What's Next for Cancer Immunotherapy

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MAY 6, 2021

Disclosures

- Consulting or Advisory Role: Iovance Biotherapeutics, IDEAYA Biosciences, Epizyme, Deciphera, Sanofi Genzyme, OncoSec, Genentech, Nektar,
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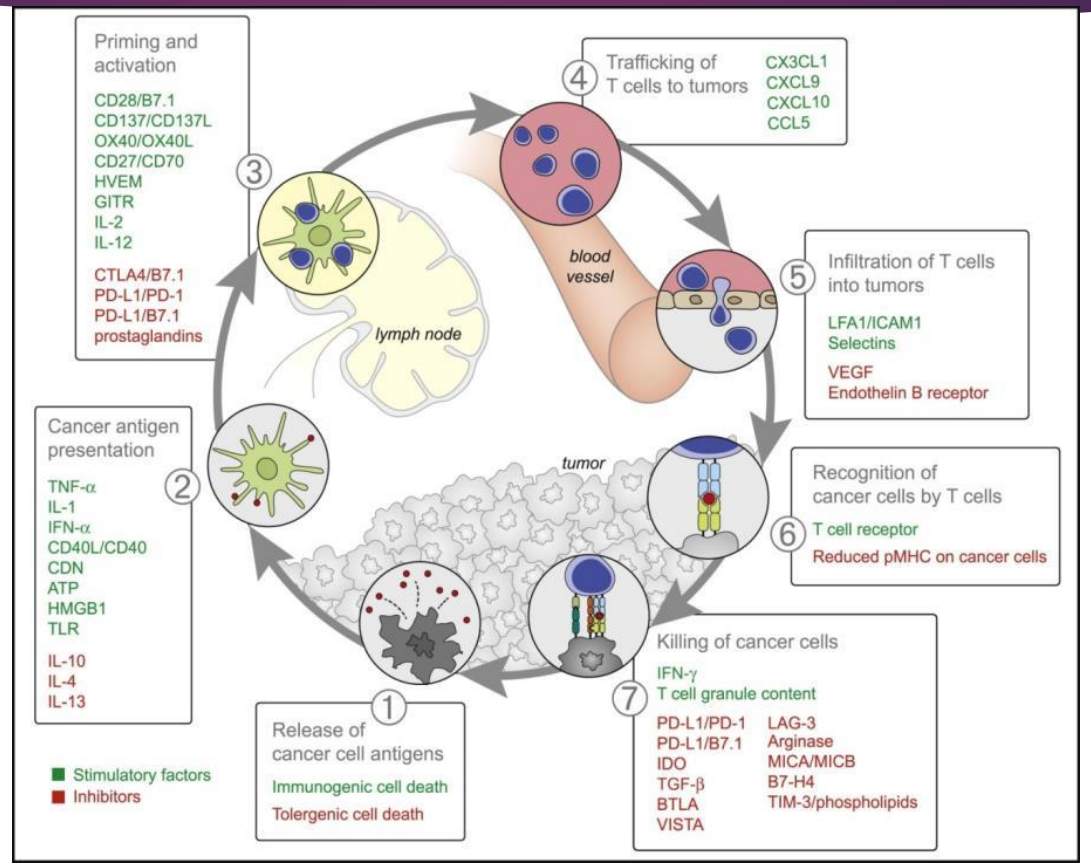
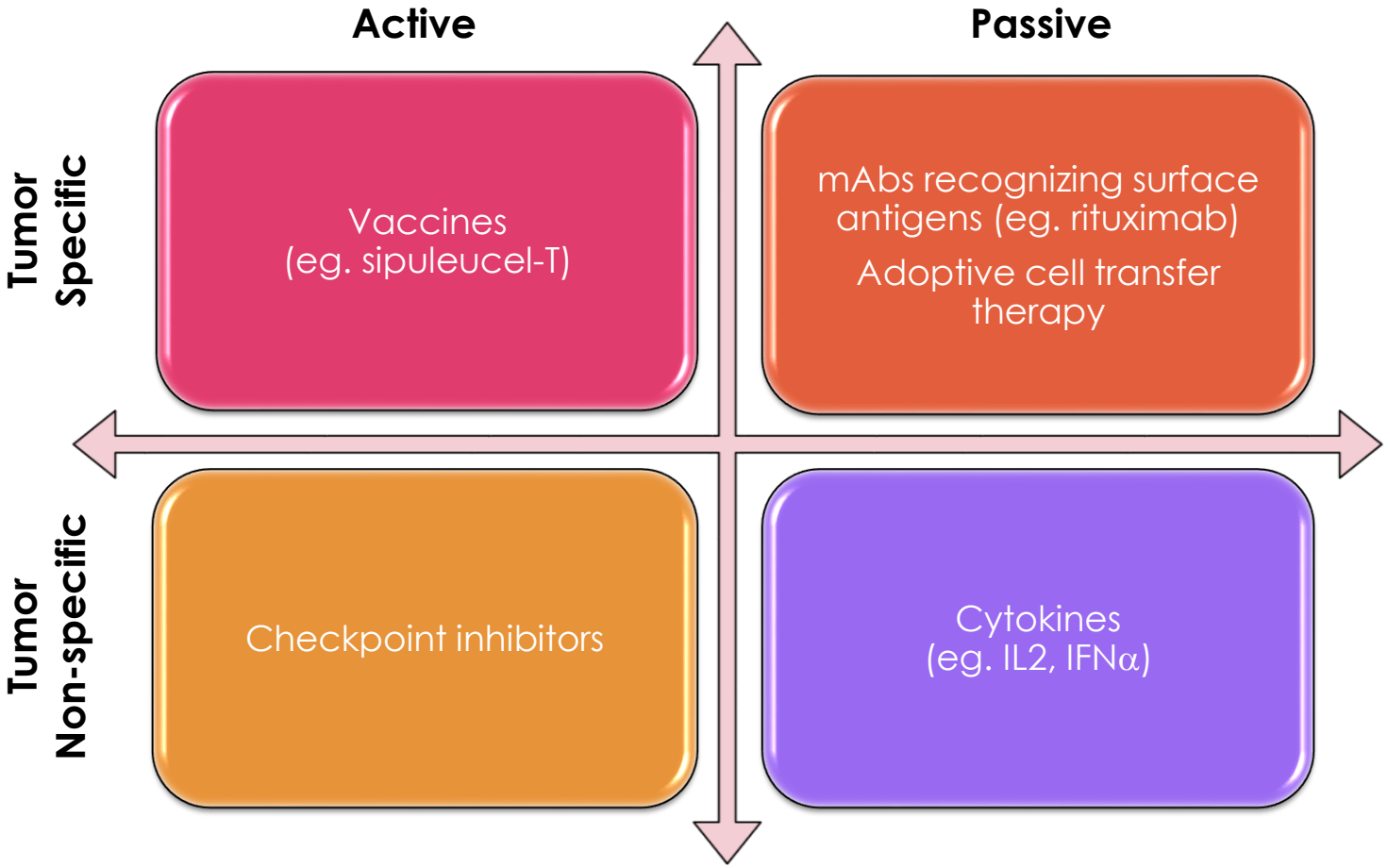
- **I will be discussing non-FDA approved indications during my presentation.**

Stimulatory and Inhibitory Molecules During Immune Tumor Surveillance

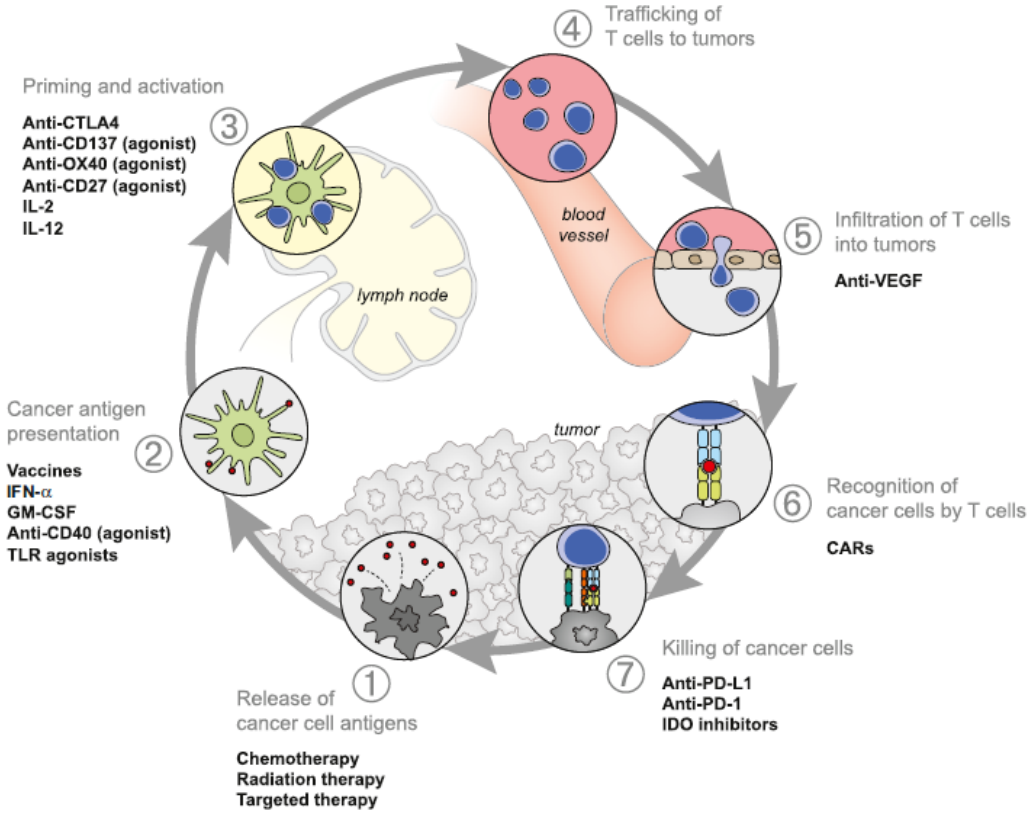


Chen DS, et al. Immunity. 2013;39:1-10.

Cancer Immunotherapy: The Basic Principles



A Roadmap of Immunotherapy Agents in the Cancer – Immune System Interaction



Chen DS, et al. Immunity. 2013;39:1-10.

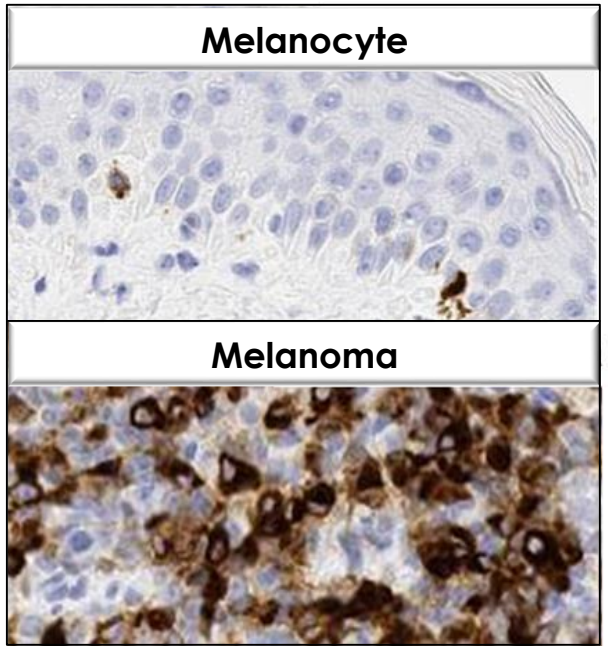
Passive, Tumor-specific Immunotherapy

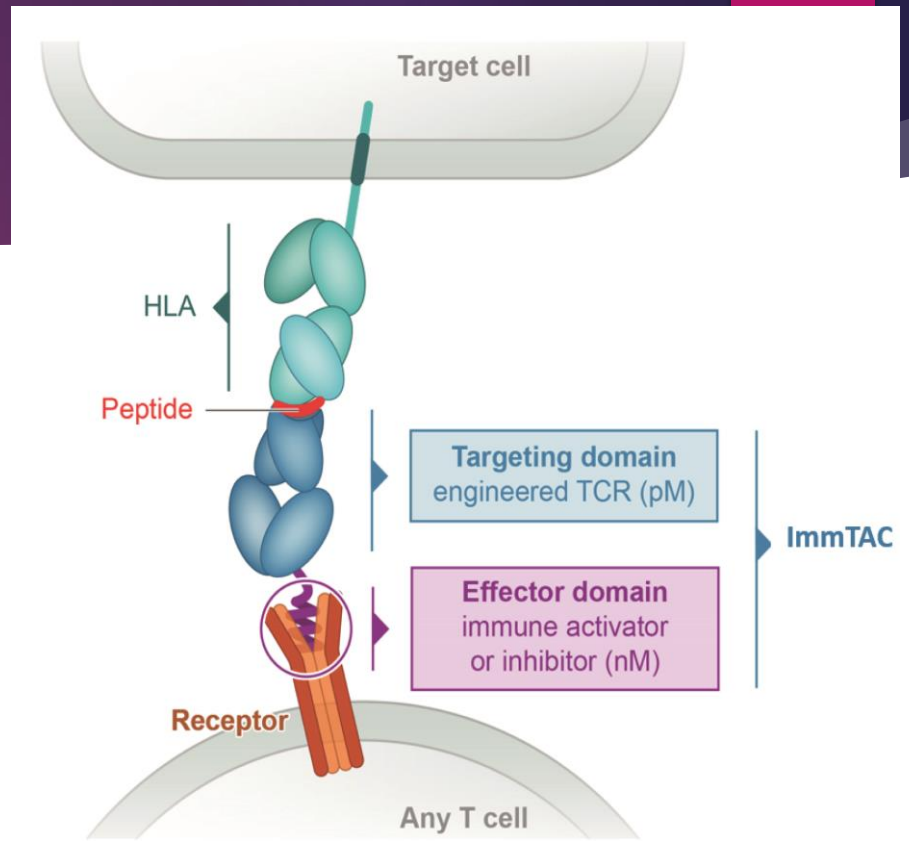
Tebentafusp

Immune-mobilizing monoclonal TCRs against cancer (ImmTACs)

Uveal Melanoma (UM)

- 12-mo OS up to 52% in first line clinical trials[1,2,3]
- Commonly expresses gp100 (melanocytic protein)





Tebentafusp

- Bispecific, soluble TCR therapeutic
- Affinity-enhanced TCR fused to anti-CD3
- Designed to redirect T cells to gp100+ melanocytic cells

1. Piulats JM, et al. *J Clin Oncol* 2021;39(6):586–98; 2. Rantala ES, et al. *Melanoma Res* 2019;29(6):561–8; 3. Khoja L, et al. *Ann Oncol* 2019;30(8):1370–80; S. Piperno-Neumann et al. AACR 2021

IMCgp100-202 – study design

Advanced UM:

- HLA-A*0201+
- No prior systemic therapy in the advanced setting
- No prior liver-directed therapy, except surgery
- Any LDH

Randomized 2:1

Stratification by LDH level
(>ULN vs ≤ULN)

Tebentafusp:

- 20 mcg C1D1
- 30 mcg C1D8
- 68 mcg C1D15+

Investigator's Choice (IC):

- Dacarbazine 1000 mg/m^2 Q3W
- Ipilimumab 3 mg/kg Q3W
- Pembrolizumab 2 mg/kg Q3W

Co-primary endpoints

- **OS in randomized patients to tebentafusp vs IC treatment (ITT)**
- **OS in randomized patients to tebentafusp with rash during Wk 1 vs IC treatment**

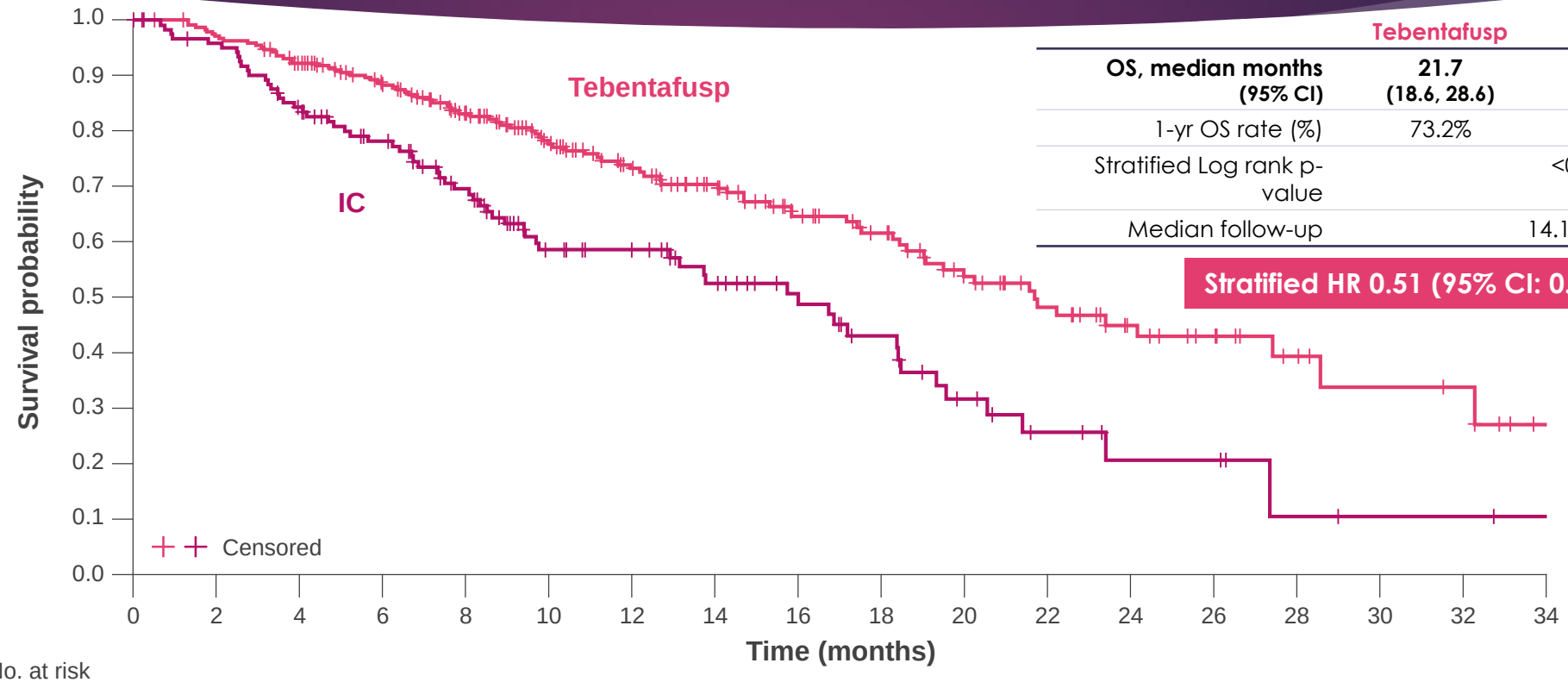
Key secondary endpoints

- **ORR and PFS by investigator assessment**

S. Piperno-Neumann et al. AACR 2021

Data cut-off date: October 13, 2020; data snapshot date: January 22, 2021.
ITT, intent-to-treat; ORR, overall response rate; PFS, progression free survival.

Primary endpoint: Overall survival



	Tebentafusp	IC
OS, median months (95% CI)	**21.7 (18.6, 28.6)**	**16.0 (9.7, 18.4)**
1-yr OS rate (%)	73.2%	58.5%
Stratified Log rank p-value	<0.0001	
Median follow-up	14.1 months	

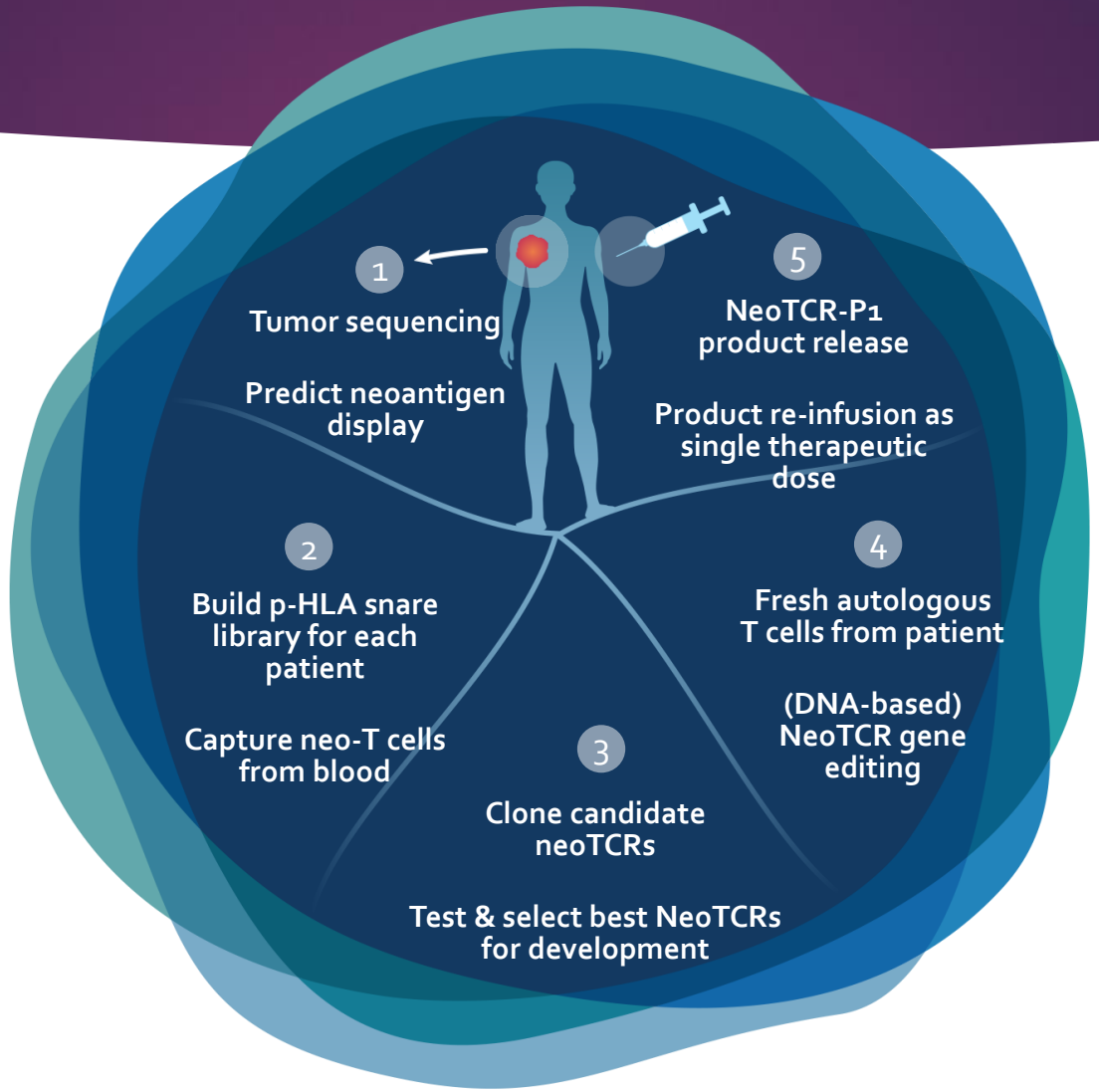
Stratified HR 0.51 (95% CI: 0.37, 0.71)

No. at risk

Tebentafusp	252	242	221	197	167	132	109	90	71	59	44	33	22	17	9	6	5	0
IC	126	116	100	86	69	48	43	34	27	20	12	7	4	4	1	1	1	0

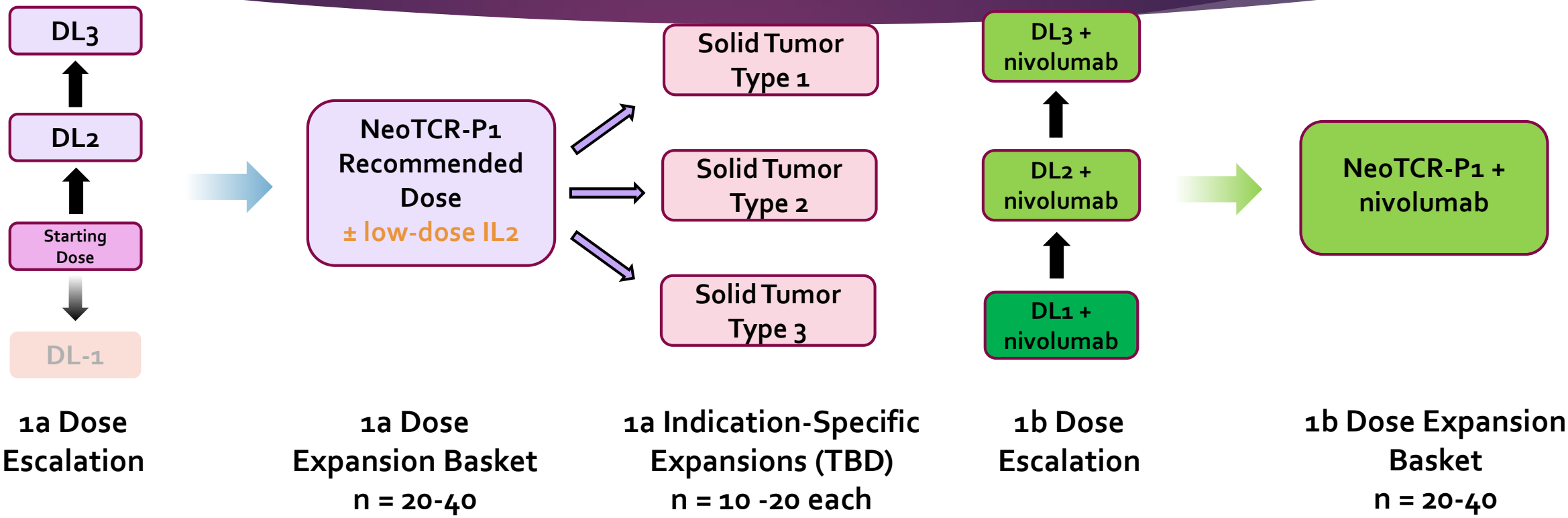
S. Piperno-Neumann et al. AACR 2021

Gene-Edited Autologous NeoTCR-T Cells



Chmielowski B et al, ASCO 2021

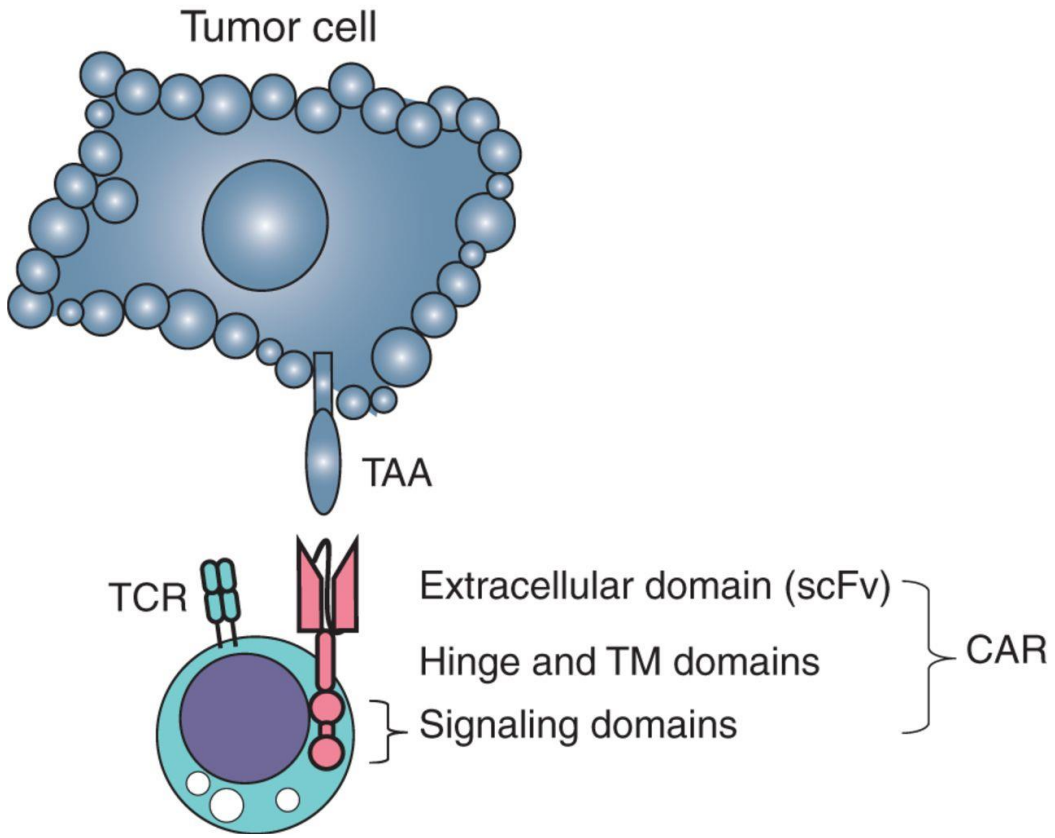
Phase 1 Study Design (NCT03970382)



Advanced melanoma, urothelial, non-small cell lung, colorectal, ovarian, prostate, or HER-2(-) breast cancer
Products contain up to 3 distinct NeoTCRs

Chmielowski B et al, ASCO 2021

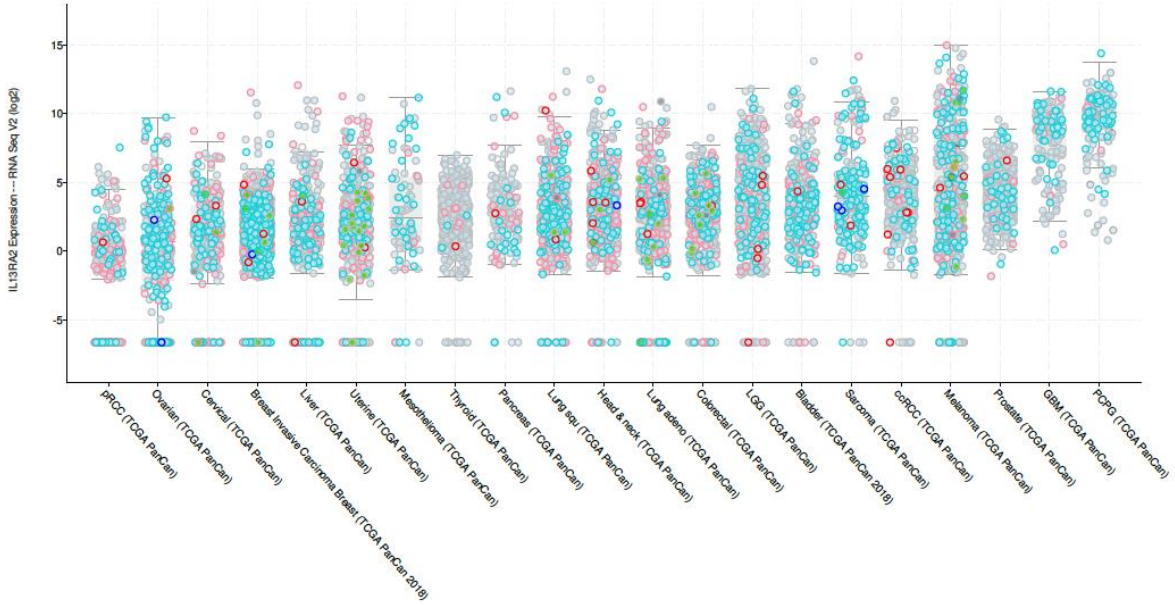
Chimeric antigen receptor (CAR) T cell therapy for solid tumors



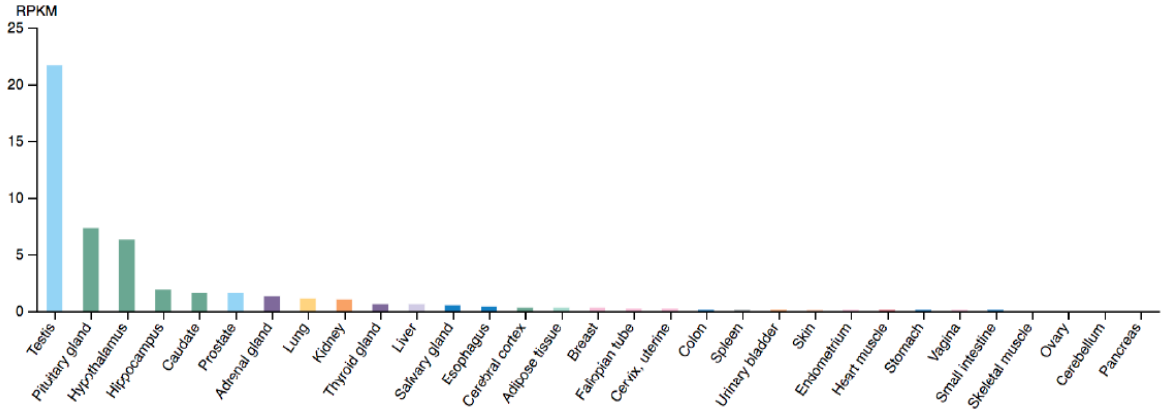
Clare Y Slaney et al. Cancer Discov 2018;8:924-934

Phase 1 Dose Escalation Study of Systemically Administered IL13Ra2 Chimeric Antigen Receptor (CAR) T cells after a Nonmyeloablative Conditioning Regimen in Patients with Metastatic Melanoma and Other Solid Tumors. PI: Dr Anusha Kalbasi

TCGA



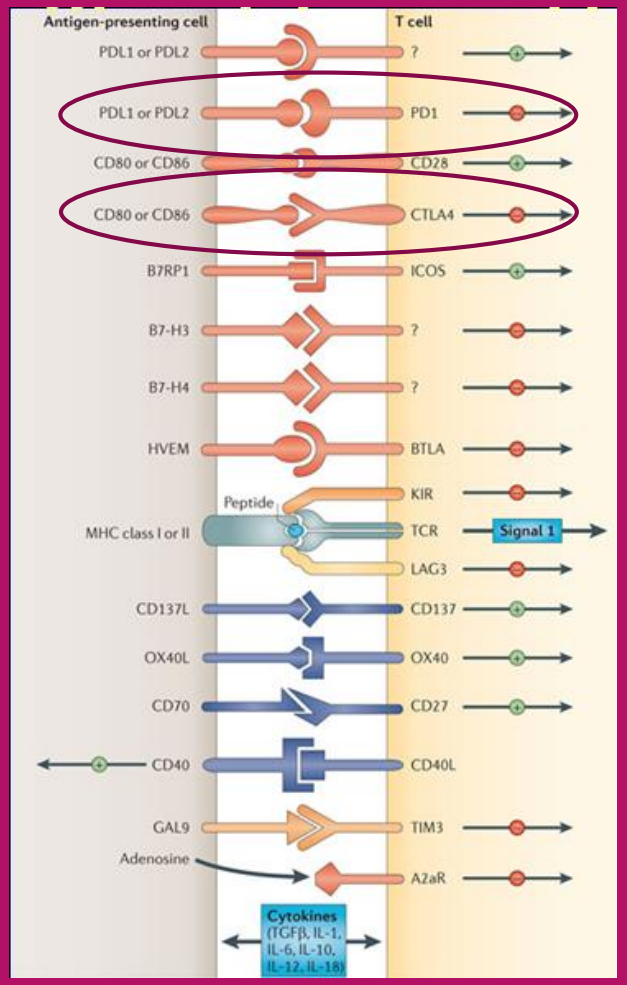
IL13Ra2 mRNA expression in normal tissues



Courtesy of Dr A. Kalbasi

Active, Tumor-non-specific Immunotherapy

Immunological synapse

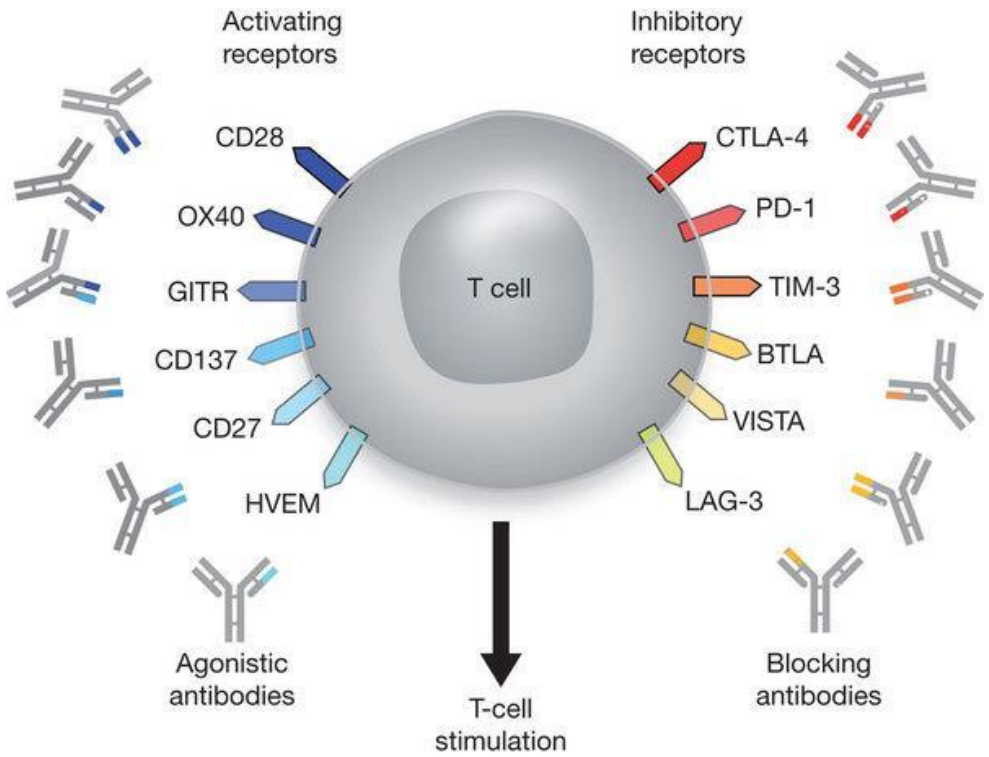


Pardoll DM. Nat Rev Cancer. 2012;12:252-264.

Approved immune checkpoint inhibitors

	melanoma	Non-small cell lung cancer	Small cell lung cancer	Head and neck cancer	Hodgkin lymphoma	Urothelial carcinoma	Gastric cancer	Esophageal cancer	Cervical cancer	Renal cell ca	Hepatocellular ca	Endometrial ca	Merkel cell ca	Cutaneous SCC	Mismatch Repair Deficient colon ca	Triple neg breast ca	Mesothelioma	Primary Mediastinal large B-cell lymphoma	Tumor Mutational Burden-High (>10/Mb)	Basal cell carcinoma
Anti-CTLA4 Ab																				
ipilimumab	■																			
Anti-PD1 Ab																				
pembrolizumab	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■		■	■	
nivolumab	■	■		■	■	■		■		■	■				■					
cemiplimab		■												■						■
Anti-PDL1 Ab																				
atezolizumab	■	■	■			■					■					■				
durvalumab		■	■																	
avelumab						■				■			■							
Anti-PD1 Ab + anti-CTLA4 Ab																				
nivolumab + ipilimumab	■	■								■	■				■		■			

Keeping the T Cells "Active": Approaches



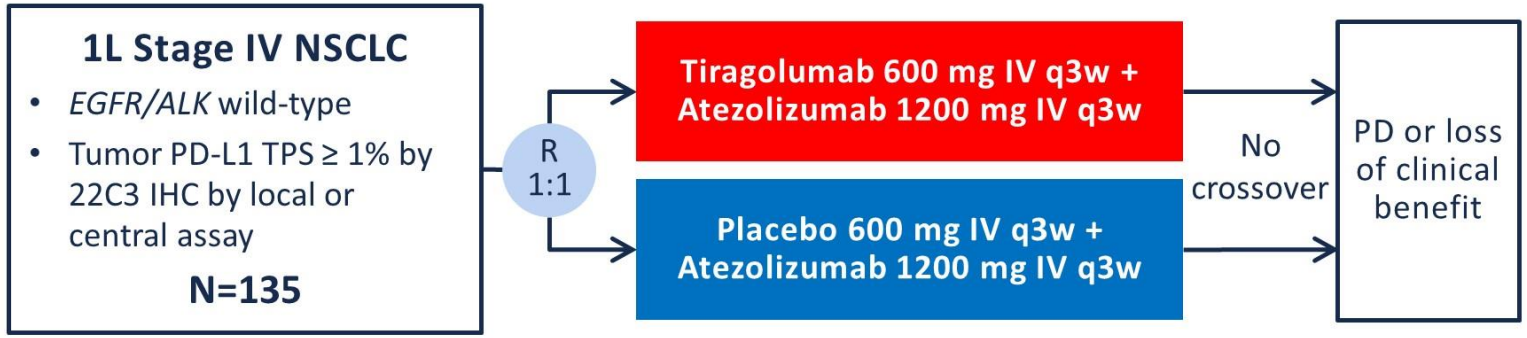
Turning up The Activating

Blocking the Inhibiting

Mellman I, et al. Nature. 2011;480:480-489

A randomized, double-blind, phase II study of the anti-TIGIT antibody tiragolumab (tira) plus atezolizumab (atezo) versus placebo plus atezo as first-line (1L) treatment in patients with PD-L1-selected NSCLC (CITYSCAPE).

CITYSCAPE Study Design



Stratification Factors:

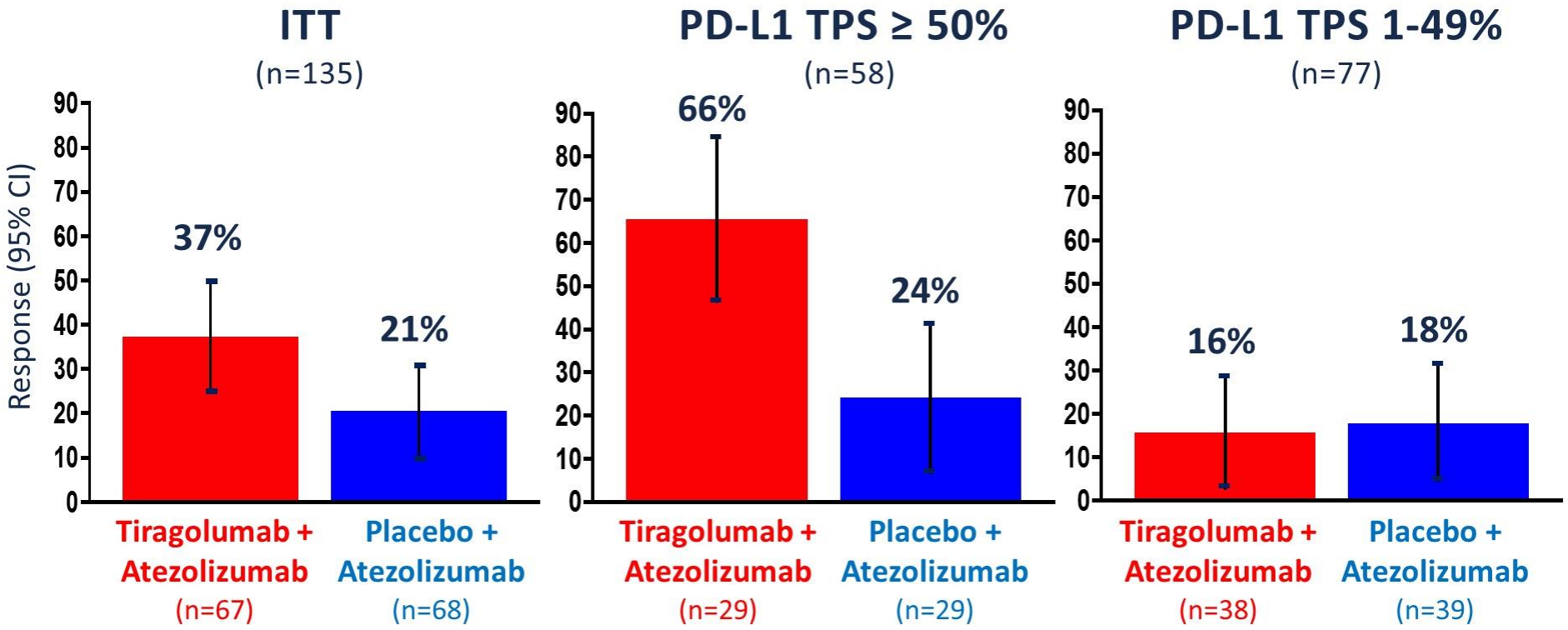
- PD-L1 TPS (1-49% vs ≥ 50%)
- Histology (Non-Squamous vs Squamous)
- Tobacco use (yes vs no)

- **Co-Primary Endpoints: ORR** and **PFS**
- **Key Secondary Endpoints: Safety**, DOR, OS, Patient-reported outcomes (PROs)
- **Exploratory Endpoints:** Efficacy analysis by PD-L1 status

DOR = duration of response; IHC = immunohistochemistry; ORR = confirmed overall response rate; OS = overall survival; PD = progressive disease; PFS = progression free survival ; q3w = every 3 weeks; R = randomized; TPS = tumor proportion score

Rodriguez-Abreu D et al. ASCO 2020, presented by Melissa Johnsson

Confirmed overall response rate

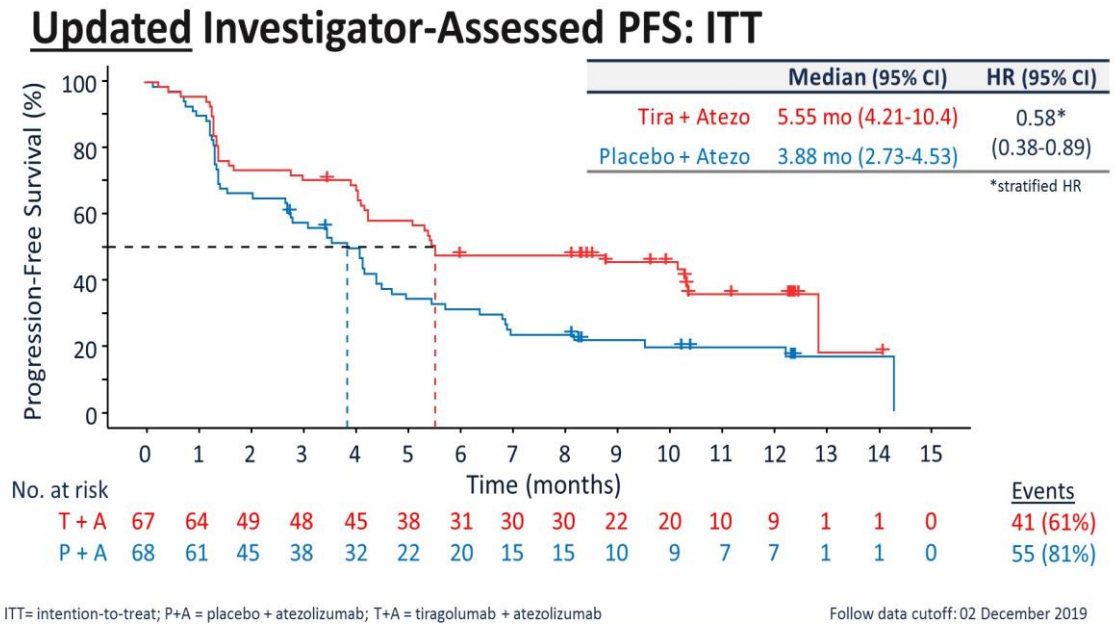


ITT = intention-to-treat; TPS = tumor proportion score

Updated data cutoff: 02 Dec 2019

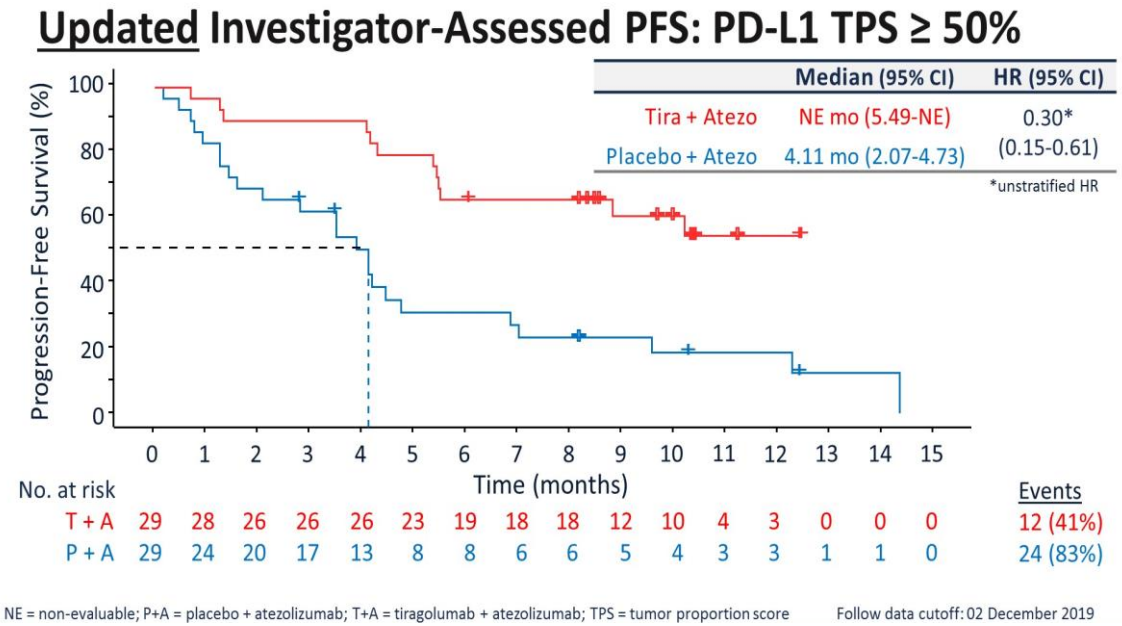
Rodriguez-Abreu D et al. ASCO 2020, presented by Melissa Johnsson

Progression-free survival



ITT= intention-to-treat; P+A = placebo + atezolizumab; T+A = tiragolumab + atezolizumab

Follow data cutoff: 02 December 2019



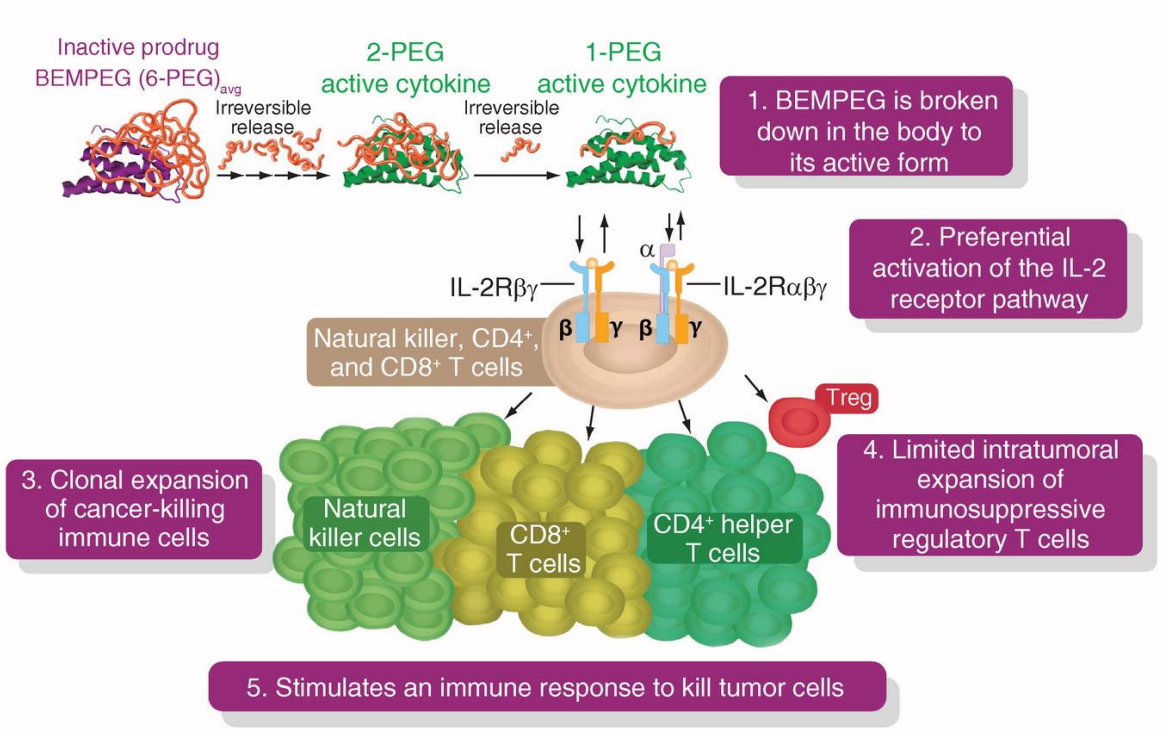
NE = non-evaluable; P+A = placebo + atezolizumab; T+A = tiragolumab + atezolizumab; TPS = tumor proportion score

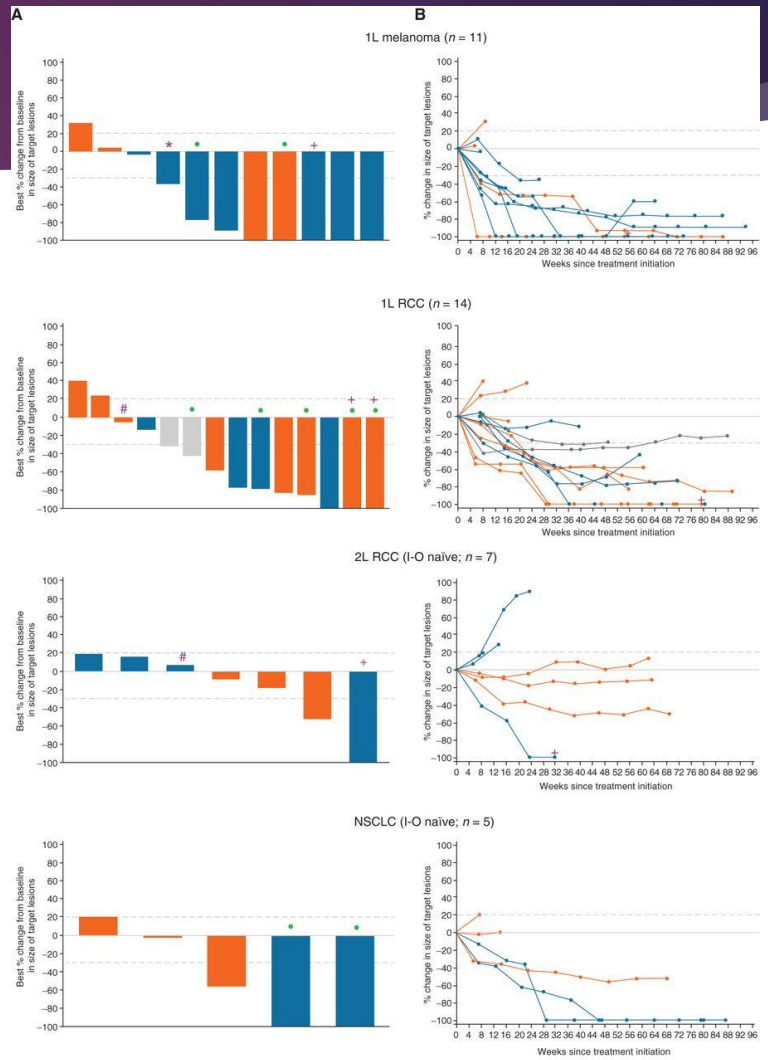
Follow data cutoff: 02 December 2019

Rodriguez-Abreu D et al. ASCO 2020, presented by Melissa Johnsson

Passive, Tumor-non-specific Immunotherapy

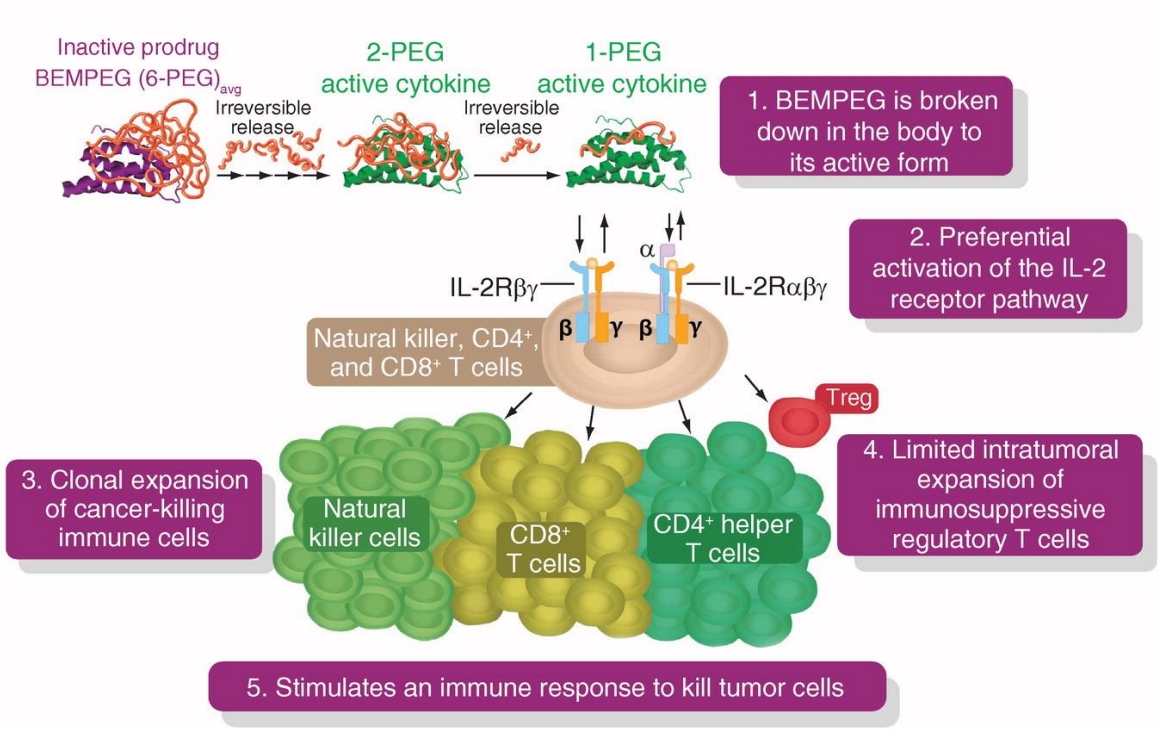
Bempegaldesleukin (NKTR-214)

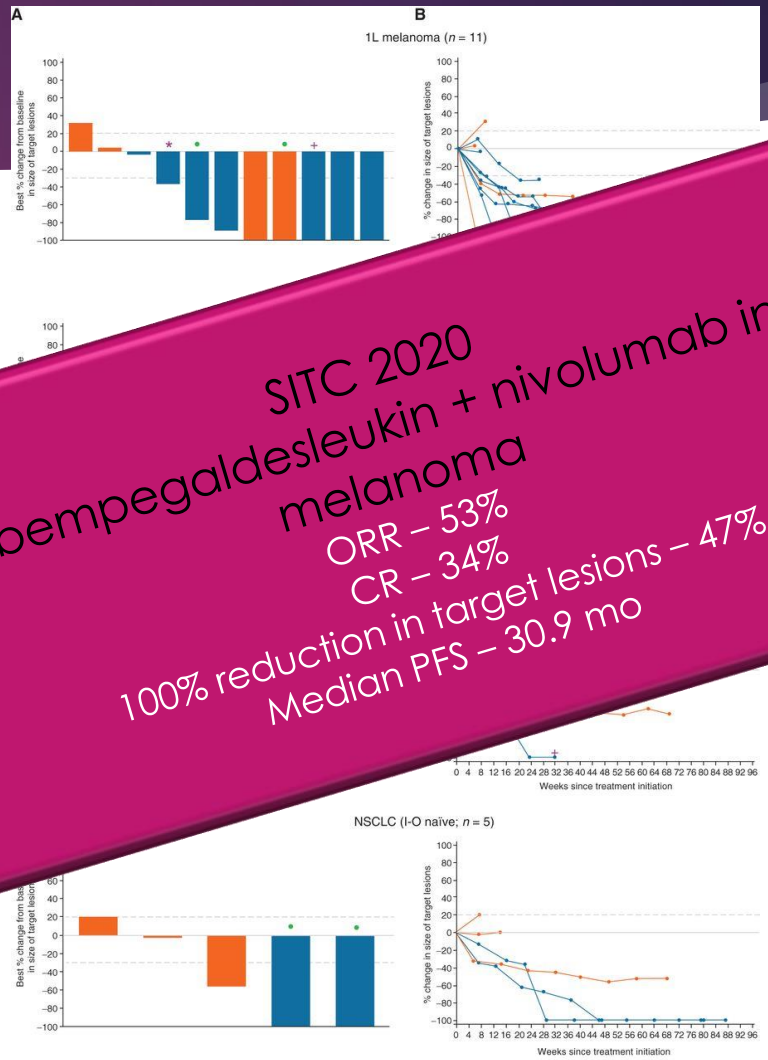




Huddart RA, et al. Future Oncol. 2021 Jan;17(2):137-149
Diab A et al. Cancer Discov. 2020 Aug;10(8):1158-1173

Bempegaldesleukin (NKTR-214)

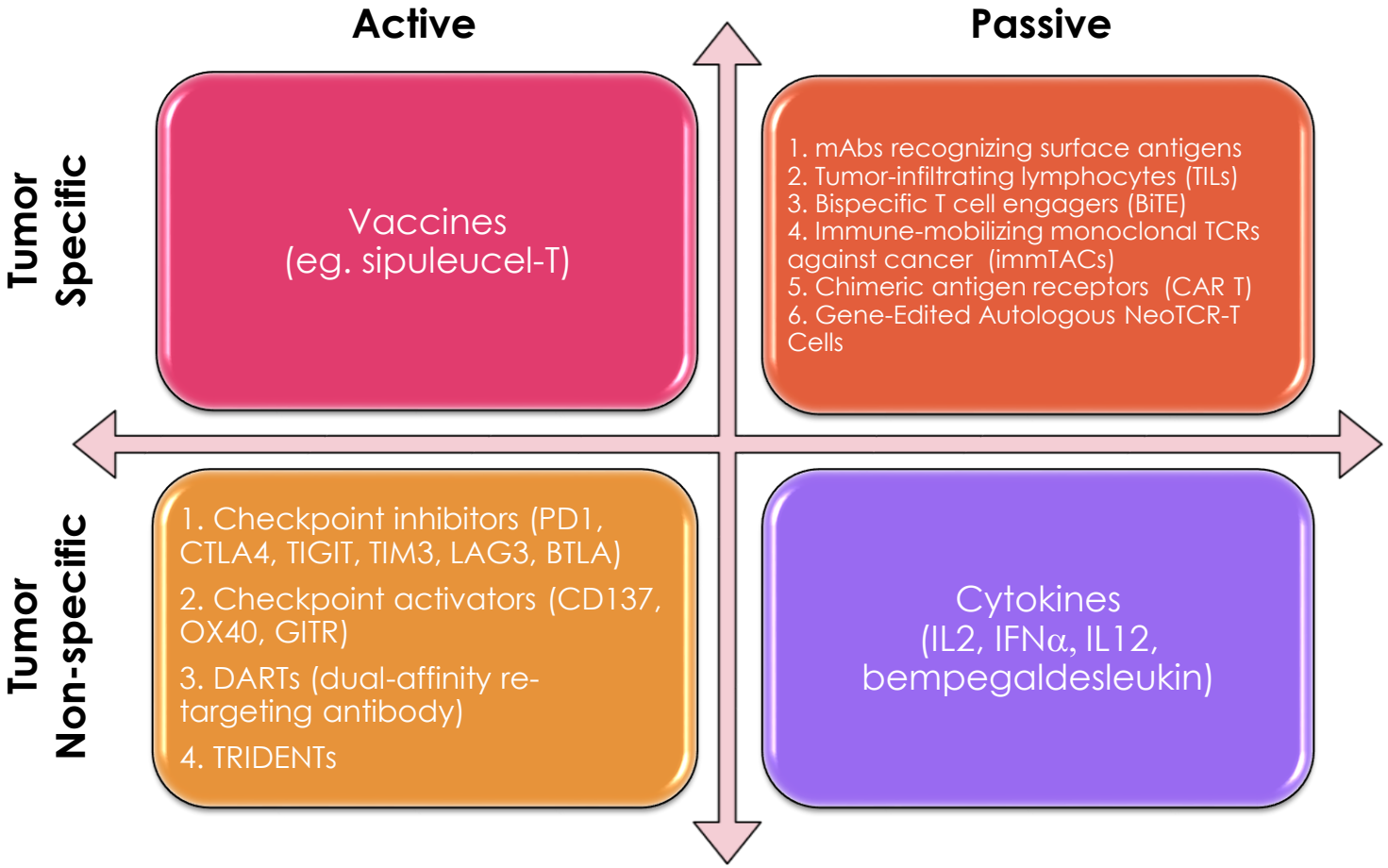




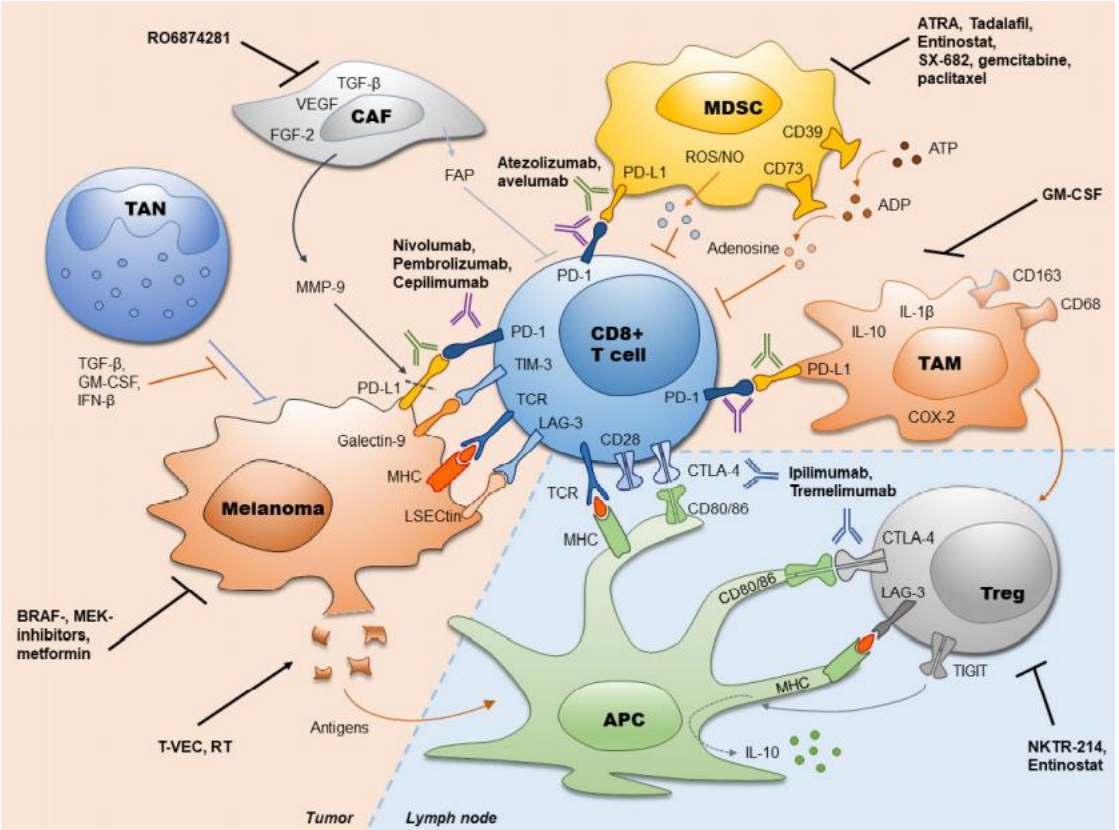
SITC 2020
bempegaldesleukin + nivolumab in melanoma
ORR – 53%
CR – 34%
100% reduction in target lesions – 47%
Median PFS – 30.9 mo

Huddart RA, et al. Future Oncol. 2021 Jan;17(2):137-149
Diab A et al. Cancer Discov. 2020 Aug;10(8):1158-1173

Cancer Immunotherapy: The Basic Principles



Immune checkpoint inhibitors in melanoma and their combination with other therapies

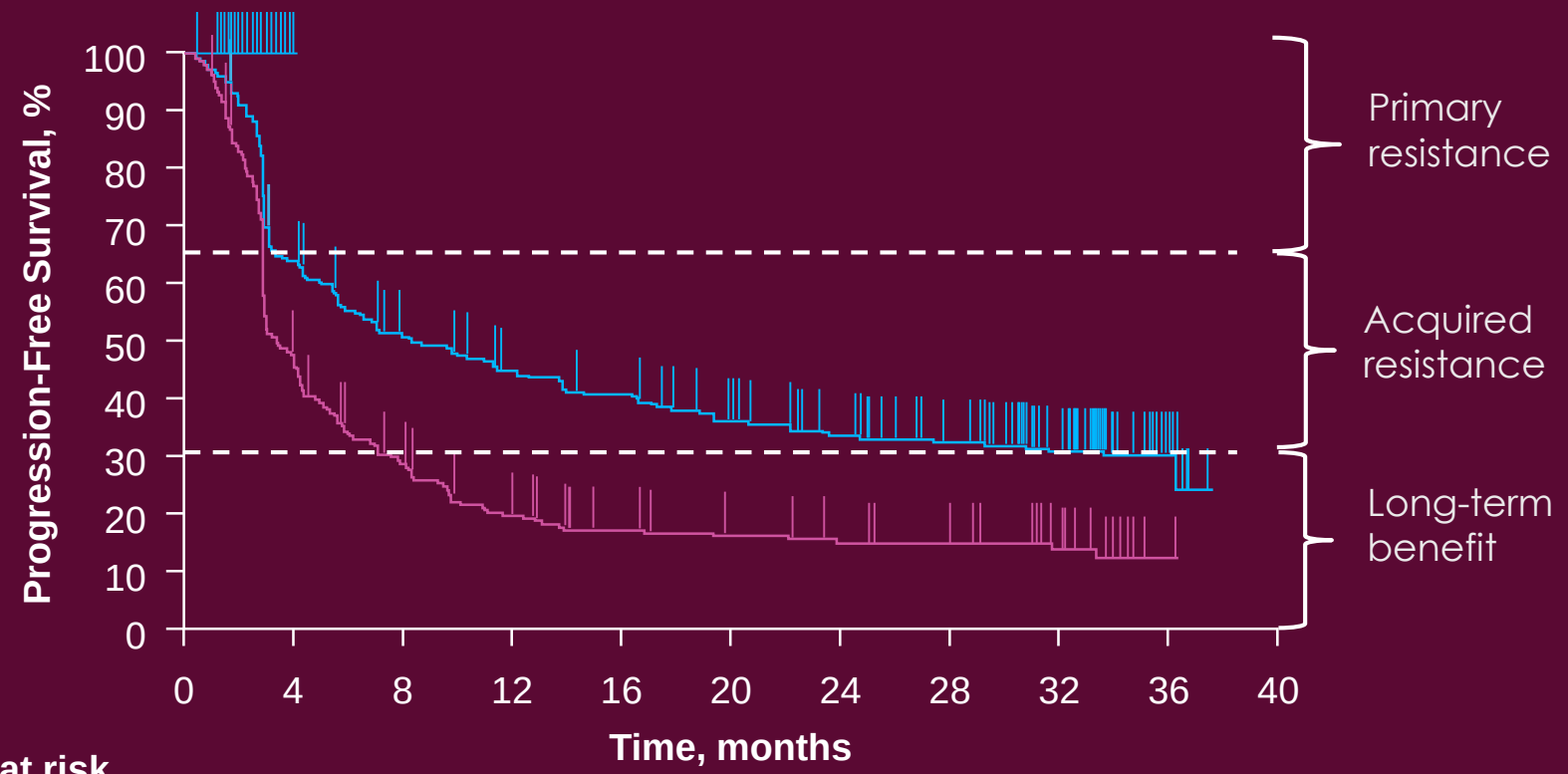


Int. J. Mol. Sci. 2020, 21, 2367

Personalized Immunotherapy

PFS on pembrolizumab in melanoma

KEYNOTE-006

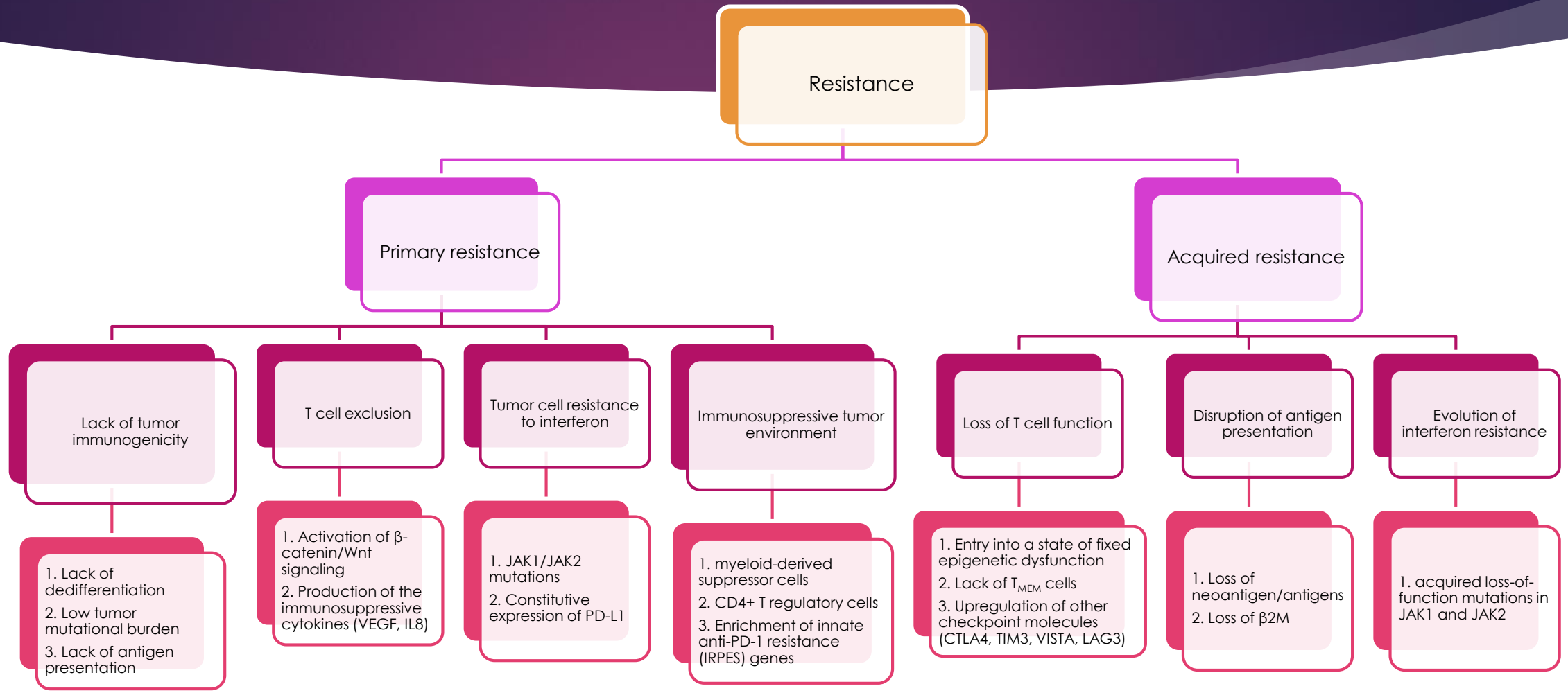


No. at risk											
Pembrolizumab	556	347	269	231	211	182	155	138	88	12	0
	278	110	64	40	32	27	23	20	14	2	0

Robert C et al. ASCO 2017, modified

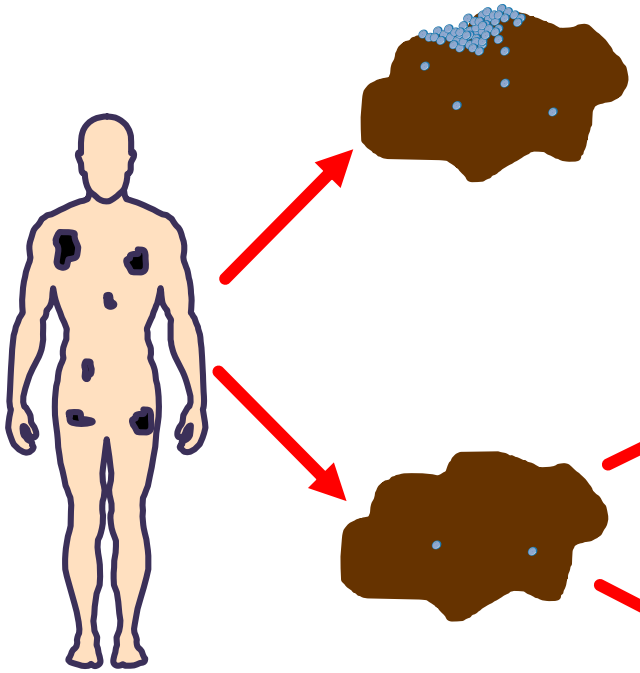
Personalized Immunotherapy

Mechanisms of resistance to PD-1/PD-L1 blockade



Nowicki TS et al. Cancer J. 2018 Jan-Feb; 24(1): 47–53.

Management of cancer in the post-anti-PD-1/L1 era



Anti-PD-1/anti-PD-L1

Bring T cells into tumors:

- + anti-CTLA4, TIGIT, TIM-3, LAG3
- + immune activating antibodie
- + cytokines
- + TLR agonists or oncolytic viruses
- + macrophage inhibitors
- + targeted therapies

Generate T cells:

- Vaccines
- TCR engineered ACT
- CAR engineered ACT
- immTACs
- BiTEs

Courtesy of Dr A. Ribas , modified

THANK YOU!

UCLA Jonsson
Comprehensive Cancer Center