Tercera Reunión Anual del grupo:

GEDEFO

Grupo de Farmacia Oncológica de la SEFH

sefh
Sociedad Española de Farmacia Hospitalaria

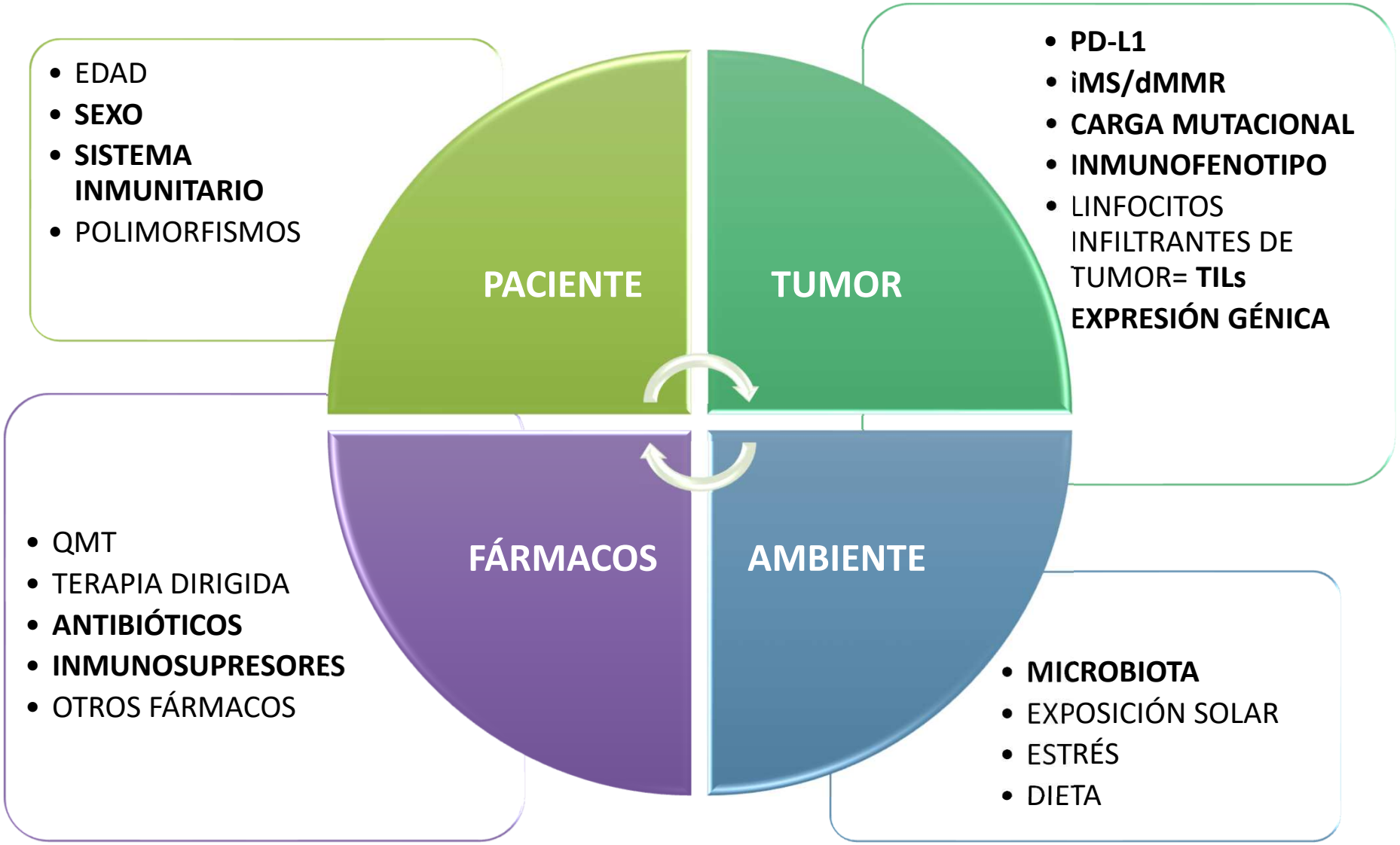
fefh
Fundación Española de Farmacia Hospitalaria

ATENCIÓN FARMACÉUTICA
AL PACIENTE
ONCOHEMATOLÓGICO

Características que condicionan la respuesta: selección de pacientes

Dra. Mª Sacra Díaz Carrasco BCOP
Servicio de Farmacia
HCU Virgen de la Arrixaca
MURCIA

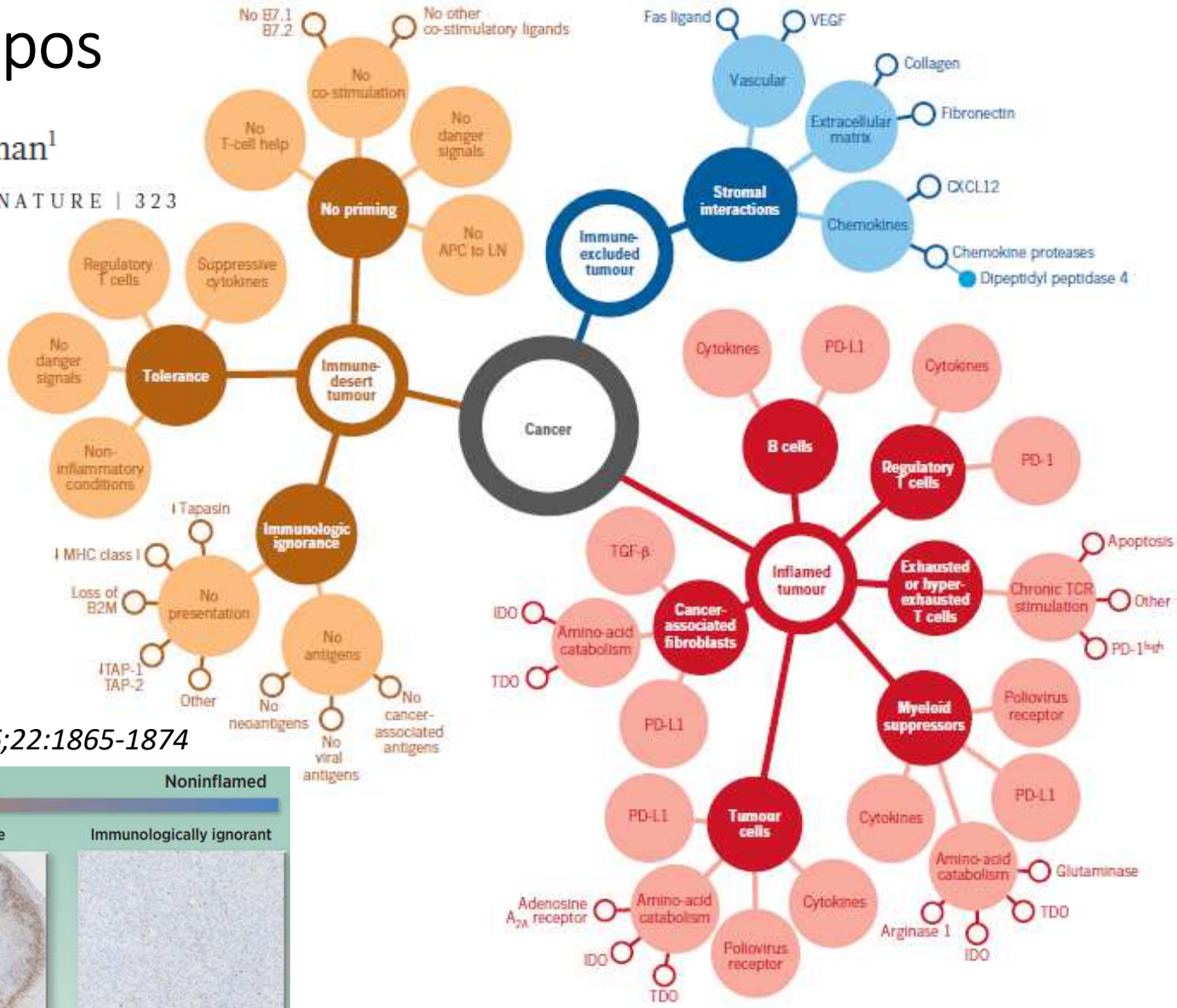
Características que condicionan la respuesta



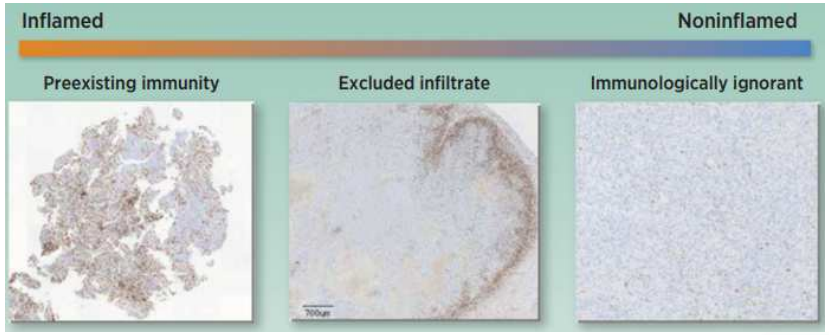
Inmunofenotipos

Daniel S. Chen[1] & Ira Mellman[1]

19 JANUARY 2017 | VOL 541 | NATURE | 323



Hegde et al. Clin Cancer Res 2016;22:1865-1874



TILs

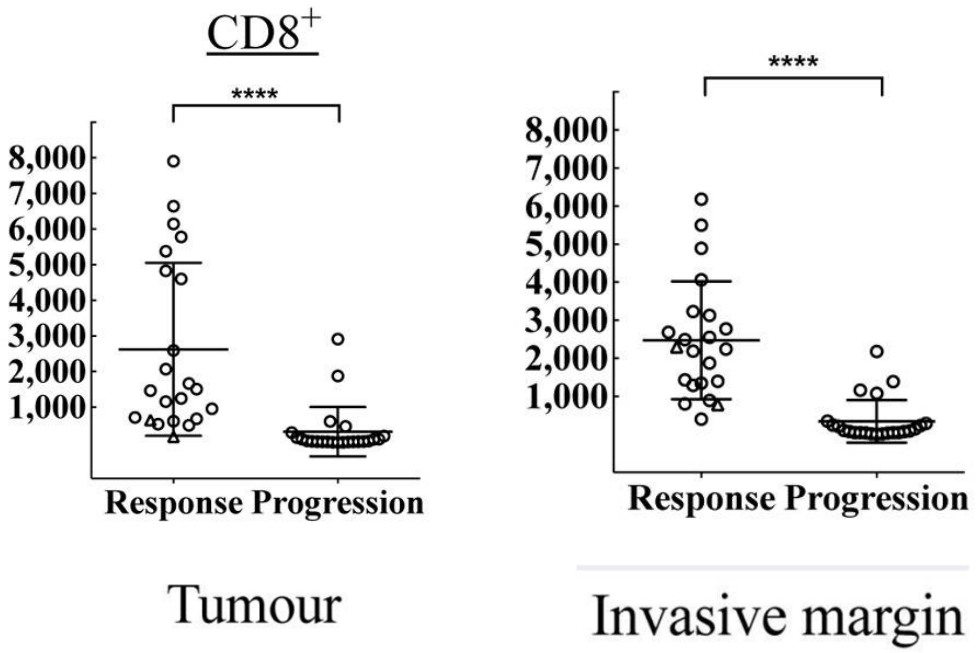
- VALOR PRONÓSTICO
  - Positivo
    - CD8+
    - CD4+
  - Negativo
    - FOXP3+ (Treg)

*Usó et al. Oncotarget. 2016; 7, 52849–61.**
*Geng et al. Cell Physiol Biochem. 2015; 37: 1560–71.**

**CPNM*

- VALOR PREDICTIVO (ICIs)
  - Positivo

Tumeh et al. Nature. 2014; 515(7528): 568–71#



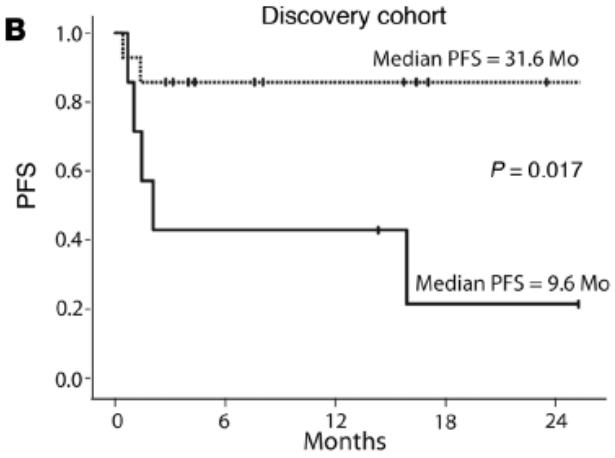
 # Melanoma M+

TILs

Tumor immune profiling predicts response to anti–PD-1 therapy in human melanoma

Daud et al. J Clin Invest. 2016;126(9):3447-3452.

Relative abundance of partially exhausted tumor-infiltrating CD8+ T cells (CTLA-4^{hi}PD-1^{hi}) predicts response to anti–PD-1 therapy.



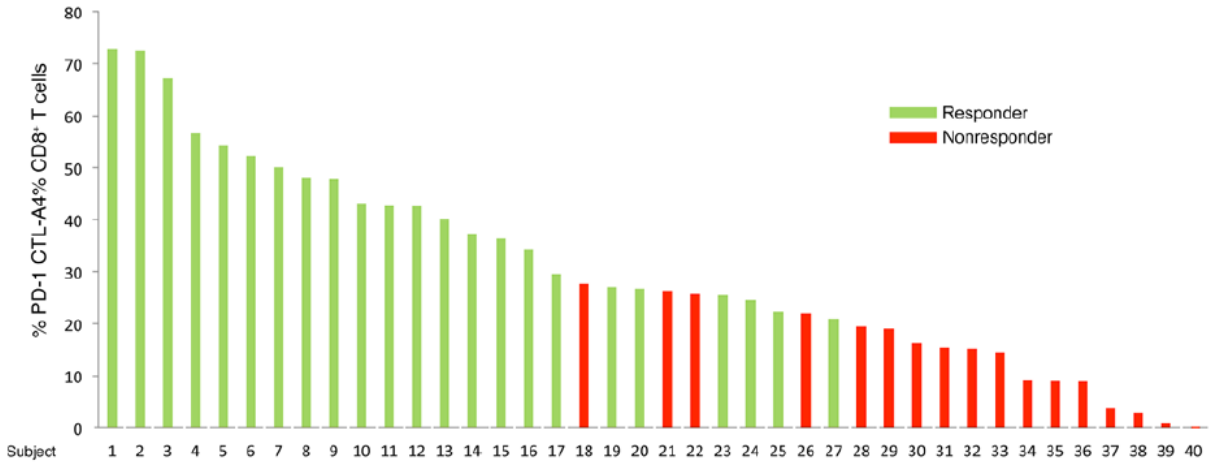
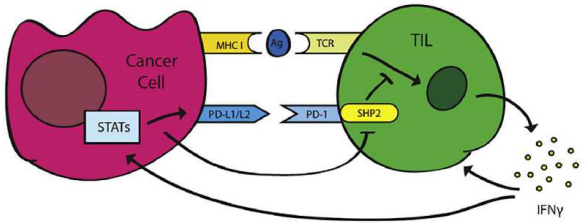


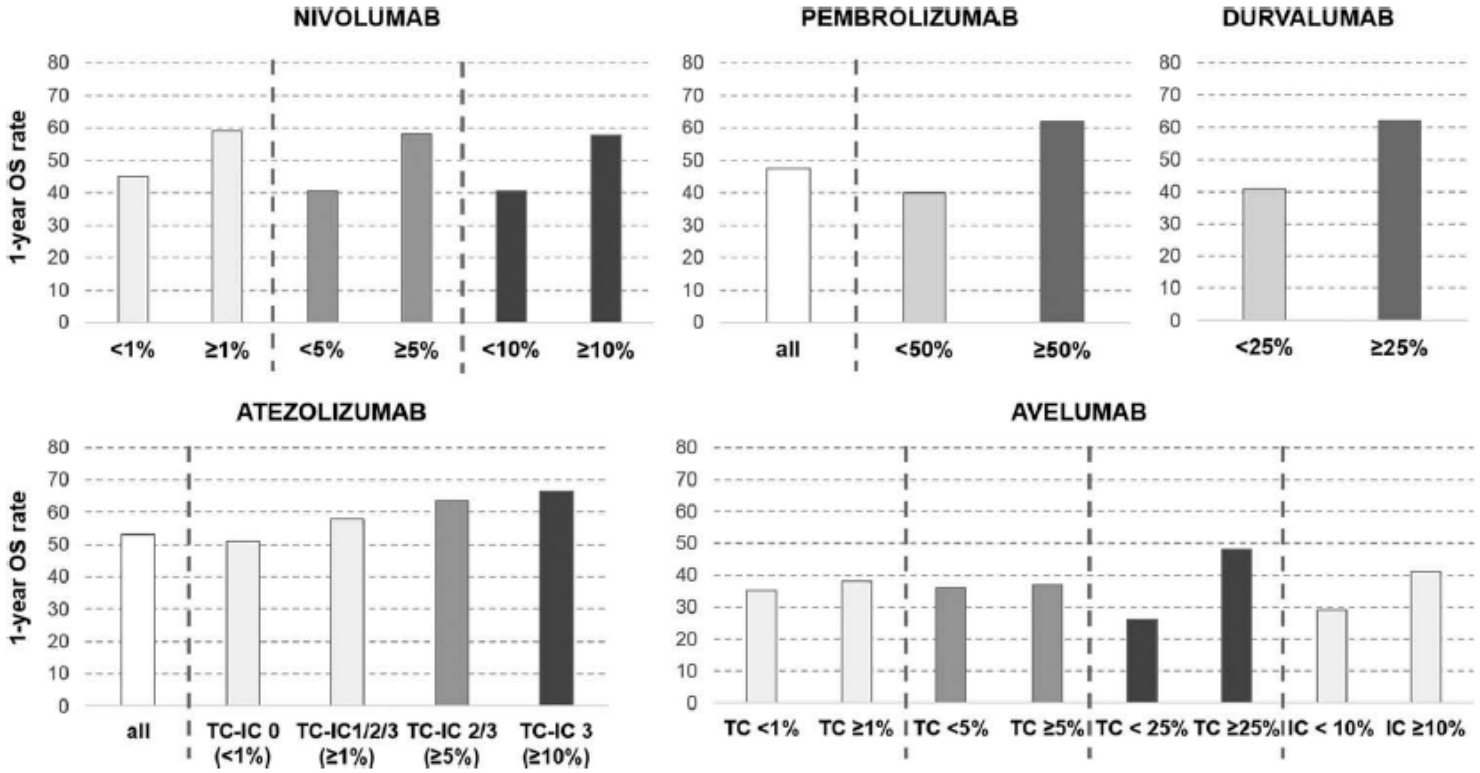
Figure 2. CTL profiles of patients with metastatic melanoma who responded or did not respond to anti–PD-1 therapy.

Figure 1. Relative abundance of CTLA-4hiPD-1hi CTLs predicts response to anti–PD-1 therapy. (B) Discovery cohort (n = 20 patients) and (C) validation cohort (n = 20 patients) of PFS for patients who had 20% or more (dotted line) or 20% or fewer (solid line) tumor-infiltrating CTLA-4hiPD-1hi CTLs.

Expresión de PDL1

G. Grizzi et al. Expert Review of Molecular Diagnostics, 2017





Correlation between PD-L1 expression and overall survival benefit in patients with **NSCLC** treated with the currently investigated PD-1/PD-L1 inhibitors

Table. Comparison of PD-L1 Assays

Characteristic	Assay			
	Pembrolizumab (Keytruda, MK-3475)	Nivolumab (Opdivo, BMS-936558)	Durvalumab (MEDI-4736)	Atezolizumab (MPDL3280A, RG7446)
Manufacturer	Merck Sharp & Dohme	Bristol-Myers Squibb	MedImmune/AstraZeneca	Genentech/Roche
mAb	Humanized IgG4	Human IgG4	Human Fc-modified IgG1	Human Fc-modified IgG1
Target	PD-1	PD-1	PD-L1	PD-L1
FDA approved	Melanoma	Melanoma, NSCLC	NA	Bladder, NSCLC[a]
coDx assay PD-L1 positive				
IHC assay developer	Dako	Dako	Ventana	Ventana
Antibody clone	22C3 mouse	28-8 rabbit	SP263 rabbit	SP142
Expression location	TCs and stroma	TCs	TCs	TICs and TCs
Cut-off	Melanoma, bladder, NSCLC: ≥1% TC (or any tumor stroma cell)	NSCLC: ≥1% to 5% TC Renal: ≥5% TC	NSCLC, SCCHN: ≥25% TC	Bladder, NSCLC, breast: IHC2+ ≥5% to <10% TC or TIC or IHC3+ ≥10% TC or TIC

- *Hansen A.R. and Siu L.L. PD-L1 Testing in Cancer. Challenges in Companion Diagnostic Development. JAMA Oncol . 2016; 2:15-6*

Expresión de PDL1

J Clin Oncol 35. © 2017 by American Society of Clinical Oncology

Programmed Death-Ligand 1 Immunohistochemistry Testing: A Review of Analytical Assays and Clinical Implementation in Non–Small-Cell Lung Cancer

Reinhard Büttner, John R. Gosney, Birgit Guldhammer Skov, Julien Adam, Noriko Motoi, Kenneth J. Bloom, Manfred Dietel, John W. Longshore, Fernando López-Ríos, Frédérique Penault-Llorca, Giuseppe Viale, Andrew C. Wotherspoon, Keith M. Kerr, and Ming-Sound Tsao

TEST IHC PD-L1

28-8 pharmDx	22C3 pharmDx	SP263 Assay	SP142 Assay

suggests possible interchangeability of their clinical use for NSCLC

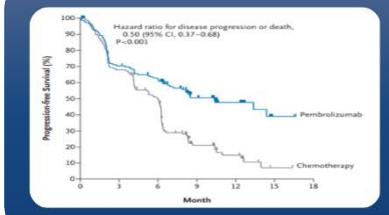
↑ CONCORDANCIA INTERENSAYO
EPRODUCIBILIDAD INTEROBSERVADOR

(EXPRESIÓN EN MEMBRANA CÉLULAS TUMORALES)

↓EXPRESIÓN PDL1

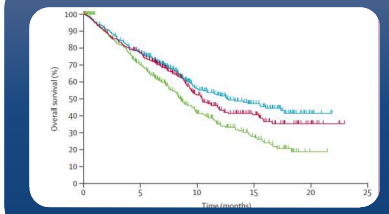
↓ CONCORDANCIA Y REPRODUCIBILIDAD EN CÉLULAS INMUNES

Expresión de PDL1



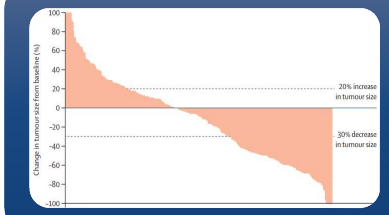
KEYNOTE 024

- PEMBROLIZUMAB CPNM 1ª LÍNEA
- EXPRESIÓN PDL1 ≥ 50%



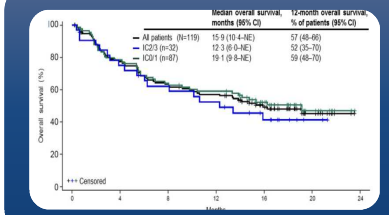
KEYNOTE 010

- PEMBROLIZUMAB CPNM 2ª LÍNEA
- EXPRESIÓN PDL1 ≥ 1%



KEYNOTE 052

- PEMBROLIZUMAB Ca. UROTELIAL NO CANDIDATO A PLATINO
- *EXPRESIÓN PDL1 ≥ 10% (Keynote-361)*



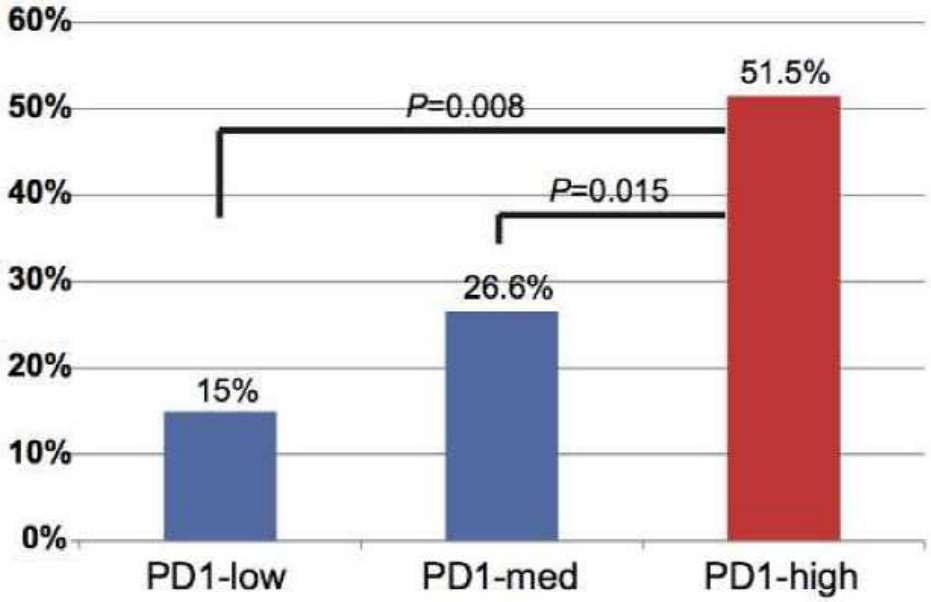
IMVIGOR 210

- ATEZOLIZUMAB Ca. UROTELIAL NO CANDIDATO A PLATINO
- *EXPRESIÓN PDL1 ≥ 5% (IMvigor130)*

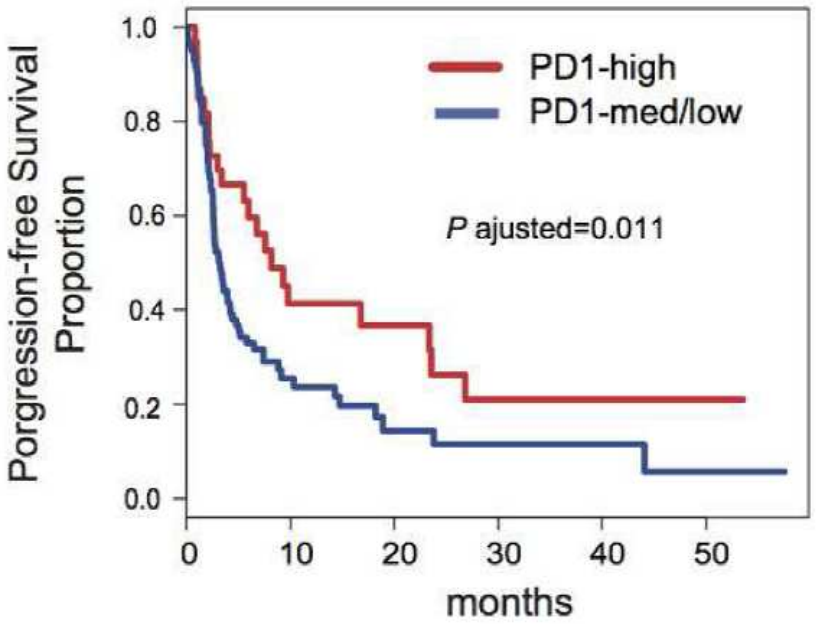
Expresión de PD1

Association between PD1 mRNA and response to anti-PD1 monotherapy across multiple cancer-types

Paré L, et al. Annals of Oncology. Aug 2018.



Overall response rates (ORR) based on PD1 mRNA expression

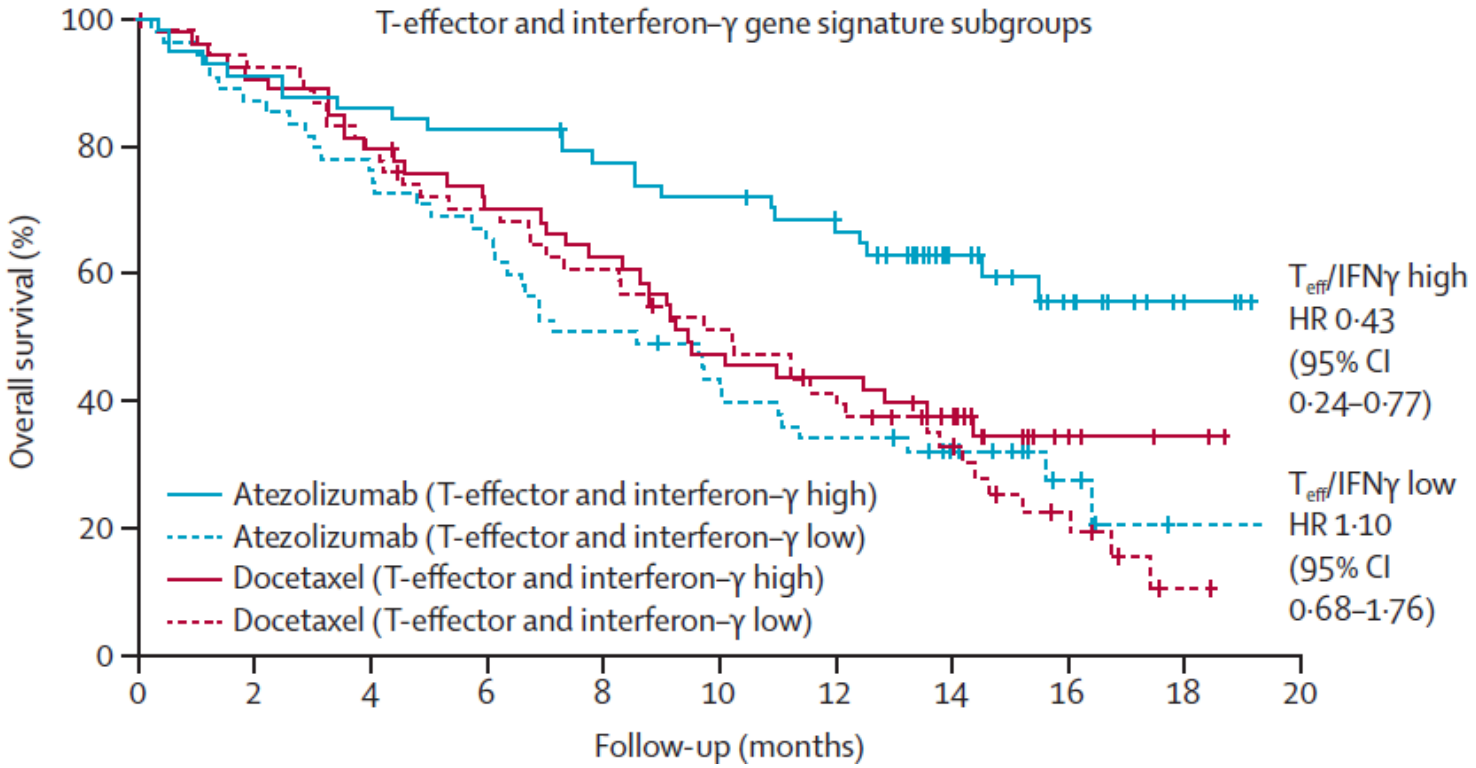


Progression-free survival (PFS) based on PD1 mRNA expression

Firmas génicas INFγ

Fehrenbacher et al. ***Lancet 2016; 387: 1837–46***

Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial



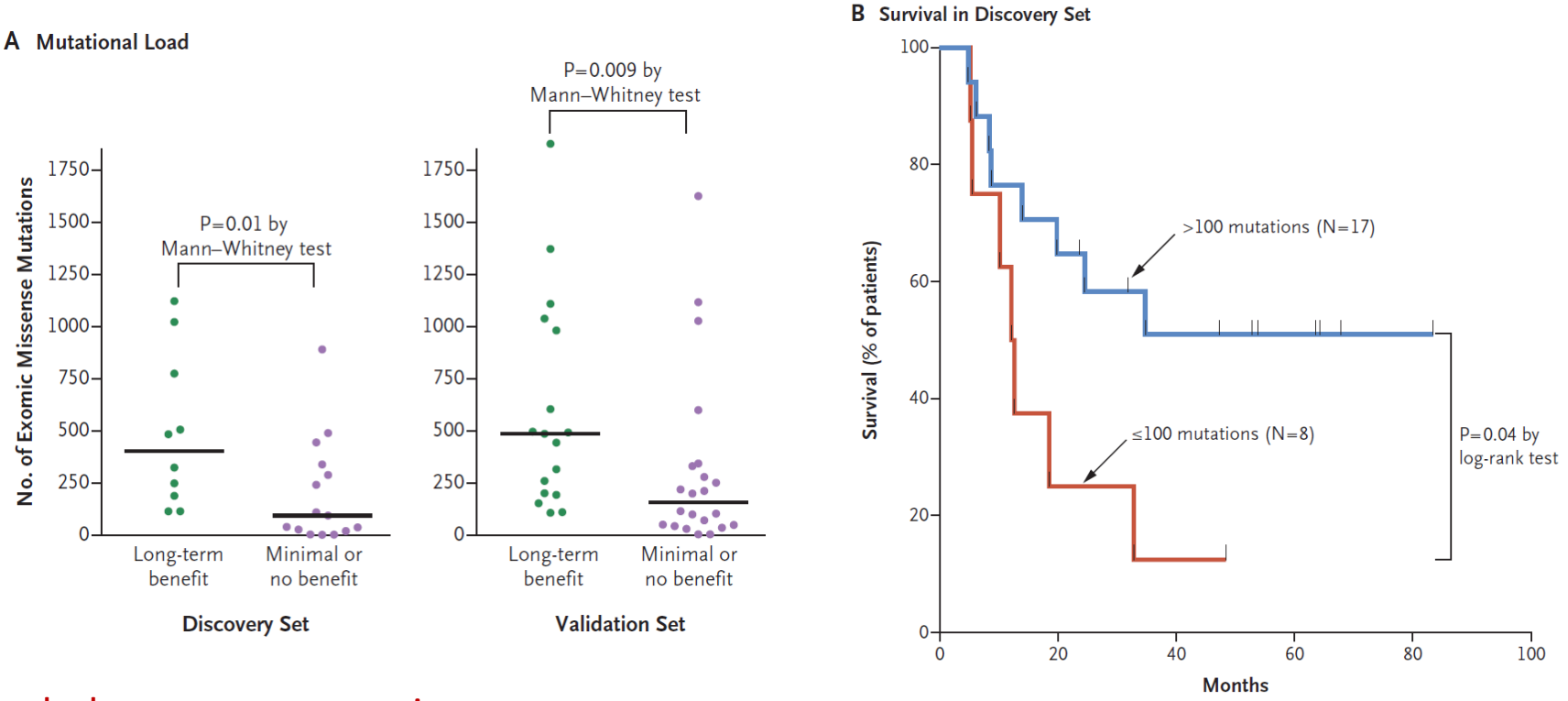
Carga mutacional

ORIGINAL ARTICLE

N ENGL J MED 371;23 NEJM.ORG DECEMBER 4, 2014

Genetic Basis for Clinical Response to CTLA-4 Blockade in Melanoma

Alexandra Snyder et al.



whole-exome sequencing

- ***Figure 2. Mutational Landscape of Tumors According to Clinical Benefit from Ipilimumab Treatment.*** *Panel A shows the mutational load (number of nonsynonymous mutations per exome) in the discovery and validation sets, according to status with respect to a clinical benefit from therapy. Panel B depicts the Kaplan–Meier curves for overall survival in the discovery set for patients with more than 100 nonsynonymous coding mutations per exome and patients with 100 or fewer mutations.*

Carga mutacional

CheckMate 026 Carbone et al.

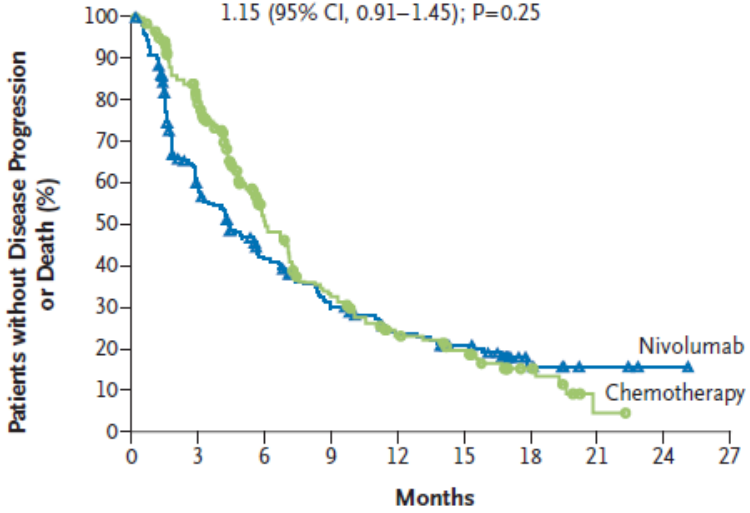
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 22, 2017 VOL. 376 NO. 25

A Progression-free Survival

	Median Progression-free Survival (95% CI)	1-Yr Progression-free Survival Rate
	mo	%
Nivolumab (N=211)	4.2 (3.0–5.6)	24
Chemotherapy (N=212)	5.9 (5.4–6.9)	23

Hazard ratio for disease progression or death, 1.15 (95% CI, 0.91–1.45); P=0.25

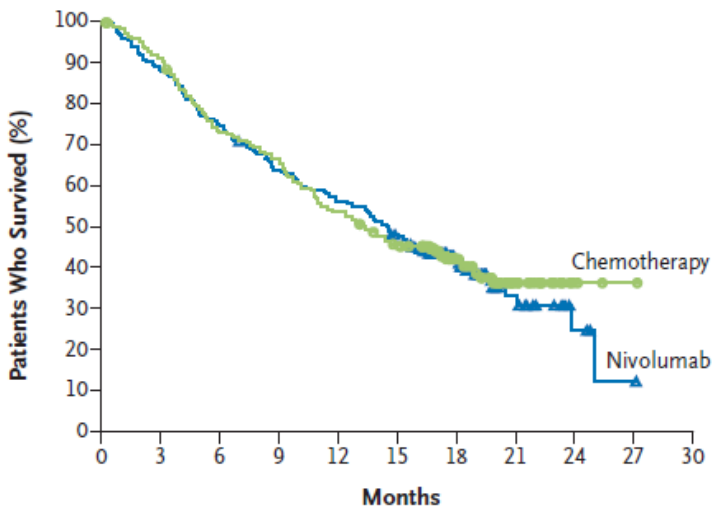


No. at Risk										
Nivolumab	211	104	71	49	35	24	6	3	1	0
Chemotherapy	212	144	74	47	28	21	8	1	0	0

B Overall Survival

	Median Overall Survival (95% CI)	1-Yr Overall Survival Rate
	mo	%
Nivolumab (N=211)	14.4 (11.7–17.4)	56
Chemotherapy (N=212)	13.2 (10.7–17.1)	54

Hazard ratio for death, 1.02 (95% CI, 0.80–1.30)



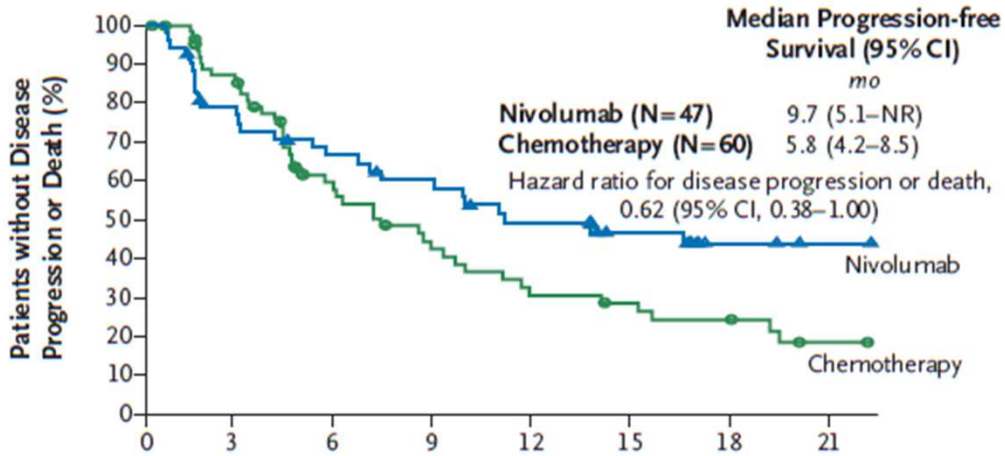
No. at Risk											
Nivolumab	211	186	156	133	118	98	49	14	4	0	0
Chemotherapy	212	186	153	137	112	91	50	15	3	1	0

Figure 1. Progression-free Survival and Overall Survival among Patients with a Programmed Death Ligand 1 Expression Level of 5% or More.

Carga mutacional

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 JUNE 22, 2017 VOL. 376 NO. 25

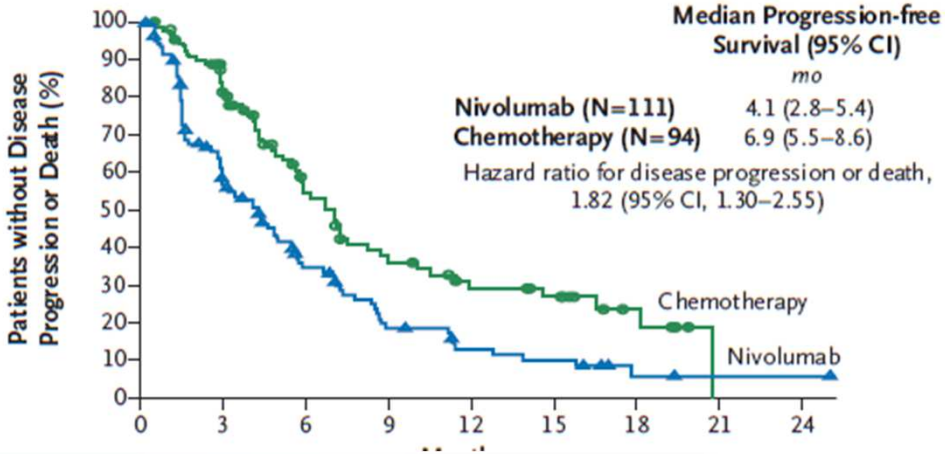
C Progression-free Survival among Patients with High Tumor-Mutation Burden



CheckMate 026 Carbone et al.

- TMB: whole-exome sequencing
- Hight TMB: ≥ 243 mut.

D Progression-free Survival among Patients with Low or Medium Tumor-Mutation Burden



- Panel **C** shows the analysis of progression-free survival among patients who could be evaluated for **tumor-mutation burden** and who had a **high** burden.
- Panel **D** shows the analysis of progression-free survival among patients who could be evaluated **for tumor-mutation burden** and who had a **low or medium** burden.

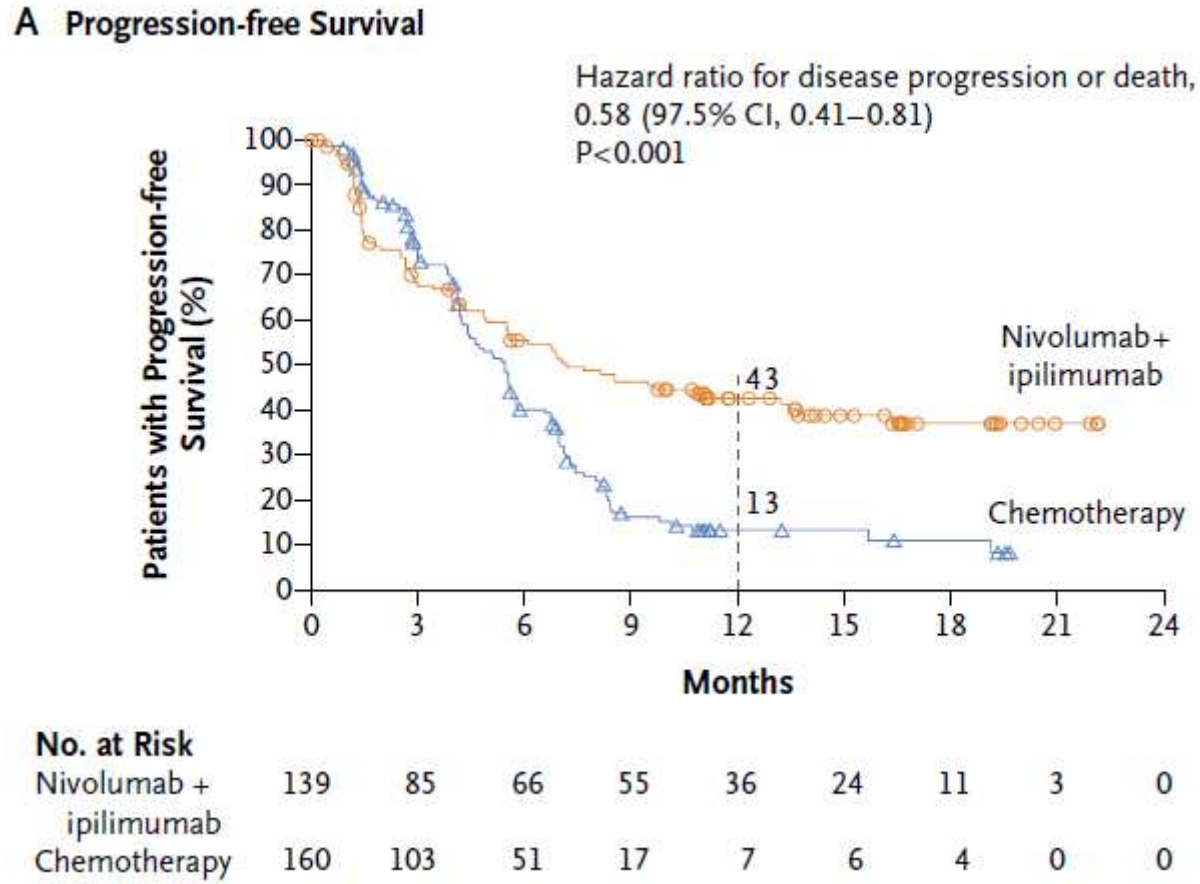
Carga mutacional

CheckMate 227 M.D. Hellmann et al.

ORIGINAL ARTICLE

N ENGL J MED 378;22 NEJM.ORG MAY 31, 2018

Nivolumab plus Ipilimumab in Lung Cancer with a High Tumor Mutational Burden



- TMB was determined by the FoundationOne CDx assay.
- High tumor mutational burden ≥10 mutations per megabase

Carga mutacional

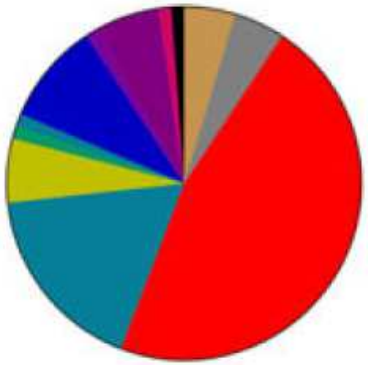
Nadal E., Hernandez Llosa. Updtes Biomarkers in immuno-oncology, 2017

Ensayo Clínico	Fármaco	Tipo Tumoral	Tecnología	Punto de corte
	Ipilimumab/ Tremelimutumab	Melanoma	WES	100 mut/tumor
FIR	Atezolizumab	1L Carcinoma no escamoso de pulmón	NGS 315 genes	9.9 mut/Mb
BIRCH	Atezolizumab	2L Carcinoma no escamoso de pulmón	NGS 315 genes	16.2 mut/Mb
POPLAR	Atezolizumab	2L Carcinoma no escamoso de pulmón	NGS 315 genes	16.2 mut/Mb
KEYNOTE 001	Pembrolizumab	1L Carcinoma no escamoso de pulmón	WES	200ns/tumor
Imvigor 210	Atezolizumab	1L Cáncer vejiga	NGS 315 genes	0.9-62.2 mut/Mb
Imvigor 211	Atezolizumab	2L Cáncer vejiga	NGS 315 genes	mut/Mb
KEYNOTE 012	Pembrolizumab	Tumor Solido Avanzado	WES	102 ns/tumor
POPLAR	Atezolizumab	2L/3L Carcinoma célula pequeña de pulmón	NGS 315 genes	16.2 mut/Mb*
OAK	Atezolizumab	2L Carcinoma no escamoso de pulmón	NGS 315 genes	16.2 mut/Mb*
CHECKMATE 026	Nivolumab	1L Carcinoma no escamoso de pulmón	WES	>243 mut
CHECKMATE 032	Ipilimumab/ Nivolumab	2L/3L Carcinoma célula pequeña de pulmón	WES	>248 mut

*Realización de TMB en sangre

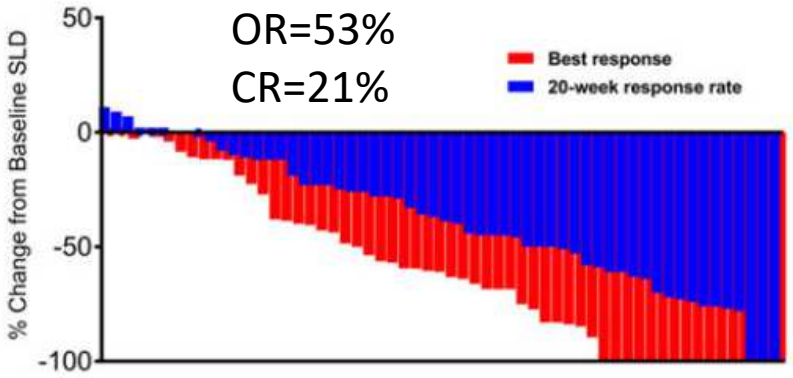
Mismatch Repair Deficiency (MMRD)

Mismatch-repair deficiency predicts response of solid tumors to PD-1 blockade Le et al. *Science*. 2017 July 28; 357(6349): 409–413.

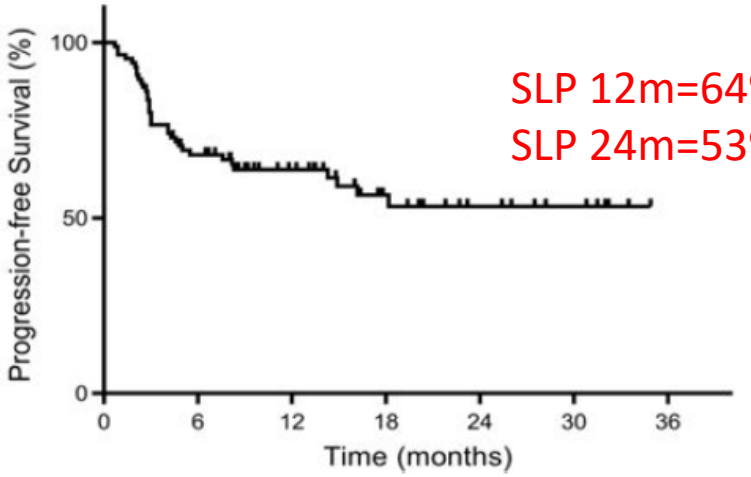


N=86

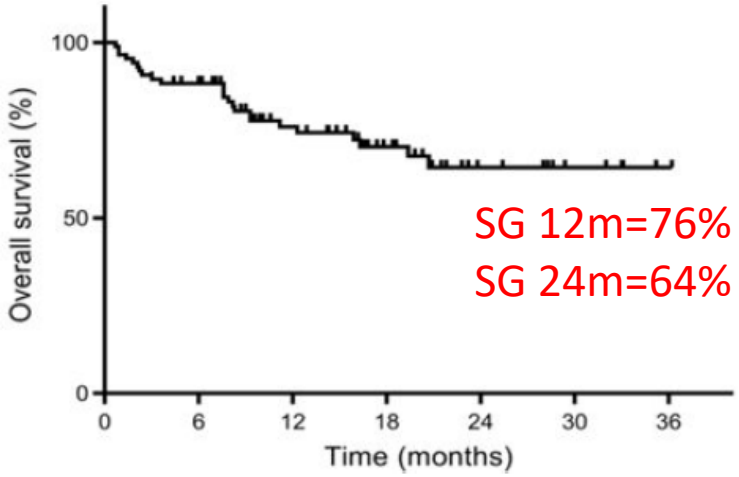
Ampulla of Vater
Cholangiocarcinoma
Colorectal
Endometrial cancer
Gastroesophageal
Neuroendocrine
Osteosarcoma
Pancreas
Prostate
Small Intestine
Thyroid
Unknown Primary



OR=53%
CR=21%



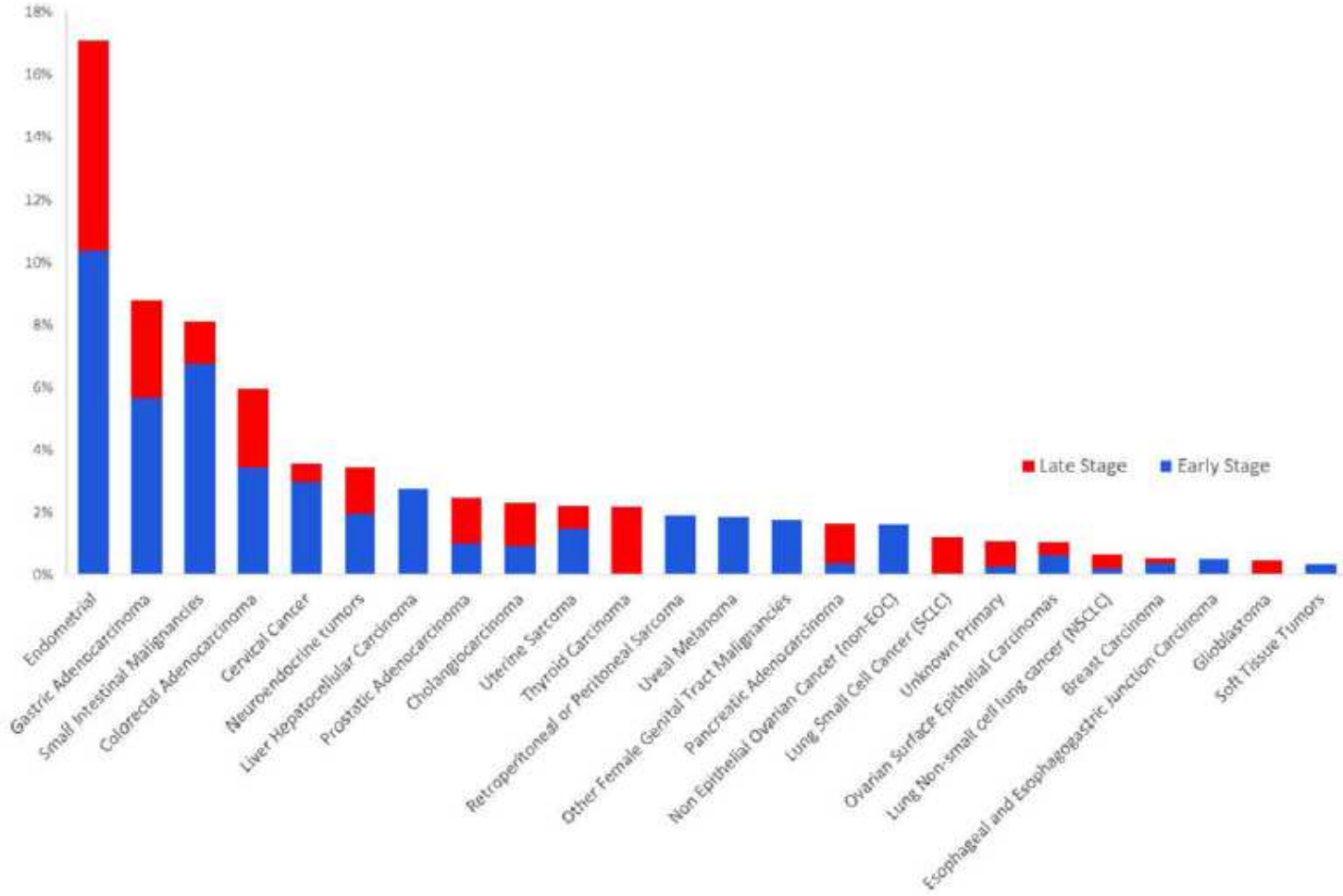
SLP 12m=64%
SLP 24m=53%



SG 12m=76%
SG 24m=64%

Mismatch Repair Deficiency (MMRD)

Mismatch-repair deficiency predicts response of solid tumors to PD-1 blockade Le et al. *Science*. 2017 July 28; 357(6349): 409–413.



The NEW ENGLAND JOURNAL of MEDICINE

First FDA Approval Agnostic of Cancer Site — When a Biomarker Defines the Indication

Perspective
OCTOBER 12, 2017

Steven Lemery, M.D., M.H.S., Patricia Keegan, M.D., and Richard Pazdur, M.D.

PEMBROLIZUMAB

Microsatellite Instability-High Cancer

- for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient
  - solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options,[1] or
  - colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.[1] (1.7)

Microbioma

Sivan et al. *Science*. 2015 November 27; 350(6264): 1084–1089.

Commensal *Bifidobacterium* promotes antitumor immunity and facilitates anti–PD-L1 efficacy

RATONES C57BL/6

TAC

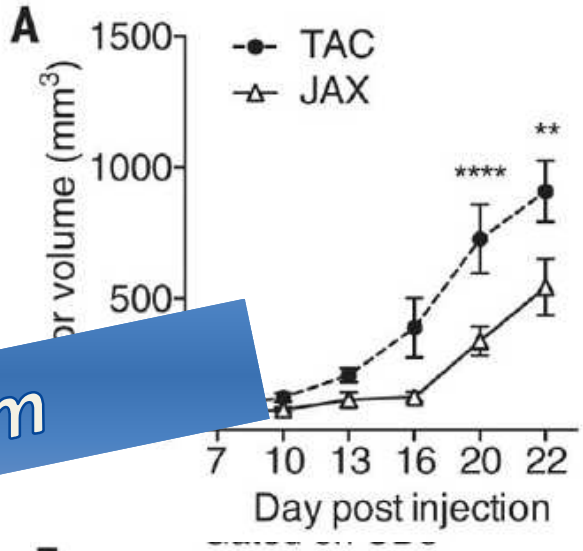
JAX

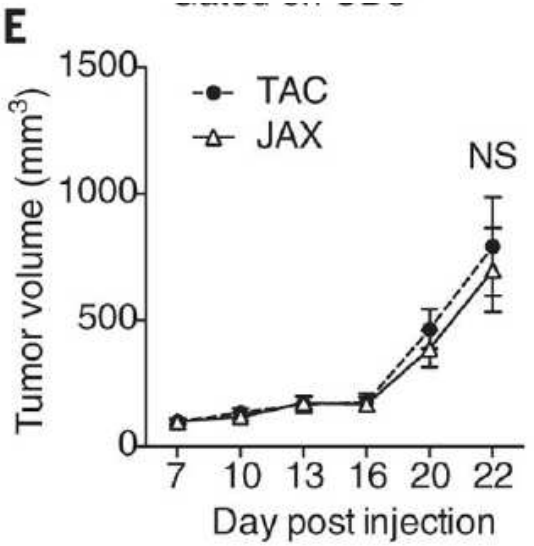
JAX

TAC

VIA S.C.

Bifidobacterium





Microbioma

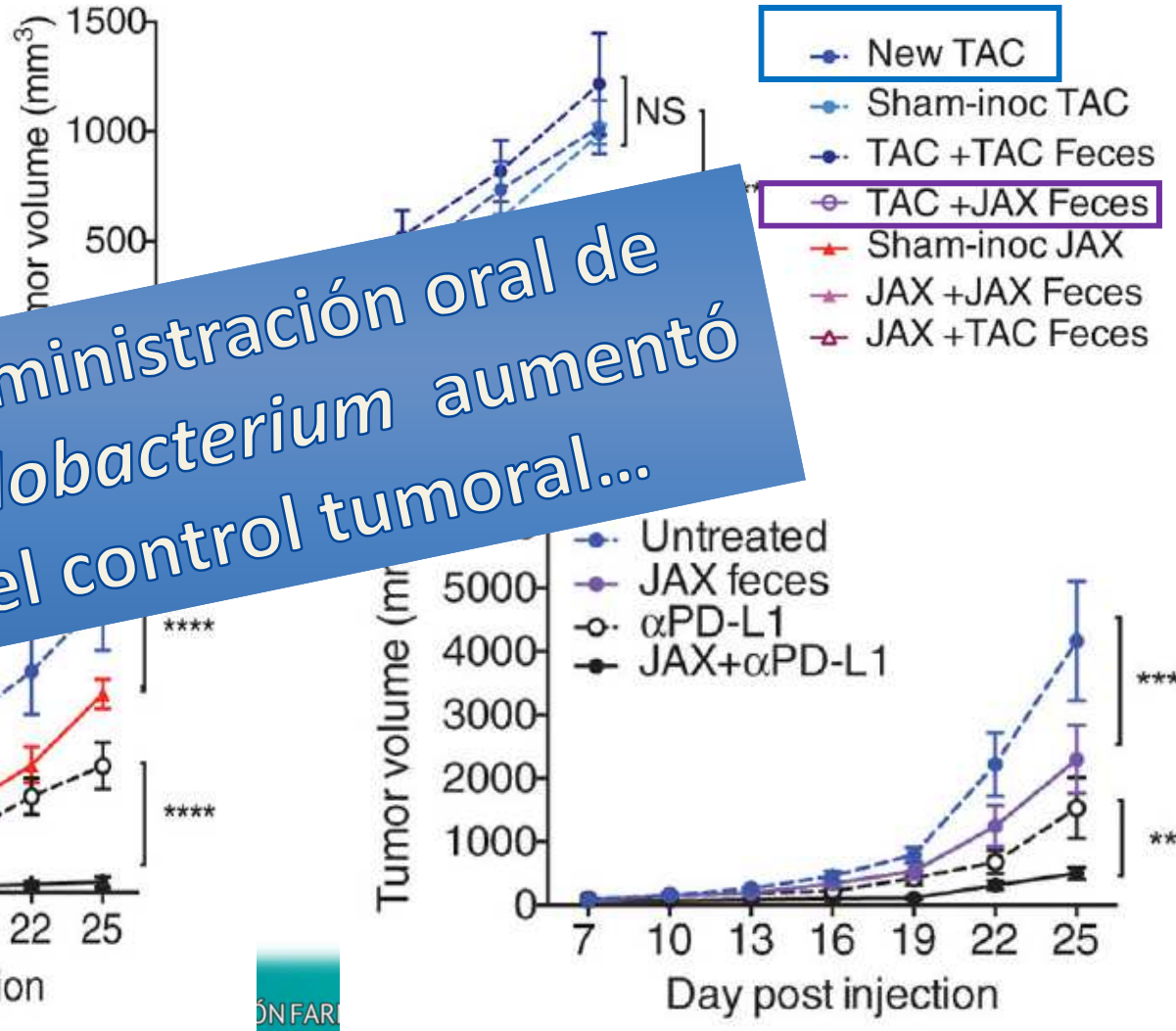
RATONES C57BL/6

TAC

JAX

Sivan et al. *Science*. 2015 November 27; 350(6264): 1084–1089.

Commensal *Bifidobacterium* promotes antitumor immunity and facilitates anti–PD-L1 efficacy



Administración oral de *Bifidobacterium* aumentó el control tumoral…

The commensal microbiome is associated with anti–PD-1 efficacy in metastatic melanoma patients

Matson *et al.*, *Science* **359**, 104–108 (2018)

Gut microbiome modulates response to anti–PD-1 immunotherapy in melanoma patients

Gopalakrishnan et al. *Science*. 2018 January 05; 359(6371): 97–103.

Gut microbiome influences efficacy of PD-1–based immunotherapy against epithelial tumors

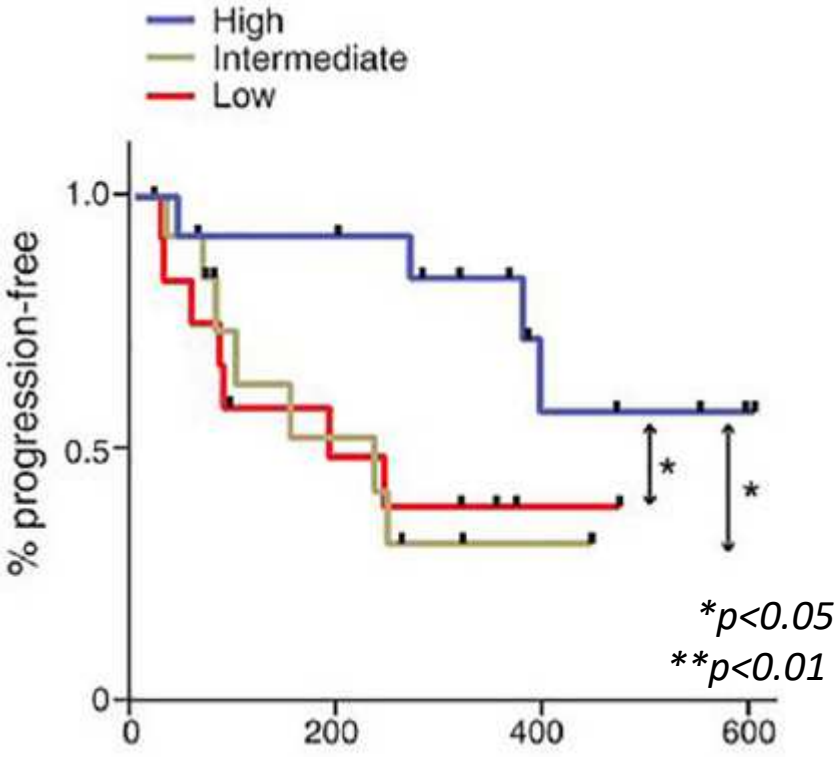
Routy *et al.*, *Science* **359**, 91–97 (2018)

Estudios que identifican asociación entre microbioma y eficacia de anti PD1/PDL1 en diferentes tumores sólidos

Microbioma

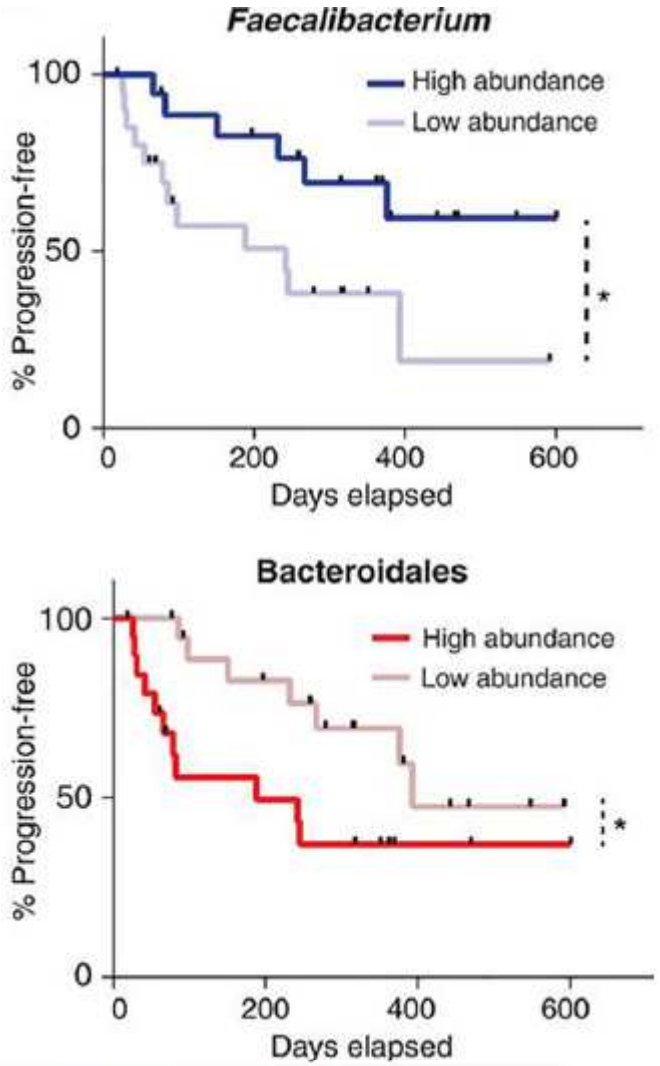
Gut microbiome modulates response to anti–PD-1 immunotherapy in melanoma patients

Gopalakrishnan et al. *Science*. 2018 January 05; 359(6371): 97–103.



**p<0.05*
***p<0.01*

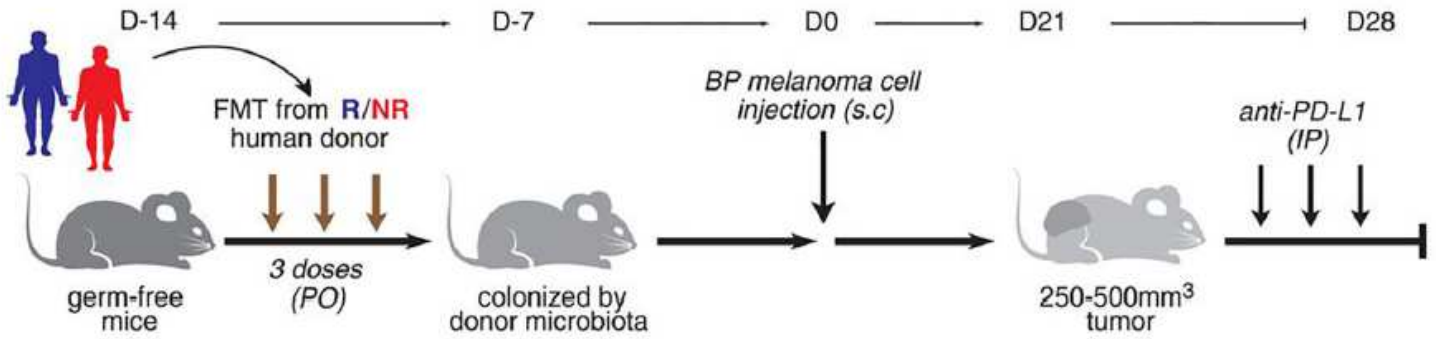
*Kaplan-Meier (KM) plot of progression-free survival (PFS) by **fecal diversity**; high (median PFS undefined), intermediate (median PFS=232 days), and low (median PFS=188 days)..*

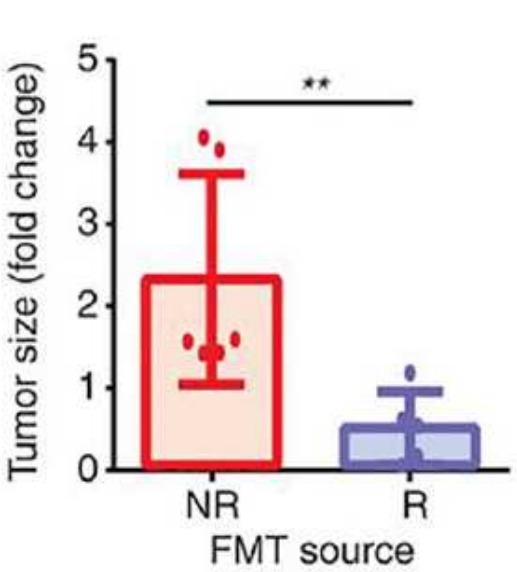


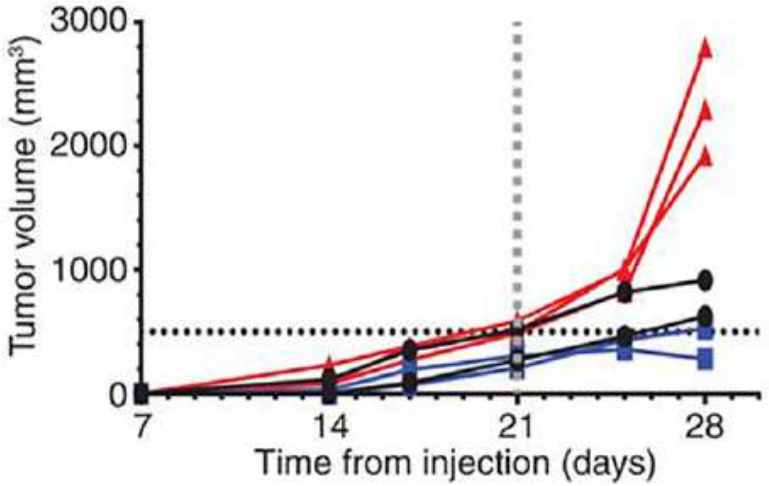
Microbioma

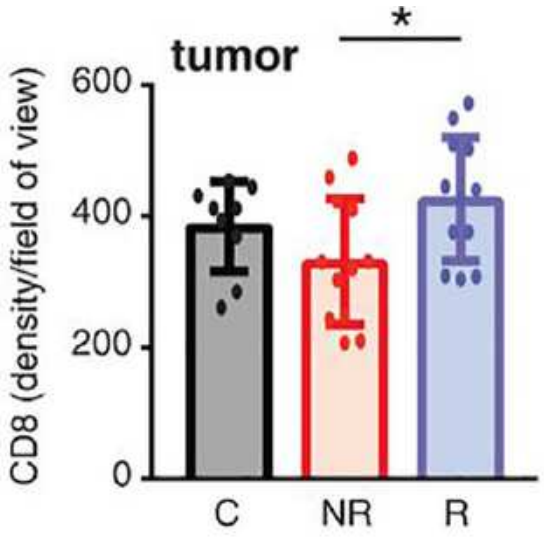
Gut microbiome modulates response to anti–PD-1 immunotherapy in melanoma patients

Gopalakrishnan et al. *Science*. 2018 January 05; 359(6371): 97–103.





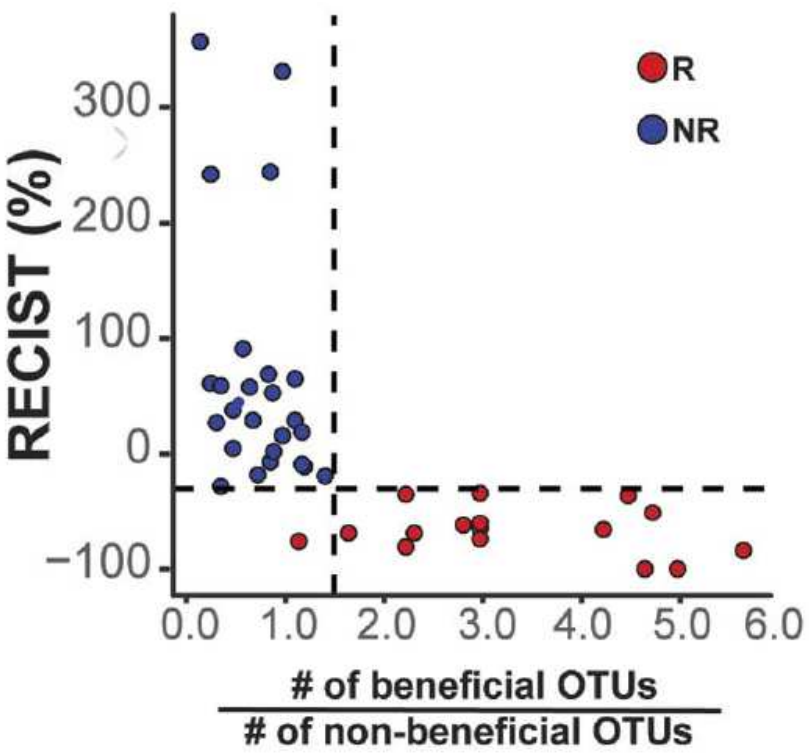




Microbioma

The commensal microbiome is associated with anti–PD-1 efficacy in metastatic melanoma patients

Matson *et al.*, *Science* **359**, 104–108 (2018)



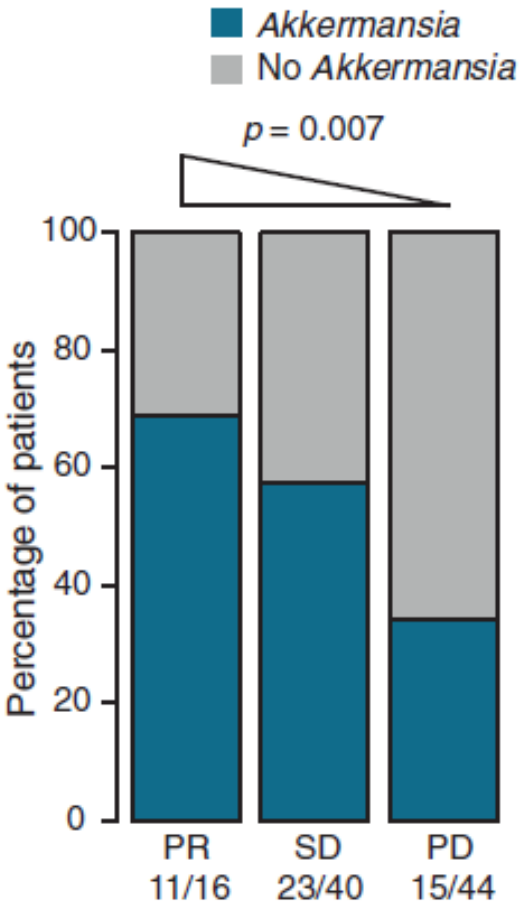
OTUs= Operational Taxonomic Units

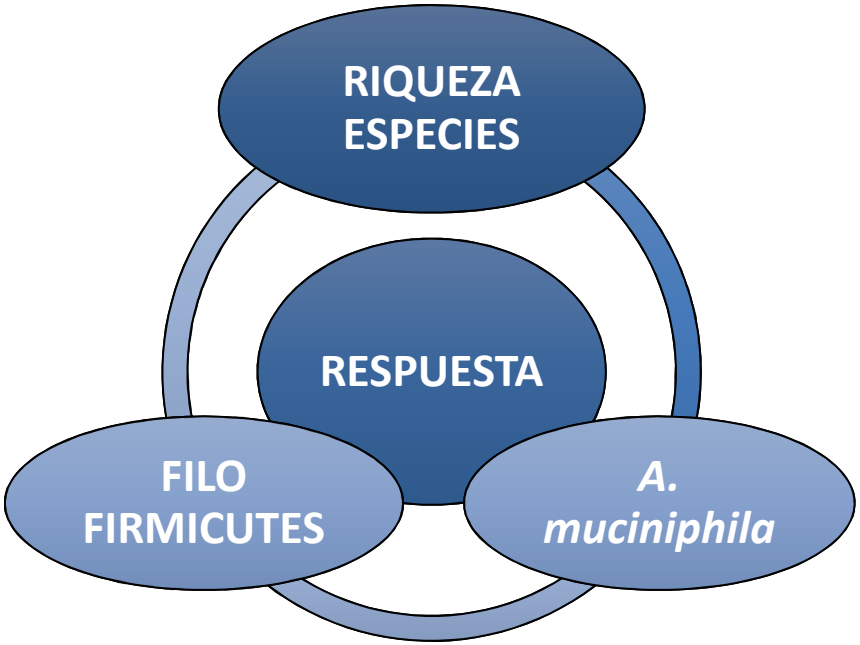
- Pacientes **R** mayor abundancia relativa de:
  - *Enterococcus faecium*
  - *Collinsella aerofaciens*
  - *Bifidobacterium adolescentis*
  - *Klebsiella pneumoniae*
  - *Veillonella parvula*
  - *Parabacteroides merdae*
  - *Lactobacillus sp.*
  - *Bifidobacterium longum*.
- Pacientes **NR** muestras enriquecidas en dos especies:
  - *Ruminococcus obeum*
  - *Roseburia intestinalis*

Microbioma

Gut microbiome influences efficacy of PD-1–based immunotherapy against epithelial tumors

Routy *et al.*, *Science* **359**, 91–97 (2018)



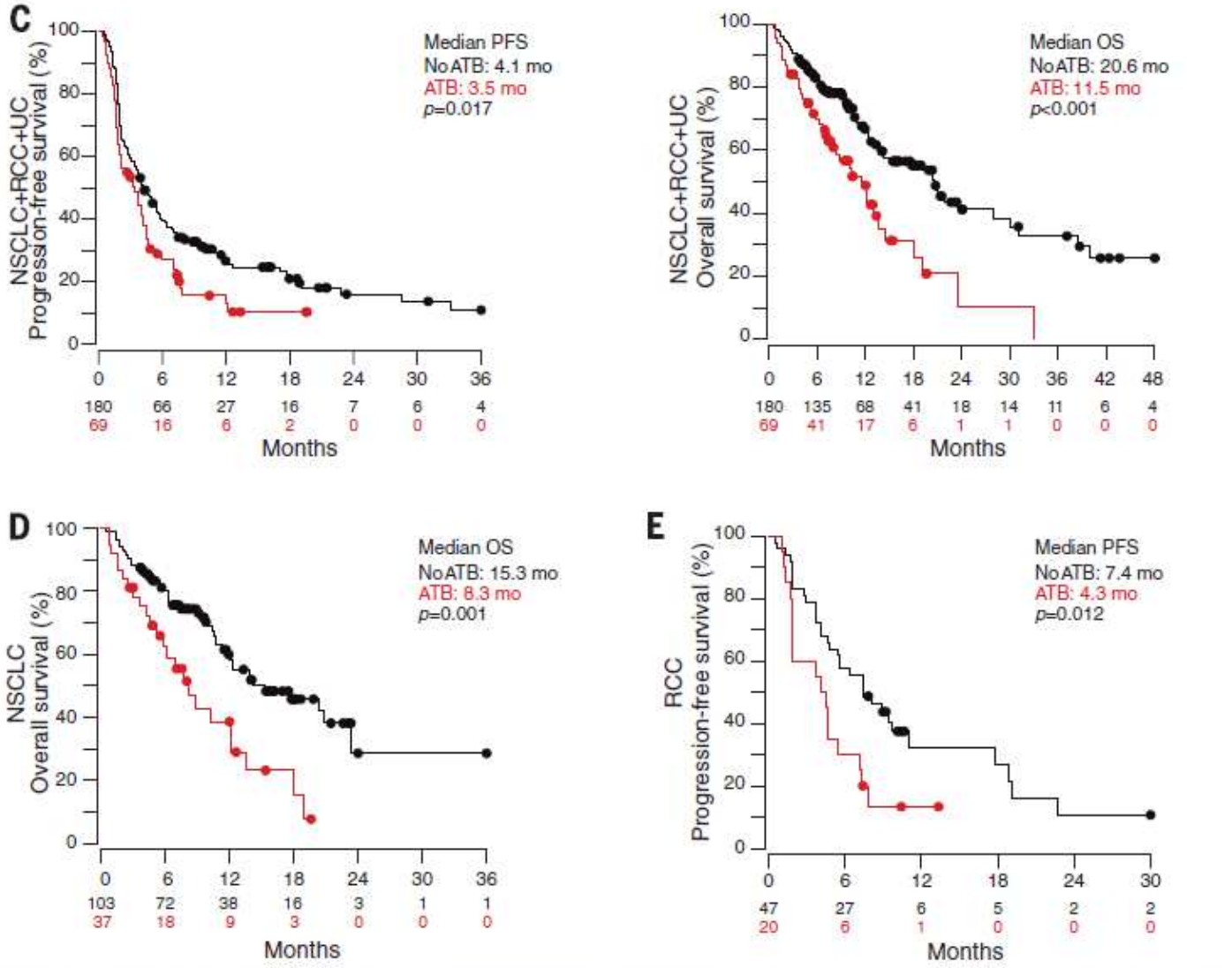


*Frequency of patients with detectable **A. muciniphila** in their feces according to PR (partial response), SD (stable disease), or PD (progressive disease) clinical status, as assessed by metagenomics.*

Microbioma

Routy *et al.*, *Science* **359**, 91–97 (2018)

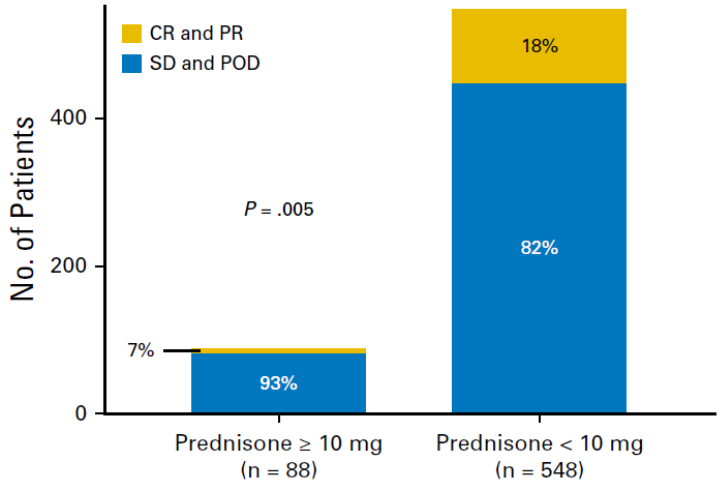
Gut microbiome influences efficacy of PD-1–based immunotherapy against epithelial tumors

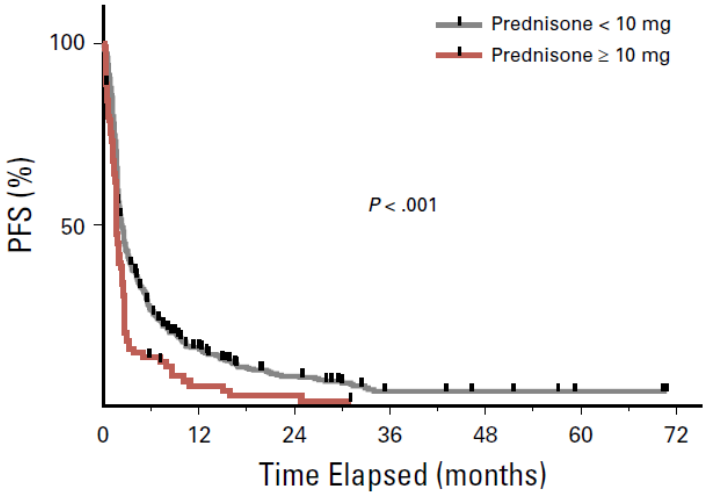


Uso de corticoides

Arbour et al. JCO 2018

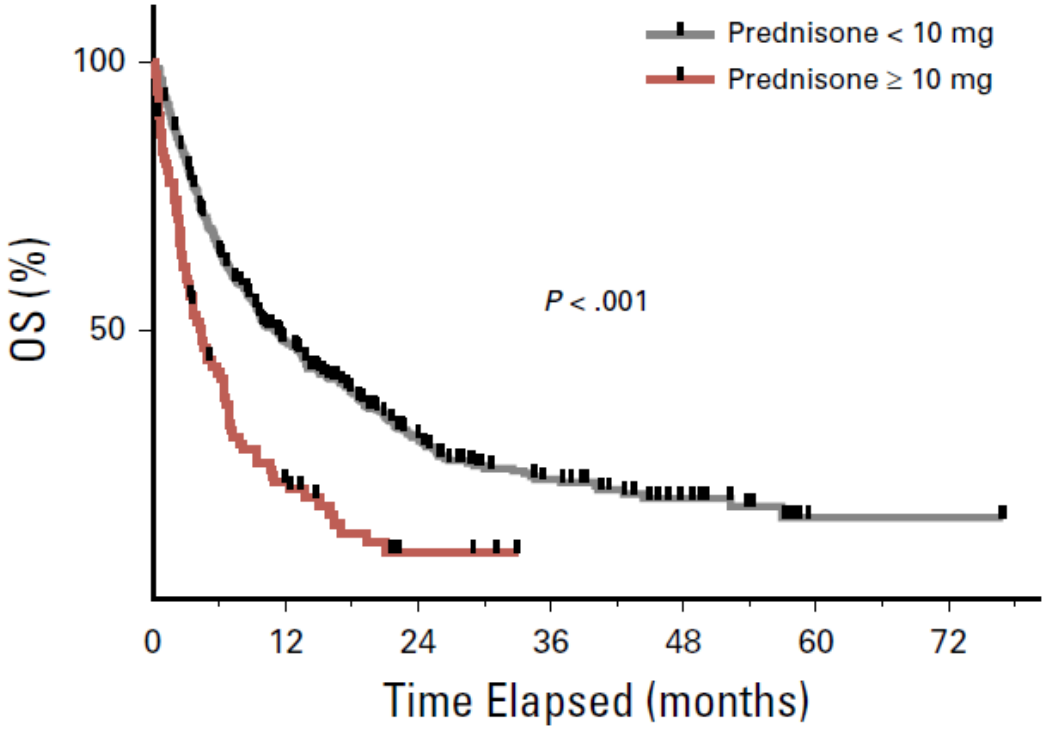
Impact of Baseline Steroids on Efficacy of Programmed Cell Death-1 and Programmed Death-Ligand 1 Blockade in Patients With Non–Small-Cell Lung Cancer





No. at risk:

< 10 mg:	550	69	24	7	5	2	0
≥ 10 mg:	90	4	2	0	0	0	0



No. at risk:

< 10 mg:	550	229	90	40	17	2	2
≥ 10 mg:	90	18	3	0	0	0	0

Grupo de Farmacia Oncológica de la SEFH

fefh

ATENCIÓN FARMACÉUTICA
AL PACIENTE ONCOHEMATOLÓGICO

Influencia del sexo

Cancer immunotherapy efficacy and patients' sex: a systematic review and meta-analysis

Conforti et al. Lancet Oncol 2018

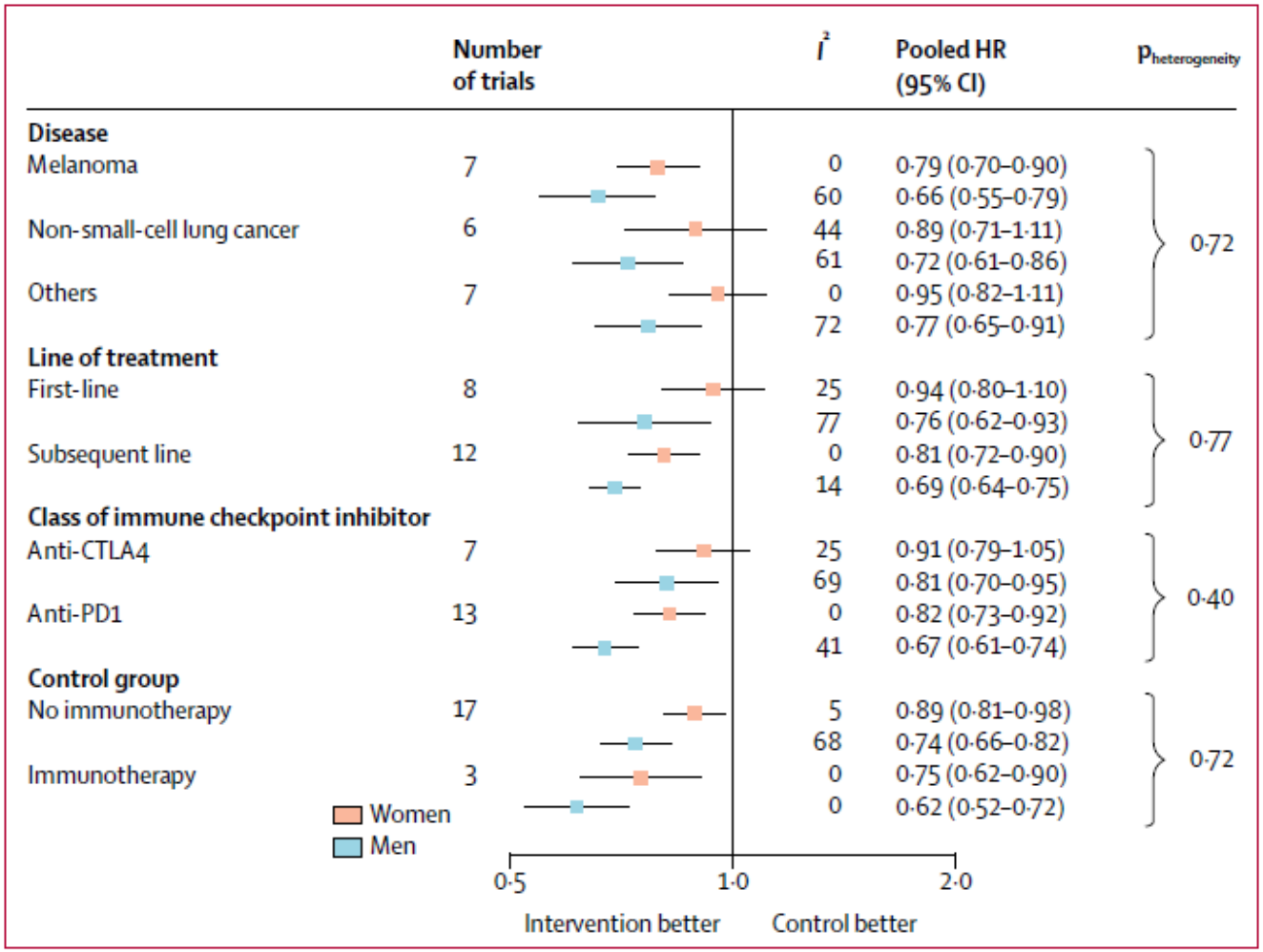


Figure 3: Analyses of sex-specific pooled hazard ratios, by subgroup

SG

HR= 0,72

HR= 0,86

Enfermedades autoinmunes

Pacientes excluidos de E.C.

Tratamiento inmunosupresor habitual

Uso factible: Efectividad similar

Riesgo exacerbación enfermedad

Riesgo reacciones inmunomediadas

Generalmente controlable con inmunosupresión

- *Gutzmer R, et al. Programmed cell death protein-1 (PD-1) inhibitor therapy in patients with advanced melanoma and preexisting autoimmunity or ipilimumab-triggered autoimmunity. Eur J Cancer. 2017; 75:24-32.*
- *Johnson DB, et al. Ipilimumab Therapy in Patients With Advanced Melanoma and Preexisting Autoimmune Disorders. JAMA Oncol. 2016 Feb;2(2):234-40.*
- *Menzies AM, et al. Anti-PD-1 therapy in patients with advanced melanoma and pre-existing autoimmune disorders or major toxicity with ipilimumab. Ann Oncol. 2017;28(2):368-376*

Sistema inmunitario del huésped

Biomarkers of response to PD-1/PD-L1 inhibition

S. Maleki Vareki et al. / Critical Reviews in Oncology/Hematology 116 (2017) 116–124

Table 1
Patient outcome based on ANC, dNLR, NLR, and ALC levels.

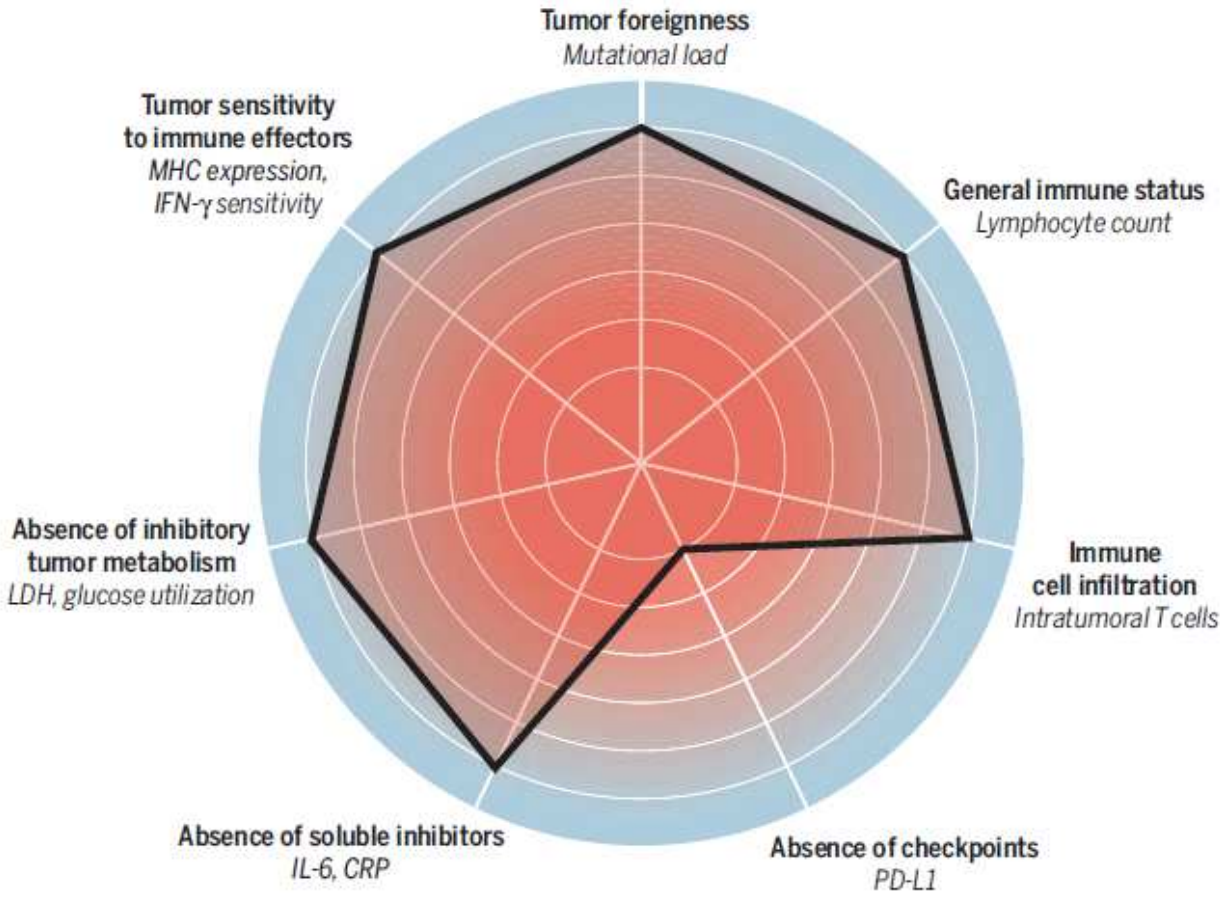
Disease	Number of patients	Treatment	Biomarker	Biomarker change	Patient outcome	Reference
Melanoma	720	Ipilimumab	ANC	Elevated Levels	Lower OS and PFS	Ferrucci et al. (2016)
Melanoma	720	Ipilimumab	dNLR	Elevated Levels	Lower OS and PFS	Ferrucci et al. (2016)
Melanoma	58	Ipilimumab	NLR	Elevated Levels	Poor prognosis	Zaragoza et al. (2016)
Melanoma	104	Ipilimumab	ALC	Elevated Levels	Prolonged PFS	Alexander et al. (2014)
Melanoma	95	Ipilimumab	ALC	Elevated Levels	Higher OS	Simeone et al. (2014)
Uveal melanoma	39	Ipilimumab	ALC	Elevated Levels	Higher OS	Luke et al. (2013)
Melanoma	616	Pembrolizumab	REC	High Levels	Favorable OS	Weide et al. (2016)
Melanoma	616	Pembrolizumab	RLC	High Levels	Favorable OS	Weide et al. (2016)
Melanoma	616	Pembrolizumab	LDH	Low Levels	Favorable OS	Weide et al. (2016)
Melanoma	117	Ipilimumab	ALC	Elevated Levels	Not predictive of OS	Postow et al. (2013)

- ANC= Absolute neutrophil counts
- dNLR= derived neutrophil-to-lymphocyte ratio
- NLR= neutrophil-to-lymphocyte ratio
- ALC= Absolute lymphocyte counts
- REC= relative eosinophil count
- RLC= relative lymphocyte count
- LDH= serum lactate dehydrogenase

Baseline-derived neutrophil-to-lymphocyte ratio (dNLR) and lactate dehydrogenase (LDH) to predict the benefit of immune checkpoint inhibitors (ICI) in advanced non-small cell lung cancer (NSCLC) patients.
Mezquita et al. J.C.O. 2017 35:15_suppl, 9089

dNLR > 3 and LDH > upper normal limit (UNL) were independent factors for poor OS and poor PFS

Inmunograma



CANCER IMMUNOLOGY

The "cancer immunogram"

Visualizing the state of cancer–immune system interactions may spur personalized therapy

By Christian U. Blank,[1,2] John B. Haanen,[1,2] Antoni Ribas,[3] Ton N. Schumacher[2]

Science **352**, 658 (2016)

The cancer immunogram. *The radar plot depicts the seven parameters that characterize aspects of cancer-immune interactions for which biomarkers have been identified or are plausible. Potential biomarkers for the different parameters are shown in italics. Desirable states are located in blue; progressively undesirable states are shown in the red gradient. The black line connecting the data values for each parameter represents a plot for a single hypothetical patient.*

Área I
Murcia Oeste
Arrixaca

Servicio
Murciano
de Salud

Tercera Reunión Anual del grupo:
GEDEFO
Grupo de Farmacia Oncológica de la SEFH

sefh
Sociedad Española de Farmacia Hospitalaria
fefh
Fundación Española de Farmacia Hospitalaria

ATENCIÓN FARMACÉUTICA
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