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IRCCS - Fondazione Pascale

Gene profile analysis of patients with metastatic melanoma treated with immune checkpoint inhibitors

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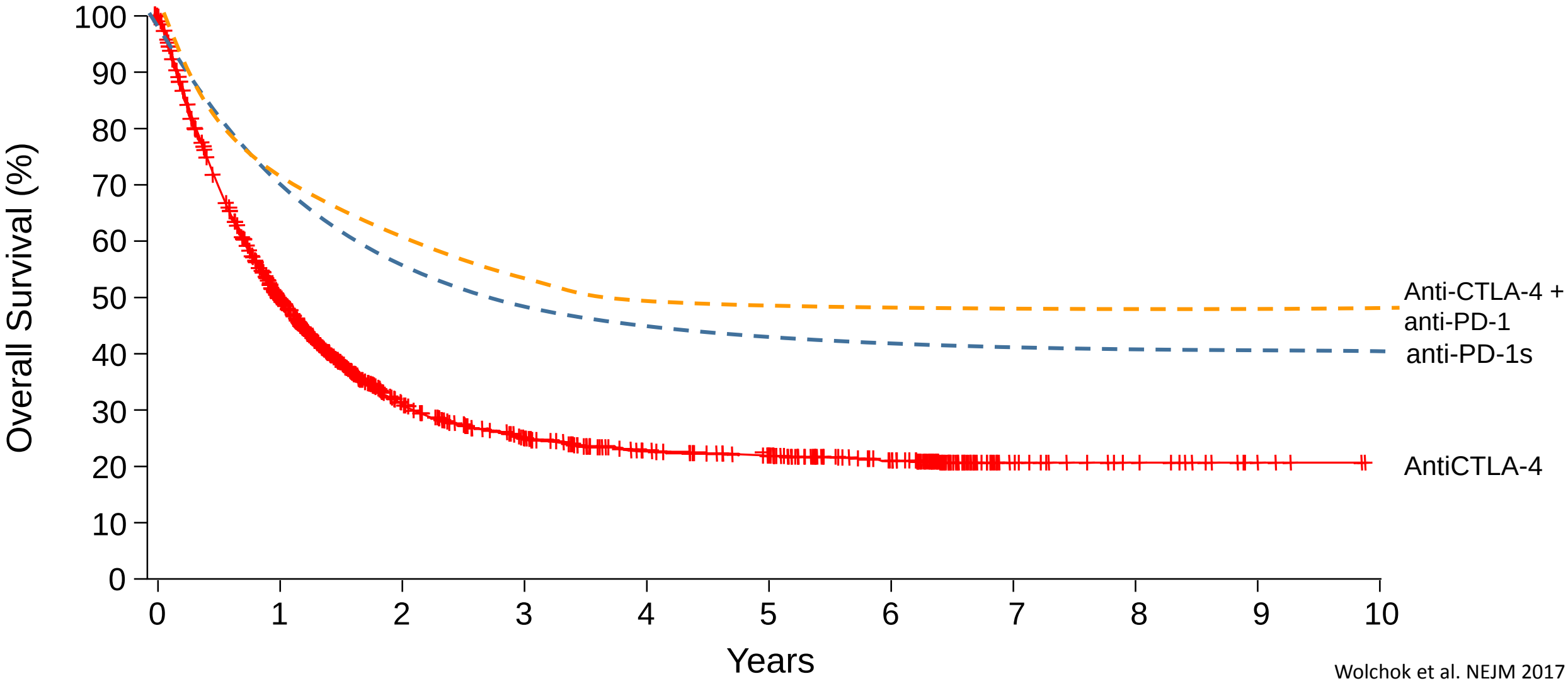
Presenter Disclosure Information

Domenico Mallardo

Project supported from NanoString Technologies

Long-term benefit …

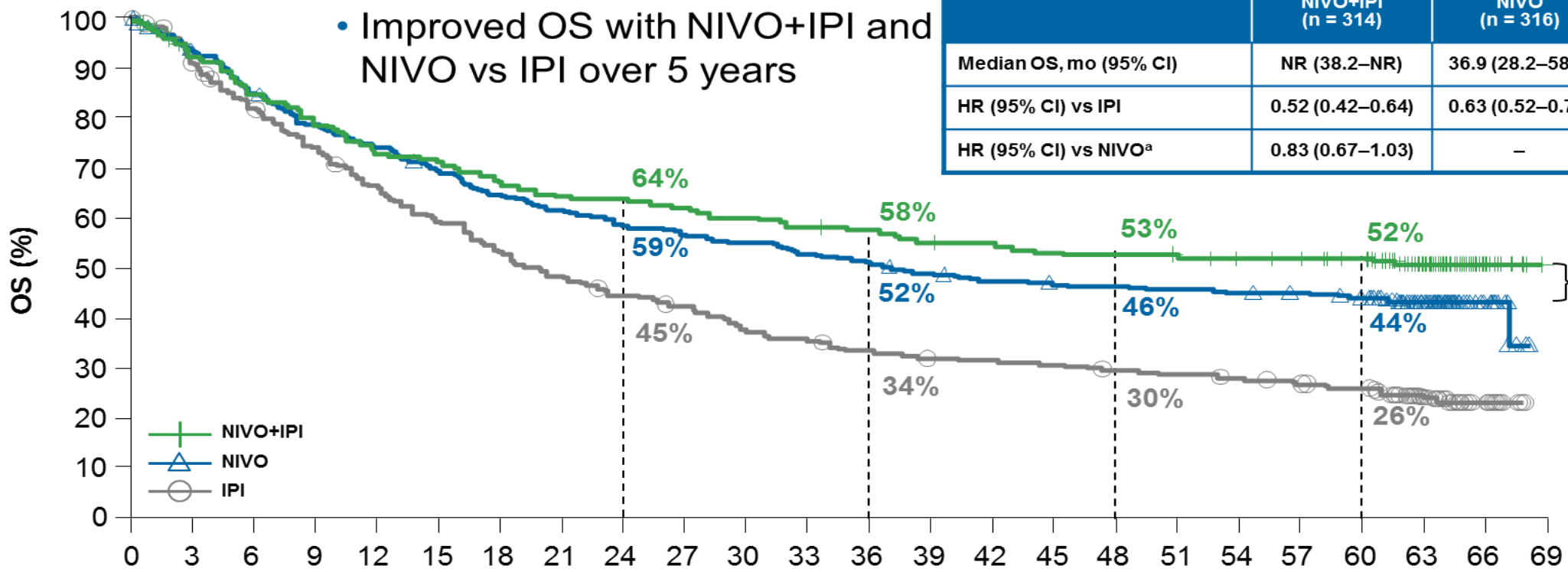


Wolchok et al. NEJM 2017

Overall Survival

- Improved OS with NIVO+IPI and NIVO vs IPI over 5 years

	NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median OS, mo (95% CI)	NR (38.2–NR)	36.9 (28.2–58.7)	19.9 (16.8–24.6)
HR (95% CI) vs IPI	0.52 (0.42–0.64)	0.63 (0.52–0.76)	–
HR (95% CI) vs NIVO[a]	0.83 (0.67–1.03)	–	–



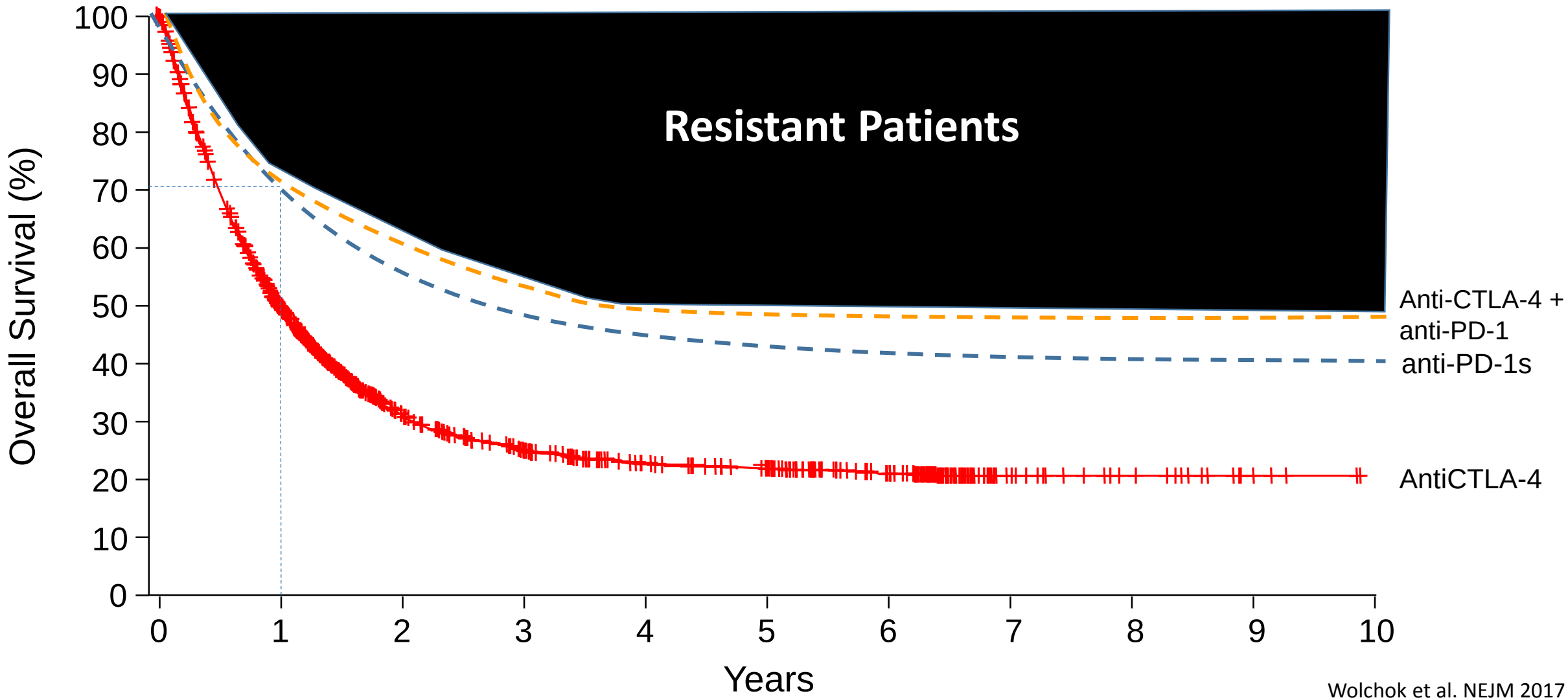
No. at risk

NIVO+IPI	314	292	265	248	227	222	210	201	199	193	187	181	179	172	169	164	163	159	157	155	150	92	14	0
NIVO	316	292	266	245	231	214	201	191	181	175	171	164	158	150	145	142	141	139	137	135	130	78	14	0
IPI	315	285	253	227	203	181	163	148	135	128	113	107	100	95	94	91	87	84	81	77	73	36	12	0

[a]Descriptive analysis. 1. Larkin J, et al. Oral presentation at the AACR Annual Meeting; April 1–5, 2017; Washington DC, USA. Abstract CT075; 2. Wolchok JD, et al. *N Engl J Med* 2017;377:1345–1356; 2. Hodi FS, et al. *Lancet Oncol* 2018;19:1480–1492.

Larkin et al. NEJM 2019

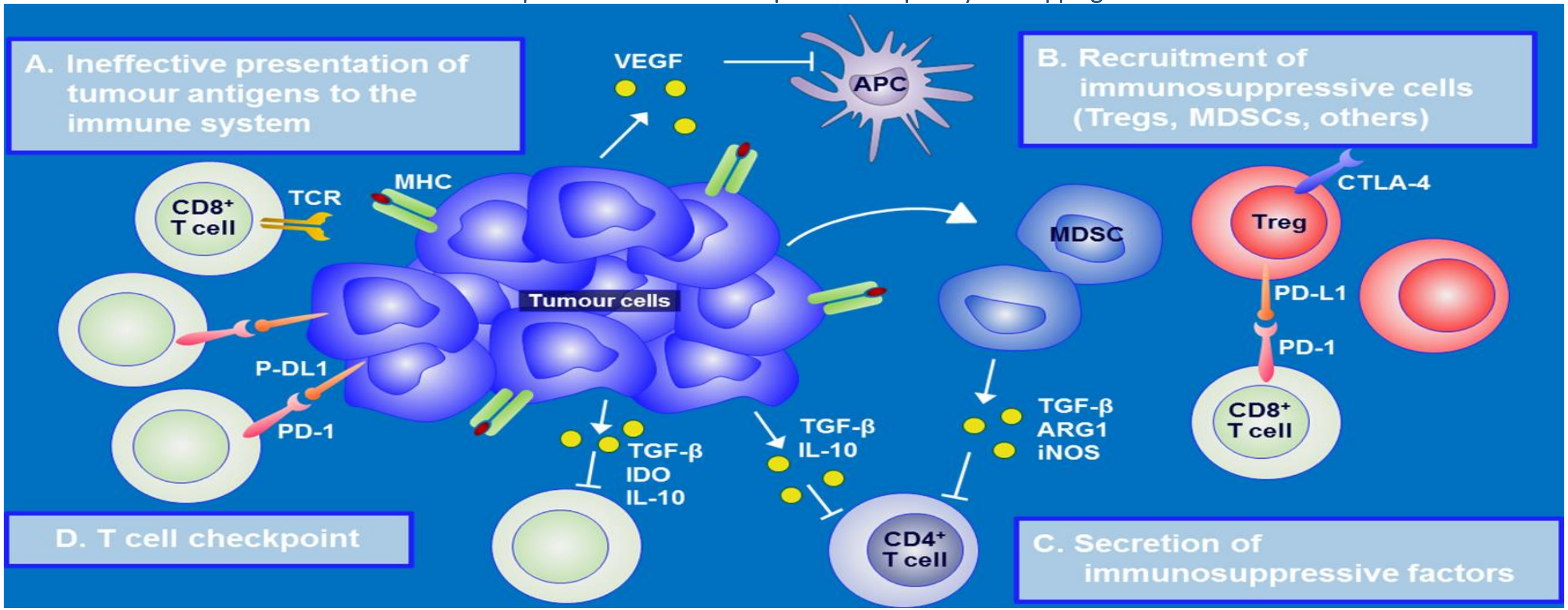
Long-term benefit …



Wolchok et al. NEJM 2017

Tumors use various mechanisms to escape the immune system

Immune escape mechanisms are complex and frequently overlapping



Vesely MD, et al. Ann Rev Immunol 2011;29:235–271

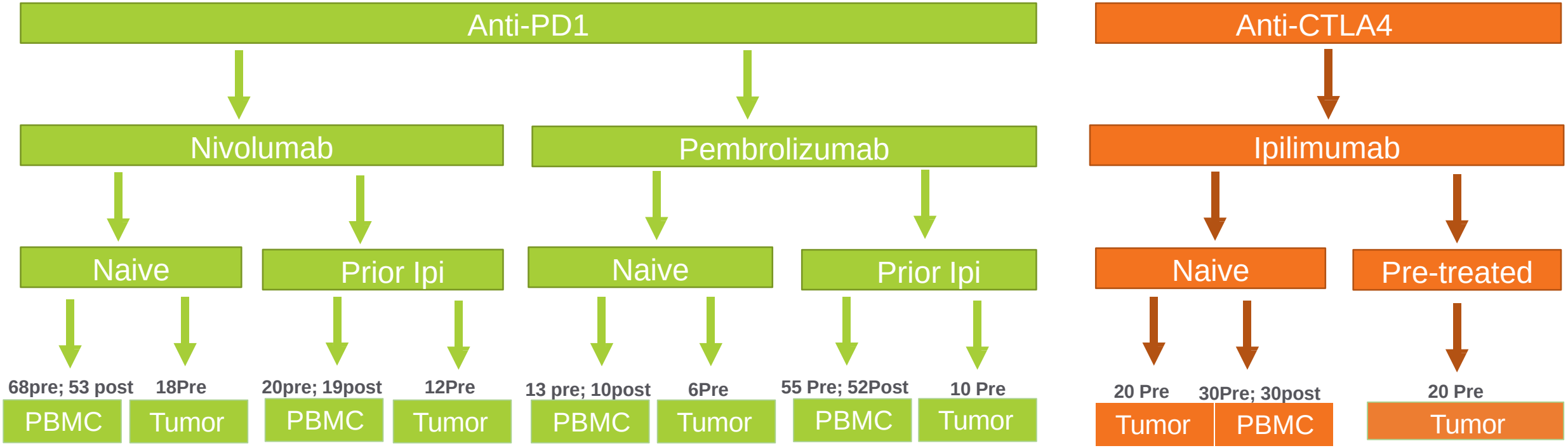
Main goal:

Identification of principal pathways involved in mechanisms of resistance to ICIs

Gene profile analysis on cohort - patients' tumor tissue

Pre-Treatment Tumor FFPE samples Baseline Characteristics	Anti-CTLA4	Anti-PD1 Pre-treated	Anti-PD1 Naive
Codeset	IO360	IO360	IO360
Mean Age, Years±SD	63±11.5	58±15	61.7±16.1
Gender: Female/Male	13/17	14/10	11/11
Prior Immunotherapy	None	anti-CTLA4	None
Stage IIIC/IV (n)	1/29	1/23	0/22
BRAF Status (WT/MUT/NA)	17/11/2	15/8/1	15/7/0
Objective Response (PR+CR)	4 (13.3%)	3 (12.5%)	10 (45.5%)
Matched PBMCs?	No	No	Yes (22)

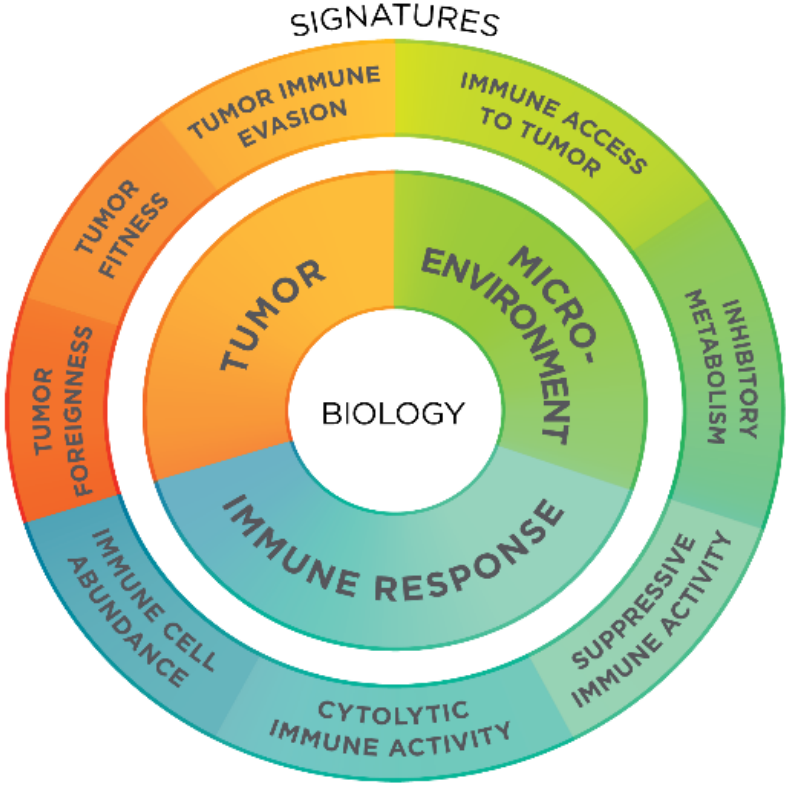
Cohort Summary: 436 samples analyzed



436 x 770 = 335 720 genes data point analyzed

PanCancer IO 360™ Gene Expression Panel

- Developed for NanoString nCounter panel
- 770 human genes
- Characterizes biology of tumor-immune interactions and pathways of immune evasion
- Companion data analysis report

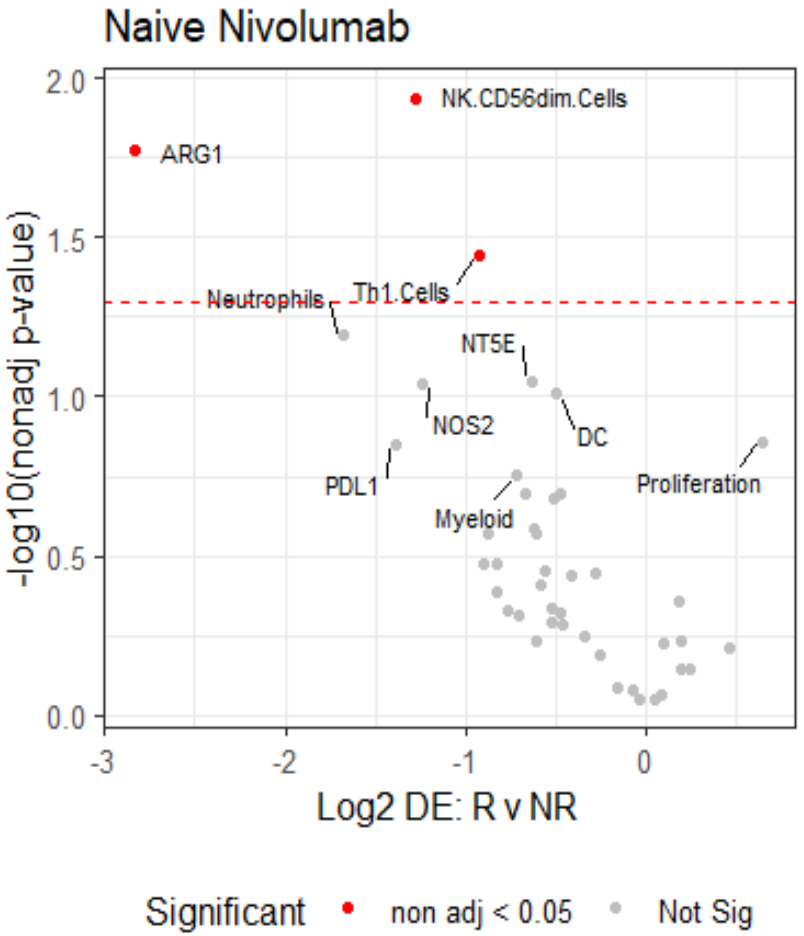


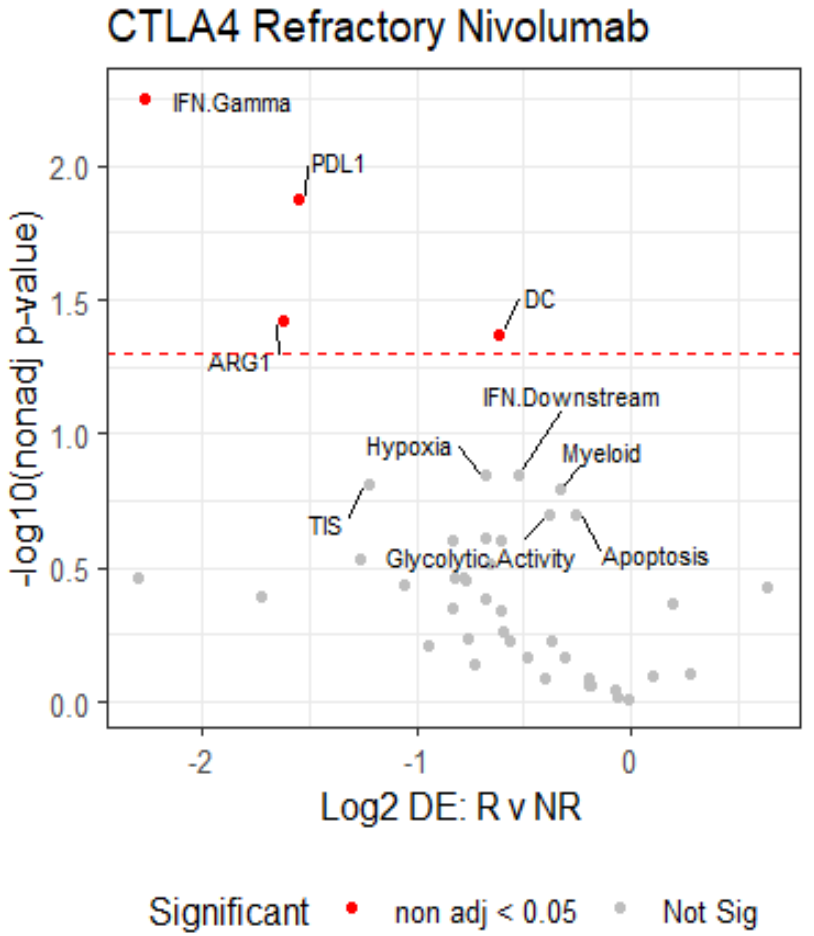
Tumor	Microenvironment	Immune Response
16 Pathways and Processes		
30+ Signatures measuring Immune and Tumor Activity		
14 Cell type abundance scores		

Tumor signature score in Nivolumab treated patients

Differential gene expression comparing responders and non-responders in naïve (R, n = 6; NR, n = 11) and CTLA-4 refractory (R, n = 2; NR, n = 8) nivolumab patients reveal different mechanisms enriching for clinical outcome.

Naïve non-responders show higher **Arg1, Th1, and NK CD56dim** signature scores, while refractory non-responders have elevated **IFN gamma, PDL1, DC, and Arg1** signature scores.



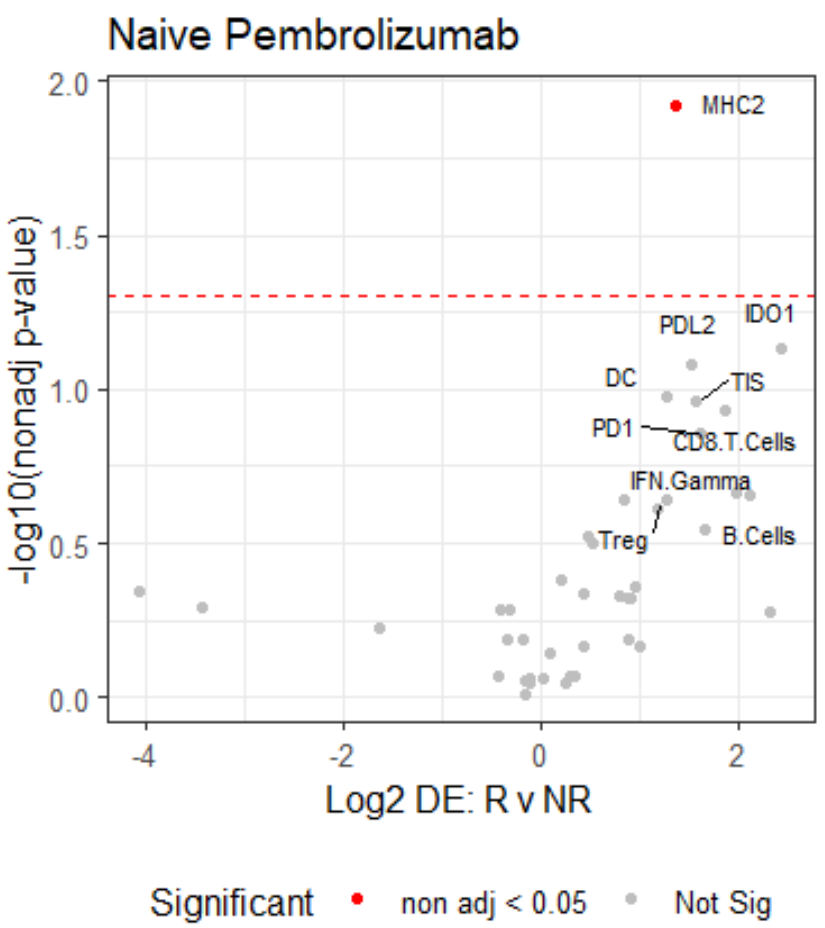


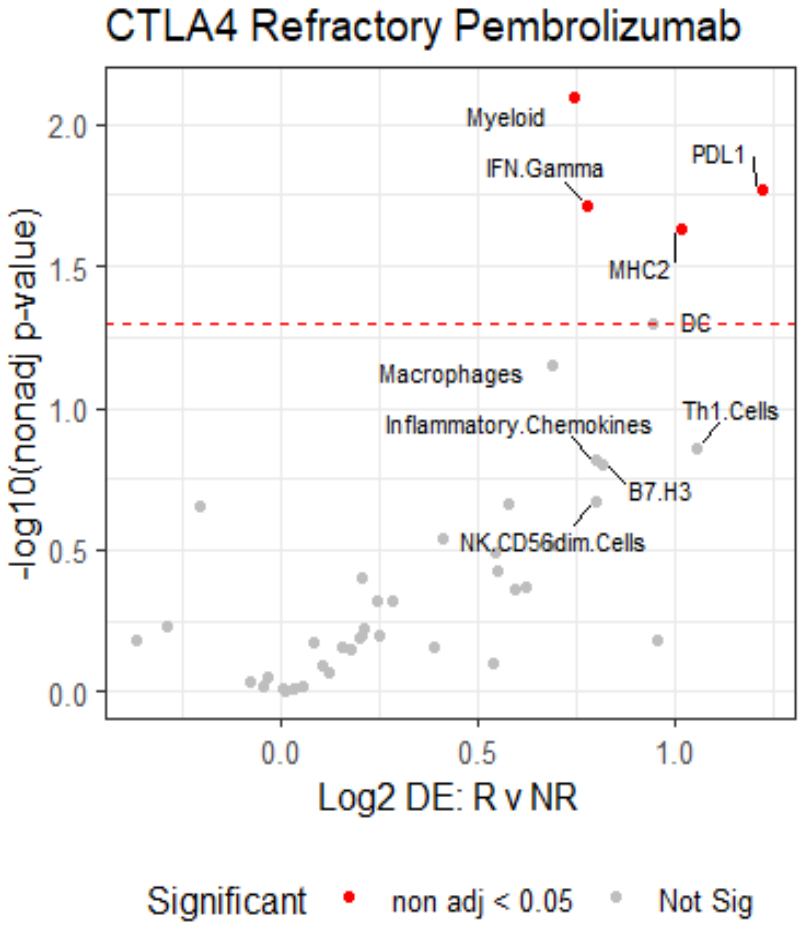
Unpublished data

Tumor signature score in Pembrolizumab treated patients

Expression analysis in responders naïve (R, n = 4; NR, n = 2) and CTLA-4 refractory (R, n = 2; NR, n = 8) cohorts compared to non-responders.

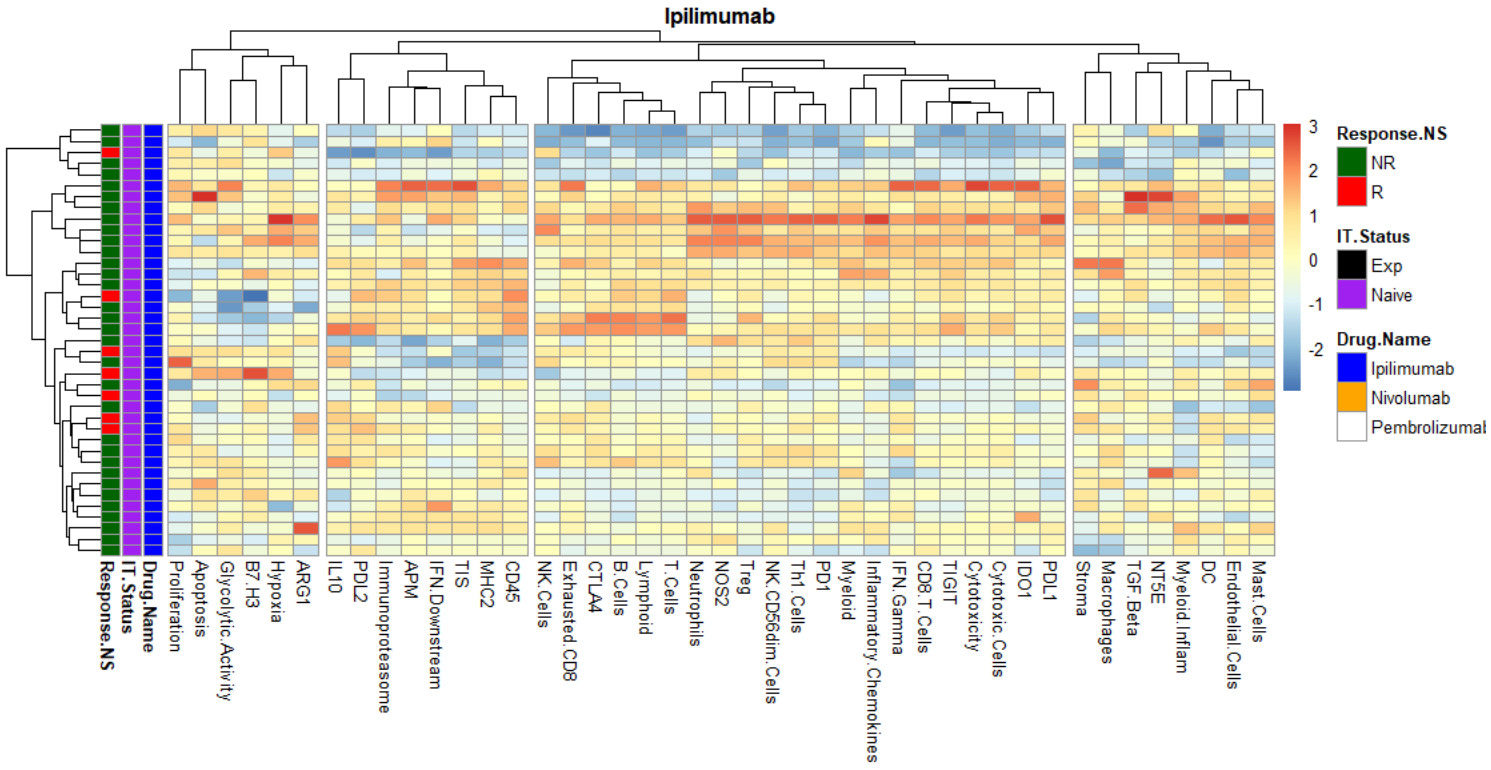
Both cohorts show higher **MHC2** signature scores in the responder groups, while responders in the refractory cohort also show higher **myeloid cell, IFN gamma, and PDL1** signature scores.

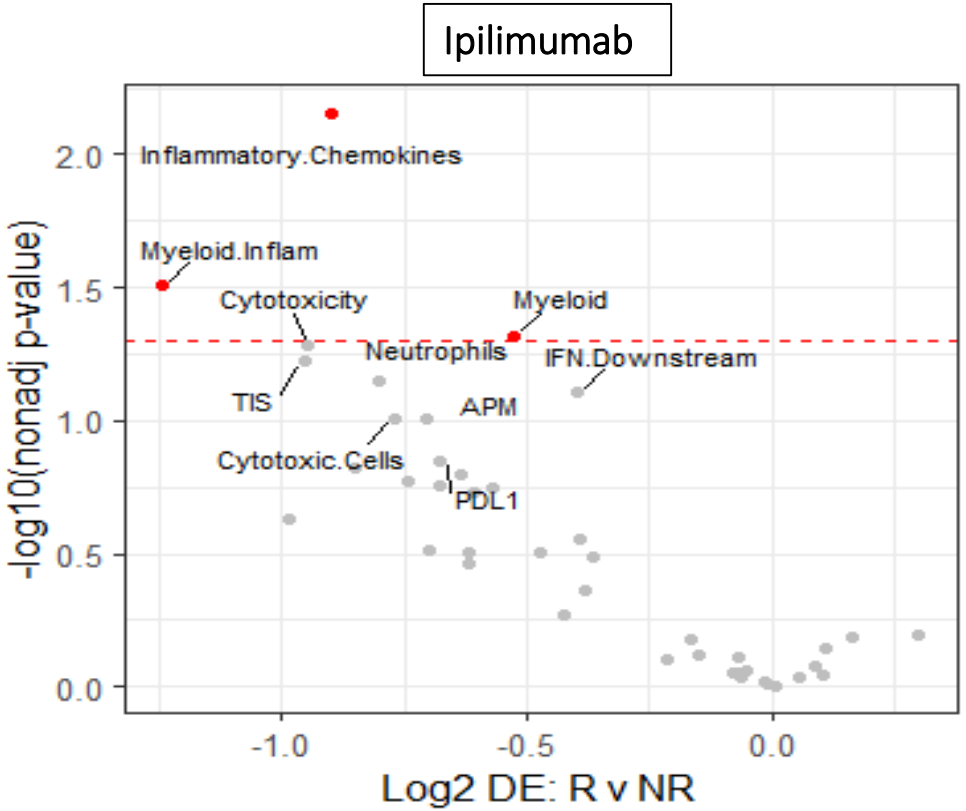




Unpublished data

Tumor signature score in ipilimumab treated patients





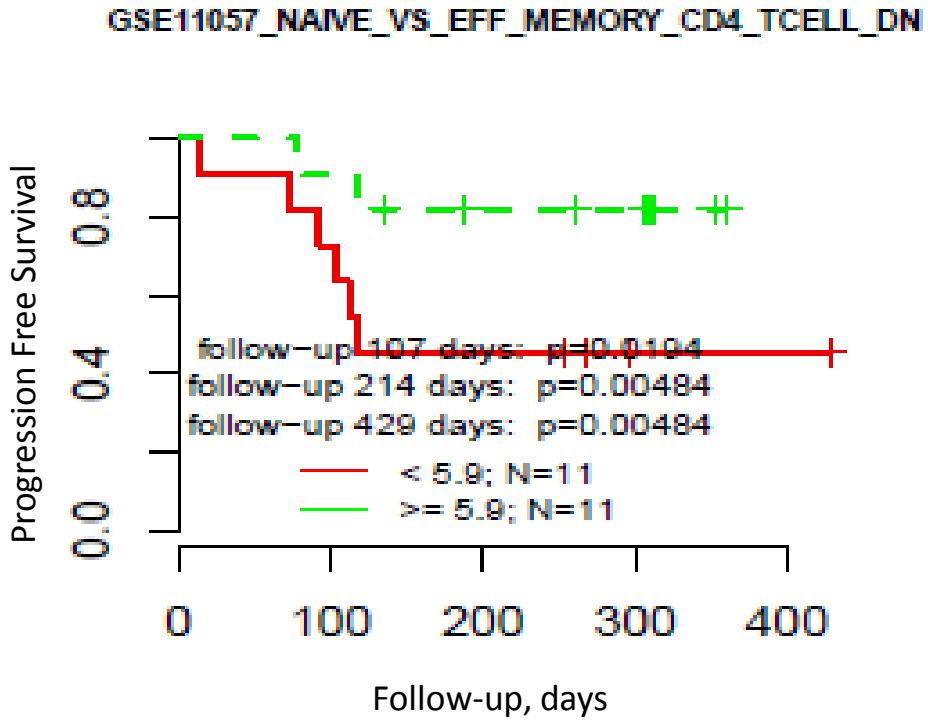
Comparison of responders (n = 7) and non-responders (n = 23) in ipilimumab-treated patients show higher inflammatory chemokine, myeloid inflammation, and myeloid cell signature scores enriched in non-responders, indicating possible suppressive immune mechanisms dominating clinical response outcomes.

Unpublished data

Immunologic signatures of Naïve patients treated with Anti-PD1 (Nivolumab and Pembrolizumab)

Expression of immunologic signatures of 199 genes associated to T cells are related with a good Progression free survival in Naïve patients treated with anti-PD1.

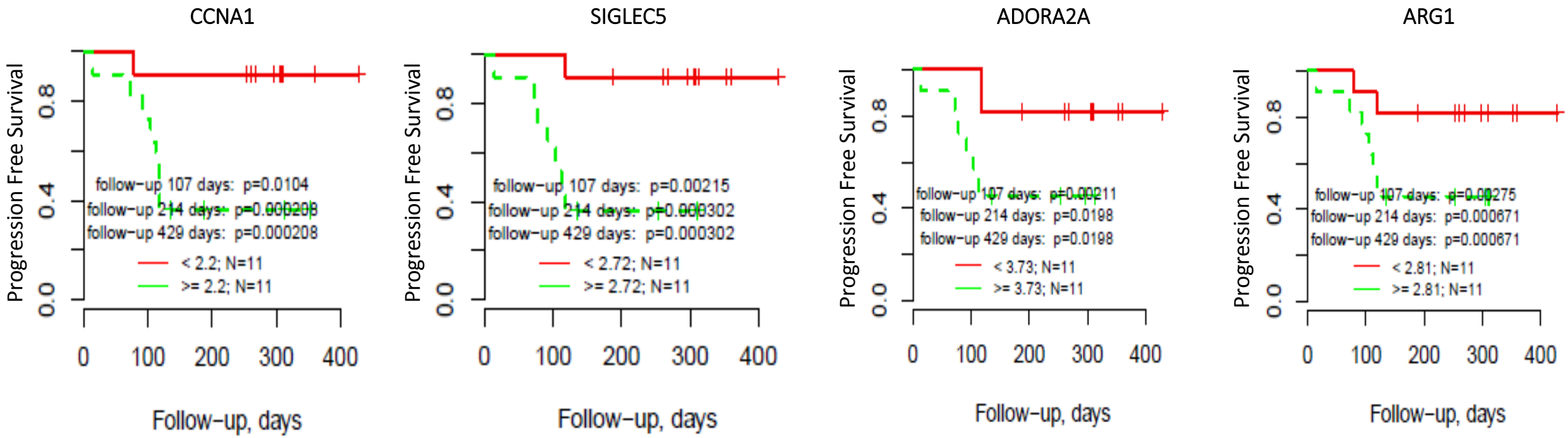
SLC35D2	SLC9A3R1	SMAP1	SPAG1	SPOPL	SRGN	SSR3	ST8SIA1
PPIF	PPP1CA	PREX1	PRR5L	PTTG1	PVRL3	RAB27A	REEP3
MYBL1	MYL6	MYO1F	NCAPH	NCF4	NETO2	NINJ2	NMU
KIF1B	KIF21A	KLRB1	LDHA	LGALS1	LGALS3	LIMS1	LIMS3
FRMD4B	GBP3	GCLM	GDPD5	GLIPR1	GOLGA7	GSTK1	GZMA
CREB3L2	CRELD2	CRIP1	CRYBG3	CTSA	CTSC	CXCR3	DNAI2
CAPG	CASK	CAST	CBLL1	CCDC107	CCL5	CCR2	CCR6
ADAM19	AHR	AKIRIN2	ALCAM	ALOX5AP	ANKRD32	ANTXR2	ANXA1
TPM4	TRAC	TRADD	TTC39C	TTYH2	TXN	TYMP	UBL3
TMEM156	TMEM200A	TMEM64	TMX4	TNF	TNFRSF4	TOR3A	TP53INP1
S100A11	S100A4	SAP30	SEC11C	SH2D1A	SH3BGRL3	SH3BP5	SLC2A3
OSBPL3	PAM	PDIA6	PEA15	PFKL	PHACTR2	PHTF2	PLXNC1
MFHAS1	MIAT	MIB1	MICAL2	MIS18BP1	MLF1	MLLT4	MTSS1
IFI27	IFNG	IL10RA	IL15RA	IQGAP1	IQGAP2	ITGB1	KIAA0895L
EPS15	EVI2B	FAM129A	FAM164A	FAM38A	FAR2	FAS	FBXL8
CDK2AP2	CHST7	CLDND1	CLIC1	CLU	CNPPD1	COTL1	CPPED1
ATXN1	B3GNT9	BTG3	C11orf75	C13orf31	C17orf91	C6orf1	CALHM2
STOM	STX11	TBCB	TBX21	TIGIT	TLR3	TMEM116	USP46
REEP5	RFTN1	RGS3	RHOU	RNF126	RNF149	RORA	UST
NOD2	NPC1	NPDC1	OBFC2A	OBFC2B	OGDH	OGFRL1	VCL
ATP2B4	LOC1002886	LOC1005061	LOC338620	LOC730184	MAP3K5	MDFIC	YWHAH
GZMK	HLA-DPA1	HMGN4	HN1	HNRPLL	HOPX	IFI16	ZBTB38
DUSP16	DUSP5	EFHD2	EIF2C4	EIF3A	EIF4EBP2	ELOVL5	ZC3HAV1L
CD226	CD28	CD58	CD63	CD74	CD84	CDC42EP3	ZNF532
ANXA2	ANXA2P1	ANXA4	AQP3	ARHGAP18	ASB2	LOC100131176	



NEA (network enrichment analysis) on GSE11057 set from MSigDB: immunology collection of >4500 gene sets

Unpublished data

Genes associated with PFS in patients treated with anti-PD1 in second line

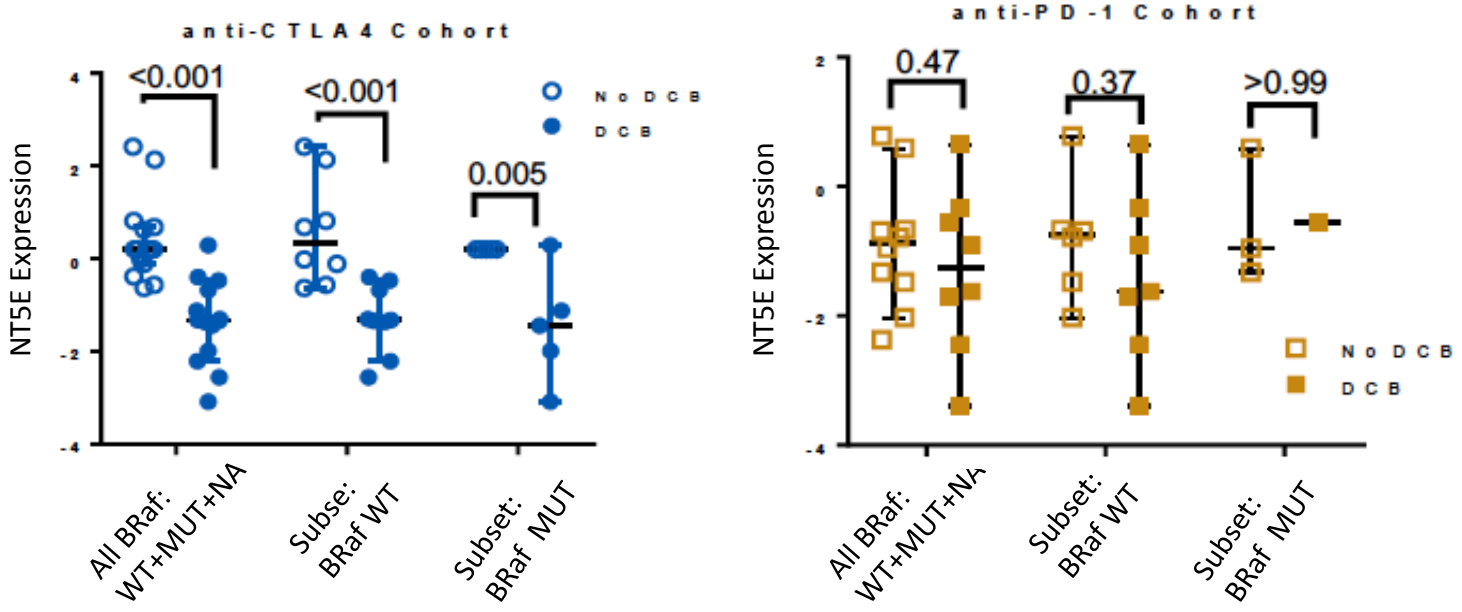


Significant genes associated to RFS in patients treated with anti-PD1 in second line, after ipilimumab progression:
CCNA1, SIGLEC5, ADORA2A, ARG1.

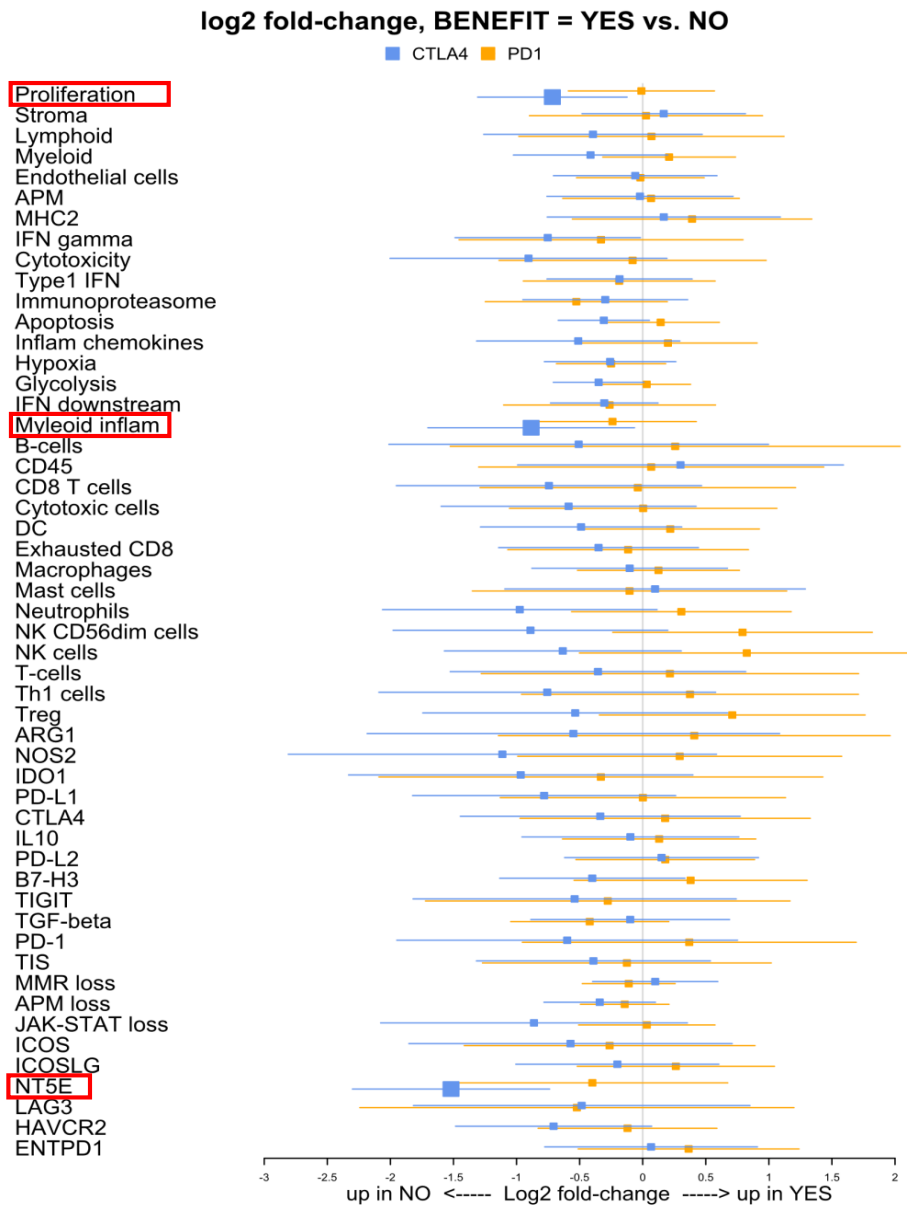
Unpublished data

CTLA4 vs PD1 Pre-Treatment Tumors Immune Indicators of Clinical Benefit

Decreased levels of proliferation scores, myeloid inflammation scores and CD73 are correlated with DCB, in anti-CTLA4 patients. Expression of CD73 is independent of BRAF status.



CD73 as a Biomarker of αCTLA4 Benefit



Unpublished data

Conclusions

- Anti-CTLA4 and anti-PD1 target different immune pathways in melanoma patients
- ICI-refractory patients undergoing a second line of immunotherapy may have responses governed by difference immune mechanisms than naïve individuals
- Anti-CTLA4 affects the peripheral immune system differently from patients who receive anti-PD1.
- Biomarkers for checkpoint inhibitor monotherapy are dependent on the specific antibody administered – anti-PD-1 and anti-CTLA-4.
- Further analysis are still ongoing in order to get additional data for finding predictive biomarkers.

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