Lung Cancer UPDATES
ASCO HIGHLIGTHS
04-08 JUNIO 2021

Iniciativa científica de:
GECP
lung cancer research

CPCNP AVANZADO: INMUNOTERAPIA

Natividad Martínez Banaclocha

Hospital General Universitario de Alicante

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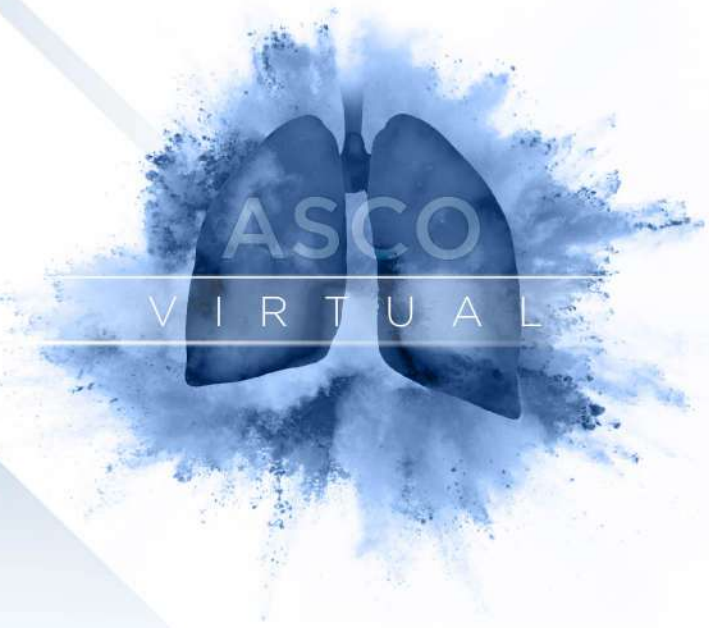

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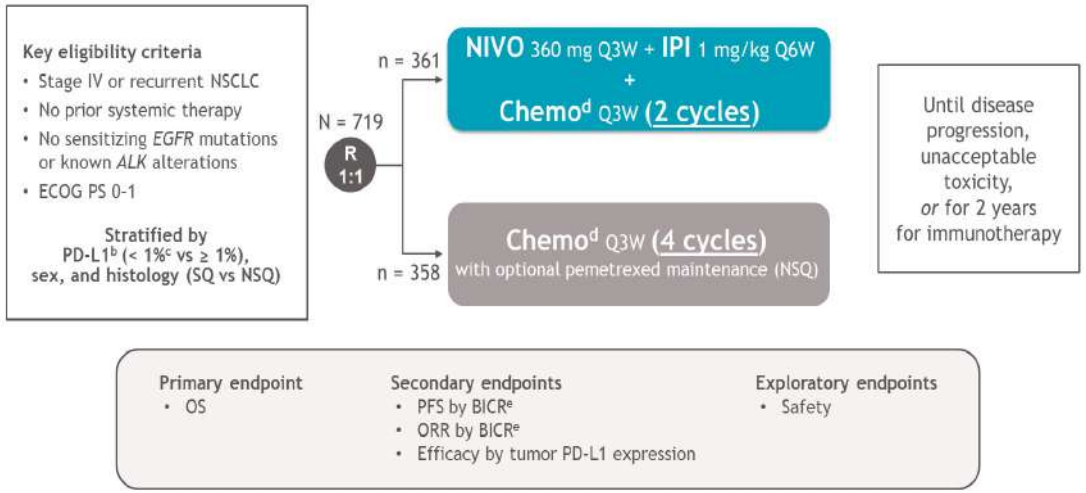
Disclosures

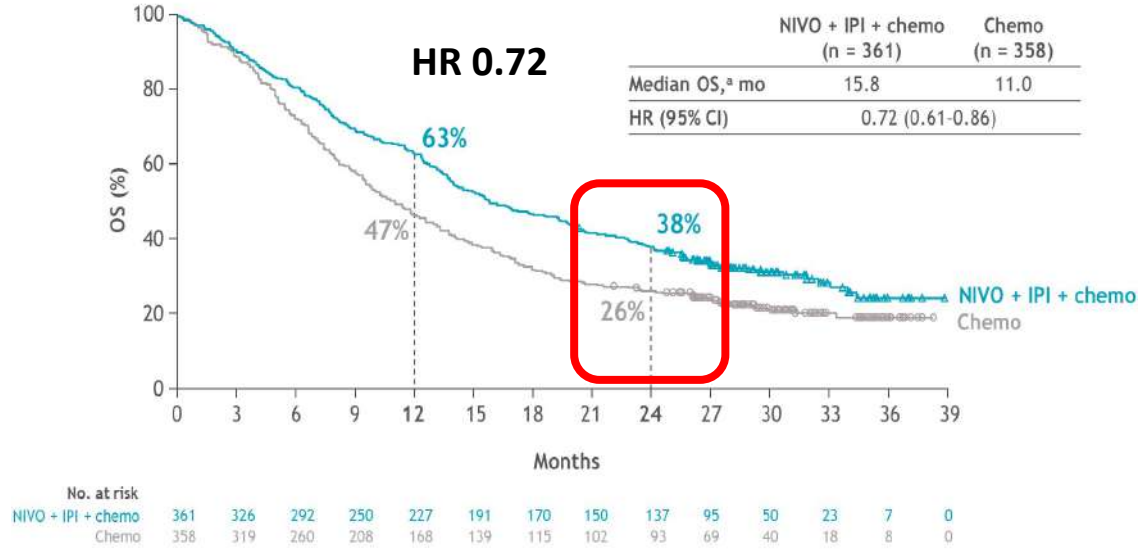
- Advisory and consultancy: Boheringher Inghelheim.
- Speaker honoraria: Roche, Boheringher Inghelheim, BMS, Astra Zeneca, Lilly, Kyowa Kirin.

First-line nivolumab (NIVO) plus ipilimumab (IPI) plus two cycles of chemotherapy (chemo) versus chemo alone (4 cycles) in patients with advanced non-small cell lung cancer (NSCLC): Two-year update from CheckMate 9LA. (M. Reck)

CheckMate 9LA study design[a]

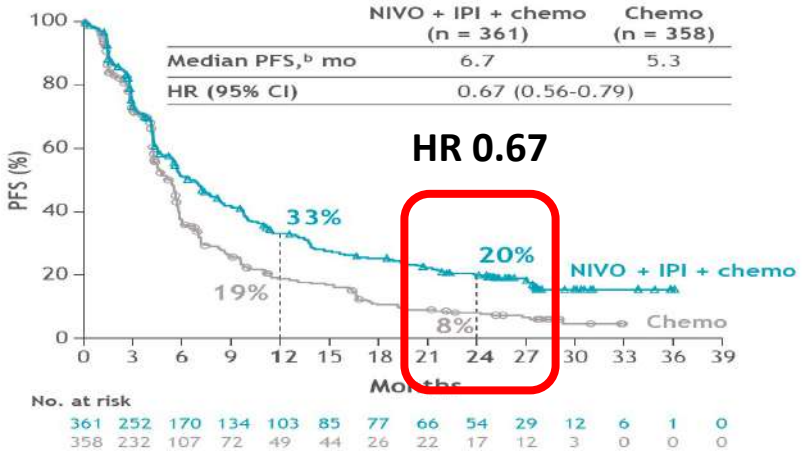


2-Year update: OS in all randomized patients

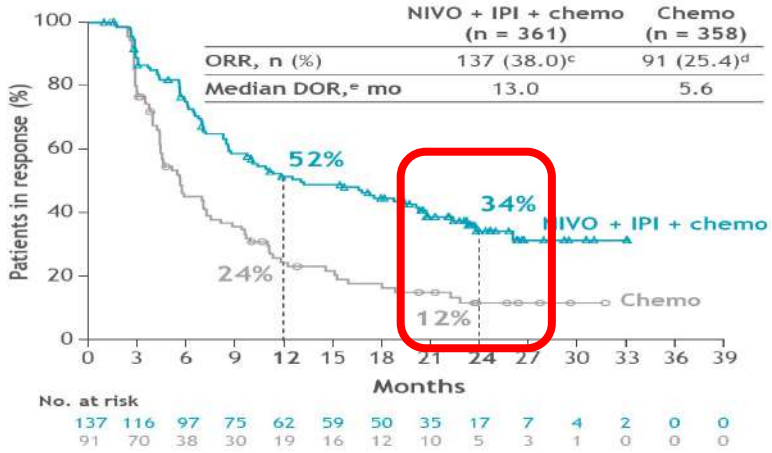


2-Year update: PFS and DOR

PFS[a]



DOR[a]



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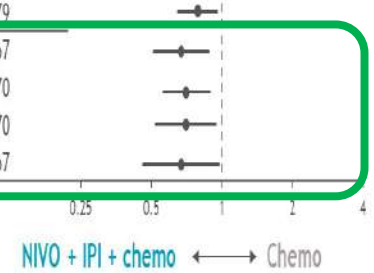
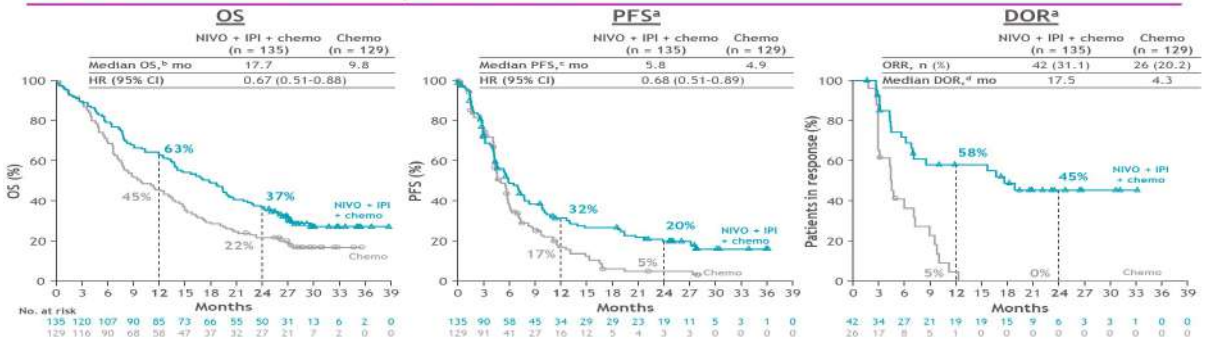
2-Year update: OS subgroup analysis

Subgroup	Median OS, mo: NIVO + IPI + chemo n = 361	Median OS, mo: Chemo n = 358	Unstratified HR	Unstratified HR (95% CI)
All randomized (N = 719)	15.8	11.0	0.73	
< 65 years (n = 354)	15.9	10.7	0.64	
≥ 65 to < 75 years (n = 295)	19.0	11.9	0.78	
≥ 75 years (n = 70)	8.5	11.5	1.04	
Male (n = 504)	14.2	9.8	0.72	
Female (n = 215)	22.2	15.9	0.75	
ECOG PS 0 (n = 225)	27.1	14.1	0.54	
ECOG PS 1 (n = 492)	13.6	9.7	0.83	
Never smoker (n = 98)	14.1	14.4	1.08	
Smoker (n = 621)	16.2	10.4	0.68	
SQ (n = 227)	14.5	9.1	0.63	
NSQ (n = 492)	17.8	12.0	0.78	
Liver metastases (n = 154)	10.2	8.1	0.85	
No liver metastases (n = 565)	19.3	12.4	0.72	
Bone metastases (n = 207)	11.9	8.3	0.73	
No bone metastases (n = 512)	19.7	12.4	0.74	
CNS metastases (n = 123)	19.9	7.9	0.47	
No CNS metastases (n = 596)	15.6	11.8	0.79	
PD-L1 < 1% (n = 264)	17.7	9.8	0.67	
PD-L1 ≥ 1% (n = 407)	15.8	10.9	0.70	
PD-L1 1-49% (n = 233)	15.2	10.4	0.70	
PD-L1 ≥ 50% (n = 174)	18.9	12.9	0.67	

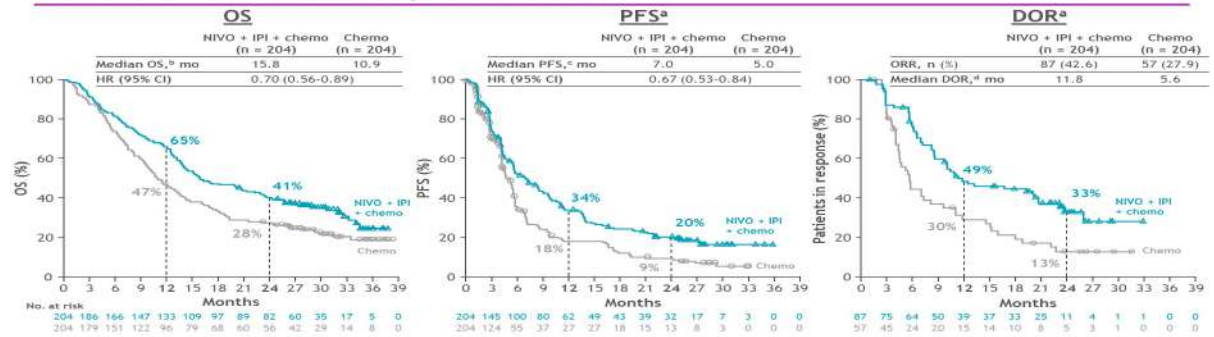


PD-L1 < 1%: efficacy outcomes



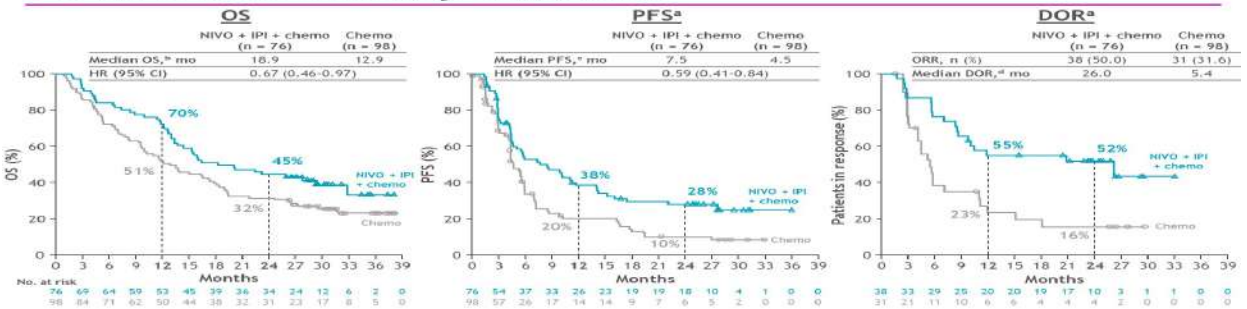
- Exploratory analysis of OS by histology in PD-L1 < 1% (HR; NIVO + IPI + chemo vs chemo): 0.75[e] (NSQ) and 0.48[f] (SQ)
  - 2-year OS rates were 38% vs 26% (NSQ) and 33% vs 11% (SQ)

PD-L1 ≥ 1%: efficacy outcomes



- Exploratory analysis of OS by histology in PD-L1 ≥ 1% (HR; NIVO + IPI + chemo vs chemo): 0.71[e] (NSQ) and 0.70[f] (SQ)
  - 2-year OS rates were 42% vs 29% (NSQ) and 38% vs 26% (SQ)

PD-L1 ≥ 50%: efficacy outcomes



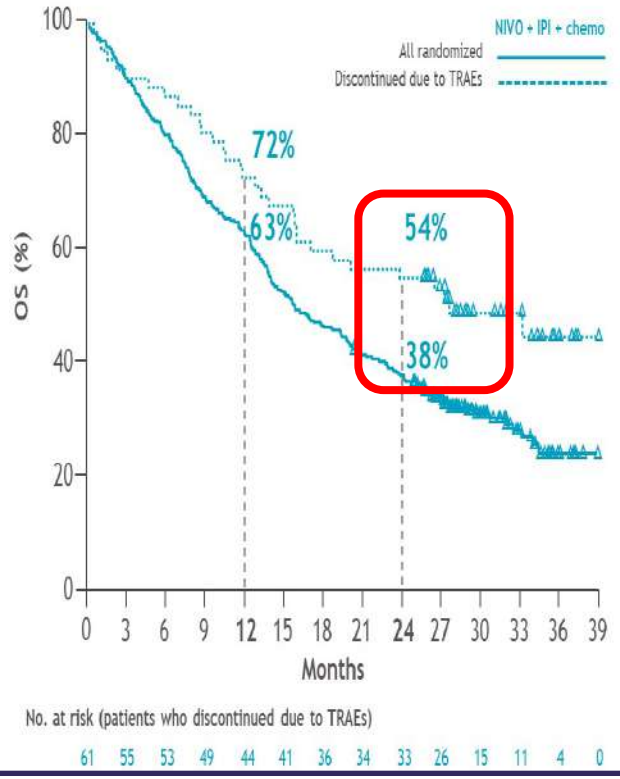
First-line nivolumab (NIVO) plus ipilimumab (IPI) plus two cycles of chemotherapy (chemo) versus chemo alone (4 cycles) in patients with advanced non-small cell lung cancer (NSCLC): Two-year update from CheckMate 9LA. (M. Reck)

2-Year update: safety and exposure summary

TRAE,[a] %	NIVO + IPI + chemo (n = 358)		Chemo (n = 349)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Any TRAE	92	48	88	38
TRAEs leading to discontinuation of any component of the regimen	22	18	8	5
TRAEs leading to discontinuation of all components of the regimen	17	14	6	3
Serious TRAEs	30	26	18	15
Treatment-related deaths[b]	2		2	

- Median (range) duration of therapy: 6.1 (0-24.4) months with NIVO + IPI + chemo; 2.5 (0-34.5) months with chemo
- In the NIVO + IPI + chemo arm, patients received a median (range) of 9.0 (1-36) doses of NIVO and 4.0 (1-18) doses of IPI; 93% of patients received 2 cycles of chemo
- Incidence of exposure-adjusted TRAEs per 100 patient-years: 714.8 (NIVO + IPI + chemo); 880.0 (chemo)

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



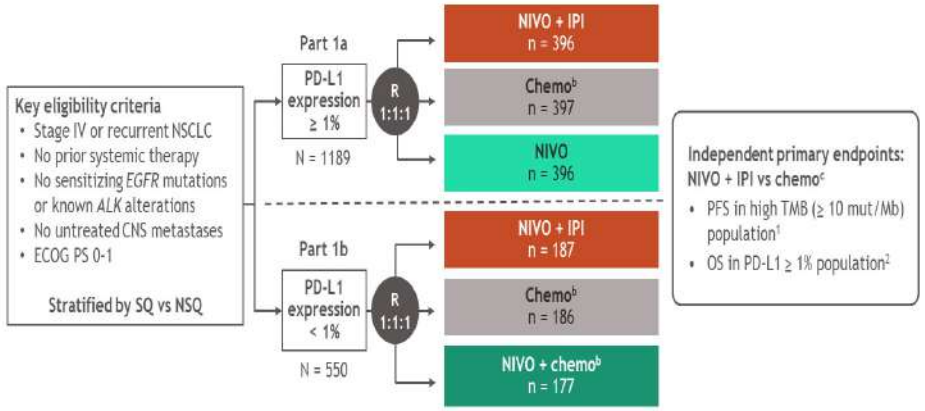
Patients who discontinued all components of NIVO + IPI + chemo due to TRAEs

	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

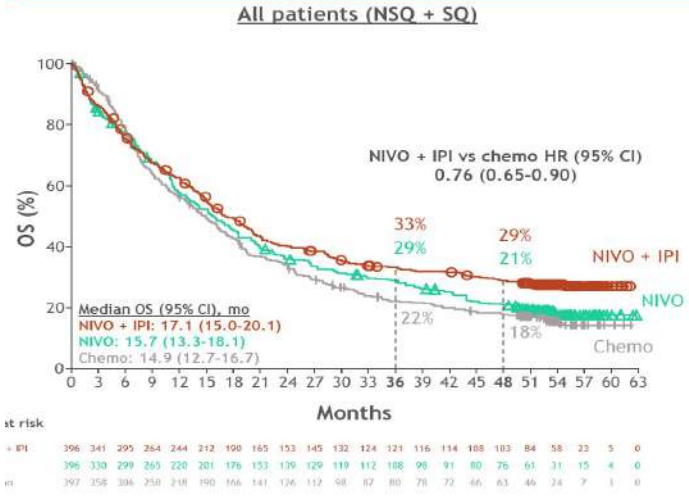
These updated results continue to support NIVO + IPI + 2 cycles of chemo as an efficacious 1L treatment option for patients with advanced NSCLC

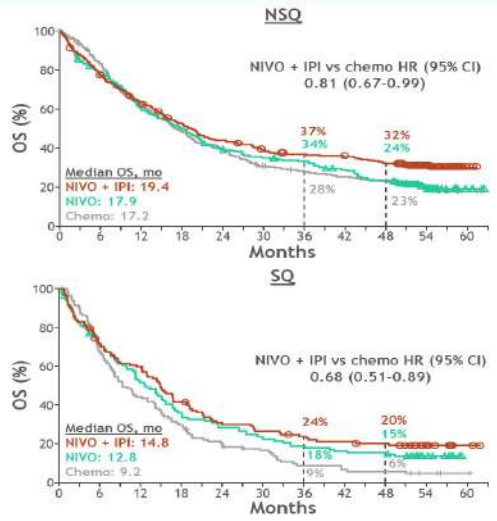
Nivolumab (NIVO) plus ipilimumab (IPI) versus chemotherapy (chemo) as first- line (1L) treatment for advanced non-small cell lung cancer (NSCLC): 4-year update from CheckMate 227



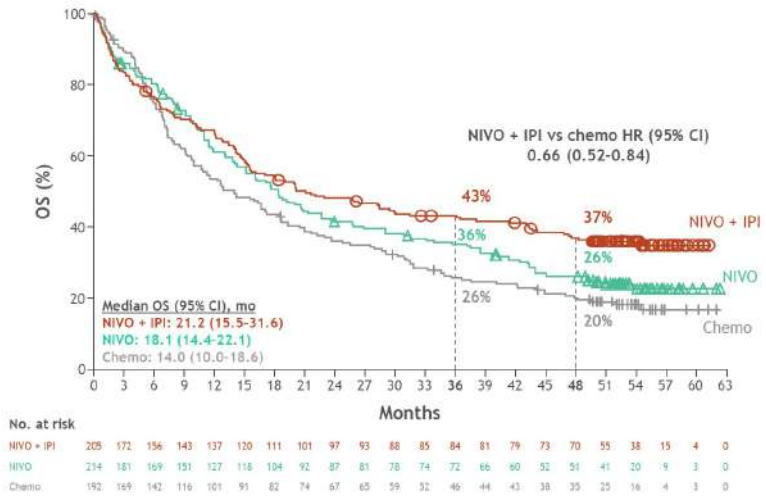
- Here we present updated 4-year efficacy and safety results for CheckMate 227 Part 1, and a post hoc efficacy analysis in patients who discontinued NIVO + IPI due to TRAEs

4-year OS in patients with PD-L1 ≥ 1%

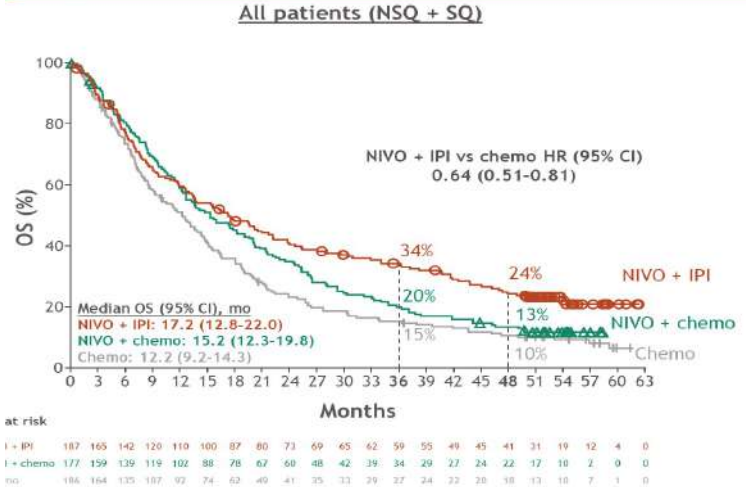


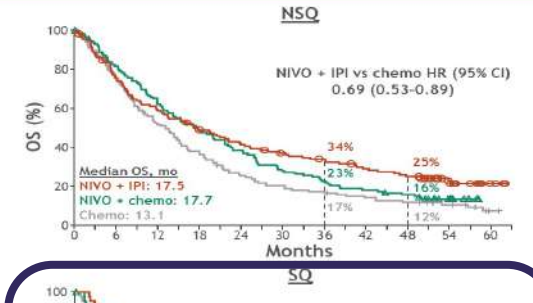


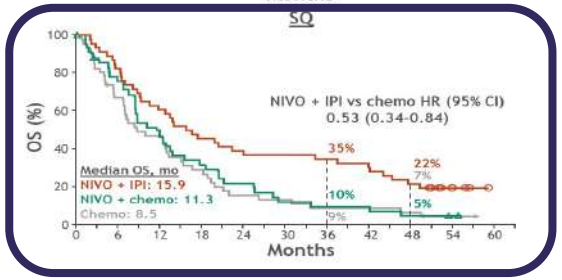
4-year OS in patients with PD-L1 ≥ 50%



4-year OS in patients with PD-L1 < 1%

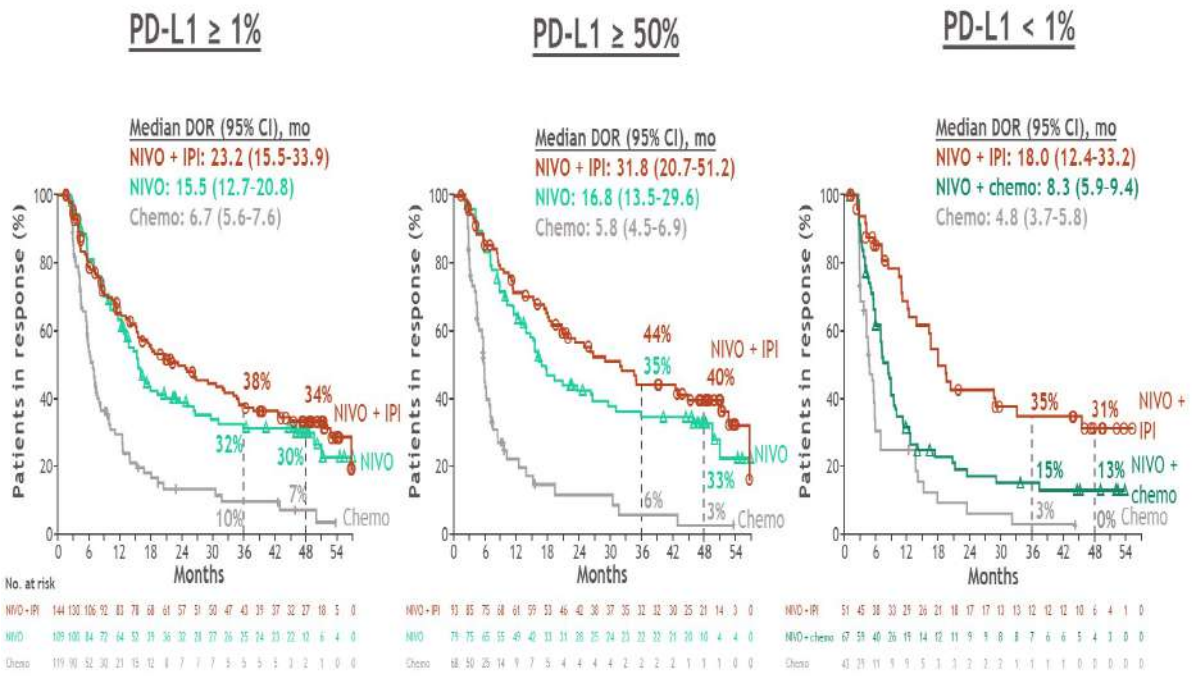




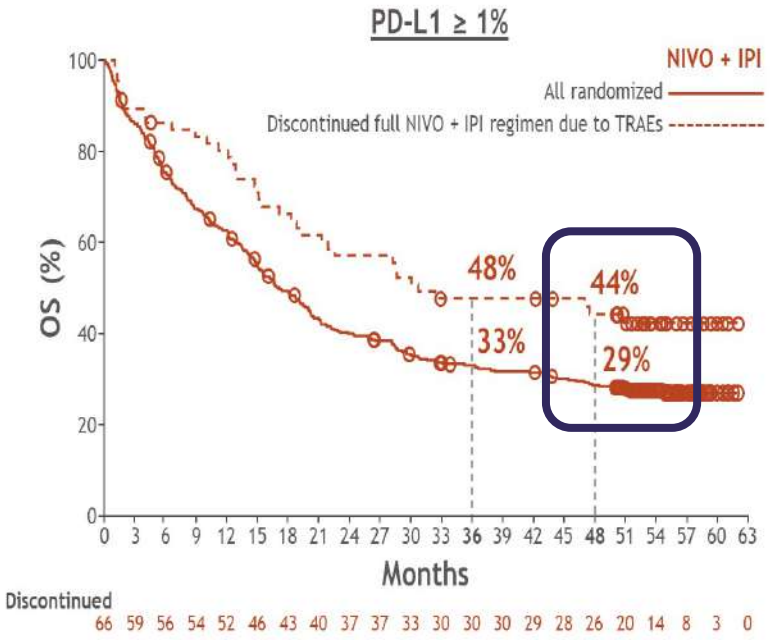


Nivolumab (NIVO) plus ipilimumab (IPI) versus chemotherapy (chemo) as first- line (1L) treatment for advanced non-small cell lung cancer (NSCLC): 4-year update from CheckMate 227

4-year update: DOR



Post hoc analysis: efficacy in patients who discontinued NIVO + IPI due to TRAEs[a]



	PD-L1 ≥ 1% (n = 66)	PD-L1 ≥ 1% and < 1% (n = 97)
Median OS, mo[b]	30.6	41.5
4-year OS rate, %	44	44
ORR, n (%)	35 (53)	50 (52)
Median DOR after discontinuation, mo[c]	52.6	34.2
Ongoing response for ≥ 3 years after discontinuation, %[c]	53	48

- 66 patients with PD-L1 ≥ 1% (17%) and 97 patients with PD-L1 ≥ 1% and < 1% (17%) treated with NIVO + IPI had TRAEs that led to discontinuation of all components of the regimen

Taken together, these updated results from CheckMate 227 continue to reinforce the positive benefit-risk profile of dual immunotherapy at 2 years after treatment discontinuation and support the use of NIVO + IPI as 1L treatment of patients with advanced NSCLC

Nivolumab (NIVO) plus ipilimumab (IPI) versus chemotherapy (chemo) as first- line (1L) treatment for advanced non-small cell lung cancer (NSCLC): 4-year update from CheckMate 227

4-year update: DOR

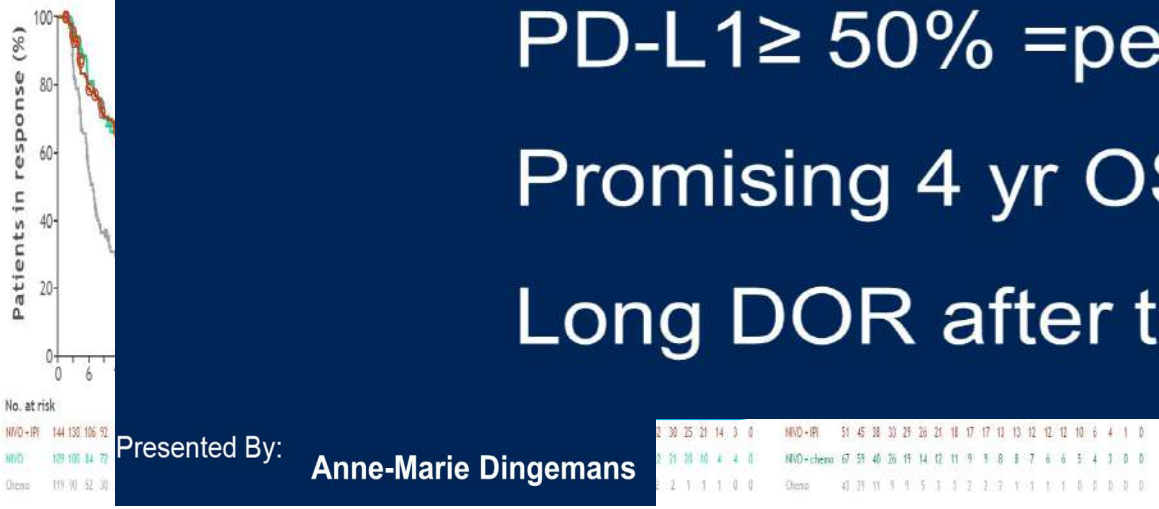
Post hoc analysis: efficacy in patients who discontinued NIVO + IPI due to TRAEs[a]

NIVO-IPI: 29% 4 yr OS in PD-L1≥1%, plateau reached?

PD-L1≥ 50% =pembro mono?

Promising 4 yr OS in PD-L1<1%

Long DOR after treatment discontinuation



	PD-L1 ≥ 1% and < 1% (n = 97)
	41.5
	44
	50 (52)
	34.2
	48

Presented By: **Anne-Marie Dingemans**

- 66 patients with PD-L1 ≥ 1% (17%) and 97 patients with PD-L1 ≥ 1% and < 1% (17%) treated with NIVO + IPI had TRAEs that led to discontinuation of all components of the regimen

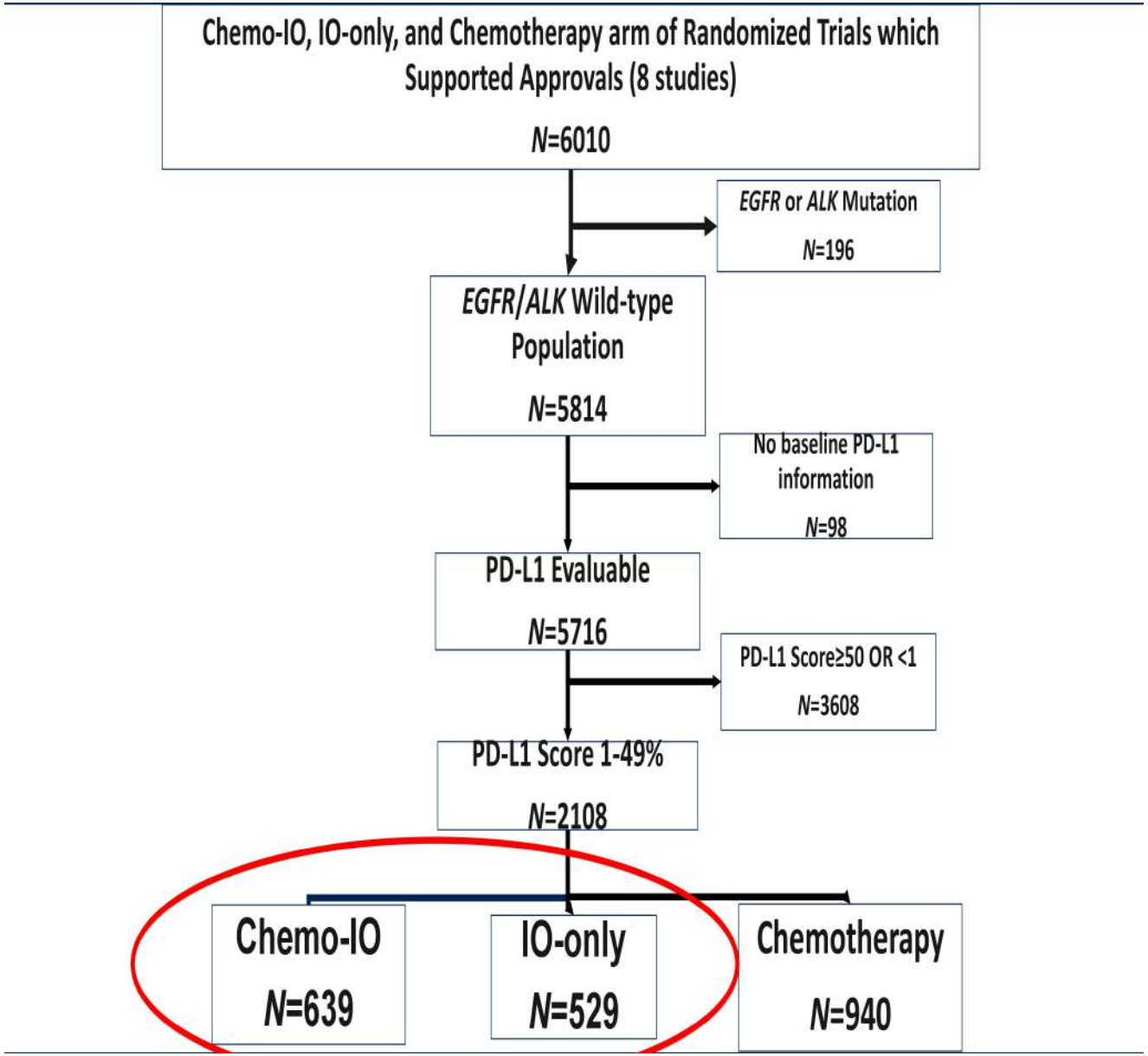
Taken together, these updated results from CheckMate 227 continue to reinforce the positive benefit-risk profile of dual immunotherapy at 2 years after treatment discontinuation and support the use of NIVO + IPI as 1L treatment of patients with advanced NSCLC

Luis G Paz-Ares

Outcomes of anti-PD-(L1) therapy in combination with chemotherapy versus immunotherapy (IO) alone for first-line (1L) treatment of advanced non-small cell lung cancer (NSCLC) with PD-L1 score 1-49%: FDA pooled analysis

Trial*	Active treatment
Immunotherapy-only (PD-L1 ≥1%)	
KEYNOTE-042	**Pembrolizumab**
CHECKMATE-227	**Nivolumab plus Ipilimumab**
Chemo-immunotherapy	
KEYNOTE-189	**Pembrolizumab** plus Platinum-doublet chemo
KEYNOTE-407	**Pembrolizumab** plus Platinum-doublet chemo
KEYNOTE-021 (cohort G)	**Pembrolizumab** plus Platinum-doublet chemo
IMPOWER-150**	**Atezolizumab** plus Bevacizumab plus Platinum-doublet chemo
IMPOWER-130	**Atezolizumab** plus Platinum-doublet chemo
CA2099LA	**Nivolumab plus Ipilimumab** plus Platinum-doublet chemo

*Control arms: Platinum-doublet chemotherapy
**Control arm in IMPOWER-150: Bevacizumab plus Platinum-doublet chemotherapy

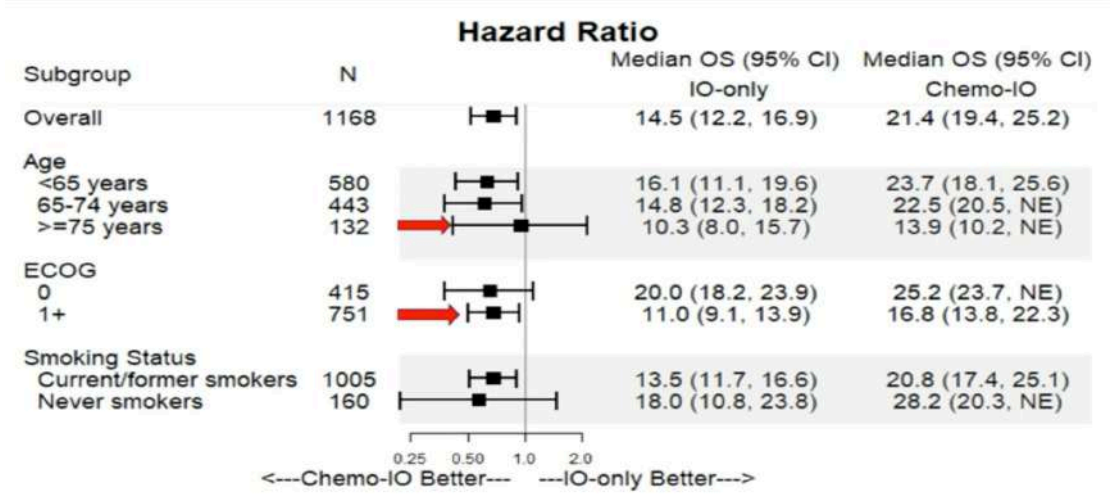


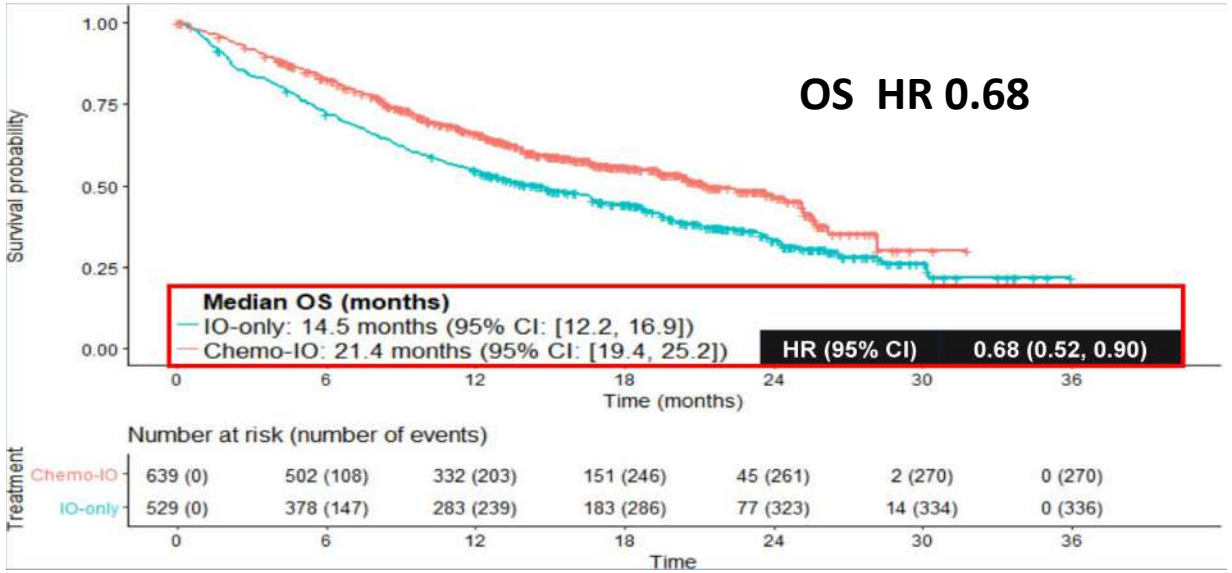
Outcomes of anti-PD-(L1) therapy in combination with chemotherapy versus immunotherapy (IO) alone for first-line (1L) treatment of advanced non-small cell lung cancer (NSCLC) with PD-L1 score 1-49%: FDA pooled analysis

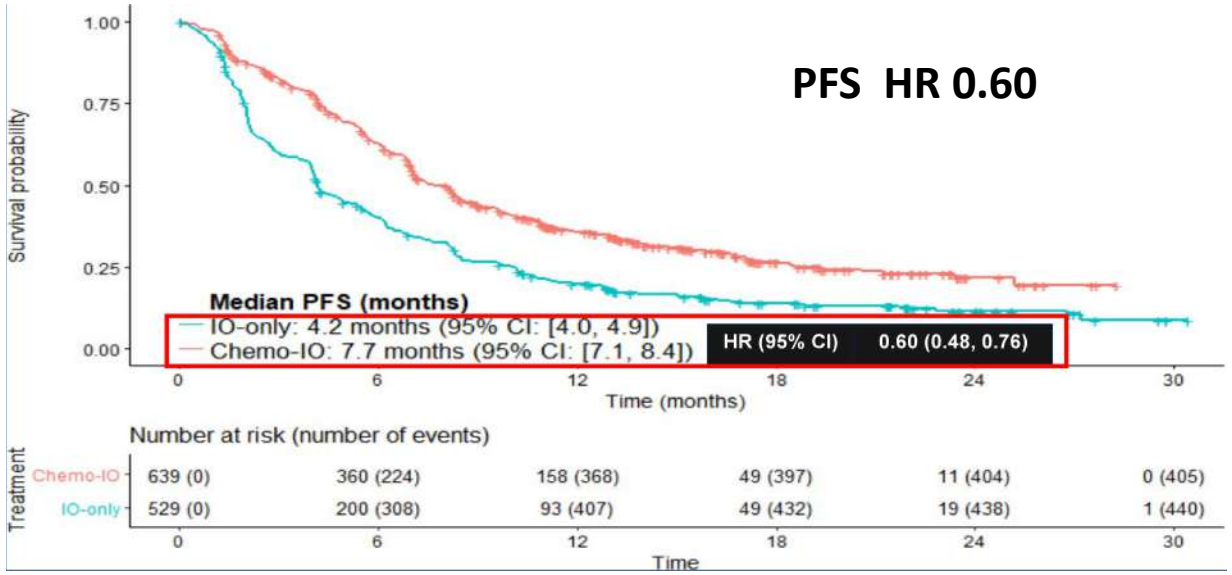
Demographic and baseline characteristics

FDA

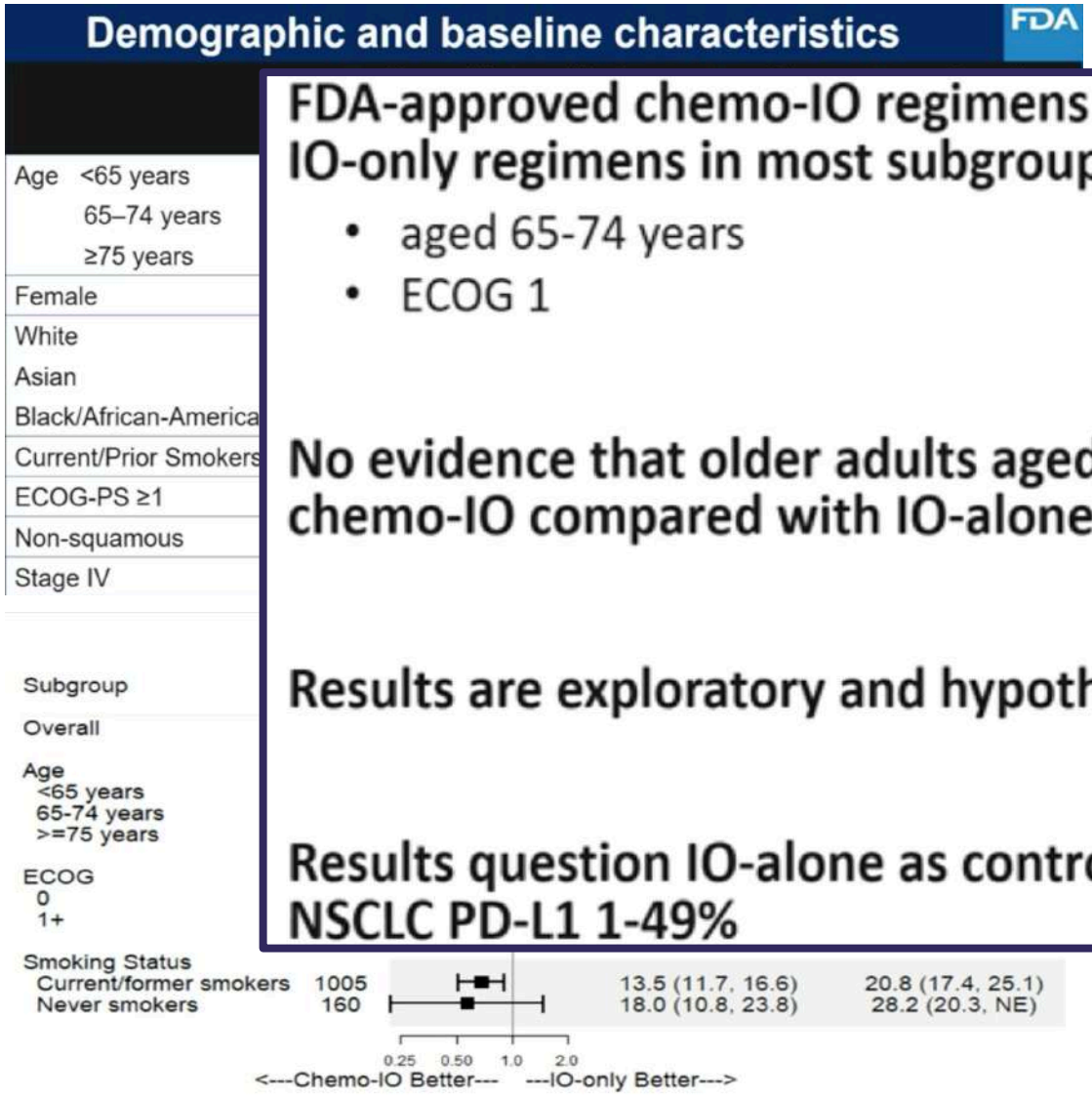
	Chemo-IO (*N*=639) %	IO alone (*N*=529) %	Chemo (*N*=940) %	Overall (*N*=2108) %
Age <65 years	48	53	53	51
65–74 years	40	36	36	37
≥75 years	11	11	12	12
Female	35	31	32	33
White	88	69	78	79
Asian	9	23	19	17
Black/African-American	2	2	2	2
Current/Prior Smokers	91	81	84	85
ECOG-PS ≥1	62	67	67	65
Non-squamous	77	63	64	68
Stage IV	89	91	92	91

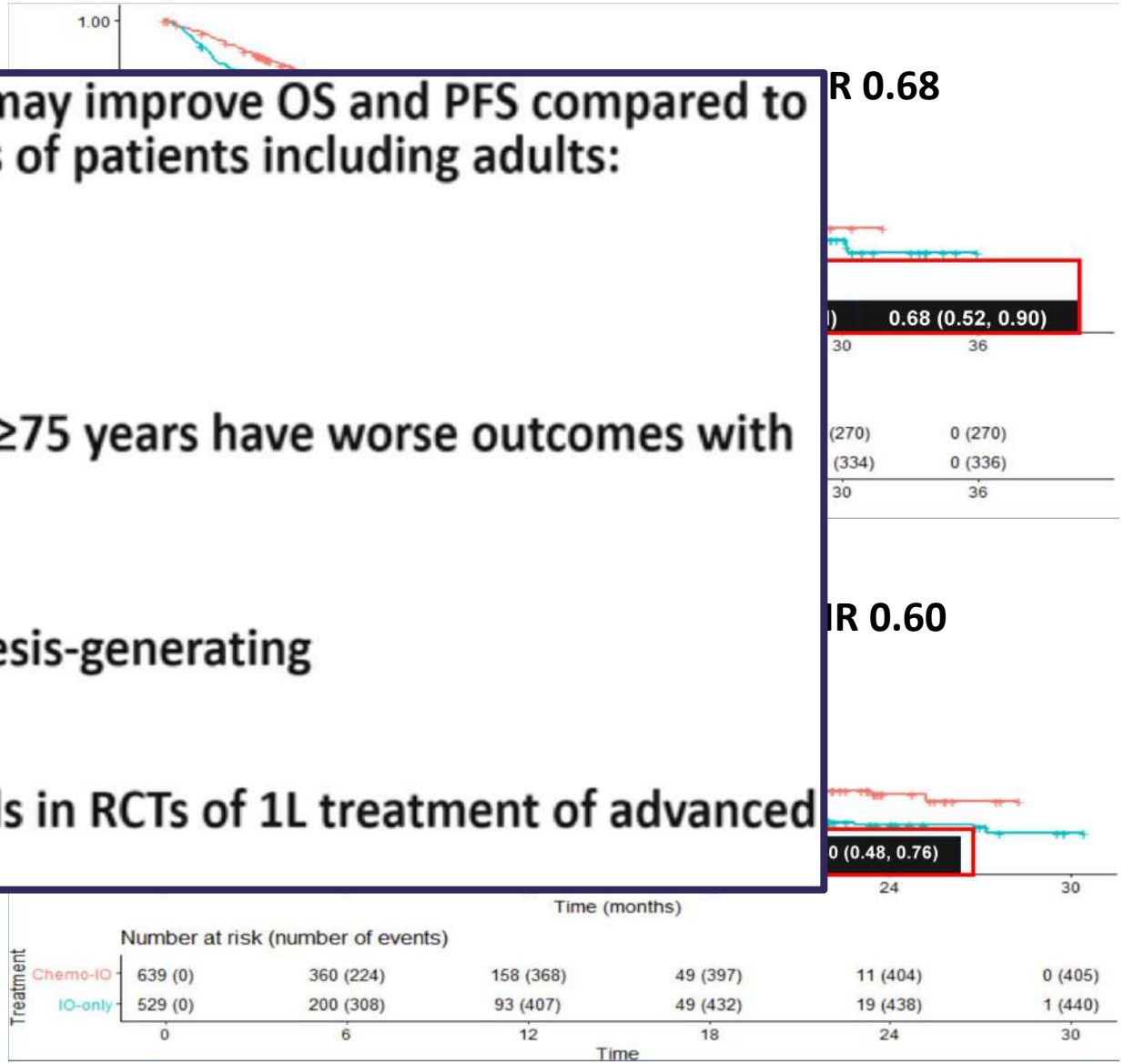






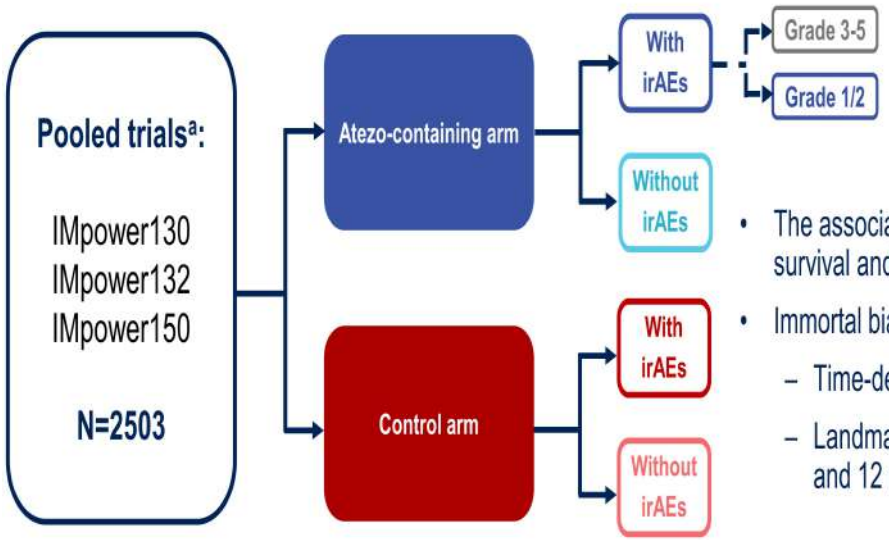
Outcomes of anti-PD-(L1) therapy in combination with chemotherapy versus immunotherapy (IO) alone for first-line (1L) treatment of advanced non-small cell lung cancer (NSCLC) with PD-L1 score 1-49%: FDA pooled analysis





Pooled analyses of immune-related adverse events (irAEs) and efficacy from the phase 3 trials IMpower130, IMpower132, and IMpower150. (Mark A. Socinski)

Methods and analysis plan



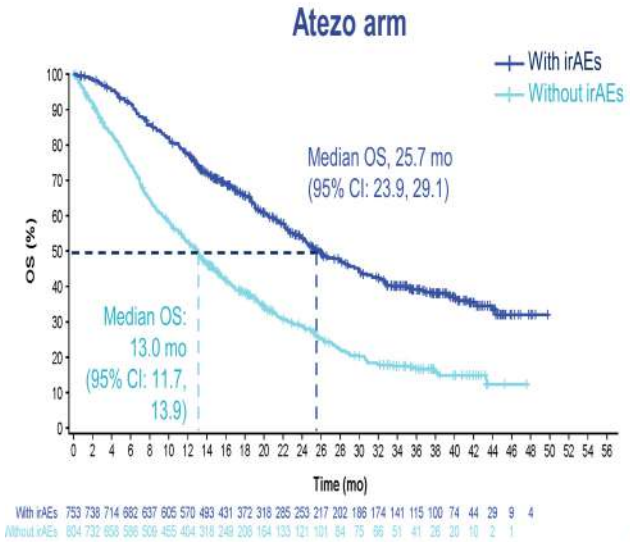
- The association between overall survival and irAEs was explored
- Immortal bias was managed by using:
  - Time-dependent Cox model
  - Landmark analyses at 1, 3, 6 and 12 months

irAEs

Defined using the Medical Dictionary for Regulatory Activities preferred terms, which included diagnosed immune conditions as well as signs and symptoms potentially representative of immune-related events regardless of investigator-assessed causality

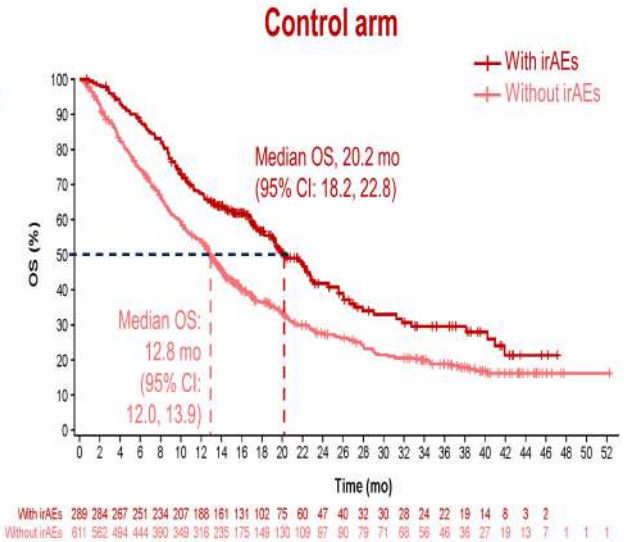
OS by irAE status[a,b]

n = 1577



Time-dependent Cox model:
HR, 0.69 (95% CI: 0.60, 0.78)

n = 926



Time-dependent Cox model:
HR, 0.82 (95% CI: 0.68, 0.99)

Patients who experienced irAEs had longer OS than those without irAEs in both the atezo-containing and control arms

Pooled analyses of immune-related adverse events (irAEs) and efficacy from the phase 3 trials IMpower130, IMpower132, and IMpower150. (Mark A. Socinski)

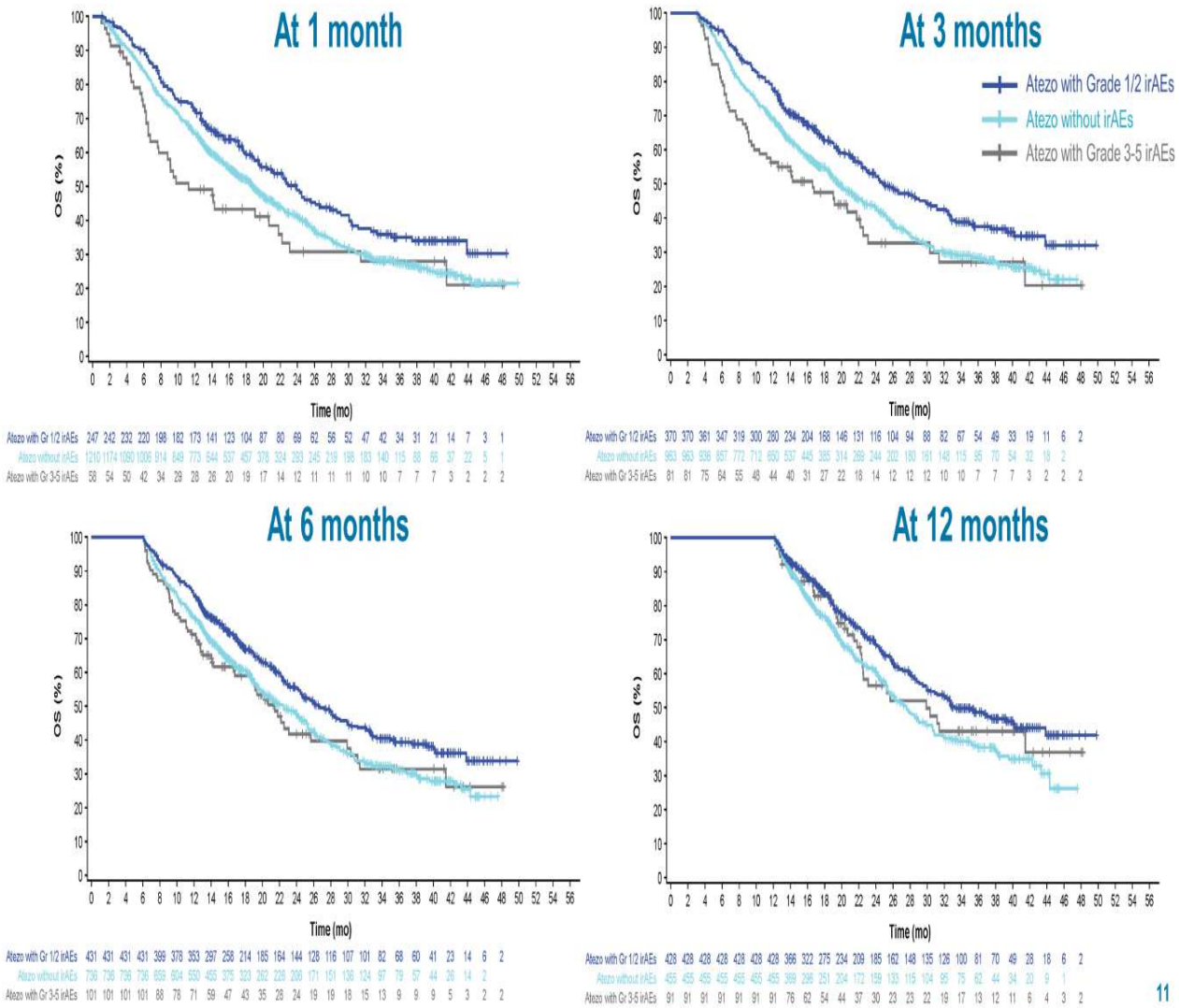
OS landmark by irAE status (cont)

		Atezo arm		Control arm		Atezo vs control HR[a] (95% CI)	
		With irAEs	Without irAEs	With irAEs	Without irAEs	With irAEs	Without irAEs
1 month	n	305	1210	116	764	**0.82** (0.61, 1.09)	**0.81** (0.72, 0.91)
	median OS, mo	22.2	18.9	19.3	14.3		
	HR[a] (95% CI)	**0.85** (0.72, 1.01)		**0.85** (0.66, 1.10)			
3 months	n	451	963	180	625	**0.74** (0.58, 0.93)	**0.84** (0.74, 0.96)
	median OS, mo	23.1	19.6	19.1	16		
	HR[a] (95% CI)	**0.81** (0.70, 0.94)		**0.92** (0.74, 1.14)			
6 months	n	532	736	197	498	**0.79** (0.63, 0.99)	**0.87** (0.75, 1.01)
	median OS, mo	25.6	22.4	21.8	19.3		
	HR[a] (95% CI)	**0.82** (0.70, 0.95)		**0.89** (0.71, 1.12)			
12 months	n	519	455	175	175	**0.91** (0.68, 1.22)	**0.84** (0.68, 1.04)
	median OS, mo	32.7	27.5	31.8	25.5		
	HR[a] (95% CI)	**0.75** (0.61, 0.91)		**0.67** (0.50, 0.91)			

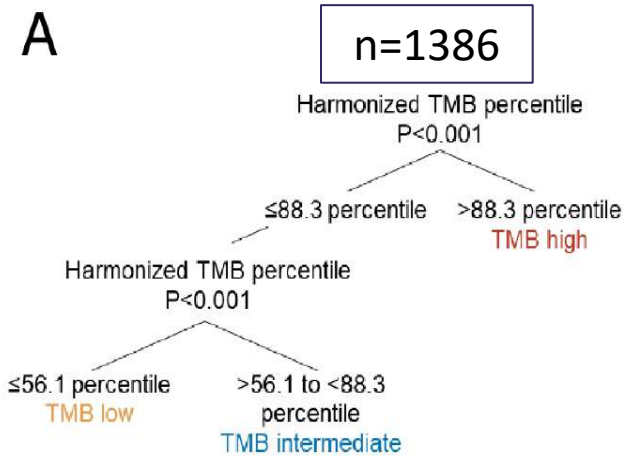
OS by irAE grade in the atezolizumab arm (cont)

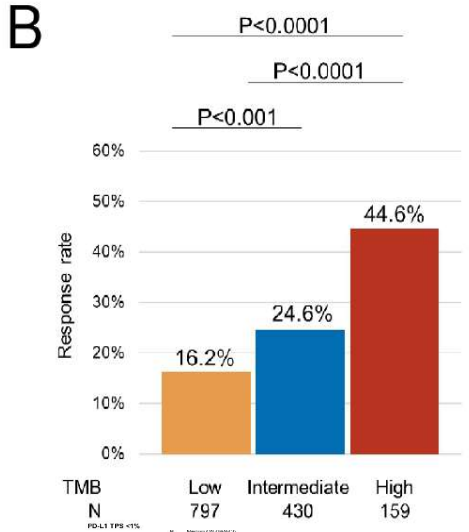
		With Grade 1/2 irAEs	With Grade 3-5 irAEs	Without irAEs
1 month	n	247	58	1210
	median OS, mo	23.8	11.3	18.9
	HR[a] (95% CI)	**0.78** (0.65, 0.94)	**1.25** (0.90, 1.72)	–
3 months	n	370	81	963
	median OS, mo	24.8	16.6	19.6
	HR[a] (95% CI)	**0.74** (0.63, 0.87)	**1.23** (0.93, 1.64)	–
6 months	n	431	101	736
	median OS, mo	26.6	21.5	22.4
	HR[a] (95% CI)	**0.77** (0.65, 0.90)	**1.1** (0.81, 1.42)	–
12 months	n	428	91	455
	median OS, mo	33.4	29.9	27.5
	HR[a] (95% CI)	**0.72** (0.59, 0.89)	**0.87** (0.61, 1.25)	–

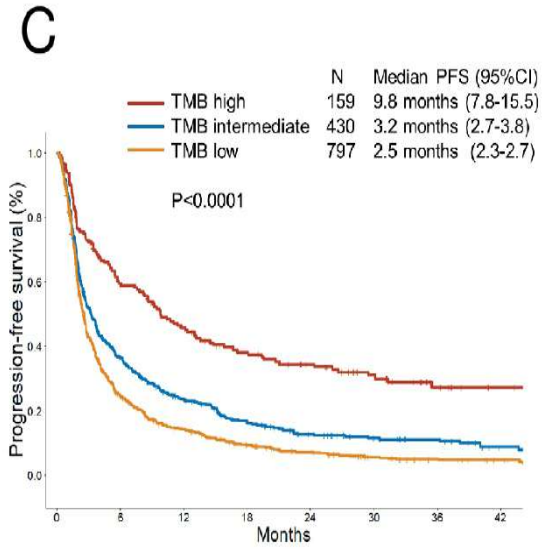
OS by irAE grade in the atezolizumab arm

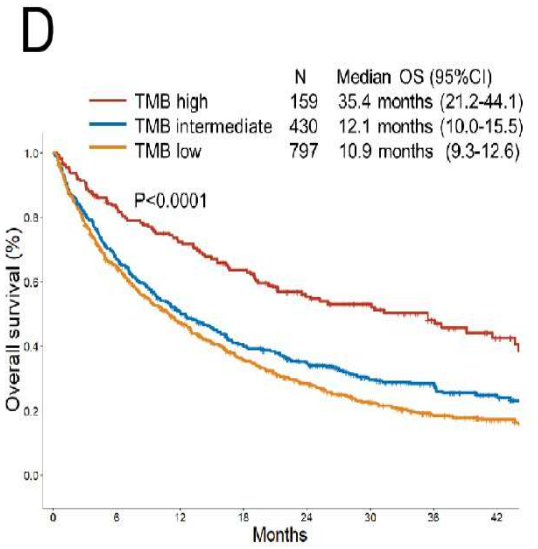


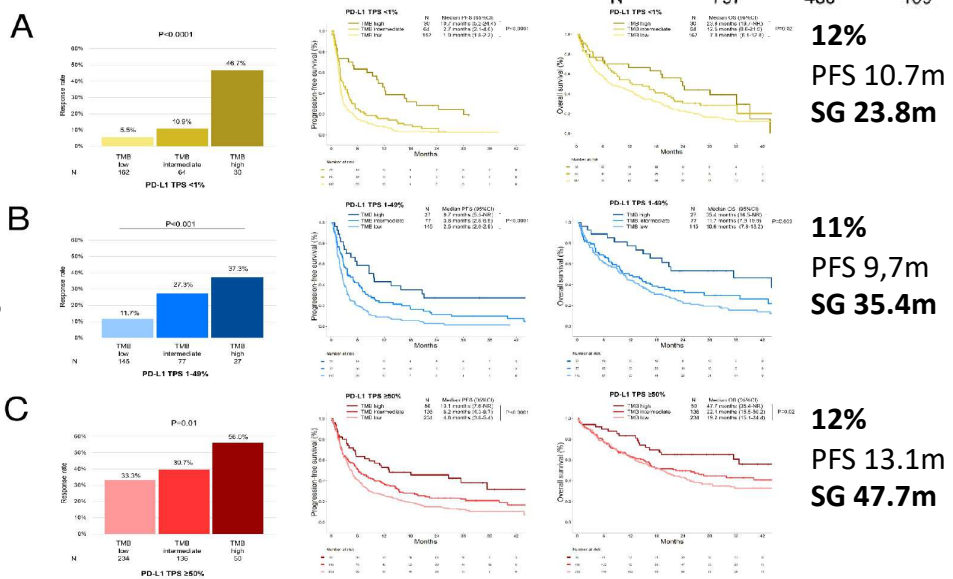
Association of a very high tumor mutational load with increased CD8+ and PD-1+ T-cell infiltration and improved clinical outcomes to PD-(L)1 blockade across different PD-L1 expression levels in non-small cell lung cáncer. (Ricciuti et al.)











PD-L1 <1%

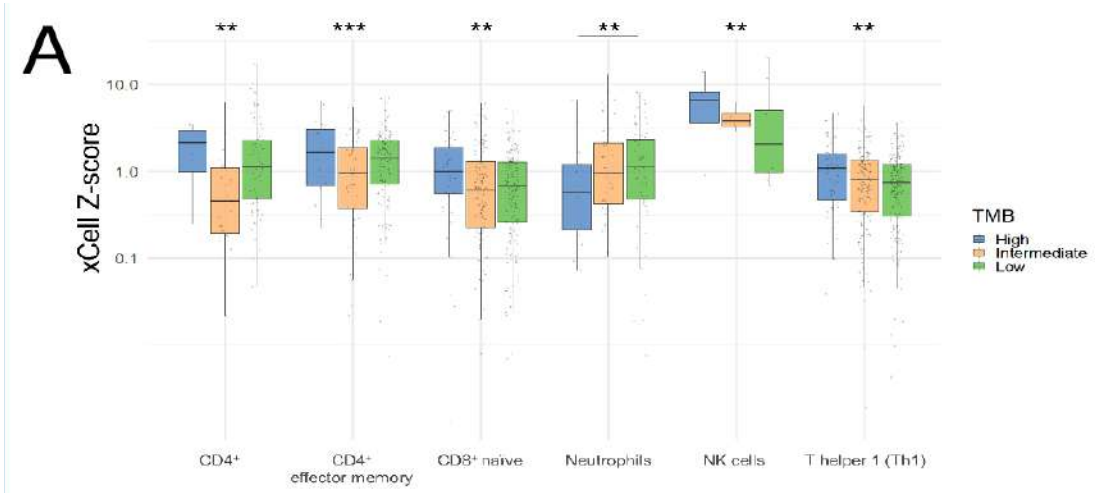
12%
PFS 10.7m
SG 23.8m

PD-L1 1-49%

11%
PFS 9,7m
SG 35.4m

PD-L1 >50%

12%
PFS 13.1m
SG 47.7m



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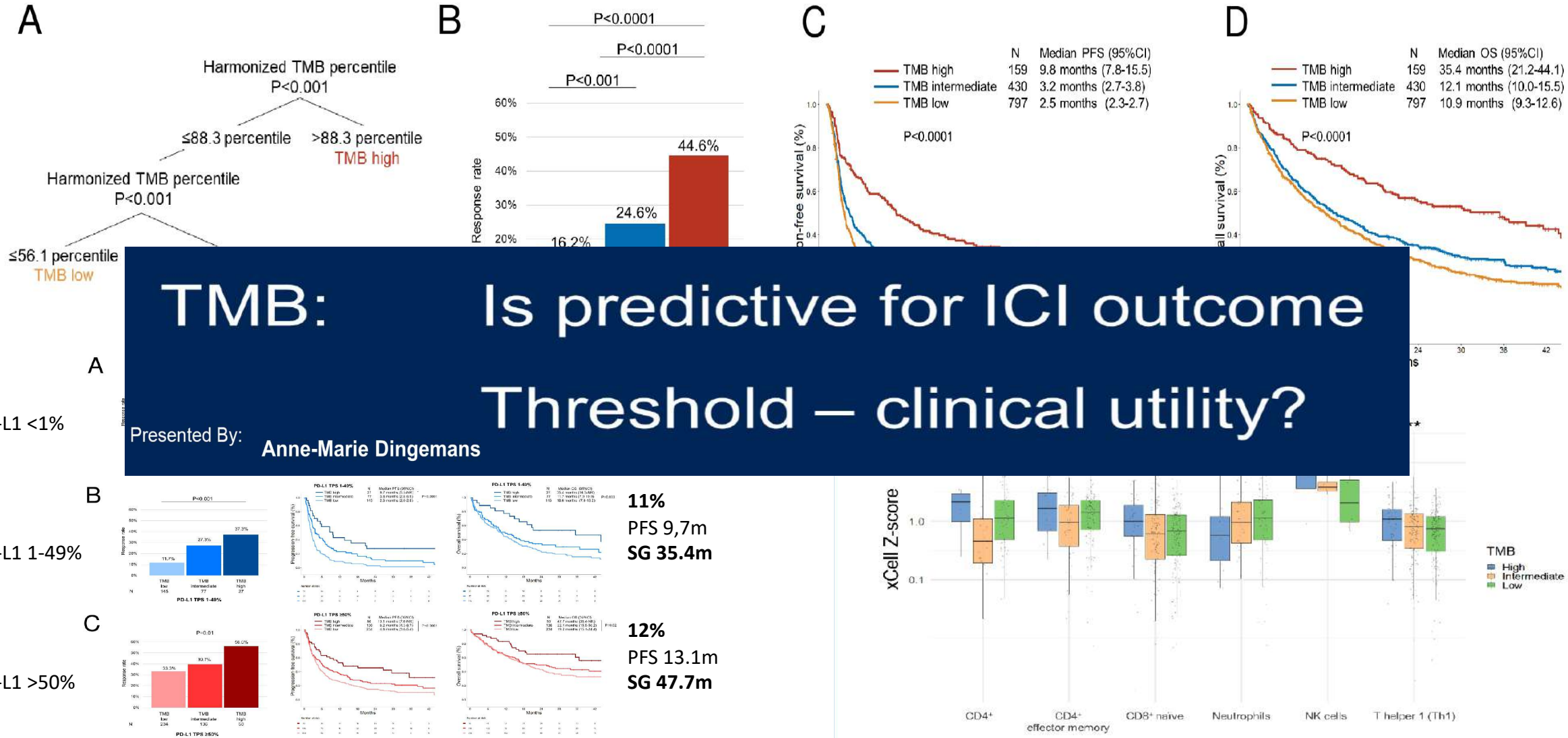

Effect of antibiotic therapy on immunotherapy outcomes for non-small cell lung cancer: Analysis from the Veterans Health Administration Database. (Strokes et al.)

Methods:

- **Retrospective cohort study** of Veterans diagnosed with NSCLC 2010-2018 and treated with ICI
- **Two Abx exposures** defined *a priori*:
  1) prior (pAbx): receipt of Abx **≤30d before** ICI start
  2) concurrent (cAbx): receipt of Abx **<60d after** ICI start
- **Primary Outcome**: overall survival (OS) from ICI start
  Kaplan-Meier, Cox Proportional Hazards,
  Propensity Score Matching

Results:

3,634 Veterans received ICI

- mostly nivolumab (59.3%) & pembrolizumab (35.1%)
- median age 69, 97% male, 73% white, 48% adenoca

Original Cohort

pAbx	No.	median OS *months*	Cox MVA HR	Cox MVA 95%CI
no	2,872	10	-	-
yes	762	7	1.31	1.20-1.44

Propensity-Score Matched Subset

pAbx	No.	median OS *months*	Cox UVA HR	Cox UVA 95%CI
no	760	9	-	-
yes	760	7	1.27	1.14-1.41

Original Cohort Surviving to 60-Day Landmark

cAbx	No.	median OS *months*	Cox MVA HR	Cox MVA 95%CI
no	2,253	10	-	-
yes	970	7	1.33	1.21-1.45

Propensity-Score Matched Subset

cAbx	No.	median OS *months*	Cox UVA HR	Cox UVA 95%CI
no	968	10	-	-
yes	968	7	1.32	1.19-1.46

Abstract 9017: William A. Stokes[1,2],

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- **Two Ab**
  1) pric
  2) con
- **Primar**
  Kaplan
  Proper

Antbiotics and ICI:

Related with worse outcome

Educate

Restore microbiome?

Presented By: **Anne-Marie Dingemans**

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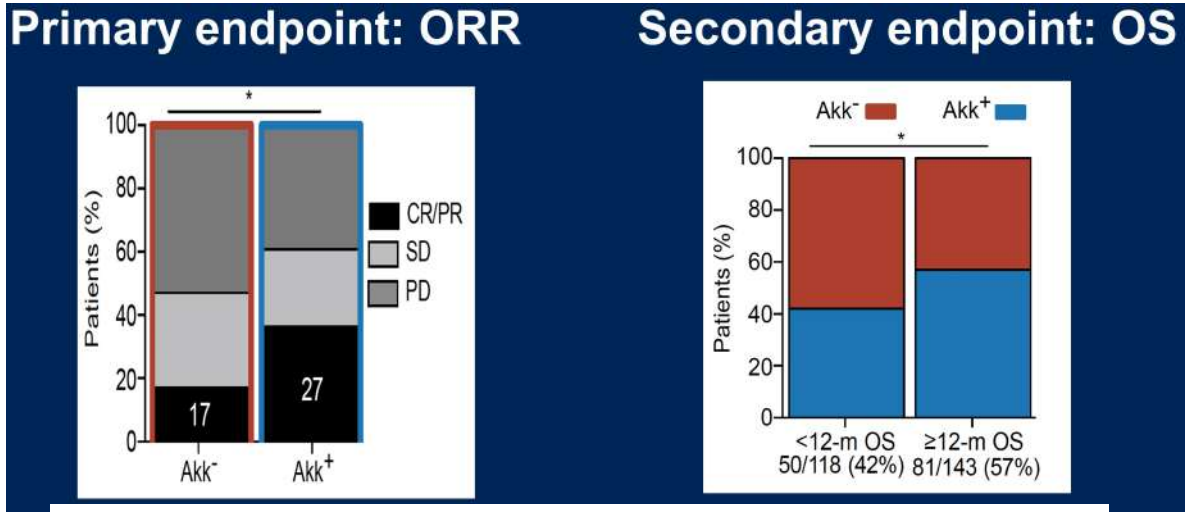

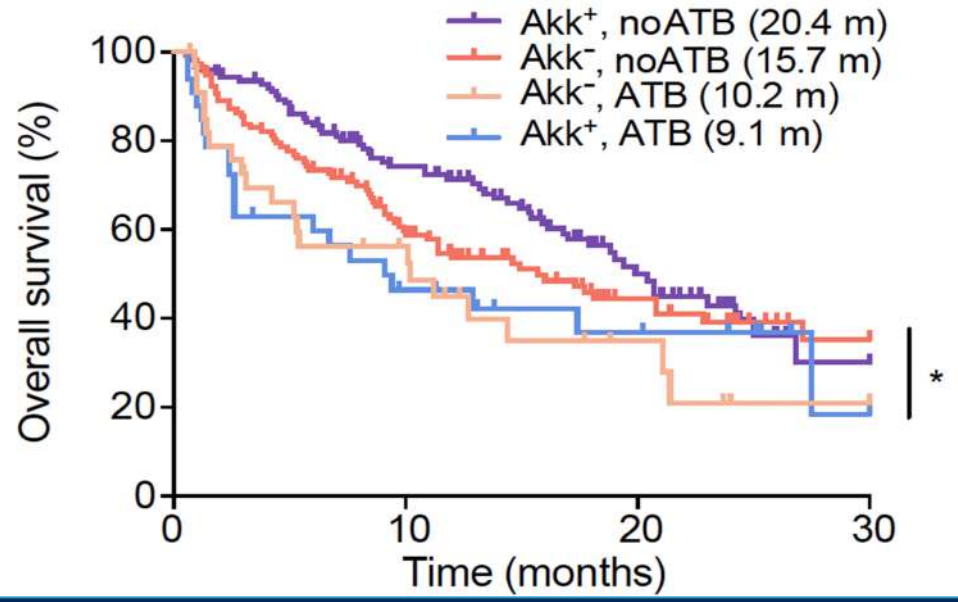

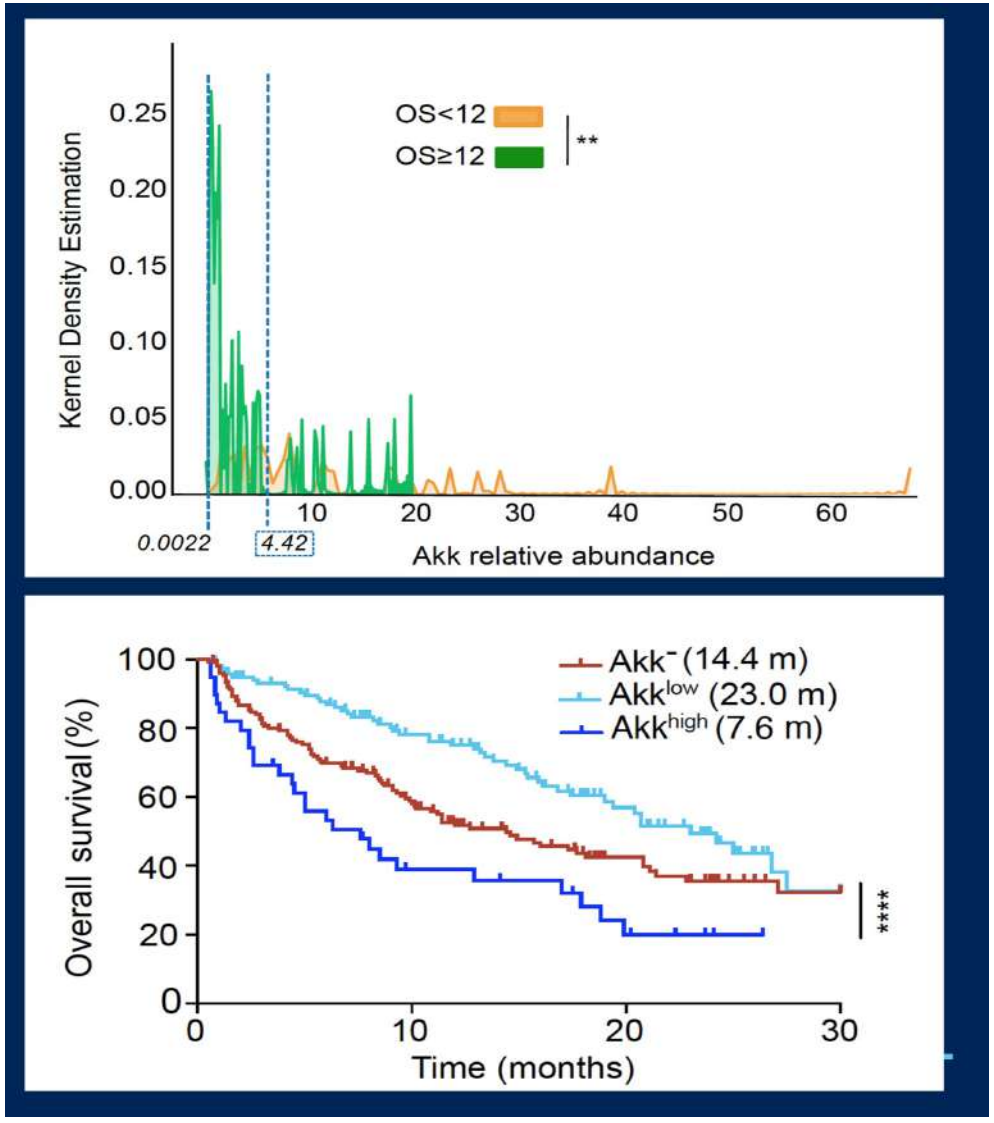

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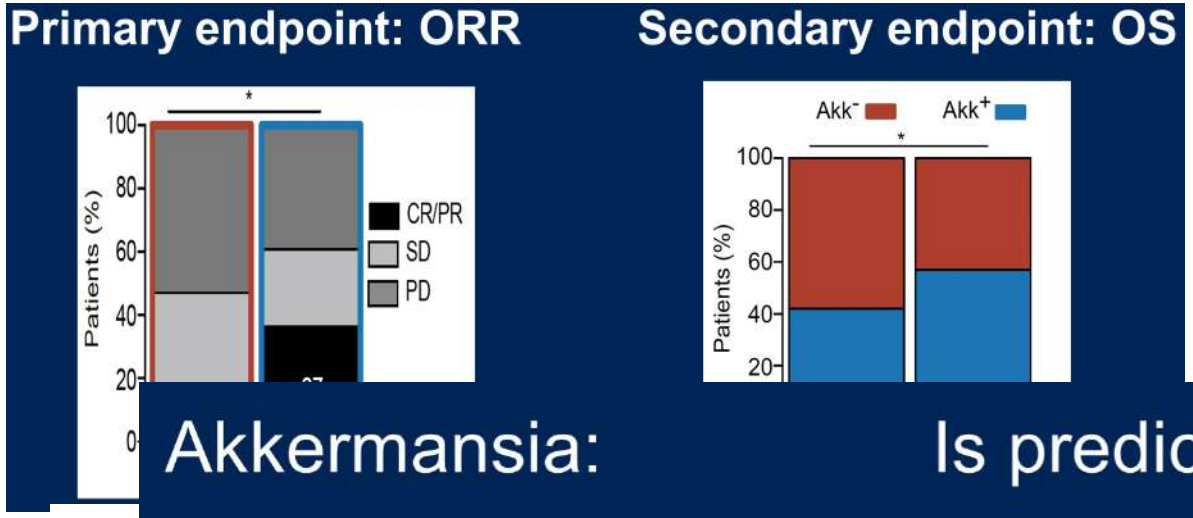
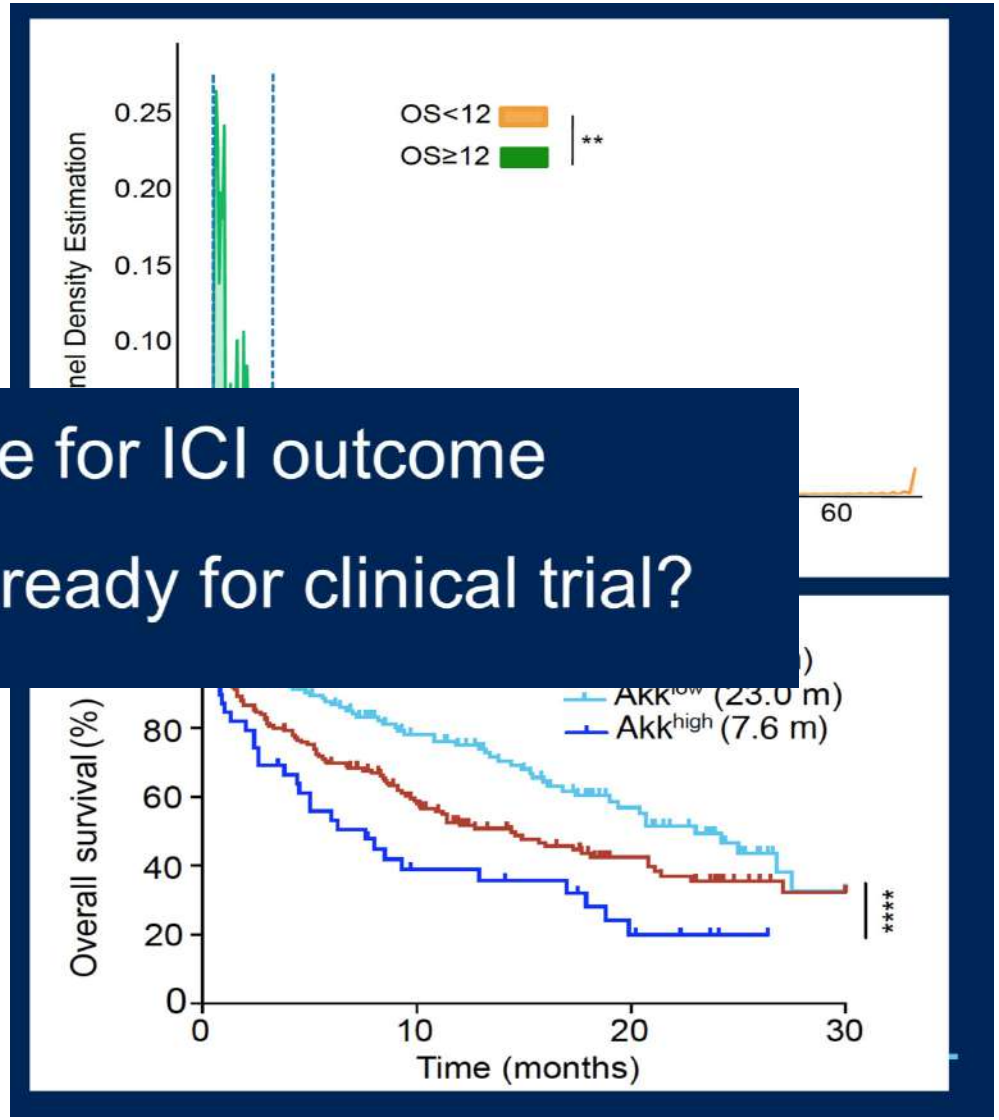
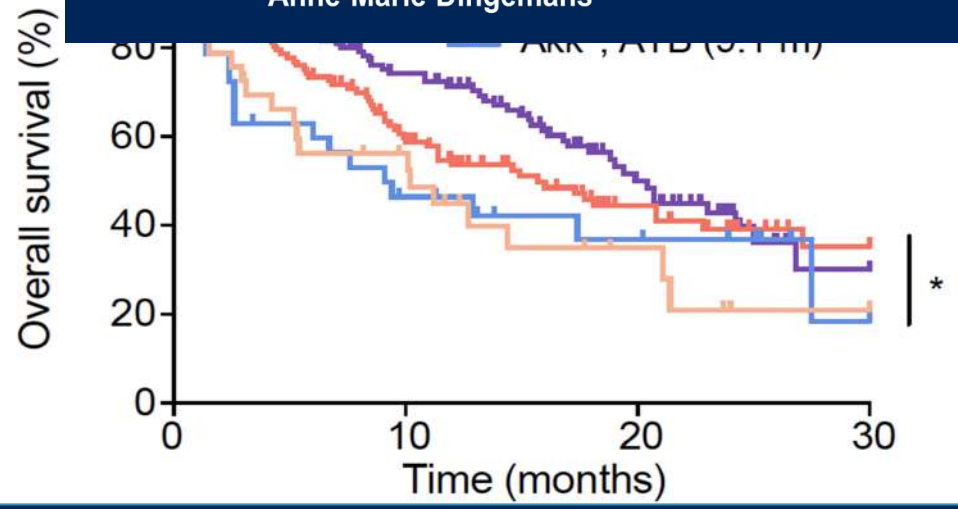




Akkermansia: Is predictive for ICI outcome

Biomarker ready for clinical trial?

Presented By: **Anne-Marie Dingemans**



Lung Cancer UPDATES
ASCO HIGHLIGTHS
04-08 JUNIO 2021

Iniciativa científica de:
GECP
lung cancer research

GRACIAS POR LA ATENCIÓN

Natividad Martínez Banaclocha

Hospital General Universitario de Alicante