IV Simposio

GETHI

Marcadores plasmáticos de respuesta a inmunoterapia

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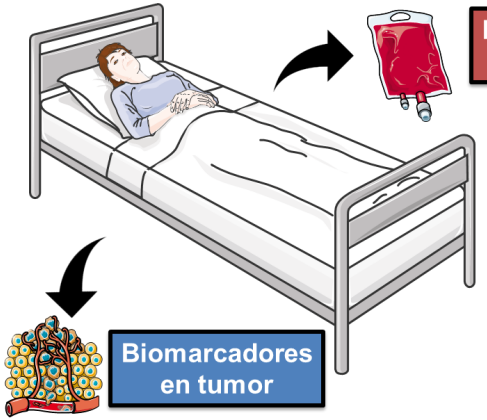
CENTRO INTEGRAL ONCOLÓGICO hm CIOCC

BIOMARCADORES



Biomarcadores en sangre

Suero	- Análisis múltiple de proteínas y proteómica
PBMCs	- Citometría de flujo /masas - Firmas genéticas - Epigenómica - Secuenciación TCR/BCR

Biomarcadores en tumor

Tumor fresco	- Xenoinjertos - Citometría de flujo /masas
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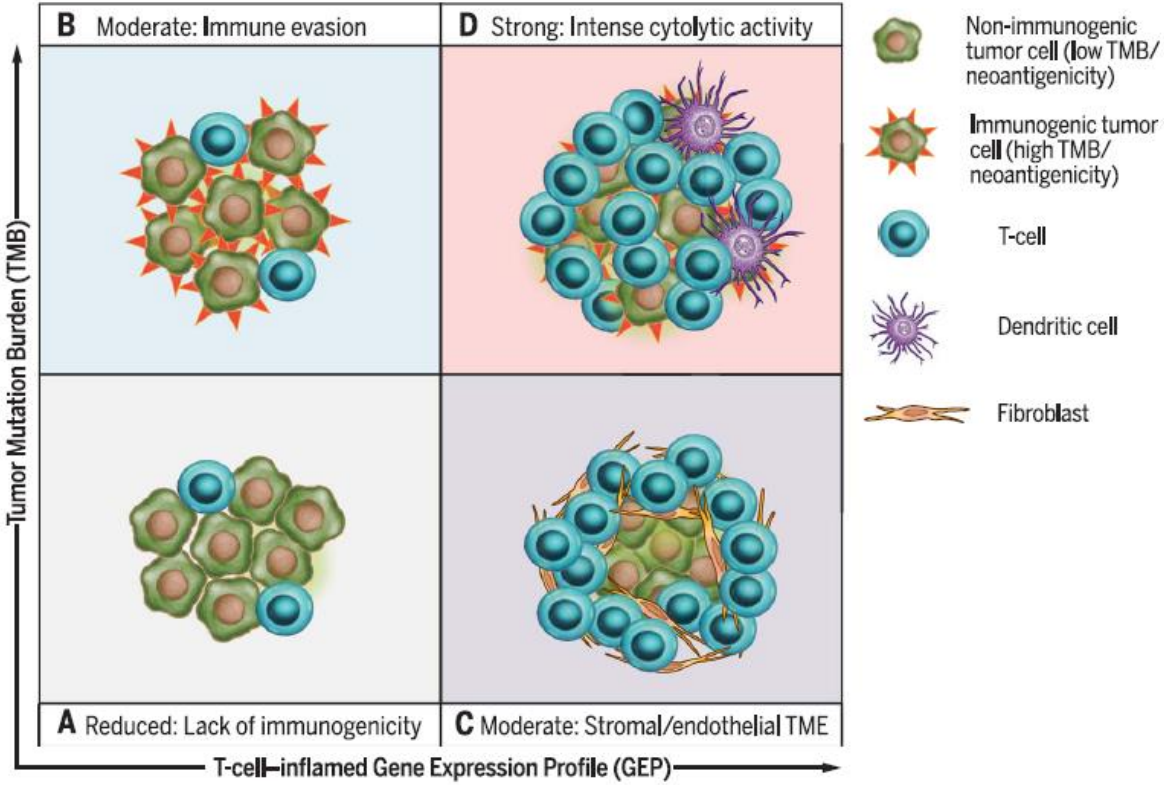
Tumor en parafina	-Inmunohistoquímica multiparamétrica

Berraondo P et al. Cáncer y Sistema Inmunológico. 2018

BIOMARCADORES EN EL TUMOR



Cristescu R et al. Science. 2018

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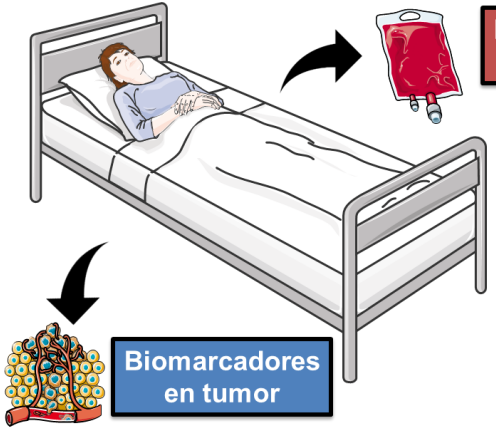

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BIOMARCADORES EN SANGRE

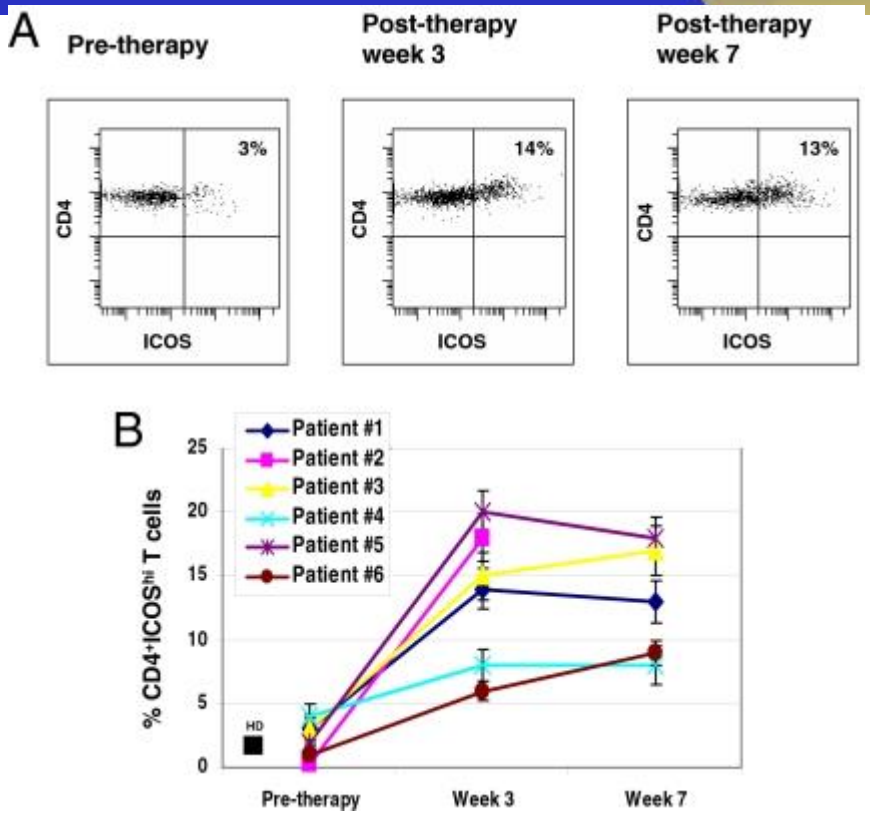
Table 1. Blood-based biomarkers described to be associated with clinical response to immunotherapies

Biomarker	Treatment	Indication	*N*	Sampling timepoints	Summary of findings	Reference
Absolute lymphocyte counts (ALC)	Ipilimumab (0.3, 3, or 10 mg/kg)	Melanoma	553	BL, every 3 weeks	Rate of ALC ↑ associated with clinical activity	(70)
	Ipilimumab (10 mg/kg)	Melanoma	53	BL, every 3 weeks	ALC after 2 doses >1,000/μL associated with clinical benefit and OS	(71)
	Ipilimumab (10 mg/kg)	Melanoma	27	BL, after weeks 4 and 7	ALC ↑ >1,500/μL at week 4 associated with response and OS	(72)
	Ipilimumab (0.3, 3, 10 mg/kg), various combinations	Melanoma	1,450	BL, every 3 weeks	Rate of ALC ↑ associated with OS, not ipi specific	(73)
Eosinophils	Ipilimumab (3 mg/kg)	Melanoma	73	BL, every 3 weeks	AEC ↑ >100/μL and ALC ↑ >1,000/μL associated with OS	(74)
	Ipilimumab (3 mg/kg)	Melanoma	123	BL	High BL AEC associated with OS	(75)
	Ipilimumab (3 mg/kg)	Melanoma	59	BL, every 3 weeks	AEC ↑ in cycle 1 associated with response	(76)
Neutrophil/ leukocyte ratio	Ipilimumab (10 mg/kg)	Melanoma	27	BL, weeks 4, 7, and 10	Low NLL ratio at weeks 7 and 10 associated with OS	(77)
Regulatory T cells	Prostate GVAX/ipilimumab (0.3 to 5 mg/kg)	Prostate cancer	28	BL, every 4 weeks	Treg ↑ between BL and week 12 negatively associated with OS	(78)
	Ipilimumab (3 mg/kg)	Melanoma	95	BL, every 3 weeks	Treg ↓ between BL and week 6 associated with OS	(54)
	Ipilimumab (10 mg/kg)	Melanoma	35	BL, 6 weeks	Treg ↑ at week 12 associated with PFS	(79)
	Nivolumab with or without multipeptide vaccine (gp100, NY-ESO-1, MART-1)	Melanoma	90	BL, week 12	Treg ↑ associated with progression	(60)
Myeloid-drived suppressor cells (MDSC)	Ipilimumab (3 or 10 mg/kg)	Melanoma	26	BL, 6 weeks	Low monocytic MDSCs at BL associated with OS	(80)
	Ipilimumab (10 mg/kg)	Melanoma	35	BL, 6 weeks	MDSC ↓ associated with PFS	(79)
	Ipilimumab (3 mg/kg)	Melanoma	59	BL, every 3 weeks	Monocytic MDSC ↓ at cycle 1 associated with response	(76)
ICOS	Ipilimumab (3 mg/kg)	Melanoma	14	BL, weeks 7 and 12	$CD4^+ICOS^+$ ↑ associated with OS	(81)
	Tremelimumab (15 mg/kg) every 90 days	Melanoma	29	BL, days 14, 30, and 60	$CD4^+ICOS^+$ ↑ associated with OS	(82)
	Ipilimumab (10 mg/kg)	Melanoma	17	BL, weeks 4, 7, and 10	$CD4^+ICOS^+$ ↑ and $CD8^+ICOS^+$ ↑ associated with disease control and OS	(77)
Th17 cells	Tremelimumab (10 or 15 mg/kg) every 90 days, 6 pts in combination with DC vaccine (MART-1)	Melanoma	27	BL, between 30 and 60 days	Th17 ↑ associated with autoimmune toxicities; no association with response	(83)
	Ipilimumab (3 or 10 mg/kg), with multipeptide vaccine	Melanoma	75	BL, 6 months	Th17 inducibility ↑ associated with freedom from relapse	(84)
MART-1, Gp100, Tyros T-cell responses	Ipilimumab (3 or 10 mg/kg), with multipeptide vaccine	Melanoma	75	BL, 6 months	Antigen-specific T-cell induction assessed by ELISPOT could not be consistently associated with any added clinical benefit	(84)
NY-ESO-1, MART-1, gp100 T cells	Nivolumab with or without multipeptide vaccine (gp100, NY-ESO-1, MART-1)	Melanoma	90	BL, 3 months	High baseline antigen-specific $CD8^+$ T cells associated with progression	(60)
Tyrosinase, gp100 and MART-1	Ipilimumab 0.3, 1.0, or 3.0 mg/kg	Melanoma	19	BL, 6 months	47% of treated patients generated specific T-cell responses	(59)
TCR Vb	Tremelimumab	Melanoma	21	BL, 1–2 months	Increase in unique T-cell clonotype not associated with clinical outcomes	(62)

Abbreviations: AEC, absolute eosinophil count; BL, baseline; Ipi, ipilimumab; NLL ratio, absolute neutrophils to lymphocytes; OS, overall survival; PFS, progression-free survival.

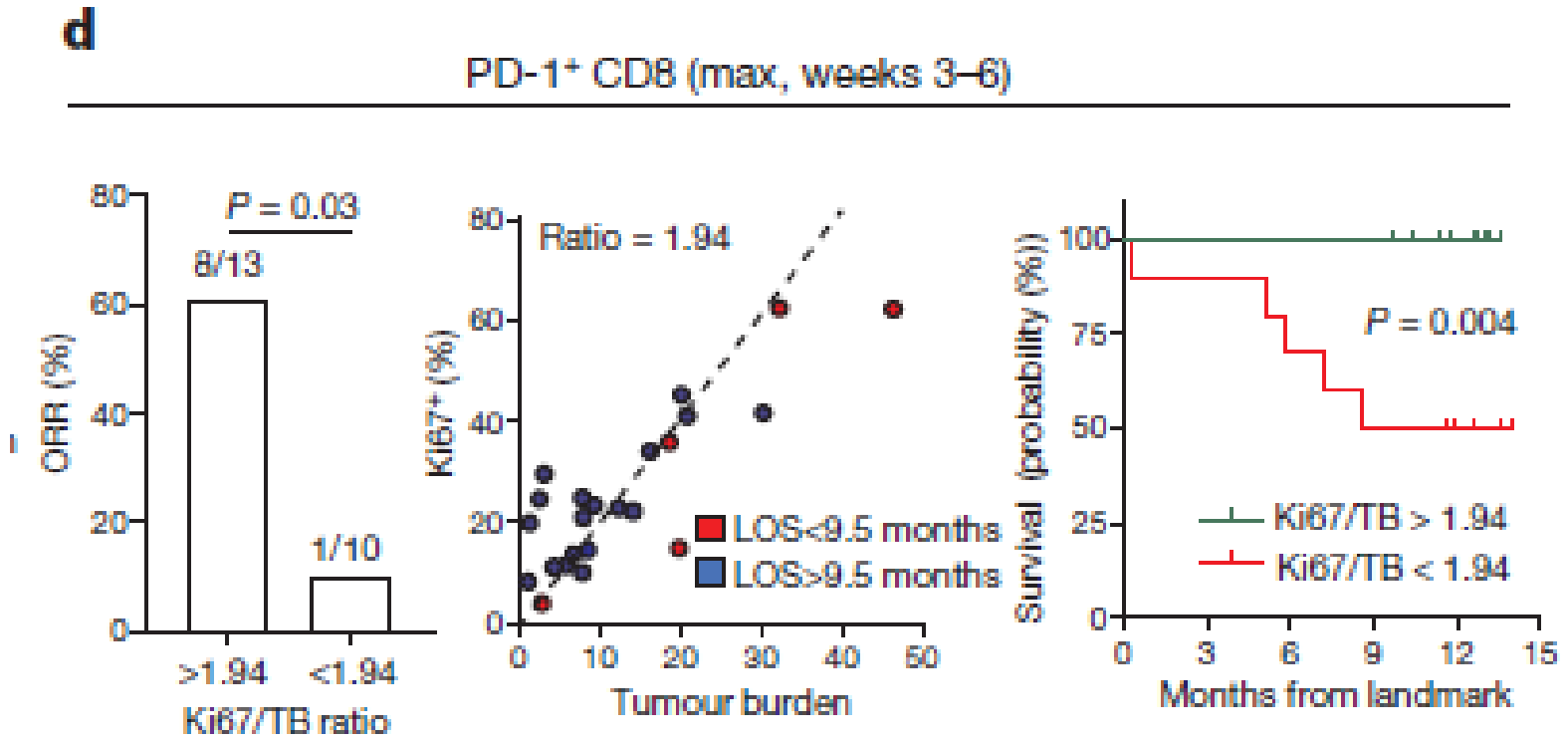
Hegde PS et al. Clin Cancer Res. 2016 22:1866-74.

CTLA-4 y ICOS

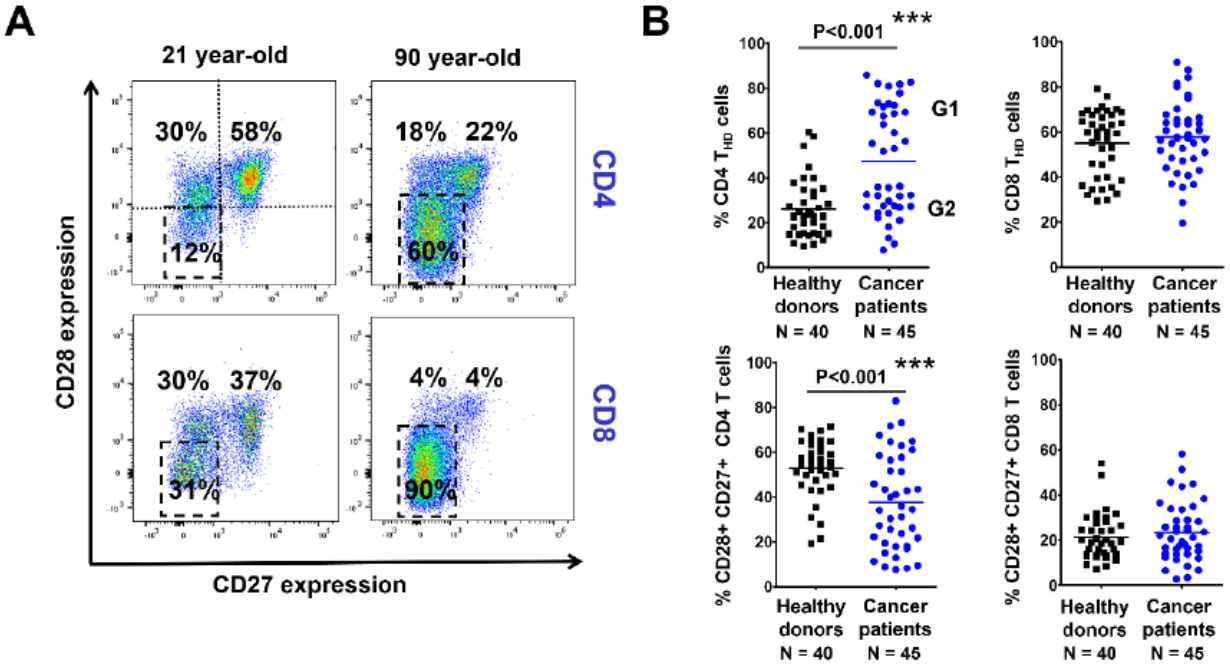


Liakou CI et al. PNAS. 2018 Sep 30;105(39):14987-92. .

BIOMARCADORES EN SANGRE

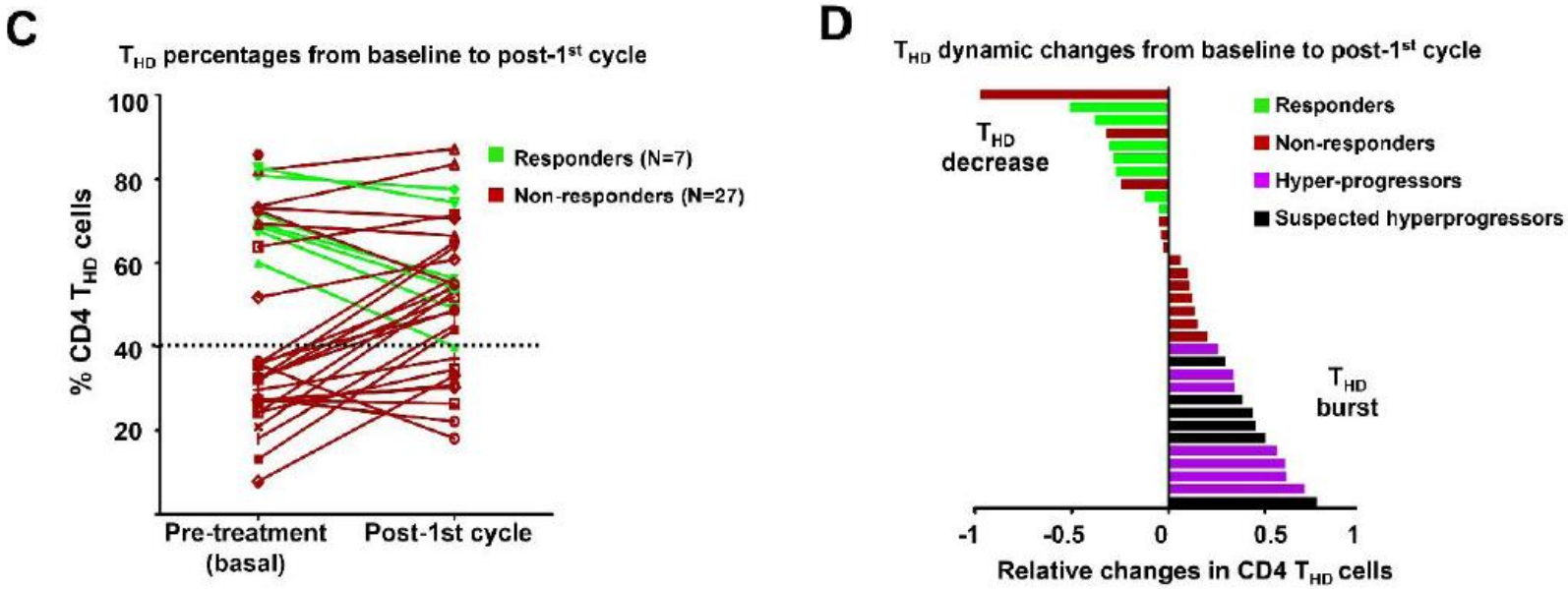


Huang AC et al. Nature. 2017 May 4;545(7652):60-65.



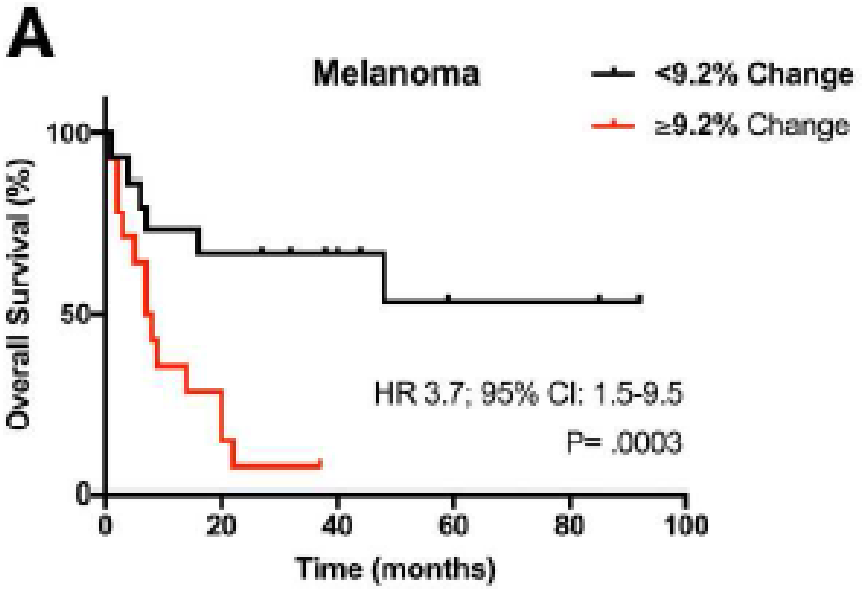
Zuazu-Ibarra M AC et al. bioRxiv. 2018 May 11

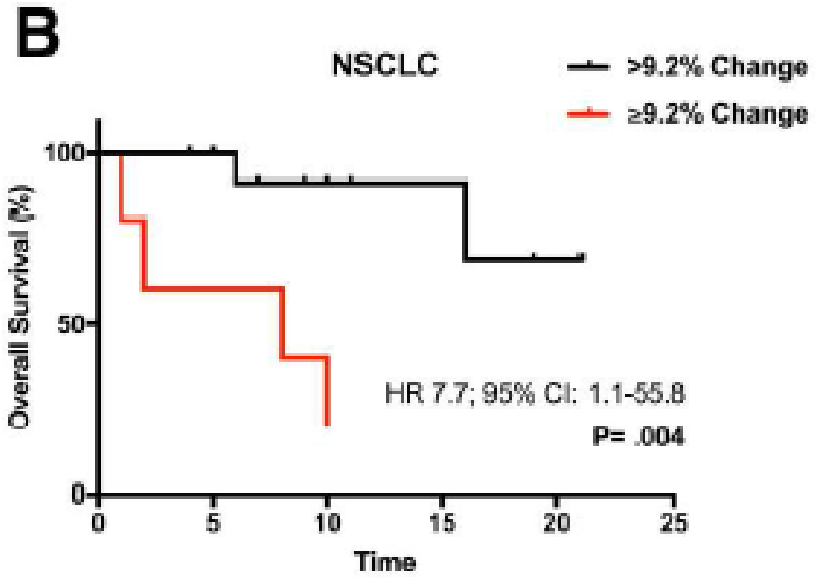
BIOMARCADORES EN SANGRE



Zuazu-Ibarra M AC et al. bioRxiv. 2018 May 11

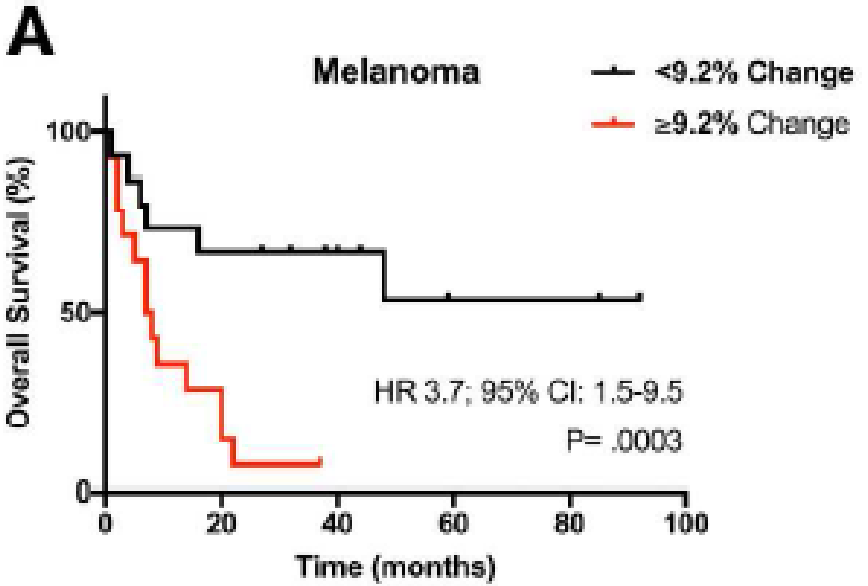
INTERLEUCINA 8

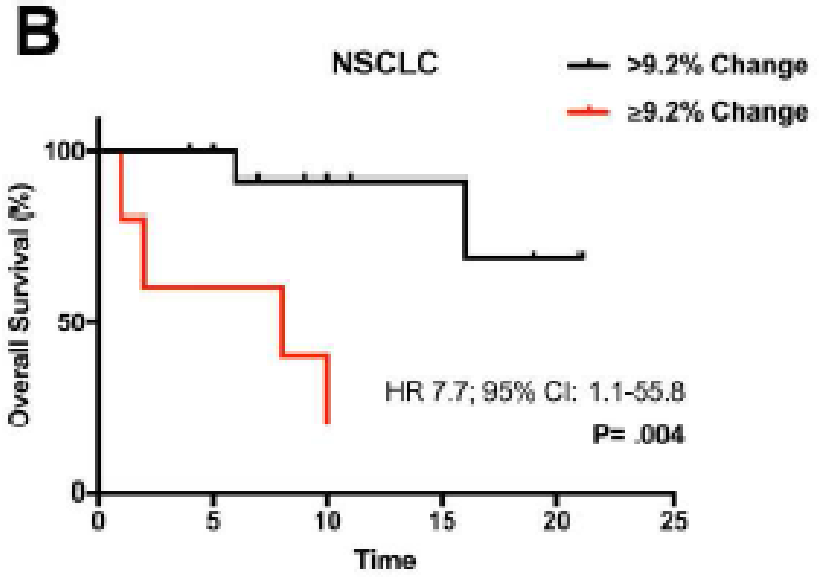




Sanmamed MF et al. Ann Oncol. 2017 Jun 8. doi: 10.1093/annonc/mdx190. .

INTERLEUCINA 8

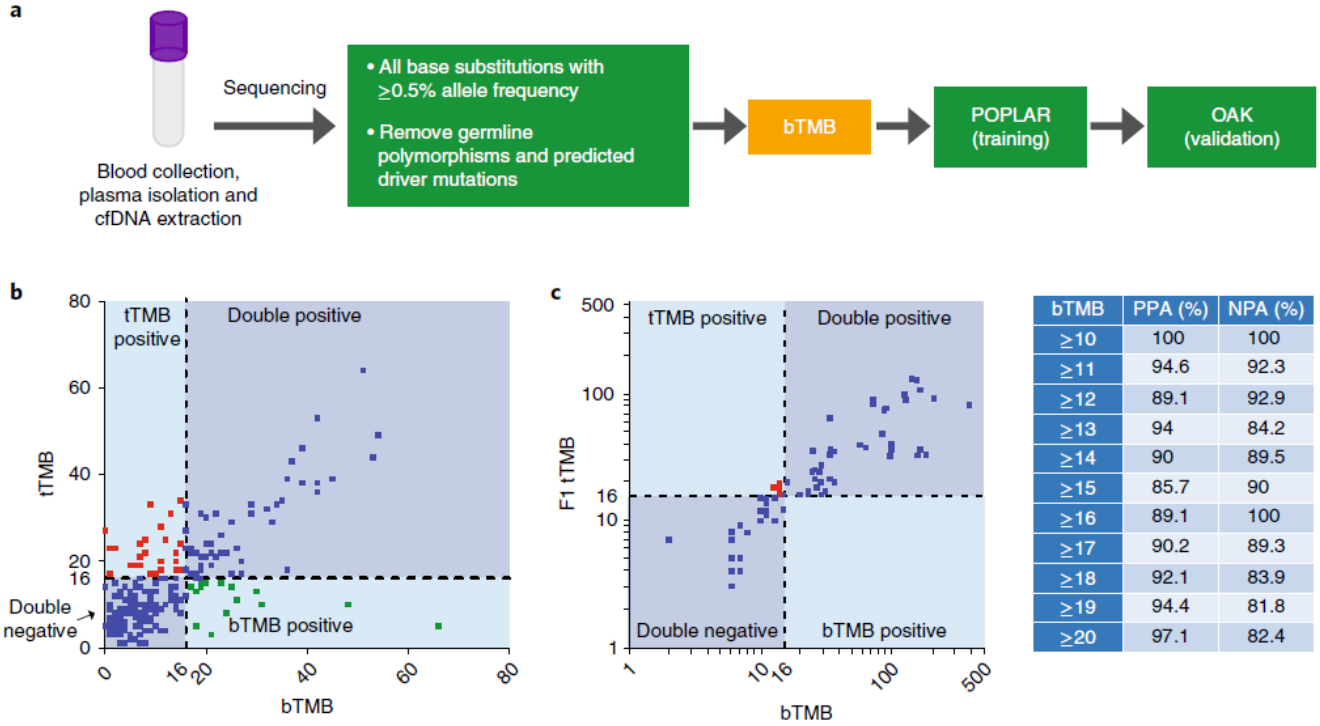




ROC analysis of NIVO-based therapy from pooled study data identified 23 pg/mL as an IL-8 threshold that could be used to enrich for pts who may be more likely to benefit from I-O.

Sanmamed MF et al. Ann Oncol. 2017 Jun 8. doi: 10.1093/annonc/mdx190.
Melero I et al. 2018 ASCO Annual Meeting. Abstract 3025.

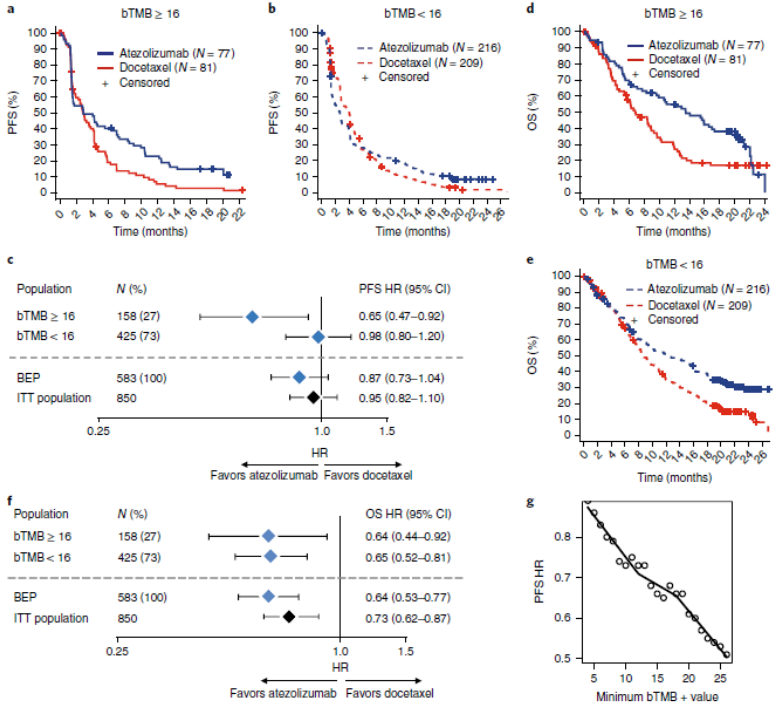
TMB



bTMB	PPA (%)	NPA (%)
≥10	100	100
≥11	94.6	92.3
≥12	89.1	92.9
≥13	94	84.2
≥14	90	89.5
≥15	85.7	90
≥16	89.1	100
≥17	90.2	89.3
≥18	92.1	83.9
≥19	94.4	81.8
≥20	97.1	82.4

Gandara DR et al. Nat Med. 2018 Sep;24(9):1441-1448.

TMB



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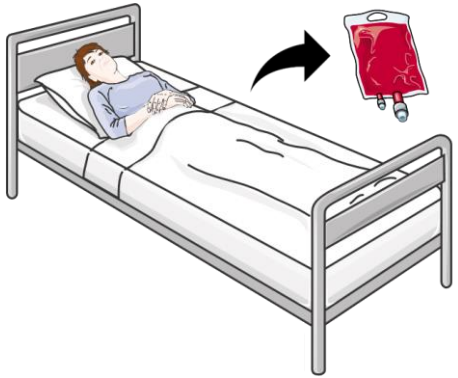
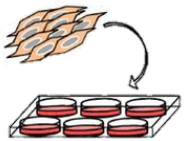


Envío en
24 h

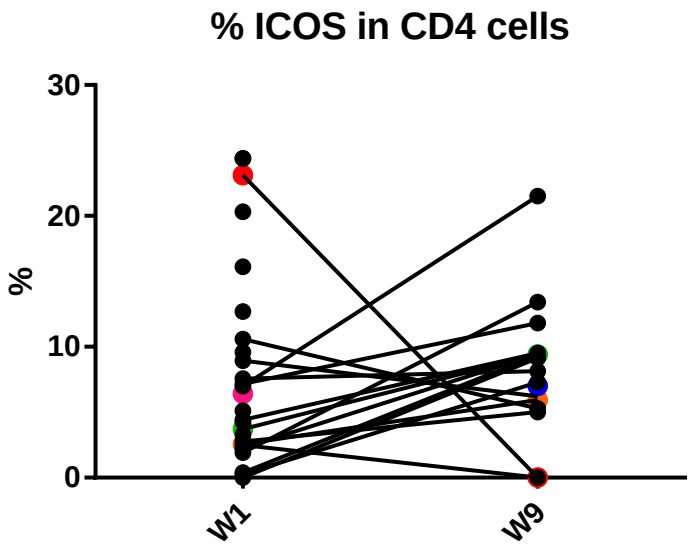
Tinción

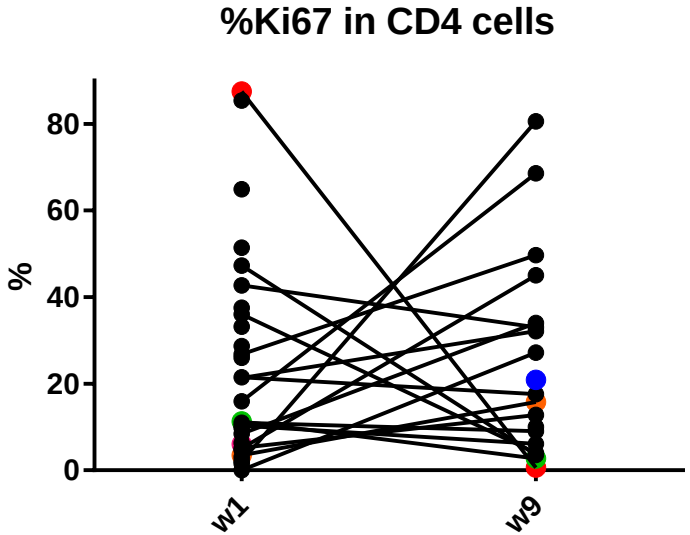


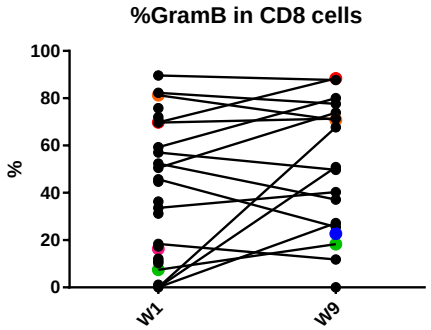
Anti-CD3/CD28
24 horas

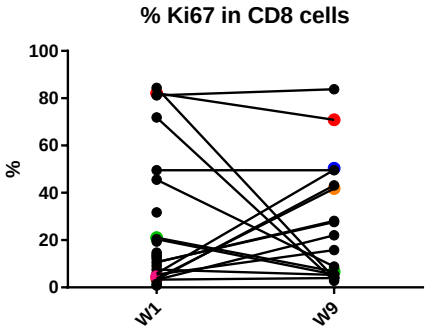
Tinción

CD4	CD25	ICOS	FoxP3		
CD4	PD-1	T-bet	Eomes	Ki67	CTLA-4
CD3	CD8	PD-1	PD-L1	GramB	
CD8	PD-1	T-bet	Eomes	Ki67	CTLA-4
CD3 neg	CD56	CD16	PD-1	PD-L1	GramB
Lin neg	CD11b	HLA-DR	CD15	CD33	Vista


% ICOS in CD4 cells
30
20
10
0
%
W1
W9


%Ki67 in CD4 cells
80
60
40
20
0
%
w1
w9


%GramB in CD8 cells
100
80
60
40
20
0
%
W1
W9


% Ki67 in CD8 cells
100
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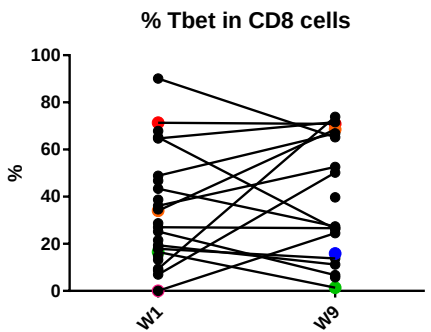
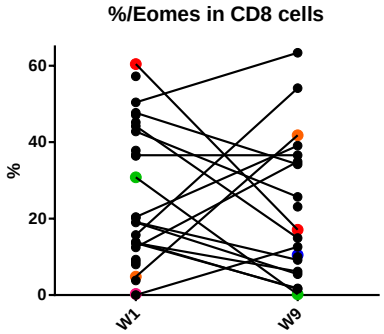
W1
W9


% Tbet in CD8 cells
100
80
60
40
20
0
%
W1
W9


%/Eomes in CD8 cells
60
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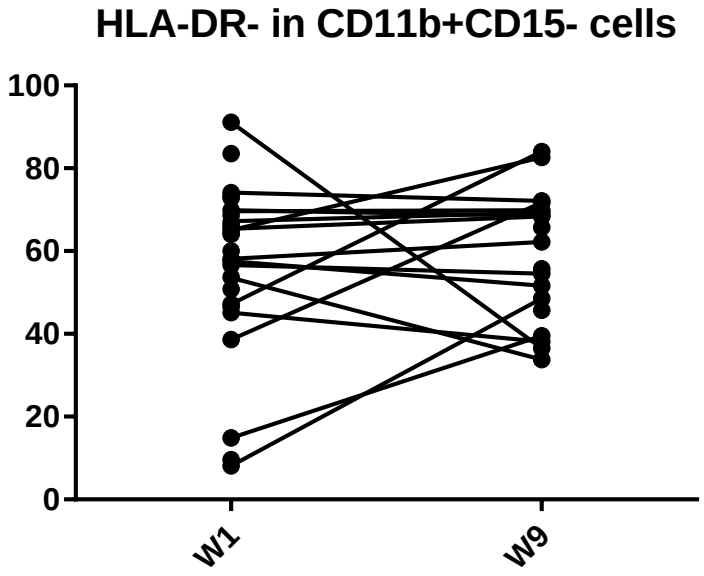
HLA-DR- in CD11b+CD15- cells
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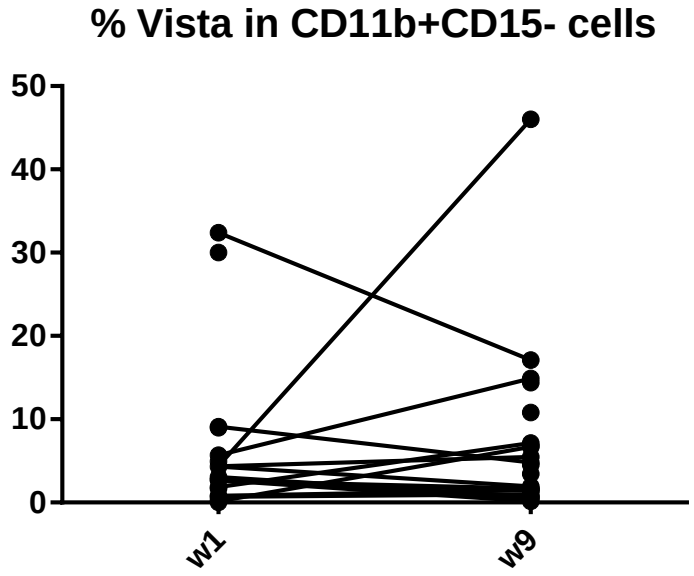
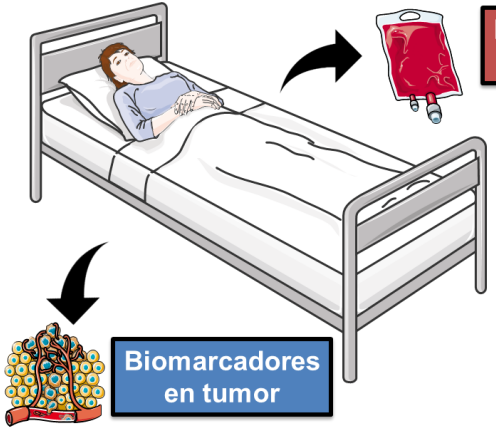
80
60
40
20
0
W1
W9


% Vista in CD11b+CD15- cells
50
40
30
20
10
0
w1
w9

CONCLUSIONES



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