CONTROVERSIAS EN ONCOLOGÍA
ALMERÍA
Almería, 28 de noviembre de 2019
SAOM
Sociedad Andaluza de Oncología Medica

Inmunoterapia en CPNCP y Melanoma metastásico

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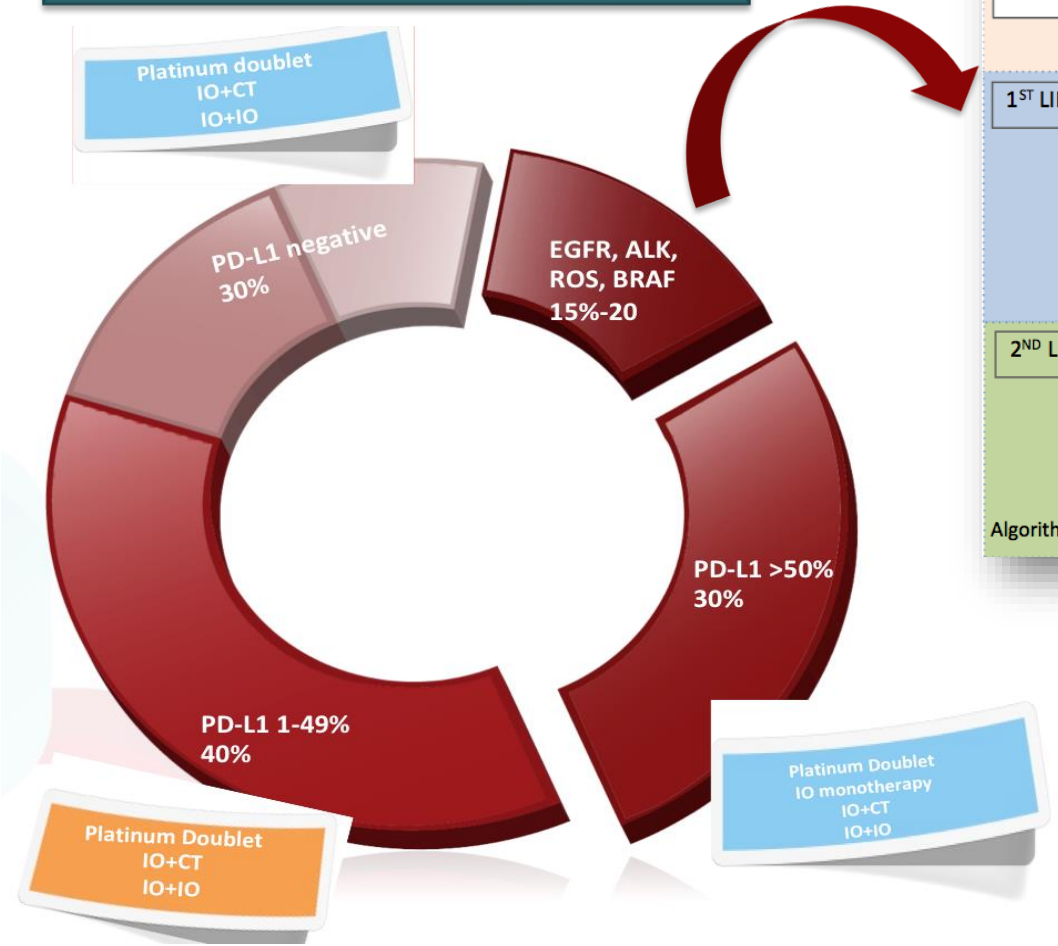
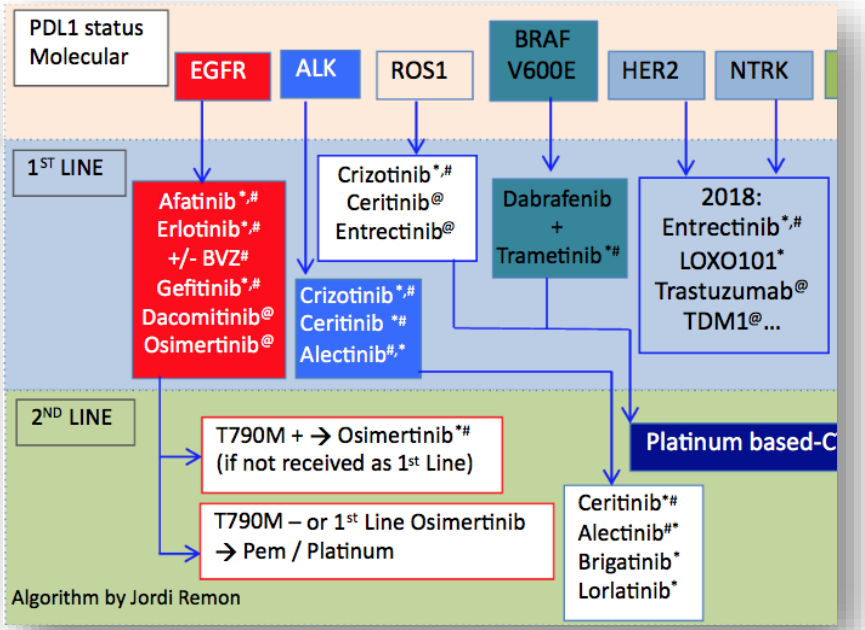
Almería Torrecárdenas Complejo Hospitalario

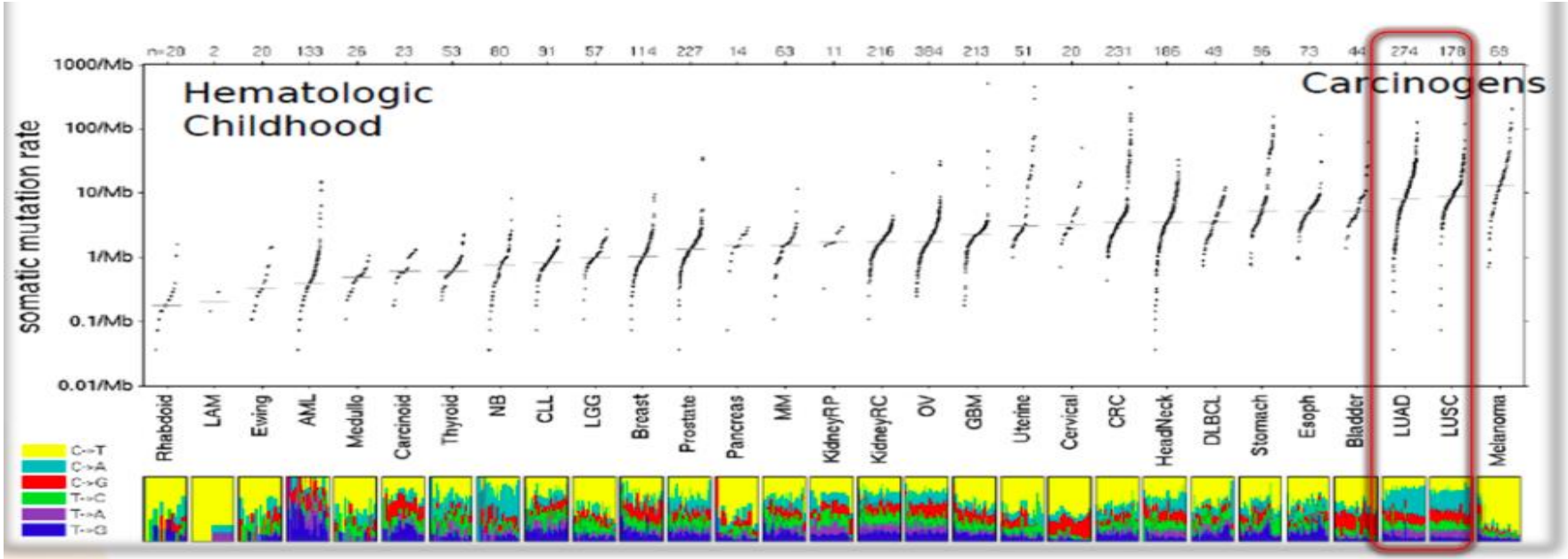
Inmunoterapia 1º línea CPNCP EIV

MOLECULAR ABNORMALITIES





Lung cancers have a very high rate of somatic mutations



Higher mutation rates have been observed in lung cancer tumors from smokers vs non-smokers

Alexandrov, et al. Nature 2013

Monoterapia con IO

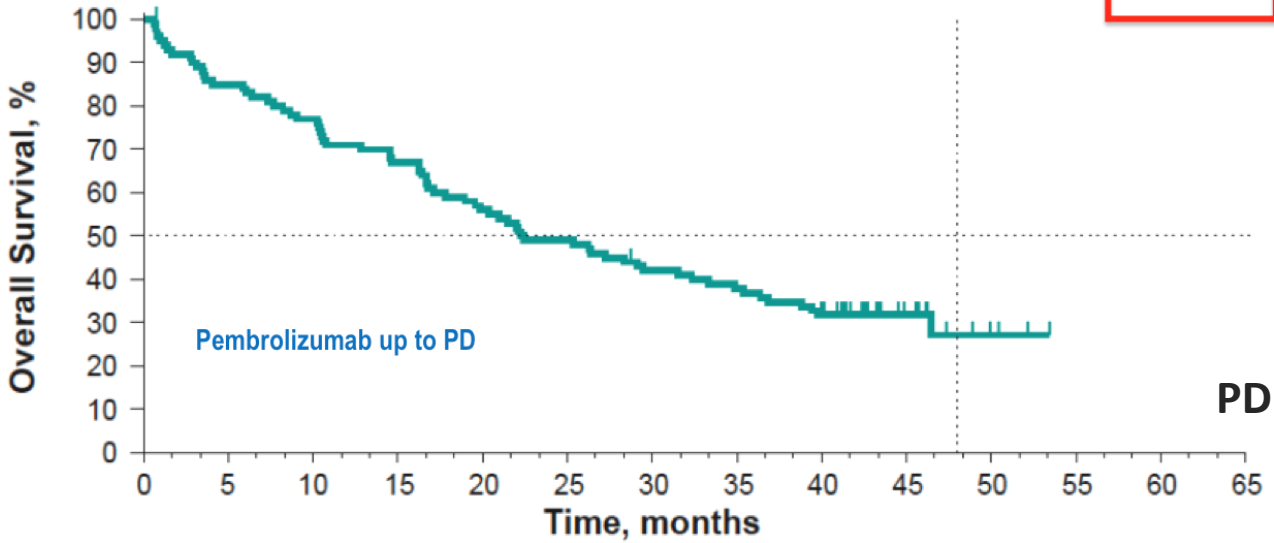
Pembrolizumab: Largos supervivientes en 1ª línea

4y OS phase I KEYNOTE 001 Trial

8th TNM IASLC Classification, 4-y OS M1c: ~4-5%

A. Treatment-naive cohort

	Events, n/N	Median, mo (95% CI)	24-mo Rate, %	36-mo Rate, %	48-mo Rate, %
Total	69/101	22.3 (17.1 to 32.3)	49.0	36.8	27.2



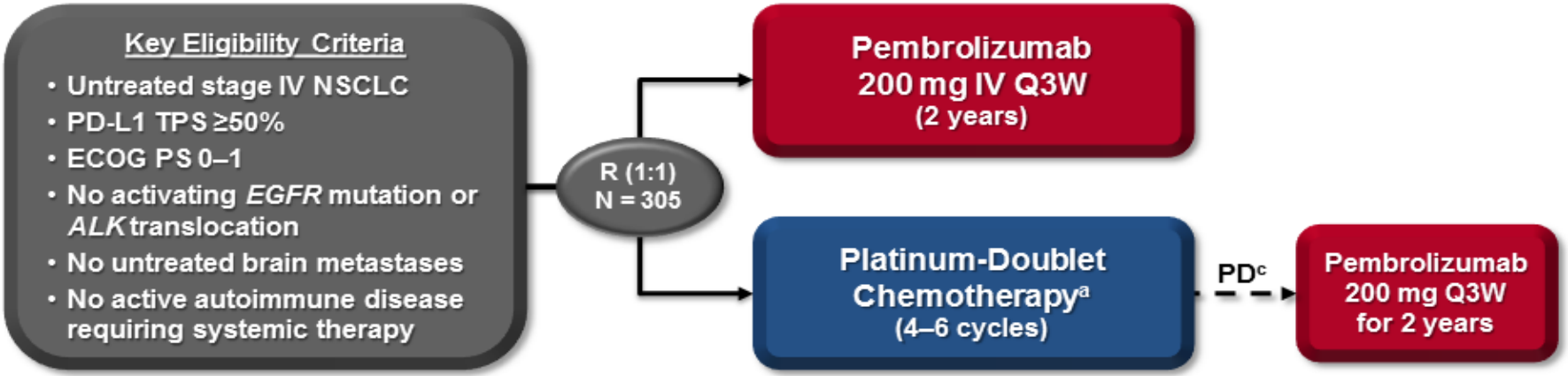
PDL-1>50%

Eberhardt – J Thorac Oncol 2015

Felip E– ASCO 2018

COPENHAGEN 2016 ESMO congress

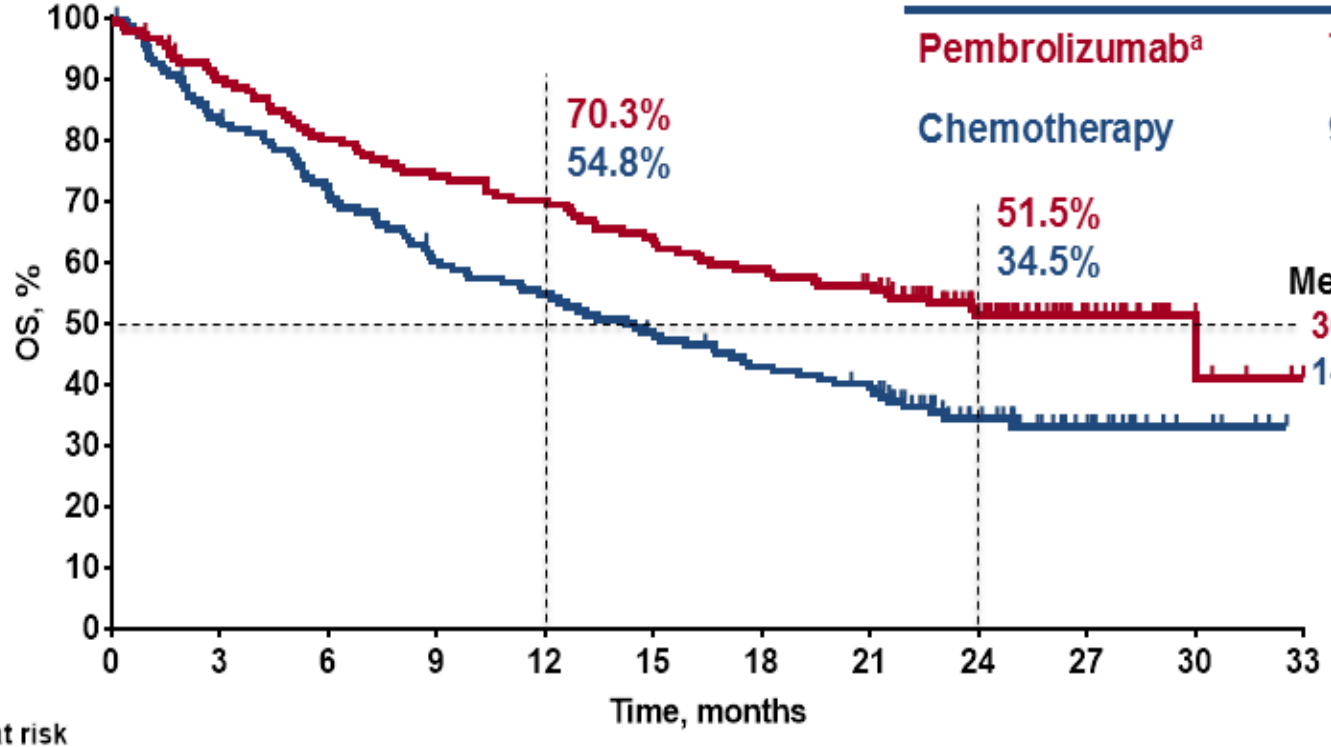
KEYNOTE-024: Pembrolizumab vs Platinum-Based Chemotherapy as First-Line Therapy for Advanced NSCLC With a PD-L1 TPS ≥50%



End Points

Primary:	PFS (RECIST v1.1, blinded independent central review)
Key secondary:	OS
Secondary:	ORR, safety
Exploratory:	DOR

Overall Survival: Updated Analysis



	Events, n	HR (95% CI)
Pembrolizumab[a]	73	0.63 (0.47–0.86)
Chemotherapy	96	*P* = 0.002[b]

Median (95% CI)

30.0 mo (18.3 mo–NR)

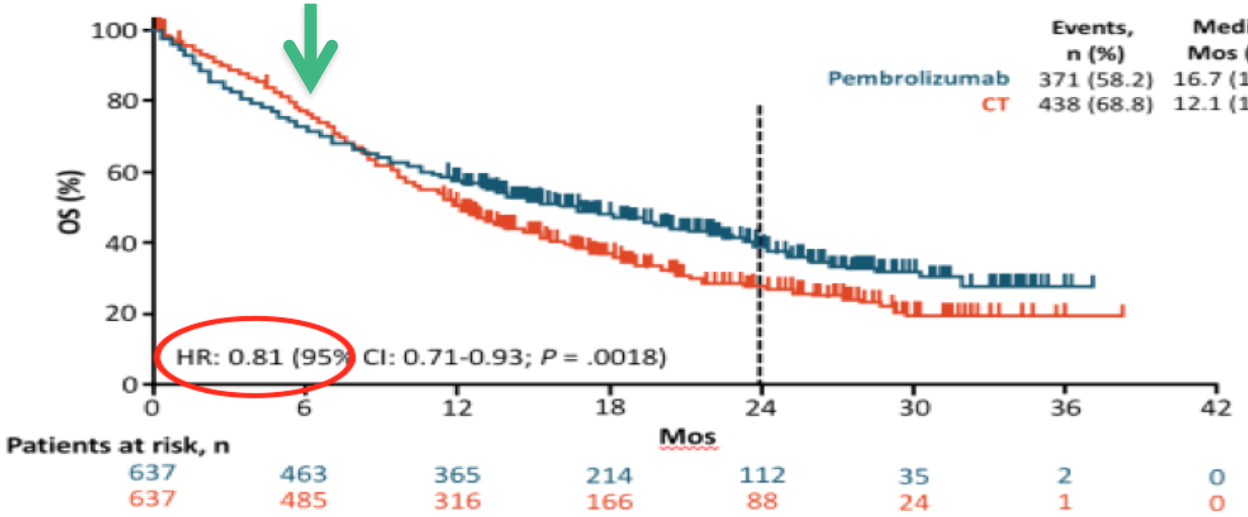
14.2 mo (9.8 mo–19.0 mo)

No. at risk

Pembro	154	136	121	112	106	96	89	83	52	22	5	0
Chemo	151	123	107	88	80	70	61	55	31	16	5	0

KEYNOTE-042
Pembrolizumab 1º LINEA PD-L1 POSITIVO

KEYNOTE-042: OS in PD-L1 TPS ≥ 1% Population (Primary Endpoint)



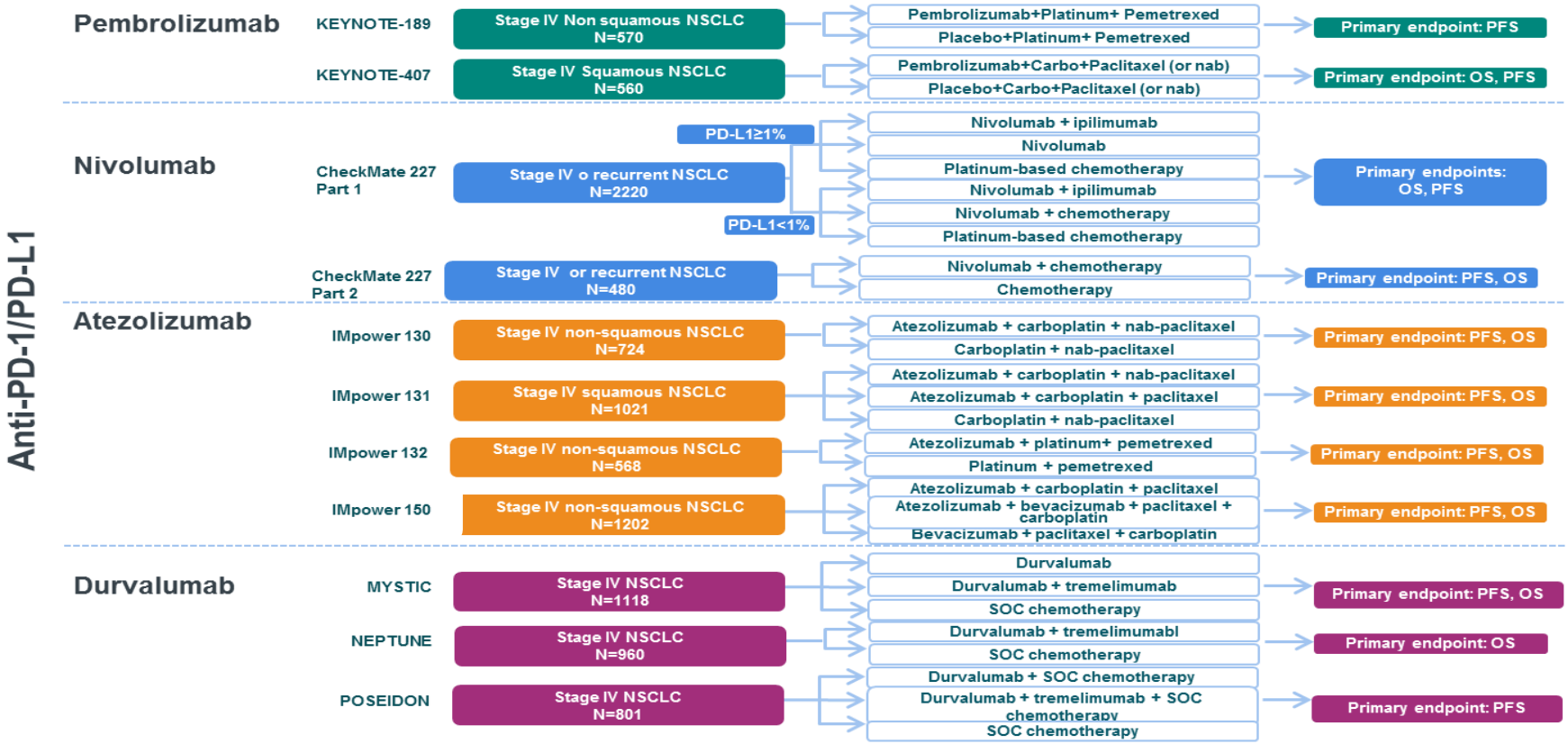
	Events, n (%)	Median OS, Mos (95% CI)	24-Mo OS, %
Pembrolizumab	371 (58.2)	16.7 (13.9-19.7)	39.3
CT	438 (68.8)	12.1 (11.3-13.3)	28.0

PD-L1 >1%

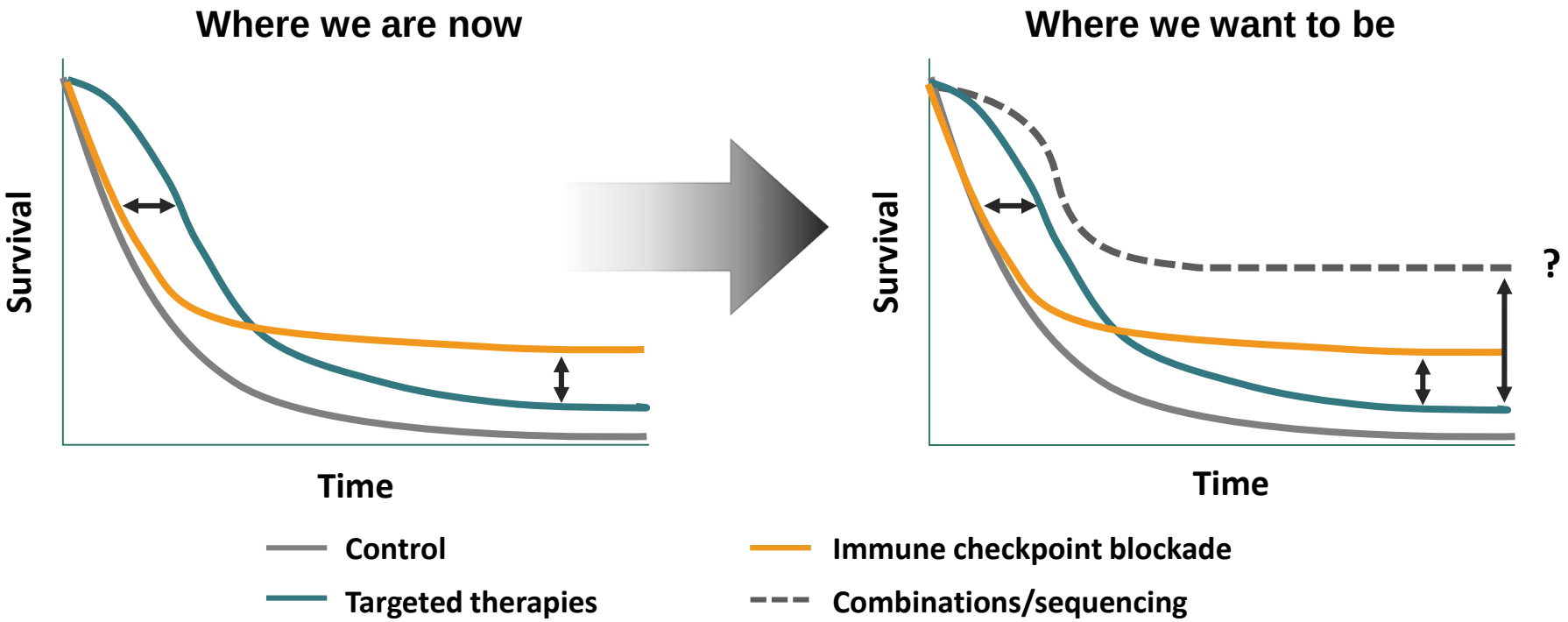
Lopes G, et al. ASCO 2018. Abstract LBA4.

Combinaciones QT + IO

Estudios fase 3 de combinaciones de Inmunoterapia en 1ª línea CPNCP EIV



Objetivos teóricos de la Inmunoterapia

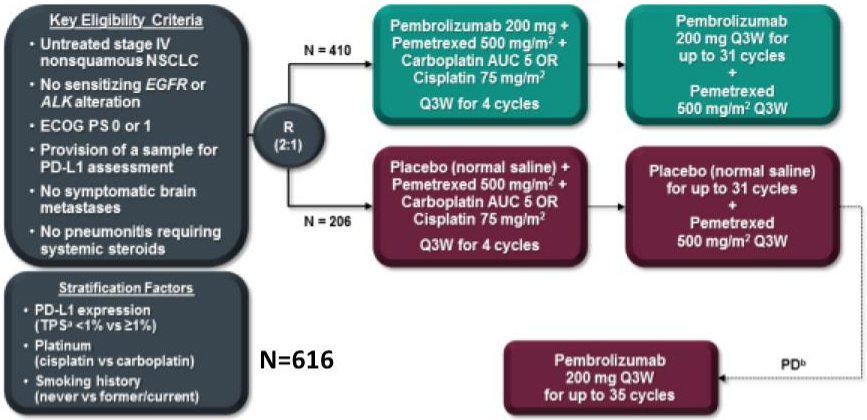


Adapted from Sharma P, Allison JP. *Cell*. 2015;161(2):205-214.

Histología no escamosa

Gandhi KN189
AACR 2018

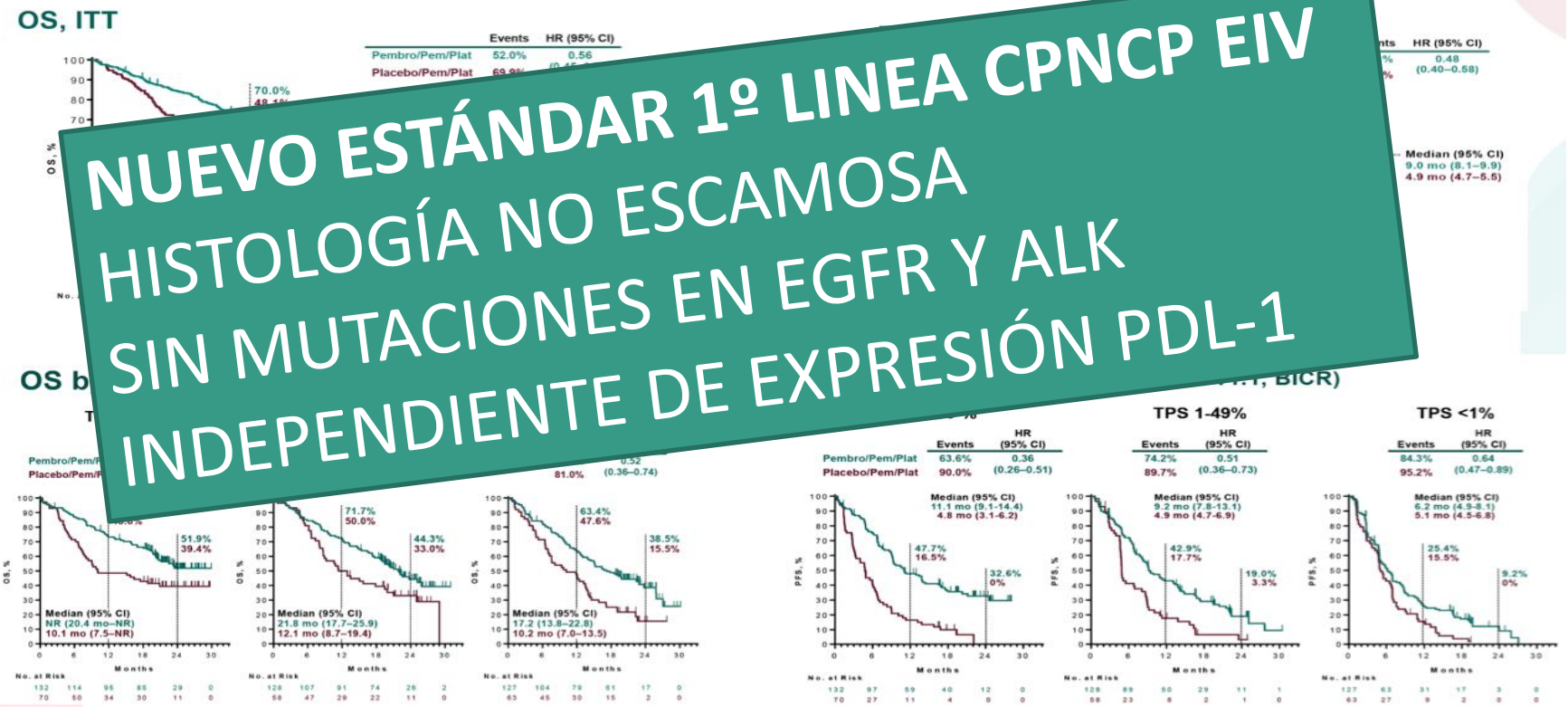
KEYNOTE-189 Study Design (NCT02578680)



[a]Percentage of tumor cells with membranous PD-L1 staining assessed using the PD-L1 IHC 22C3 pharmDx assay. [b]Patients could crossover during the induction or maintenance phases. To be eligible for crossover, PD must have been verified by blinded, independent central radiologic review and all safety criteria had to be met.

KEYNOTE-189

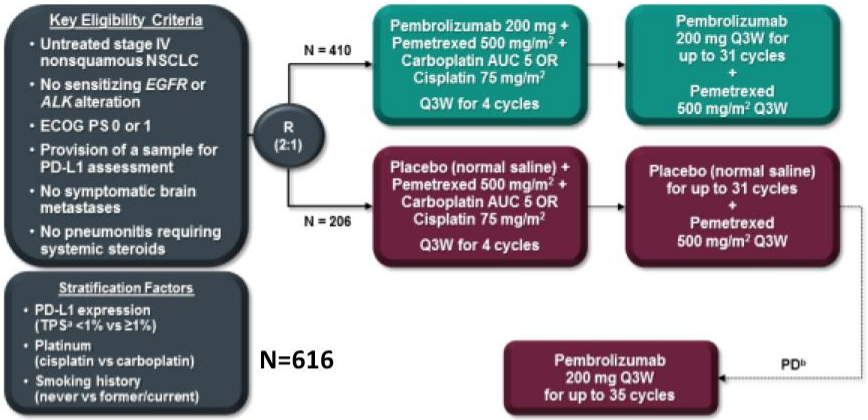
KN 189: Pembro+Platinum+Pem is superior to Platinum+Pem in non-SCC irrespective of PD-L1 expression



NUEVO ESTÁNDAR 1º LINEA CPNCP EIV
HISTOLOGÍA NO ESCAMOSA
SIN MUTACIONES EN EGFR Y ALK
INDEPENDIENTE DE EXPRESIÓN PDL-1

Gandhi KN189
AACR 2018

KEYNOTE-189 Study Design (NCT02578680)



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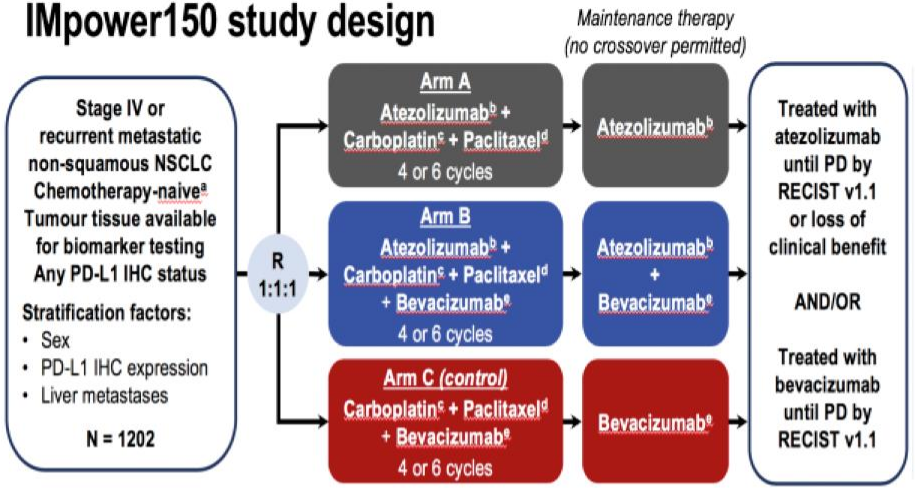
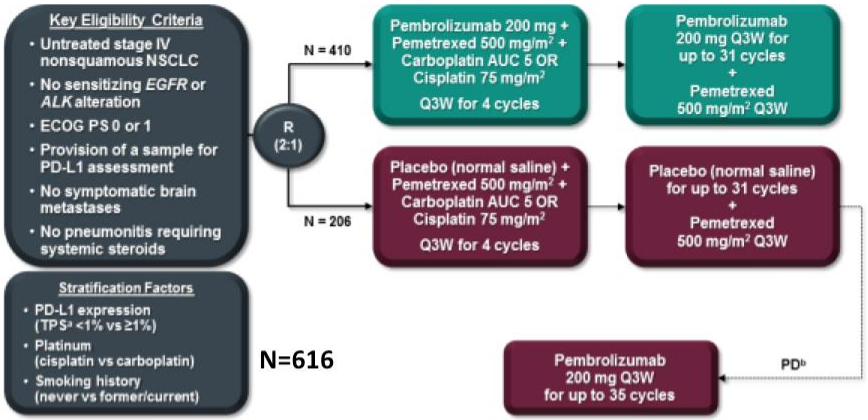
IMpower150 study design



Gandhi KN189
AACR 2018

KEYNOTE-189 Study Design (NCT02578680)



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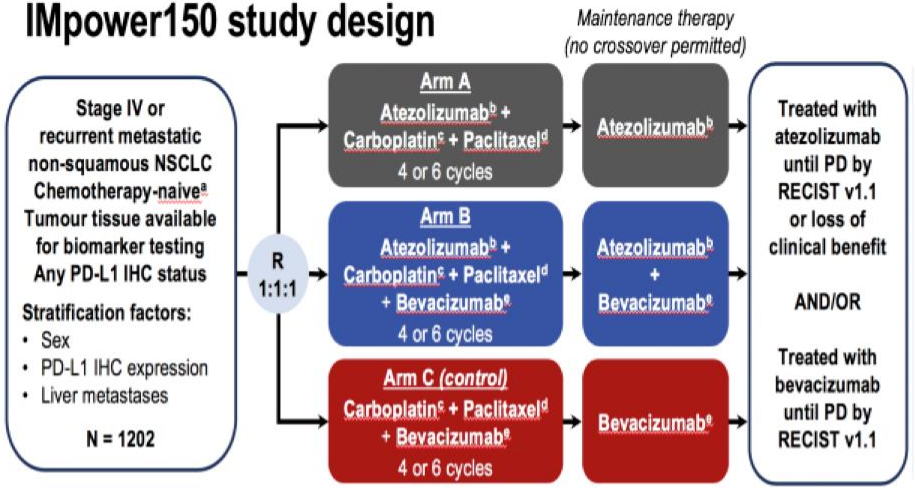
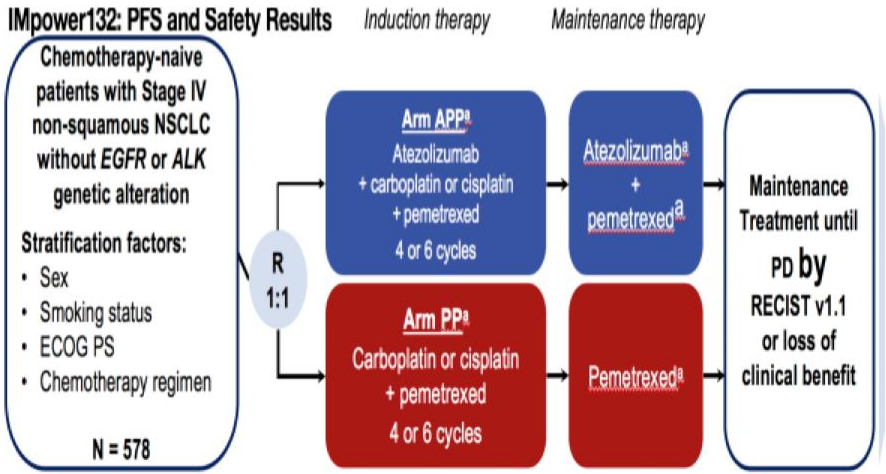
IMpower150 study design



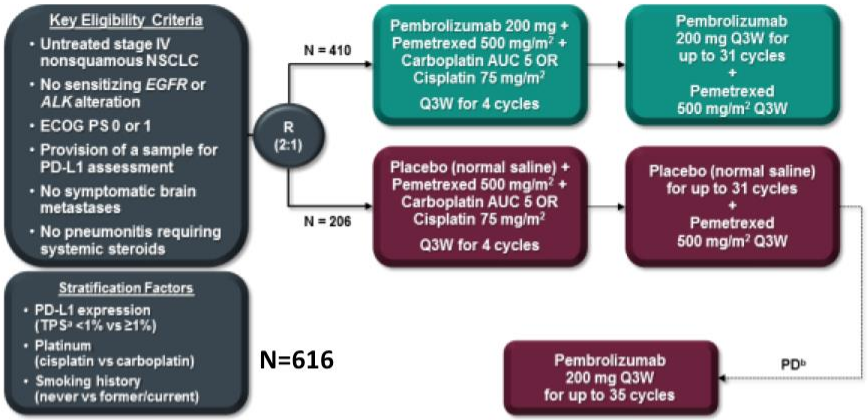
IMpower132: PFS and Safety Results



Gandhi KN189 AACR 18. Reck M. IMpower150. ESMO2017. Vassiliki A. Papadimitrakopoulou. WCLC2018

Gandhi KN189
AACR 2018

KEYNOTE-189 Study Design (NCT02578680)



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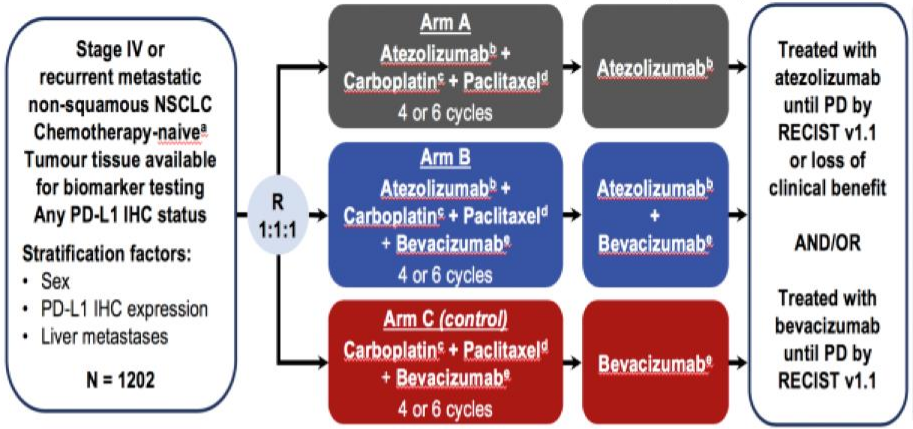
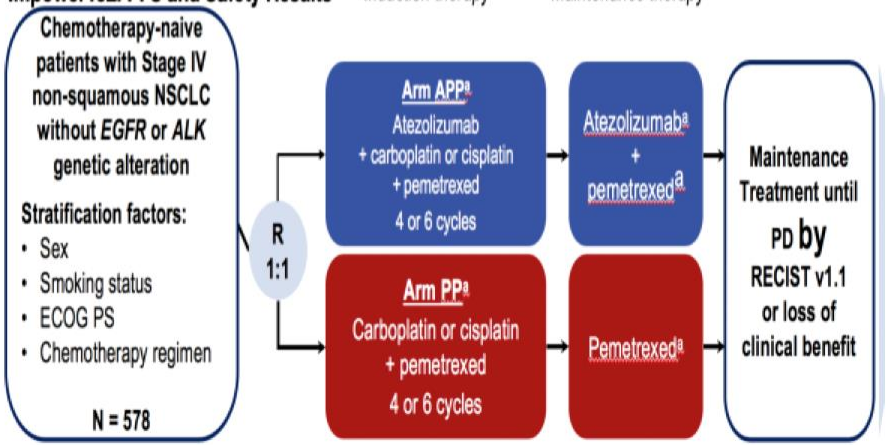
IMpower150 study design

Maintenance therapy (no crossover permitted)

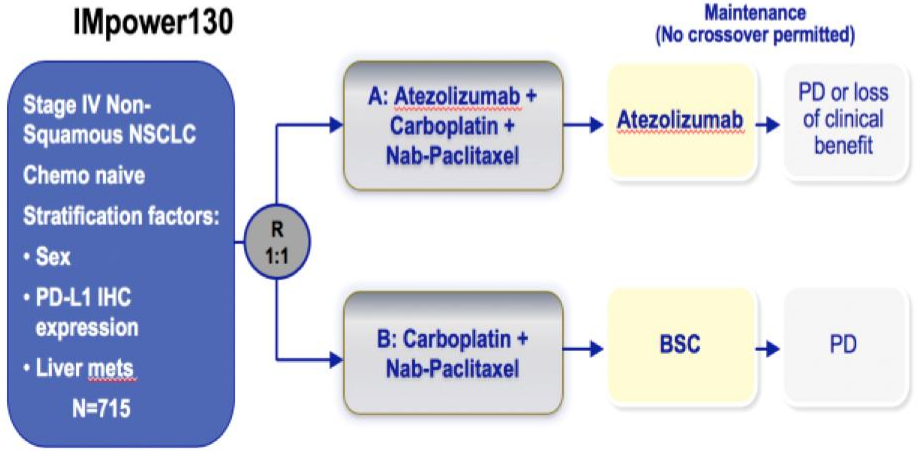


IMpower132: PFS and Safety Results

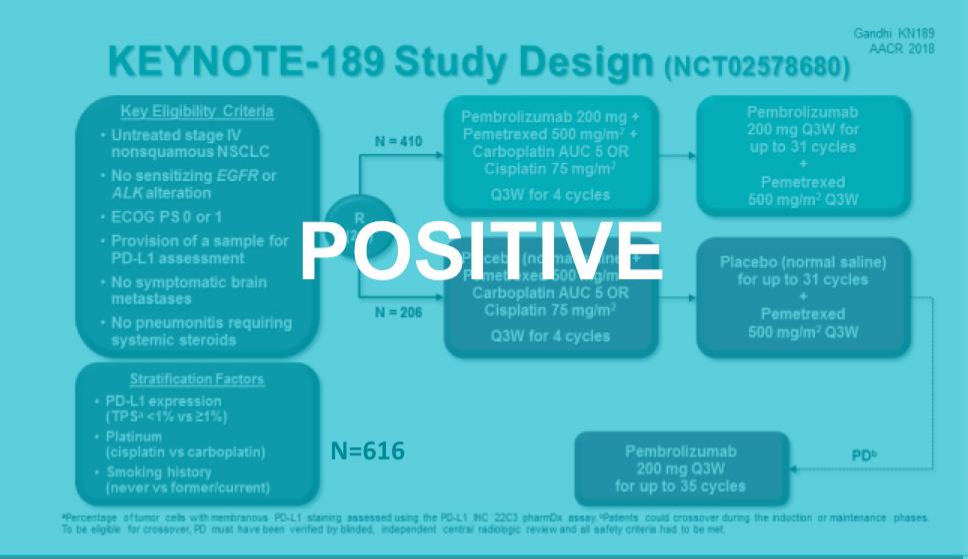
Induction therapy *Maintenance therapy*

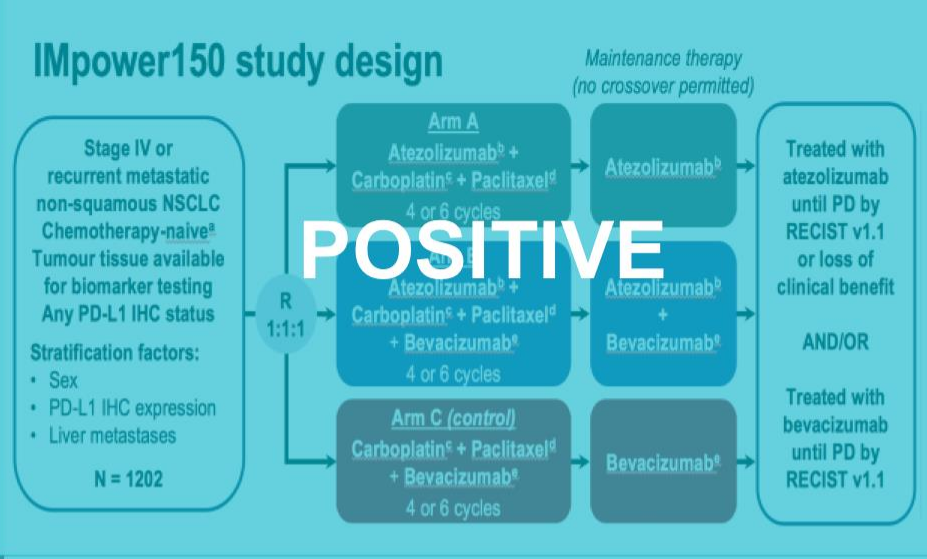


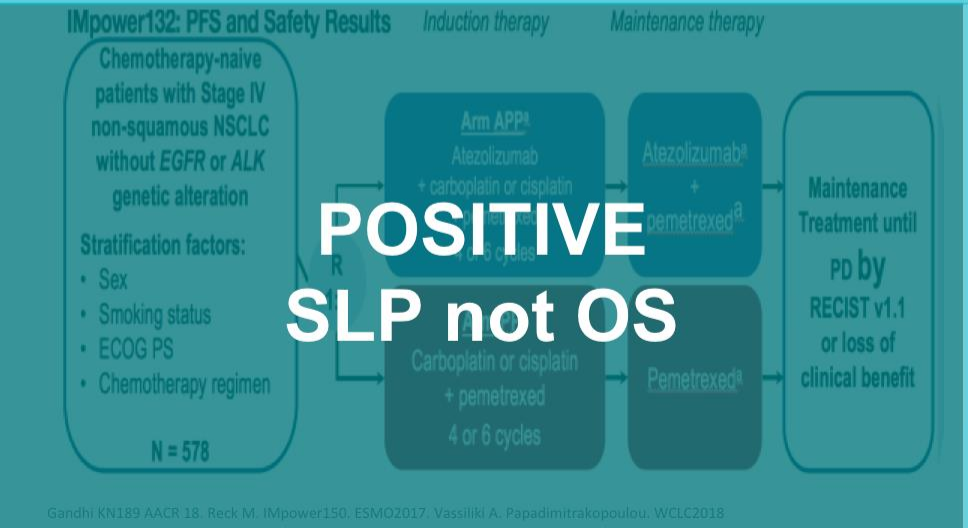
IMpower130

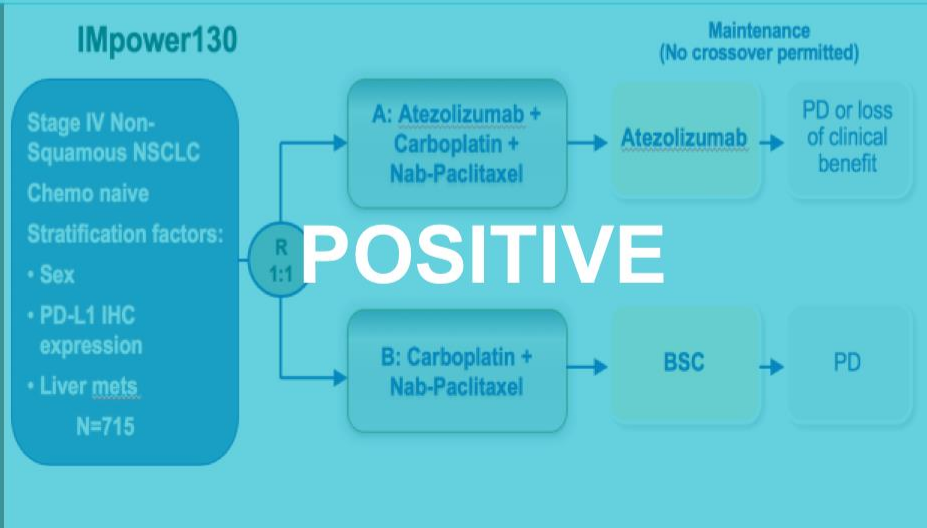


Gandhi KN189 AACR 18. Reck M. IMpower150. ESMO2017. Vassiliki A. Papadimitrakopoulou. WCLC2018







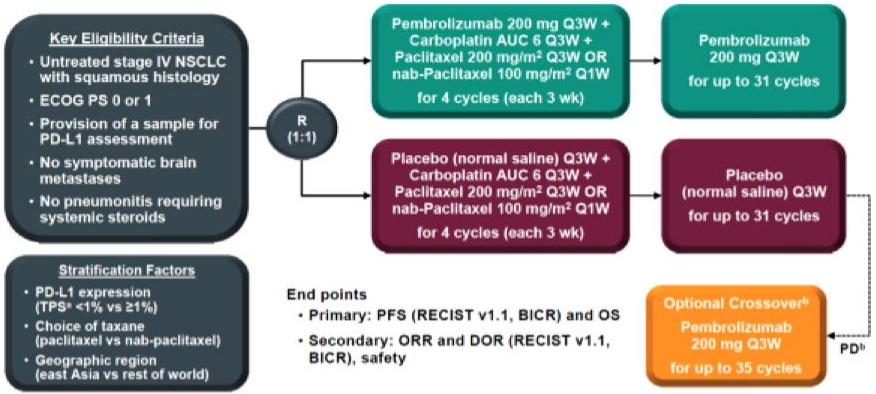


Gandhi KN189 AACR 18. Reck M. IMpower150. ESMO2017. Vassiliki A. Papadimitrakopoulou. WCLC2018

Histología escamosa

Paz-Ares KN407 ASCO 2018

KEYNOTE-407 Study Design (NCT02775435)

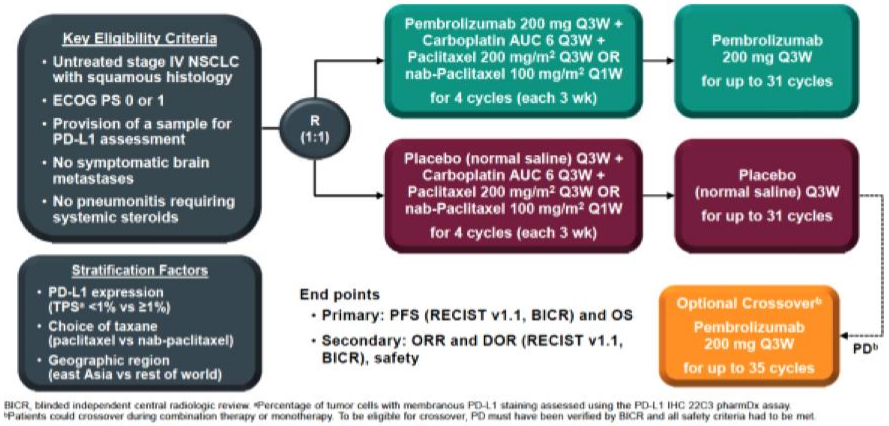


BICR, blinded independent central radiologic review. [a]Percentage of tumor cells with membranous PD-L1 staining assessed using the PD-L1 IHC 22C3 pharmDx assay. [b]Patients could crossover during combination therapy or monotherapy. To be eligible for crossover, PD must have been verified by BICR and all safety criteria had to be met.

Jotte RM, et al. J Clin Oncol 2018; Paz-Ares LG, et al. J Clin Oncol 2018. Hellman MD, NEJM 2018,

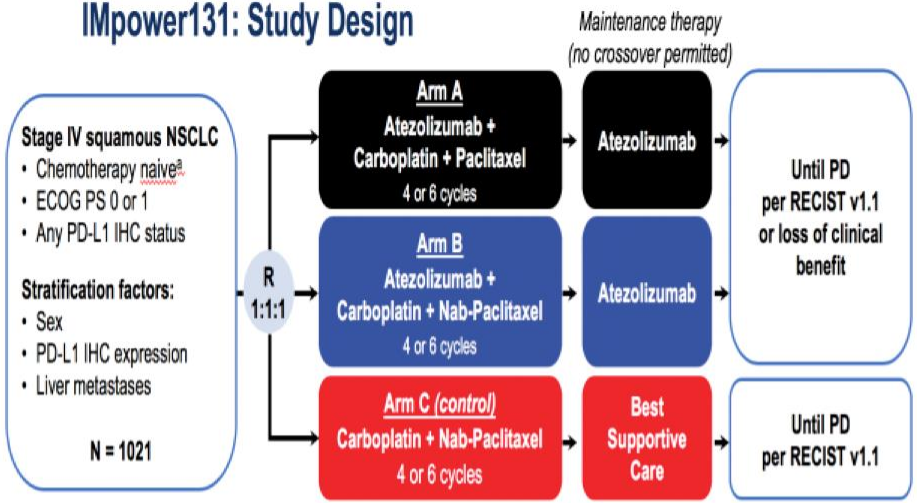
Paz-Ares KN407 ASCO 2018

KEYNOTE-407 Study Design (NCT02775435)

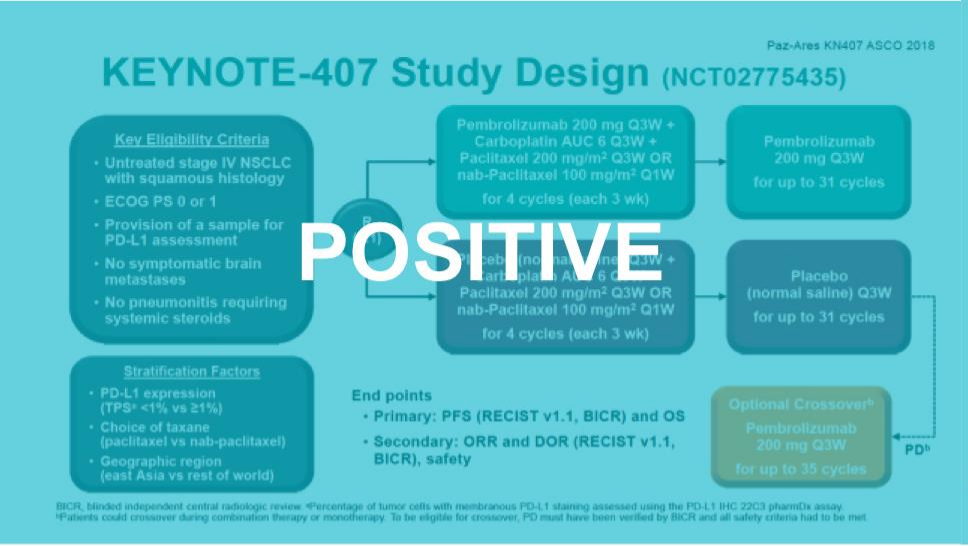


BICR, blinded independent central radiologic review. [a]Percentage of tumor cells with membranous PD-L1 staining assessed using the PD-L1 IHC 22C3 pharmDx assay. [b]Patients could crossover during combination therapy or monotherapy. To be eligible for crossover, PD must have been verified by BICR and all safety criteria had to be met.

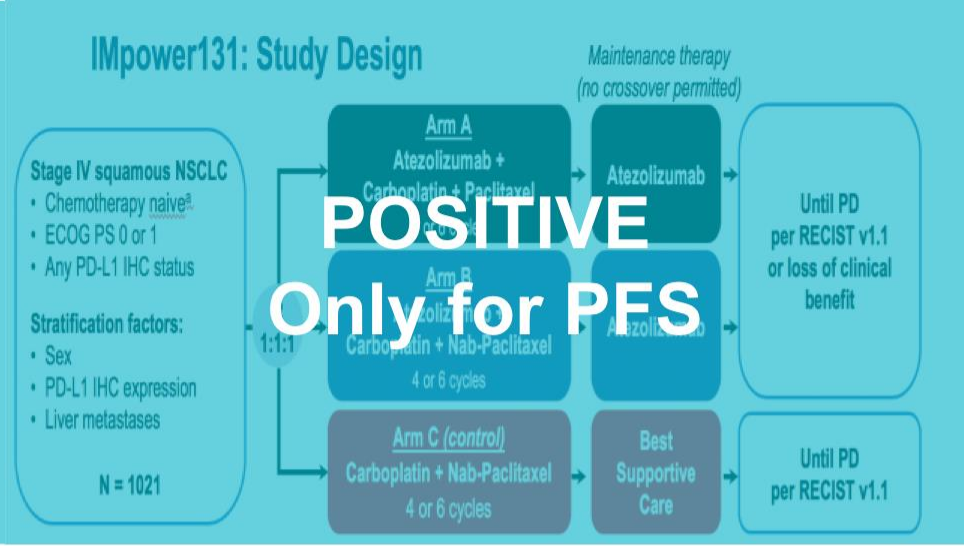
IMpower131: Study Design



Jotte RM, et al. J Clin Oncol 2018; Paz-Ares LG, et al. J Clin Oncol 2018. Hellman MD, NEJM 2018,



POSITIVE



POSITIVE
Only for PFS

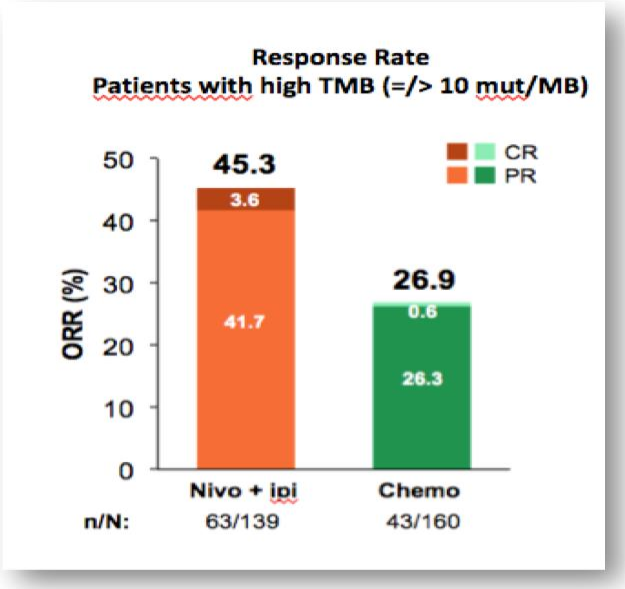
Jotte RM, et al. J Clin Oncol 2018; Paz-Ares LG, et al. J Clin Oncol 2018. Hellman MD, NEJM 2018,

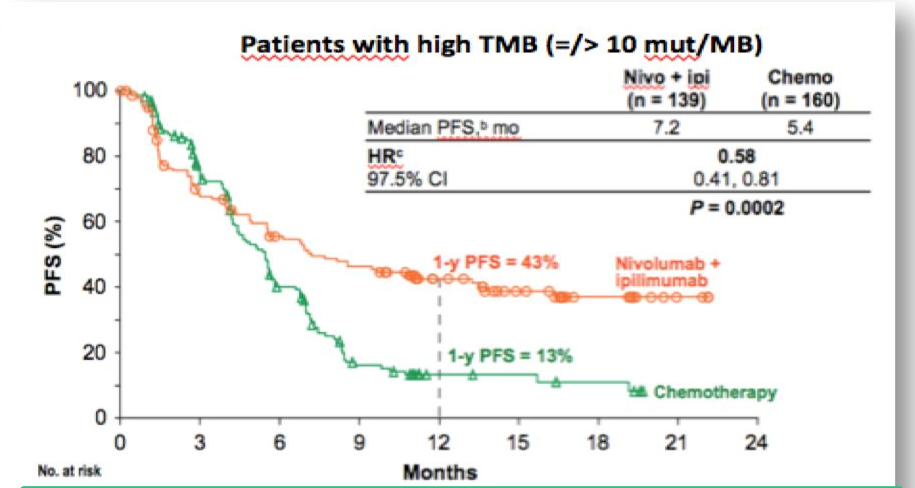
Escamoso y no escamoso

Nivo+Ipi vs QT en 1º LINEA CPNCP TMB > 10 mut/Mb

CheckMate 227: Nivo + Ipi in 1L NSCLC With High TMB (≥10 mut/Mb)

CM-227: First Results





PD-1> 1% y TMB > 10 mut

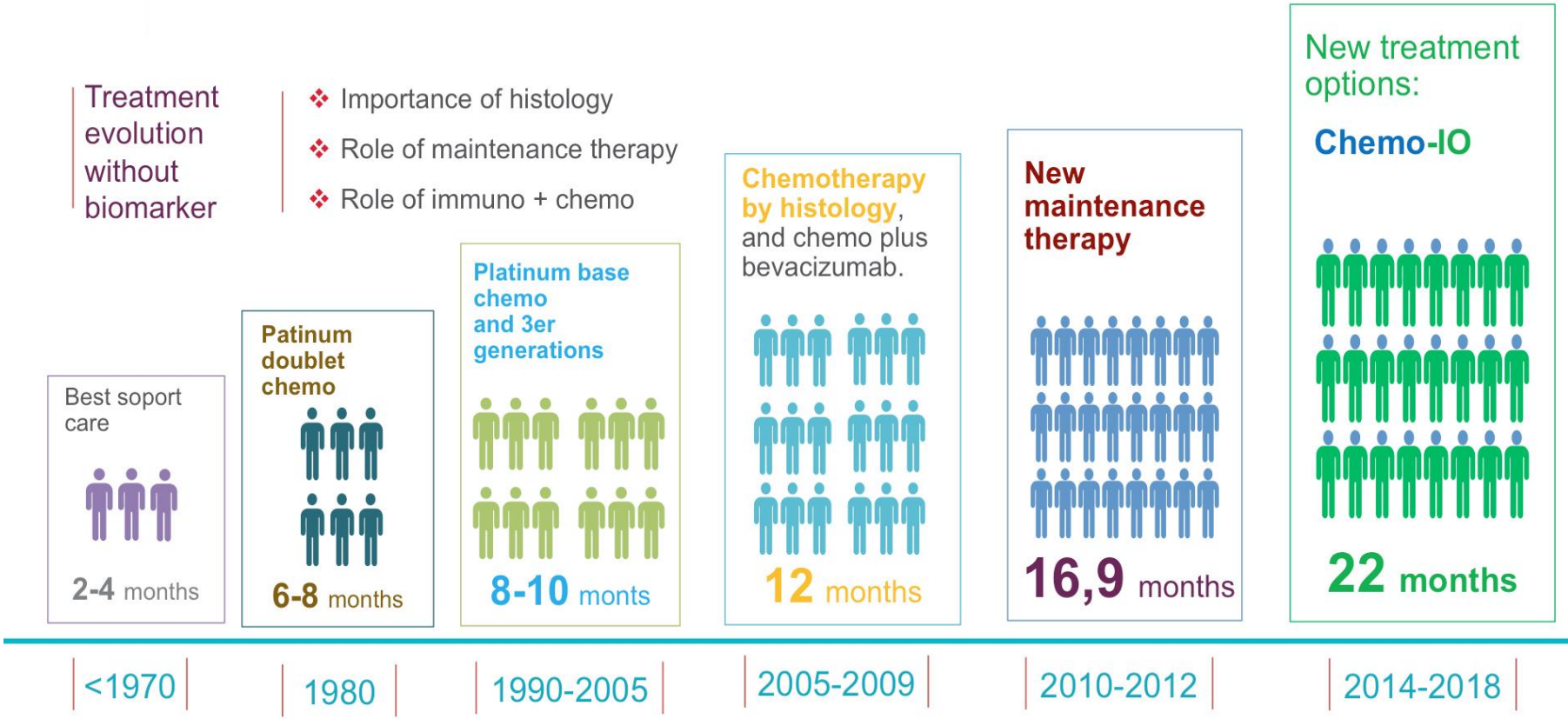
Hellman M et al, AACR 2018

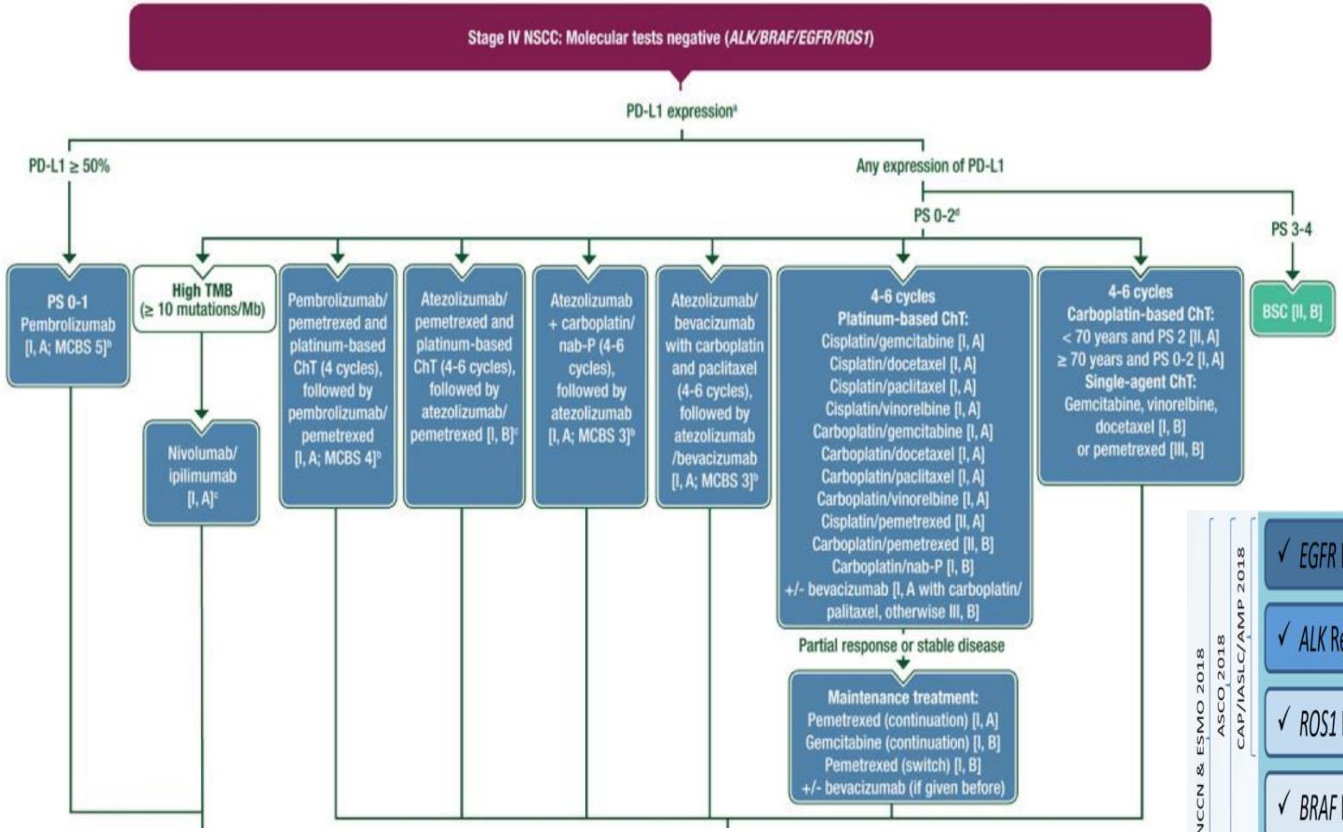
Histology	Trial	N (Int vs Cont)	ORR (%)	PFS (months)	HR PFS	OS (months)	HR OS	PFS PD-L1 >50% HR	OS PD-L1 >50% HR
Non-squamous	KN 189	410 vs 206	47.6 vs 18.9	8.8 vs 4.9	0.52	NR vs 11.3	0.49	0.36	0.42
	ImP150*	400 vs 400	63.5 vs 48.0	8.3 vs 6.8	0.59	19.2 vs 14.7	0.78	0.48	0.70(NS)
	[illegible]	292 [illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	ImP130	451 vs 228	49.2 vs 31.9	7.0 vs 5.5	0.64	18.6 vs 13.8	0.79	0.51	0.84 (NS)
Squamous	KN 407	101 vs 103	58.4 vs 35	4.8 vs 6.4	0.56	15.9 vs 11.3	0.64	0.37	0.64(NS)
	ImP131*	343 vs 340	59.4 vs 51.3	6.3 vs 5.6	0.71	14.0 vs 13.9	0.96 (NS)	0.44	0.56
All histologies	Mystic[a]	728 vs 364	35.6 vs 37.7	4.7 vs 5.4[a]	0.87	16.3 vs 12.9	0.76-0.85 (NS		0.76
	CM227**	139 vs 160	45.3 vs 26.9	7.2 vs 5.4	0.58	23 vs 16	0.77(NS)		

¡Good Bye D-Platinum alone!

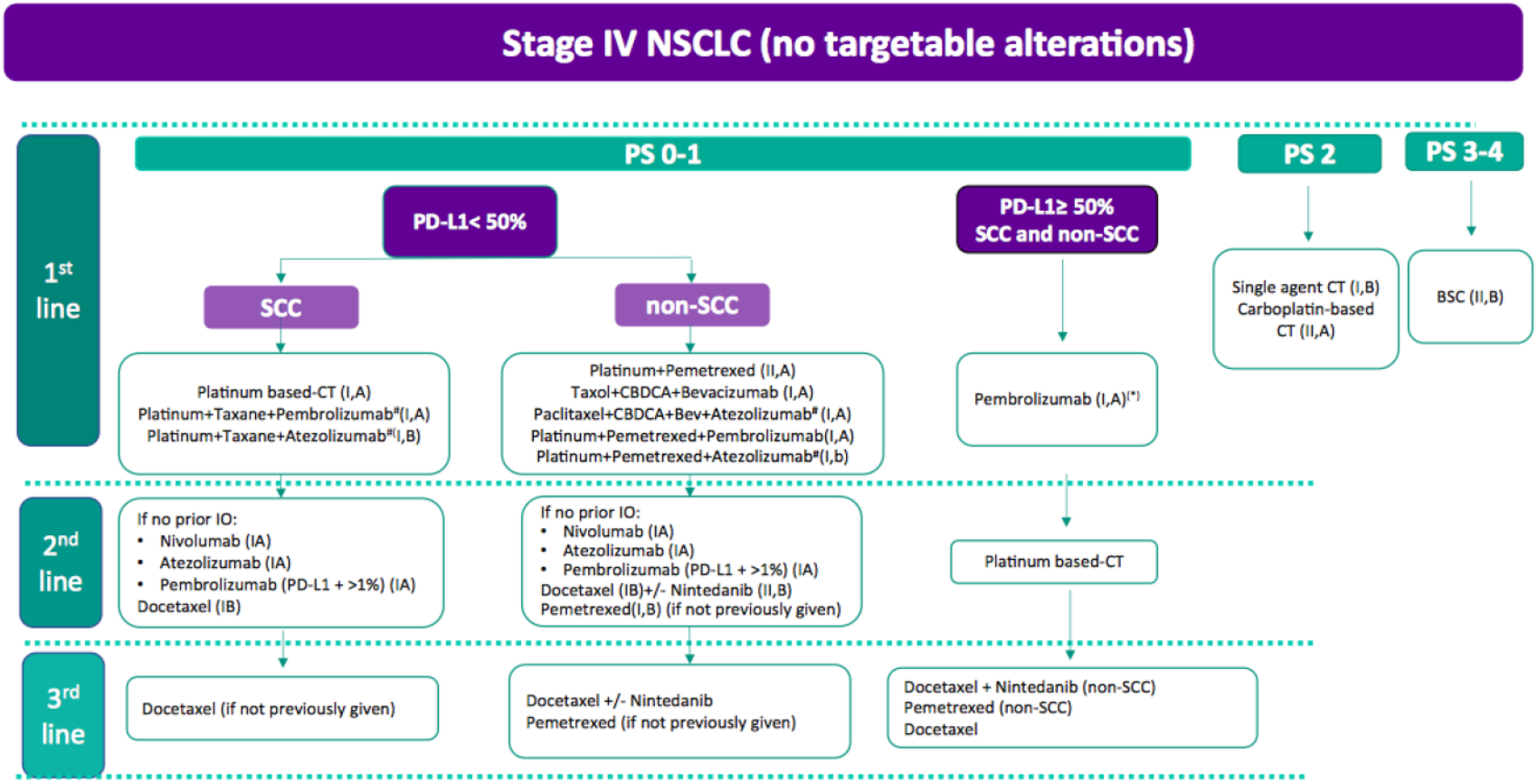
¿Cómo podemos seguir aumentando la SG en CP?

¿Cómo hemos conseguido aumentar la SG?





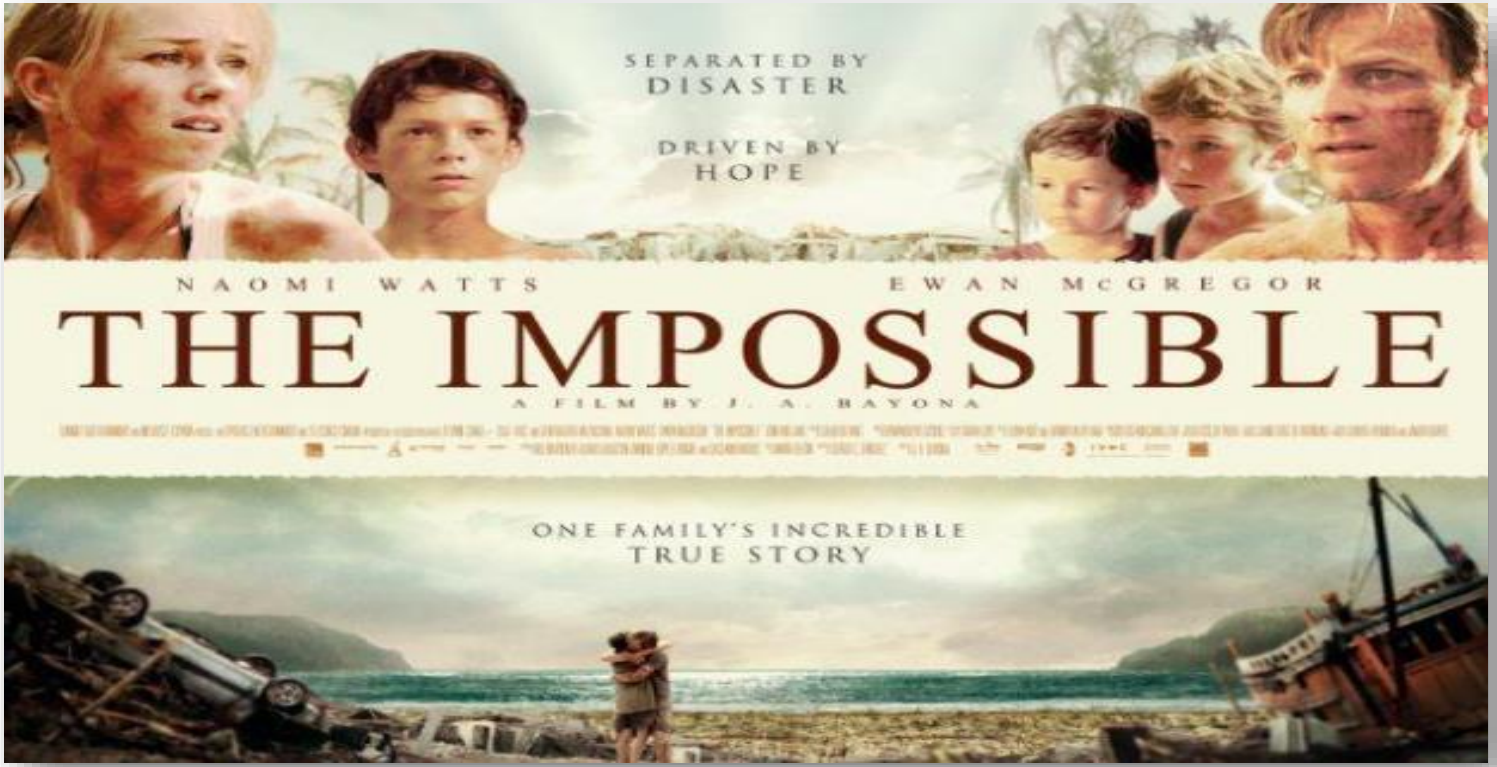
ESMO guidelines lung cancer. Sep 2019


Stage IV NSCLC (no targetable alterations)
1st line
PS 0-1
PS 2
PS 3-4
PD-L1< 50%
PD-L1≥ 50% SCC and non-SCC
SCC
non-SCC
Single agent CT (I,B)
Carboplatin-based CT (II,A)
BSC (II,B)
Platinum based-CT (I,A)
Platinum+Taxane+Pembrolizumab#(I,A)
Platinum+Taxane+Atezolizumab#(I,B)
Platinum+Pemetrexed (II,A)
Taxol+CBDCA+Bevacizumab (I,A)
Paclitaxel+CBDCA+Bev+Atezolizumab# (I,A)
Platinum+Pemetrexed+Pembrolizumab(I,A)
Platinum+Pemetrexed+Atezolizumab#(I,b)
Pembrolizumab (I,A)(*)
2nd line
If no prior IO:
• Nivolumab (IA)
• Atezolizumab (IA)
• Pembrolizumab (PD-L1 + >1%) (IA)
Docetaxel (IB)
If no prior IO:
• Nivolumab (IA)
• Atezolizumab (IA)
• Pembrolizumab (PD-L1 + >1%) (IA)
Docetaxel (IB)+/- Nintedanib (II,B)
Pemetrexed(I,B) (if not previously given)
Platinum based-CT
3rd line
Docetaxel (if not previously given)
Docetaxel +/- Nintedanib
Pemetrexed (if not previously given)
Docetaxel + Nintedanib (non-SCC)
Pemetrexed (non-SCC)
Docetaxel

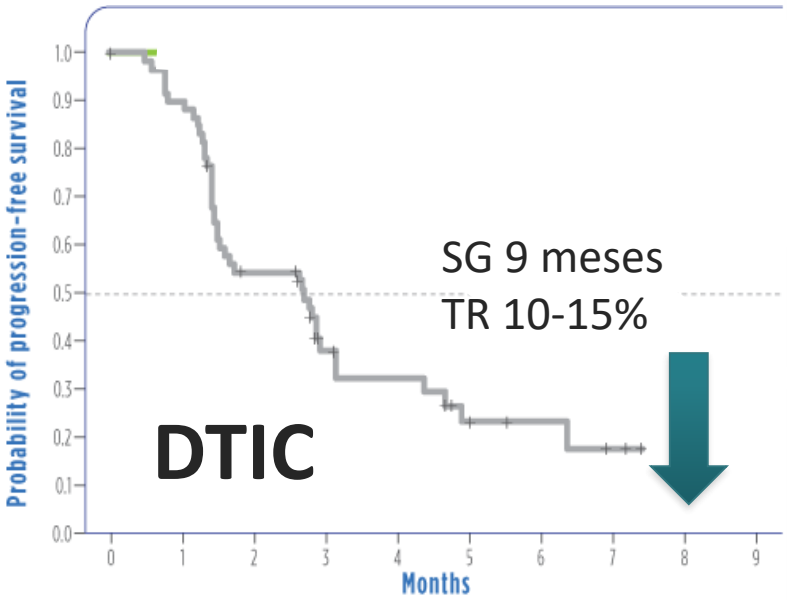
SEOM 2018

Inmunoterapia
Melanoma metastásico

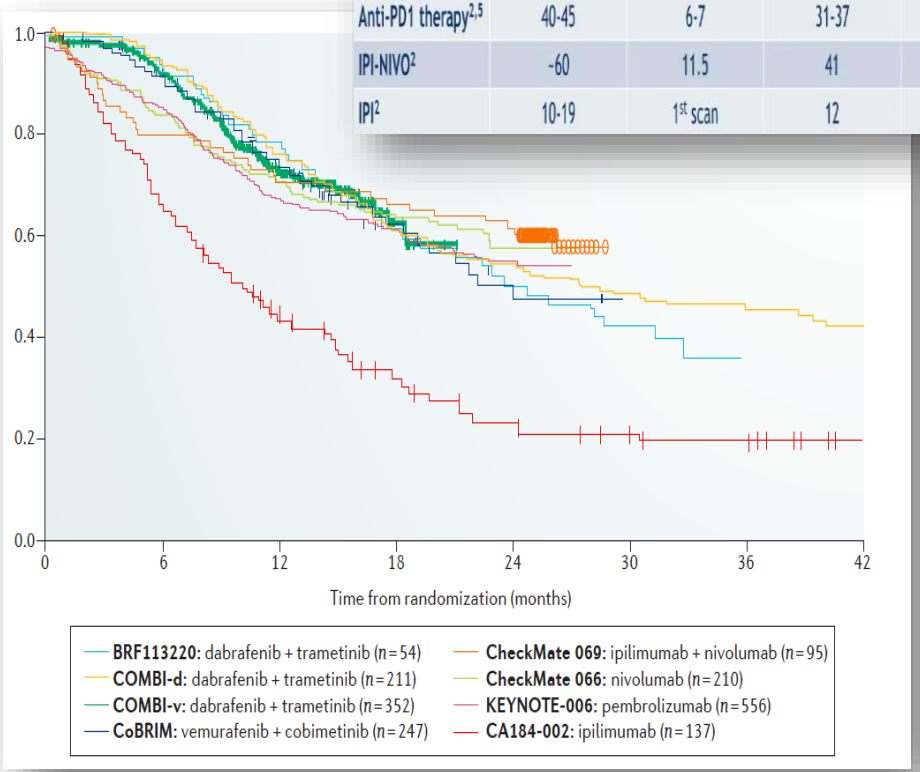
En los últimos años en melanoma…



En los últimos años en melanoma…

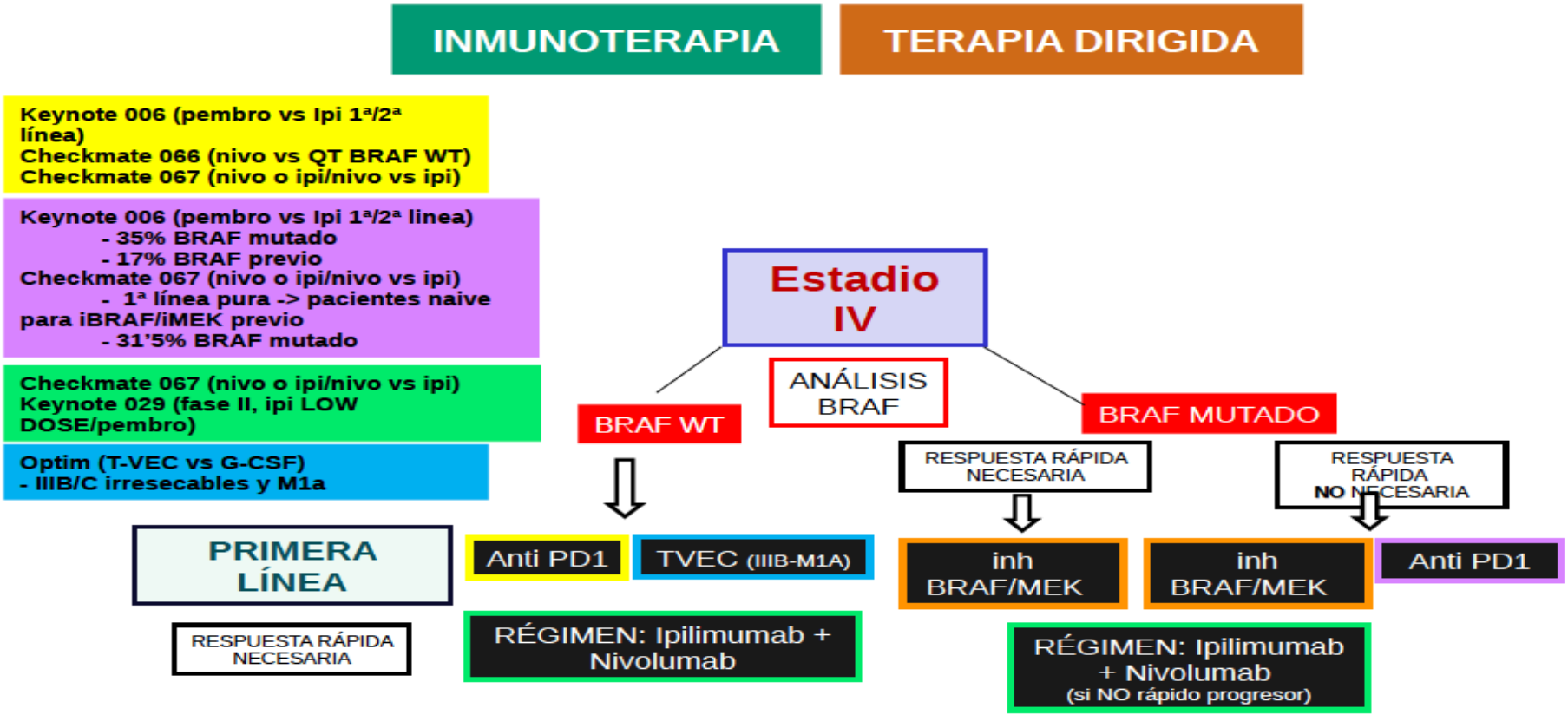


Therapy	Response rate (%)	Median PFS (Months)	2-year PFS (%)	2-yr OS (%)
BRAFi/MEKi[1,3,4]	65-70	11-15	30	53-57
Anti-PD1 therapy[2,5]	40-45	6-7	31-37	57-58
IPI-NIVO[2]	~60	11.5	41	64
IPI[2]	10-19	1st scan	12	45



Luke. Nature Reviews Clinical Oncology, 2017

TRATAMIENTO ACTUAL 1º LINEA MELANOMA METASTÁSICO



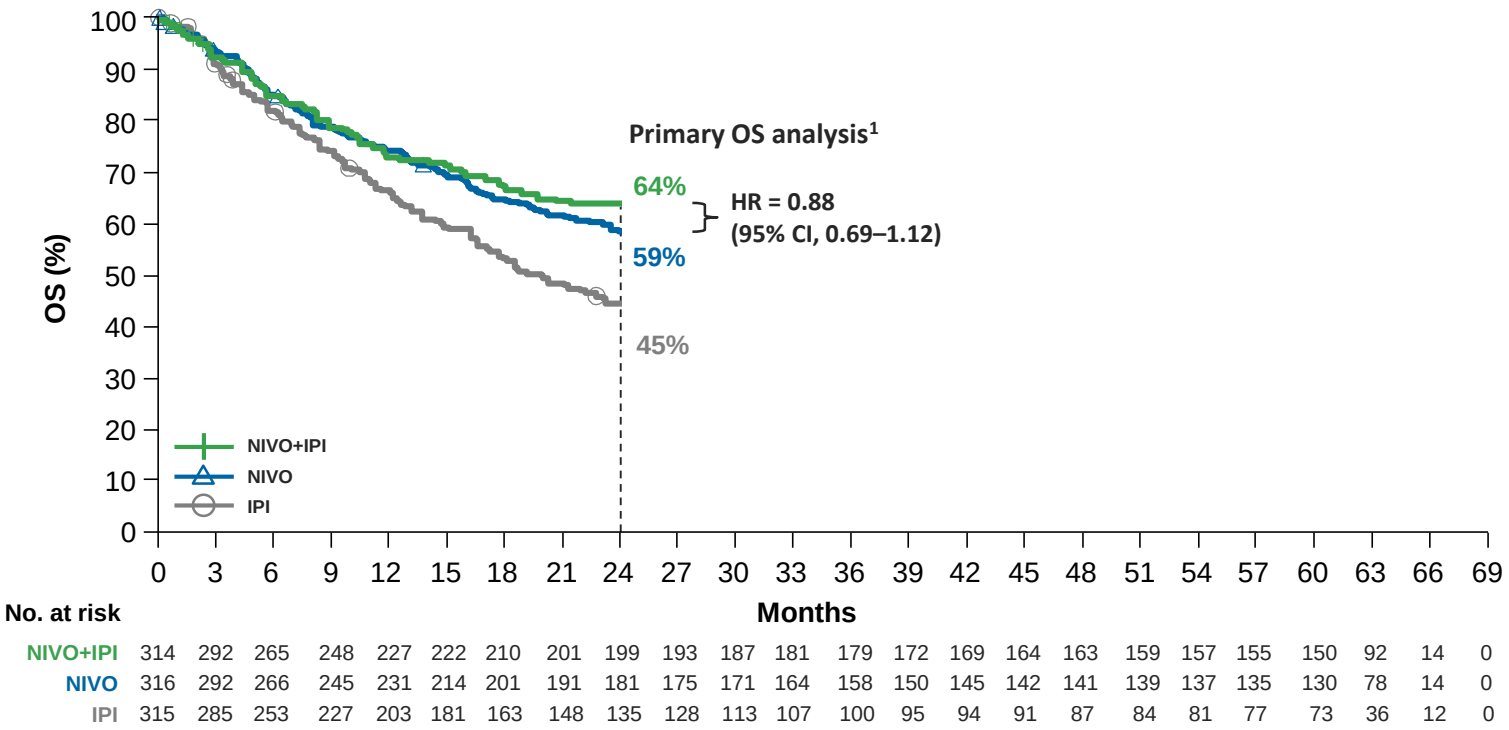
Evidencia de SG y/o SLP en ensayos fase III

Inmunoterapia Melanoma Metastásico

Algunas cuestiones…

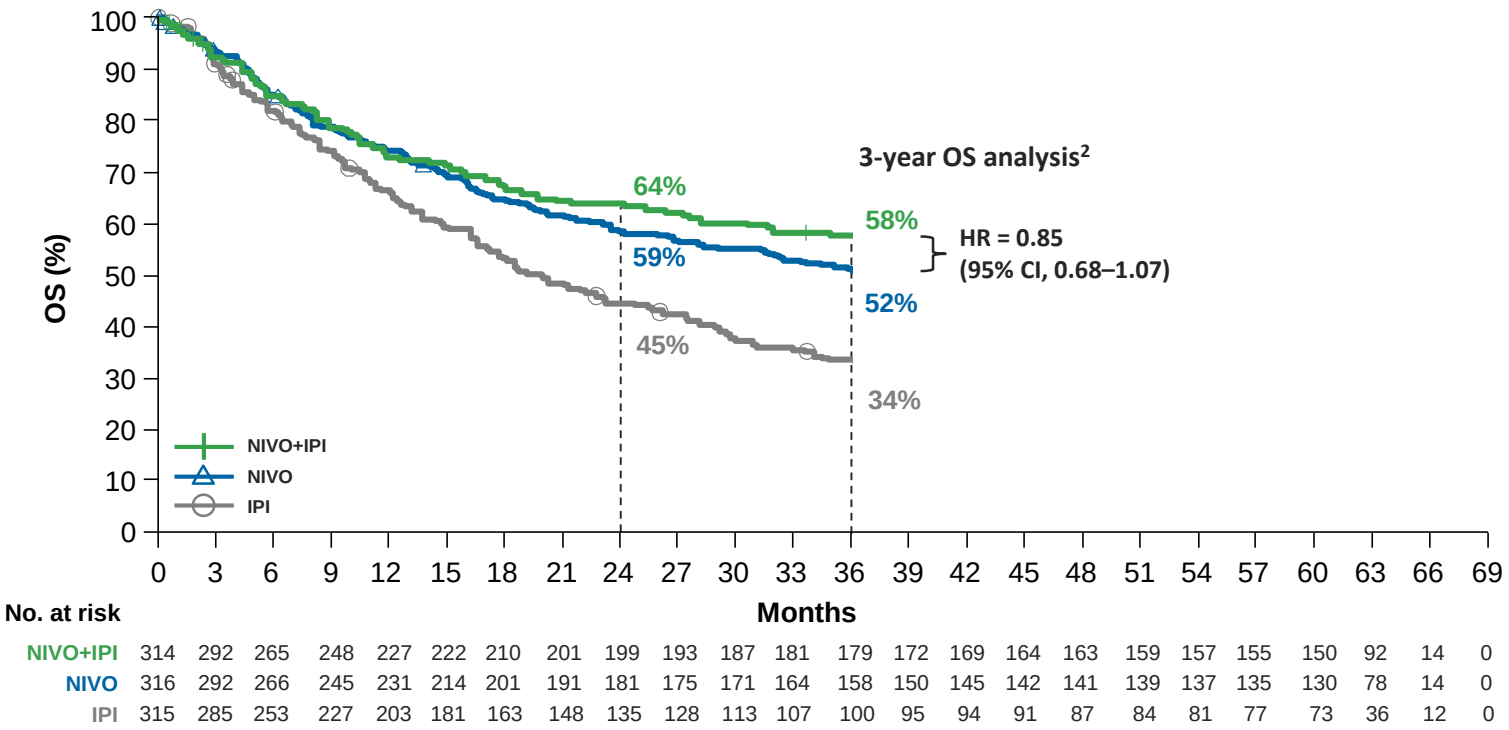
- **¿Largos supervivientes con inmunoterapia?**

CHECK-MATE 067: *SUPERVIVENCIA A 5 AÑOS*



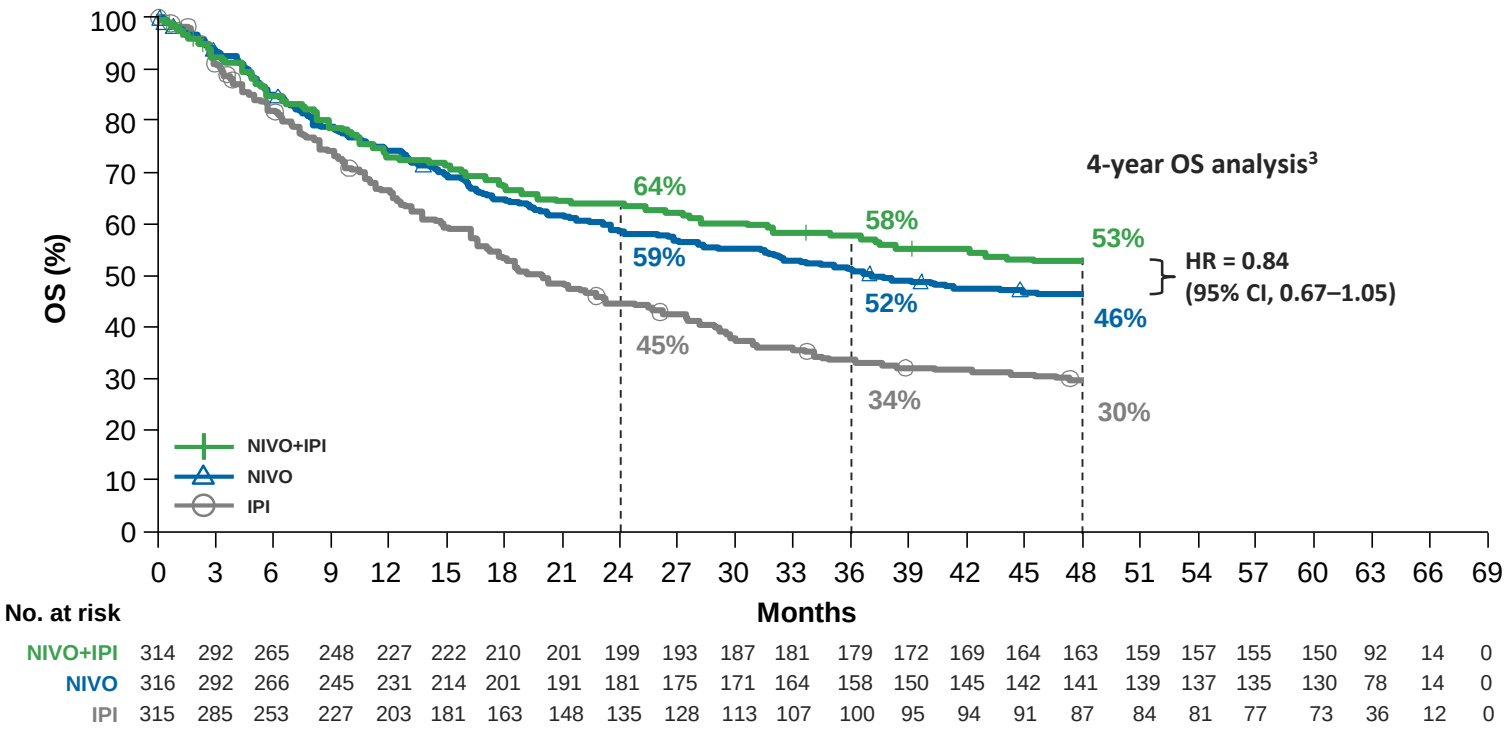
Abstract 2545. Larkin, et al. ESMO 2019

CHECK-MATE 067: *SUPERVIVENCIA A 5 AÑOS*



Abstract 2545. Larkin, et al. ESMO 2019

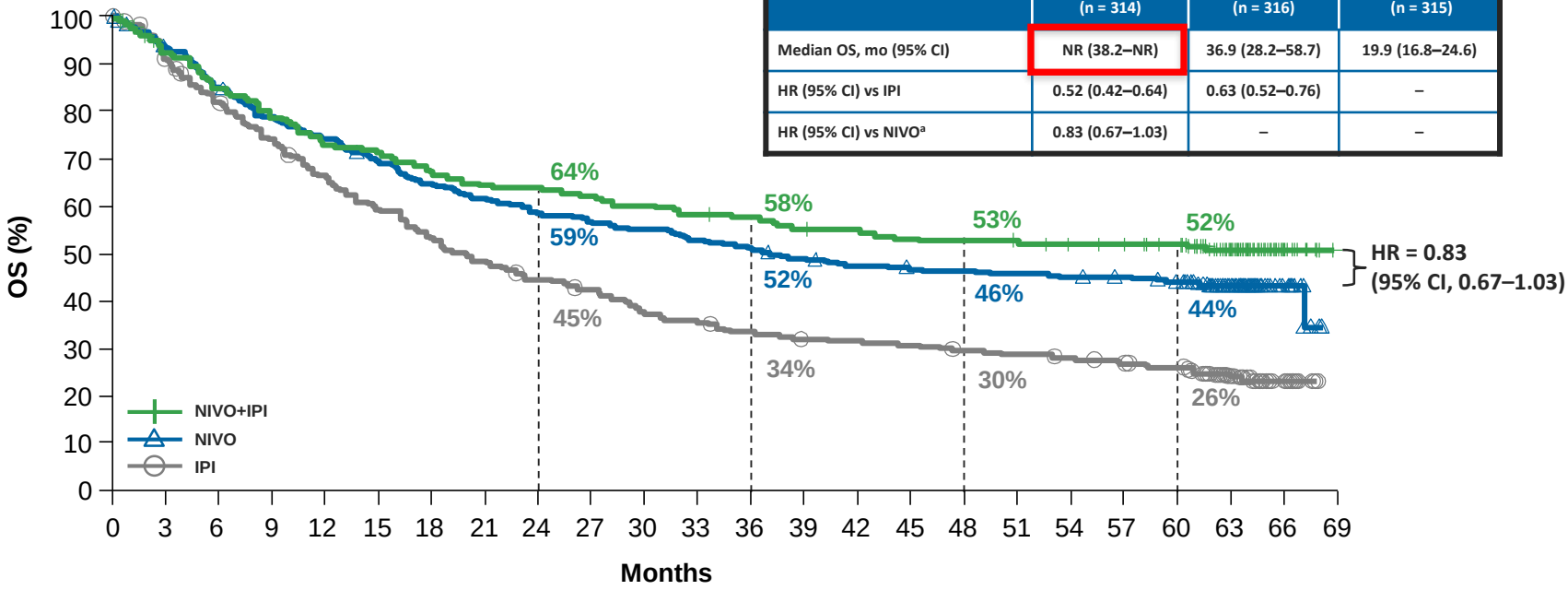
CHECK-MATE 067: *SUPERVIVENCIA A 5 AÑOS*



Abstract 2545. Larkin, et al. ESMO 2019

CHECK-MATE 067: *SUPERVIVENCIA A 5 AÑOS*

	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)	–	–



TOXICIDAD Grado 3-4	NIVO	NIVO-IPI	IPI
	23%	59%	28%

Abstract 2545. Larkin, et al. ESMO 2019

Inmunoterapia Melanoma Metastásico

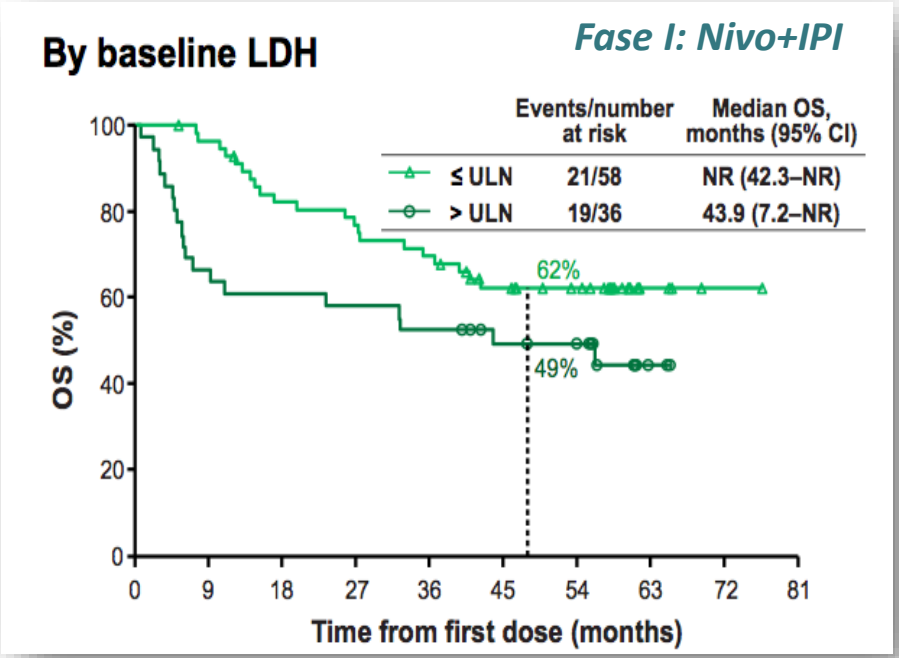
Algunas cuestiones…

- ¿Largos supervivientes con inmunoterapia?

- **¿Identificación de los largos supervivientes?**

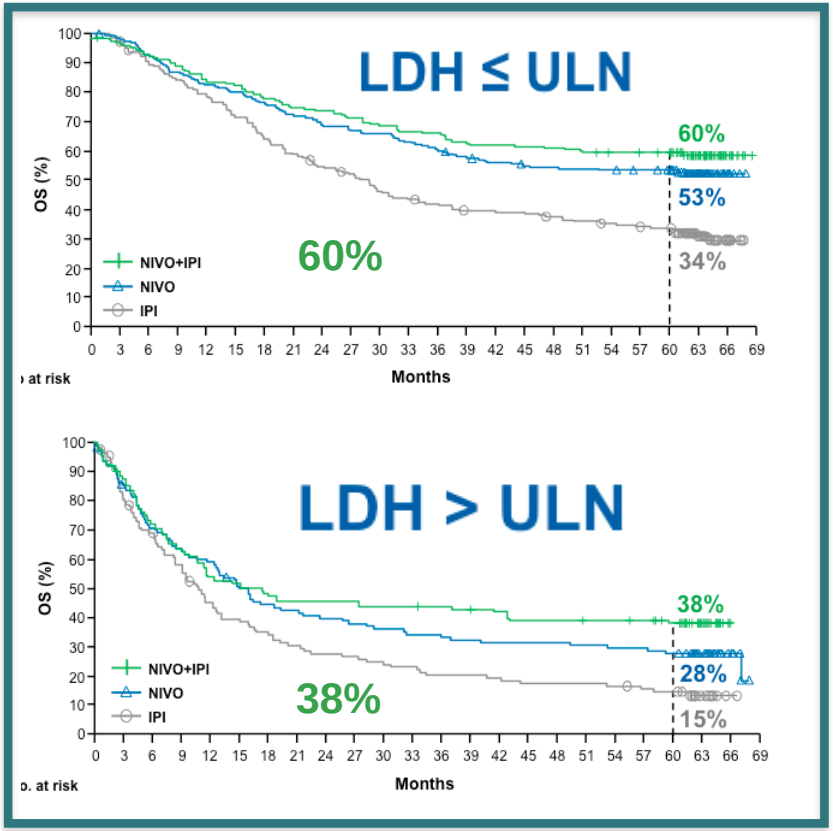
LDH: Factor pronóstico

Fase I: Nivo+IPI



Abstract 9533. Atkins et al. ASCO 2019

Fase III: Nivo+IPI



Abstract 2545. Larkin, et al. ESMO 2019

Inmunoterapia Melanoma Metastásico

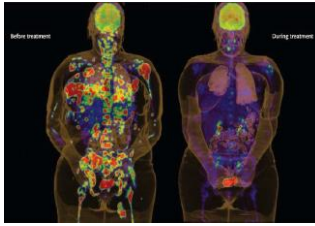
Algunas cuestiones…

- ¿Largos supervivientes con inmunoterapia?

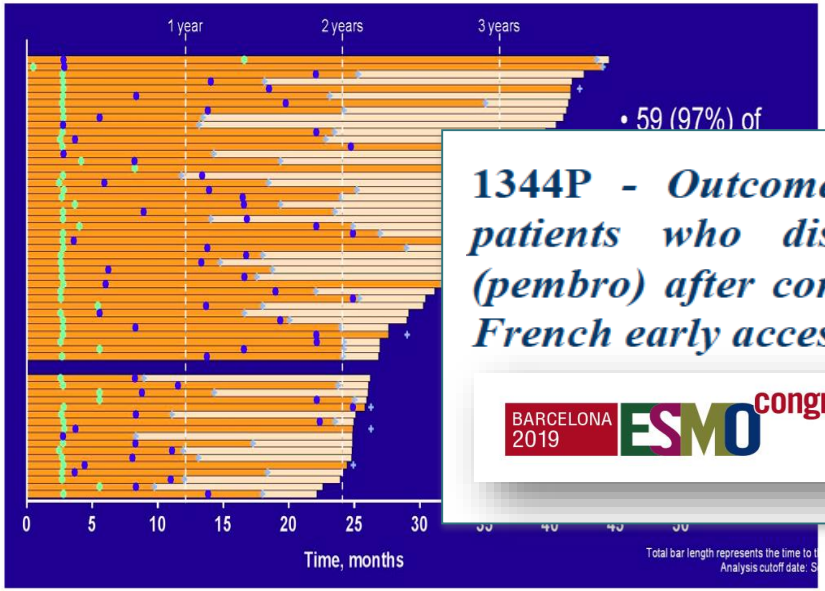
- ¿Identificación de los largos supervivientes?

- **¿Se puede parar la inmunoterapia? ¿Parar compromete la eficacia?**

Discontinuación inmunoterapia en respuesta



KEYNOTE-001: SEGUIMIENTO TRAS PARAR PEMBROLIZUMAB EN RC

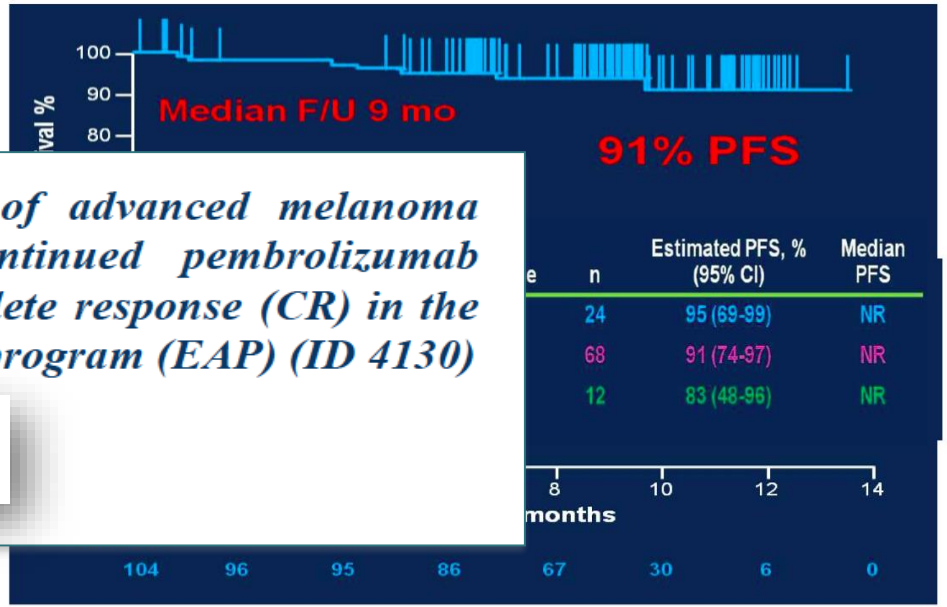


1344P - *Outcomes of advanced melanoma patients who discontinued pembrolizumab (pembro) after complete response (CR) in the French early access program (EAP) (ID 4130)*

BARCELONA 2019 ESMO congress

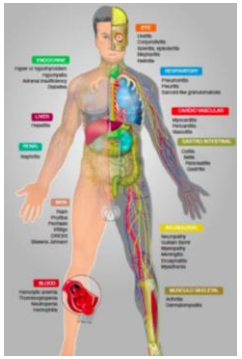
Robert C, et al. ASCO 2017

KEYNOTE-006: SEGUIMIENTO TRAS COMPLETAR TRATAMIENTO CON PEMBROLIZUMAB 24 meses



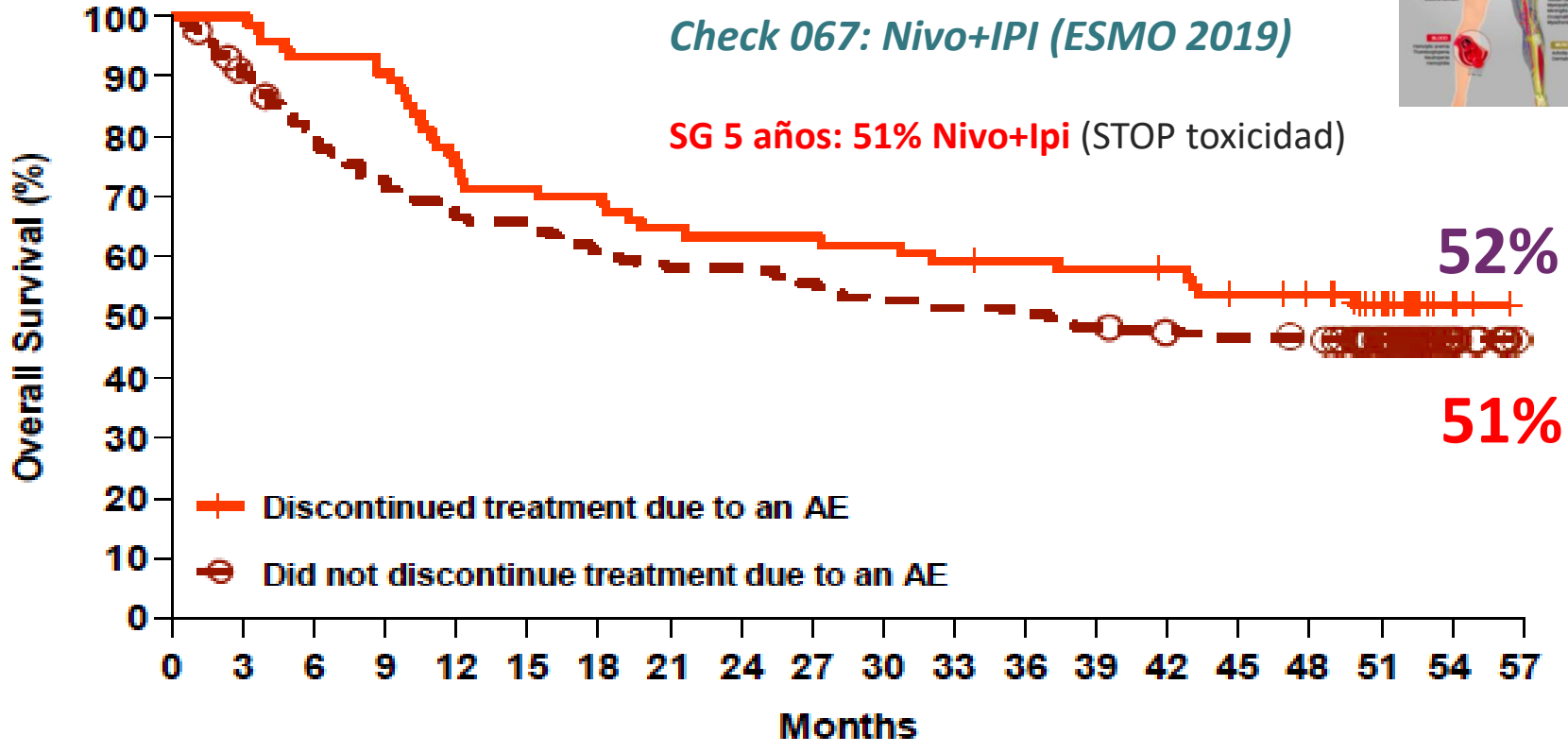
Abstract 9504. Robert, C et al. ASCO 2017

Discontinuación inmunoterapia por toxicidad



Check 067: Nivo+IPI (ESMO 2019)

SG 5 años: 51% Nivo+Ipi (STOP toxicidad)



¿Hacia dónde vamos?...algunos obstáculos

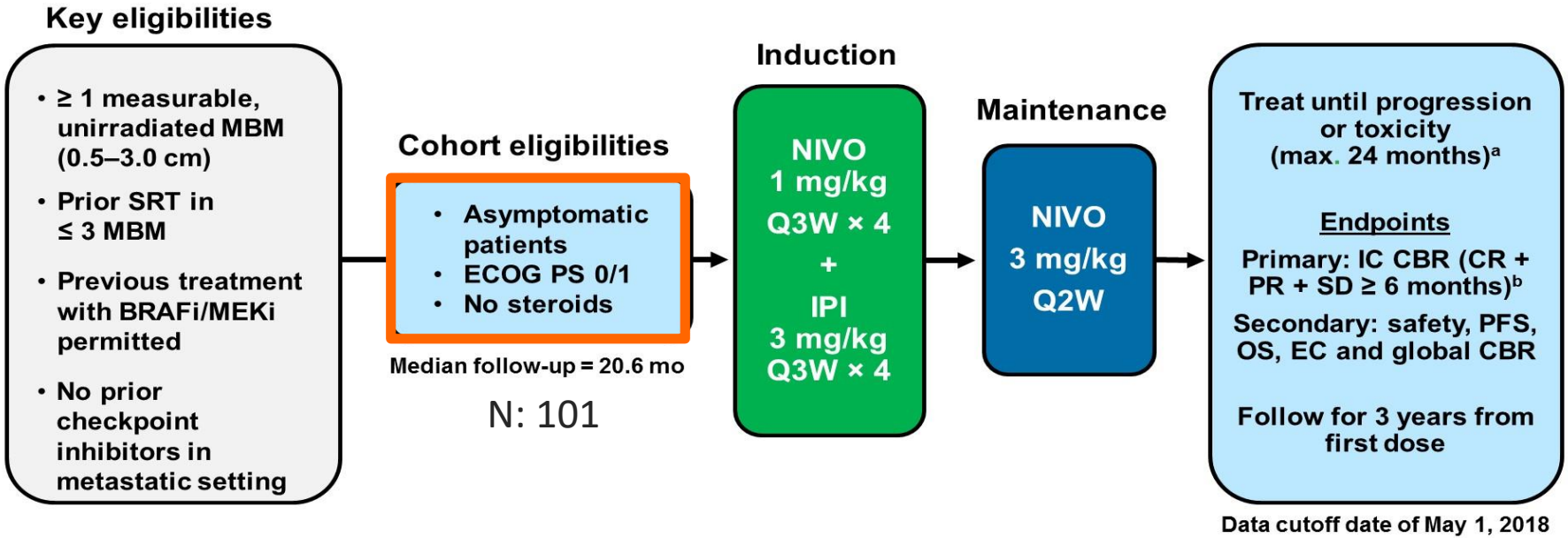
Metástasis Cerebrales

Melanoma uveal

Secuencias o Combinaciones

Biomarcadores

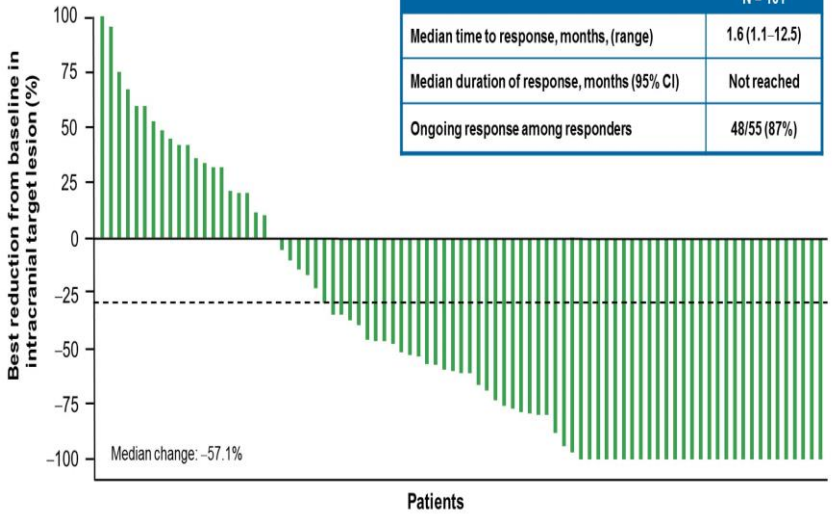
Efficacy and Safety of the Combination of Nivolumab Plus Ipilimumab in Patients With Melanoma and Asymptomatic or Symptomatic Brain Metastases (CheckMate 204)



Abstract 9501. Tawbi et al. ASCO 2019

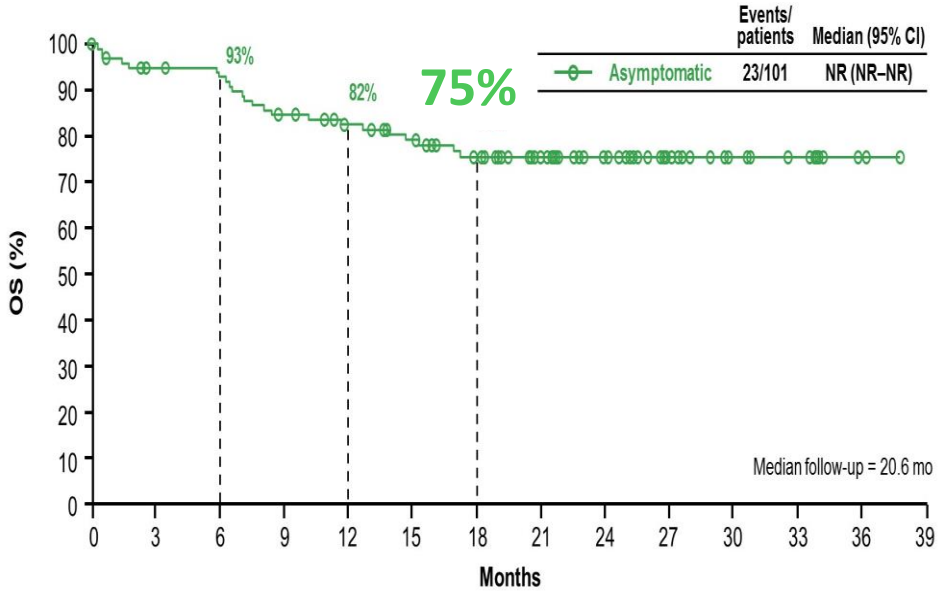
Intracranial Tumor Burden Change and Characteristics of Intracranial Response – Asymptomatic Patients

	N = 101
Median time to response, months, (range)	1.6 (1.1–12.5)
Median duration of response, months (95% CI)	Not reached
Ongoing response among responders	48/55 (87%)



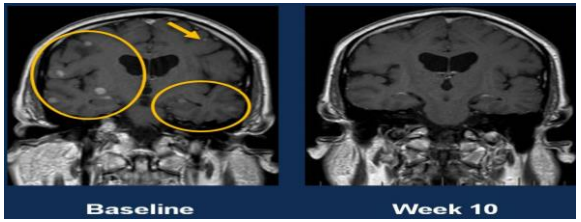
RC 29 (29%)
RP 26 (26%)
ORR 55/101 (54%)

Overall Survival – Asymptomatic Patients



Abstract 9501. Tawbi et al. ASCO 2019

Metástasis Cerebrales



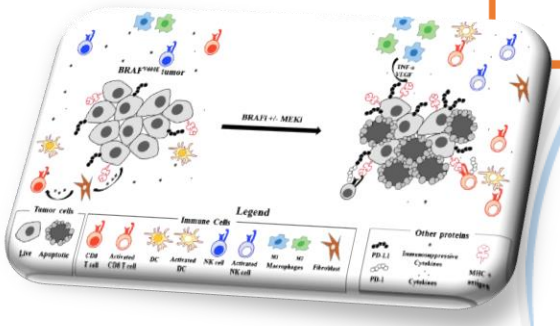
Ensayo	Combinación	Respuesta intracraneal en 1ºL	Respuestas Completas	n
ABC[1]	NIVO-IPI vs NIVO	59% N-I 21% N	26% N-I 16% N	75
Check 204[2]	NIVO-IPI	58%	29%	101

¿Podemos obviar la RT holocraneal?

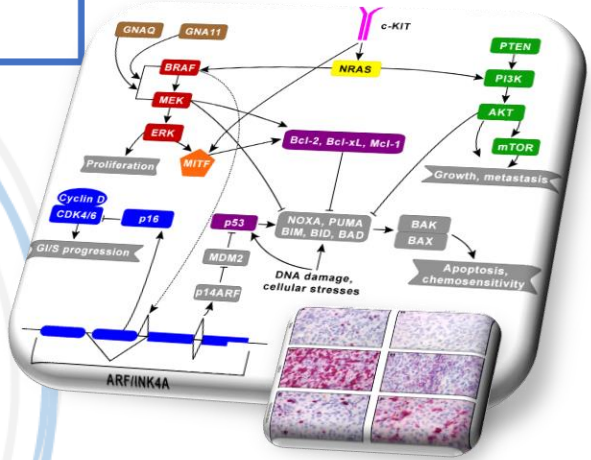
POBLACIÓN SELECCIONADA

[1] 13110. Long et al. ESMO 2019. [2]9501. Tawbi et al. ASCO 2019

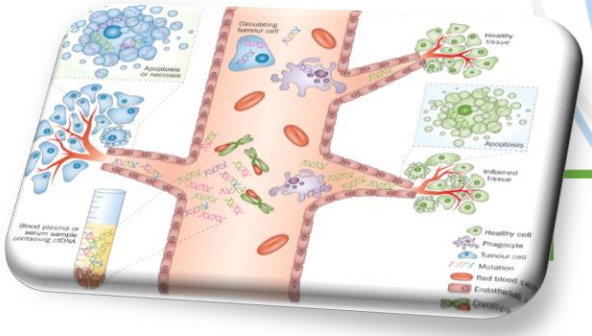
Microambiente tumoral



Tumor



Biomarcador



Sangre periférica

Huésped

Treatment based on patient's characteristics

Patient history (eg, autoimmune disease)

Organ system function, especially cardiac function

Patient's wishes and lifestyle factors

Mutational status

Performance status

Brain mtx

Tumor burden

LDH level

Courtesy of P. Ascierto, ESMO 2018


Muchas Gracias