XXIV SIMPOSIO DE REVISIONES EN CÁNCER

"Tratamiento médico del cáncer en el año 2022"

10 años de experiencia: retos y éxitos del tratamiento con la doble inmunoterapia

Almudena García Castaño
Hospital Universitario Marqués de Valdecilla

10 años…

10 años… de experiencia

Editorial

Revista Mexicana de Pediatría
Vol. 78, Núm. 3 • Mayo-junio 2011
pp 99-101

¿Qué es la medicina?: ¿Una ciencia? ¿Un arte? ¿o un oficio?

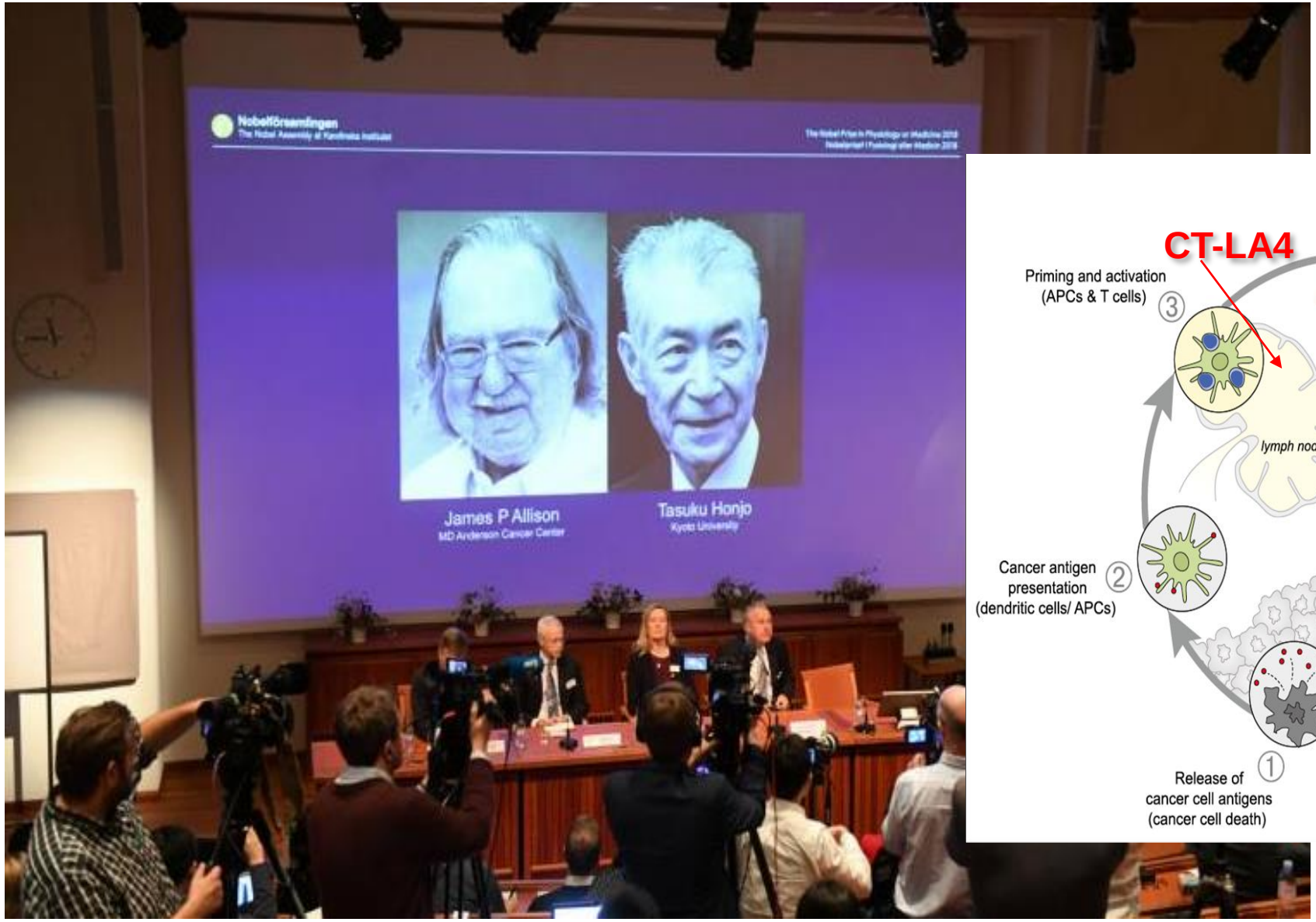
(What's medicine: a science, an art or a craft?)

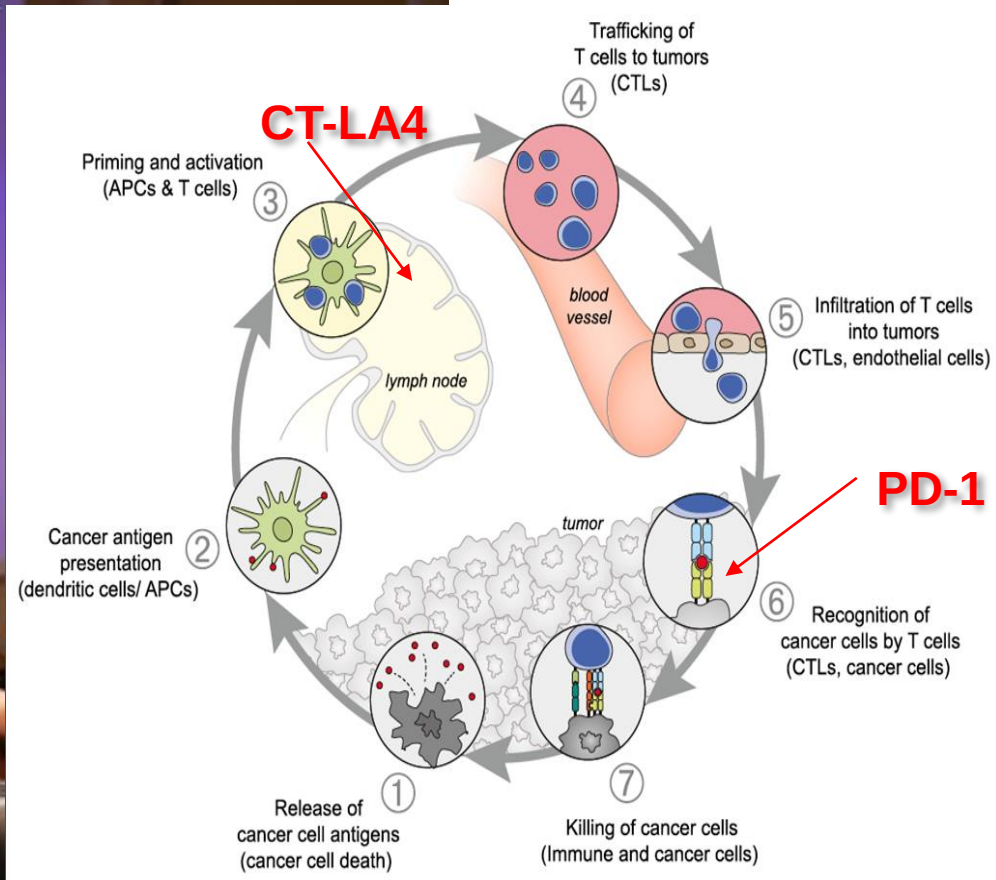
Leopoldo Vega Franco

La medicina no es sólo una ciencia, sino que también es un arte.
No consiste de componer píldoras y yesos; se trata de los mismos procesos de la vida,
que deben ser entendidos antes de que puedan ser guiados

Paracelso

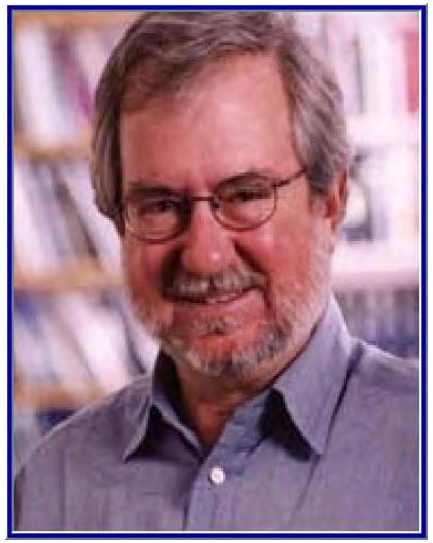
10 años… de experiencia con inmunoterapia





No vemos jamás las cosas tal cual son, las vemos tal cual somos”
Anaïs Nin

Todo empezó con esto…



Enhancement of Antitumor Immunity by CTLA-4 Blockade

Dana R. Leach, Matthew F. Krummel, James P. Allison*

One reason for the poor immunogenicity of many tumors may be that they cannot provide signals for CD28-mediated costimulation necessary to fully activate T cells. It has recently become apparent that CTLA-4, a second counterreceptor for the B7 family of costimulatory molecules, is a negative regulator of T cell activation. Here, in vivo administration of antibodies to CTLA-4 resulted in the rejection of tumors, including preestablished tumors. Furthermore, this rejection resulted in immunity to a secondary exposure to tumor cells. These results suggest that blockade of the inhibitory effects of CTLA-4 can allow for, and potentiate, effective immune responses against tumor cells.

SCIENCE • VOL. 271 • 22 MARCH 1996

Improved survival with **ipilimumab** in patients with metastatic melanoma **MDX010-20**

Hodi FS, *et al*. N Engl Med 2010

676 pacientes

HLA-A*0201

III irresecable/IV

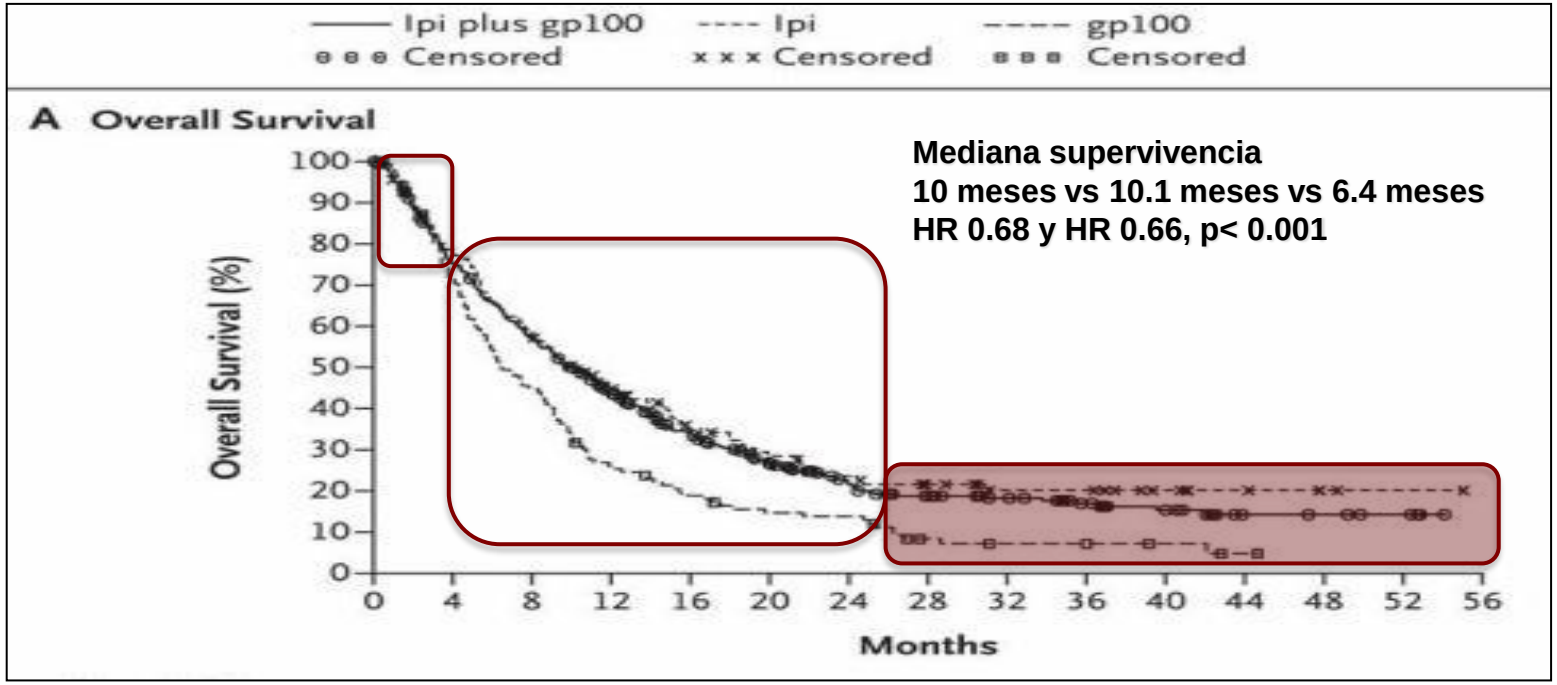
2ª línea

Objetivo principal: SG

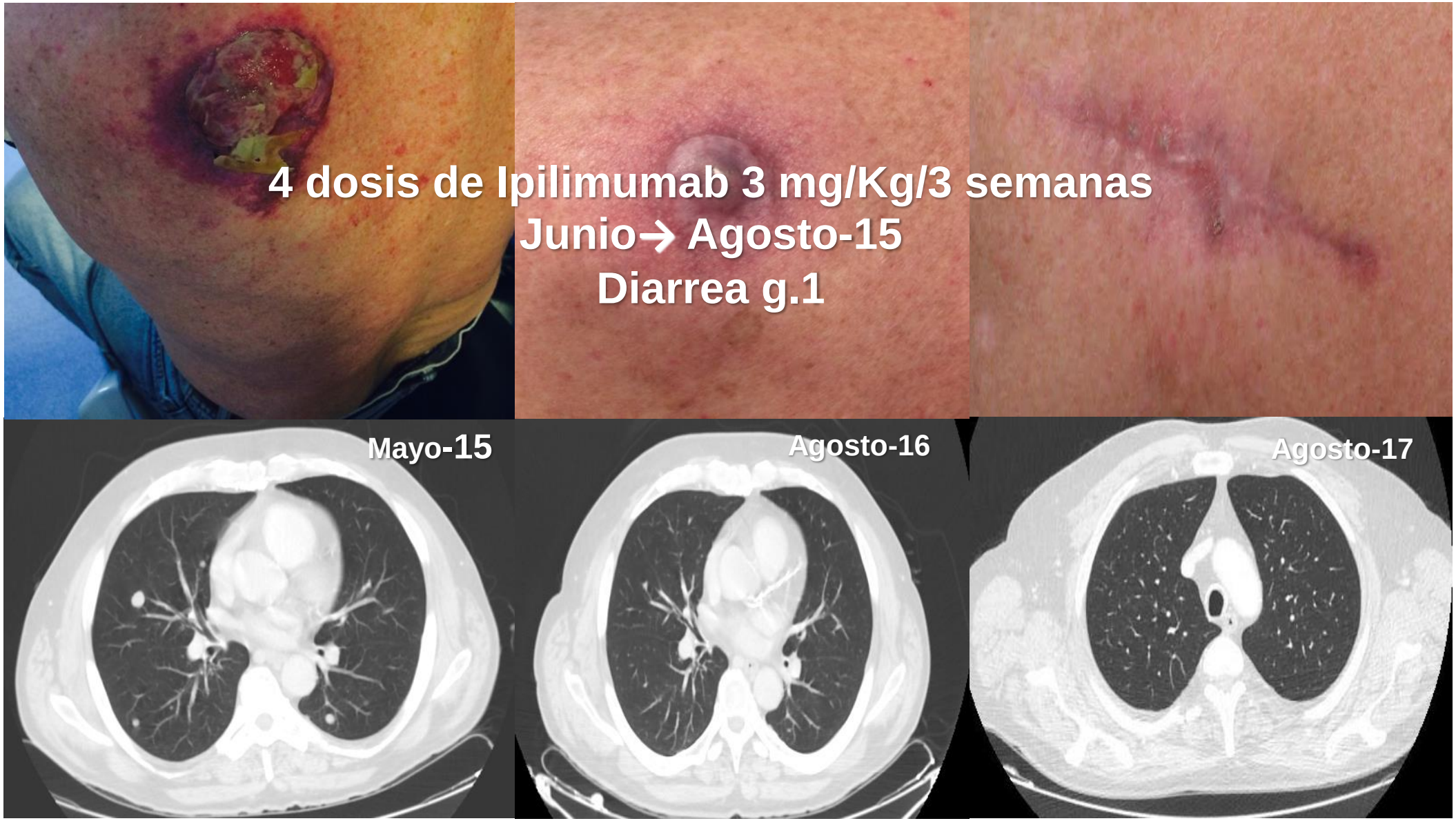
R

- **Ipilimumab + gp100 N= 403**
- **Ipilimumab N= 137**
- **gp100 N= 136**

Variable	Ipilimumab + gp100 (N=403)	Ipilimumab (N=137)	gp100 (N=136)
Respuestas (%)	5,7	**10,9**	1,5
Control enfermedad (%)	20,1	**28,5**	11,0
Duración respuesta (meses)	11,5	NR	NR



Paciente Nº 1



Drug of the year: Programmed Death-1 receptor/Programmed Death-1 Ligand-1 receptor monoclonal antibodies

Caroline Robert, Jean-Charles Soria, Alexander M.M. Eggermont*

Gustave Roussy Comprehensive Cancer Center, 114 Rue Edouard Vaillant, 94800 Villejuif/Paris-Sud, France

European Journal of Cancer (2013) 49, 2968–2971

Corrected 26 March 2018. See full text.

SPECIAL SECTION CANCER IMMUNOTHERAPY

REVIEW

Cancer immunotherapy using checkpoint blockade

Antoni Ribas[1]* and Jedd D. Wolchok[2,3]*

The release of negative regulators of immune activation (immune checkpoints) that limit antitumor responses has resulted in unprecedented rates of long-lasting tumor responses in patients with a variety of cancers. This can be achieved by antibodies blocking the cytotoxic T lymphocyte–associated protein 4 (CTLA-4) or the programmed cell death 1 (PD-1) pathway, either alone or in combination. The main premise for inducing an immune response is the preexistence of antitumor T cells that were limited by specific immune checkpoints. Most patients who have tumor responses maintain long-lasting disease control, yet one-third of patients relapse. Mechanisms of acquired resistance are currently poorly understood, but evidence points to alterations that converge on the antigen presentation and interferon-g signaling pathways. New-generation combinatorial therapies may overcome resistance mechanisms to immune checkpoint therapy.

Clinical effects of PD-1– and PD-L1–blockade therapies

The underlying biology and durable response rates in patients with multiple types of cancer indicate that therapeutic blockade of the PD-1 pathway is arguably one of the most important advances in the history of cancer treatment. There are currently five anti–PD-1 or anti–PD-L1 antibodies approved by the FDA in 11 cancer indications (Table 1 and Fig. 2). The first evidence of the antitumor activity of PD-1 blockade

SMR 2021

7-Year Follow-Up of KEYNOTE-006: Pembrolizumab Versus Ipilimumab in Advanced Melanoma

C. Robert[1]; M. S. Carlino[2]; C. McNeil[3]; A. Ribas[4]; J. J. Grob[5]; J. Schachter[6]; M. Nyakas[7]; D. Kee[8]; T. M. Petrella[9]; A. Bleustein[10]; M. Lotem[11]; A. Arance Fernandez[12]; A. I. Daud[13]; O. Hamid[14]; J. Larkin[15]; J. Anderson[16]; C. Krepler[16]; D. Gnjenmik[16]; G. V. Long[17]

[1]Gustave Roussy and Paris-Saclay University, Villejuif, France; [2]Melanoma Institute Australia, The University of Sydney, Westmead and Blacktown Hospitals, Sydney, NSW, Australia; [3]Chris O'Brien Lifehouse Skin and Melanoma Institute Australia, Camperdown, NSW, Australia; [4]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [5]Aix-Marseille University, Hospital of the Timone, Marseille, France; [6]Sheba Medical Center-Tel HaShomer, Ramat Gan, Israel; [7]Oslo University Hospital, Oslo, Norway; [8]Austin Health-Austin Hospital, Heidelberg, VIC, Australia; [9]Sunnybrook Health Sciences Centre, Toronto, ON, Canada; [10]Mount Sinai Medical Center Comprehensive Cancer Center, Miami Beach, FL, USA; [11]Sharett Institute of Oncology, Hadassah University Hospital Ein Kerem, Jerusalem, Israel; [12]Hospital Clinic of Barcelona, Barcelona, Spain; [13]University of California San Francisco, San Francisco, CA, USA; [14]The Angeles Clinic and Research Institute, a Cedars-Sinai Affiliate, Los Angeles, CA, USA; [15]The Royal Marsden NHS Foundation Trust, London, United Kingdom; [16]Merck & Co., Inc., Kenilworth, NJ, USA; [17]Melanoma Institute Australia, The University of Sydney, Royal North Shore and Mater Hospitals, Sydney, NSW, Australia

Figure 3. Modified PFS

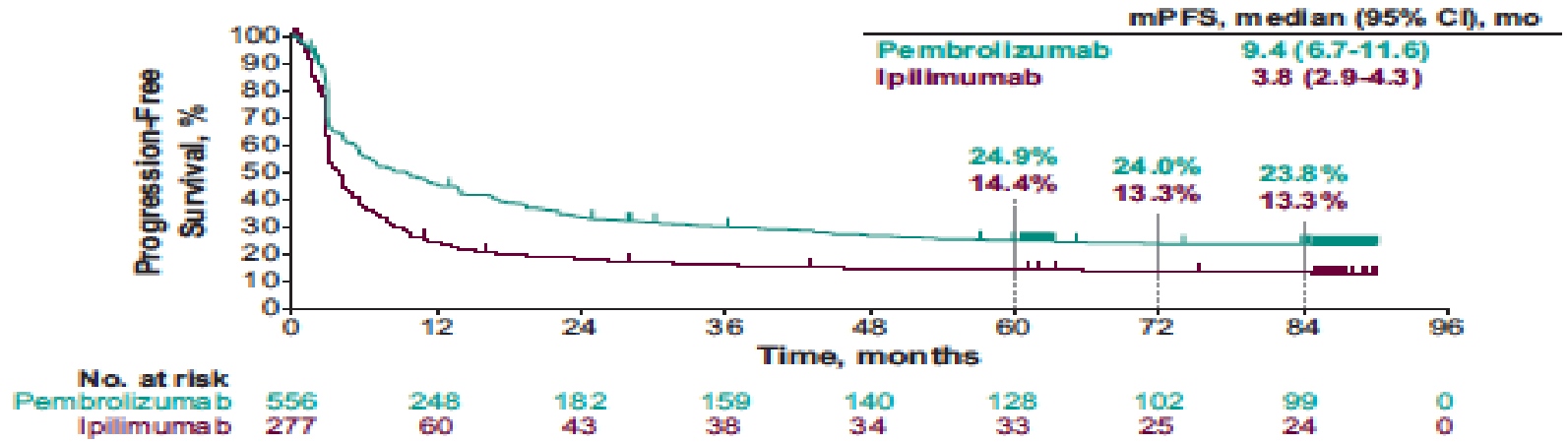
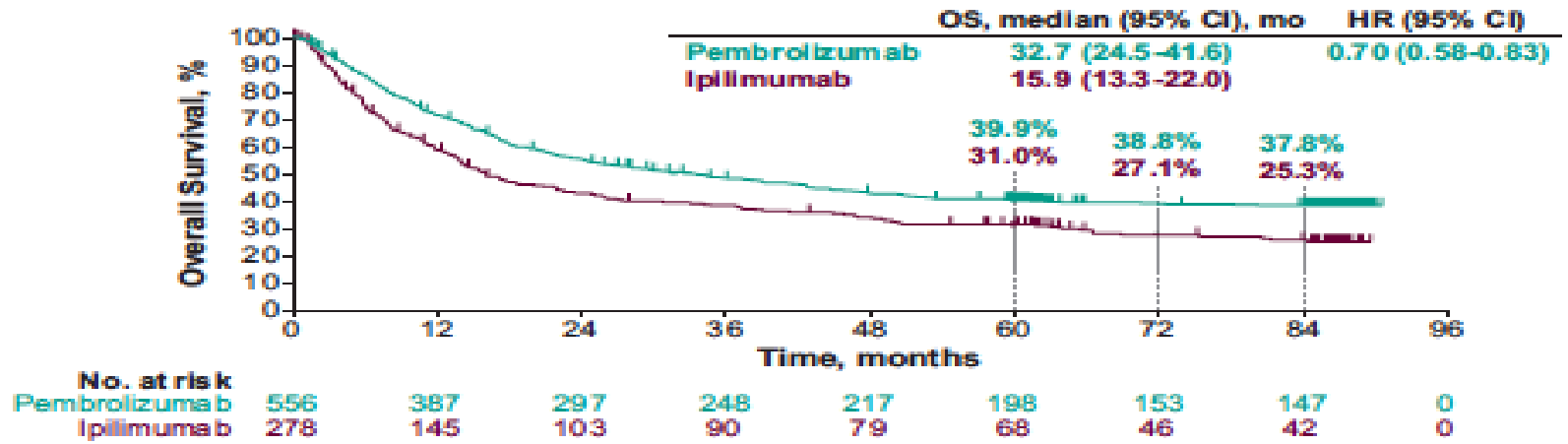


Figure 4. OS by Randomized Treatment in the Overall Population



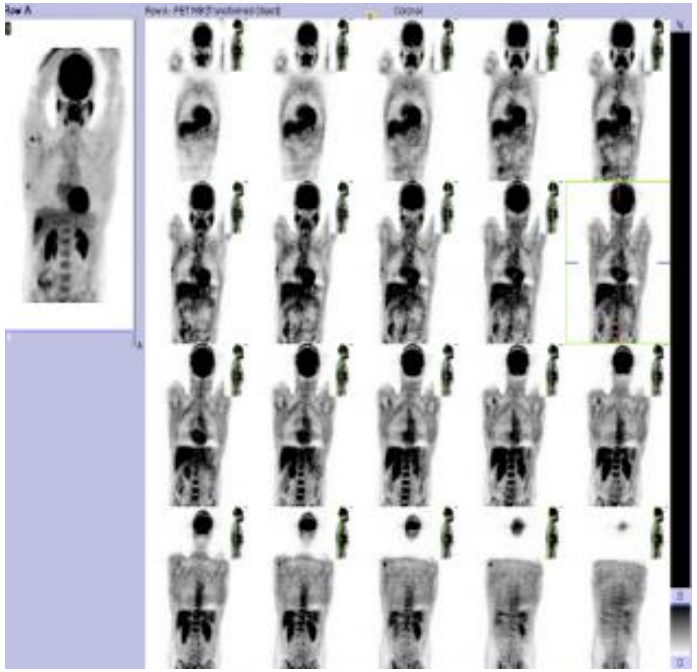
HR, hazard ratio.

Paciente Nº2

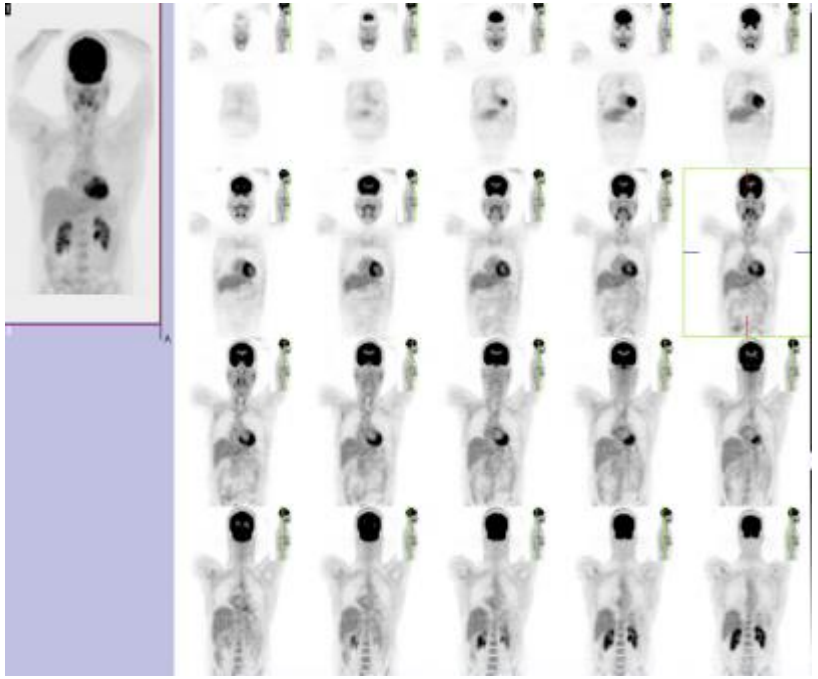
- Varón de 45 años
- Psoriasis con artritis psoriásica desde 2012
- Fototipo cutáneo tipo II

10-Junio-18 *Respuesta completa*
ECOG 0
Continua con Nivolumab hasta Marzo-20
Vivo, sin tratamiento y sin enfermedad

- **Abril-17**→ Melanoma maligno nodular pT4b pN3 (8/10) M0, estadio IIIC (AJCC 7ª)
- **Oct-17**→ Recaída hepática y subcutánea



- Mutación BRAF +
- ECOG 0
- RMN cerebral sin datos de interés
- LDH 161 U/L (105-215 U/L)
- **Nivolumab**→ Nov-17



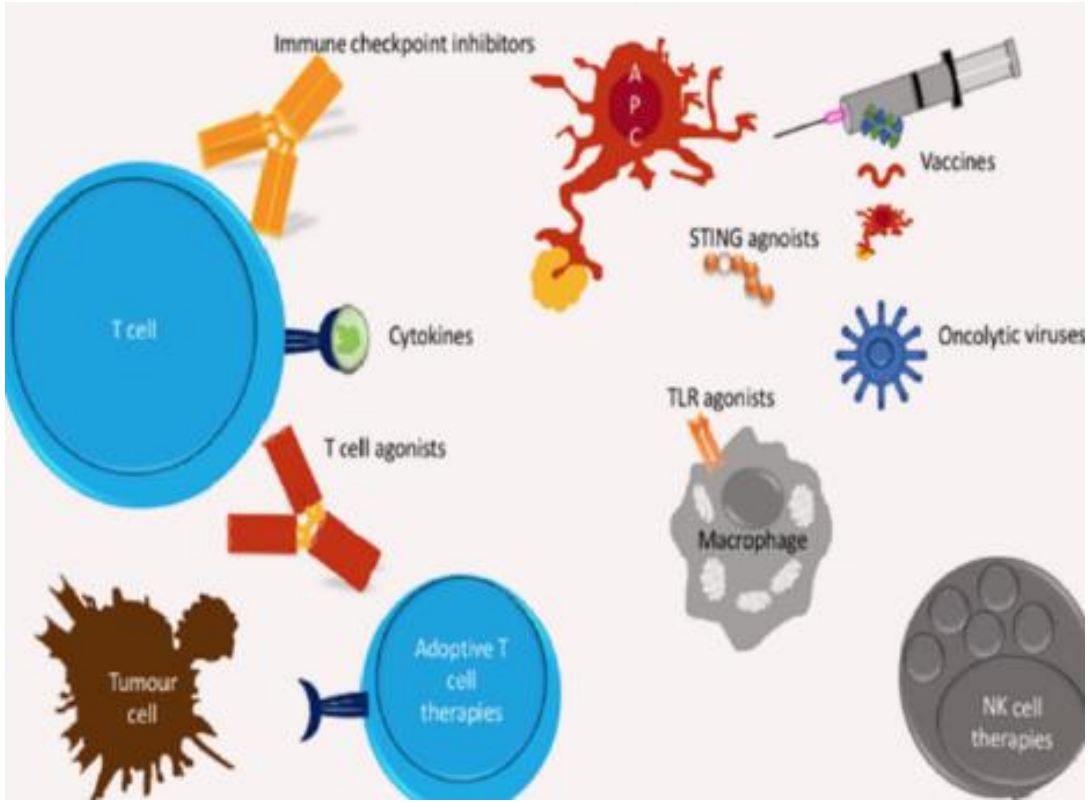
Paciente Nº3

- **Varón 46 años**
- **2011**→ Melanoma maligno nodular tronco pT4a pN0 M0, estadio IIB, 7ª AJCC
- **Dic-16**→ Recaída ganglionar inguinal izquierda tratada con cirugía y RT
- **Jun-17**→ Recidiva pulmonar y subcutánea en recto izquierdo

- Mutación BRAF negativa
- ECOG 0
- No M1 cerebrales
- LDH 180 U/L (105-215 U/L)
- **Nivolumab**→ Julio-17
- Dic-17→ **Progresión subcutánea y ganglionar**→ **Ipilimumab**

- Abril-18→ **Progresión pulmonar** → **Fotemustina**
- **Sep-18**→ **Exitus**

De esta necesidad→ “Estrategias de combinación”



Diferentes clases inmunoterapia
Diferentes fármacos

Objetivos

Mejorar eficacia de inmunoterapia
Aumenta inmunogenicidad del tumor
“dejar de esconderse”
Aumentar respuestas
Disminuir resistencias primarias
Retrasar resistencia adquirida
Racional

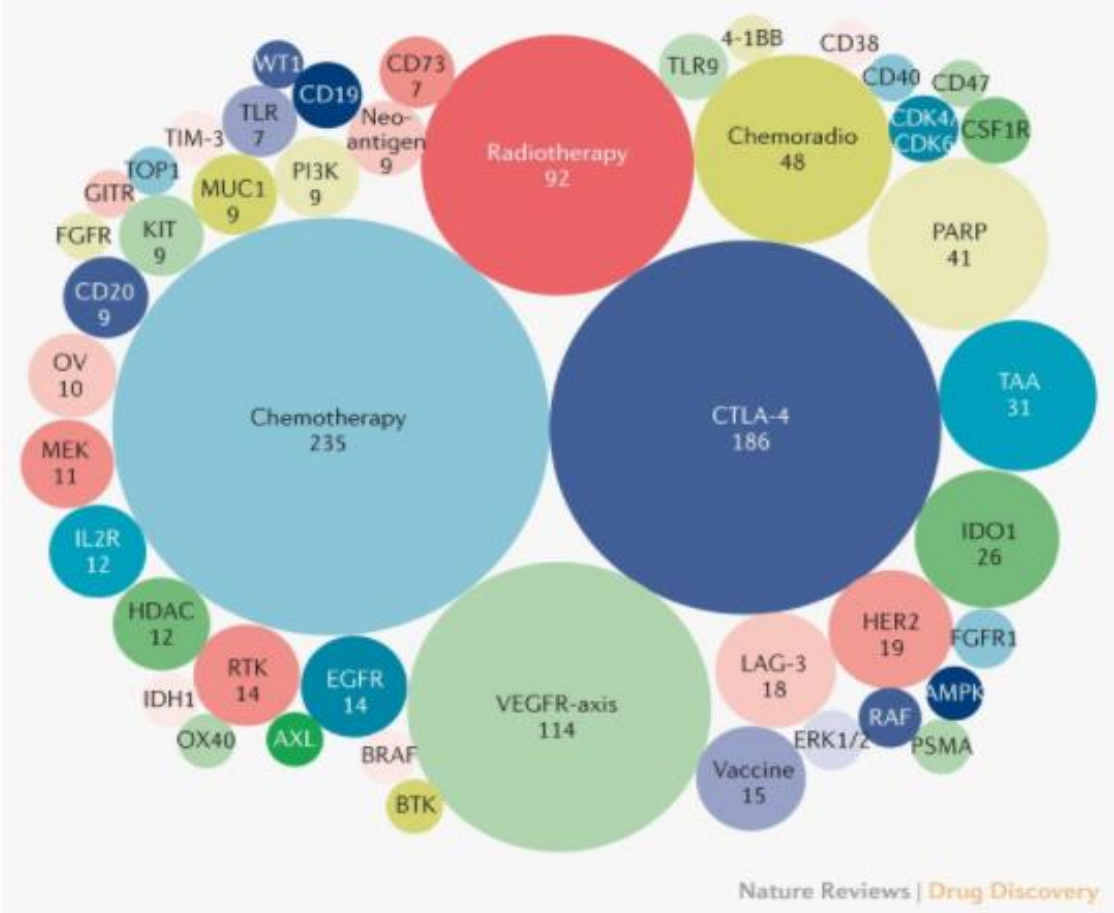
Paciente Nº 2 ⟵ ***Paciente Nº 3***

Garces A, *et al.* Building on the anti-PD1/PD-L1 backbone: combination immunotherapy for cáncer. Expert Opin Investig Drugs. 2019;28(8):695-708.

10 años… de experiencia con doble inmunoterapia

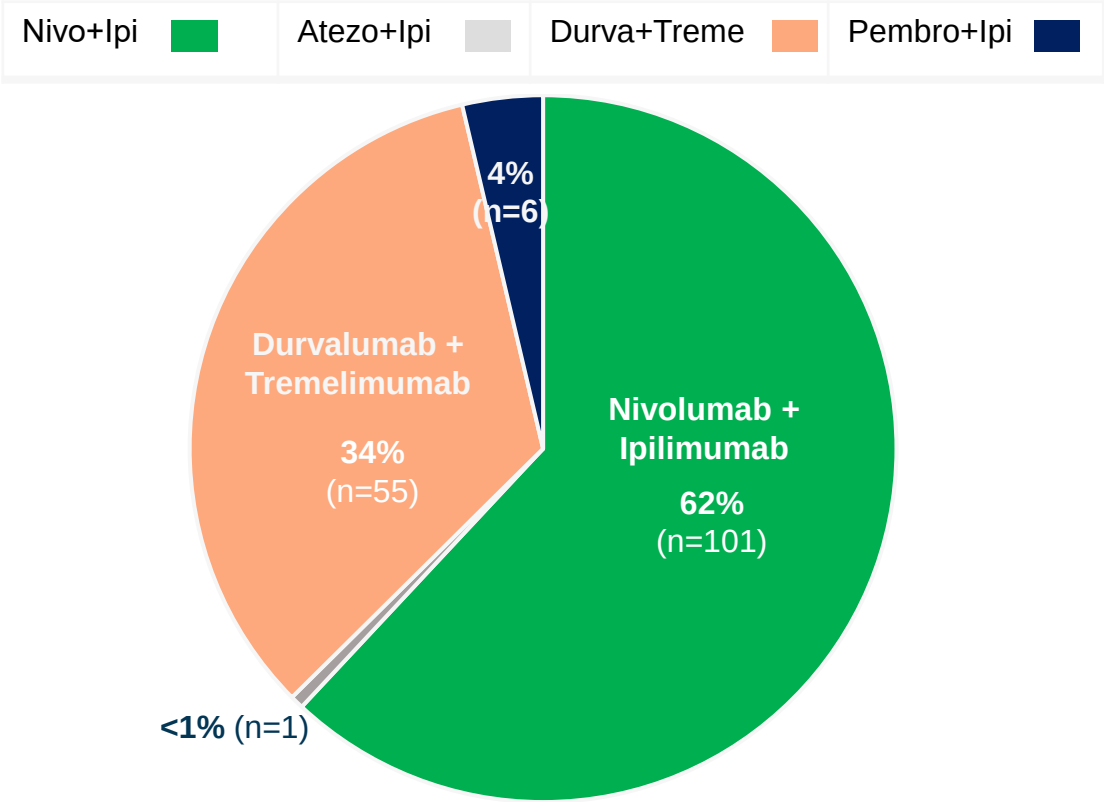
Analysis of new combination trials with

PD-1/PD-L1 inhibitors started in the past 2 years



Jia Xin Yu, *et al.* Nat Rev Drug Discov 2020

Landscape of combination checkpoint inhibition agents



Chae, *et al.* J Immunother Cancer 2018

Nivolumab + Ipilimumab, ¿juntos mejor?

Anti-CTLA-4	Anti-PD-1
• Hard wired	• Induced resistance
• Targets CD28 pathway	• Targets TCR pathway
• Works during priming	• Works on differentiated T cells
• Expand conal diversity	• Does not expand clonal diversity
• Responses often slow	• Responses usually rapid
• Primarily effects CD4 T cells	• Only effects CD8 T cells
• Can move T cells into “cold” tumors	• Does not move T cells into tumors
• Adverse events relatively frequent	• Adverse events less frequent
• Disease recurrence after response rare	• Disease recurrence after response significant

Allison J, *et al.* ASCO 2019 del 31 mayo- 4 junio. Chicago, EEUU

Cambios inmunológicos → Anti-PD-1 vs anti-CTLA-4 vs anti-PD-1 más anti-CTLA-4

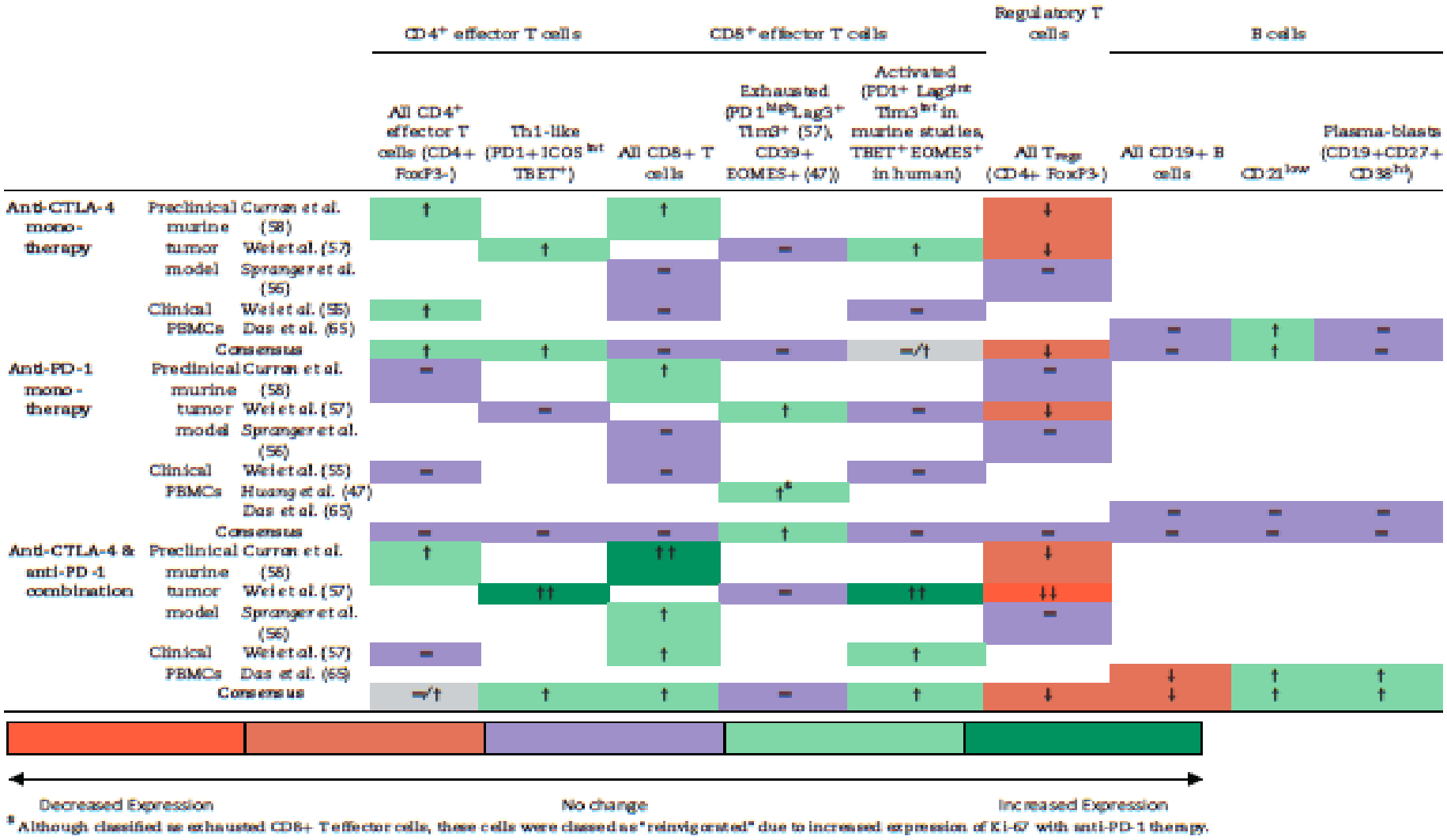


Figura extraída de Willsmore ZN, *et al.* Eur J Immunol 2021

Nivolumab + Ipilimumab, ¿juntos mejor?

Efectos sinérgicos

Respuesta immune más robusta

Eficacia clínica demostrada*

Primera línea melanoma avanzado/metastásico

Primera línea cáncer de pulmón combinación dos ciclos quimioterapia

Primera línea mesotelioma irresecable

Hepatocarcinoma segunda línea tras sorafenib

Primera línea cáncer renal avanzado con intermedio/mal pronóstico

Segunda línea cáncer colon MSI-H/dMMR

* https://www.ema.europa.eu/en/documents/product-information/opdivo-epar-product-information_es.pdf

* https://www.ema.europa.eu/en/documents/overview/yervoy-epar-medicine-overview_es.pdf

¿Y esta eficacia en qué se ha traducido?

- Aumento tasa respuestas

Eficacia→ Tasa de respuestas

CheckMate 067 6.5 y

Response to treatment at 6.5 years

	NIVO + IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
ORR (95% CI), %	58 (53-64)	45 (39-51)	19 (15-24)
Best overall response, %			
Complete response	23	19	6
Partial response	36	26	13
Stable disease	12	9	22
Progressive disease	24	38	50
Unknown	6	8	9
Median duration of response (95% CI), months	NR (61.9-NR)	NR (45.7-NR)	19.2 (8.8-47.4)

CI, confidence interval; NR, not yet reached.

Y en algunos pacientes la respuesta es un objetivo clínico (y una necesidad)…

Wolchock JD, *et al.* ASCO 2021

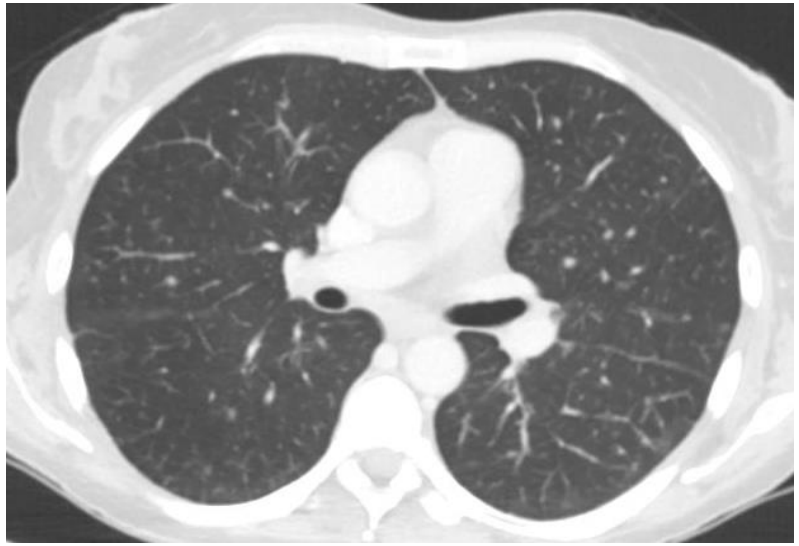
Paciente Nº4

Mujer, 39 años
Melanoma cuero cabelludo
estadio IIIC→ 2016
BRAF mutado

ILP tras nivo-Ipi→ 24meses
2ª línea→ Terapia dirigida
ILP terapia dirigida→ 18 meses

Junio-17→ Recaída pulmonar/hepática
- LDH >2 LSN
- Tos continua y disnea

Sep-17→ 4 ciclos Nivolumab + Ipilimumab
- LDH normal
- Mejoría síntomas evidente

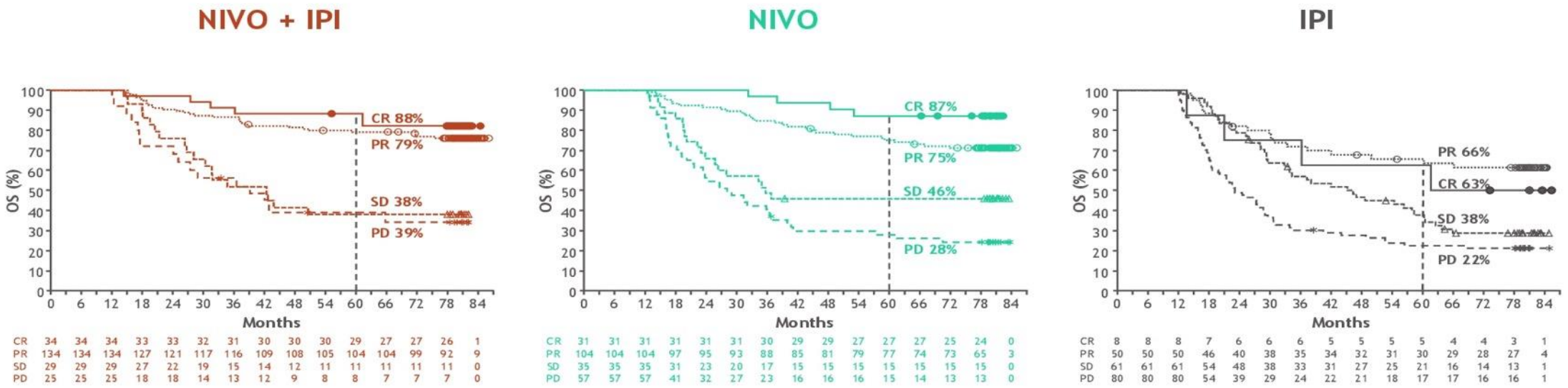


¿Y esta eficacia en qué se ha traducido?

- Aumento tasa respuestas (y de la calidad de las mismas)

Eficacia→ Supervivencia global según respuesta

OS by best overall response, 12-month landmark analysis[a]

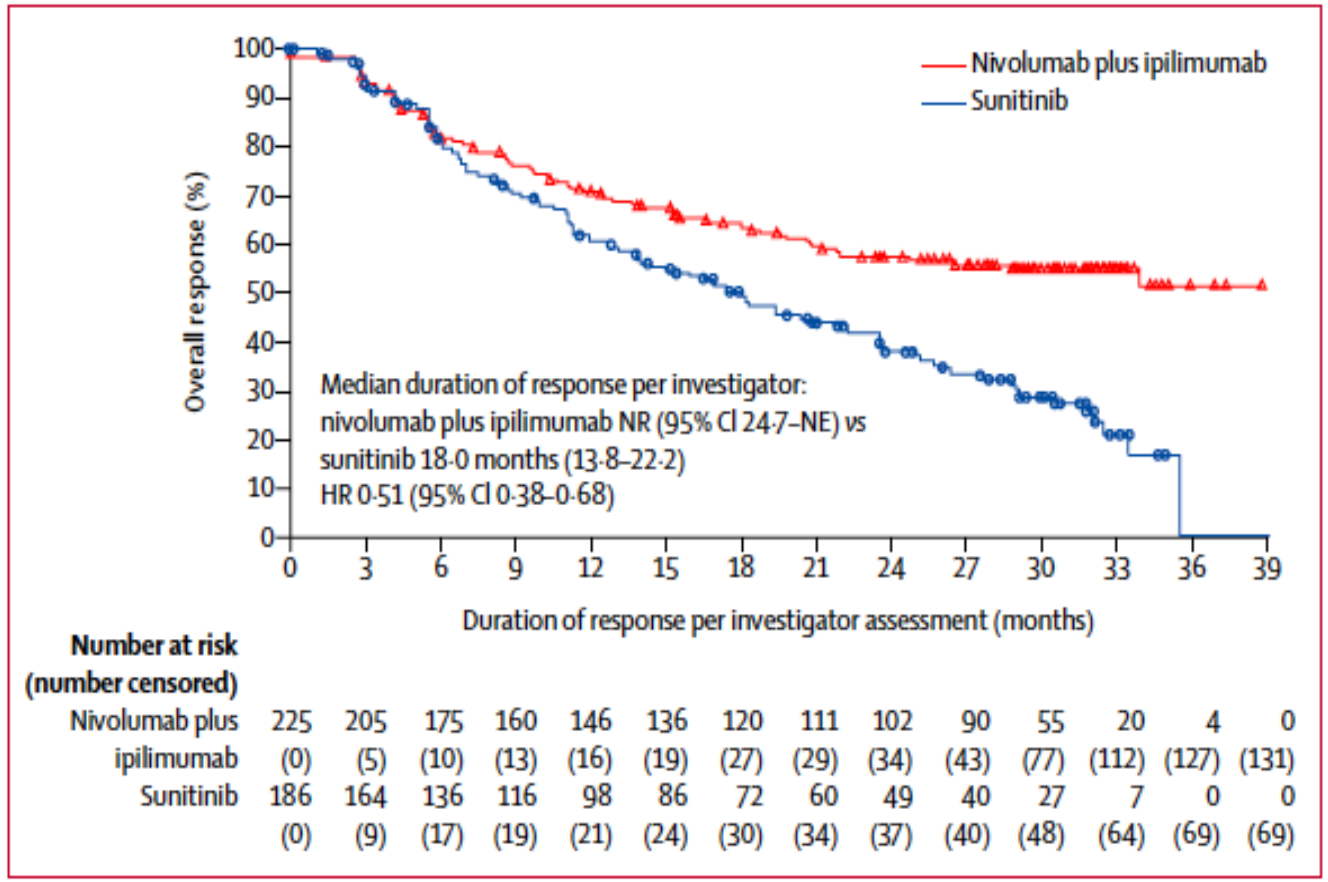


- **Patients with a best overall response of a CR, PR, SD, or PD at 12 months were followed for OS**

[a]To address guarantee-time bias, landmark analysis excluded patients who had an event during the first 12 months.
PD, progressive disease.

Wolchock JD, *et al.* ASCO 2021

Nivolumab plus ipilimumab versus sunitinib in first-line treatment for advanced renal cell carcinoma: extended follow-up of efficacy and safety results from a randomised, controlled, phase 3 trial



Pacientes cáncer renal intermedio-mal pronóstico	Nivolumab + Ipilimumab (%)	Sunitinib (%)
Mejor respuestas (%)		
Respuesta completa	**11**	**1**
Respuesta parcial	**31**	**28**
Enfermedad estable	**26**	**41**
Progresión	**25**	**19**
NA	**7**	**10**
Pacientes duración respuesta > 18 meses (%)	**52**	**28**

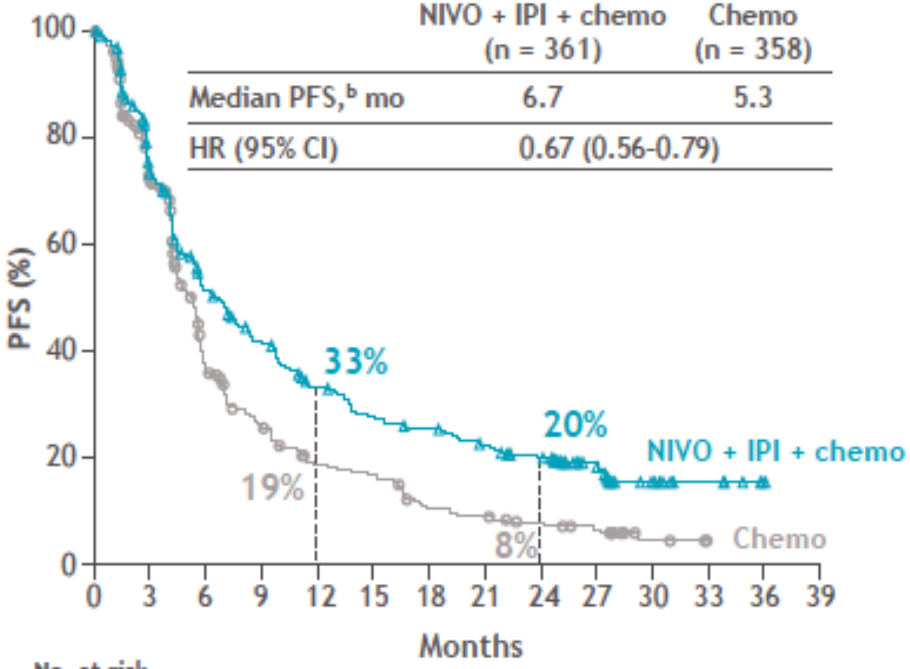
Motzer RJ, *et al.* Lancet Oncol 2019

First-line nivolumab + ipilimumab + 2 cycles of chemotherapy versus chemotherapy alone (4 cycles) in patients with advanced non-small cell lung cancer: **2-year update from CheckMate 9LA**

2-Year update: PFS and DOR

PFS[a]

	NIVO + IPI + chemo (n = 361)	Chemo (n = 358)
Median PFS,[b] mo	6.7	5.3
HR (95% CI)	0.67 (0.56-0.79)	

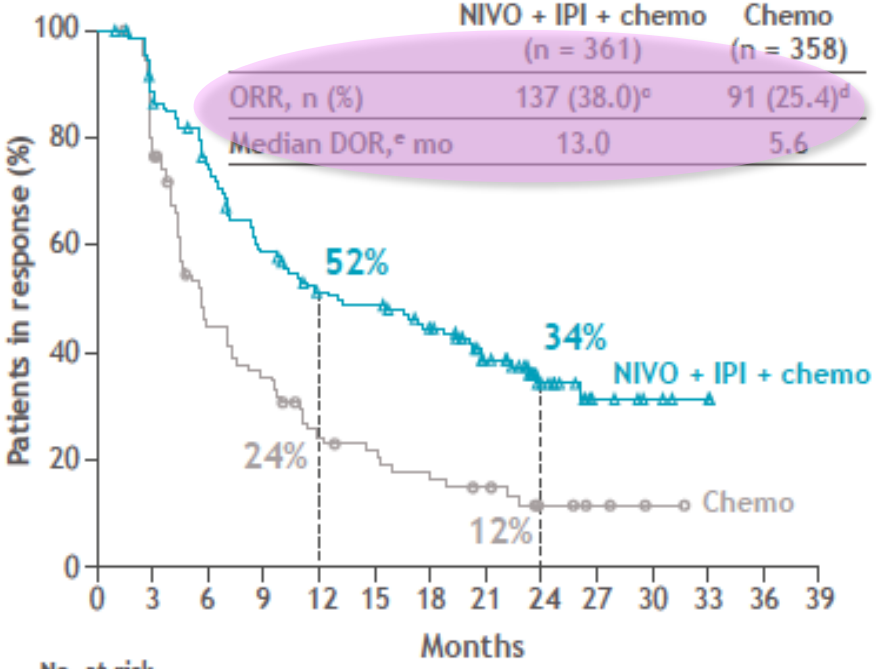


No. at risk

NIVO + IPI + chemo	361	252	170	134	103	85	77	66	54	29	12	6	1	0
Chemo	358	232	107	72	49	44	26	22	17	12	3	0	0	0

DOR[a]

	NIVO + IPI + chemo (n = 361)	Chemo (n = 358)
ORR, n (%)	137 (38.0)[c]	91 (25.4)[d]
Median DOR,[e] mo	13.0	5.6



No. at risk

NIVO + IPI + chemo	137	116	97	75	62	59	50	35	17	7	4	2	0	0
Chemo	91	70	38	30	19	16	12	10	5	3	1	0	0	0

Minimum follow-up: 23.3 months.
[a]Per BICR; [b]95% CI = 5.6-7.8 (NIVO + IPI + chemo) and 4.4-5.6 (chemo); [c]Includes 3.3% CR and 34.6% PR; 4 patients who had a PR as best response at a previous DBL (12.2 months minimum follow-up for response) improved to CRs; [d]Includes 1.1% CR and 24.3% PR; [e]95% CI = 8.7-20.2 (NIVO + IPI + chemo) and 4.4-7.2 (chemo).

8

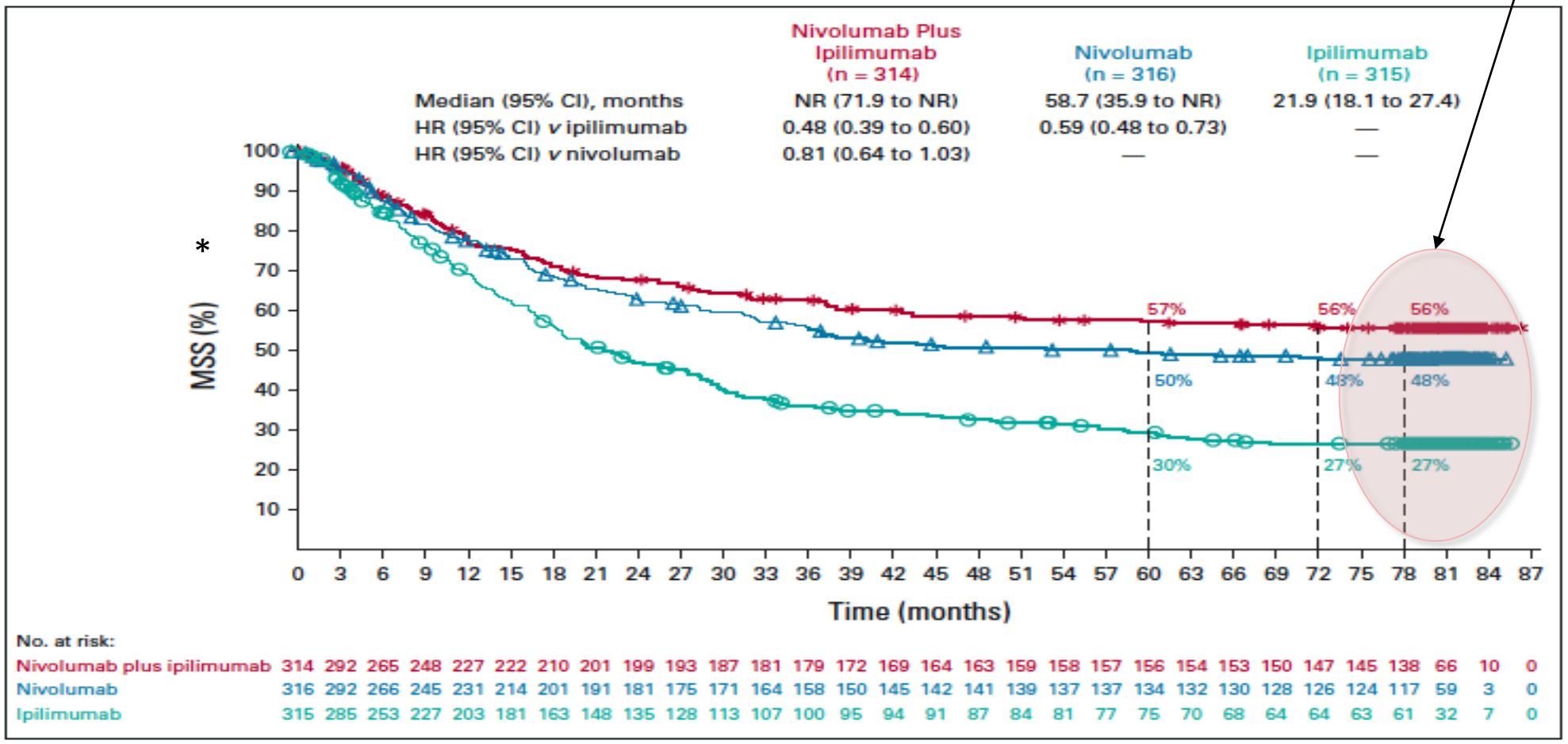
Reck M, *et al.* ASCO 2021, #9000

¿Y esta eficacia en qué se ha traducido?

- Aumento tasa respuestas (y de la calidad de las mismas)
- Beneficio en supervivencia global

Long-Term Outcomes With Nivolumab Plus Ipilimumab or Nivolumab Alone Versus Ipilimumab in Patients With Advanced Melanoma

Nos fijamos en esto…

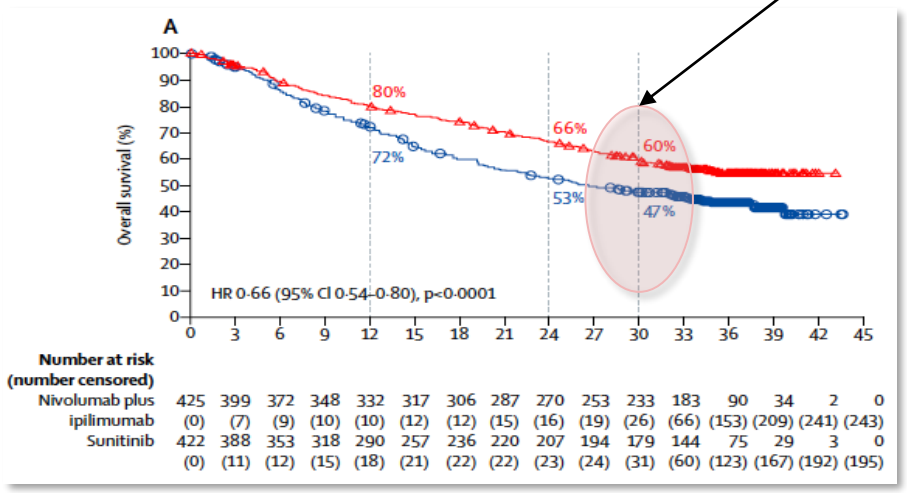


* Supervivencia específica de melanoma (análisis descriptivo)

Wolchock JD, *et al.* J Clin Oncol 2021

Nivolumab plus ipilimumab versus sunitinib in first-line treatment for advanced renal cell carcinoma: extended follow-up of efficacy and safety results from a randomised, controlled, phase 3 trial

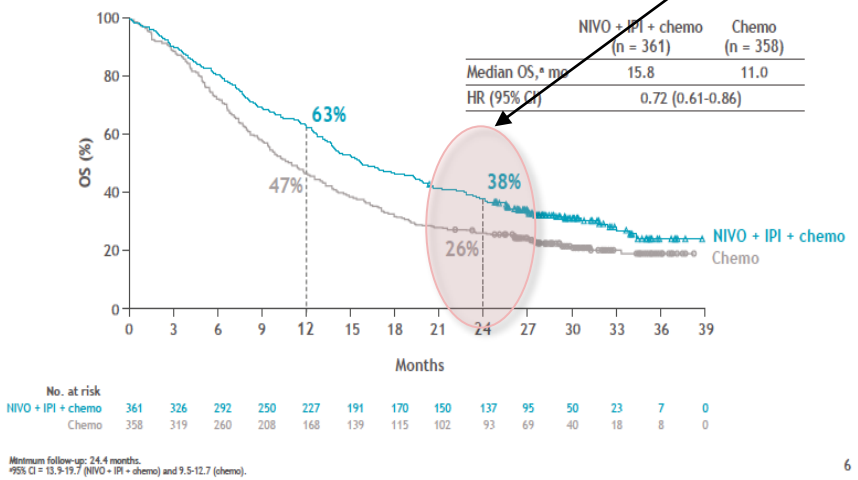
Y en esto…



Motzer RJ, *et al.* Lancet Oncol 2019

First-line nivolumab + ipilimumab + 2 cycles of chemotherapy versus chemotherapy alone (4 cycles) in patients with advanced non-small cell lung cancer: **2-year update from CheckMate 9LA**

Y en esto…



Reck M, *et al.* ASCO 2021, #9000

The Oncologist
Regulatory Issues: FDA

FDA Approval Summary: Nivolumab Plus Ipilimumab for the Treatment of Patients with Hepatocellular Carcinoma Previously Treated with Sorafenib

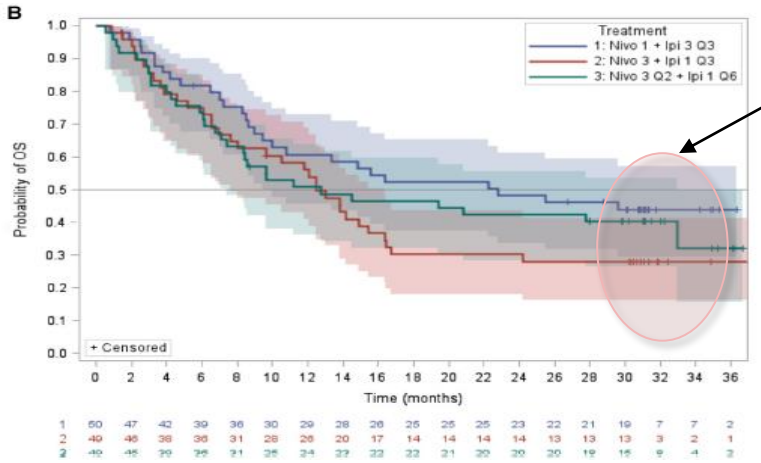
May Tun Saung,[a] Lorraine Pelosof,[a] Sandra Casak,[a] Martha Donoghue,[a] Steven Lemery,[a,b] Mengdie Yuan,[a] Lisa Rodriguez,[a] Peter Scholtand,[a] Meredith Chuk,[a] Gina Davis,[a] Kirsten B. Goldberg,[a] Marc R. Theoret,[a,b] Richard Pazdur,[a,b] Lola Fashoyin-Aje[a]
[a]Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, Maryland, USA; [b]Oncology Center of Excellence, U.S. Food and Drug Administration, Silver Spring, Maryland, USA

Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Hepatocellular carcinoma • CheckMate 040 • Nivolumab • Ipilimumab

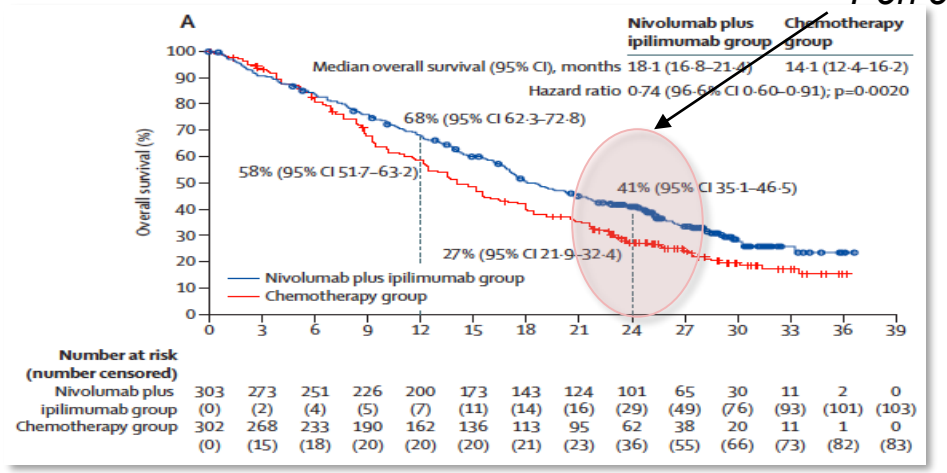
The Oncologist 2021;26:797–806

Y en esto…



First-line nivolumab plus ipilimumab in unresectable malignant pleural mesothelioma (CheckMate 743): a multicentre, randomised, open-label, phase 3 trial

Y en esto…



Baas P, *et al.* The Lancet 2021

¿Y esta eficacia en qué se ha traducido?

- Aumento tasa respuestas (y de la calidad de las mismas)
- Beneficio en supervivencia global
- Beneficio en pacientes “de especial mal pronóstico”

	IMDC intermediate-risk or poor-risk patients			Intention-to-treat population			IMDC favourable-risk patients		
	Nivolumab plus ipilimumab (n=425)	Sunitinib (n=422)	p value	Nivolumab plus ipilimumab (n=550)	Sunitinib (n=546)	p value	Nivolumab plus ipilimumab (n=125)	Sunitinib (n=124)	p value
Proportion of patients with confirmed objective responses, % (95% CI)	42% (37–47)	29% (25–34)	0·0001	41% (37–46)	34% (30–38)	0·015	39% (31–48)	50% (41–59)	0·14
Best overall response									
Complete response	48 (11%)	5 (1%)	..	58 (11%)	10 (2%)	..	10 (8%)	5 (4%)	..
Partial response	130 (31%)	119 (28%)	..	169 (31%)	176 (32%)	..	39 (31%)	57 (46%)	..
Stable disease	110 (26%)	174 (41%)	..	165 (30%)	222 (41%)	..	55 (44%)	48 (39%)	..
Progressive disease	106 (25%)	80 (19%)	..	121 (22%)	86 (16%)	..	15 (12%)	6 (5%)	..
Unable to determine or not reported	31 (7%)	44 (10%)	..	37 (7%)	52 (10%)	..	6 (5%)	8 (6%)	..
Median time to confirmed objective response (IQR), months*	n=176; 2·8 (2·7–3·1)	n=124; 4·0 (2·8–5·5)	..	n=225; 2·8 (2·7–4·0)	n=186; 4·0 (2·8–6·0)	..	n=49; 2·9 (2·7–5·5)	n=62; 4·2 (2·8–6·9)	..
Median time to confirmed complete response (IQR), months	n=48; 5·8 (2·9–10·5)	Not calculated	..	n=58; 7·6 (3·8–11·2)	Not calculated	..	n=10; 10·5 (7·0–14·0)	Not calculated	..
Patients with duration of response ≥18 months*	92/176 (52%)	35/124 (28%)	..	120/225 (53%)	72/186 (39%)	..	28/49 (57%)	37/62 (60%)	..
Patients with ongoing response*	104/176 (59%)	43/124 (35%)	..	131/225 (58%)	69/186 (37%)	..	27/49 (55%)	26/62 (42%)	..
Patients with ongoing complete response	42/48 (88%)	4/5 (80%)	..	51/58 (88%)	6/10 (60%)	..	9/10 (90%)	2/5 (40%)	..

Data are n (%) or n/N (%) unless otherwise specified. p value calculated only for the co-primary endpoint. IMDC=International Metastatic Renal Cell Carcinoma Database Consortium. *Characterisation of response kinetics could not be calculated for two intermediate-risk or poor-risk partial responders to nivolumab plus ipilimumab because of missing date of partial response.

Table 1: **Investigator-assessed objective response rates by the Response Evaluation Criteria in Solid Tumors (version 1.1)**

Motzer RJ, *et al.* Lancet Oncol 2019

Melanoma: from incurable beast to a curable bet. The success of immunotherapy

¿Combinaciones mejor aquí?

*Maria Libera Ascierto [1], Ignacio Melero [2] and Paolo Antonio Ascierto [3]**

Frontiers in Oncology 2015

[1] Department of Oncology, Johns Hopkins University, Baltimore, MD, USA, [2] Department of Oncology, Centro de Investigación Médica Aplicada (CIMA), Clinica Universidad de Navarra, Pamplona, Spain, [3] Unit of Melanoma, Cancer Immunotherapy and Innovative Therapy, Istituto Nazionale Tumori Fondazione "G. Pascale", Napoli, Italy

Poblaciones de peor pronóstico

Niveles elevados LDH

Metástasis cerebrales

Tropismo cerebral

- 20-30% al diagnóstico
- 50% a lo largo de la enfermedad
- 70% series autopsias

Mal pronóstico→ Mediana SG 4 meses

Melanoma mucosas/uveal

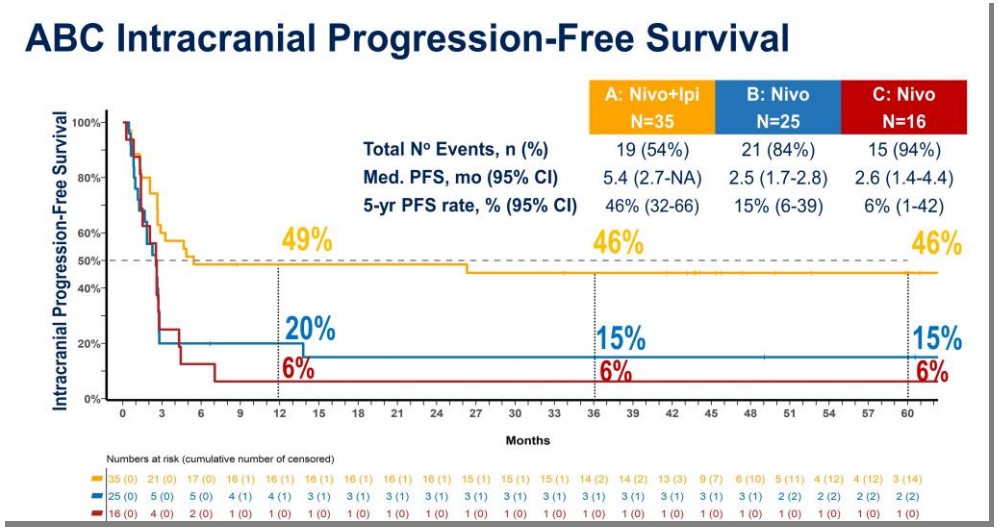
Melanomas especial mal pronóstico

Anti-PD1 poco eficaz

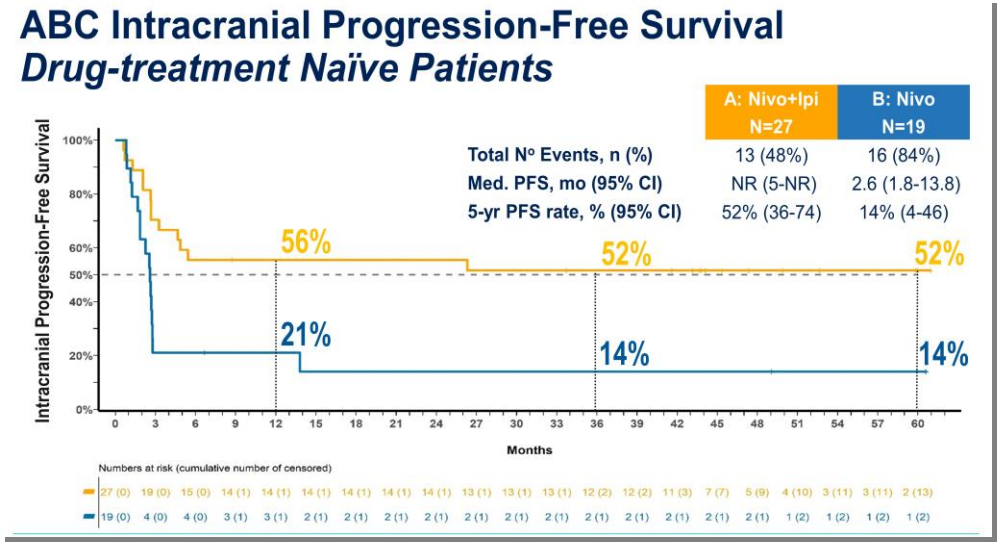
Nivolumab + Ipilimumab
eficacia significativa M1 asintomáticas no tratadas

Estudio ABC (mediana seguimiento 52.8 meses). Long G, *et al. ASCO 2021*

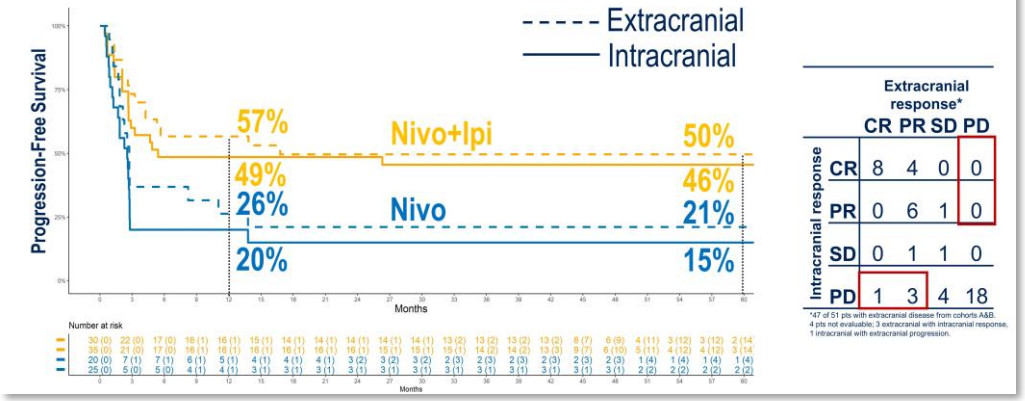
ABC Intracranial Progression-Free Survival



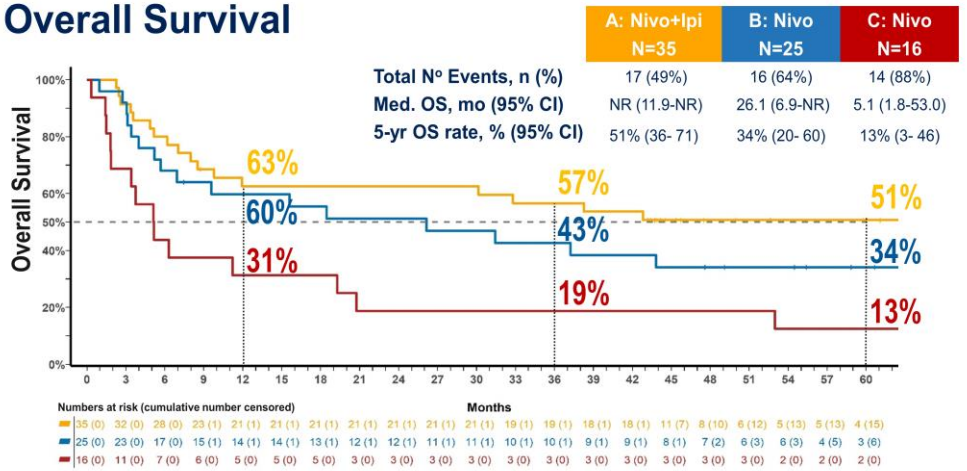
ABC Intracranial Progression-Free Survival
Drug-treatment Naïve Patients



ABC Intracranial and Extracranial Concordance
All Patients Cohort A and B



Overall Survival

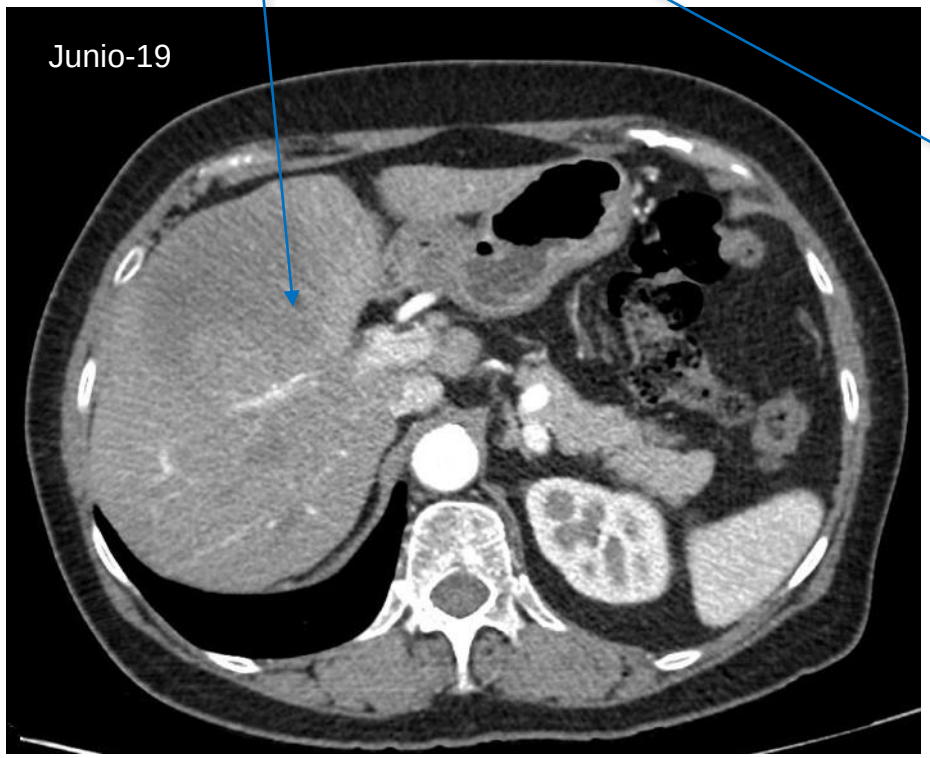


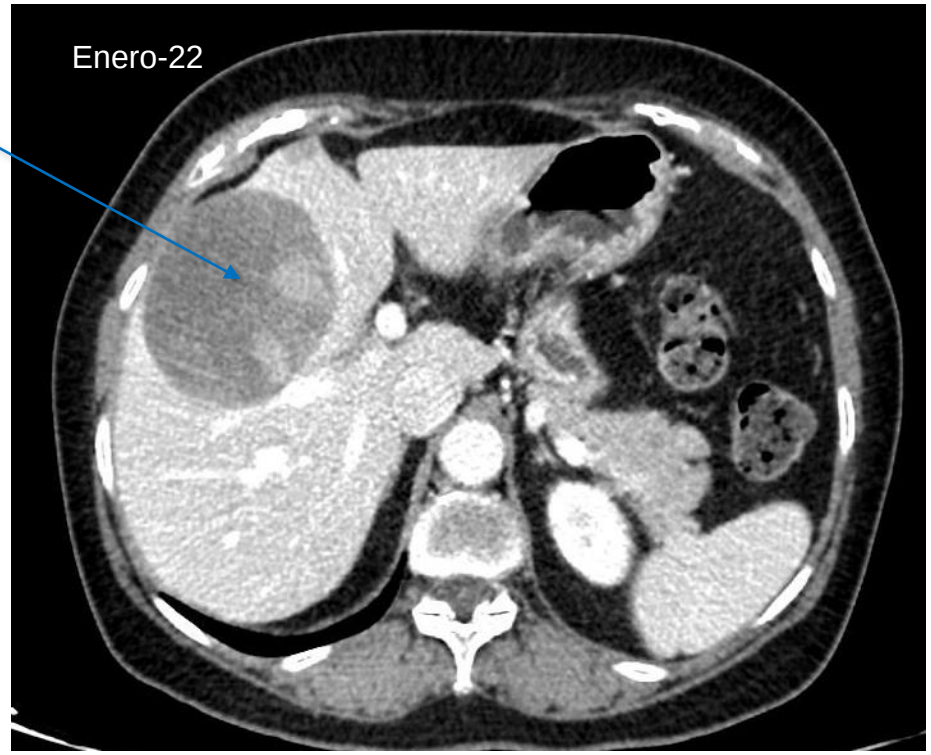
- Death solely due to intracranial progression in 8/76 (17%) patients (1 Cohort A, 4 Cohort B, 3 Cohort C)

Paciente Nº5

Mujer de 59 años

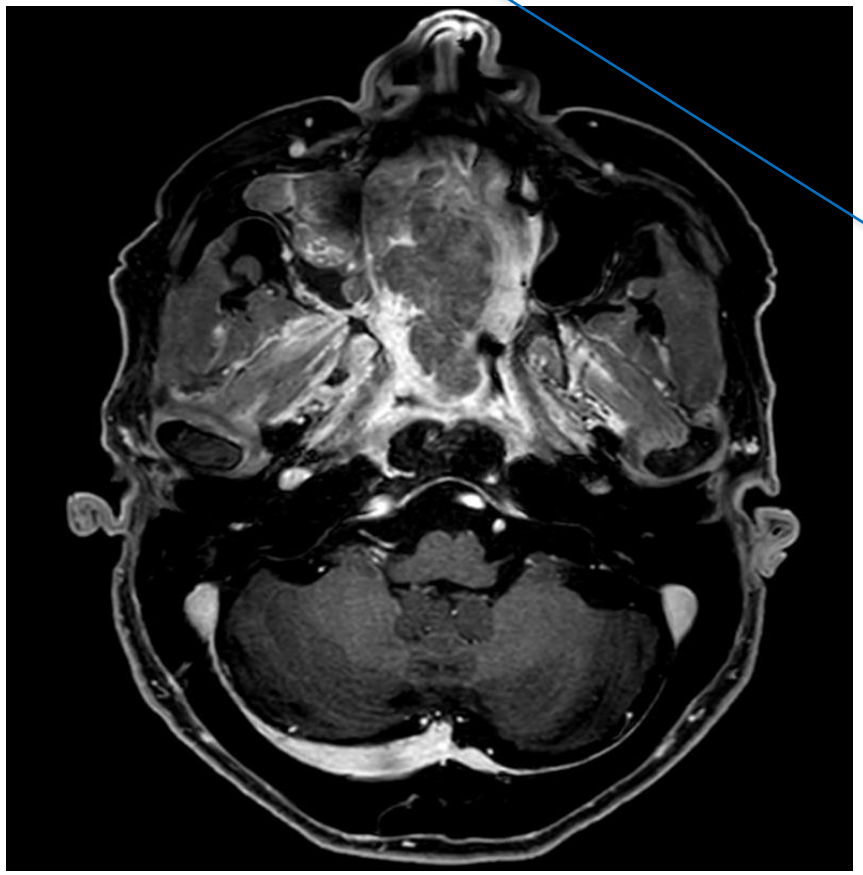
- Melanoma ocular de ojo izquierdo sometido a enucleación (2011)
- Recaída local tratada con braquiterapia (2013).
- Recaída hepática (junio-19) tratada con Nivolumab (1 mg/Kg)-Ipilimumab (3 mg/Kg)/3 semanas x 4C y actualmente Nivolumab en monoterapia con EE
- ECOG 0

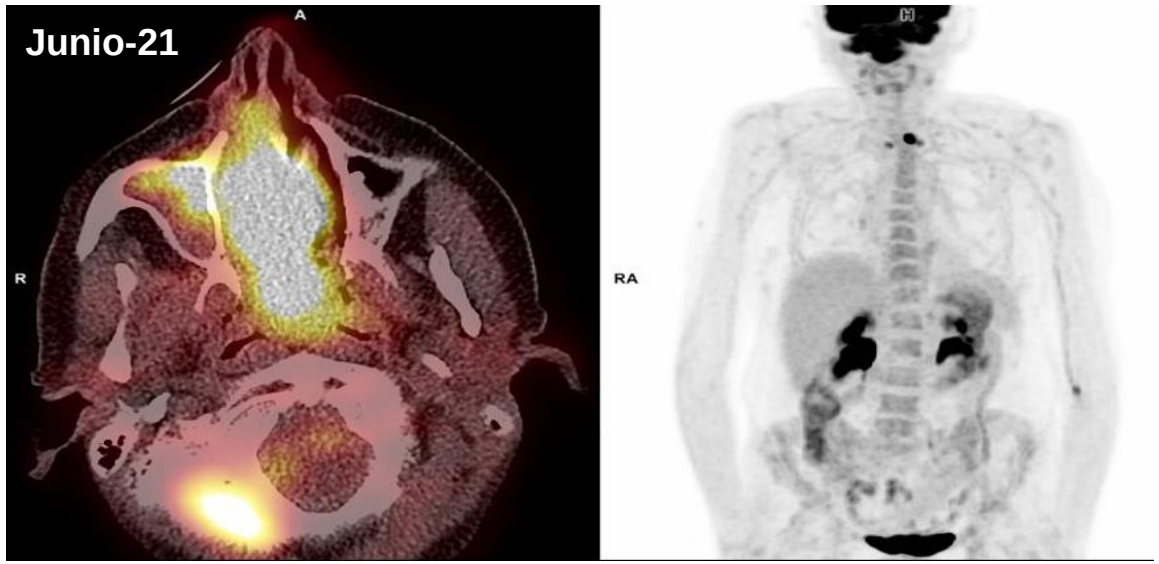


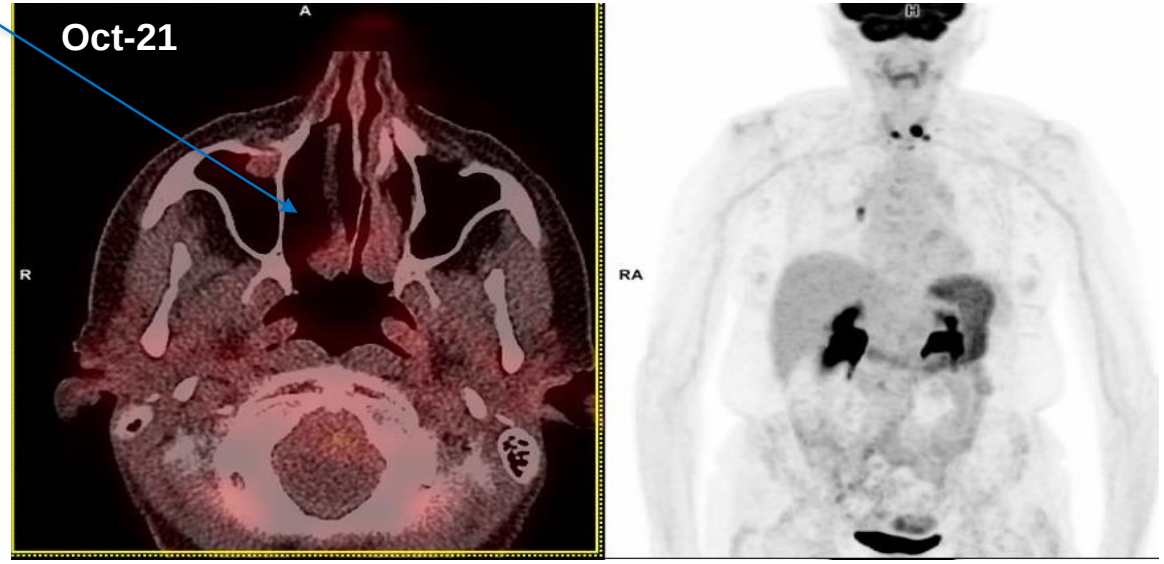


Paciente Nº6

Mujer de 78 años
- Melanoma mucosa nasal derecha en junio-21 con
- ECOG 1, obstrucción nasal y rinolalia
- Nivolumab (1 mg/Kg)-Ipilimumab (3 mg/Kg)/3 s x 4C







¿Y esta eficacia en qué se ha traducido?

- Aumento tasa respuestas (y de la calidad de las mismas)
- Beneficio en supervivencia global
- Beneficio en pacientes “de especial mal pronóstico”
- Posibilidad parar tratamientos (sin comprometer la eficacia)

¿We can?

Un nuevo concepto…

Treatment-Free Survival: A Novel Outcome Measure of the Effects of Immune Checkpoint Inhibition—A Pooled Analysis of Patients With Advanced Melanoma

¿ Por qué?

- Porque SLP y la SG han guiado las aprobaciones y decisiones clínicas

…aunque quizás no valoren adecuadamente el beneficio de la inmunoterapia

- Pacientes que discontinúan

…periodos de remisión, sin necesidad de tratamientos subsecuentes

- Memoria inmunológica

Regan M, *et al.* J Clin Oncol 2019

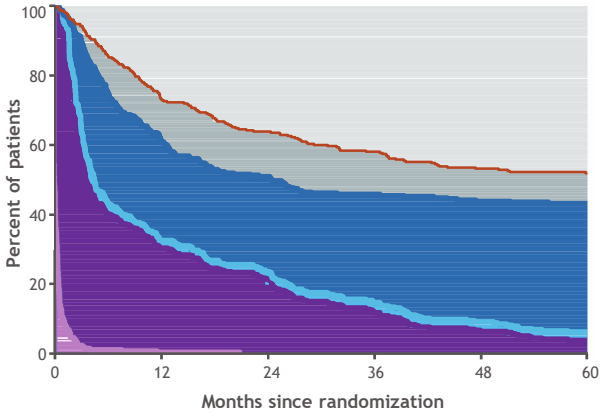
Estimating Treatment-Free Survival Over Extended Follow-up in Patients With Advanced Melanoma Treated With Immune Checkpoint Inhibitors: 5-Year Follow-up of CheckMate 067

Abstract Number 10043

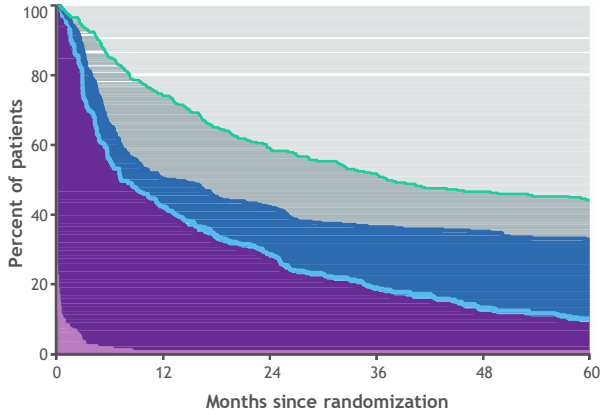
Meredith M. Regan,[1,2] Charlene Mantia,[3] Lillian Werner,[1] Ahmad A. Tarhini,[4] Sumati Rao,[5] Andriy Moshyk,[5] Corey Ritchings,[5] Sandra Re,[5] Agnes Balogh,[5] Michael B. Atkins,[6] David F. McDermott[2,3]

[1]Dana-Farber Cancer Institute, Boston, MA, USA; [2]Harvard Medical School, Boston, MA, USA; [3]Beth Israel Deaconess Medical Center, Boston, MA, USA; [4]Moffitt Cancer Center and Research Institute, Tampa, FL, USA; [5]Bristol Myers Squibb, Princeton, NJ, USA; [6]Georgetown Lombardi Comprehensive Cancer Center, Washington, DC, USA

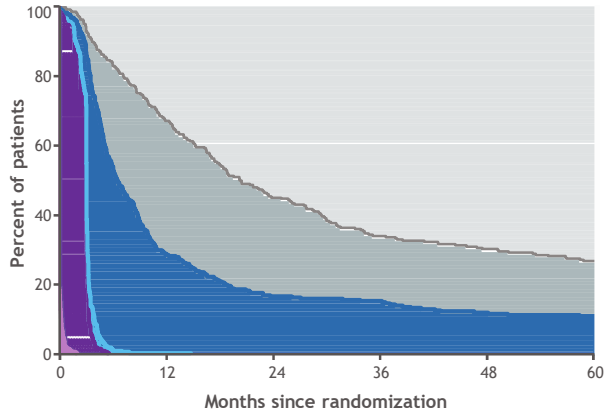
A. NIVO+IPI



B. NIVO



C. IPI



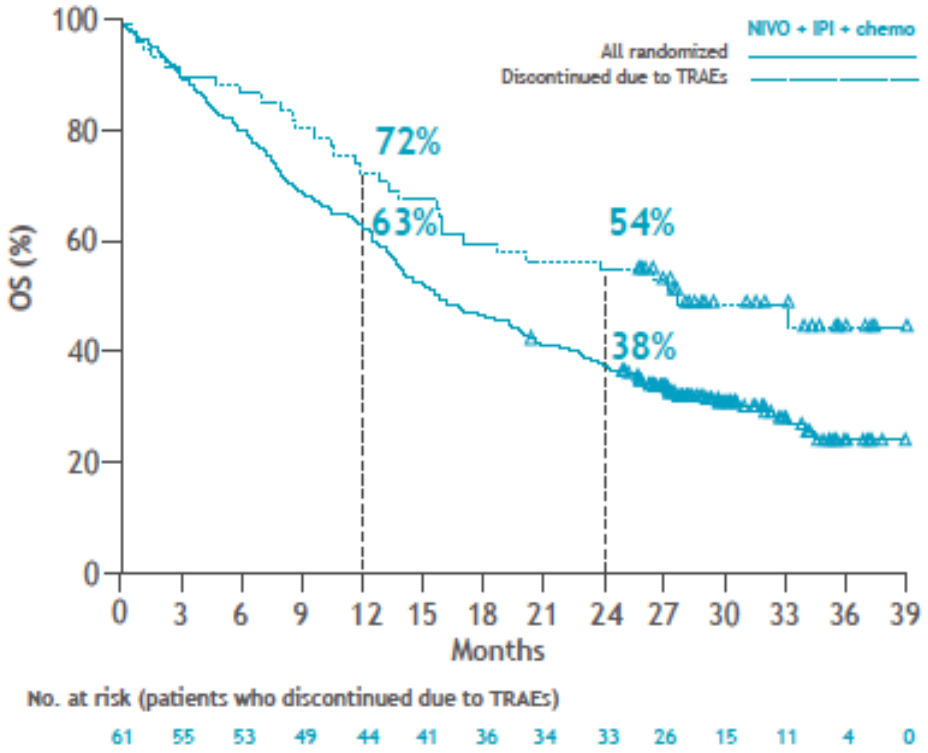
TFS→ SG dentro y fuera de tratamiento, con y sin toxicidad.

- Actualización 5 años TFS
- 33% tiempo sin tratamiento Nivolumab+Ipilimumab, 17% NIVO y 20% IPI
- Mayoría tiempo TFS transcurrió sin ≥ TRAEs grado 3 en todos los brazos
- NIVO+IPI continuó teniendo doble TFS que los pacientes tratados con NIVO (19,7 meses vs 9,9 meses)

	NIVO+IPI		NIVO			IPI		
Overall survival	38.6	64%	36.1	60%	2.5 (−1.1 to 6.2)	28.4	47%	10.2 (6.6 to 13.9)
Survival after subsequent therapy initiation	6.6	11%	9.3	15%	−2.7 (−4.9 to −0.4)	13.9	23%	−7.3 (−9.8 to −4.8)
TFS	19.7	33%	9.9	17%	9.8 (6.7 to 12.8)	11.9	20%	7.8 (4.6 to 11.0)
Without grade ≥ 3 TRAE	18.1	30%	9.0	15%	9.0 (6.1 to 12.0)	11.7	19%	6.4 (3.3 to 9.5)
With grade ≥ 3 TRAE	1.6	3%	0.9	2%	0.7 (−0.4 to 1.8)	0.2	< 1%	1.4 (0.5 to 2.3)
Time on protocol therapy	12.3	21%	16.9	28%	−4.6 (−7.3 to −1.8)	2.6	4%	9.8 (7.9 to 11.6)
Without grade ≥ 3 TRAE	11.8	20%	16.2	27%	−4.4 (−7.1 to −1.7)	2.5	4%	9.3 (7.5 to 11.1)
With grade ≥ 3 TRAE	0.5	1%	0.7	1%	−0.2 (−0.8 to 0.5)	0.1	< 1%	0.4 (0.2 to 0.6)

First-line nivolumab + ipilimumab + 2 cycles of chemotherapy versus chemotherapy alone (4 cycles) in patients with advanced non-small cell lung cancer: **2-year update from CheckMate 9LA**

Efficacy in patients who discontinued NIVO + IPI + chemo due to TRAEs[a]



Patients who discontinued all components of NIVO + IPI + chemo due to TRAEs

	NIVO + IPI + chemo (n = 61)
Median OS,[b] mo	27.5
2-year OS rate, %	54
ORR, n (%)	31 (51)
Median DOR after discontinuation,[c] mo	14.5
Ongoing response for ≥ 1 year after discontinuation,[c] %	56

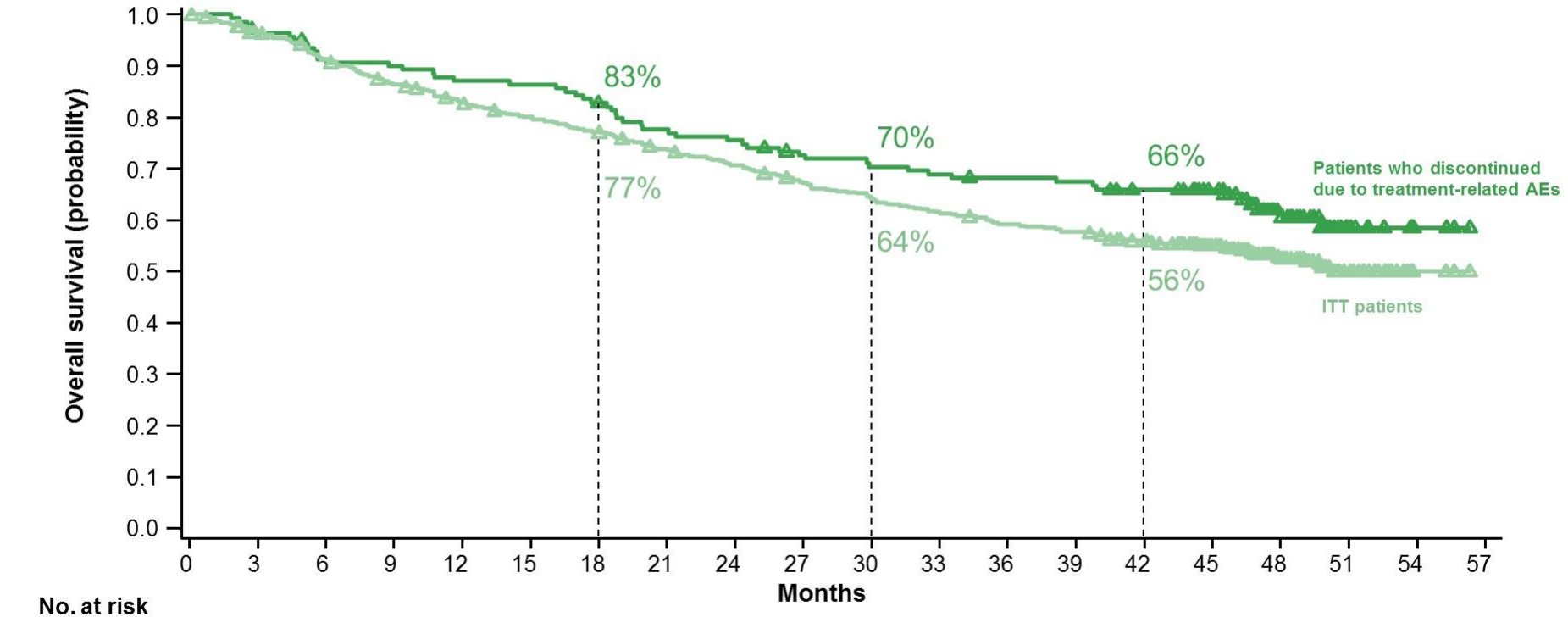
Among patients who discontinued all components of NIVO + IPI + chemo due to TRAEs:

- Median (range) number of doses was 7 (1–33) for NIVO and 3 (1–17) for IPI
- Median (range) duration of treatment was 4.4 (0–23.3) months

Reck M, *et al.* ASCO 2021, #9000

OS in Patients Who Discontinued Due to Treatment-Related AEs

Post hoc analyses in the NIVO+IPI arm



No. at risk																			
Pts who discontinued	141	135	127	125	121	120	115	107	104	98	95	93	91	90	85	74	46	13	3	0
ITT Pts	550	523	493	465	444	426	411	390	372	353	337	323	309	302	286	241	135	49	3	0

Tannir N, *et al.* 2020 Genitourinary Cancers Symposium

Paciente Nº 7

Varón de 68 años
Osteoartritis
Agosto-19→ Adenocarcinoma células claras riñón derecho estadio IV

Ipilimumab 1 mg/Kg
+
Nivolumab 3 mg/Kg/ 3 semanas

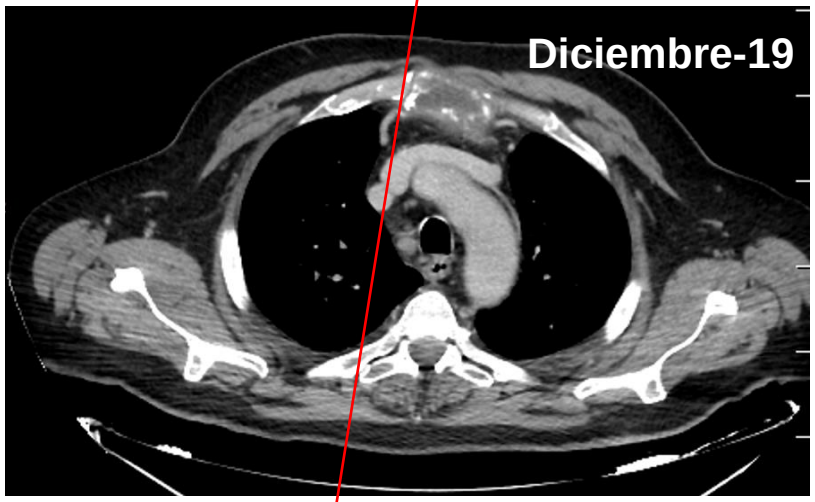
Tras 3 ciclos…

- Toxicidad hepática G4
- Artralgias refractarias a esteroides→ inmunosupresores

Suspensión definitiva

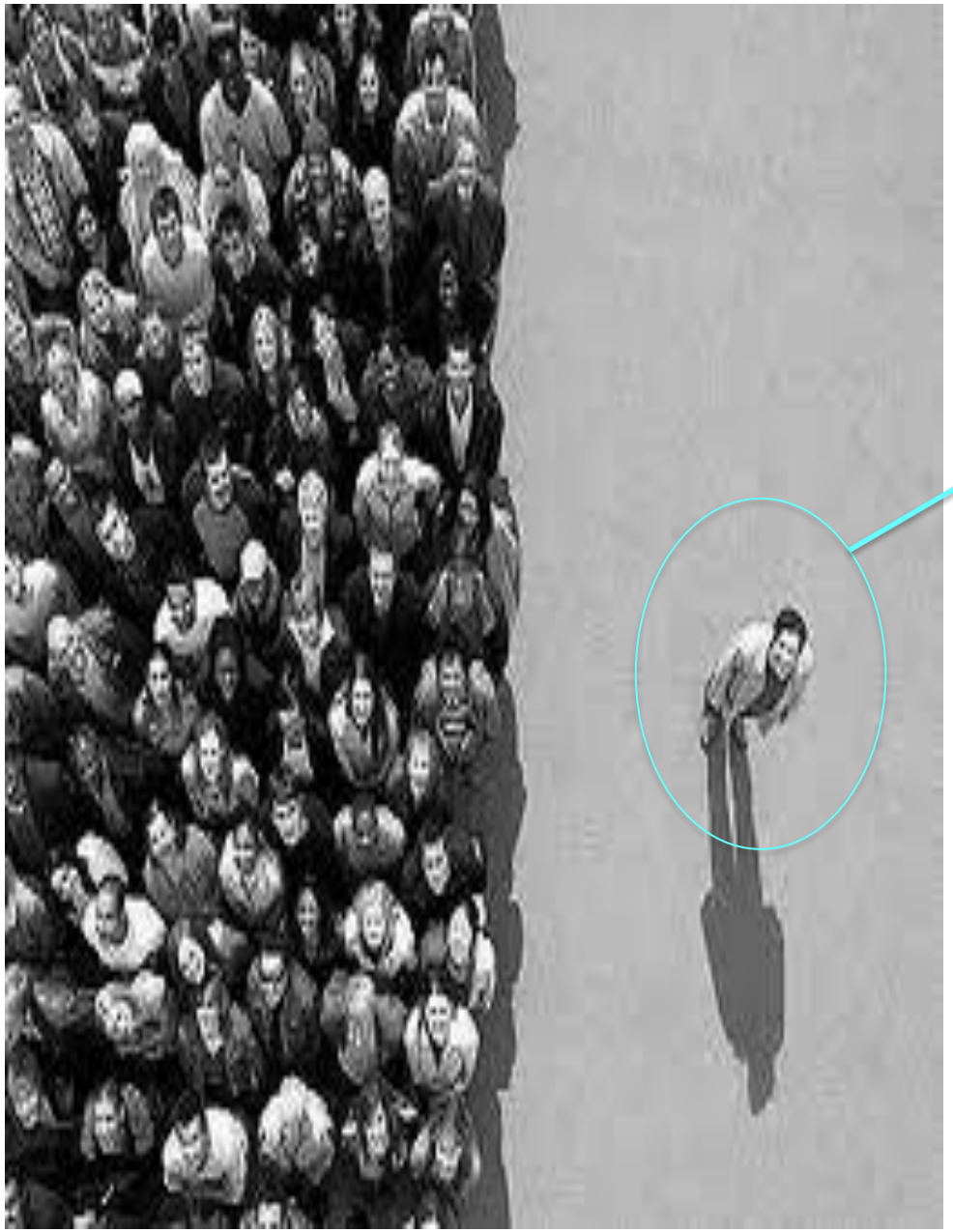
Vivo, sin enfermedad

Nefrectomía (Agosto-20)→
Necrosis, no tumor viable



¿Y qué nos queda?

- Selección pacientes



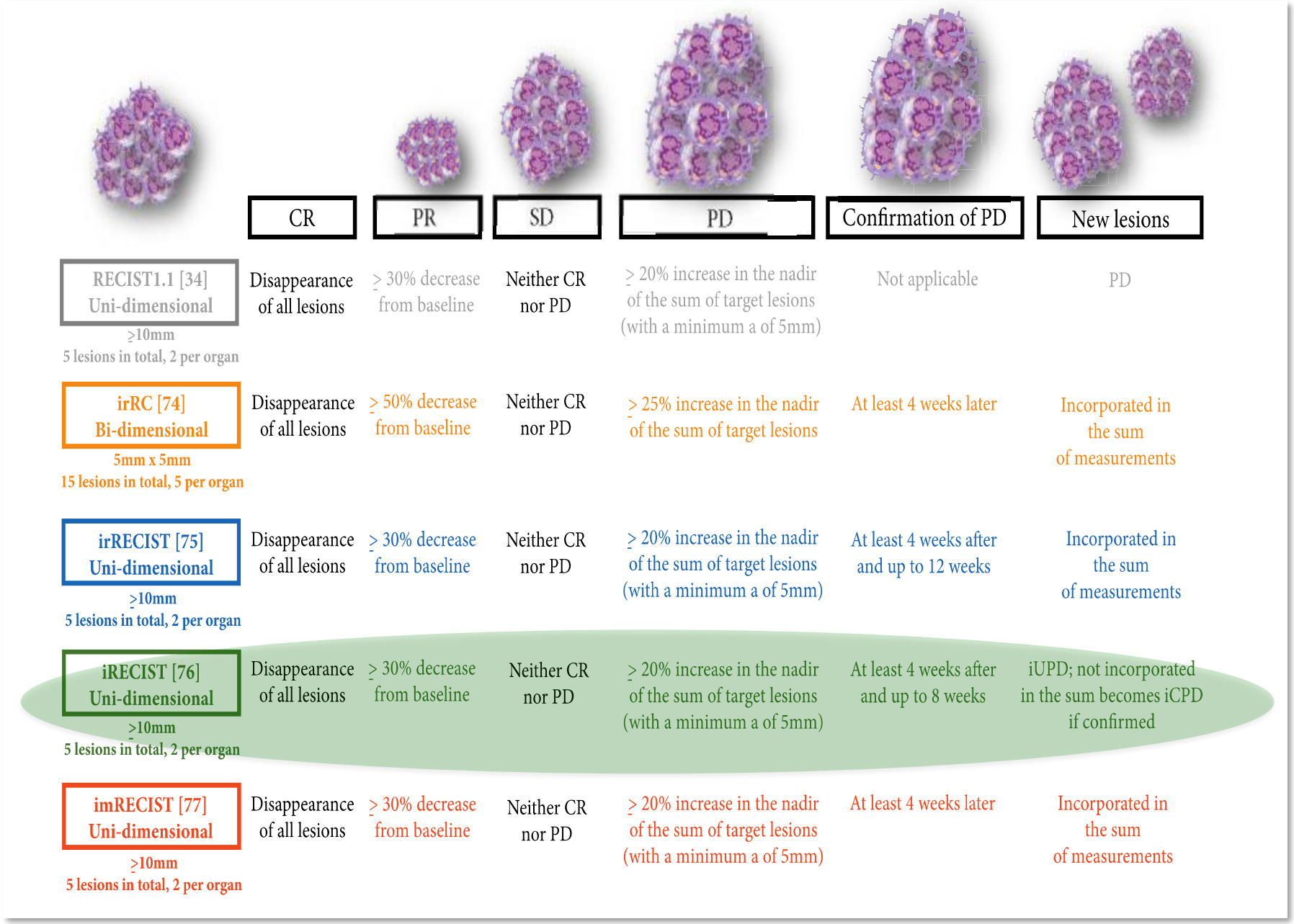
Adecuada selección pacientes

Necesidad perentoria desarrollo biomarcadores

“A cada paciente lo que necesite”

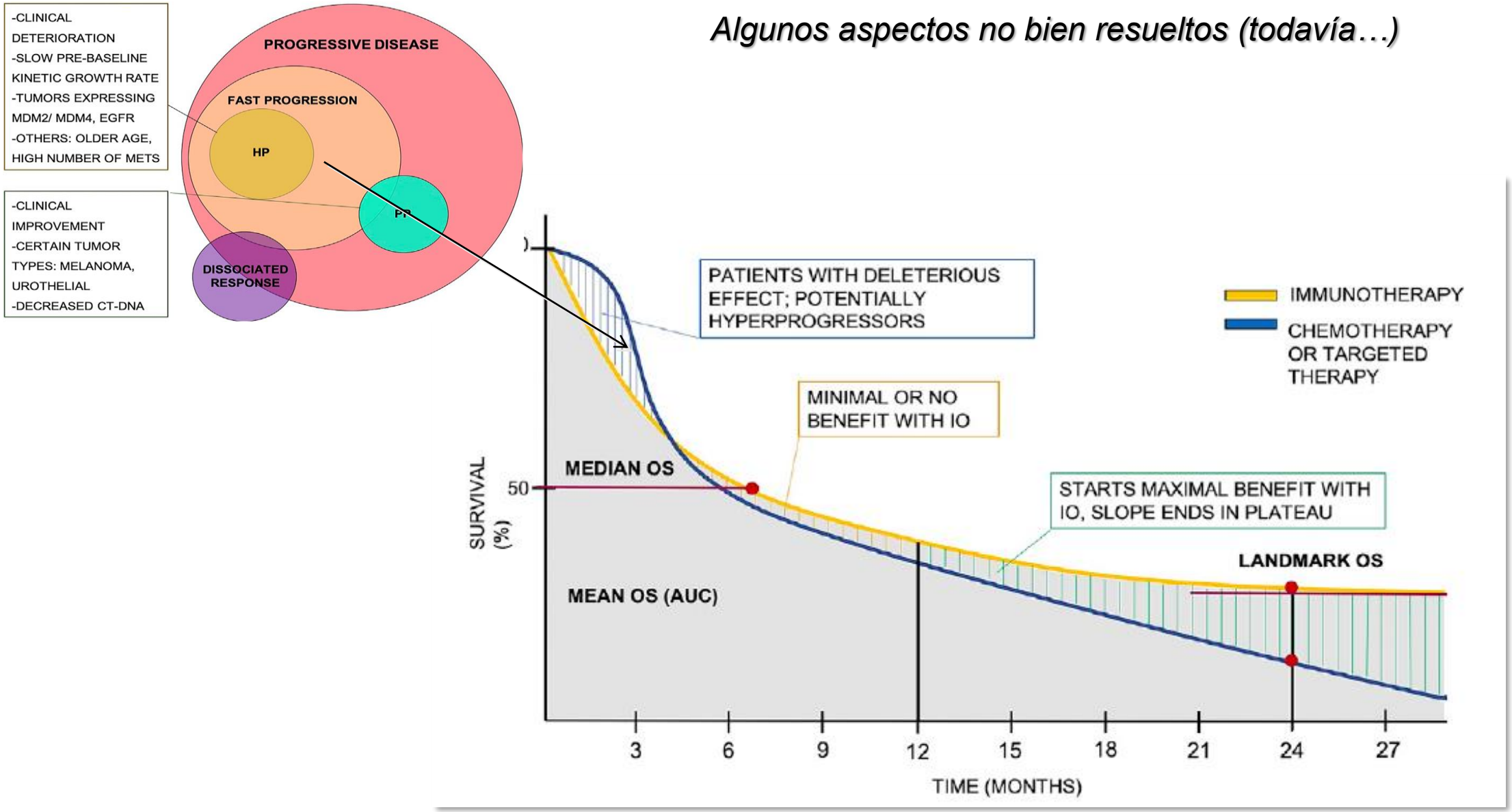
¿Y qué nos queda?

- Selección pacientes
- Optimizar medición eficacia



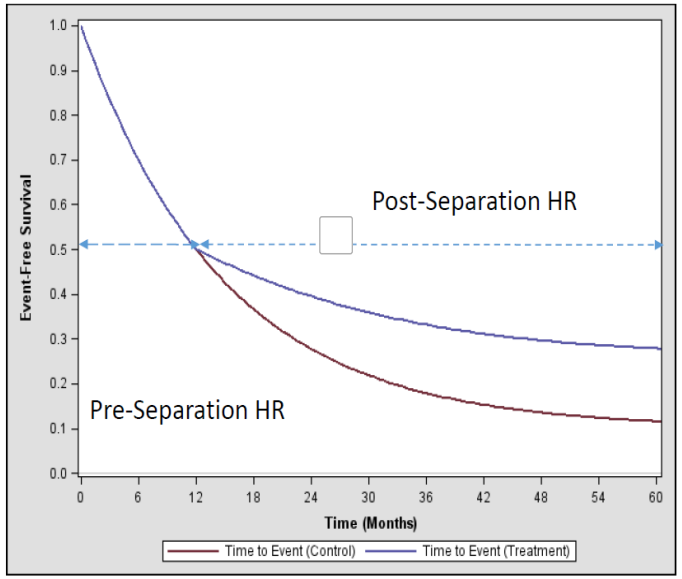
Borcoman E, *et al.* Annals of Oncology 2019

Algunos aspectos no bien resueltos (todavía…)



Calvo E, *et al.* Cell 2020

¿Deberíamos redefinir la estadística?



Chen *BMC Medical Research Methodology* (2016) 16:12
DOI 10.1186/s12874-016-0117-3

BMC Medical Research Methodology

RESEARCH ARTICLE Open Access

Predicting analysis times in randomized clinical trials with cancer immunotherapy

Tai-Tsang Chen[1,2]

Chen *Journal for ImmunoTherapy of Cancer* 2013, 1:18
http://www.immunotherapyofcancer.org/content/1/1/18

Journal for ImmunoTherapy of Cancer

RESEARCH ARTICLE Open Access

Statistical issues and challenges in immuno-oncology

Tai-Tsang Chen[1,2]

¿Y qué nos queda?

- Selección pacientes
- Optimizar medición eficacia
- Mejor conocimiento toxicidad y su manejo *(y su dosificación)*

Seguridad

CheckMate 067 6.5 y

Safety summary

- No new safety signals were observed
- No additional treatment-related deaths were reported since the 36-month analysis

	NIVO + IPI (n = 313)		NIVO (n = 313)		IPI (n = 311)	
	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4
Treatment-related AE, %	96	59	87	24	86	28
Treatment-related AE leading to discontinuation, %	42	31	14	8	15	13
Treatment-related death,[a] n (%)	2 (1)		1 (< 1)		1 (< 1)	

[a]Previously reported treatment-related deaths were cardiomyopathy and liver necrosis for NIVO + IPI (n = 1 each; both occurred > 100 days after last treatment), neutropenia for NIVO (n = 1), and colonic perforation for IPI (n = 1).
AE, adverse event.

No más toxicidad ni muertes tóxicas relacionadas con el tratamiento…

Time to dissect the autoimmune etiology of cancer antibody immunotherapy

irAE	Potentially life-threatening?	Autoimmunity or inflammation?	Mechanistic evidence	HLA association?	irAE treatment	Response to therapy?
Predominantly CTLA-4 blockade						
Colitis (5)	Yes	Unclear	Unknown	Yes	High-dose steroids; infliximab for steroid-refractory patients	Yes
IBD (89, 90)	Rare	Unclear	Genetic evidence implicates barrier integrity, pathogen detection, and autophagy	No	Steroids, immune modulators, anti–TNF-α antibodies, integrin inhibitors, anti–IL-23 antibodies	Yes
Hypophysitis (23, 109)	Yes, if misdiagnosed	Autoimmune	Normal pituitary cells express ectopic CTLA-4; activation of the classic complement pathway	Yes	High-dose steroids; IV. replacement therapy; if severe, ICI discontinuation	Yes
Fulminant T1D (73)	Yes, if misdiagnosed	Autoimmune	Unknown	Yes	Insulin therapy	Yes
Predominantly PD-1/PD-L1 blockade						
T1D (56, 67, 74, 75)	Yes, if in DKA	Autoimmune	PD-L1 upregulation on islet cells that may resist T cell–mediated apoptosis	Strong association	Insulin therapy	Yes
T2D (69)	No	Unknown	Unknown	No	Dietary control; oral hypoglycemic agents	Yes
Pancreatitis (80)	Yes, if severe	Immune-mediated	Unknown	Unknown	Usually medical management	Yes
Thyroiditis (47, 48)	Yes, if untreated	Autoimmune	Strong association with thyroid Ab	No	Symptomatic, frequently lifelong thyroid hormone replacement	Yes
Graves' disease (59–61)	Yes, if untreated	Autoimmune	TSH receptor Ab	No	Antithyroid therapy, beta blockers, RAI, or surgery if necessary	Yes
Autoimmune polyendocrine syndrome type 2 (77)	Yes, if untreated	Autoimmune	Unknown	Insufficient evidence	Hormone replacement based on endocrine disorder	Yes
Primary adrenal insufficiency (adrenalitis) (63)	Yes	Autoimmune	Unknown	No	Hydrocortisone replacement therapy; fludrocortisone if necessary	Excellent response
ICI-induced immune arthritis (48)	No	Autoimmune	Unknown	Unknown	NSAIDs, DMARDs, biologic agents, steroids	Yes
Myocarditis (118)	Yes	Autoimmune	Unknown	No	High-dose steroids, IVIg, plasmapheresis	High mortality

DMARD, disease-modifying antirheumatic drug; IVIg, intravenous immunoglobulin; RAI, radioactive iodine therapy; TSH, thyroid-stimulating hormone.

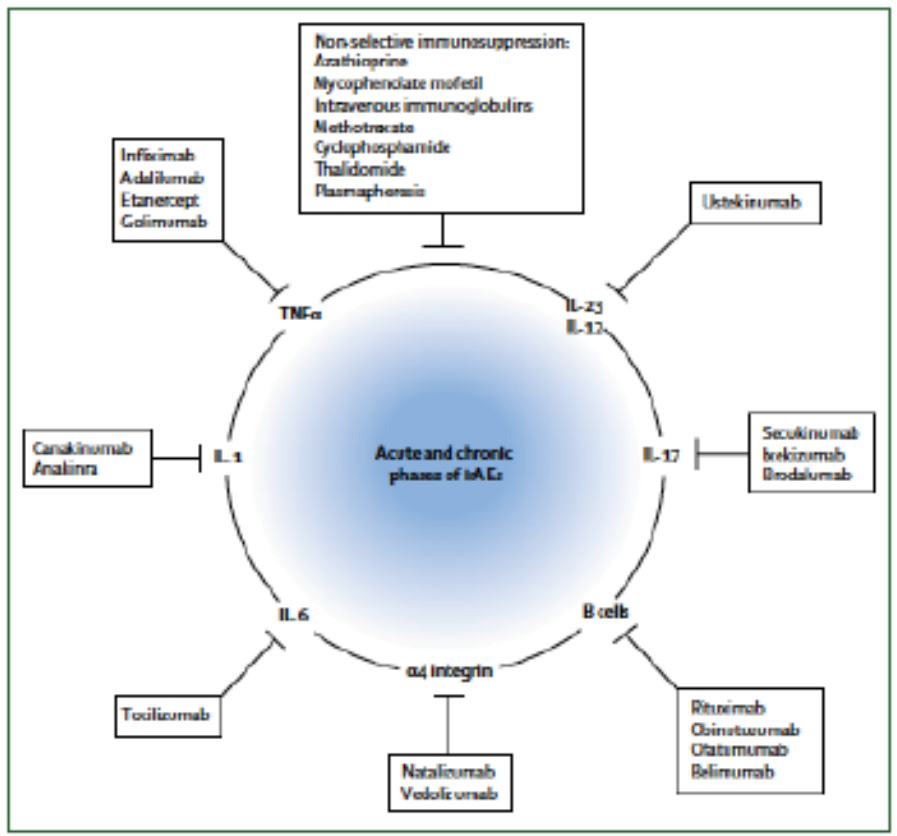
Dougan M, *et al.* J Clin Invest 2020

New therapeutic perspectives to manage refractory immune checkpoint-related toxicities

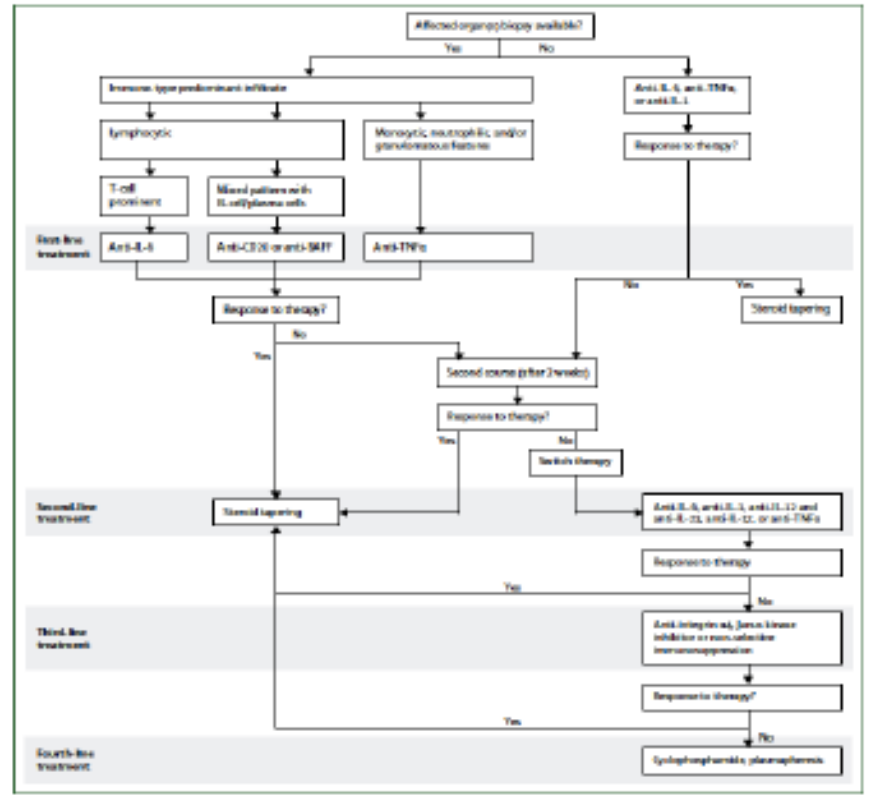
Filipe Martins, Gerasimos P Sykiotis, Michel Maillard, Montserrat Fraga, Camillo Ribi, Thierry Kuntzer, Olivier Michielin, Solange Peters, Georges Coukos, Francois Spertini, John A Thompson, Michel Obeid

Lancet Oncol 2019

Diferentes mecanismos desencadenantes de la toxicidad inmune



Tipo infiltrado inmune guia el tratamiento



Inhibición fase aguda reacción inflamatoria
Limita dependencia corticoides
Inhibición progresión tumoral→ IL1 e IL6

¿Y qué nos queda?

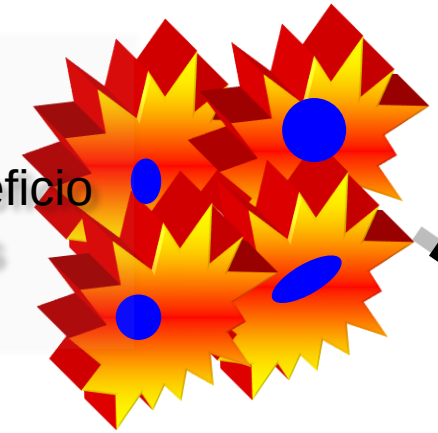
- Selección pacientes
- Optimizar medición eficacia
- Mejor conocimiento toxicidad y su manejo
- Traslado beneficio estadios precoces

¿Qué te sugiere esto?

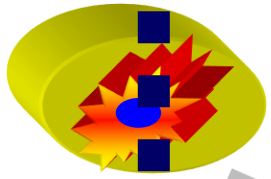
¿Podemos trasladar este beneficio de la inmunoterapia a estadios tempranos?

Tres objetivos

1. Tratar cáncer antes que sea metastásico
2. ↓ mortalidad específica
3. ↑ posibilidades curación



Tumor

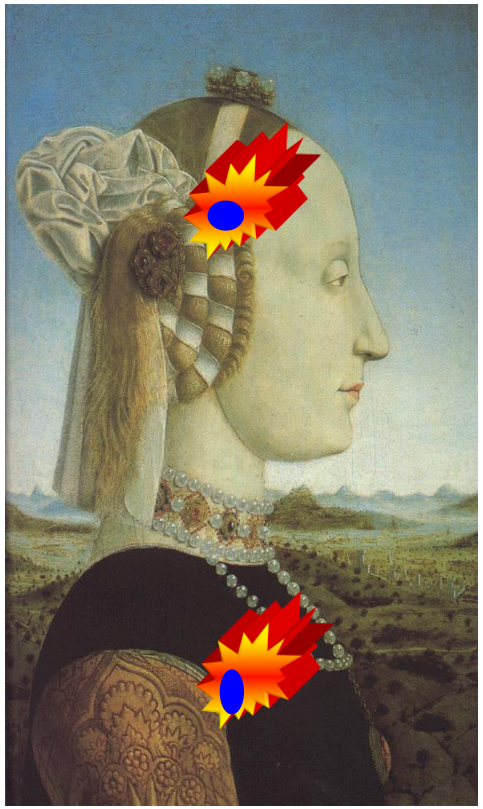


Ganglios

Enfermedad Diseminada

Medicamentos

Curación “más” probable



Metástasis

Enfermedad Locorregional

Cirugía/Radioterapia + Medicamentos

Más posibilidades de curación

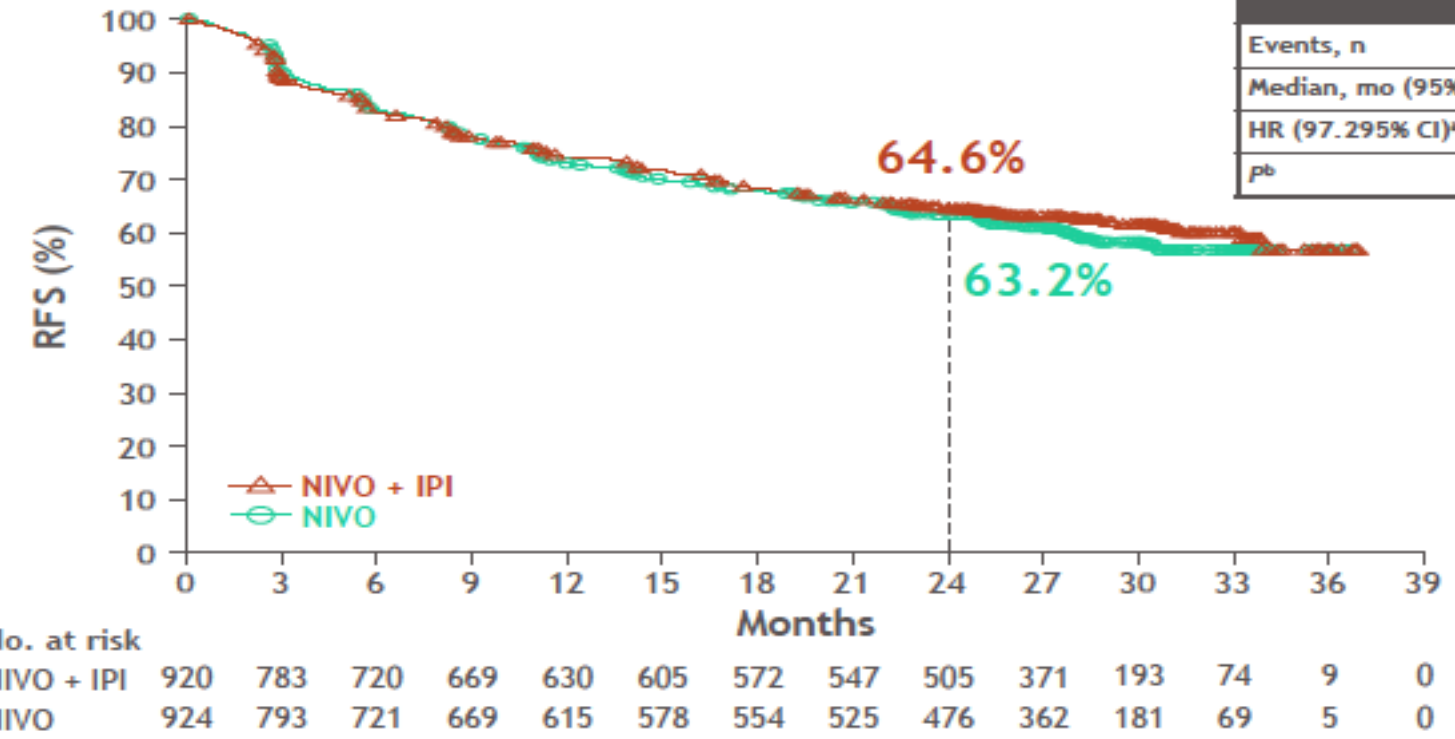
Adyuvancia

CheckMate 915→ Nivolumab + Ipilimumab vs Nivolumab estadios IIIB-IIID y IV resecados melanoma

¿Qué ha pasado?

Dual primary endpoint: RFS in ITT population

AACR American Association for Cancer Research
FINDING CURES TOGETHER



	NIVO + IPI (n = 920)	NIVO (n = 924)
Events, n	327	347
Median, mo (95% CI)	NR	NR
HR (97.295% CI)[a]	0.92 (0.77-1.09)	
P[b]	0.269	

Long GV, *et al.* AACR 2021

Neoadyuvancia

OPACIN-NEO

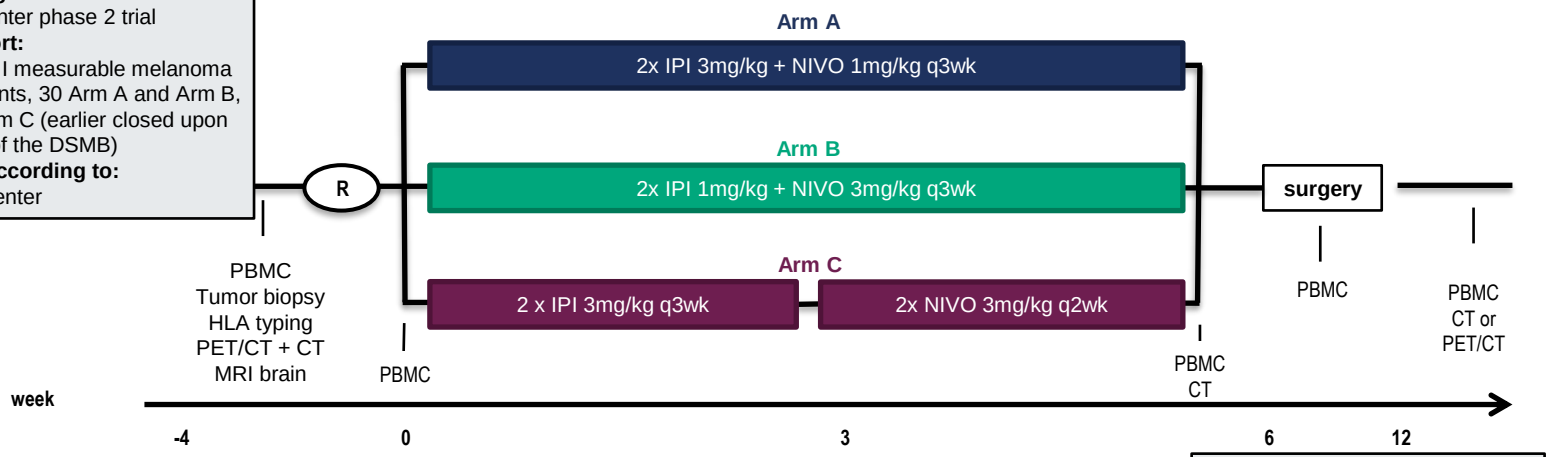
Rozeman EA, *et al.* ESMO 2018

86 pacientes
Brazo A→ 30 pacientes
Brazo B→ 30 pacientes
Brazo C→ 26 pacientes

Study design:
- Multi-center phase 2 trial

Study cohort:
- Stage IIII measurable melanoma
- 86 patients, 30 Arm A and Arm B, 26 in Arm C (earlier closed upon advice of the DSMB)

Stratified according to:
- Study center

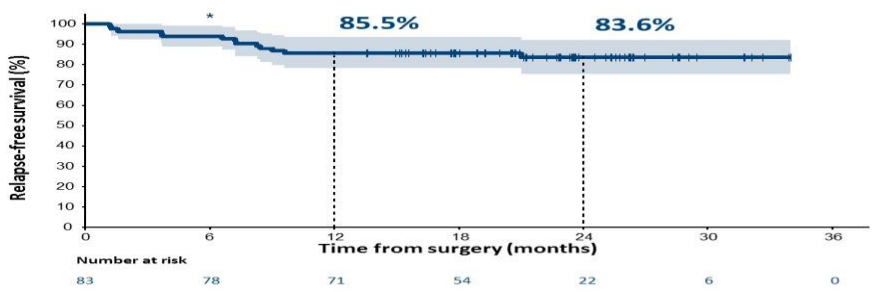


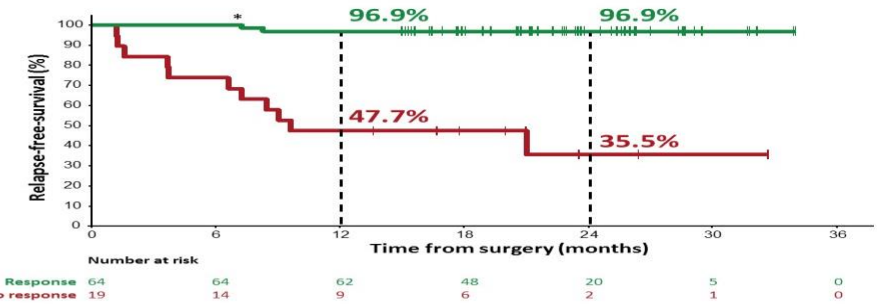
Dosing in Arm A, B, and C based on data from Blank, Rozeman, et al., Nat Med 2018, Long, et al., Lancet Oncol 2017, Meerveld-Eggink, Rozeman, et al., Ann Oncol, 2017

Data lock: 28 Sep 2018
Median follow-up 8.3 months

Promising RFS after 2 years follow-up and pathologic response predicts outcome

- **OpACIN-neo:** After a median follow-up of 24.6 months, only 1/64 (2%) patients with pathologic response has relapsed





(near-)pCR = (near) pathologic complete response, pPR = pathologic partial response, pNR = pathologic non-response

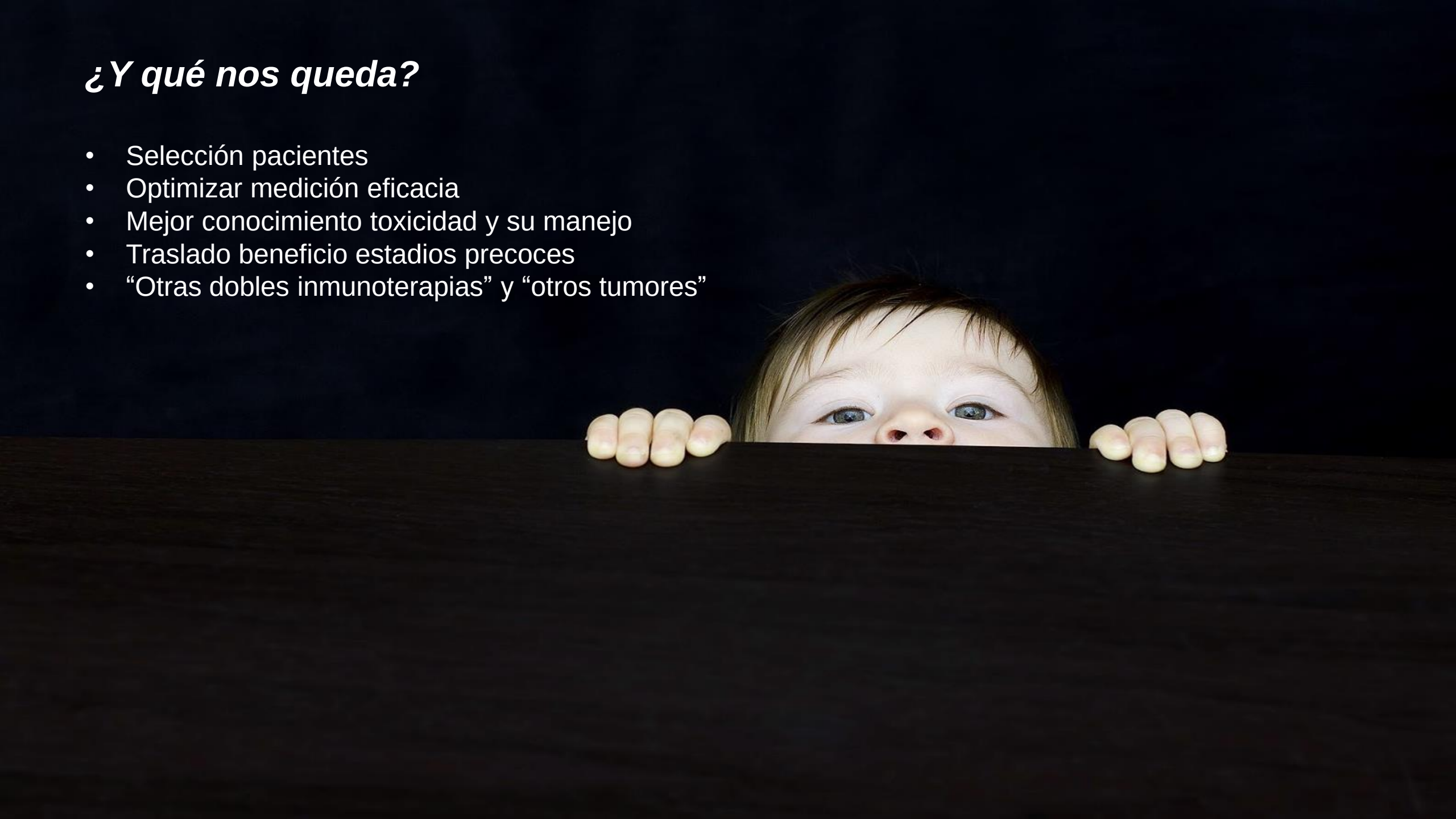
Rozeman et al., abstract 10015, ASCO 2020

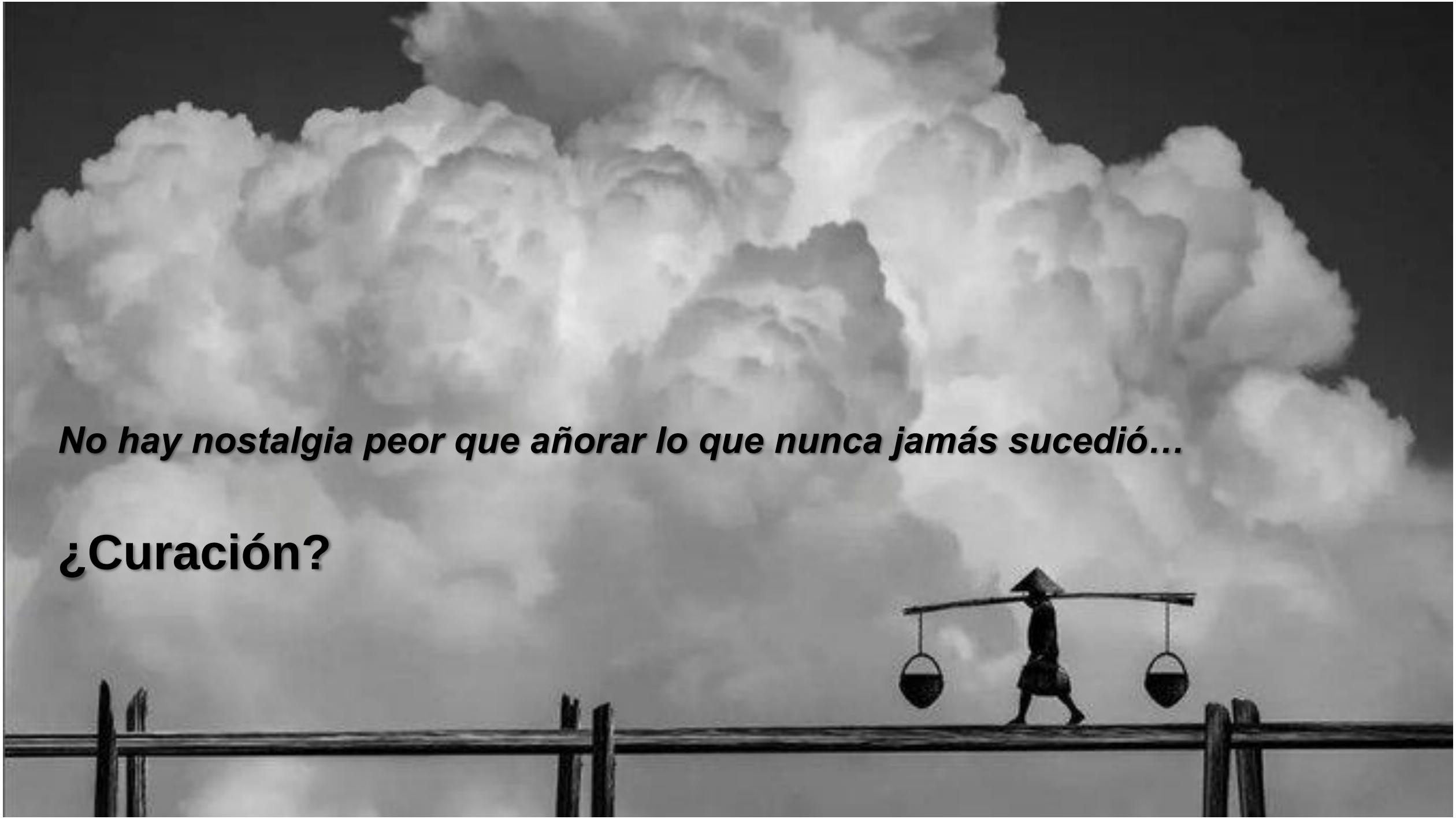
PRESENTED AT: 2020 ASCO ANNUAL MEETING #ASCO20 Slides are the property of the author, permission required for reuse. PRESENTED BY: Prof. dr. C.U. Blank

* patient died due to toxicity without signs of melanoma relapse

¿Y qué nos queda?

- Selección pacientes
- Optimizar medición eficacia
- Mejor conocimiento toxicidad y su manejo
- Traslado beneficio estadios precoces
- “Otras dobles inmunoterapias” y “otros tumores”




No hay nostalgia peor que añorar lo que nunca jamás sucedió…
¿Curación?

… tus pies sobre la tierra antes no hollada,
tus ojos frente a lo antes nunca visto…

Luis Cernuda, “Peregrino”

Gracias por vuestra atención