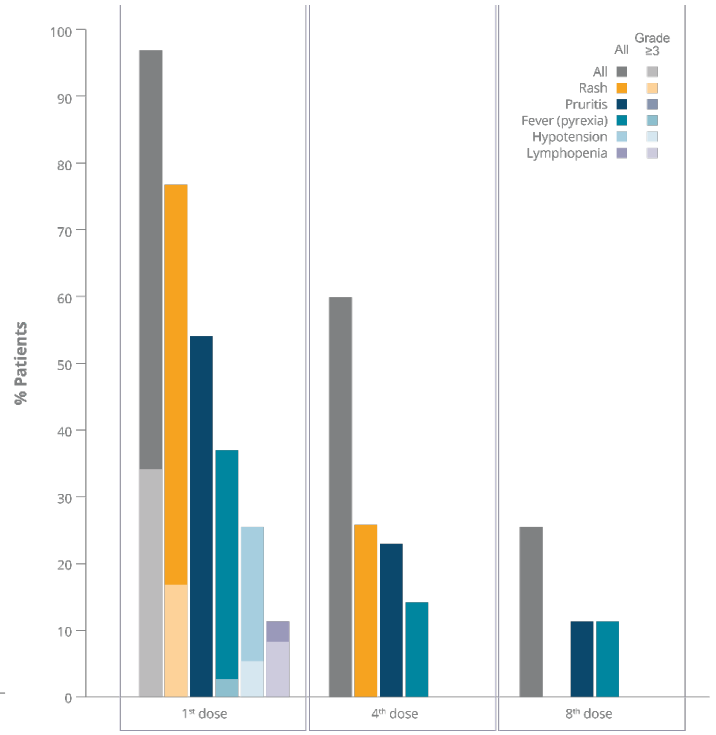
Response



Middleton MR, et al.
ASCO 2019

Cytokine kinetics paralleled mechanism-based AEs





Memorial Sloan Kettering Cancer Center

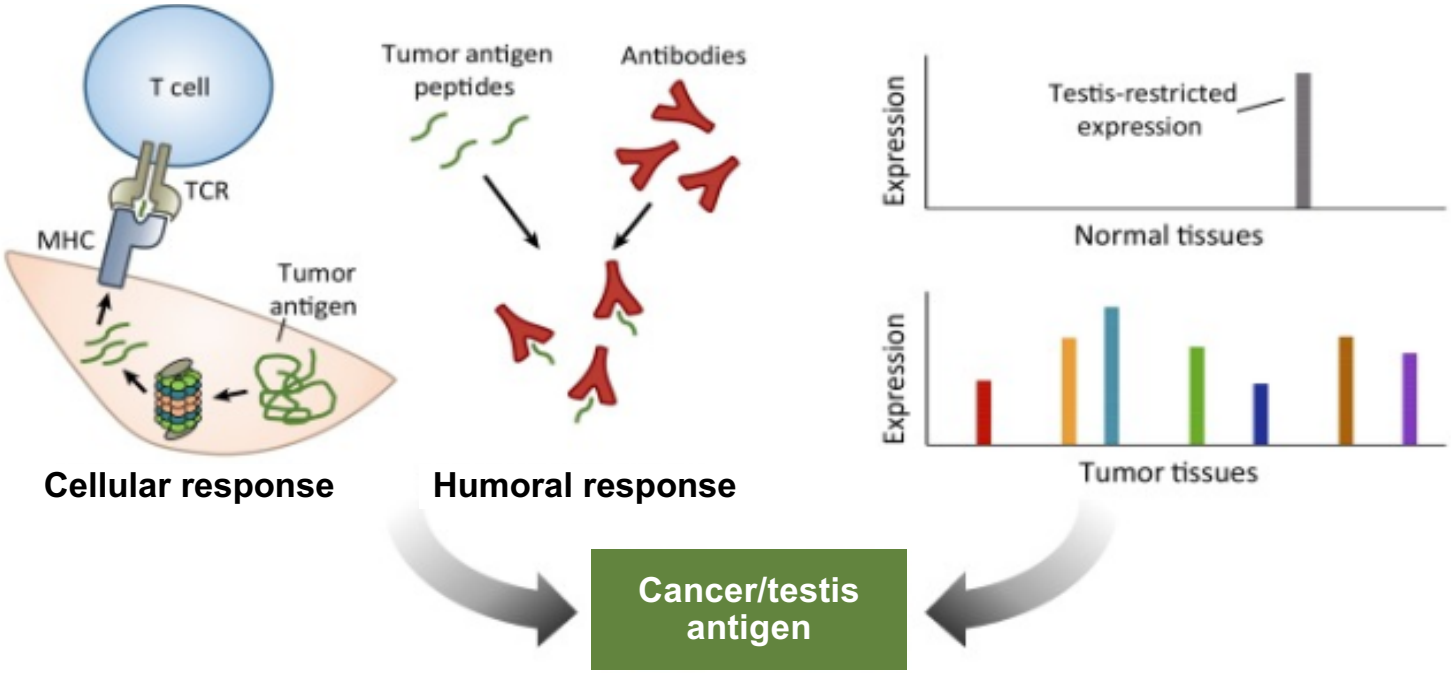
Middleton MR, et al.
ASCO 2019

Safety Profile

	Number (%) of Patients (N=83)	
Preferred Term	Any Grade	≥Grade 3
Patients with any related TRAE	79 (95.2%)	50 (60%)
Pyrexia	65 (78.3%)	3 (4%)
Chills	49 (59.0%)	0
Nausea	46 (55.4%)	1 (1%)
Pruritus	45 (54.2%)	2 (2%)
Fatigue	41 (49.4%)	4 (4%)
Hypotension	41 (49.4%)	9 (11%)
Periorbital oedema	33 (39.8%)	0
Dry skin	32 (38.6%)	0
Oedema peripheral	29 (49.4%)	0
Erythema	26 (31.3%)	3 (4%)
Vomiting	23 (27.7%)	1 (1%)
Headache	20 (24.1%)	0
Rash	20 (24.1%)	2 (2%)
Hair colour changes	19 (22.9%)	2 (2%)
Rash maculo-papular	17 (20.5%)	5 (6%)
Abdominal pain	17 (20.5%)	1 (1%)
Face edema	15 (18.1%)	0
Pruritis generalised	14 (16.9%)	1 (1%)
Skin exfoliation	14 (16.9%)	0

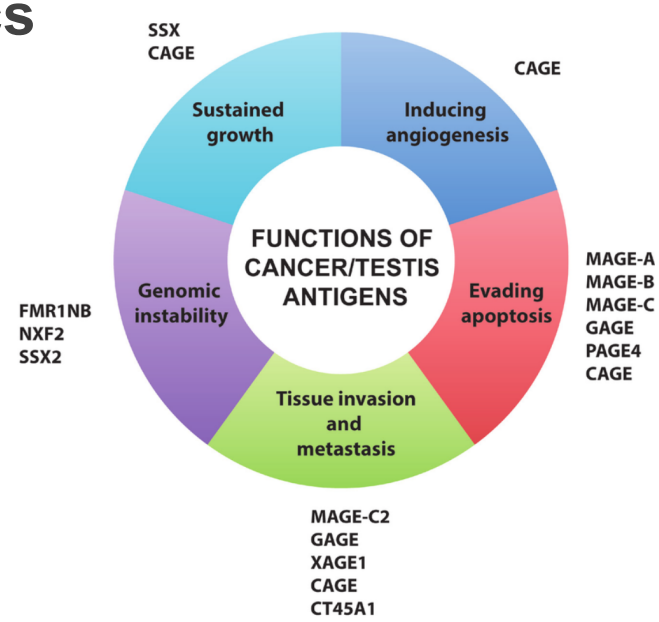
Middleton MR, et al.
ASCO 2019

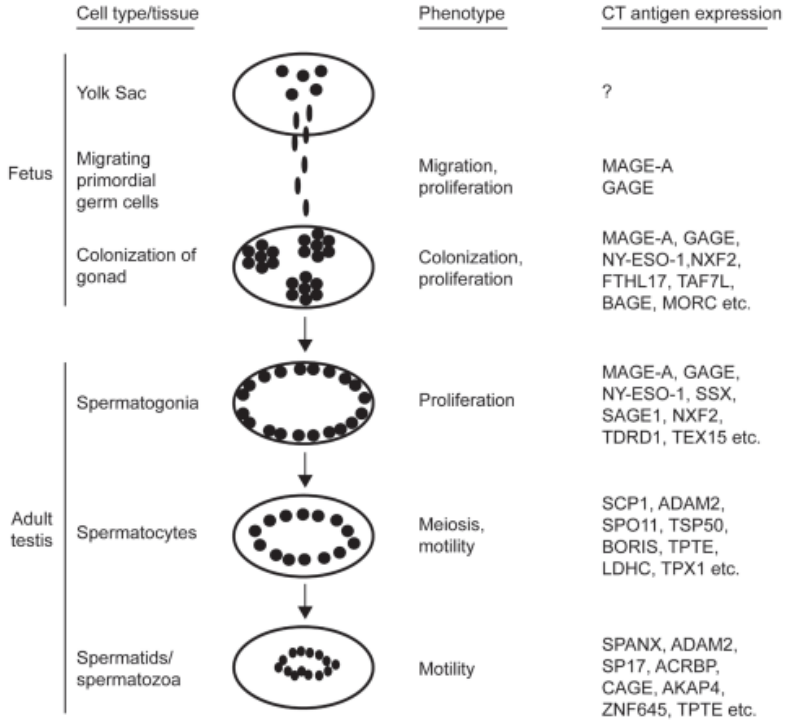
Cancer testis antigens: promising therapeutic targets



Gibbs et al. Trends in Cancer 2018

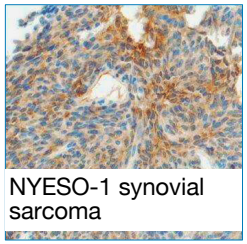
Numerous characteristics shared with germ cells & potential oncogenic function



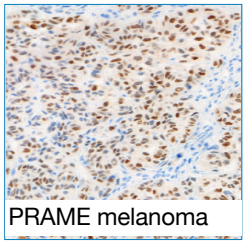


Gjerstoff M et al. Oncotarget 2015,Gibbs et al. Trends in Cancer 2018

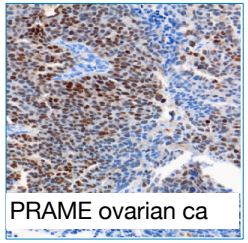
Widely expressed amongst numerous malignancies



NYESO-1 synovial sarcoma



PRAME melanoma

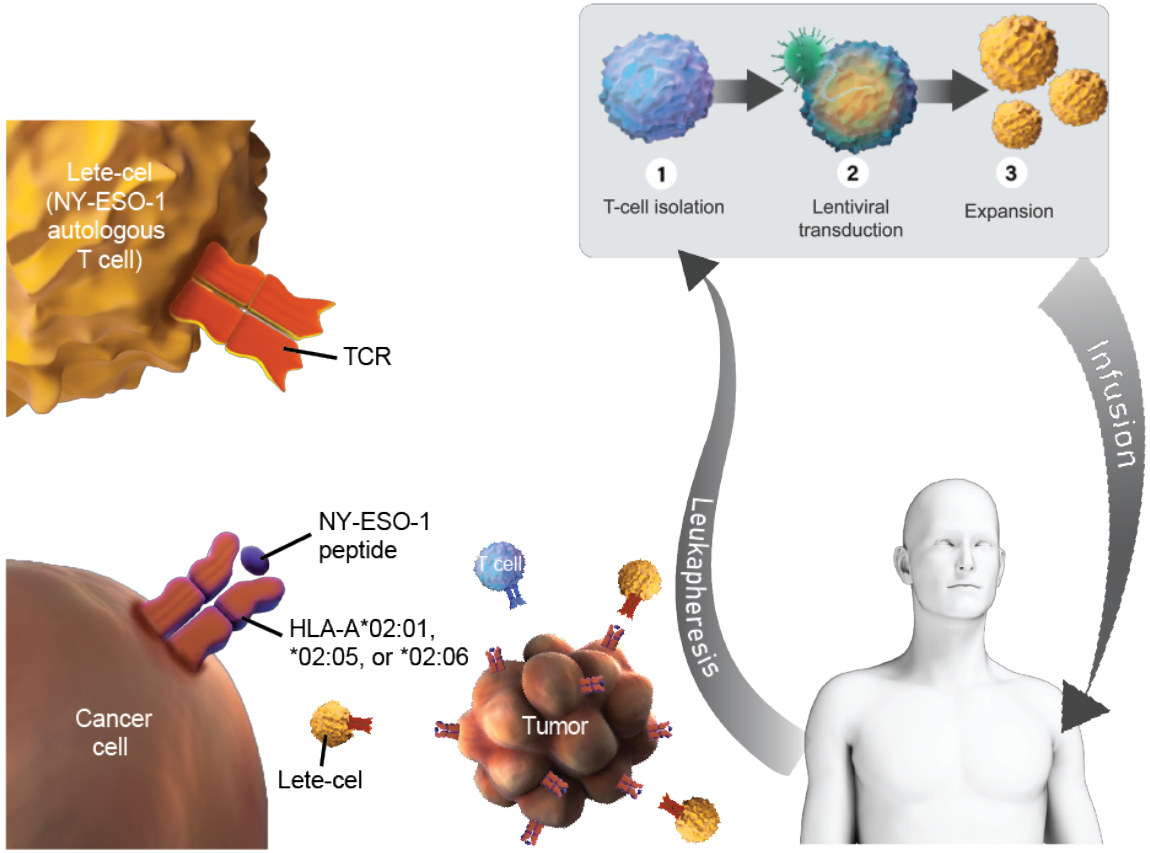


PRAME ovarian ca

Salmanienejad A et al. Immunol Invest Oct 2016

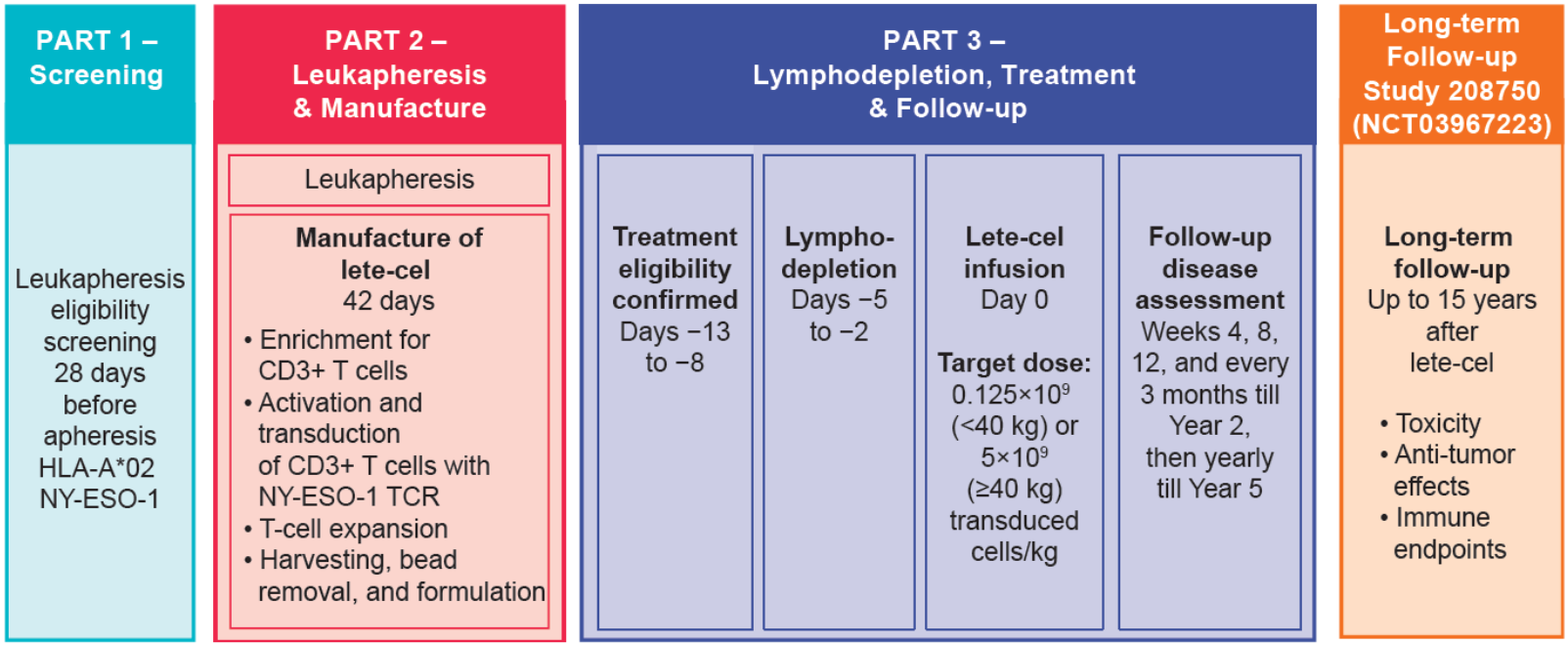
Investigated CTA	Tumor type	Expression level	References
NY-ESO-1	Melanoma	17–42%	(Chen et al., 1997; Van Der Bruggen et al., 2002; Vaughan et al., 2004)
	Bladder cancer	32–80%	(Kurashige et al., 2001; Scanlan et al., 2004)
	NSCLC	27%	(Gure et al., 2005); (Groeper et al., 2007)
	Colon cancer	2–10%	(Li et al., 2005; Mashino et al., 2001)
	Renal cell carcinoma	Not detected	(Chen et al., 1997)
	Lymphoma	Not detected	(Chen et al., 1997)
	Esophageal squamous cell carcinoma (ESCC)	41.4%	(Forghanifard et al., 2011)
MAGE-A3	Melanoma	57–76%	(Brasseur et al., 1995; Roeder et al., 2005)
	NSCLC	35–60%	(Melloni et al., 2004; Scanlan et al., 2000)
	Bladder cancer	57%	(Van Der Bruggen et al., 2002)
	Squamous esophageal cancer	75%	(Weinert et al., 2009)
	Hepatocarsinoma	42%	(Chen et al., 1997)
BAGE	Hepatocarsinoma	21%	(Kobayashi et al., 2000)
	Melanoma	14–28%	(Boël et al., 1995; Ruault et al., 2002)
	NSCLC	17–20%	(Melloni et al., 2004; Tajima et al., 2003)
	Bladder cancer	15%	(Scanlan et al., 2002b)
MAGE-A4	ESCC	92%	(Forghanifard et al., 2011)
	NSCLC	42%	(Groeper et al., 2007)
SSX2	liposarcoma	%16	(Hemminger et al., 2014)
LAGE1	ESCC	39%	(Forghanifard et al., 2011)

Lete-cel: autologous CD4+ and CD8+ T cells genetically modified to express a TCR recognizing NY-ESO-1 bound to human leukocyte antigen A*02 (HLA-A*02)



D'Angelo SP, et al. SITC 2020

Study design



D'Angelo SP, et al. SITC 2020

Results

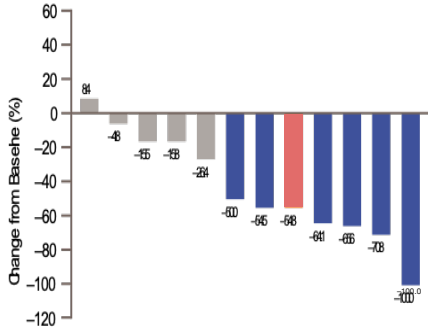
	Cohort 1 (n=12)	Cohort 2 (n=13)	Cohort 3 (n=5)	Cohort 4 (n=15)
Median (range) transduced cell dose ($x10^9$)	**3.60** (0.45–14.36)	**2.42** (1.60–5.01)	**3.02** (1.53–5.00)	**2.40** (1.00–4.95)
Efficacy				
Overall response rate[a] (95% CI)	**6 (50)** (0.21–0.79)	**4 (31)** (0.09–0.61)	**1 (20)** (0.01–0.72)	**4 (27)** (0.08–0.55)
Complete response	1 (8)	0	0	0
Partial response	5 (42)	4 (31)	1 (20)	4 (27)
Stable disease	5 (42)	7 (54)	3 (60)	10 (67)
Progressive disease	1 (8)	1 (8)	0	1 (7)
Not evaluable	0	1 (8)	1 (20)	0
Median DoR (range), weeks	**31.0** (13–72)	**8.6** (8–13)	**32.1** (32–32)	**16.4** (14–94)
Median PFS (95% CI), weeks	**15.4** (7.7–38.0)	**13.1** (7.9–13.9)	**8.6** (0.7–36.1)	**22.4** (11.3–26.6)
Median OS (95% CI), months[a]	**24.3** (8.5–48.8)	**9.9** (3.9–19.6)	**19.9** (8.8–NA)	Not mature; to be reported later
Peak persistence, median (range), DNA copies/µg				
Responders[b]	**106,174** (76,185–192,445)	**65,875** (13,365–197,546)	**123,314** (123,314–123,314)	**40,137** (5677–131,176)
Non-responders[c]	**30,601** (11,265–119,883)	**72,564** (22,627–145,791)	**15,688** (9453–43,015)	**19,650** (164–111,260)

D'Angelo SP, et al. SITC 2020

Depth of response

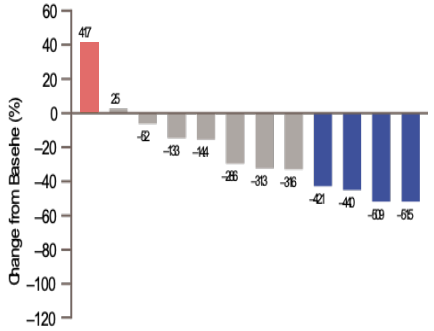
Cohort 1

ORR **50%**



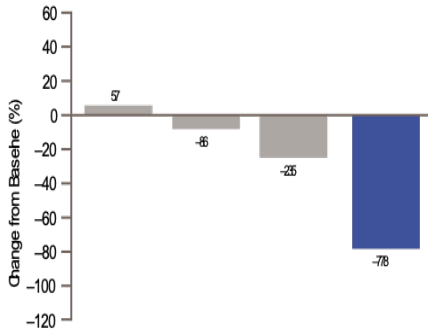
Cohort 2[b]

ORR **31%**



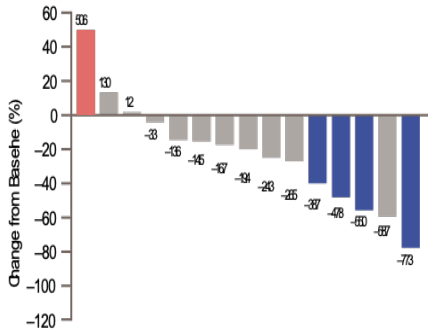
Cohort 3[b]

ORR **20%**



Cohort 4

ORR **27%**

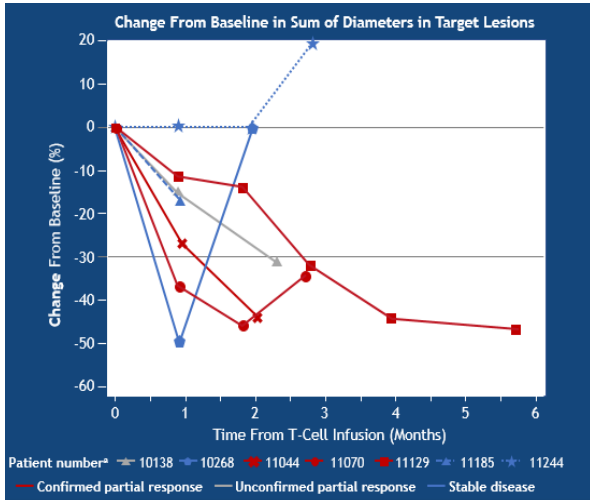


Best Response: **Progressive Disease** **Confirmed Complete or Partial Response** **Stable Disease**

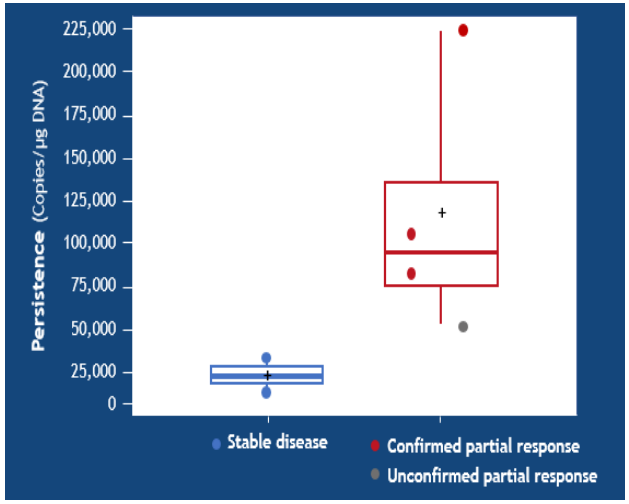
D'Angelo SP, et al. SITC 2020

NYESO1 TCR demon-strates efficacy in myxoid LPS

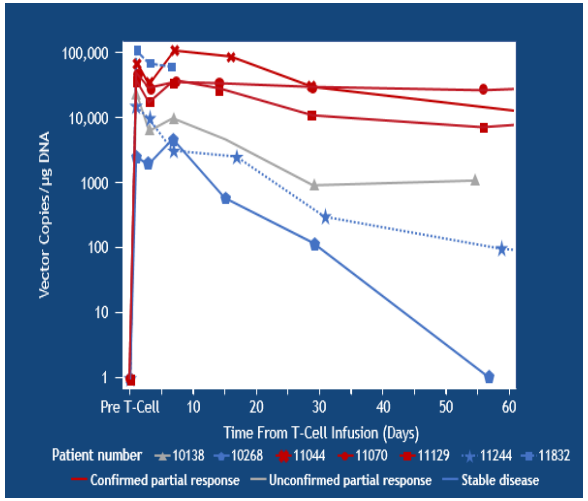
50% ORR in myxoid LPS



Higher expansion in responding patients

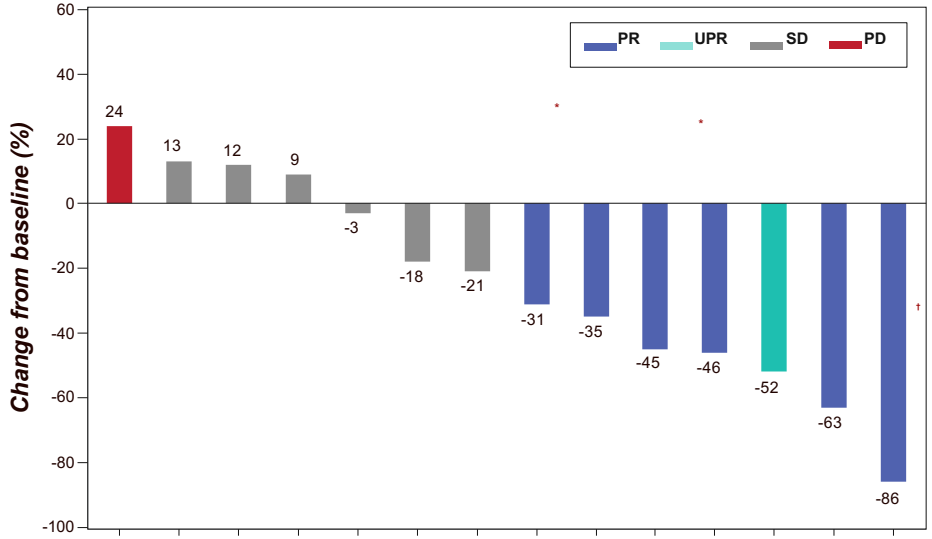


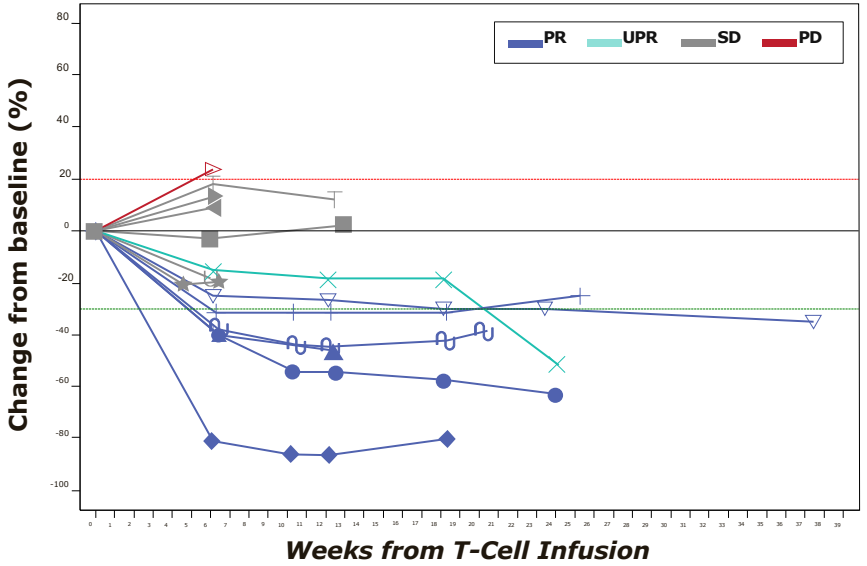
Higher persistence in responding patients



D'Angelo SP, et al. ASCO 2018

MAGE4 TCR Induce Clinical Responses in Synovial sarcoma





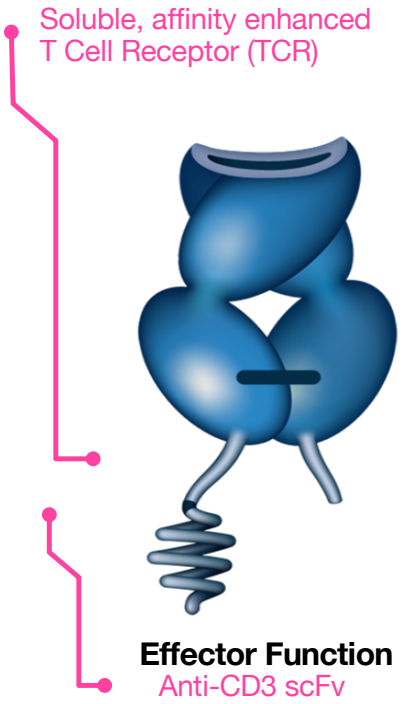
Van Tine B, CTOS 2020

NASDC
NCI Awardee Skills Development Consortium

Bispecific Antibodies Targeting Cancer Testis Antigens

Targeting cancer testis antigens with bispecific antibodies

NY-ESO-1/LAGE-1A TCR
MCnyeso
MSK PI: S D'Angelo
NCT:



MAGE-A4 TCR
IMC-C103C
MSK PI: Neil Segal
NCT:

PRAME TCR
IMC-F106C
MSK PI: Matthew Hellman
NCT:

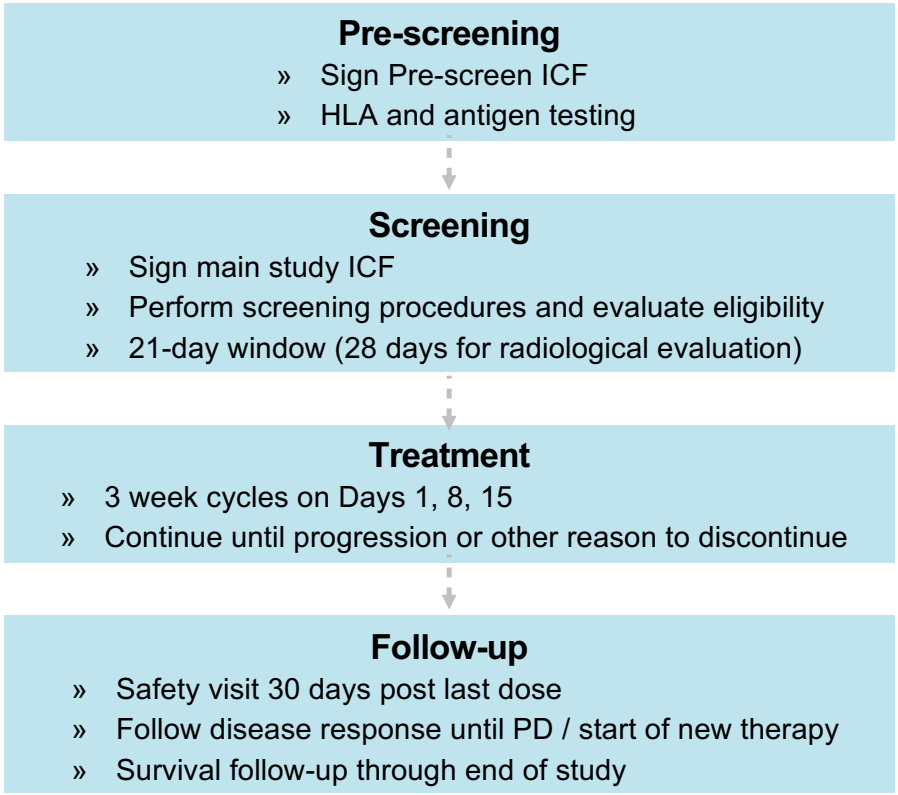
Memorial Sloan Kettering Cancer Center

Antigen expression across malignancies

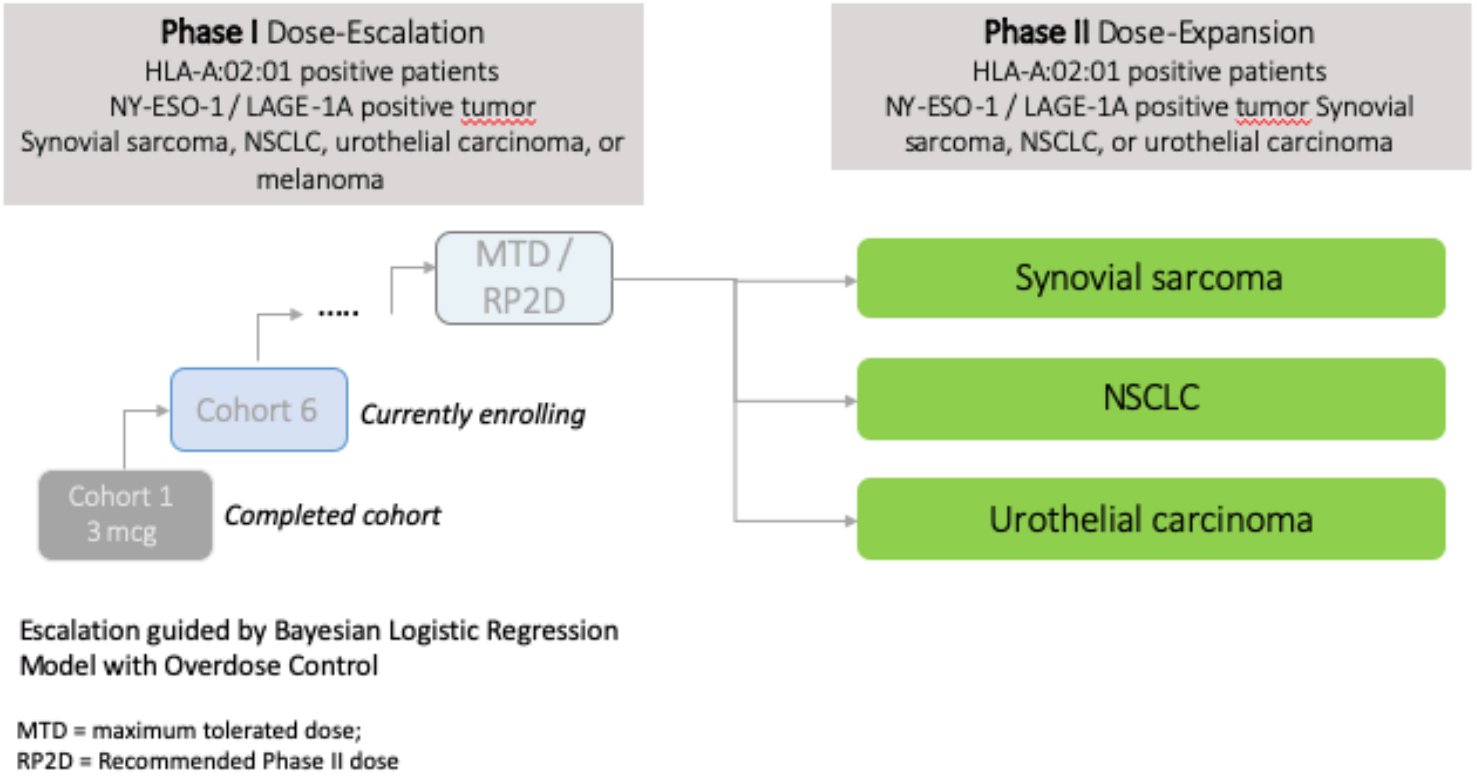
Indication	NY-ESO-1/LAGE-1A	MAGE-A4	PRAME
Melanoma - cutaneous	35%	Not eligible	80%*
Melanoma - uveal	<10%	Not eligible	To be determined
NCSLC - adenocarcinoma	<10%	<10%	47%
NSCLC - squamous cell carcinoma	15%	53%	68%
Ovarian - high-grade serous	Not eligible	75%*	97%*
Ovarian - other histologies	Not eligible	To be determined	To be determined
Synovial sarcoma	65%	76%*	Not eligible
Urothelial carcinoma	25%	30%	10%

Overview of study periods

Pre-screening tests may be performed at any time, including while patient is on prior cancer treatment



Study Design

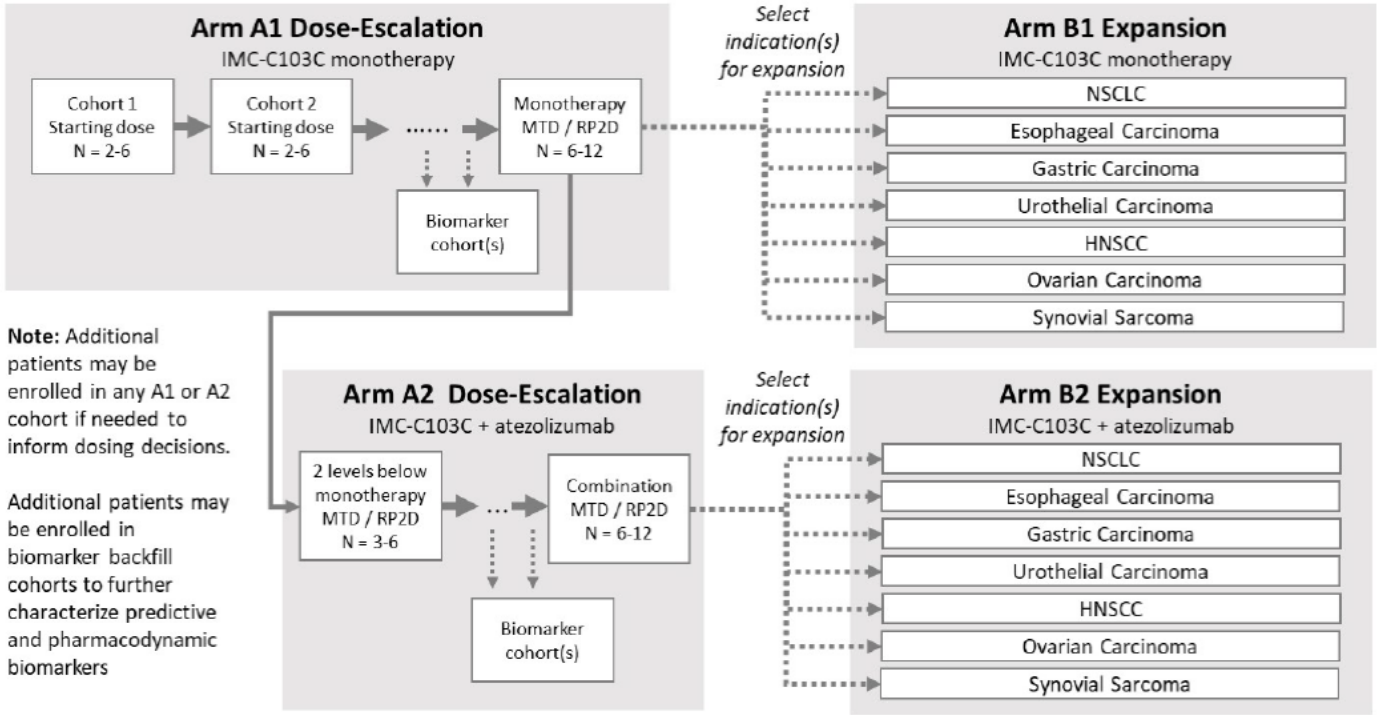


Escalation guided by Bayesian Logistic Regression Model with Overdose Control

MTD = maximum tolerated dose;
RP2D = Recommended Phase II dose

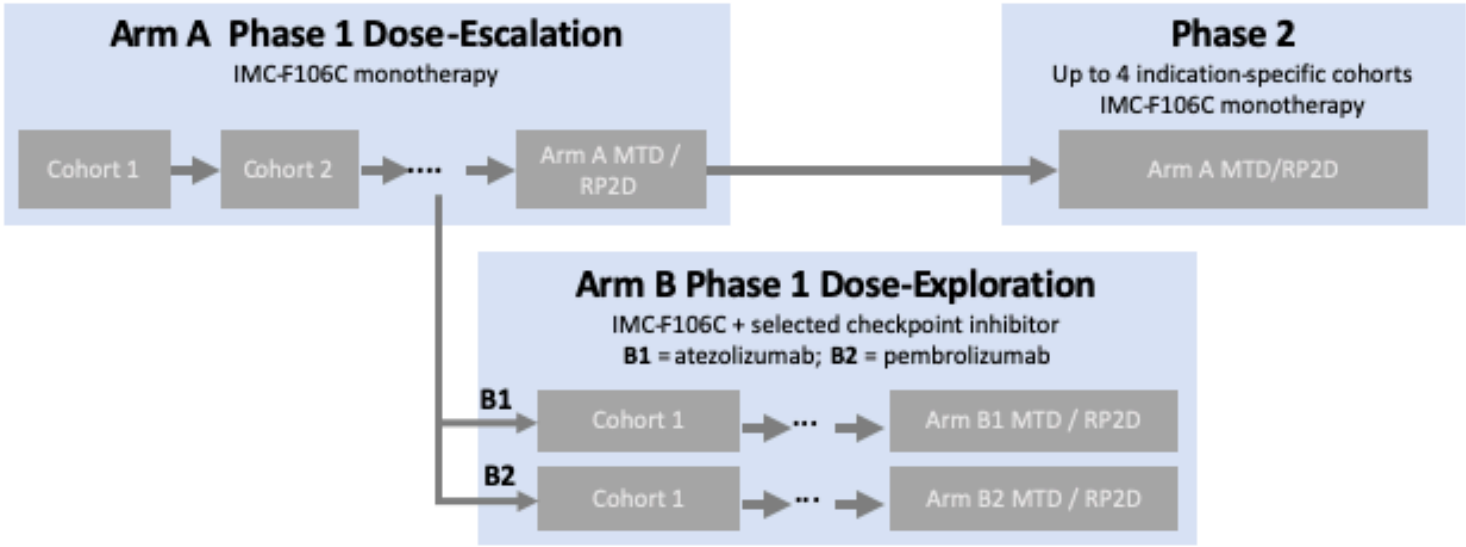
MAGE4 (IMC-C103C-101) Study Design PI: Neal Segal

Note: Two expansion cohorts are planned' additional cohorts may be opened at the discretion of the Sponsor. Expansion cohorts will initially enroll up to 9 patients; may enroll 15 additional patients (N=24) if ≥ 1 response.



PRAME (IMC-F106C-101): Study Design, PI: Matt Hellman

Metastatic or Unresectable
Melanoma
Ovarian
Uterine
NSCLC
SCLC
Breast
Urothelial
Other solid

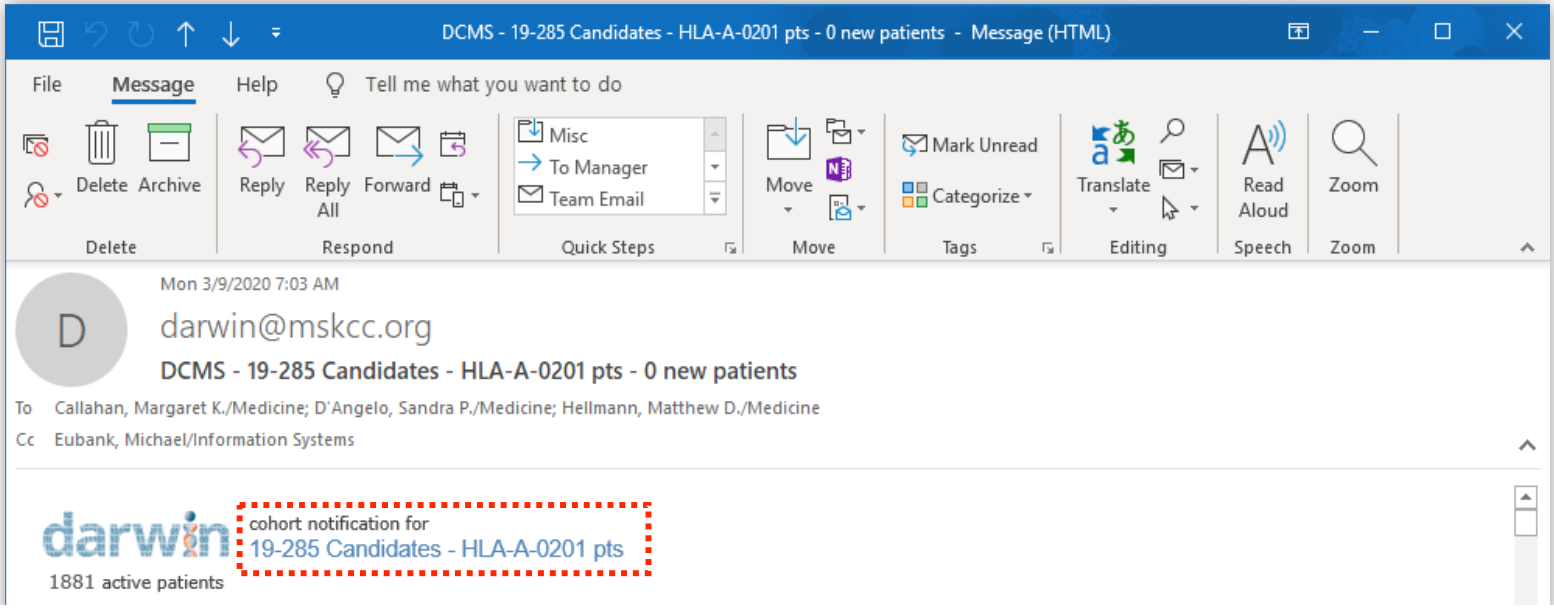


Limitations: HLA-A*02:01 frequency

Population(United States of America)	Sample Size	Allele Frequency	Approximate % Positive
African	28,557	0.1146	22%
African American	416,581	0.1235	23%
Caribbean Black	33,328	0.1107	21%
Caribbean Hispanic	115,374	0.1688	31%
Chinese	99,672	0.0946	18%
European Caucasian	1,242,890	0.2755	48%
Filipino	50,614	0.0671	13%
Hispanic South or Central American	146,714	0.2095	38%
Korean	77,584	0.1857	34%
Mexican or Chicano	261,235	0.223	40%
Middle Eastern or North Coast of Africa	70,890	0.1973	36%
North American Amerindian	35,791	0.2776	48%
South Asian Indian	185,391	0.0492	10%
Southeast Asian	27,978	0.0578	11%
Vietnamese	43,540	0.0349	7%

Data from the National Marrow Donor Program,http://www.allelefrequencies.net/

Utilizing MSK IMPACT, Next generation sequencing assay to identify HLA + patients

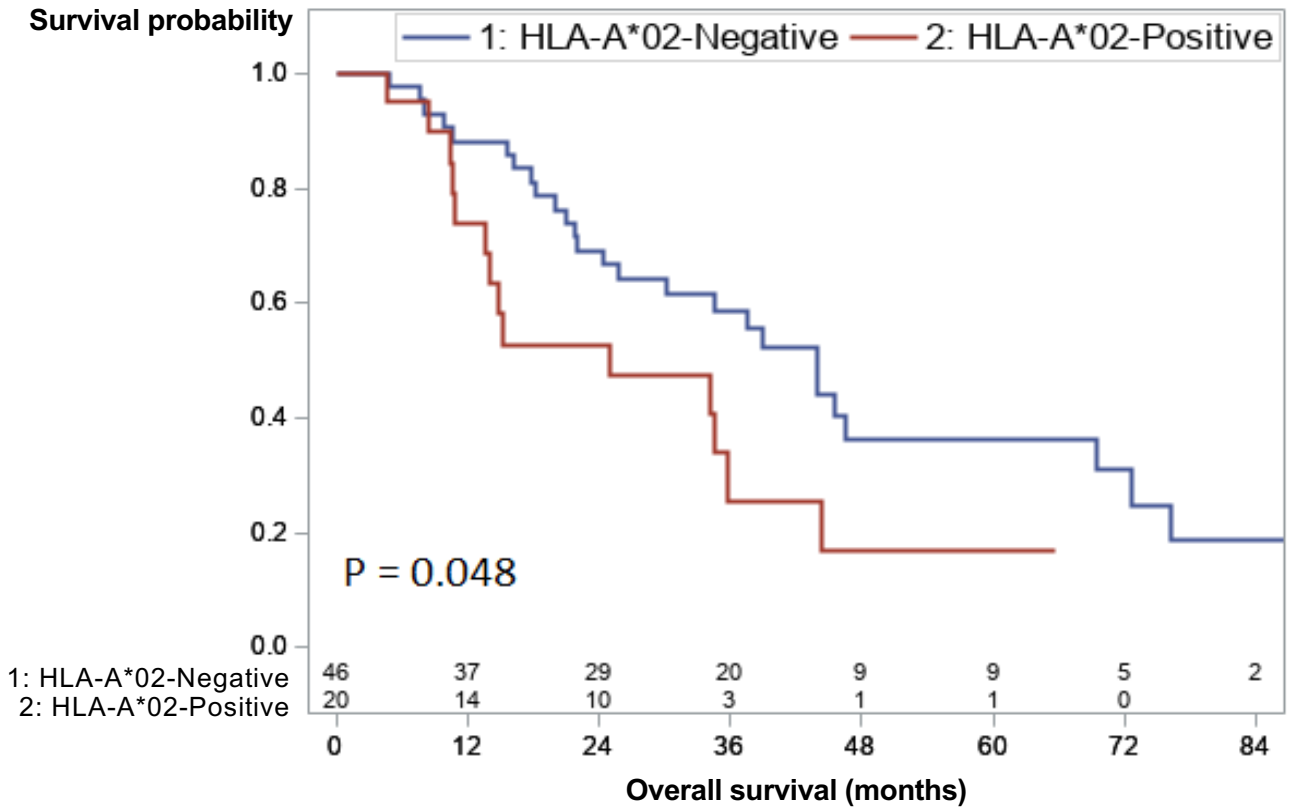


HLA Genotype as Measured by MSK-IMPACT and Outside CLIA-certified Laboratory is consistent

Patient ID	CLIA-certified Laboratory						MSK-IMPACT					
	HLA_A1	HLA_A2	HLA_B1	HLA_B2	HLA_C1	HLA_C2	HLA_A1	HLA_A2	HLA_B1	HLA_B2	HLA_C1	HLA_C2
P-0007522	01:01	31:01	13:02	35:02	06:DDAR	04:JKTU	01:01	31:01	35:02	13:02	04:01	06:02
P-0010759	01:01	30:04	35:02	57:03	04:JKTU	07:AAGAJ	30:04	01:01	57:03	35:02	04:01	07:01
P-0039186	02:01	02:02	39:05	44:03	03:05	14:02	02:02	02:01	39:01	44:03	14:02	03:04
P-0003440	01	02	07	08	07	15	01:01	02:01	07:05	08:01	15:05	07:01
P-0005828	01	03	07	08	07	07	03:01	01:01	07:02	08:01	07:02	07:01
P-0005310	33	68	15	50	02	06	68:01	33:01	50:01	15:03	02:10	06:02
P-0008520	02:02:01	33:01:01	15	44	05	14	02:02	33:01	44:02	15:16	14:02	05:01
P-0003060	23	31	35	44	02	04	23:01	31:01	44:03	35:01	02:02	04:01
P-0010353	32	33	42	44	04	17	32:01	33:01	42:01	44:03	04:01	17:01
P-0027364	02:01	11:01	07:TDVB	35:TDS	07:ABSED	04:JKTU	11:01	02:01	07:02	35:01	07:02	04:01
P-0020517	02:01	24:02	18:RRG	44:HTH	07:AJKDW	05:01	24:02	02:01	18:01	44:02	05:01	07:01
P-0018549	02:01	24:02	39:01	44:27	07:ABSED	07:ET	24:02	02:01	39:01	39:01	07:04	07:02
P-0003036	03	25	07	39	07	12	03:01	26:01	07:02	39:01	12:03	07:02
P-0001101	01:01	68:01	NA	NA	NA	NA	01:01	68:01	14:02	35:02	08:02	04:01
P-0013119	02:01	24:10	NA	NA	NA	NA	24:10	02:01	15:25	15:01	04:01	04:03
P-0017556	03:01	26:01	NA	NA	NA	NA	03:01	26:01	07:02	15:17	07:02	07:01
P-0019860	03:01	29:02	NA	NA	NA	NA	03:01	29:02	07:02	44:03	16:01	07:02
P-0021211	68:02	02:01	NA	NA	NA	NA	68:02	02:01	53:01	49:01	04:01	07:01
P-0021465	11:01	33:03	NA	NA	NA	NA	11:01	33:03	15:02	18:01	08:01	12:03
P-0027765	01:01	02:01	NA	NA	NA	NA	01:01	02:01	08:01	15:03	02:10	07:01
P-0003328	03	23	07	08	07	07	03:01	11:01	57:01	13:02	06:02	06:02
P-0025830	NA	NA	NA	NA	NA	NA	24:03	24:02	40:06	18:01	15:02	12:03

Rosenbaum et al. CCR 2020

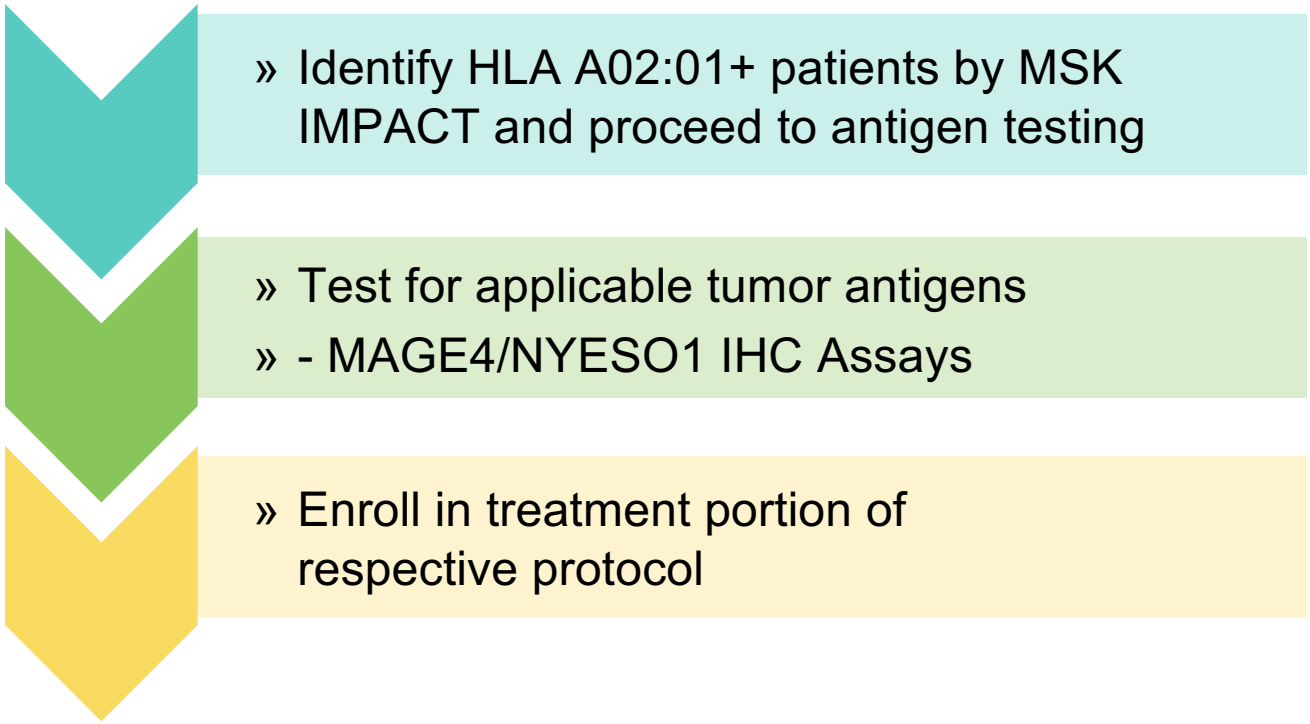
HLA genotype doesn't impact overall survival in cohort of patients with synovial sarcoma



Memorial Sloan Kettering Cancer Center

Rosenbaum et al. CCR 2020

Ideally….
a universal screening master protocol can further expedite patient enrollment



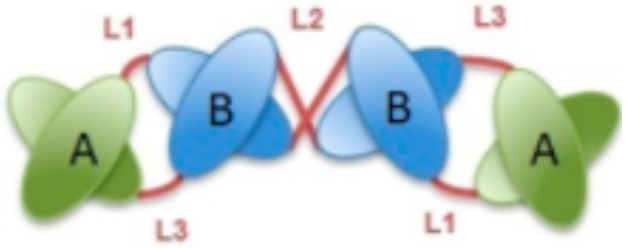
NK cell redirectors

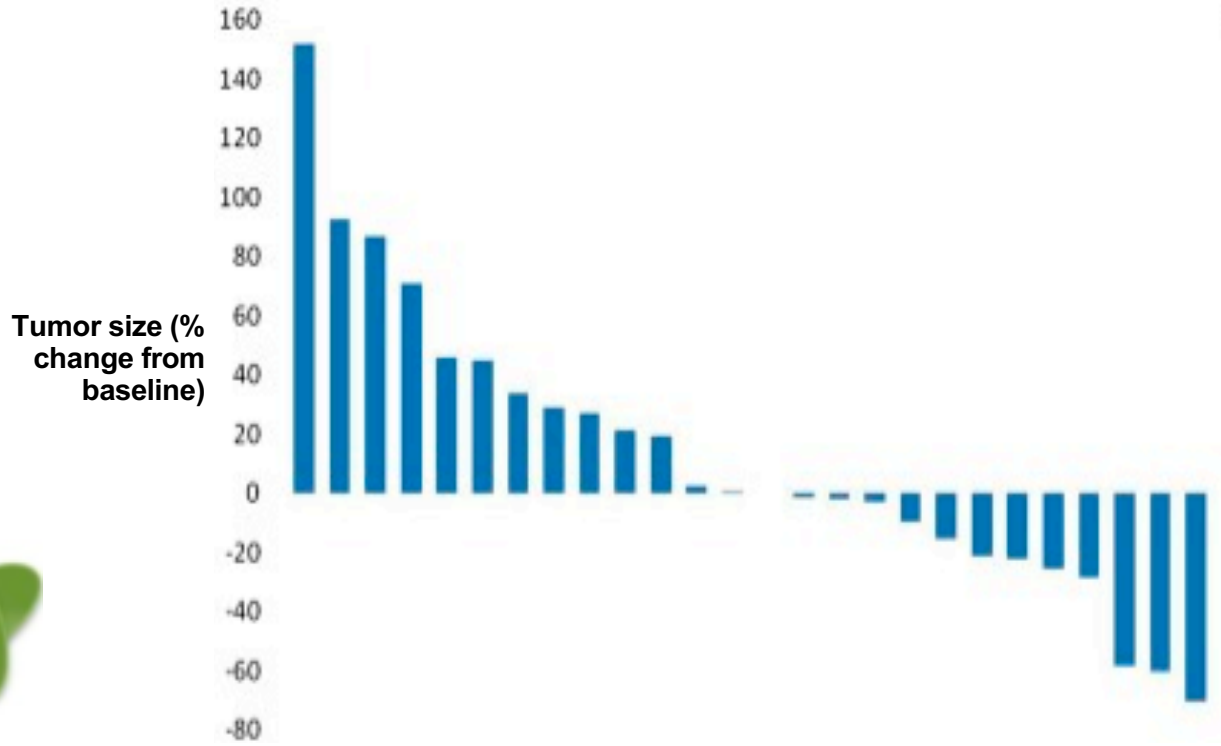
Redirect NK cells to malignant cells by targeting tumor antigens and CD16A

Target	Example	Stage
CD30 x CD16A	AFM13	II
EGFR x CD16A	AFM24	Pre-clinical
BCMA x CD16A	AFM26	Pre-clinical

AFM13: For CD30 + Malignancies

Bispecific, tetravalent chimeric antibody construct





Tumor Targeted

Directs co-stimulation to the tumor infiltrating immune cells by targeting a tumor antigen and con-stimulator molecule

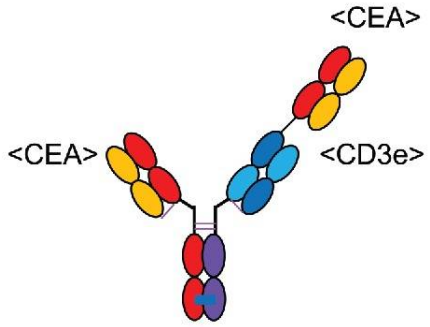
Target	Example	Stage
TA x CD40	ABBV-428	I
HER2 x 4-1BB	PRS343	I
FAP x 4-1BB	4-1BB agonist	PC
5T4 x 4-1BB	MGD006, JNJ-63709178, Xmab14045	I

Dahlen E et al. Therapeutic Advances in Vaccines and immunotherapy. 2018

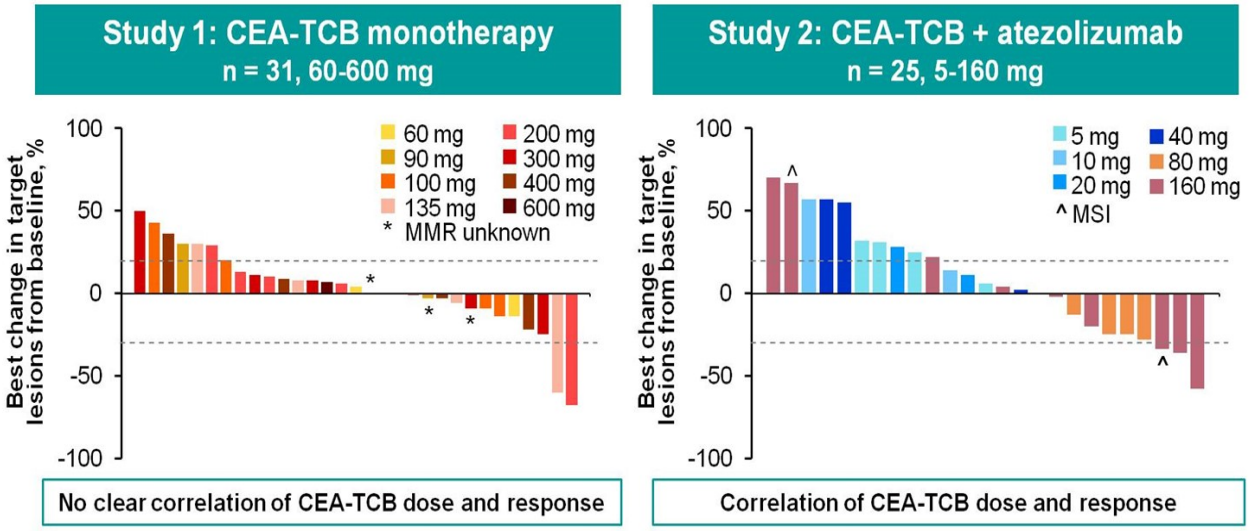
CEA-TCB

2-to-1 format

Binds w 1 arm to CD3 on T cells and with 2 arms to CEA on tumor cells

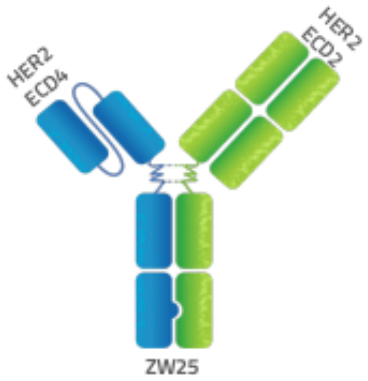


Tabernero J et

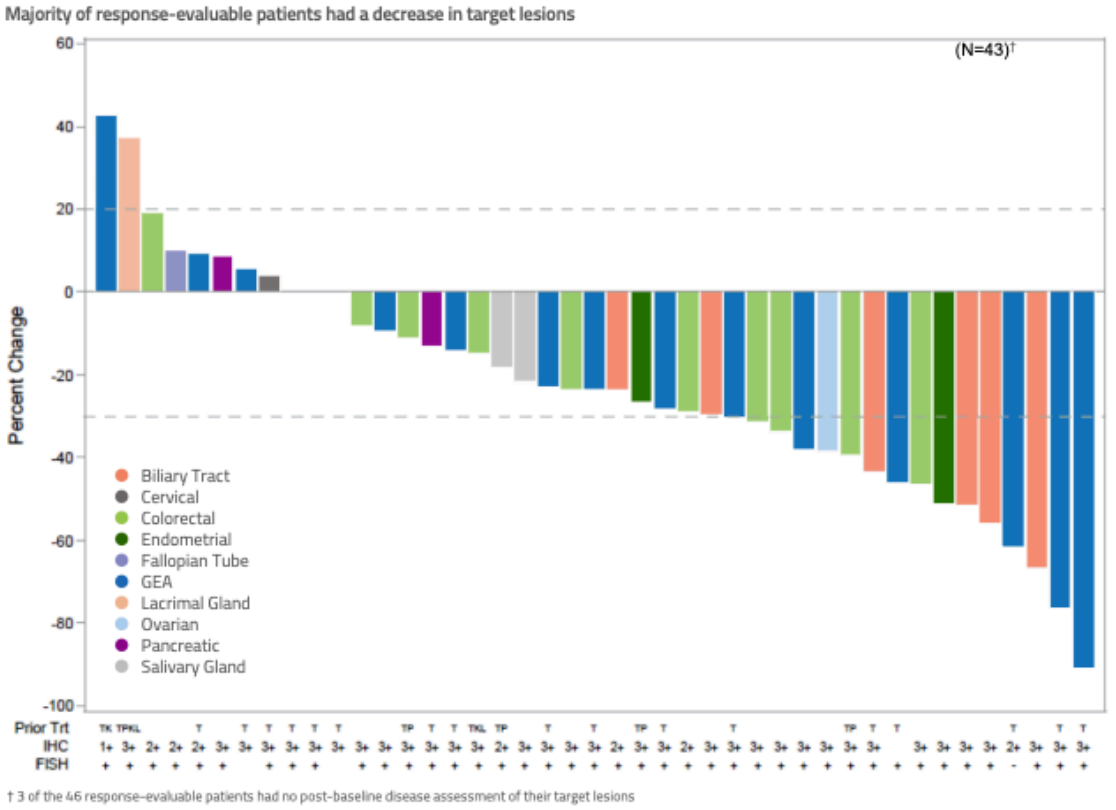


ZW25: bispecifc Her-2 targeted antibody

Cross-linked trans HER2 binding and HER2 receptor clustering



Meric-Bernstam F, ESMO 2019



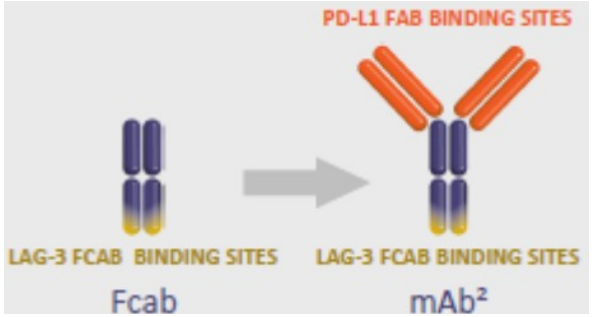
Dual Immunomodulators

Simultaneous targeting of two immunomodulating targets resulting in blockade of inhibitory targets, depletion of suppressive cells or activation of effector cells

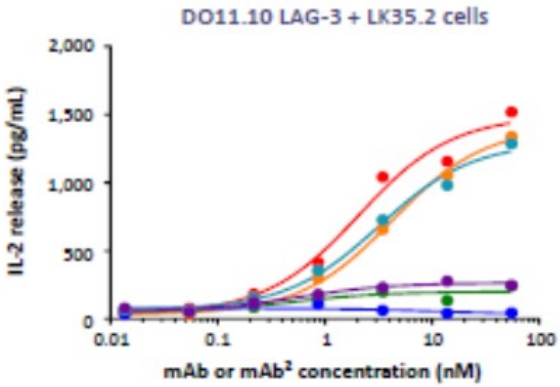
Target	Example	Stage
PD1 x LAG-3	MGD013, FS118	I
PD-1 x TIM-3	MCLA-134	Pre-clinical
PD1 x CTLA-4	XmAb20717	Pre-clinical
CTLA-4 x OX40	ATOR-1015	Pre-clinical

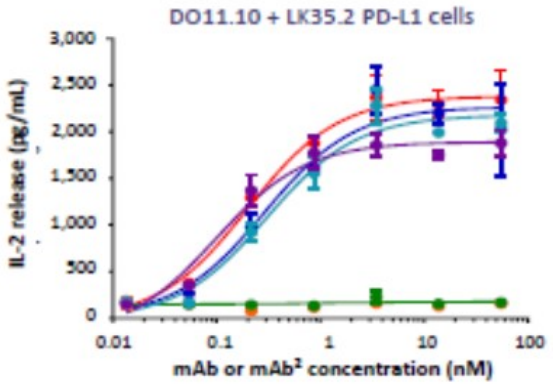
Dahlen E et al. Therapeutic Advances in Vaccines and immunotherapy. 2018

LAG/PD-L1 bispecific antibody blocks immune suppression in-vitro



Kraman M, SITC 2016





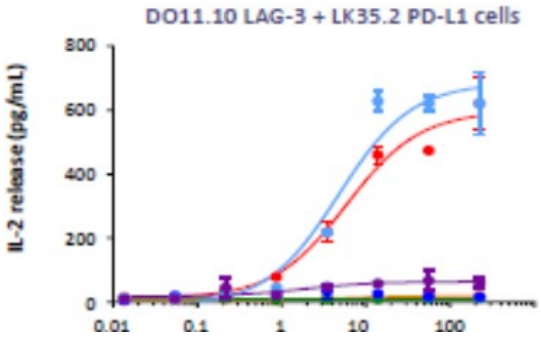
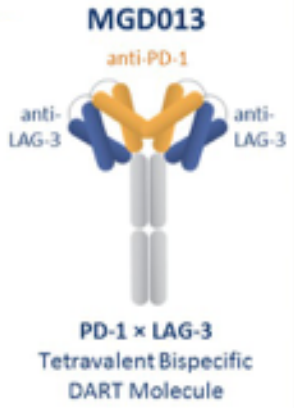
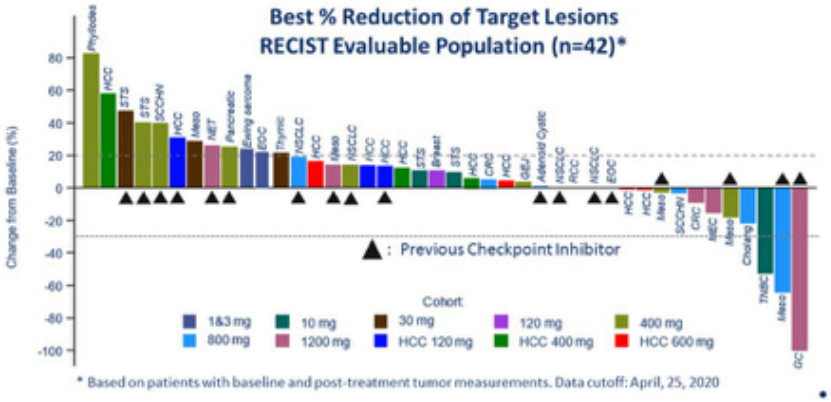


Figure 11. DO11.10 cells were incubated with the indicated mAb or mAb² while LK35.2 cells were incubated with OVA peptide and then combined. Cells were incubated at 37°C for 24 hours prior to measuring IL-2 levels in the supernatant by ELISA.

MGDO13





* Based on patients with baseline and post-treatment tumor measurements. Data cutoff: April, 25, 2020

Confirmed Partial Responses (n=1, each):

- TNBC (10 mg)
- Mesothelioma (800 mg)
- Gastric Cancer (1200 mg)

Refractory to anti-PD-1 treatment

- 18 patients with SD as best overall response (DCR = 48.8%)

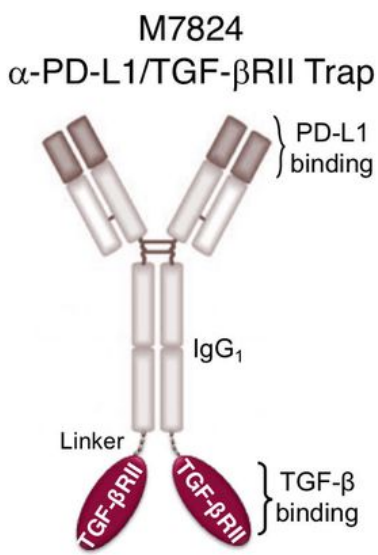
Immune-Related Adverse Events of Special Interest (AESIs)

	No. (%) of Patients	
	All Grades (N=53)	≥ Grade 3 (N=53)
Rash	7 (13.2)	1 (1.9)
Hypothyroidism	6 (11.3)	0
Immune-mediated hepatitis	2 (3.8)	2 (3.8)
Pancreatitis	1 (1.9)	1 (1.9)
Colitis	1 (1.9)	1 (1.9)
Adrenal insufficiency	1 (1.9)	1 (1.9)
Hyperthyroidism	1 (1.9)	0

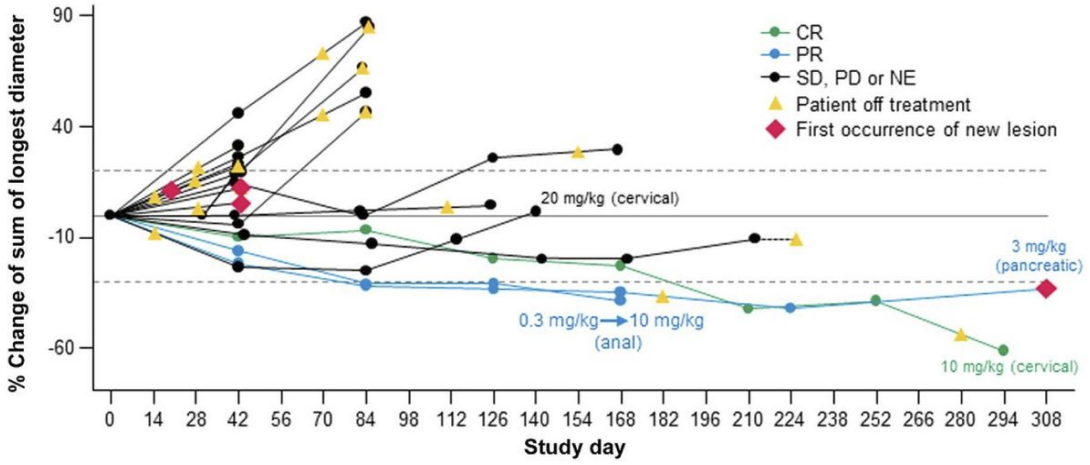
- Well-tolerated with manageable irAEs
- Safety consistent with anti-PD-(L)1 toxicity profile
- MTD not exceeded or defined at up to 1200 mg Q2W
- Dose limiting toxicities:
  - Immune-mediated hepatitis (1200 mg – primary dose escalation); resolved without sequelae
  - Lipase increase with radiographic evidence of pancreatitis (600 mg – HCC escalation); dose level subsequently cleared

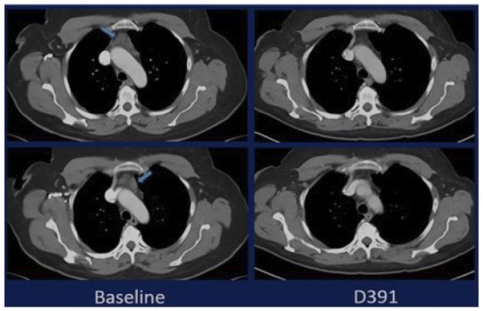
Ulahannan S et al. ASCO 2020

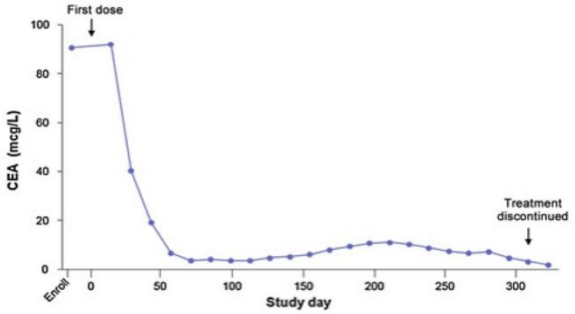
PD-L1 × TGFbeta



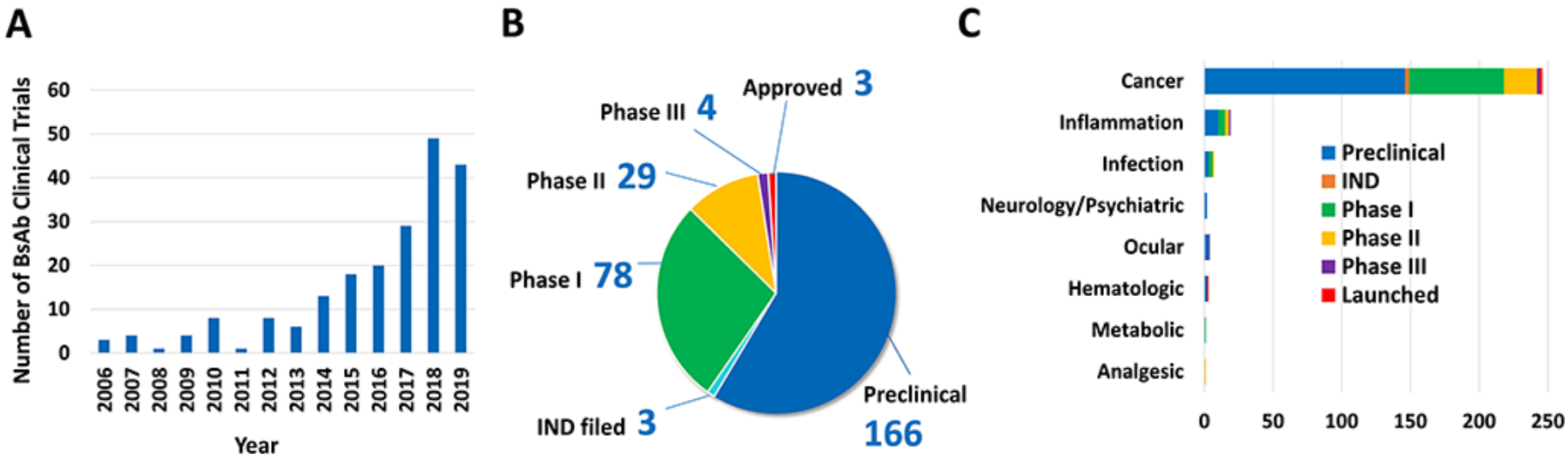
Lind et al. JITC 2020





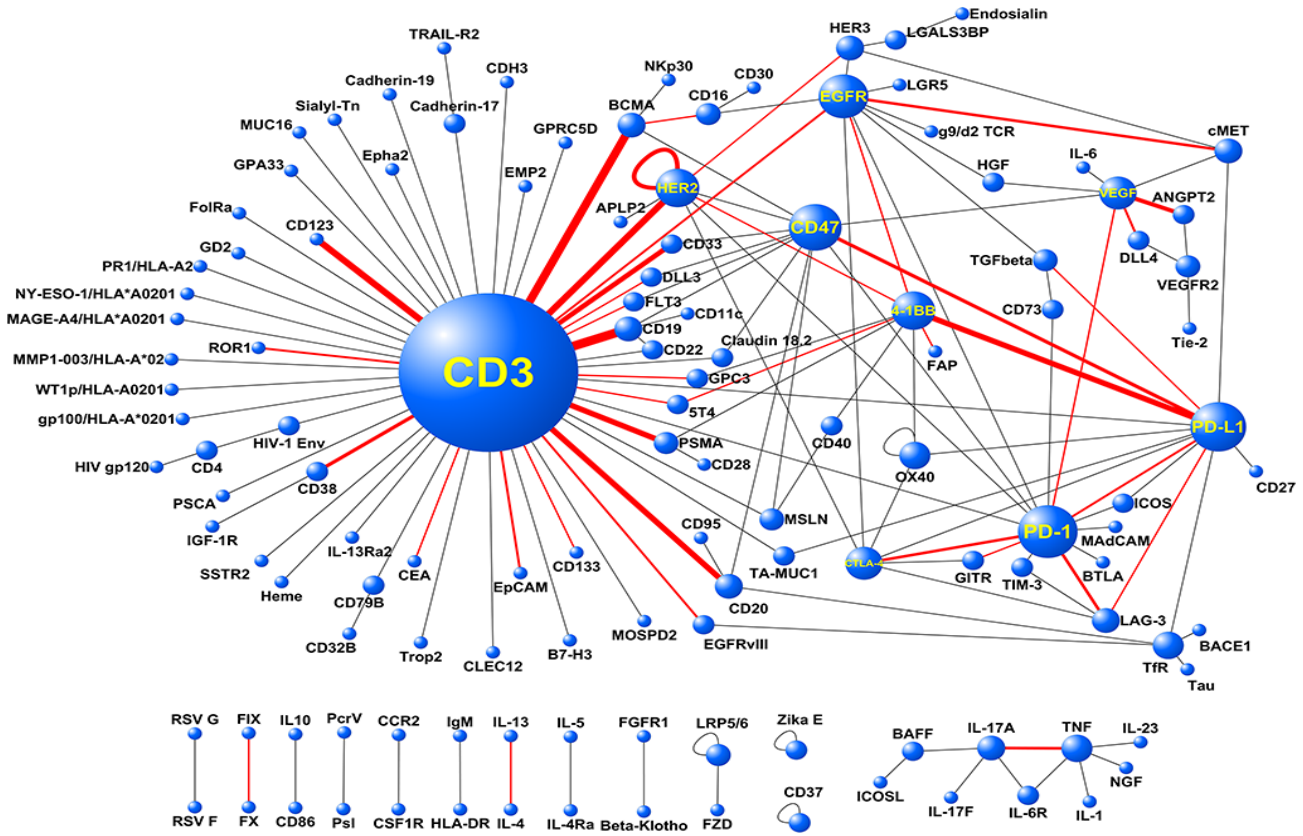


Rising Bispecific Antibody Programs



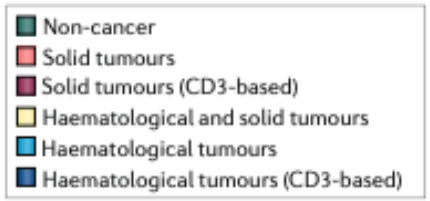
Nie S et al. Antibody Ther, 2020

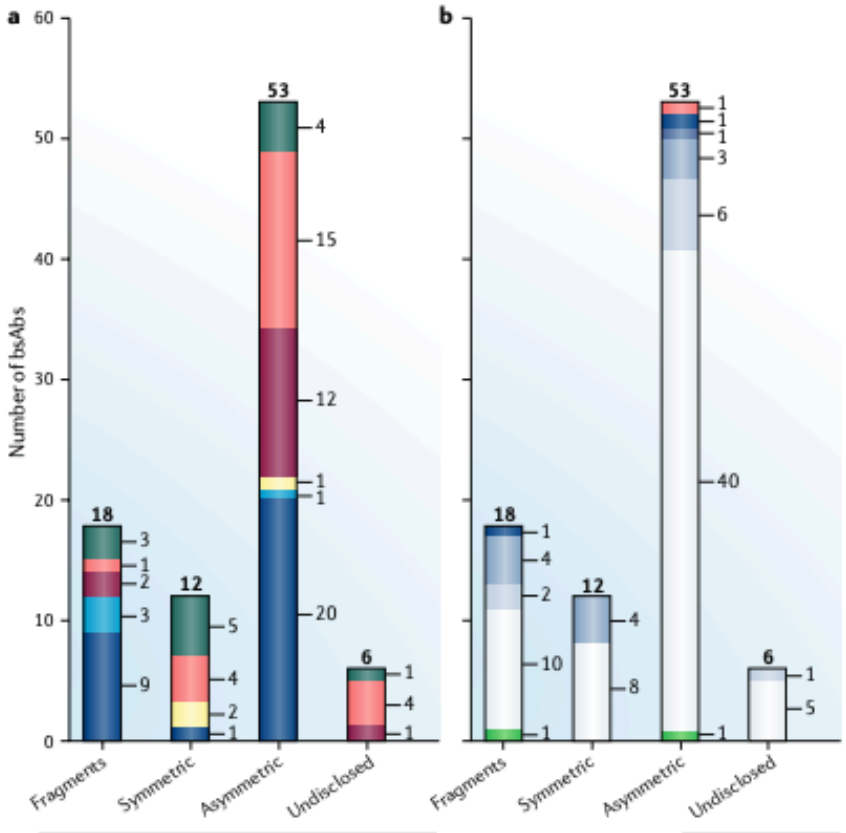
Potential target pairs of bispecific programs in pre-clinical/clinical space



Nie S et al. Antibody Ther, 2020

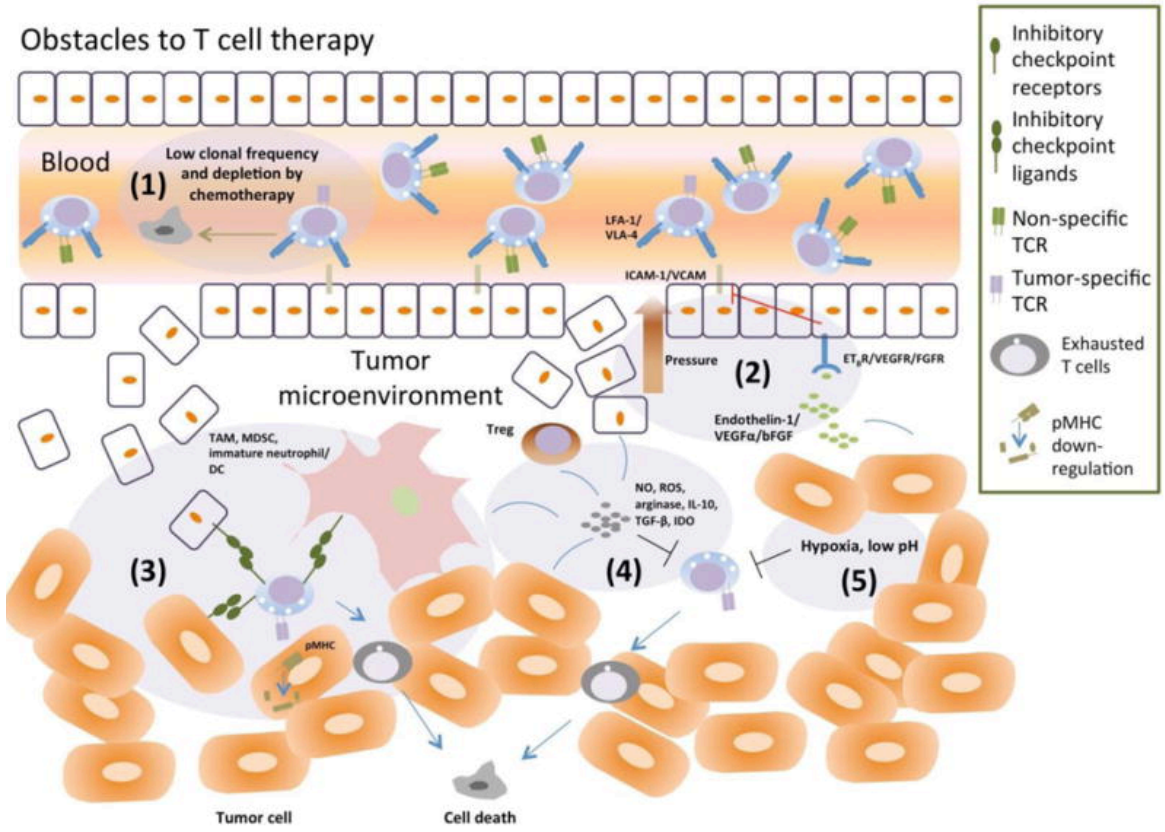
Clinical Development Pipeline





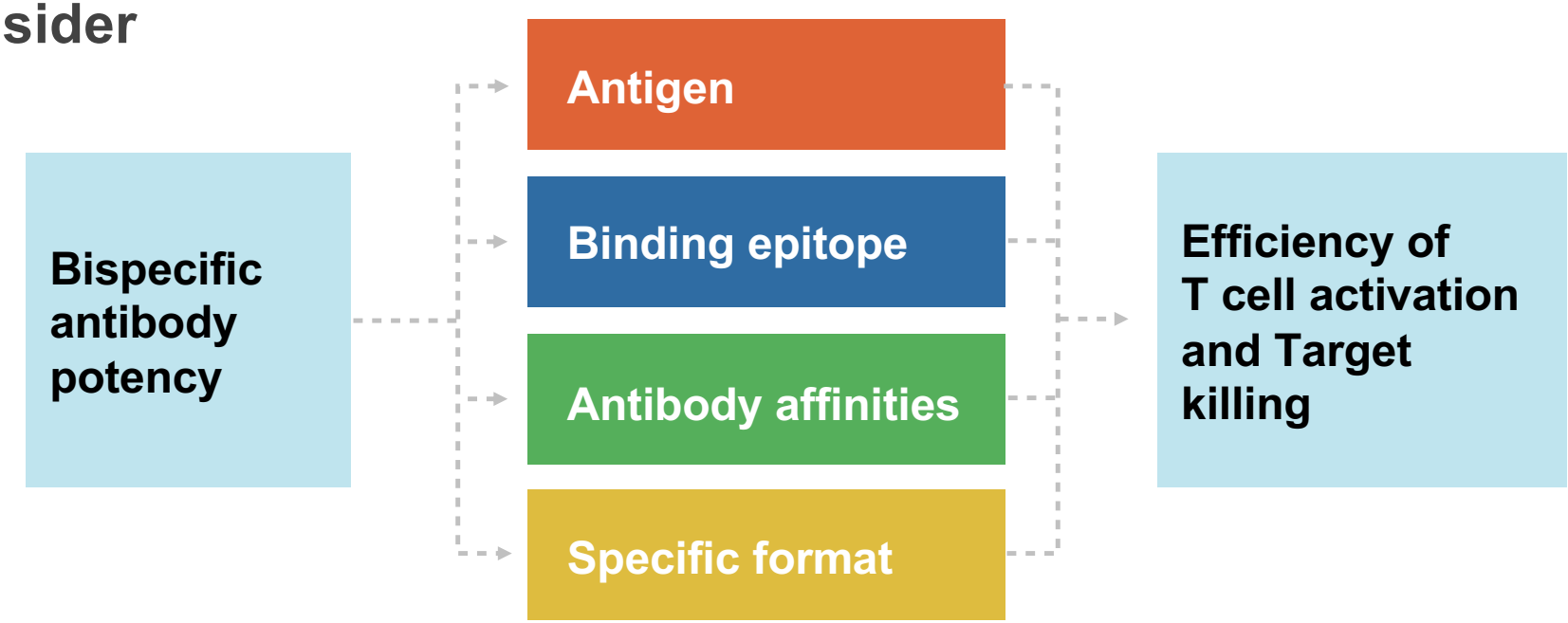
Labrijn A et al. Nature Review 2019

Challenges to overcome

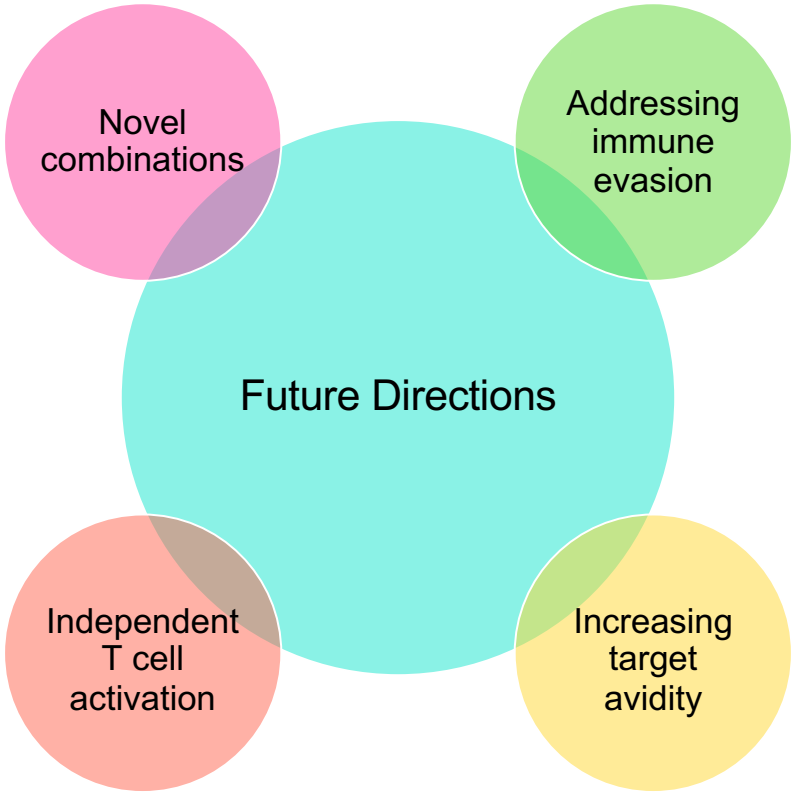


Memorial Sloan Kettering Cancer Center

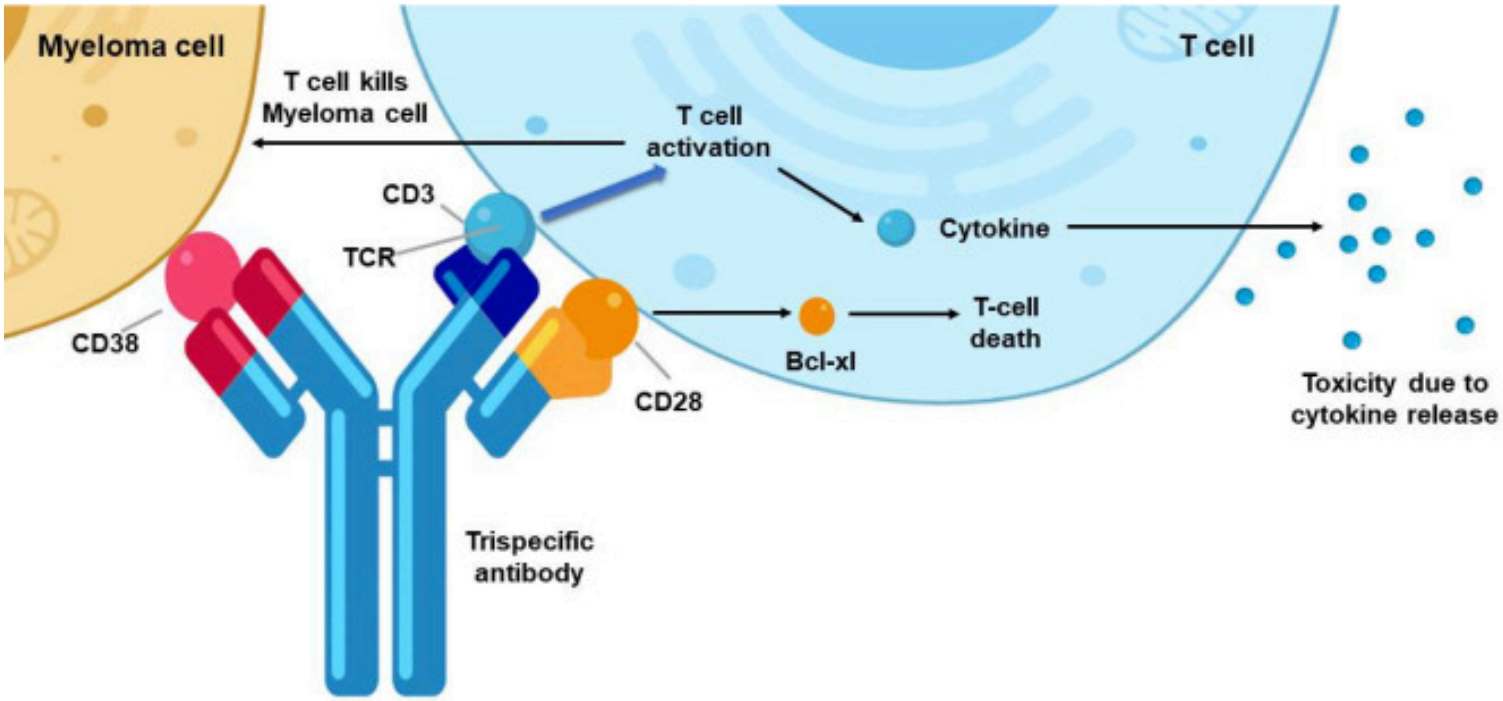
Factors to consider



Future directions

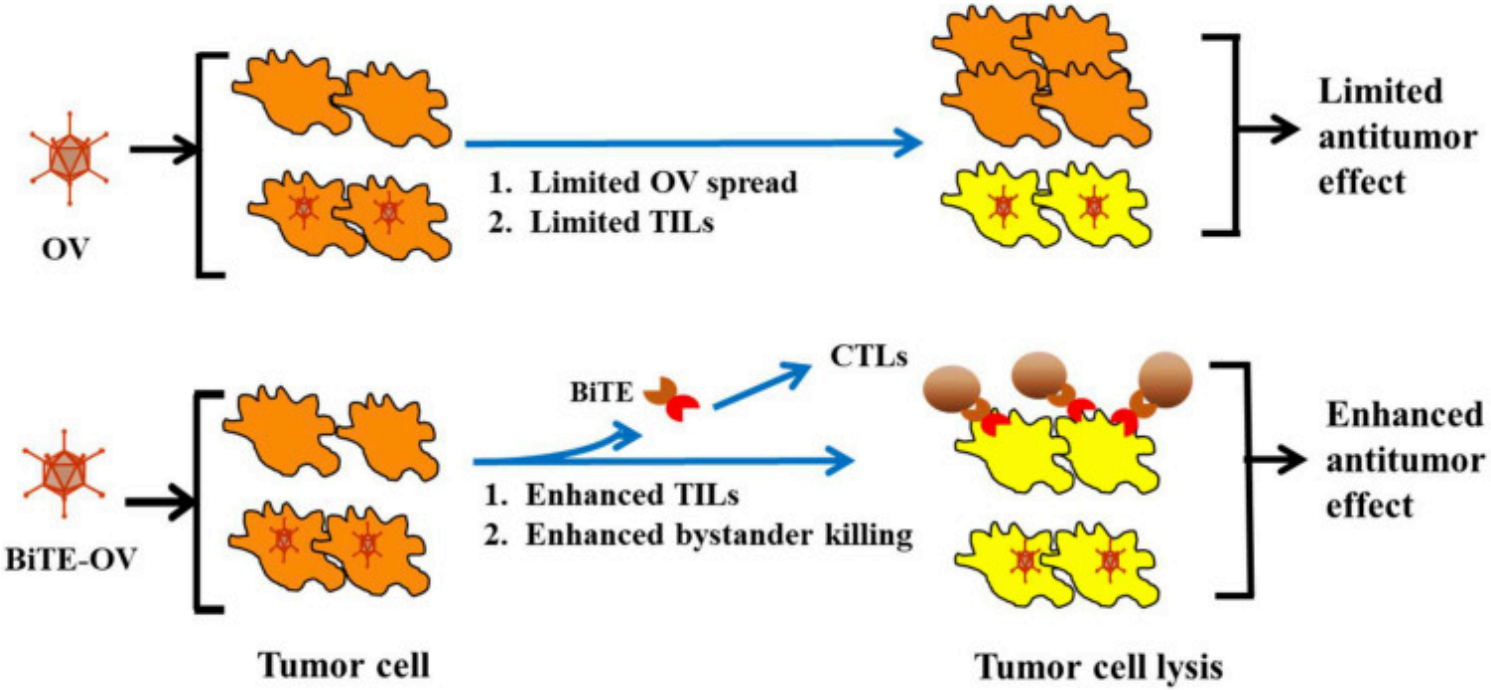


Triple specific T cell engager



Guo et al. Biomedicine 2020

BiTE-armed oncolytic virus



Guo et al. Biomedicine 2020

Conclusions

- **Bispecific antibodies will continue to evolve as promising cancer therapeutics**
- **Capitalizing on targetable cellular markers or genomic susceptibilities will further contribute to the progress**
- **Addressing safety, the complex solid tumor immune microenvironment and mechanisms of immune resistance/escape will be essential**
- **Future directions will incorporate novel approaches such as triple specific engagers or BITE-armed oncolytic viruses**

MSK Team

Sarcoma Medical Oncology
- Lauren Banks
- Jason Chan
- Ping Chi
- Mark Dickson
- Mrinal Gounder
- Mary Louise Keohan
- Ciara Kelly
- Benjamin Nacev
- Evan Rosenbaum
- William D. Tap
- Katherine Thornton
- Viswatej Avutu

Surgical Oncology
- Samuel Singer
- Sam Yoon
- Aimee Crago
- Edmund Bartlett
- Murray Brennan

Cellular Therapeutics
- Christopher Klebanoff
- Renier Brentjens
- Roisin O'Cearbhaill
- Chris Hackett

Sarcoma Pathology
- Cristina Antonescu
- Meera Hameed
- Narsi Agaram

Pediatric Oncology
- Julia Glade-Blender
- Emily Slotkin
- Leonard Wexler
- Paul Meyers

Early Drug Development
- Alex Drilon
- Margaret Callahan

Support

NIH Supplement
Alliance 3U10-CA180821-03

dangelos@mskcc.org
@sandrapdangelo

NASDC
NCI Awardee Skills Development Consortium

Bispecific Antibodies As Cancer Therapeutics

Questions