Checkpoint Blockers and Repurposing Cancer Drugs : *What can we learn from the oncology field?*

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Center for Clinical Investigations (BIOTHERIS), INSERM CIC1428
French society for Immuno-Therapy of Cancers (FITC)

Session 6: Managing Malignancies in PIDs

Nov 10th 2023

DISCLOSURES - *OVER THE PAST 5 YEARS (2018-2023)*

Principal Investigator of Clinical Trials from the following companies: Roche/Genentech, BMS, Merck (MSD), Pfizer, Lytix pharma, Eisai, Astra Zeneca/Medimmune, Tesaro, Chugai, OSE immunotherapeutics, SOTIO, Molecular Partners, IMCheck.

Principal Investigator of the following academic trials: ACSE NIVOLUMAB/NCT03012581 (funding: INCa, Ligue contre le Cancer & BMS; drug supply: BMS, Ligue contre le Cancer & BMS; sponsor Unicancer), ISI-JX/NCT02977156 (funding & drug supply: Transgene; sponsor Leon Berard Cancer Center), NIVIPIT/NCT02857569 (funding & drug supply: BMS; sponsor Gustave Roussy), PEMBIB/NCT02856425 (funding Boehringer Ingelheim; drug supply: Boehringer Ingelheim & MSD; sponsor Gustave Roussy); PRIMO/ NCT04270864 (funding: Charities; drug supply: BMS & IDERA; sponsor Gustave Roussy).

Member of Clinical Trial Steering Committee: NCT02528357 (GSK), NCT03334617 (AZ).

Member of Data Safety and Monitoring Board: NCT02423863 (Sponsor: Oncovir), NCT03818685 (Sponsor: Centre Léon Bérard).

Member of Scientific Advisory Boards : Merck Serono, Lytix pharma, Novartis, BMS, Symphogen, Genmab, Amgen, Tesaro/GSK, Pfizer, Astra Zeneca/Medimmune, Servier, Gritstone, Molecular Partners, Bayer, Sanofi, Pierre Fabre, RedX pharma, OSE Immunotherapeutics, Medicxi, HiFiBio, IMCheck, Deka Biosciences, HotSpot Therapeutics, Clover, Grey Wolf, BiolineRx, Innate Pharma, J&J, Adagene, Marengo Therapeutics, Pathios, Pega One.

Teaching/Speaker activities: Roche/Genentech, BMS, Merck (MSD), Merck Serono, Astra Zeneca/Medimmune, Amgen, Sanofi, Servier, Innate Pharma.

Scientific & Medical Consulting : Roche, Pierre Fabre, EISAI, Bayer, Rigontec, Daichii Sankyo, Sanofi/BioNTech, Molecular Partners, Pillar Partners, BPI, Faron, Sanofi, Atreca, Takeda.

Non-Financial Support (travel expenses): Astra Zeneca, BMS, Merck (MSD), Roche.

Shareholder: Centessa, HiFiBio, Shattuck Labs, BiolineRx, Lytix Biopharma, Imcheck, Deka Biosciences, Adagene, Hot Spot, Marengo.

Patent holder: Patent Issued (not licensed): “Humanized and Chimeric Monoclonal Antibodies to CD81”, Stanford Office of Technology Licensing, 3000 El Camino Real, Bldg. 5, Suite 300, Palo Alto, CA 94306-2100. U.S. Application Serial No. 62/351,054.

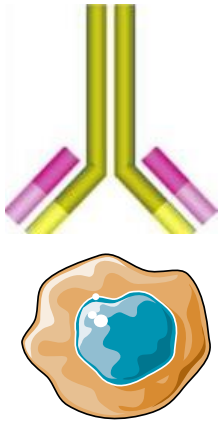
Member of the following scholar societies: European Society for Medical Oncology (ESMO), American Society for Clinical Oncology (ASCO), American Association for Cancer Research (AACR), European Academy for Tumor Immunology (EATI). Founder and president of the French society for Immunotherapy of Cancer (FITC). Member of the board of the Immuno-Oncology Group at the French Network of Comprehensive Cancer Centers (Unicancer).

Member of the Editorial Boards of the European Journal of Cancer and ESMO IO Tech.

Immuno-Oncology 1.0: Paradigm Shift

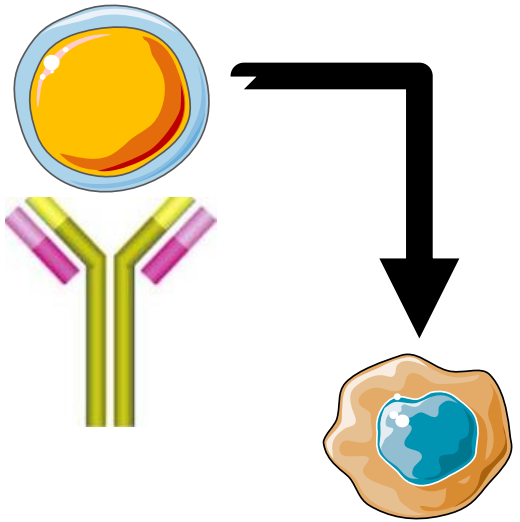
Cancer is an Auto-Dysimmune Disease

Historical Paradigm: Targeting Cancer Cells	New Paradigm: Targeting Immune Cells

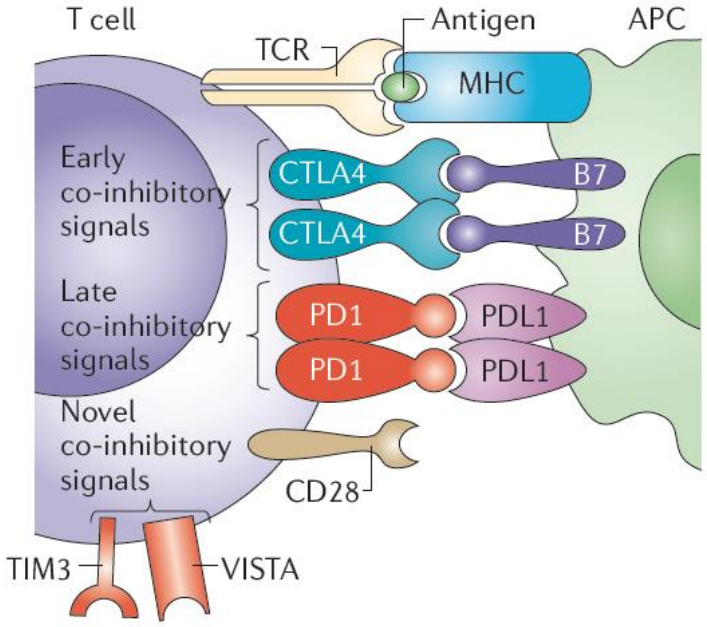


Cancer Cell

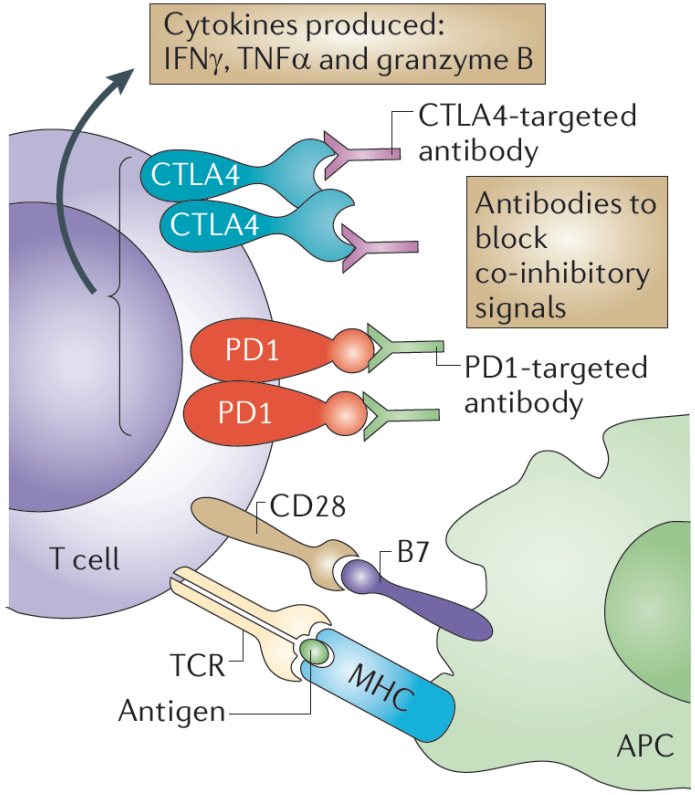
Lymphocyte



Lymphocyte Inhibition



Immune Checkpoint Targeted Therapy



FDA/EMA Approved Immune Checkpoint Targeted Antibodies

Anti-CTLA-4

Ipilimumab (BMS)

YERVOY™

Tremelimumab (AZ)

IMJUDO®

Anti-PD-1

Nivolumab (BMS)

OPDIVO™

Pembrolizumab (MSD)

KEYTRUDA®

Cemiplimab (Regeneron/Sanofi)

LIBTAYO®

Dostarlimab (GSK)

Jemperli (dostarlimab-gxly) Injection 500 mg

Anti-PD-L1

Atezolizumab (Roche/Genentech)

TECENTRIQ™

Durvalumab (AZ/Medimmune)

IMFINZI™

Avelumab (Pfizer)

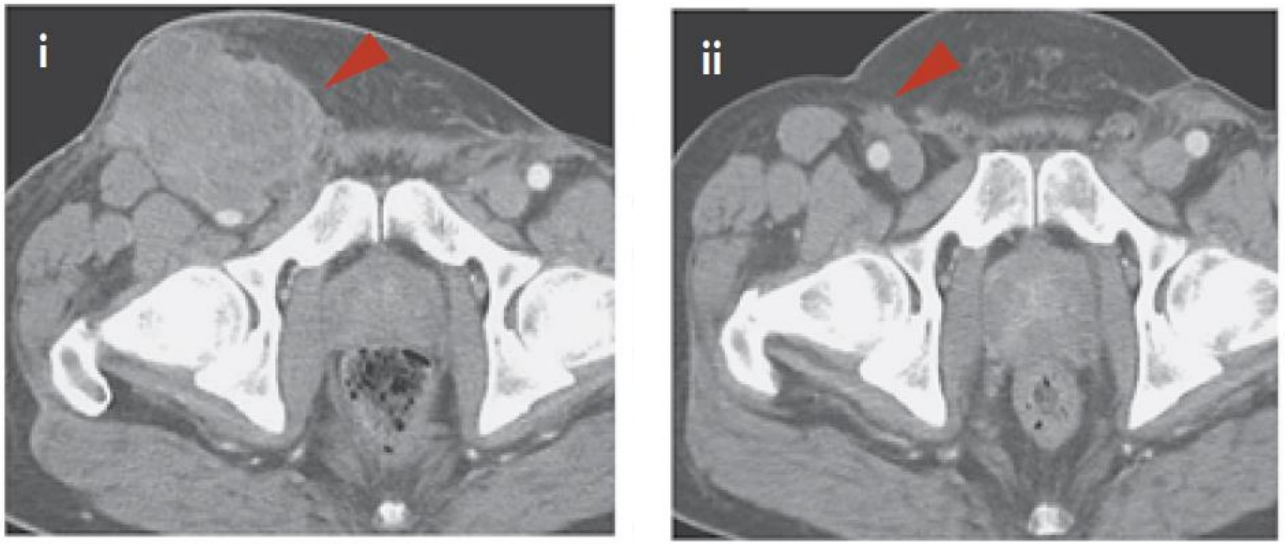
BAVENCIO®

The NEW ENGLAND JOURNAL of MEDICINE

Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer

Suzanne L. Topalian, M.D., F. Stephen Hodi, M.D., Julie R. Brahmer, M.D., Scott N. Gettinger, M.D.,

N Engl J Med 2012;366:2443-54.

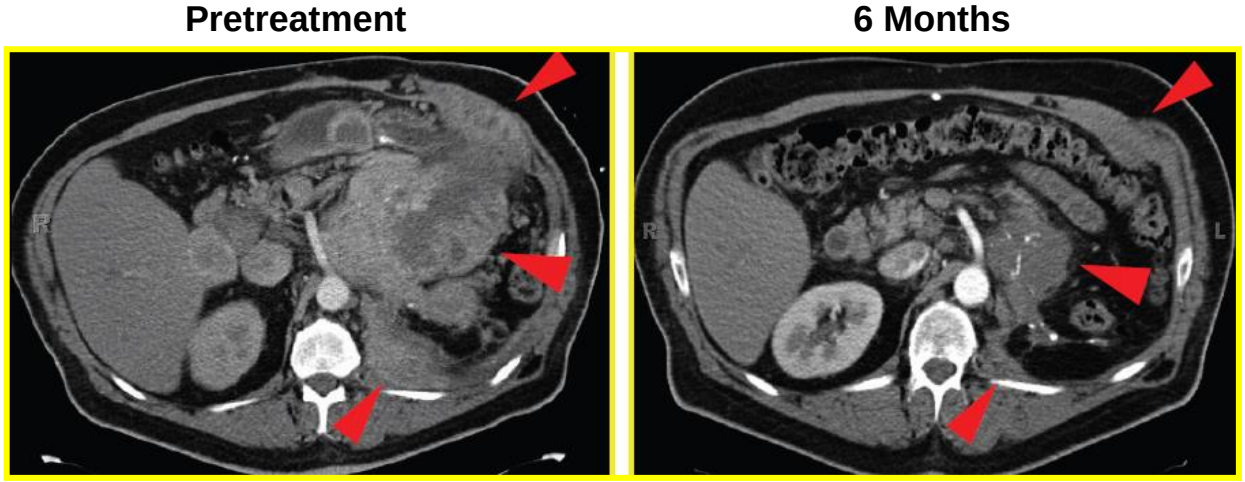


Patient with Melanoma

Metastatic RCC (Nivolumab, Anti-PD1)

Case studies

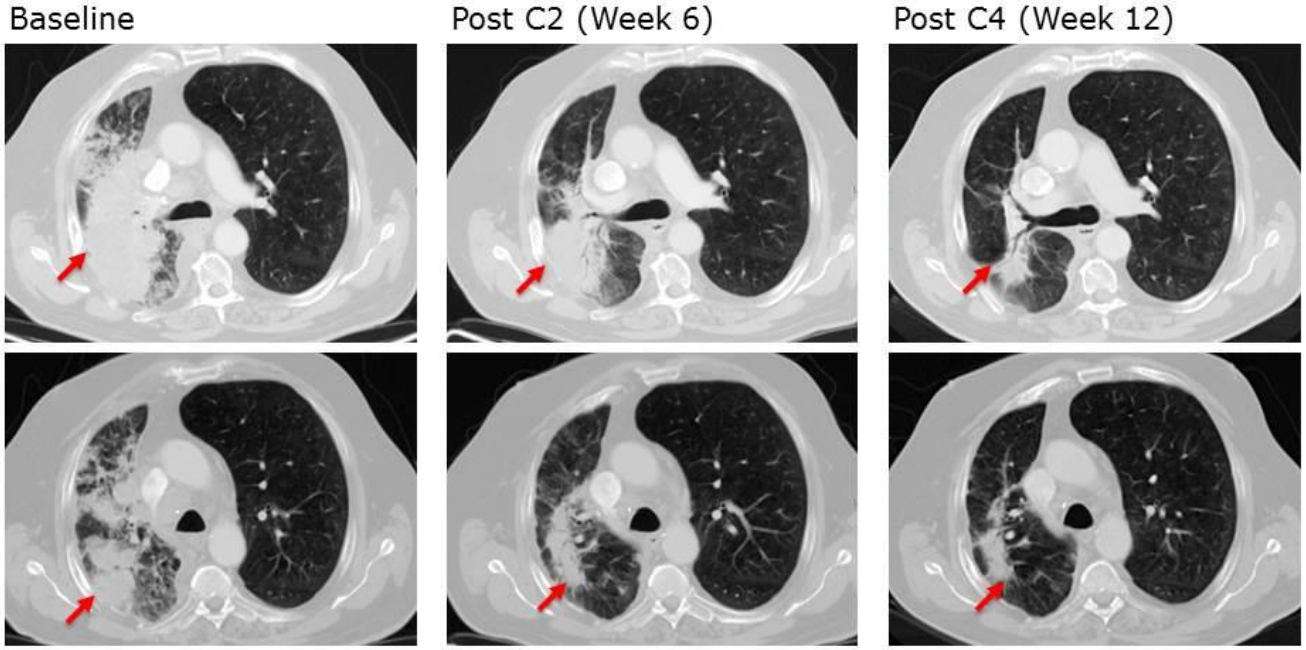
- 57-year-old male patient
- Developed progressive disease following radical surgery and treatment with sunitinib, temsirolimus, sorafenib, and pazopanib



RCC = renal cell cancer

McDermott D ESMO 2012

Rapid Response in an NSCLC Patient Treated With MPDL3280A Monotherapy

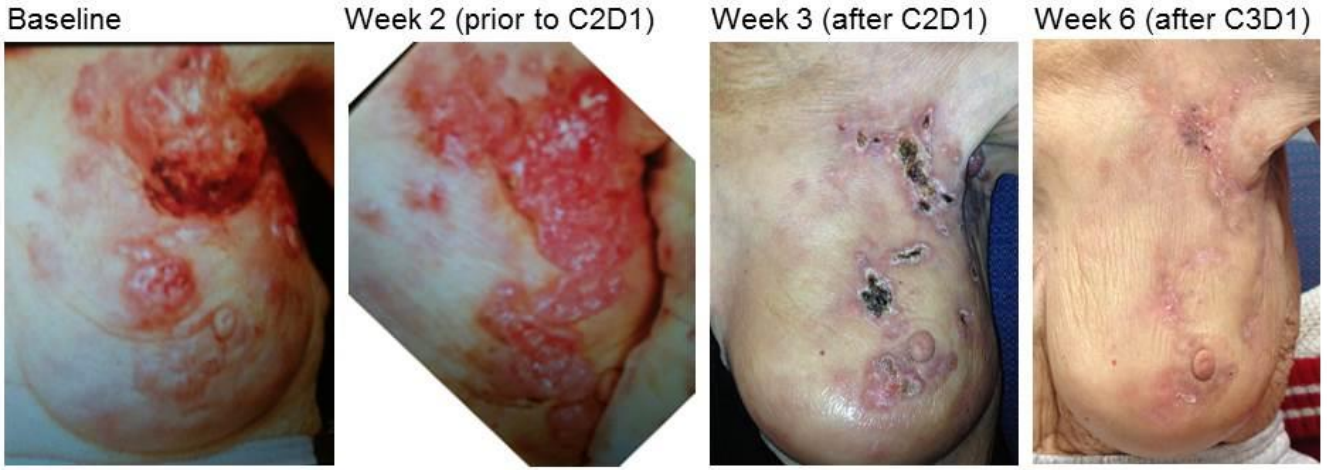


64-year-old male with squamous NSCLC s/p R lobectomy, cisplatin + gemcitabine, docetaxel, erlotinib, PD-L1 positive

Images represent data from patient enrolled after Aug 1, 2012.
Hospital Universitario Vall D´Hebron (Cruz/Tabernero).

Presented By Roy S. Herbst, MD, PhD at 2013 ASCO Annual Meeting

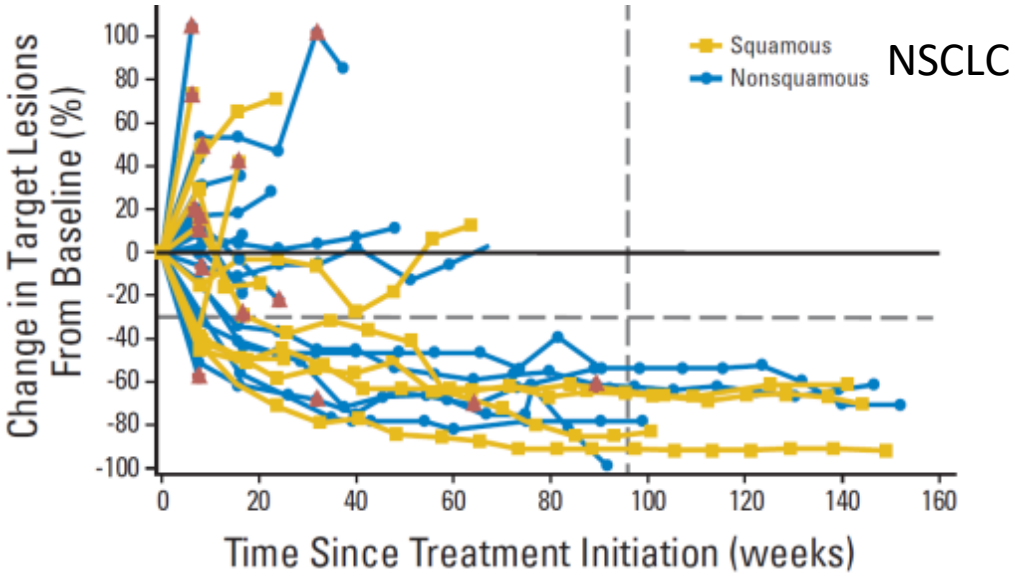
Rapid Response to MPDL3280A in Head and Neck Cancer With Metastatic SCC of the Tongue



78-year-old female with HNSCC s/p carboplatin + radiation, paclitaxel + cetuximab, carboplatin + paclitaxel + cetuximab, cisplatin + 5FU, PD-L1 positive

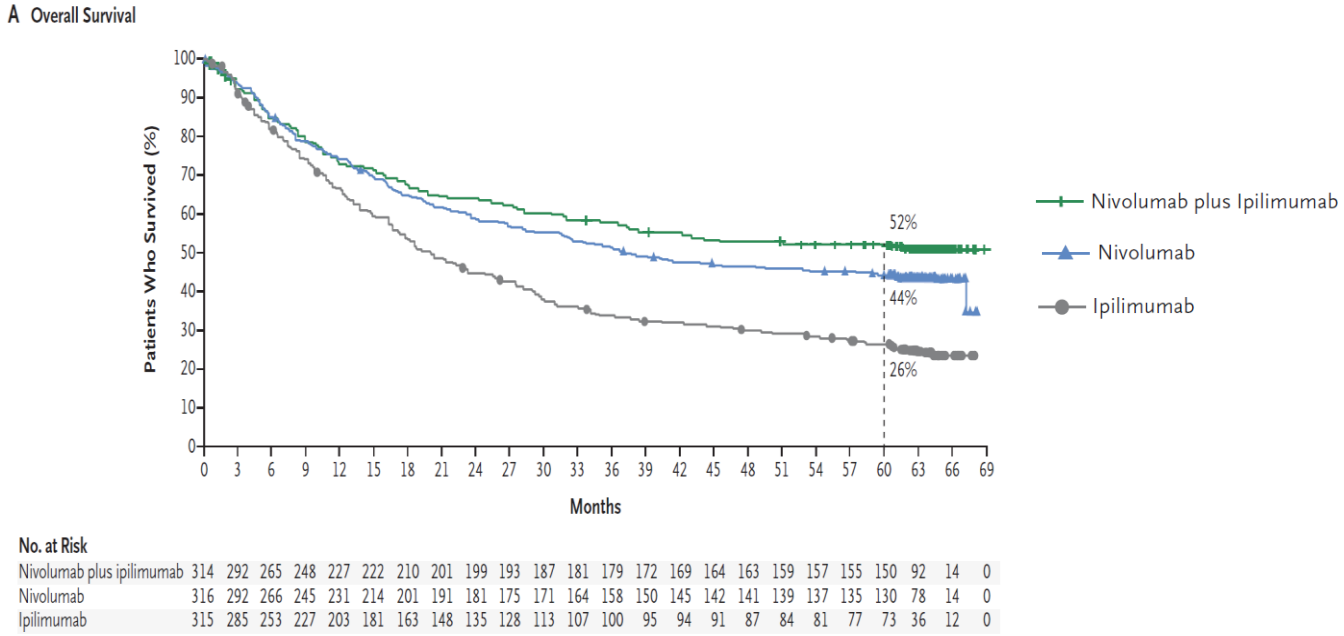
Images represent data from patient enrolled after Aug 1, 2012.
Comprehensive Cancer Center of Nevada (Braiteh).

Long Duration of Responses



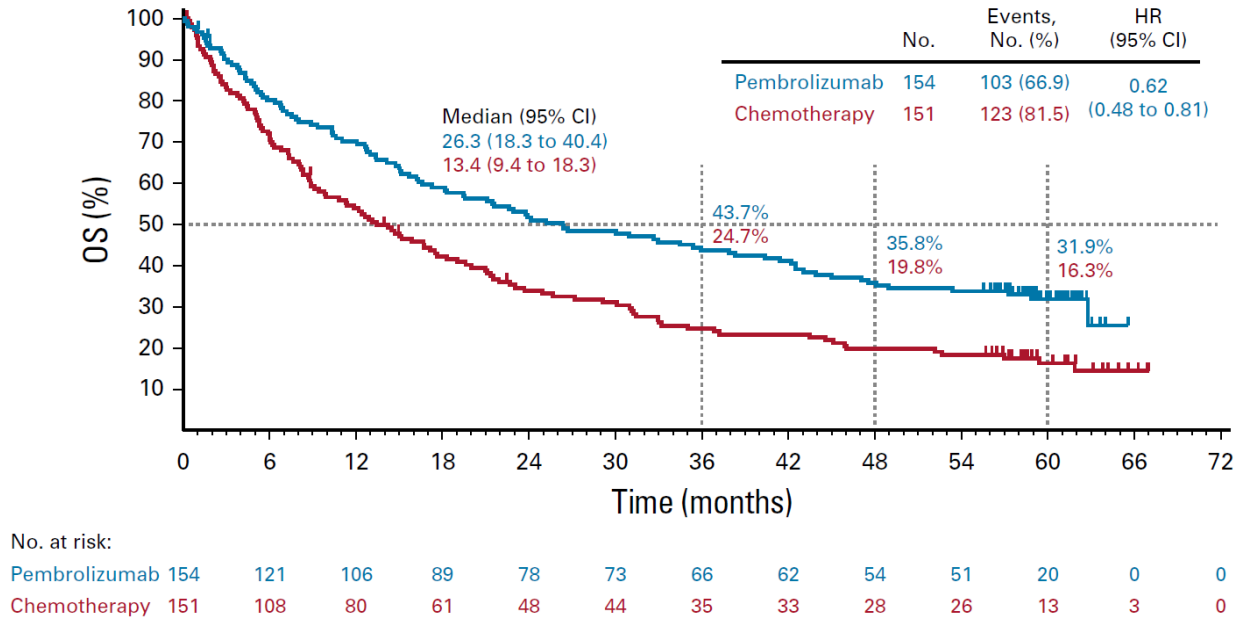
JCO, April 20, 2015.

5 years OS benefits in Metastatic Melanoma



Larkin J, et al. Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. N Engl J Med 2019:NEJMoa1910836.

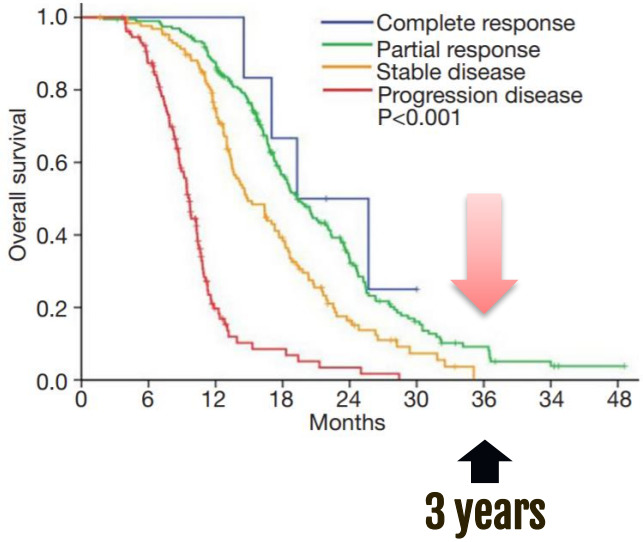
Anti-PD1 for 1L M+ NSCLC with PD-L1>50%



Reck, M., et al. (2021). Five-Year Outcomes With Pembrolizumab Versus Chemotherapy for Metastatic Non–Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score ≥ 50%. J. Clin. Oncol. 39, 2339–2349.

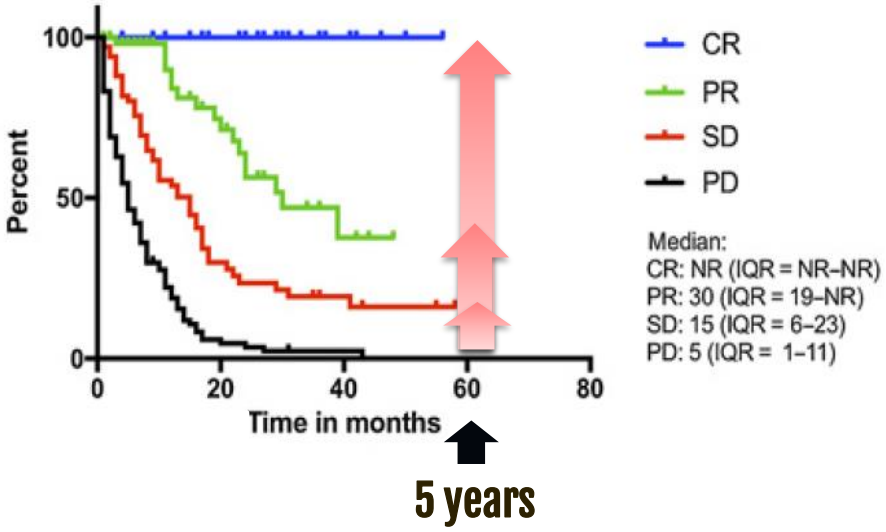
Paradigm Shift in Clinical Cancer Research Methodology

CHEMO+RADIO THERAPIES



Chen Y, et al. Outcomes of concurrent chemoradiotherapy versus chemotherapy alone for esophageal squamous cell cancer patients presenting with oligometastases. J Thorac Dis Vol 11, No 4 (April 2019) J Thorac Dis 2019.

IMMUNOTHERAPIES



Gauci M-L, et al. Long-Term Survival in Patients Responding to Anti-PD-1/PD-L1 Therapy and Disease Outcome upon Treatment Discontinuation. Clin Cancer Res 2019;25:946–56.

Why Immune Checkpoint Targeted Therapies provide Survival Benefits?

Adaptive anti-tumor immunity is polyclonal:

➔ ***better control of tumor heterogeneity***

Adaptive anti-tumor immunity has memory:

➔ ***durable remissions***

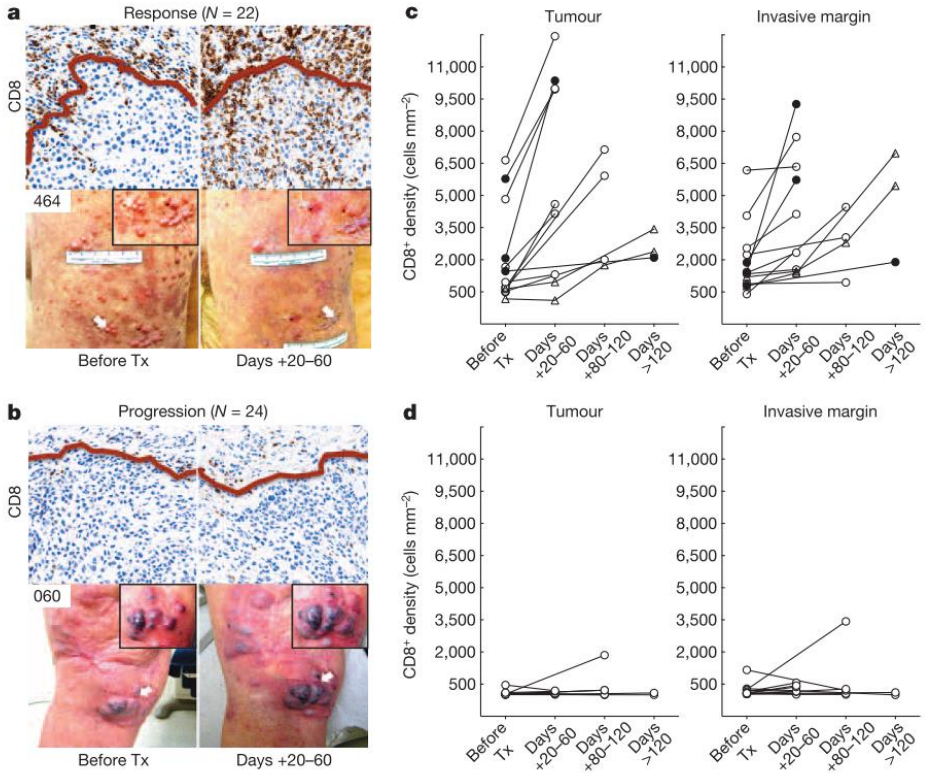
And immune cells can cross the BBB

(whereas most drugs can't)

Anti-PD(L)1 & CD8+ T-Cell Anti-Tumor Immunity

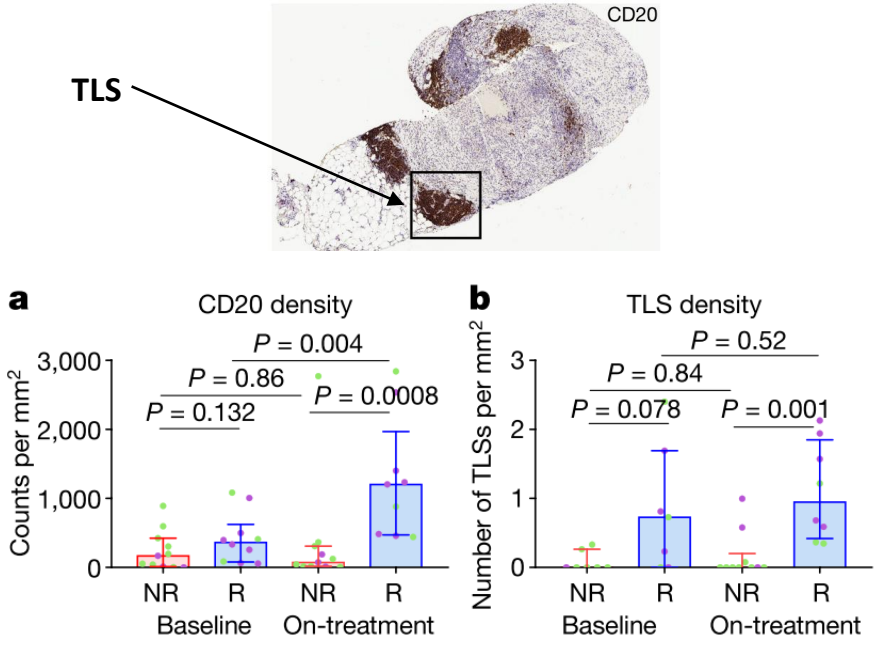
Responding Patient

Non Responding Patient

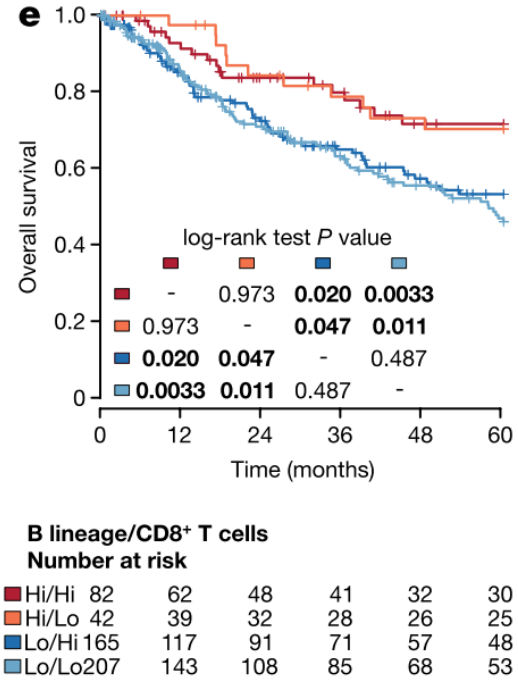


Tumeh PC, et al. PD-1 blockade induces responses by inhibiting adaptive immune resistance. Nature. 2014;515:568–71.

Anti-PD(L)1 & B-Cell Anti-Tumor Immunity

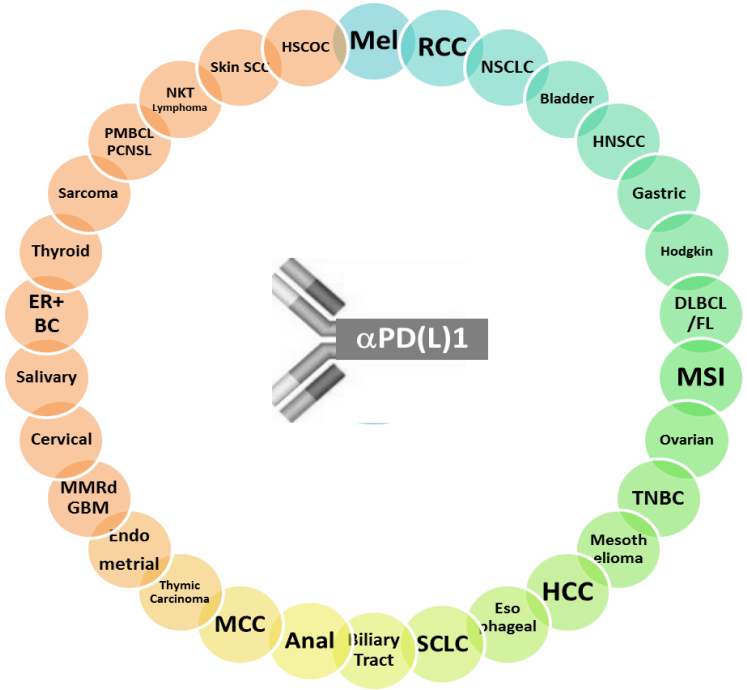


Helmink BA, et al. B cells and tertiary lymphoid structures promote immunotherapy response. Nature. 2020;577:549–55.

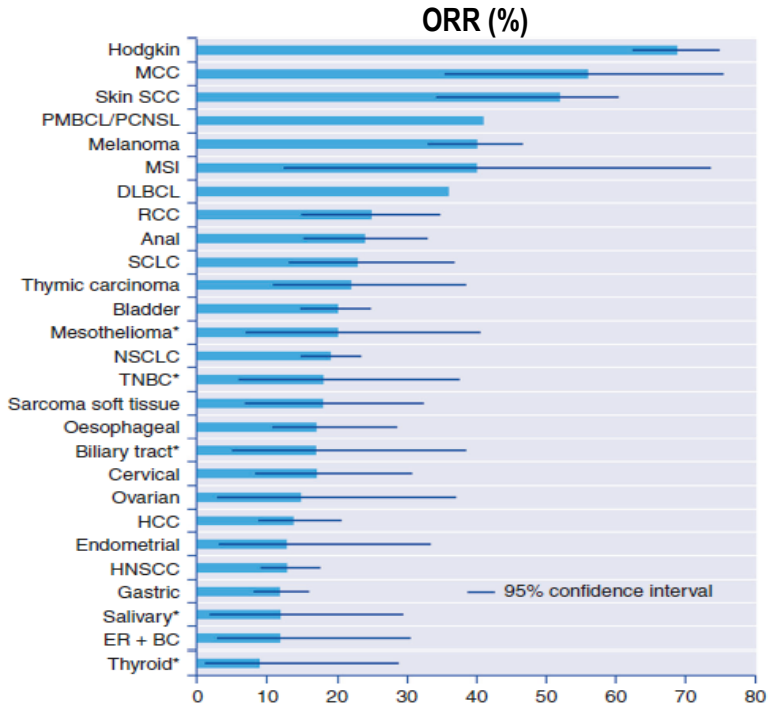


Petitprez F, et al. B cells are associated with survival and immunotherapy response in sarcoma. Nature. 2020;577:556–60.

All Cancer Types can be sensitive to Cancer Immunotherapies

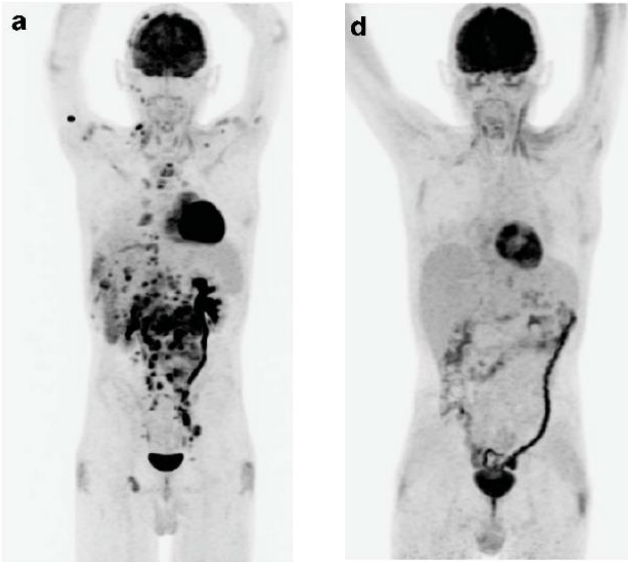


ORR varies across indications, lines of treatment, patients subgroups

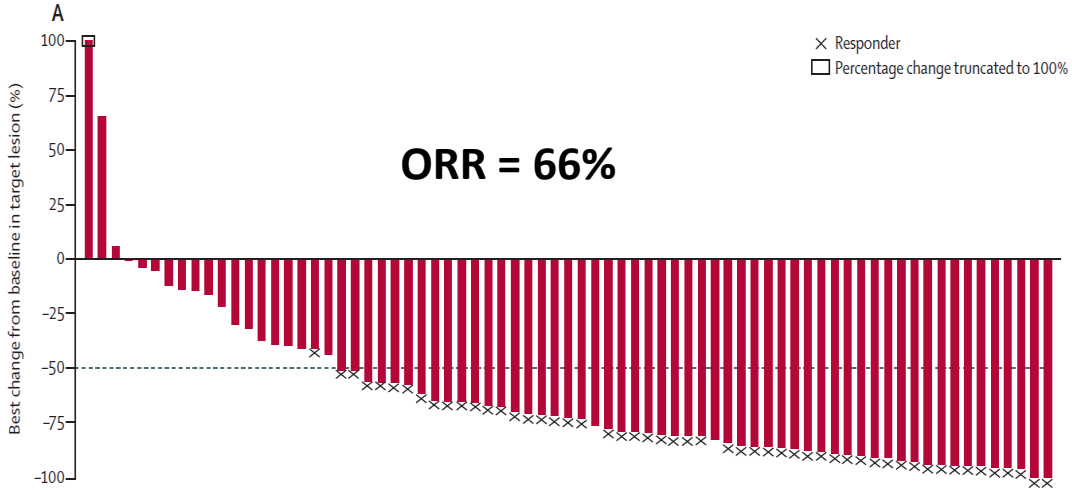


Hirsch L, Zitvogel L, Eggermont A, Marabelle A. Br J Cancer 2019;120:3–5.

Anti-PD1 (Nivolumab)
in Relapsing / Refractory classical Hodgkin's lymphoma

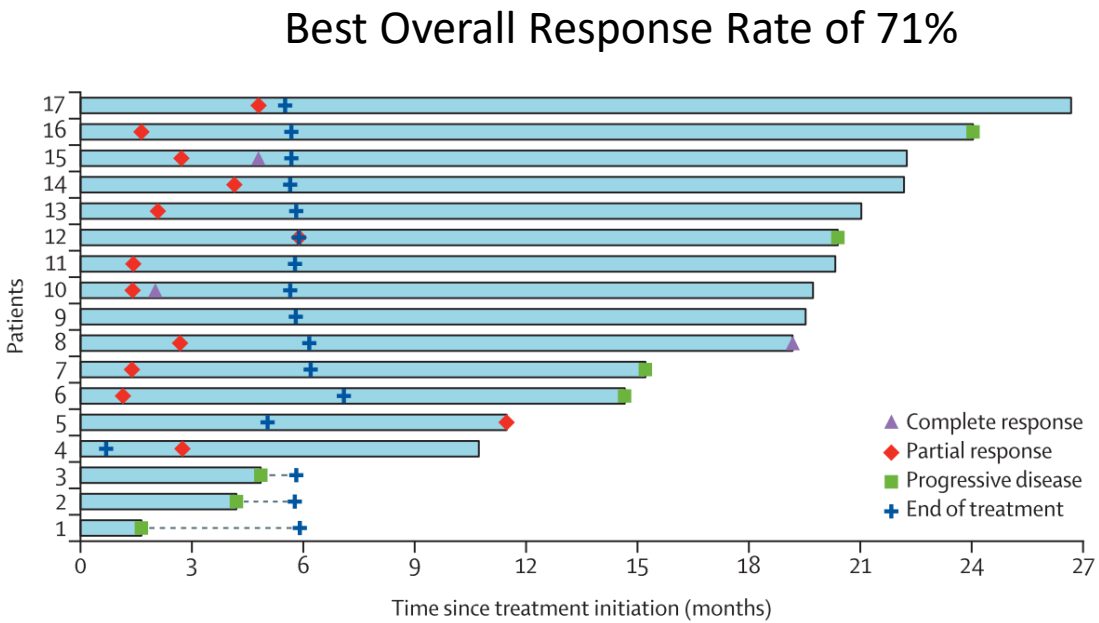


Angenendt, L., T., et al. (2016). Nivolumab in a patient with refractory Hodgkin's lymphoma after allogeneic stem cell transplantation.
Bone Marrow Transplant. 51, 443–445.



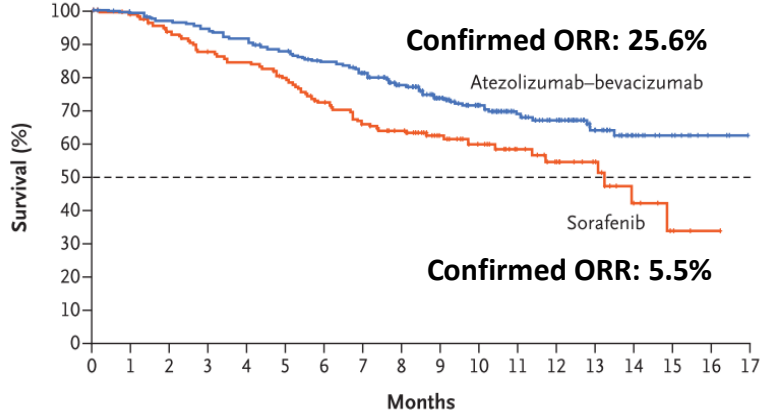
Younes, A., et al. (2016). Nivolumab for classical Hodgkin's lymphoma after failure of both autologous stem-cell transplantation and brentuximab vedotin: a multicentre, multicohort, single-arm phase 2 trial.
Lancet Oncol. 17, 1283–1294.

Anti-PD1 in *Classic or Endemic* Kaposi Sarcoma



Delyon, J., et al. (2022). PD-1 blockade with pembrolizumab in classic or endemic Kaposi's sarcoma: a multicentre, single-arm, phase 2 study. Lancet Oncol. 23, 491–500.

Anti-PD-L1 (atezolizumab) & Anti-VEGF (bevacizumab) in HCC

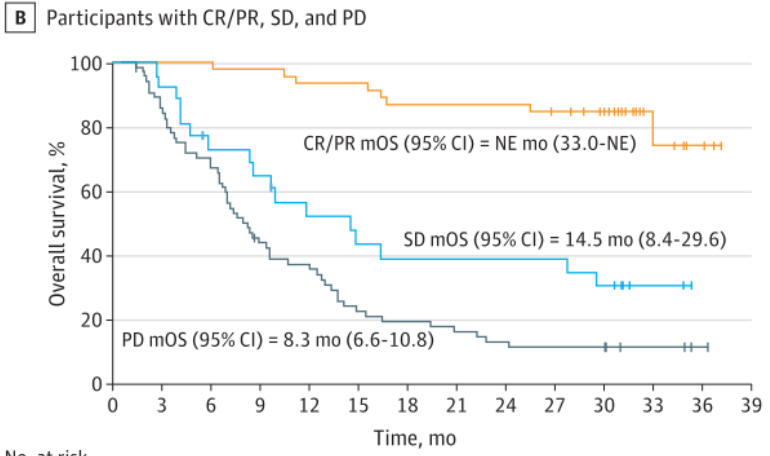


No. at Risk

Atezolizumab–bevacizumab	336	329	320	312	302	288	275	255	222	165	118	87	64	40	20	11	3	NE
Sorafenib	165	157	143	132	127	118	105	94	86	60	45	33	24	16	7	3	1	NE

Finn, R.S., et al. (2020). Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N. Engl. J. Med. 382, 1894–1905.

Anti-P1 (nivolumab) + Anti-CTLA4 (ipilimumab) in HCC

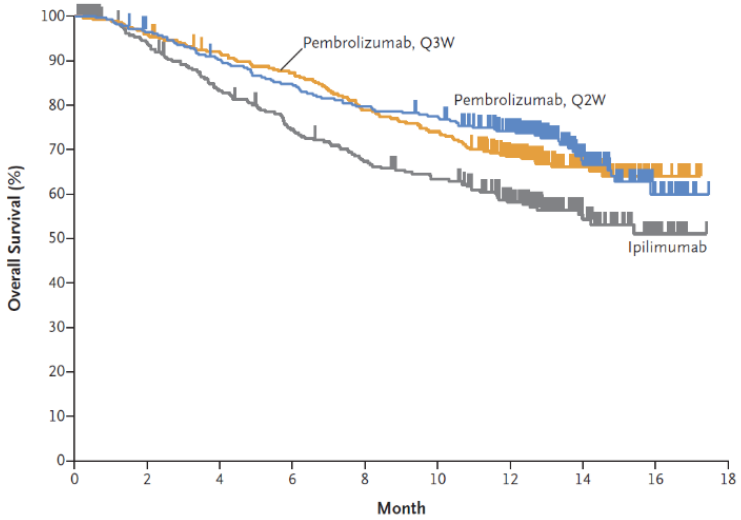


No. at risk (censored)[a]

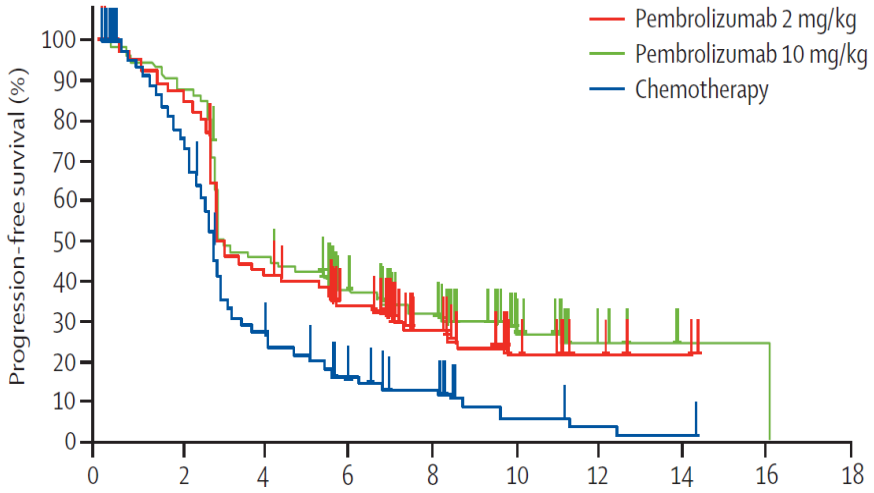
CR/PR	46	46	46	45	43	43	40	40	40	38	33	7	3	0
	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(6)	(31)	(35)	(38)
SD[b]	26	24	18	16	12	10	9	9	9	9	7	2	0	0
	(0)	(0)	(1)	(1)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(7)	(9)	(9)
PD	65	55	45	27	23	14	12	10	8	7	7	4	2	0
	(0)	(1)	(1)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(5)	(7)	(9)

Yau, T., et al. (2020). Efficacy and Safety of Nivolumab plus Ipilimumab in Patients with Advanced Hepatocellular Carcinoma Previously Treated with Sorafenib: The CheckMate 040 Randomized Clinical Trial. JAMA Oncol. 6, 1–8.

αPD-1/αPD-L1:
No Dose/Efficacy/Toxicity Correlation



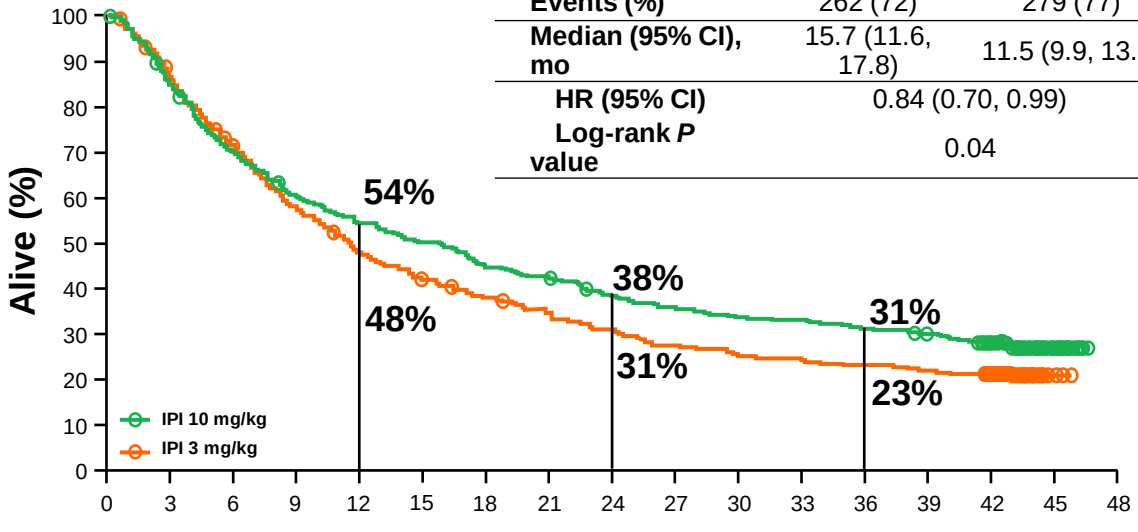
Robert C, et al. Pembrolizumab versus Ipilimumab in Advanced Melanoma.
N Engl J Med. 2015;372:2521–32.



Ribas A, et al. Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. Lancet Oncol. 2015;

Anti-CTLA4 (ipilimumab) 10 mg/kg *vs* 3 mg/kg

OS	IPI 10 mg/kg n = 365	IPI 3 mg/kg n = 362
Events (%)	262 (72)	279 (77)
Median (95% CI), mo	15.7 (11.6, 17.8)	11.5 (9.9, 13.3)
HR (95% CI)	0.84 (0.70, 0.99)	
Log-rank *P* value	0.04	



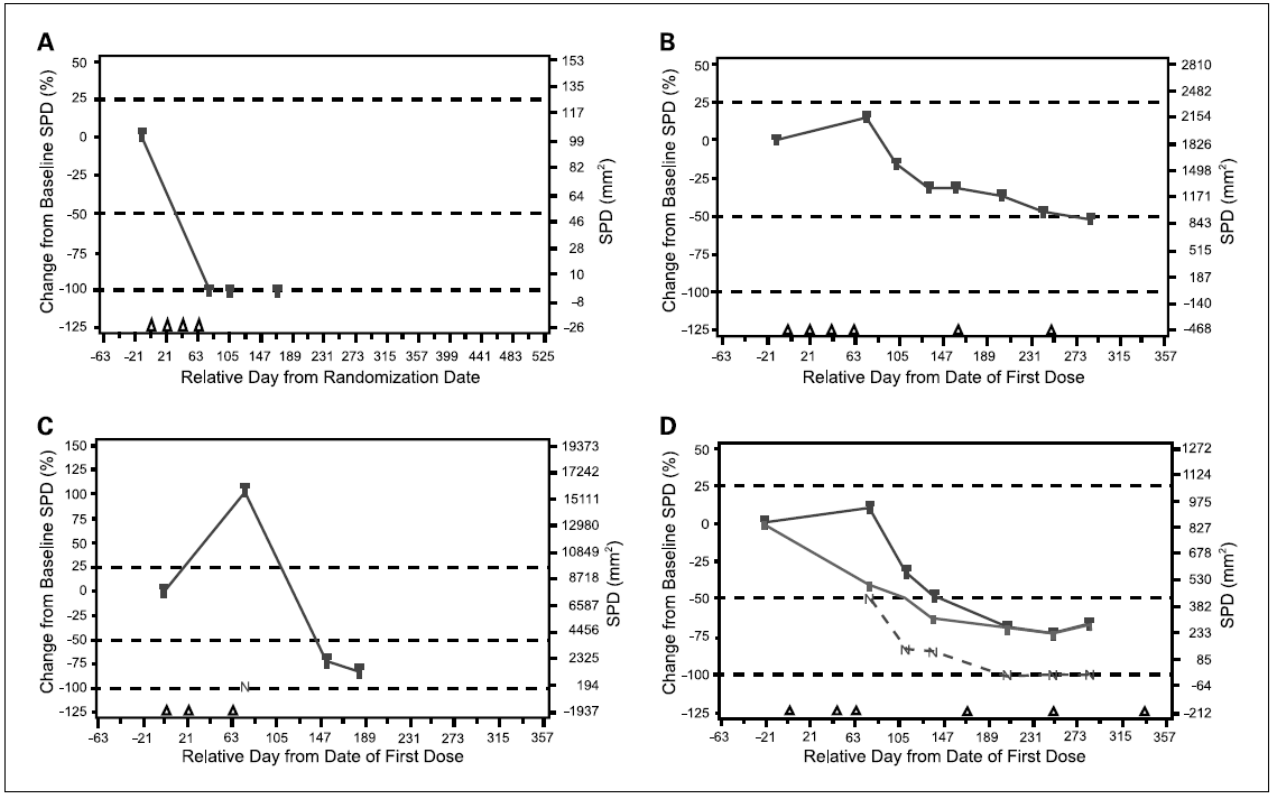
Number of patients at risk

IPI 10 mg/kg	365	306	253	217	196	181	161	151	137	126	120	118	111	105	94	16	0
IPI 3 mg/kg	362	310	253	205	168	146	131	118	107	95	87	83	80	76	71	8	0

Minimum OS follow-up: ~43 months

Ascierto PA *et al. ESMO* 2016

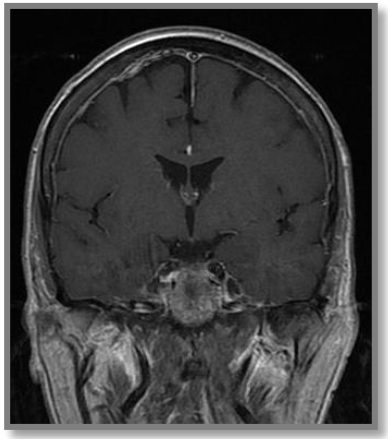
New Types of Responses in Oncology



Immune-Related Response Criteria

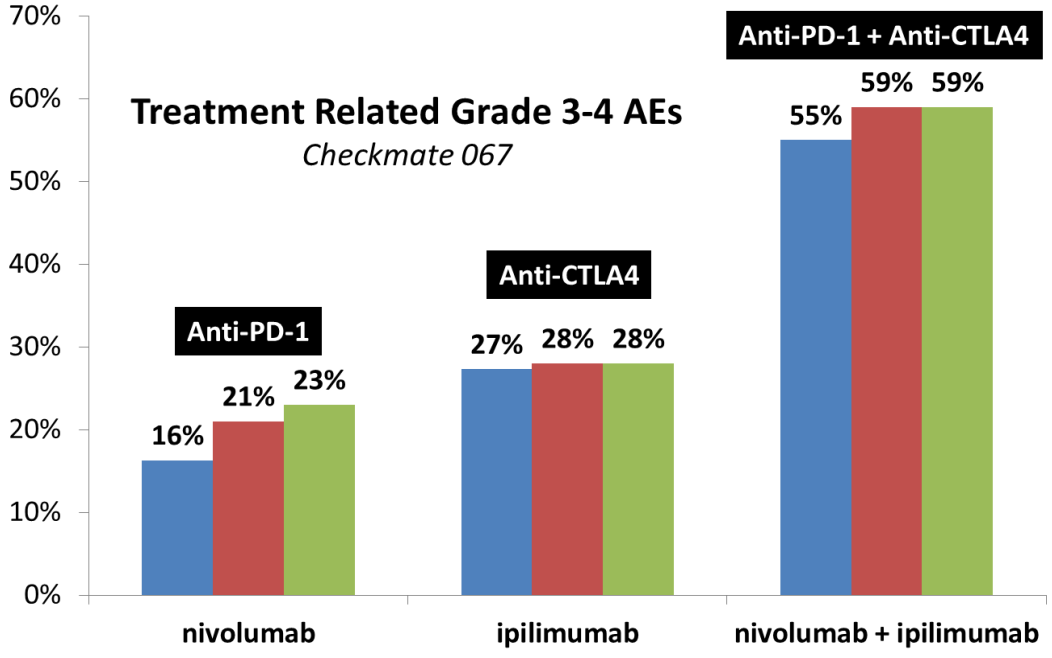
Clin Cancer Res 2009;15(23) December 1, 2009

New Types of Toxicities in Oncology



Bompaire et al Invest New drugs 2012

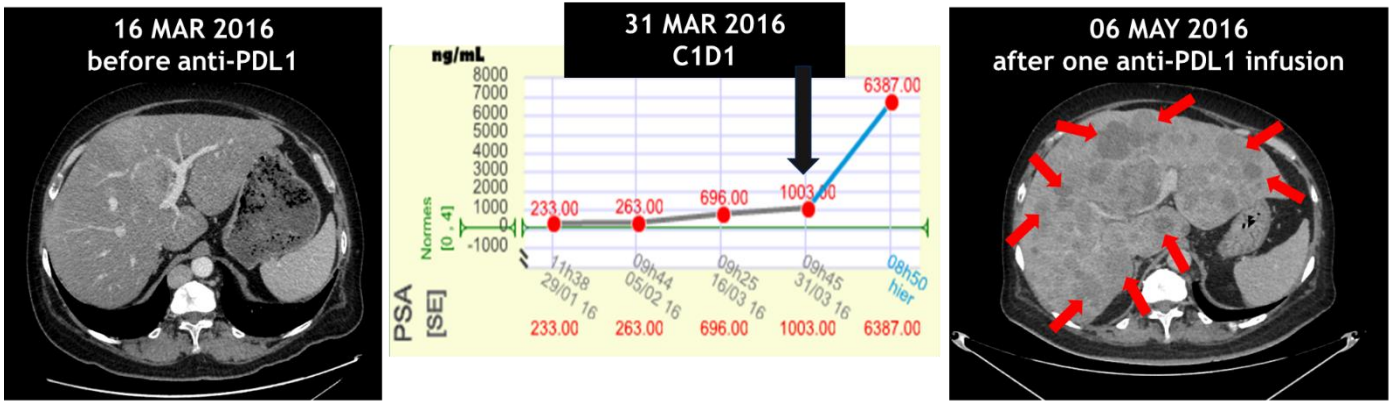
Immune Related Adverse Events
On-target /*Off-tumor* Effects



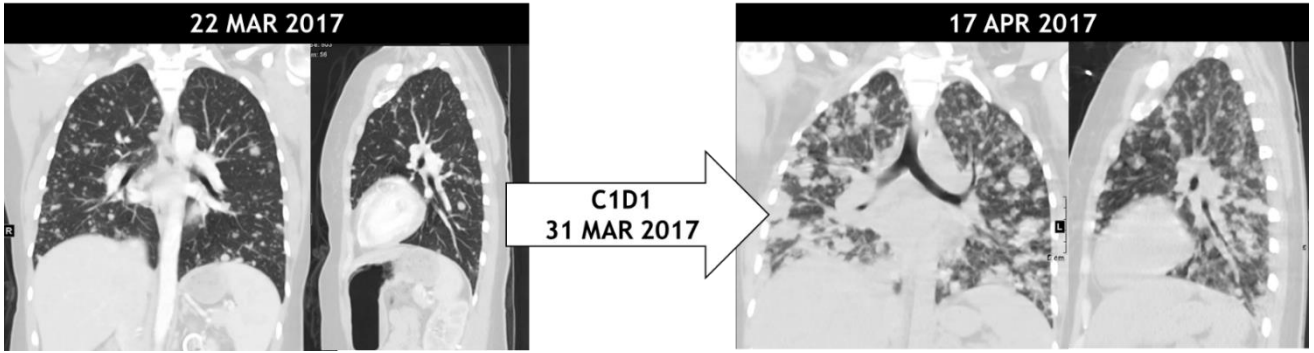
Larkin, J., *et al.* NEJM. (**2015**); *373*, 23–34.
Wolchok, J. D. *et al.* NEJM. (**2017**); 377, 1345–1356.
Larkin J, *et al.* NEJM. (**2019**); 381:1535–46.

Hyperprogression:
Paradoxical Cancer Acceleration on Immunotherapy

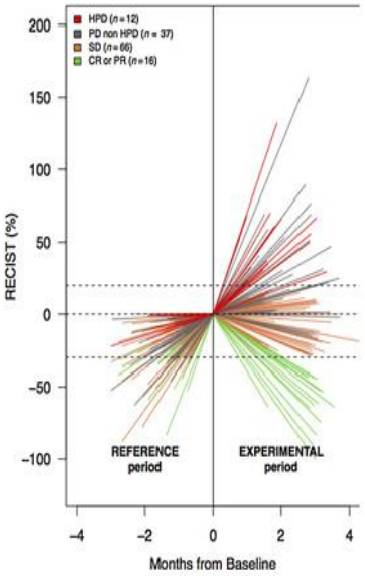
Prostate Cancer on Anti-PD-L1



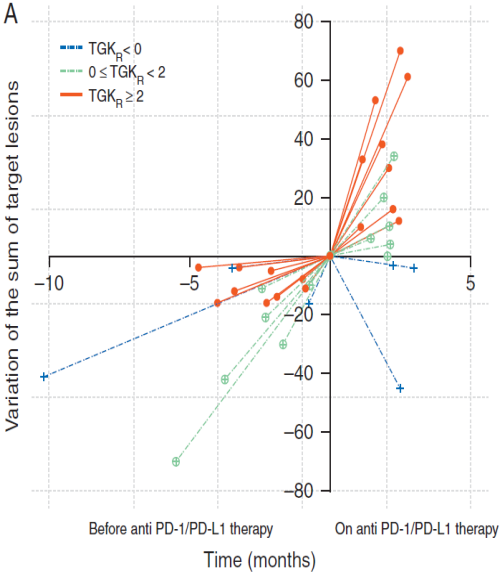
Urothelial carcinoma on anti-PD-1



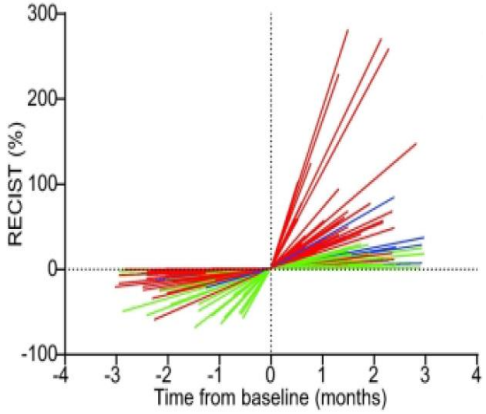
Some Patient Increase their Tumor Growth Under Anti-PD(L)1



Champiat S, et al.
Clin Cancer Res 2017;23:1920–8.



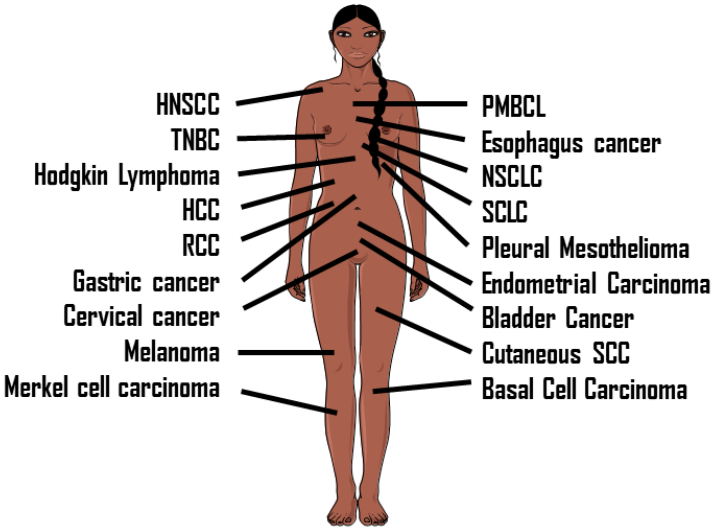
Saâda-Bouzid E, et al. Ann Oncol 2017:1605–11.
doi:10.1093/annonc/mdx178.



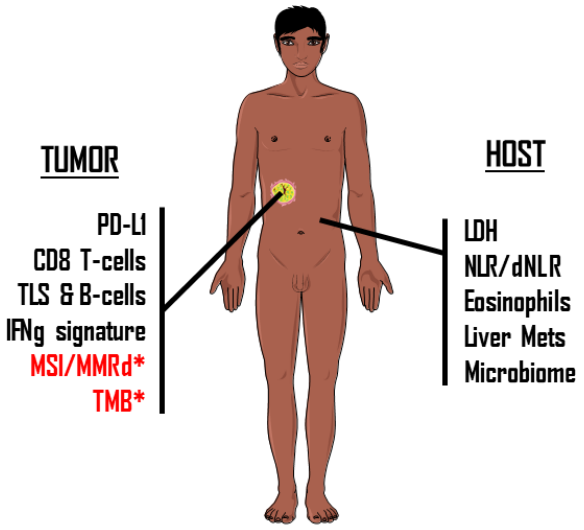
Kim CG, et al. Ann Oncol 2019.
doi:10.1093/annonc/mdz123.

Biology (not Histology) Drives the Efficacy of Cancer Immunotherapies

Histology Based Approvals for Immunotherapy



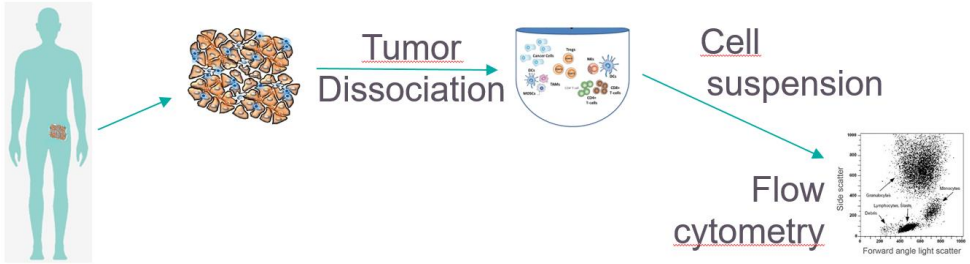
Histology Independent Biomarkers Driving Efficacy of Immunotherapies

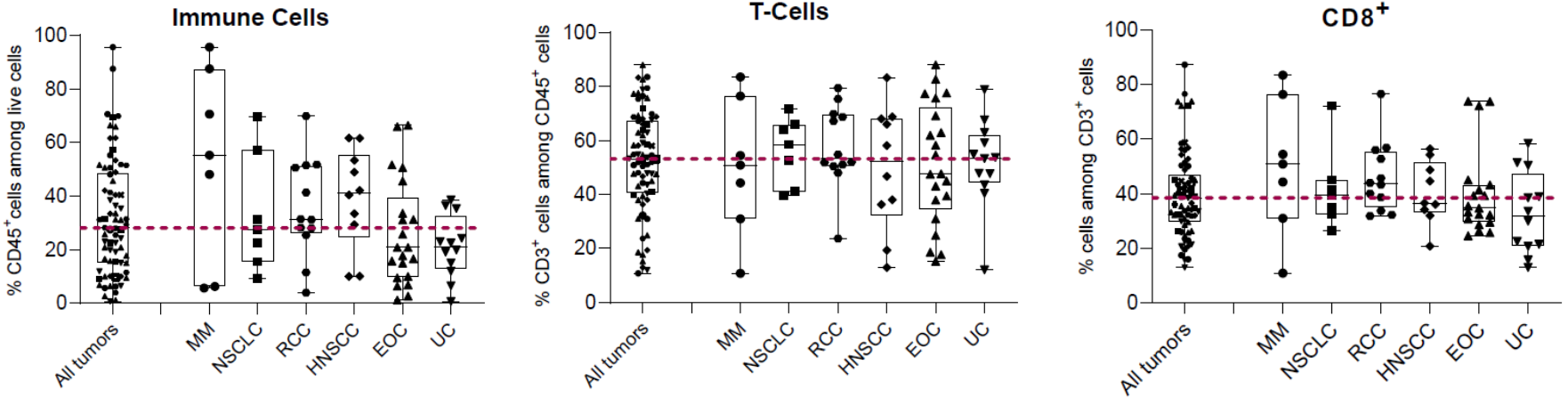


*Approved by the FDA but not by the EMA

Bonvalet et al. Cancer immunotherapy efficacy is driven by tumour biology, not by its histology. Impact on drug development and approvals. Eur. J. Cancer 162, 130–132. (2022).

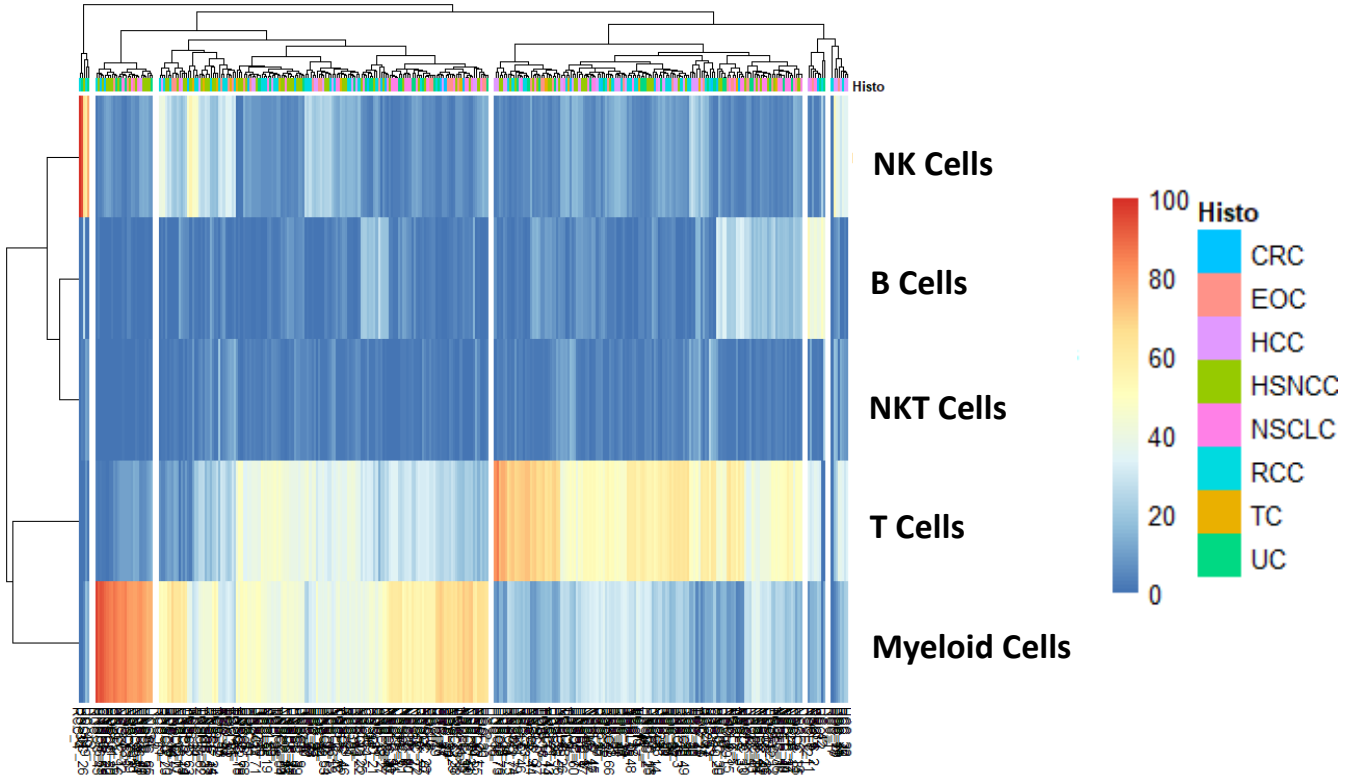
Pathology Does Not Dictate Tumor Immune Infiltrates





Bredel et al. (2023); Immune Checkpoints are Predominantly Co-Expressed by Clonally Expanded CD4+FoxP3+ Intratumoral T-cells in Human Cancers. (under review)

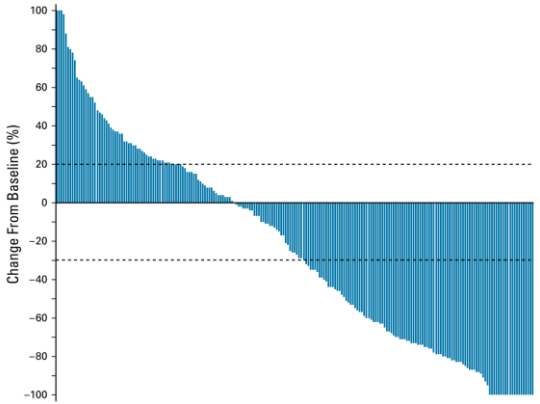
But Common Immune Contextures are found across Indications



Bonvalet et al. Subset of Immune Cells in 300+ Human Cancers (Flow Cytometry). Unpublished Data.

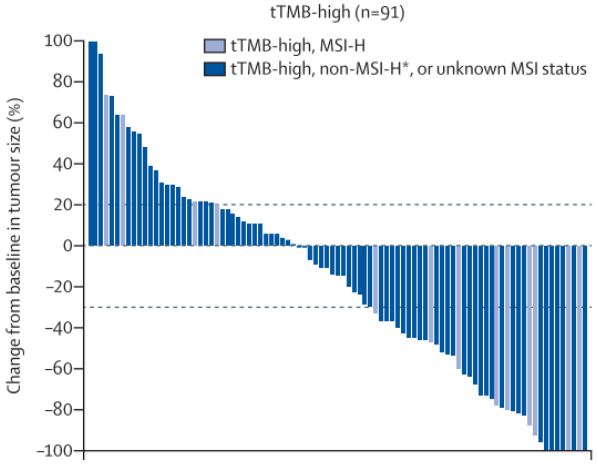
Tumor Agnostic Indications Are Accumulating

MSI-H / MMRd



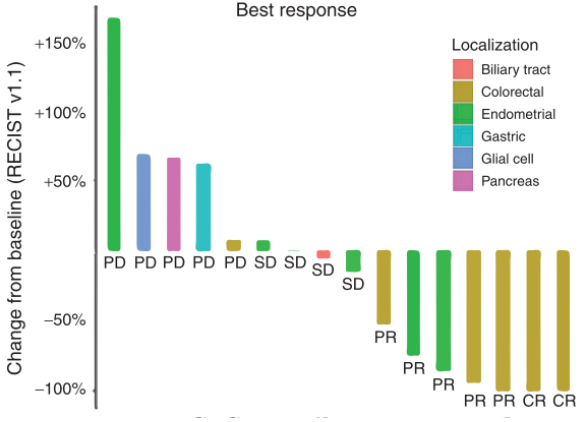
Marabelle, A., et al. (2020). J. Clin. Oncol. 38, 1–10.

TMB-H



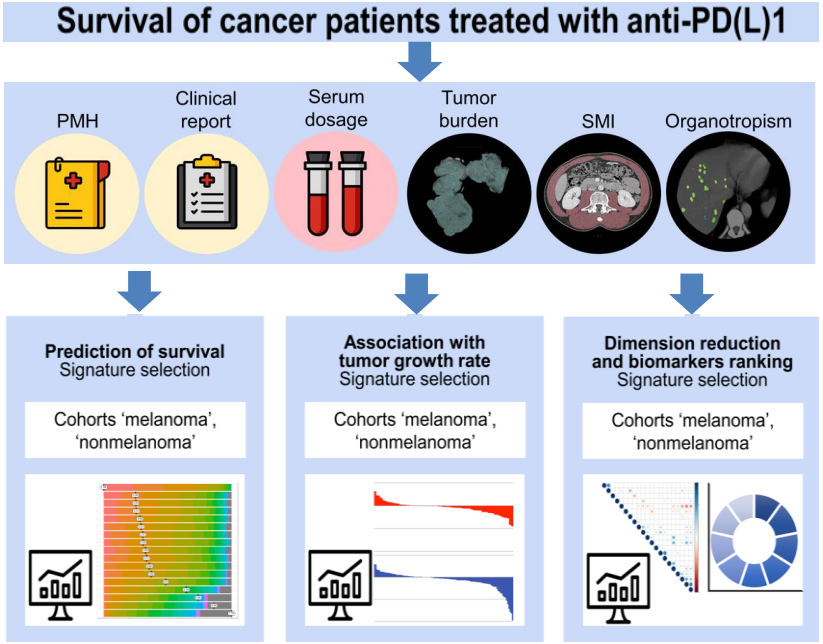
Marabelle, A.,et al. (2020). Lancet Oncol. 21, 1353–1365.

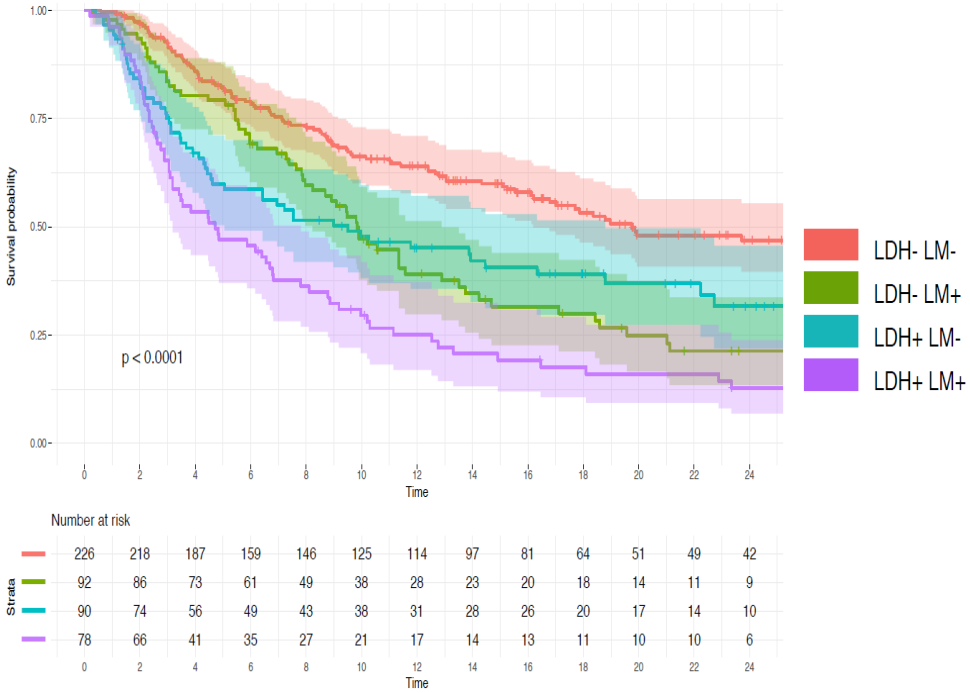
POLEd



Rousseau, B., et al. (2022). Cancer Discov. 12, 1435–1448.

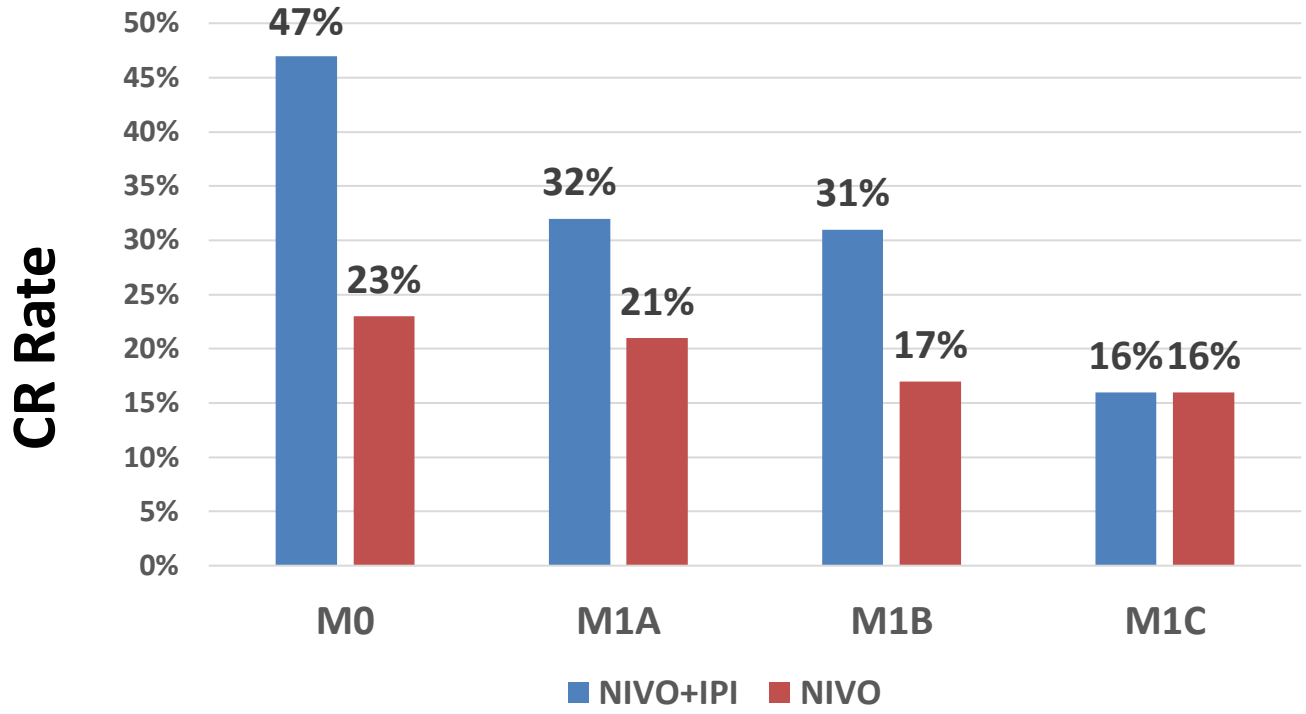
All Patients in a Given Indication are not Equivalent: LDH & Liver Mets





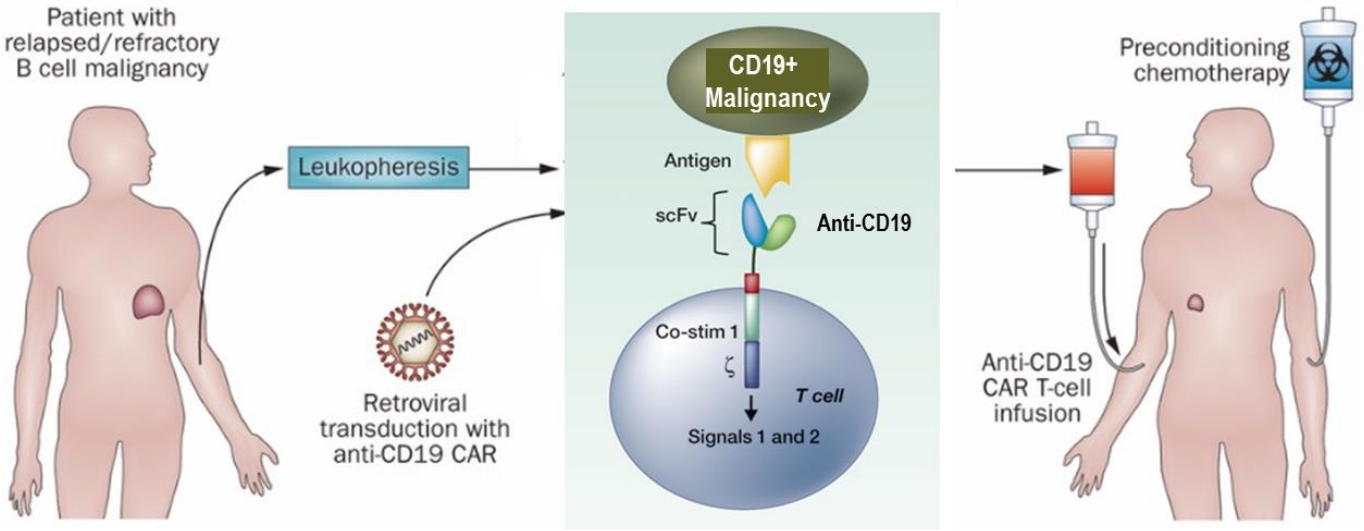
Dercle L. et al. (2022). High serum LDH and liver metastases are the dominant predictors of primary cancer resistance to anti-PD(L)1 immunotherapy. Eur. J. Cancer *177*, 80–93.

Efficacy of anti-CTLA4 in Melanoma is stage dependent

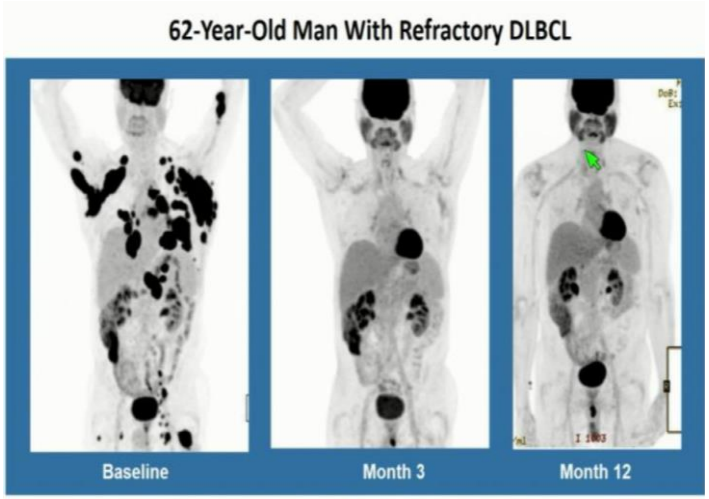


Robert, C. *et al.* 1082MO 5-year characterization of complete responses in patients with advanced melanoma who received nivolumab plus ipilimumab (NIVO+IPI) or NIVO alone. *Ann. Oncol.* **31**, S734–S735 (2020).

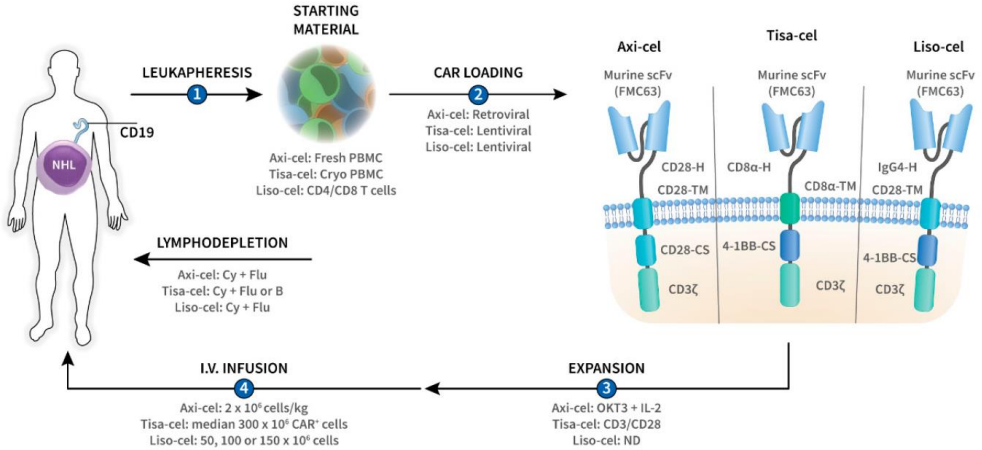
Chimeric Antigen Receptor (CAR-T) Cell Therapy



αCD19 CAR-T in R/R B-Cell Lymphoma



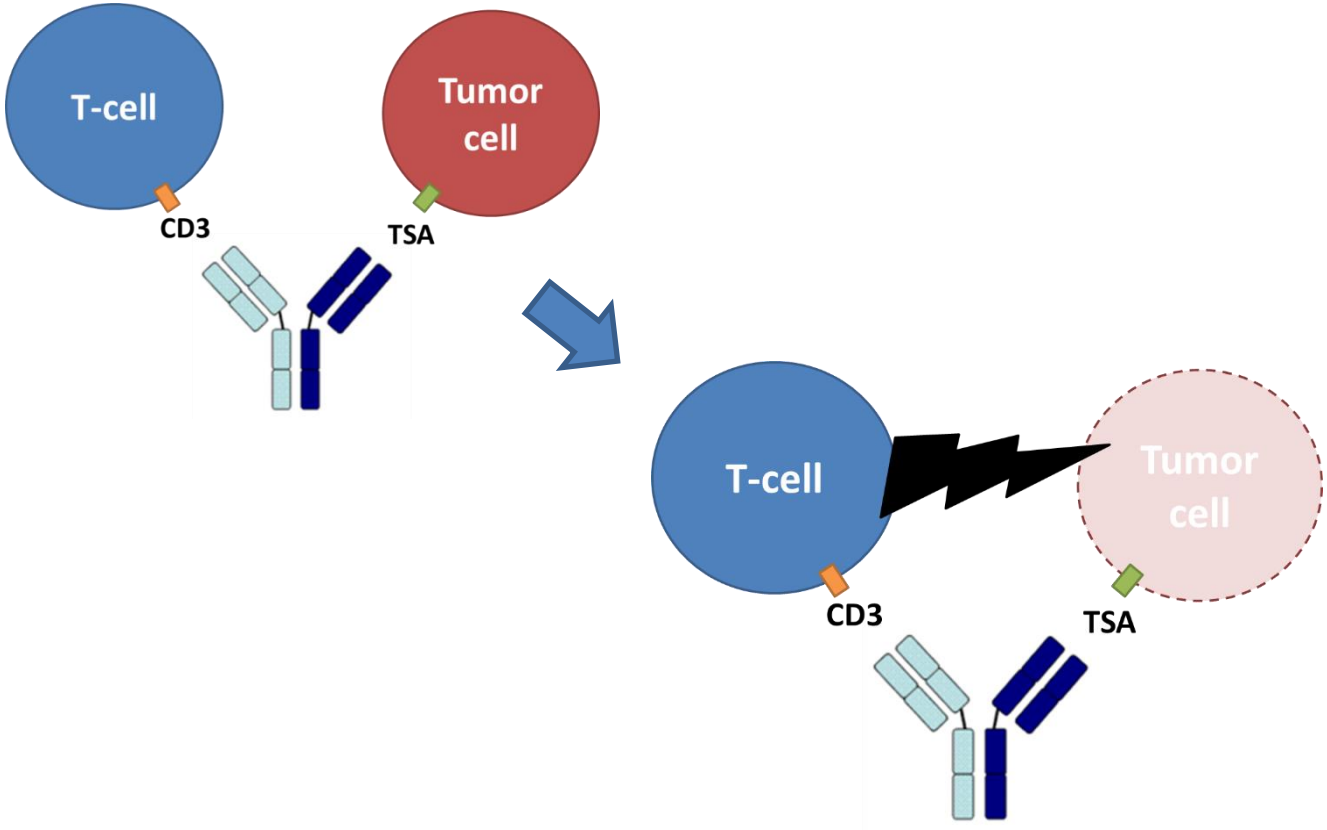
Locke et al. AACR 2017.



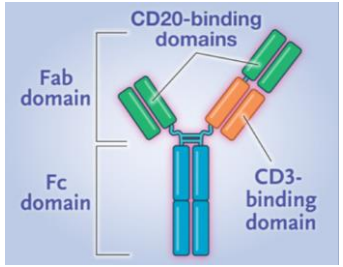
Cell Product	axi-cel	tisa-cel	liso-cel
Trial [ref.]	ZUMA-1 [17,18]	JULIET [19,20]	TRANSCEND [21–23]
N enrolled (infused)	111 (101)	165 (111)	344 (269 + 25 #)
N response-evaluable	101	93	256
Best ORR (CR)	83% (58%)	52% (40%)	73% (53%)

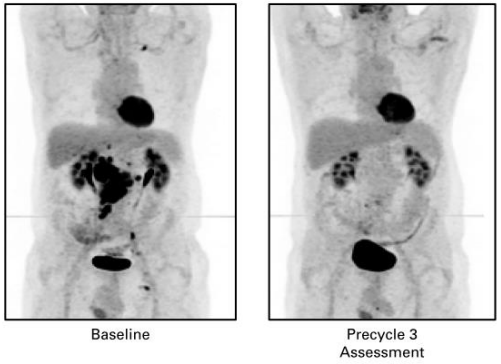
Roex, G., et al. (2020). Chimeric antigen receptor-T-cell therapy for B-cell hematological malignancies: An update of the pivotal clinical trial data. Pharmaceutics 12.

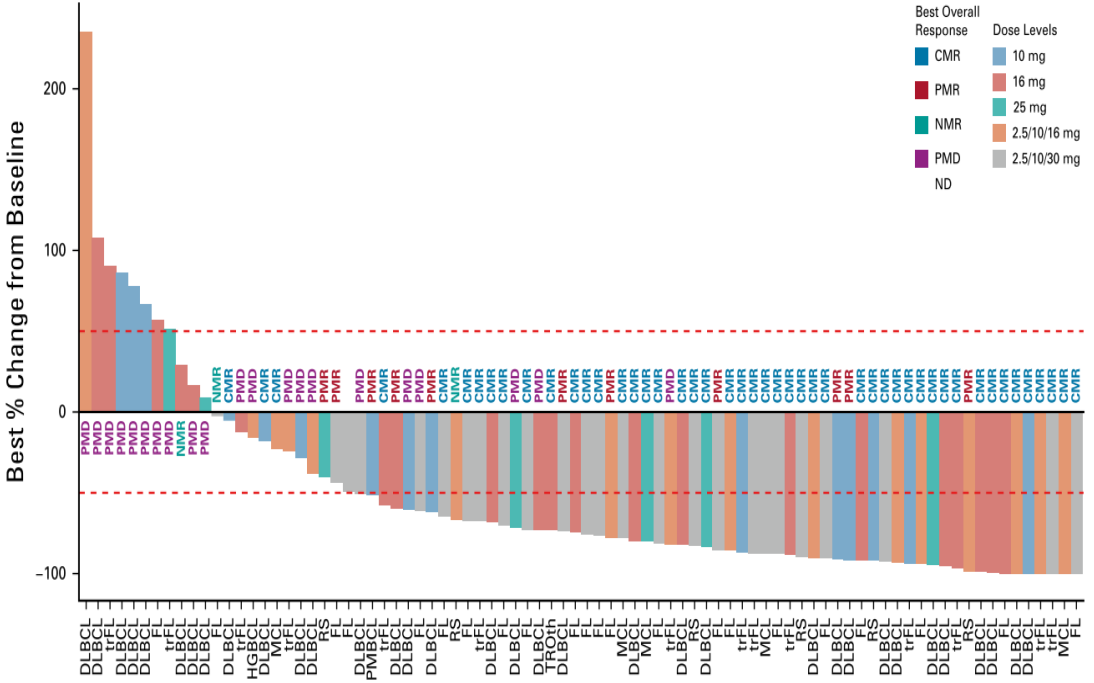
Bispecific T-cell Activating mAbs



Anti-CD20 x Anti-CD3 (Glofitamab) for Relapsed or Refractory Diffuse Large B-Cell Lymphoma



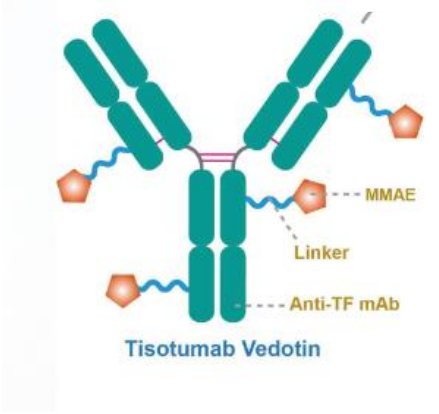


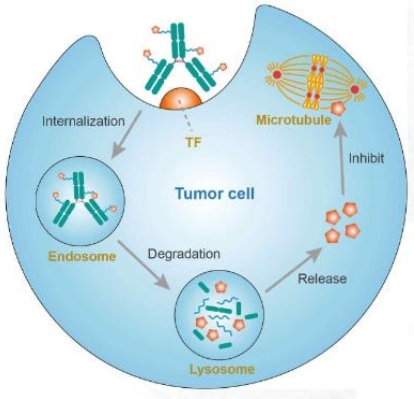


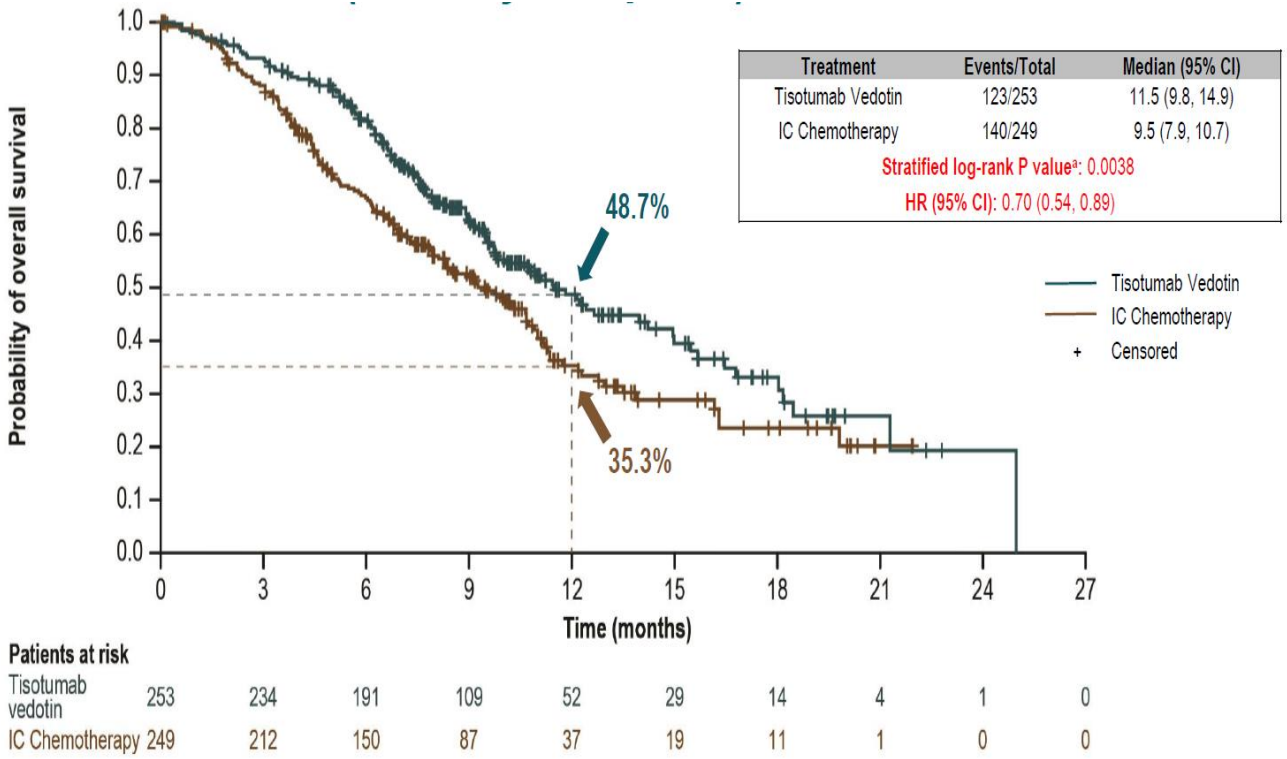
Hutchings, M., et al. (2021). Glofitamab, a Novel, Bivalent CD20-targeting t-cell-engaging bispecific antibody, induces durable complete remissions in relapsed or refractory B-Cell Lymphoma: A phase i trial. J. Clin. Oncol. 39, 1959–1970.

CAR-Ts	BISPECIFIC T-CELL ENGAGERS
MHC-I BYPASS	
POTENT ON TARGET ACTIVITY	LIMITED ON TARGET ACTIVITY
HIGH OFF TARGET TOXICITY	
LIMITED (IF ANY) ANTIGEN SPREADING / CLONAL SELECTION	
CAN CROSS THE BBB	DO NOT CROSS THE BBB
COMPLICATED TO IMPLEMENT	EASIER TO IMPLEMENT
VERY EXPENSIVE	CHEAPER

Antibody Drug Conjugate (ADC) against Tissue Factor in Cervical Cancer







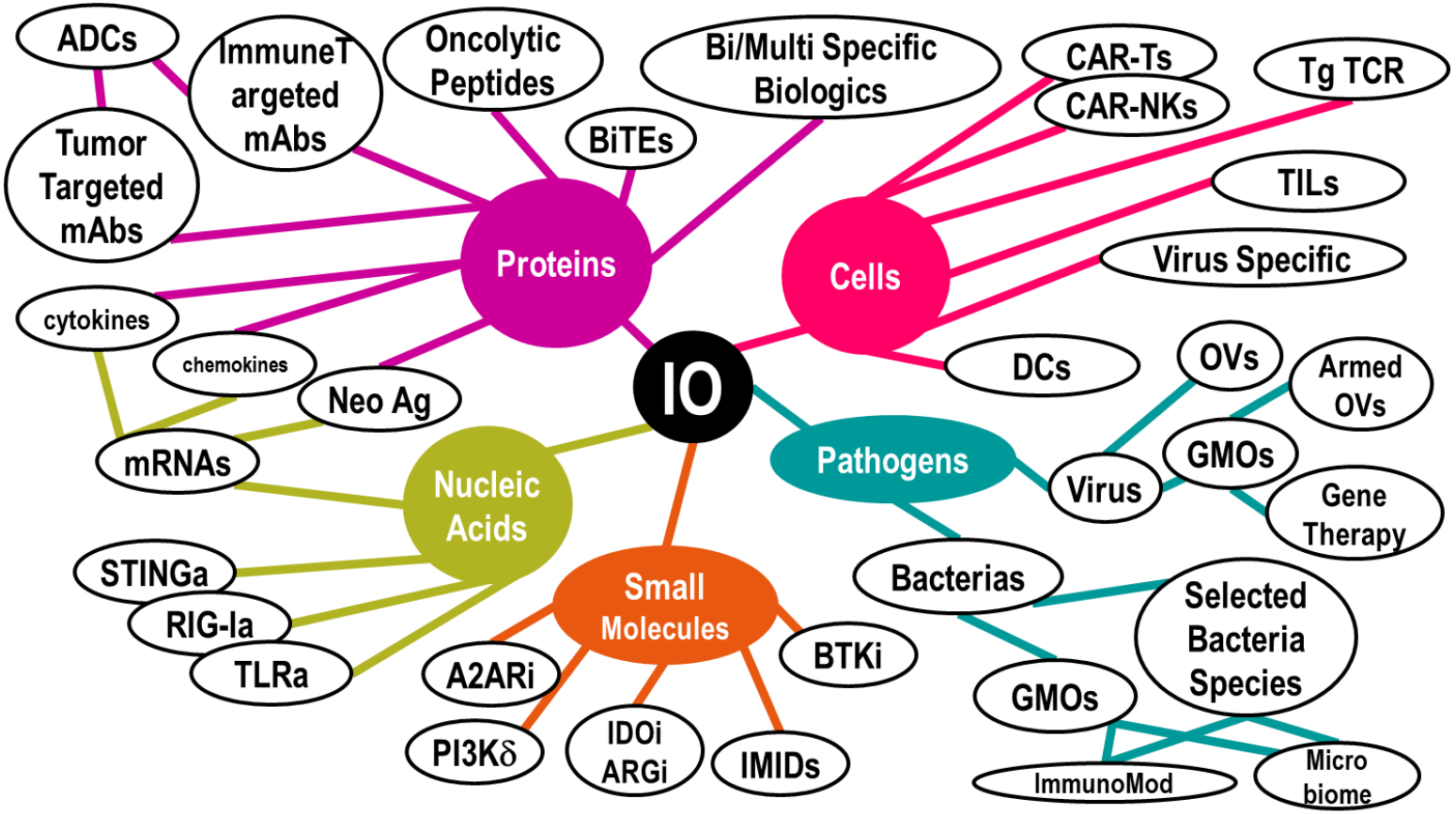
Treatment	Events/Total	Median (95% CI)
Tisotumab Vedotin	123/253	11.5 (9.8, 14.9)
IC Chemotherapy	140/249	9.5 (7.9, 10.7)

Stratified log-rank P value[a]: 0.0038

HR (95% CI): 0.70 (0.54, 0.89)

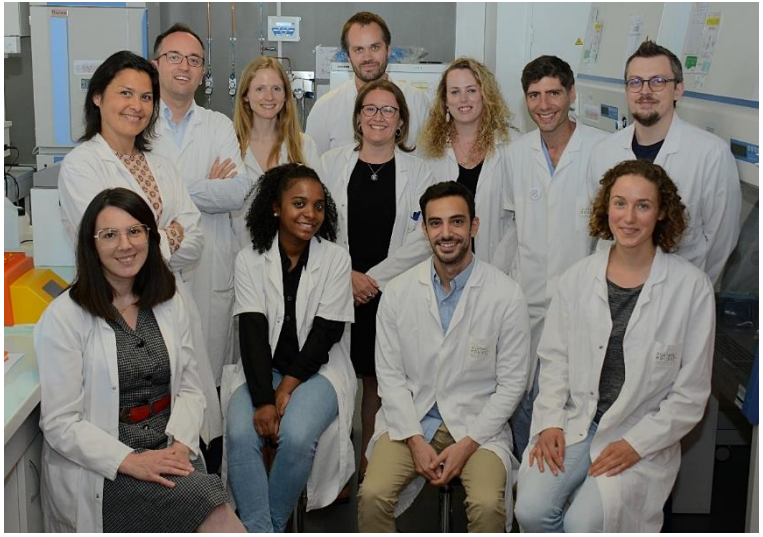
[a]The threshold for statistical significance is 0.0226 (2-sided), based on the actual number of OS events at interim analysis.

Immuno-Oncology 2.0: Versatility



Laboratoire de Recherche Translationnelle en Immunothérapie

CIC BIOTHERIS: Biotherapies for Anti-Tumor *In Situ* Immunization



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