TUMORI TORACICI: NUOVE PROSPETTIVE

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Modulo dichiarazione conflitto di interessi

Tutti i rapporti finanziari intercorsi negli ultimi due anni devono essere dichiarati.

☐ Non ho rapporti (finanziari o di altro tipo) con le Aziende del farma

☐ x Ho / ho avuto rapporti (finanziari o di altro tipo) con le Aziende del farmaco

Relationship	Company/Organization
Advisory board	Eli Lilly, Astra Zeneca, Boheringer,
Speaker	BMS, Astra Zeneca, Roche
Clinical trials investigator	Spectrum farmaceutics, Roche, Merck, BMS, Takeda, Astra Zeneca

AGENDA

mNSCLC

ONCOGENE ADDICTED

- FLAURA OS
- FINAL OS AURA 3

IMMUNOTHERAPY

- IO-IO COMBO (CM 227)
- IO vs CHEMO (IMP 110)
- TMB (PEMBRO TRIALS)

Extended SCLC

- CHEMO-IMMUNO

Mesothelioma

- IMMUNO

Thymic carcinoma

- REMORA trial

AGENDA

mNSCLC

ONCOGENE ADDICTED

- FLAURA OS
- FINAL OS AURA 3 (ESMO ASIA)

IMMUNOTHERAPY

- TMB (PEMBRO TRIALS)
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Extended SCLC

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EGFR+

ORIGINAL ARTICLE

Overall Survival with Osimertinib in Untreated, *EGFR*-Mutated Advanced NSCLC

This article was published on November 21, 2019, at NEJM.org.

EGFR+

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FLAURA DOUBLE-BLIND STUDY DESIGN

Patients with locally advanced or metastatic NSCLC

Key inclusion criteria
- ≥18 years (≥20 years in Japan)
- WHO performance status 0 / 1
- Ex19del / L858R (enrolment by local or central EGFR testing)
- No prior systemic anticancer / EGFR-TKI therapy
- Stable CNS metastases allowed

Stratification by **mutation status** (Ex19del / L858R) and **race** (Asian / non-Asian)

Randomised 1:1

- **Osimertinib** (80 mg p.o. qd) (n=279)
- Comparator EGFR-TKI **Gefitinib** (250 mg p.o. qd) or **Erlotinib** (150 mg p.o. qd) (n=277)

RECIST 1.1 assessment every 6 weeks until objective progressive disease. Following the primary PFS analysis, progression events by RECIST 1.1 were no longer centrally collected

Crossover was allowed for patients in the **comparator EGFR-TKI** arm, who could receive open-label osimertinib upon central confirmation of progression* and T790M positivity

OS was a key secondary endpoint

20%

- Final OS analysis planned for when approximately 318 death events had occurred
- For statistical significance, a p-value of less than 0.0495, determined by O'Brien-Fleming approach, was required
  - Alpha spend for interim OS analysis was 0.0015
- At data cut-off, 61 patients (22%) in the osimertinib arm and 13 patients (5%) in the comparator arm were ongoing study treatment

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Data cut-off: 25 June 2019

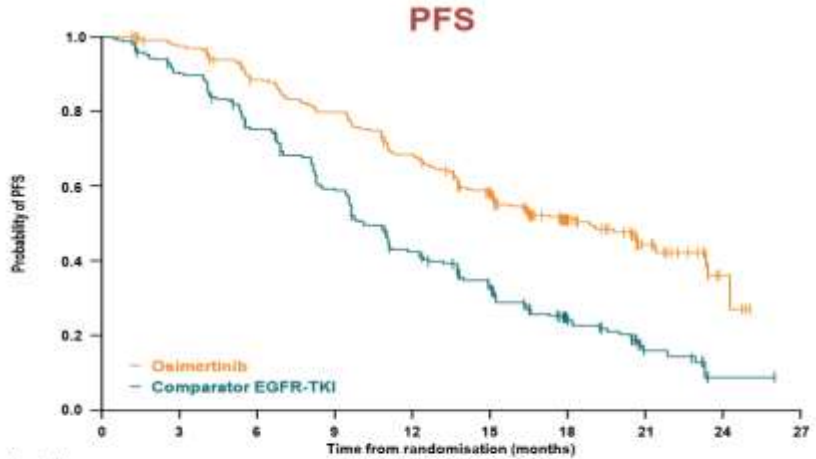
Soria et al. N Engl J Med 2018;378:113-25

*By investigator assessment if disease progression occurred after the primary analysis data cut-off

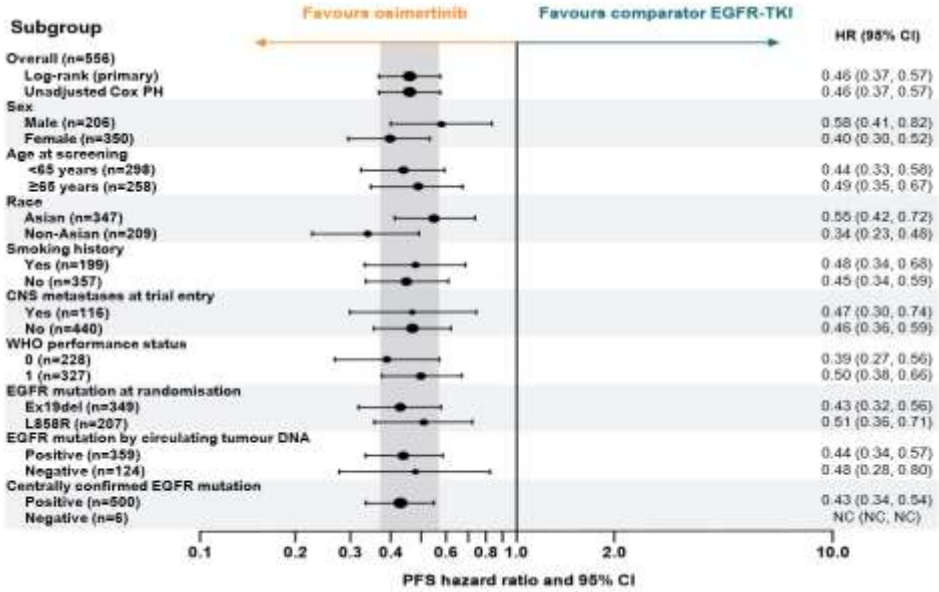
p.o., orally; qd, once daily; RECIST 1.1, Response Evaluation Criteria In Solid Tumors version 1.1; WHO, World Health Organization

EGFR+

PRIMARY ANALYSIS: PROGRESSION-FREE SURVIVAL



	Median PFS, months (95% CI)	HR (95% CI)
Osimertinib	18.9 (15.2, 21.4)	0.46 (0.37, 0.57); p<0.001
Comparator EGFR-TKI	10.2 (9.6, 11.1)	



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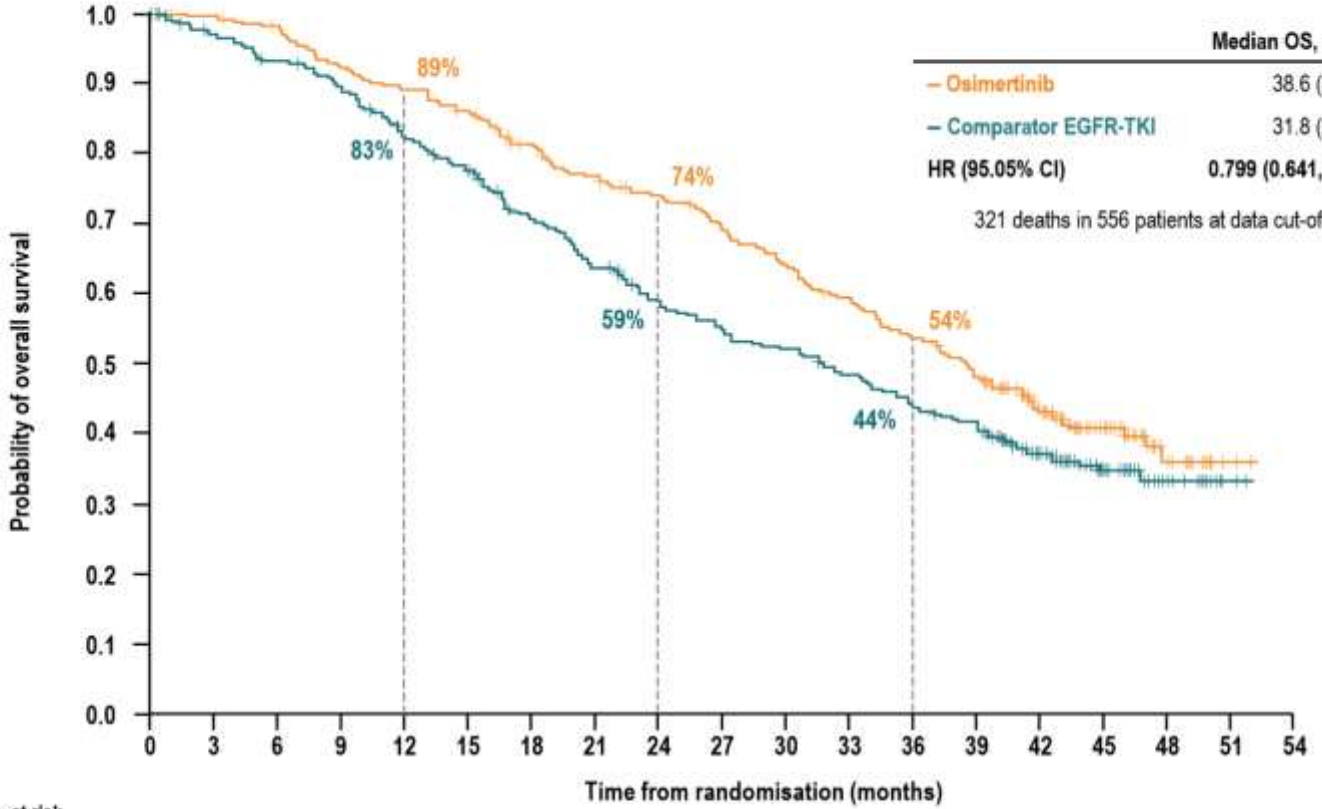
Data cut-off: 12 June 2017

Soria et al. N Engl J Med 2018;378:113-25

CI, confidence interval; ctDNA, circulating tumour DNA; NC, not calculable; PH, proportional-hazards

FINAL ANALYSIS: OVERALL SURVIVAL

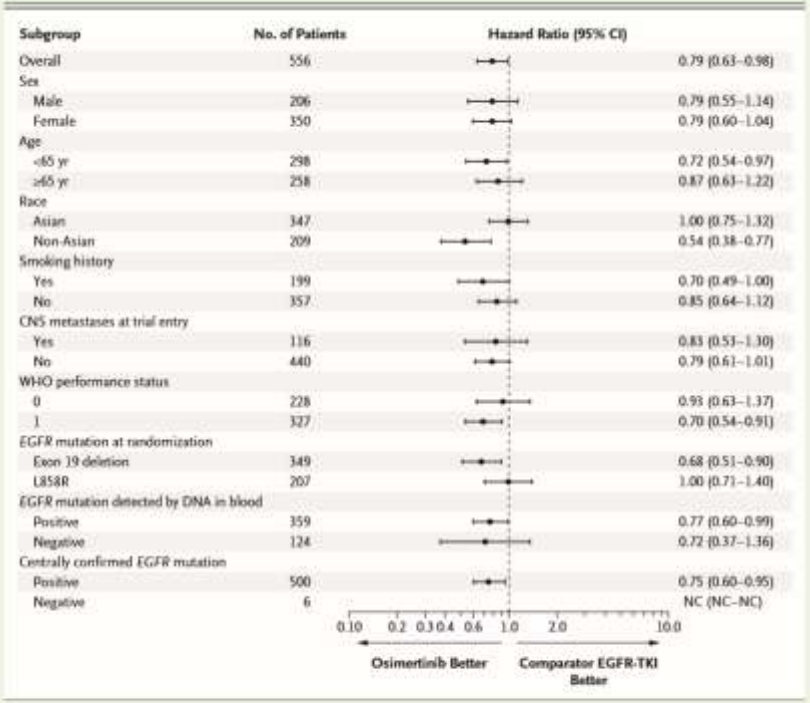


After three years, 28% of patients in the osimertinib arm and 9% of patients in the comparator EGFR-TKI arm remained on first-line study treatment

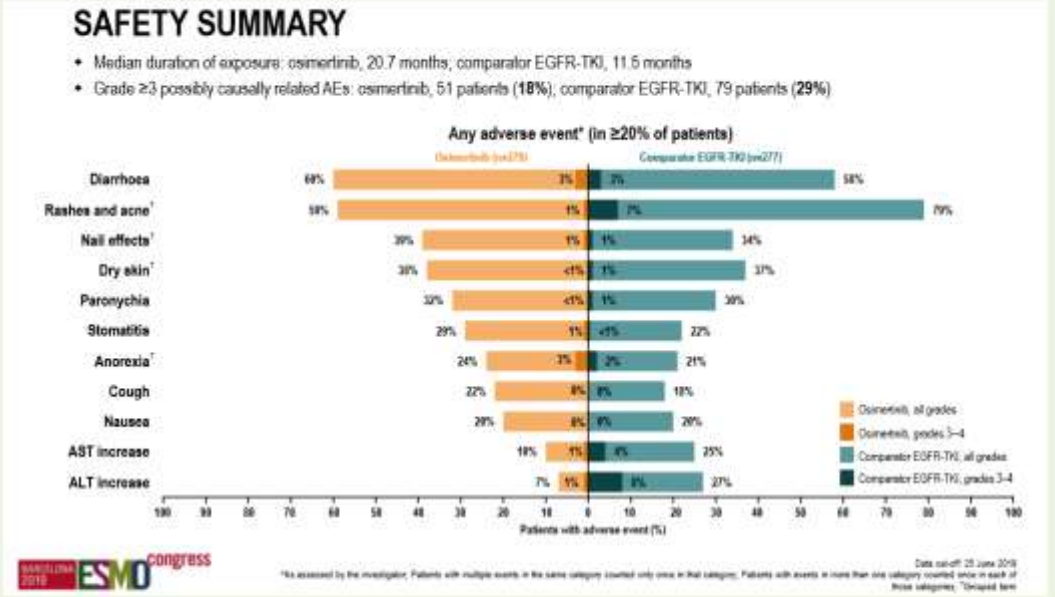
S Ramalingam ESMO 2019

EGFR+

SUBGROUP ANALYSIS FOR OS

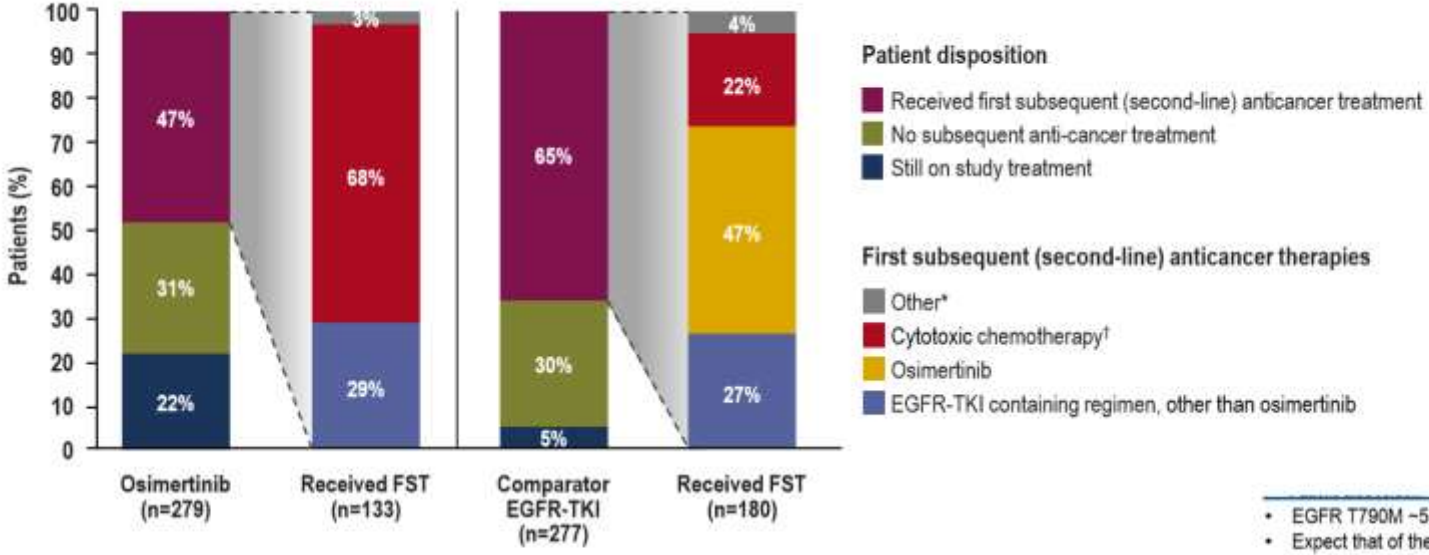


SAFETY



SECOND-LINE TREATMENT FOLLOWING PROGRESSION

- Of the 180 patients in the comparator EGFR-TKI arm who received a first subsequent treatment, **85 patients (47%) crossed over to osimertinib** (31% of all patients randomised from the comparator EGFR-TKI arm)



*Refers to those patients who did not receive either chemotherapy or an EGFR-TKI; †The majority of patients who received cytotoxic chemotherapy received a platinum

- EGFR T790M ~50% of resistance to SOC TKIS
- Expect that of the eligible patients ~ 50% receive osimertinib; in FLAURA 47%

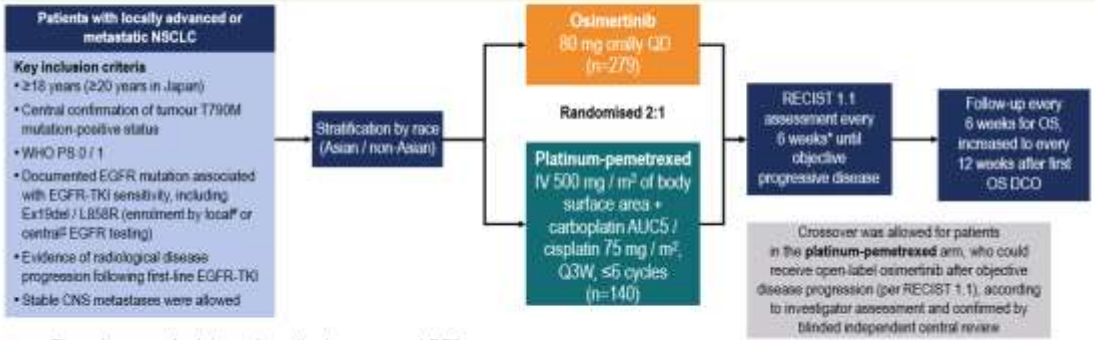
- Only 31% of all patients received osimertinib
  - 30% received no therapy
  - 5% still on SOC TKI
  - In some biopsy not feasible or clinical condition warrants starting chemotherapy

STUDIO FLAURA: TAKE HOME MESSAGE

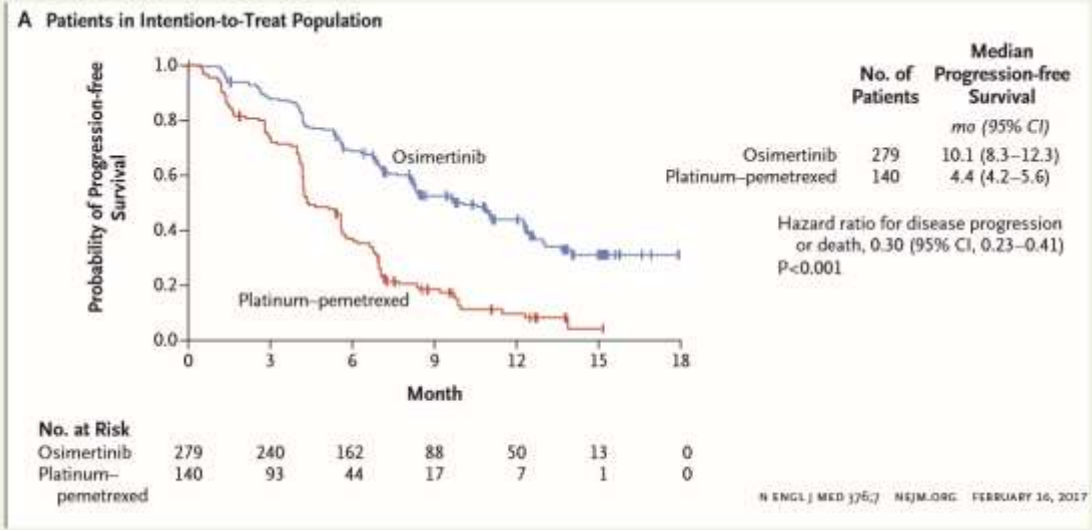
- Beneficio di Osimertinib anche in OS
- Profilo di tossicità competitivo
- Numero dei pazienti che non accede a linee successive e che non sviluppa la T790M a progressione
- Metastasi cerebrali: valutazione multidisciplinare caso per caso
- Come migliorare il dopo OSIMERTINIB I linea, studi clinici in corso (SAVANNAH-ELIOS-ORCHARD)
- Uncommon mutations non inserite nello studio

Overall survival from the AURA3 Phase III study: osimertinib vs platinum-pemetrexed in patients with EGFR T790M advanced NSCLC and progression on a prior EGFR-TKI

Yi-Long Wu[1], Tony S. Mok[2], Ji-Youn Han[3], Myung-Ju Ahn[4], Angelo Delmonte[5], Suresh S. Ramalingam[6], Sang-We Kim[7], Frances A. Shepherd[8], Janessa Laskin[9], Yong He[10], Hiroaki Akamatsu[11], Willemijn S. M. E. Theelen[12], Wu-Chou Su[13], Thomas John[14], Martin Sebastian[15], Helen Mann[16], Miguel Miranda[16], Gianluca Laus[17], Yuri Rukazenkov[17], Vassiliki A. Papadimitrakopoulou[18]

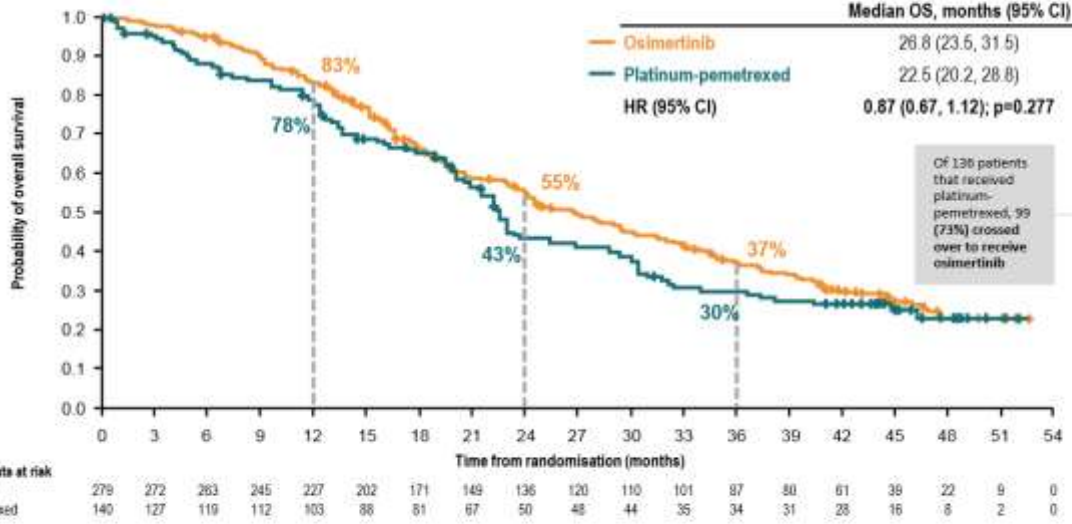


- The primary endpoint was investigator-assessed PFS
- OS and safety were secondary endpoints
- AURA3 final OS DCO: 15 March 2019 (progression events were not collected from this DCO)



EGFR+

AURA3 overall survival



Data cut-off: 15 March 20

Patients not known to have died at the time of analysis are censored at the last recorded date that the patient was known to be alive. Crosses indicate censored observations. *As this was not the first testing of OS, the 95% CI level was adjusted to 95.564%. confidence interval, HR, hazard r

Patients who received post-treatment therapy (≥5% of patients[a])	Osimertinib, % n=165 (59%)	Platinum-pemetrexed, % n=114 (81%)
EGFR inhibitor	15	97
Osimertinib crossover	0	86[b]
EGFR protein kinase inhibitors[b]	11	8
Cytotoxic chemotherapy platinum compounds	65	1
Cytotoxic chemotherapy folic acid analogues	66	2
Cytotoxic chemotherapy taxanes	8	1
Antibody against VEGF	8	0

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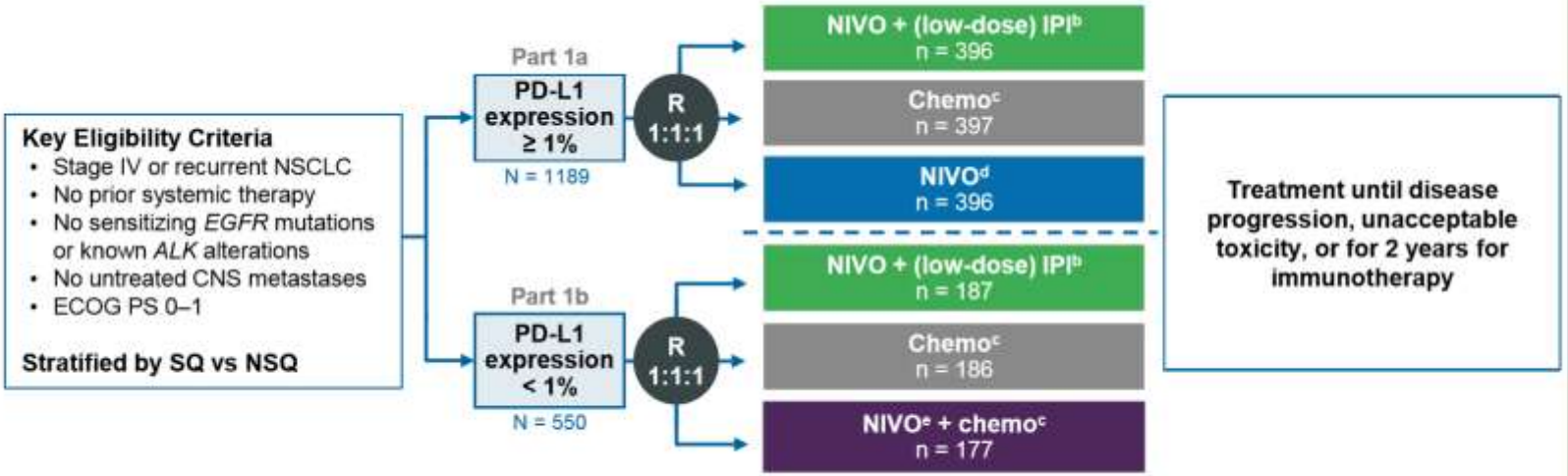
CM227: ESMO 2019

CheckMate 227 Part 1 Study Design[a]



Independent co-primary endpoints: NIVO + IPI vs chemo
- PFS in high TMB (≥10 mut/Mb) population[f]
- OS in PD-L1 ≥ 1% population[g]

Secondary endpoints (PD-L1 hierarchy):
- PFS: **NIVO + chemo vs chemo** in PD-L1 < 1%
- OS: **NIVO + chemo vs chemo** in PD-L1 < 1%
- OS: **NIVO vs chemo** in PD-L1 ≥ 50%

Database lock: July 2, 2019; **minimum follow-up for primary endpoint: 29.3 months**

[a]NCT02477826; [b]NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W); [c]**NSQ:** pemetrexed + cisplatin or carboplatin, Q3W for ≤ 4 cycles, with optional pemetrexed maintenance following chemo or NIVO + pemetrexed maintenance following NIVO + chemo; **SQ:** gemcitabine + cisplatin, or gemcitabine + carboplatin, Q3W for ≤ 4 cycles; [d]NIVO (240 mg Q2W); [e]NIVO (360 mg Q3W); [f]TMB primary endpoint analysis conducted at January 24, 2018 database lock in subset of patients randomized to NIVO + IPI or chemo; alpha allocated was 0.025; [g]Alpha allocated was 0.025 overall (0.023 for final analysis)

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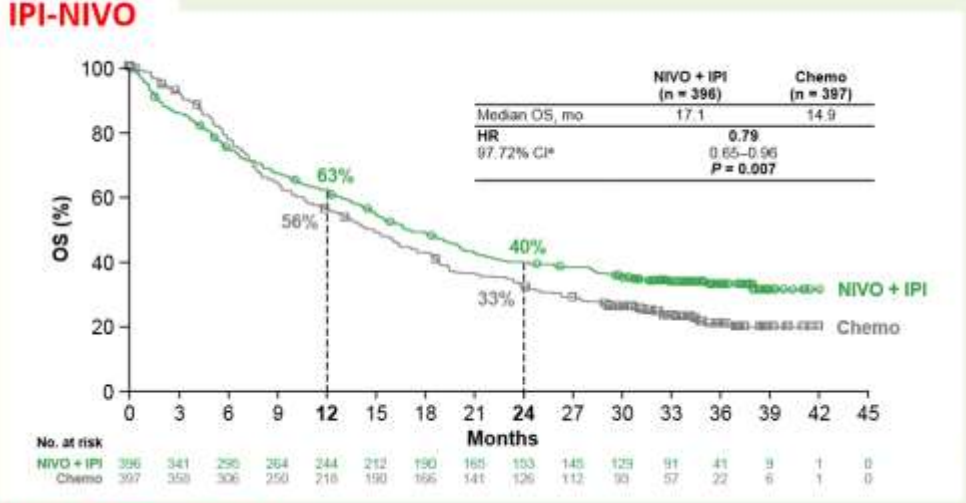
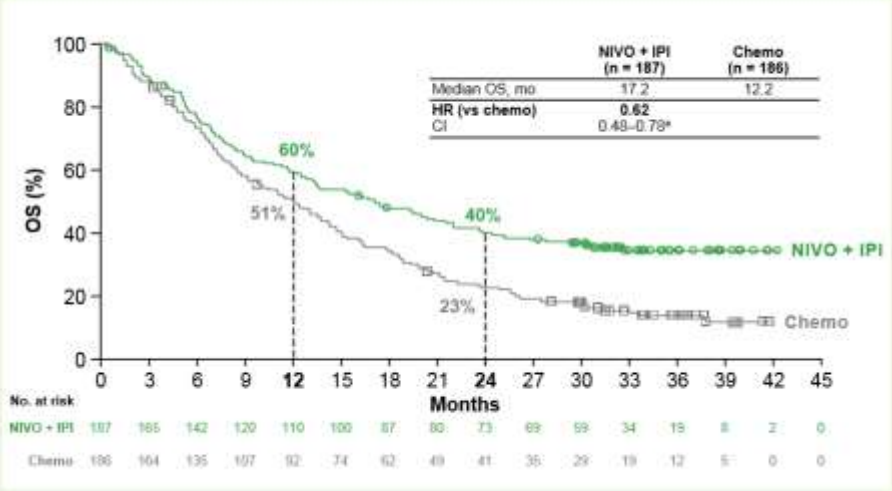
IPI-NIVO





OS IN PDL-1≥1%

OS IN PDL-1<1% (???)

CheckMate 227 Part 1: NIVO + IPI in NSCLC

Safety Summary of Treatment-Related AEs in All Patients Treated With NIVO + IPI, Chemo, or NIVO

TRAE,[a] %	NIVO + IPI (n = 576)		Chemo (n = 570)		NIVO[b] (n = 391)	
	Any grade	Grade 3–4	Any grade	Grade 3–4	Any grade	Grade 3–4
Any TRAE	77	33	82	36	66	19
TRAE leading to discontinuation[c]	18	12	9	5	12	7
Most frequent TRAEs (≥ 15%)						
Diarrhea	17	2	10	1	12	< 1
Rash	17	2	5	0	11	1
Fatigue	14	2	19	1	11	< 1
Decreased appetite	13	1	20	1	7	0
Nausea	10	< 1	36	2	6	< 1
Anemia	4	1	33	12	3	< 1
Constipation	4	0	15	< 1	2	0
Neutropenia	< 1	0	17	10	< 1	0
Treatment-related deaths[d]	1		1		< 1	

- With 18 months more follow-up, safety was consistent with the previous report[1] and did not increase
- Median duration of therapy (range) was 4.2 mo (0.03–25.5) with NIVO + IPI, 2.6 mo (0.03–37.6+) with chemo, and 4.6 mo (0.03–26.5) with NIVO

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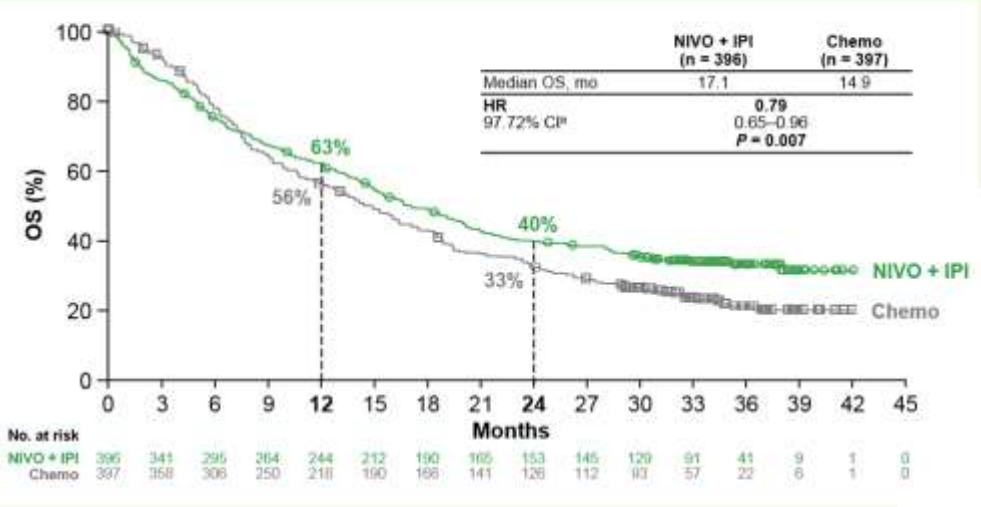
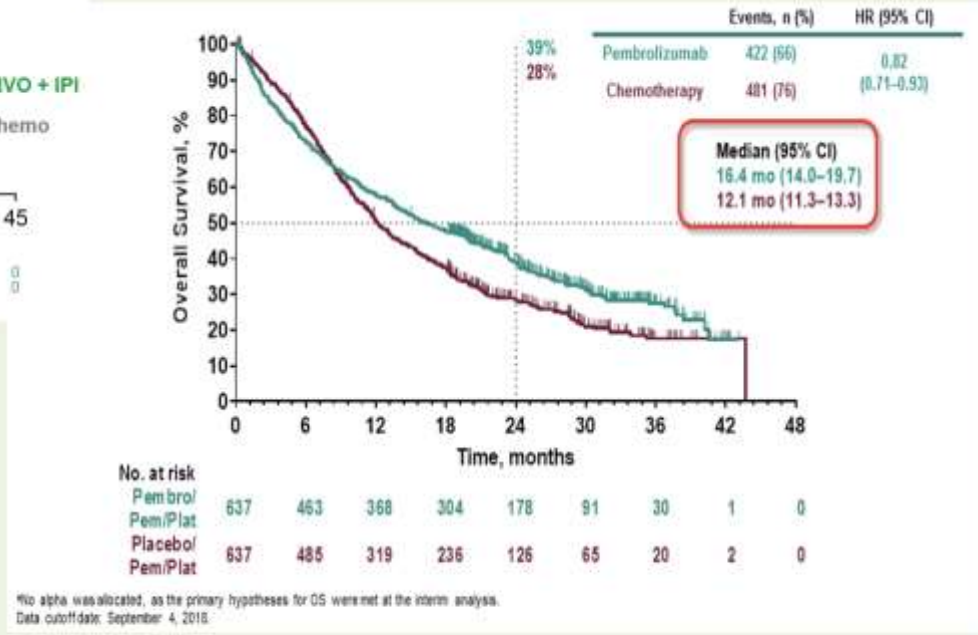
IPI-NIVO



OS PDL-1≥%



Nivo ipi 227

Pembro KN 042

Part 1a

NIVO + IPI

Chemo

NIVO

Peters ESMO 2019

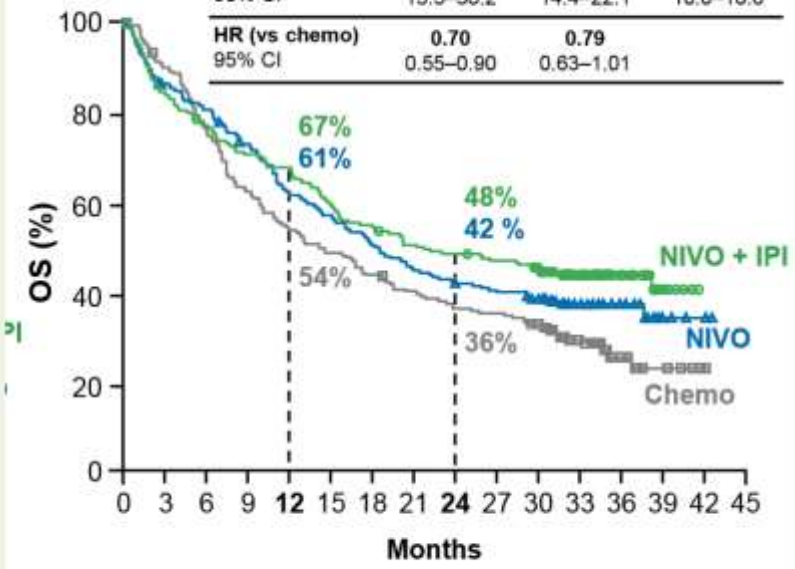
Mok et al Lancet 2019

IPI-NIVO

OS IN PDL-1≥50

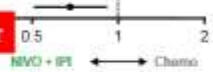
OS

	NIVO + IPI (n = 205)	NIVO (n = 214)	Chemo (n = 192)
Median OS, mo	21.2	18.1	14.0
95% CI	15.5–38.2	14.4–22.1	10.0–18.6
HR (vs chemo)	**0.70**	**0.79**	
95% CI	0.55–0.90	0.63–1.01	



OS for NIVO + IPI vs Chemo by Tumor PD-L1 Expression, TMB Status, and Combined Subgroups in All Randomized Patients

		Median OS, months NIVO + IPI n = 583	Chemo n = 583	HR	HR (95% CI)
Randomized groups				Stratified	Stratified
PD-L1	All randomized (N = 1166)	17.1	13.9	0.73	
	PD-L1 < 1% (n = 373)	17.2	12.2	0.62	
	PD-L1 ≥ 1% (n = 793)	17.1	14.9	0.79[a]	
Additional exploratory subgroups analyses[b,c]				Unstratified	Unstratified
PD-L1	1–49% (n = 396)	15.1	15.1	0.94	
	≥ 50% (n = 397)	21.2	14.0	0.70	
TMB[c] (mut/Mb)	low, < 10 (n = 380)	16.2	12.6	0.75	
	high, ≥ 10 (n = 299)	23.0	16.4	0.68	



TMB is not discriminatory for OS and cannot be used as a predictive biomarker

- No consistent correlation was observed between survival outcomes with NIVO + IPI vs chemo and PD-L1 or TMB alone or in combination[1]

[a]Stratified HR (97.72% CI). [b]Patients were not stratified by TMB or PD-L1 ≥ or < 50% – subgroup analyses therefore may be impacted by imbalances and should be interpreted with caution. [c]Not controlled by randomization. [d]Unstratified HR for NIVO + IPI vs chemo in TMB-evaluable (n = 678) and non-evaluable (n = 487) patients was 0.74 (95% CI, 0.61–0.90) and 0.74 (95% CI, 0.60–0.92), respectively.
[1]Hellmann MD, et al. N Engl J Med 2019. doi: www.nejm.org/doi/full/10.1056/NEJMoa1910231. 2019 Sept 26 [Epub ahead of print]

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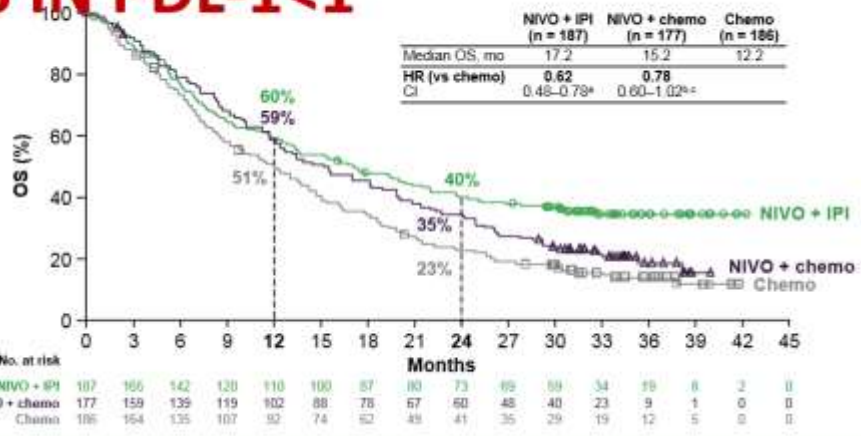
OS IN PDL-1<1

	NIVO + IPI (n = 187)	NIVO + chemo (n = 177)	Chemo (n = 186)
Median OS, mo	17.2	15.2	12.2
HR (vs chemo)	**0.62**	**0.78**	
CI	0.48–0.79[a]	0.60–1.02[b,c]	



CM 227: CONSIDERATIONS

- PDL-1≥1 non è più un criterio di selezione (ma 1-49) e chemio non deve essere braccio di confronto nei PDL-1>50%. Infatti in questo gruppo lo standard è monoimmuno con pembro
- Sembra che IPI-NIVO funzioni nei PDL-1 negativi e molto positivi (≥50) (OS non pianificata)
- Troppe domande, poche risposte, troppi emendamenti al disegno dello studio
- Molti dei dati estrapolati sono hypothesis generating

OVERALL SURVIVAL: INDIRECT TRIAL COMPARISON

STUDY	HR	CI	MEDIAN OS	1Y	2Y
CM227<1	0.62	0.48-0.78	17.2	60	40
KN189<1	0.52	0.36-0.74	17.2	63.4	38.5
CM227≥1	0.79	0.65-0.96	17.1	63	40
IMP 150 all	0.78	0.64-0-96	19.2	67	43
KN189 1-49	0.62	0.42-0.92	21.8	71.7	44.3
KN189≥50	0.59	0.39-0.88	NR	73.3	51.59
CM227≥50	0.70	0.55-0.90	21.2	67	48
KN024≥50	0.65	0.50-0.86	26.3	70.3	51.7

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Mesothelioma

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Thymic carcinoma

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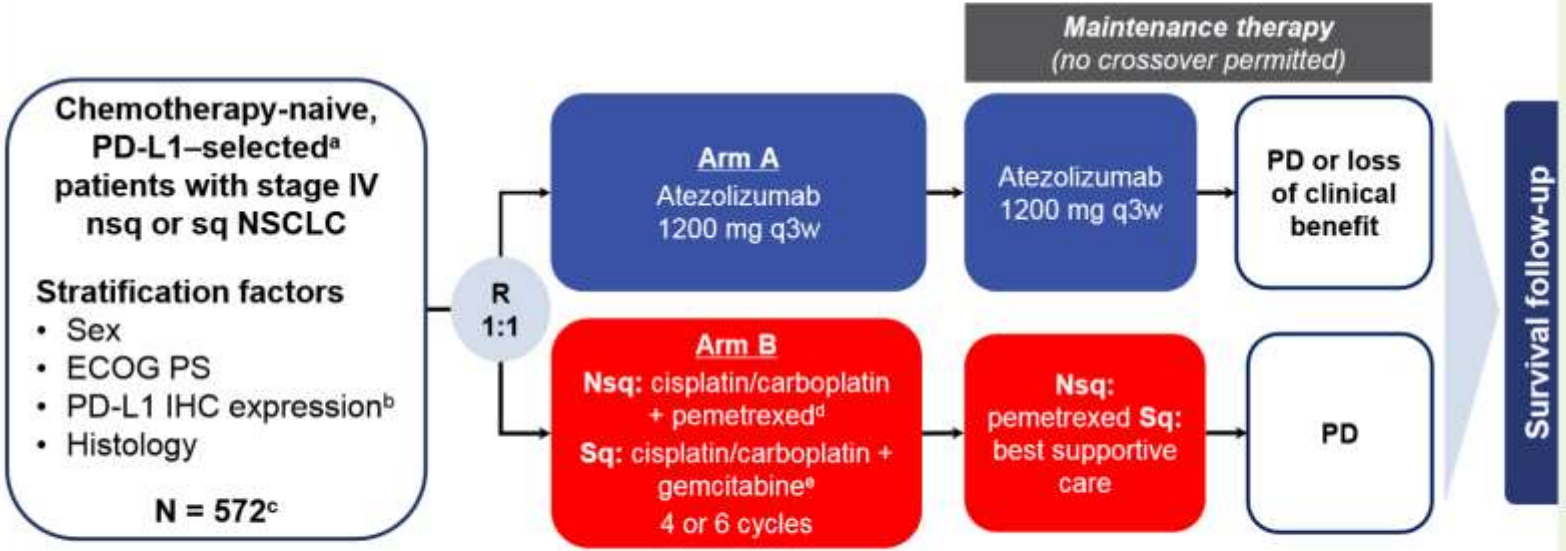
IMpower110: Interim OS Analysis of a Phase III Study of Atezolizumab (atezo) vs Platinum-Based Chemotherapy (chemo) as 1L Treatment (tx) in PD-L1–selected NSCLC

David R Spigel,[1] Filippo De Marinis,[2] Giuseppe Giaccone,[3] Niels Reinmuth,[4] Alain Vergnenegre,[5] Carlos Henrique Barrios,[6] Masahiro Morise,[7] Enriqueta Felip,[8] Zoran Andric,[9] Sarayut Geater,[10] Mustafa Özgüroğlu,[11] Simonetta Mocci,[12] Mark McCleland,[12] Ida Enquist,[12] Kim Komatsubara,[12] Yu Deng,[12] Hiroshi Kuriki,[12] Xiaohui Wen,[12] Jacek Jassem,[13] Roy S Herbst[14]

[1]Sarah Cannon Research Institute, Nashville, TN, USA; [2]European Institute of Oncology, Milan, Italy; [3]Weill Cornell Medical Center, New York, NY, USA; [4]Asklepios Lung Clinic, Munich-Gauting, Germany; [5]Centro de Pesquisa Clínica, Hospital São Lucas, Porto Alegre, Brazil; [6]PUCRS School of Medicine, Porto Alegre, Brazil; [7]Nagoya University Graduate School of Medicine, Aichi, Japan; [8]Vall d'Hebron University Hospital, Barcelona, Spain; [9]Clinical Hospital Center Bezanijska Kosa, Belgrade, Serbia; [10]Prince of Songkla University – Hat Yai, Songkhla, Thailand; [11]Istanbul University-Cerrahpaşa, Cerrahpaşa School of Medicine, Istanbul, Turkey; [12]Genentech, Inc., South San Francisco, CA, USA; [13]Medical University of Gdansk, Gdansk, Poland; [14]Yale School of Medicine, New Haven, CT

IMpower110 Study Design

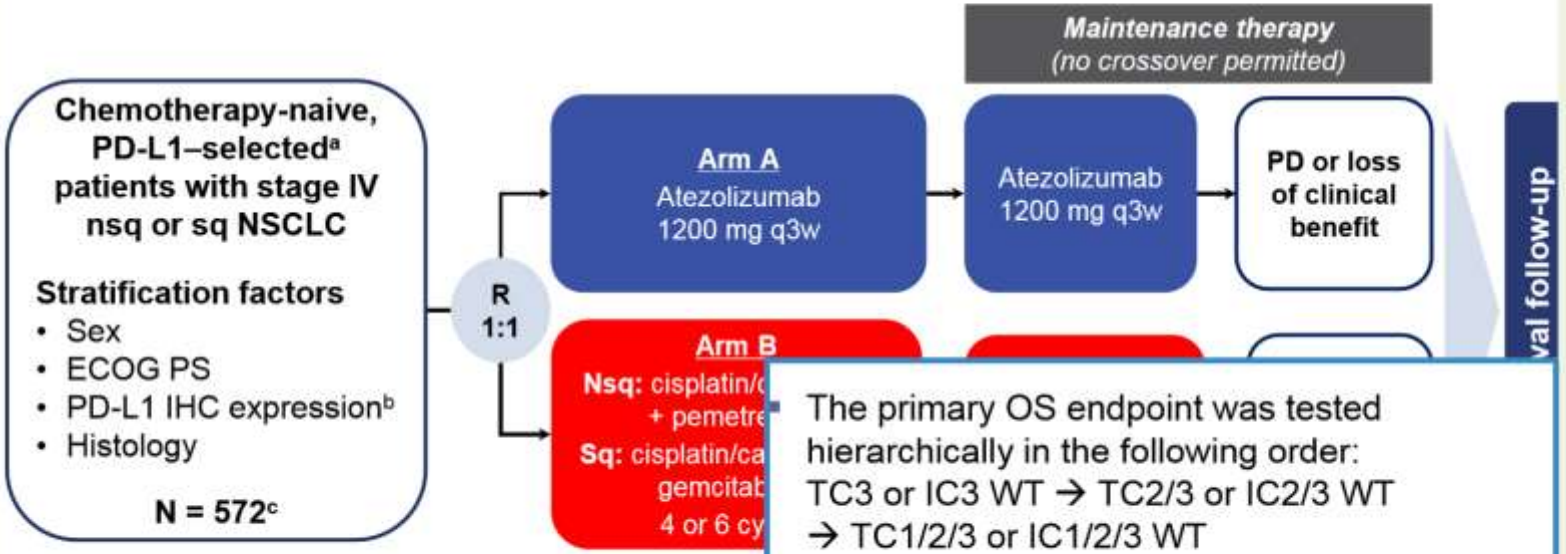


- Primary endpoint: OS in WT population[f]
- Key secondary endpoints: investigator-assessed PFS, ORR and DOR (per RECIST version 1.1)

IC, tumour-infiltrating immune cells; IHC, immunohistochemistry; nsq, non-squamous; PD, progressive disease; q3w, every 3 weeks; R, randomised; sq, squamous; TC, tumour cells; WT, wild-type. [a] PD-L1 expression (VENTANA SP142 IHC assay) ≥ 1% on TC or IC. [b] TC1/2/3 and any IC vs TC0 and IC1/2/3. [c] 554 patients in the WT population. [d] Cisplatin 75 mg/m^2 or carboplatin area under the curve (AUC) 6 + pemetrexed 500 mg/m^2 IV q3w. [e] Cisplatin 75 mg/m^2 + gemcitabine 1250 mg/m^2 or carboplatin AUC 5 + gemcitabine 1000 mg/m^2 IV q3w. [f] WT population excludes patients with *EGFR*+ and/or *ALK*+ NSCLC.

Spigel et al. IMpower110 Interim OS Analysis https://bit.ly/2IxRNHQ

IMpower110 Study Design



- Primary endpoint: OS in WT population[f]
- Key secondary endpoints: investigator-assessed

IC, tumour-infiltrating immune cells; IHC, immunohistochemistry; nsq, non-squamous; PD, 3 weeks; R, randomised; sq, squamous; TC, tumour cells; WT, wild-type. [a] PD-L1 expressi ≥ 1% on TC or IC. [b] TC1/2/3 and any IC vs TC0 and IC1/2/3. [c] 554 patients in the WT popu carboplatin area under the curve (AUC) 6 + pemetrexed 500 mg/m² IV q3w. [e] Cisplatin 75 r or carboplatin AUC 5 + gemcitabine 1000 mg/m² IV q3w. [f] WT population excludes patients

- The primary OS endpoint was tested hierarchically in the following order: TC3 or IC3 WT → TC2/3 or IC2/3 WT → TC1/2/3 or IC1/2/3 WT
- The secondary endpoint of PFS can be formally tested only when the primary endpoint is positive among all 3 populations

OS: TC3 or IC3 WT

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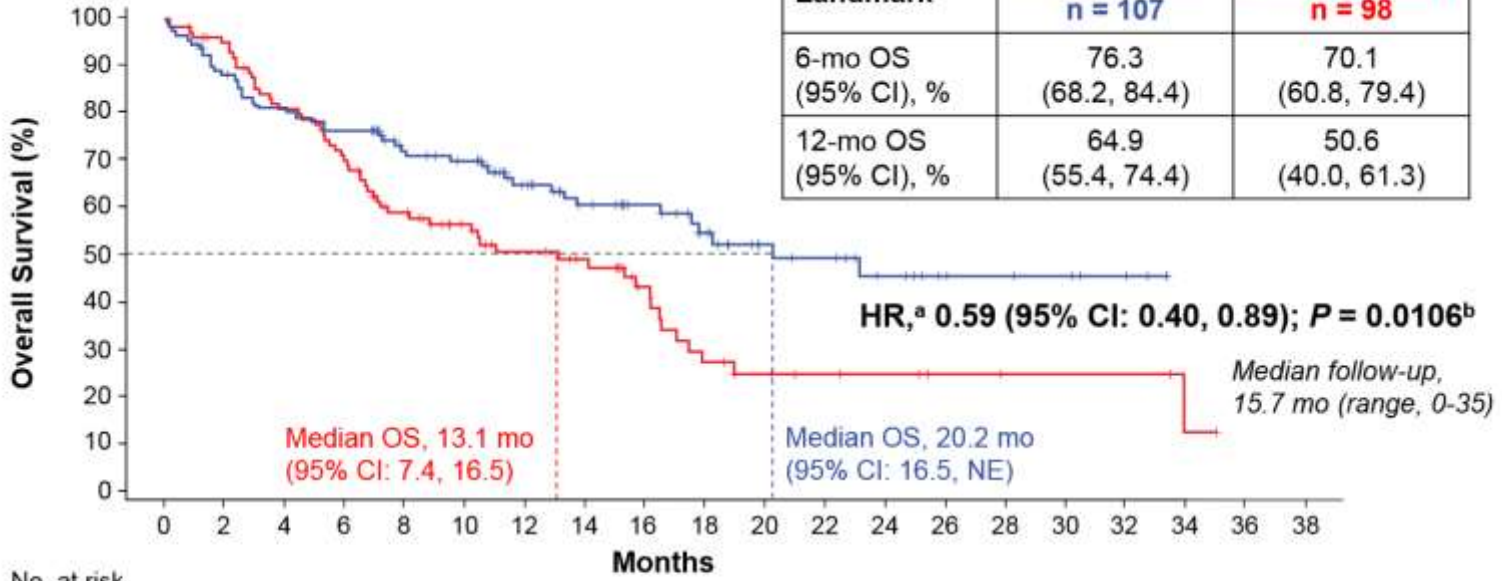
Landmark	Arm A (atezo) n = 107	Arm B (chemo) n = 98
6-mo OS (95% CI), %	76.3 (68.2, 84.4)	70.1 (60.8, 79.4)
12-mo OS (95% CI), %	64.9 (55.4, 74.4)	50.6 (40.0, 61.3)



No. at risk

Atezolizumab	107	94	85	80	66	61	48	40	34	25	18	16	11	7	6	5	2	
Chemotherapy	98	89	75	65	50	40	33	28	19	12	9	7	6	4	3	3	3	1

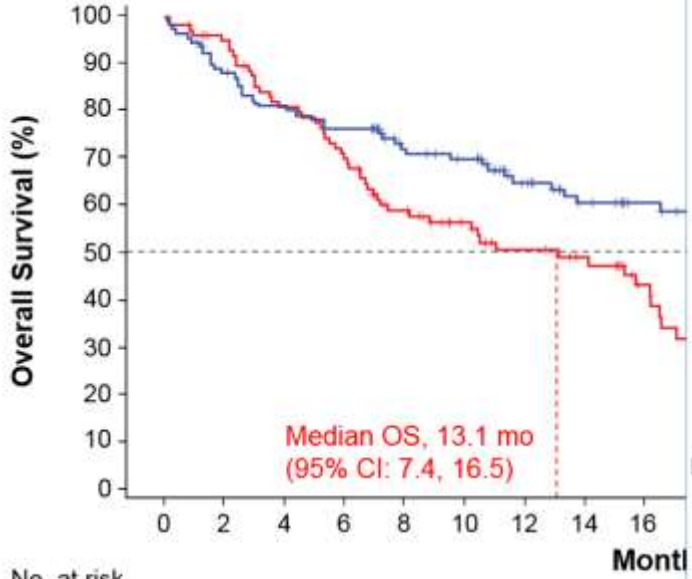
Spigel ESMO 2019

NE, not estimable. [a] Stratified. [b] Stratified log-rank.
Data cutoff: 10 September 2018.

Spigel et al. IMpower110 Interim OS Analysis https://bit.ly/2IxRNHQ

ATEZO I LINE

OS: TC3 or IC3 WT



No. at risk

Atezolizumab	107	94	85	80	66	61	48	40	34	25	18	16	11	7	6	5	2	
Chemotherapy	98	89	75	65	50	40	33	28	19	12	9	7	6	4	3	3	3	1

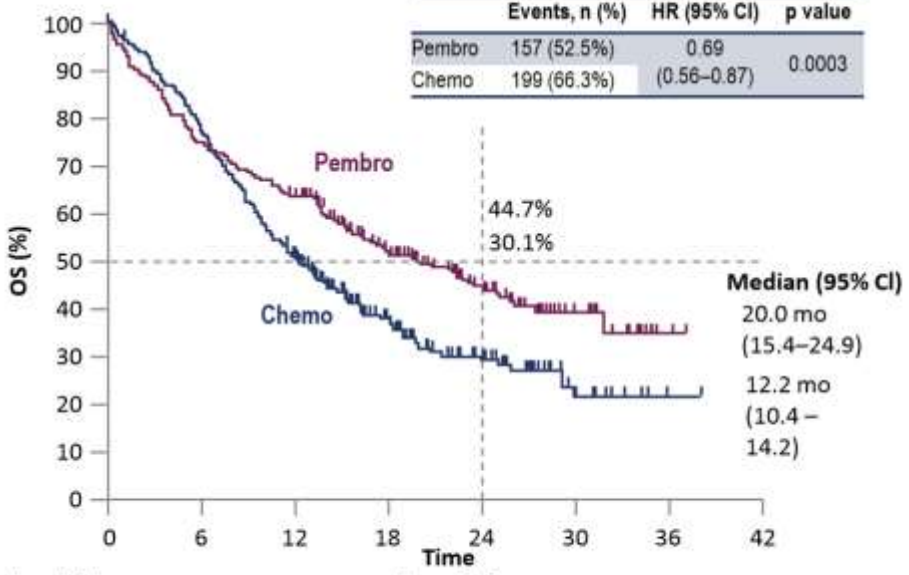
NE, not estimable. [a] Stratified. [b] Stratified log-rank.
Data cutoff: 10 September 2018.

Spigel ESMO 2019

Spigel et al. IMpower110 Interim OS Analysis
https://bit.ly/2IxRNHQ

KEYNOTE-042

	Events, n (%)	HR (95% CI)	p value
Pembro	157 (52.5%)	0.69 (0.56–0.87)	0.0003
Chemo	199 (66.3%)		



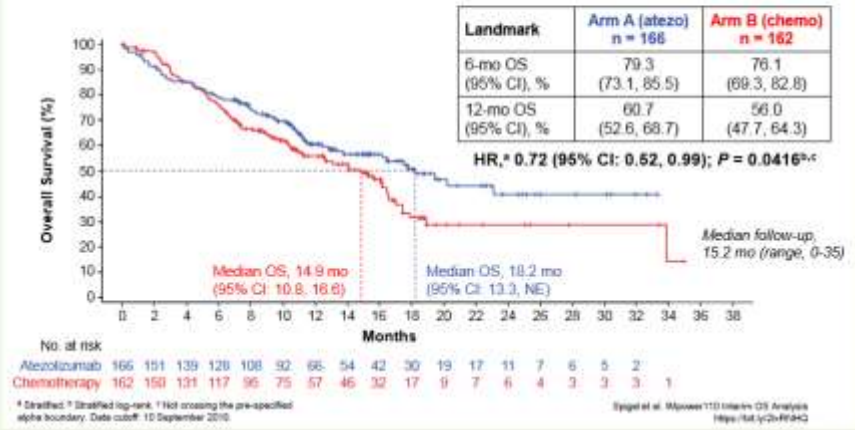
Median (95% CI)
20.0 mo (15.4–24.9)
12.2 mo (10.4 – 14.2)

Number at risk

Pembro	299	224	189	107	59	22	2	0
Chemo	300	231	149	75	40	11	1	0

ATEZO I LINE

OS: TC2/3 or IC2/3 WT



Landmark	Arm A (atezo) n = 166	Arm B (chemo) n = 162
6-mo OS (95% CI), %	79.3 (73.1, 85.5)	76.1 (69.3, 82.8)
12-mo OS (95% CI), %	60.7 (52.6, 68.7)	56.0 (47.7, 64.3)

HR,[a] 0.72 (95% CI: 0.52, 0.99); $P = 0.0416$[b,c]

[a] Stratified. [b] Stratified log-rank. [c] Not crossing the pre-specified alpha boundary. Data cutoff: 10 September 2016.

Spigel et al. IMpower110 Interim OS Analysis
https://bit.ly/2sRRHQ

Safety Summary

	Arm A (atezo) n = 286	Arm B (chemo) n = 263			
Median treatment duration (min-max), mo	5.3 (0-33)	Pem 3.5 (0-20)	Gem 2.6 (0-5)	Carb 2.3 (0-5)	Cis 2.1 (0-5)
Any-cause AE, n (%)	258 (90.2)	249 (94.7)			
Related AE	173 (60.5)	224 (85.2)			
Grade 3-4 AE, n (%)	91 (31.8)	141 (53.6)			
Related Grade 3-4 AE	37 (12.9)	116 (44.1)			
Serious AE, n (%)	81 (28.3)	75 (28.5)			
Related serious AE	24 (8.4)	41 (15.6)			
Grade 5 AE, n (%)	11 (3.8)	11 (4.2)			
Related Grade 5 AE	0	1 (0.4)			
AE leading to any treatment withdrawal, n (%)	18 (6.3)	43 (16.3)			
Atezo AESI, n (%)	115 (40.2)	44 (16.7)			
Grade 3-4 atezo AESI	19 (6.6)	4 (1.5)			
Atezo AESI requiring use of corticosteroids, n (%)	22 (7.7)	1 (0.4)			

AE, adverse event; AESI, adverse event of special interest; carb, carboplatin; cis, cisplatin; gem, gemcitabine; pem, pemetrexed. Data cutoff: 10 September 2016.

Spigel et al. IMpower110 Interim OS Analysis
https://bit.ly/2sRRHQ

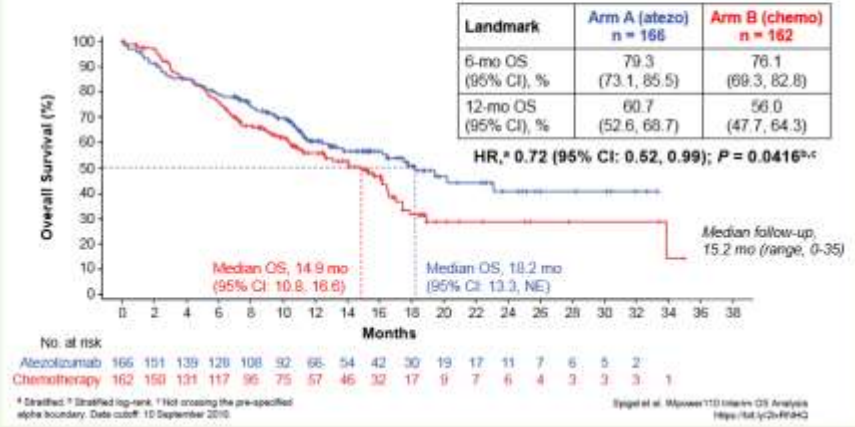
TC1/2/3 or IC1/2/3 WT

	Arm A (atezo) n = 277	Arm B (chemo) n = 277
Patients with ≥ 1 therapy, n (%)	82 (29.6)	137 (49.5)
Chemotherapy	77 (27.8)	68 (24.5)
Immunotherapy	7 (2.5)	80 (28.9)
Targeted therapy	14 (5.1)	12 (4.3)

proportion of patients who received different classes of subsequent cancer
apies was similar across the PD-L1 subgroups

ATEZO I LINE

OS: TC2/3 or IC2/3 WT



Landmark	Arm A (atezo) n = 166	Arm B (chemo) n = 162
6-mo OS (95% CI), %	79.3 (73.1, 85.5)	76.1 (69.3, 82.8)
12-mo OS (95% CI), %	60.7 (52.6, 68.7)	56.0 (47.7, 64.3)

HR,[a] 0.72 (95% CI: 0.52, 0.99); $P = 0.0416$[b,c]

Safety Summary

	Arm A (atezo) n = 286	Arm B (chemo) n = 263			
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AE, adverse event; AESI, adverse event of special interest; carb, carboplatin; cis, cisplatin; gem, gemcitabine; pem, pemetrexed. Data cutoff: 10 September 2018.

Spigel et al. IMpower110 Interim OS Analysis https://bit.ly/2sR94HQ

TC1/2/3 or IC1/2/3 WT

	Arm A (atezo) n = 277	Arm B (chemo) n = 277
Patients with ≥ 1 therapy, n (%)	82 (29.6)	137 (49.5)
Chemotherapy	77 (27.8)	68 (24.5)
Immunotherapy	7 (2.5)	80 (28.9)
Targeted therapy	14 (5.1)	12 (4.3)

proportion of patients who received different classes of subsequent cancer apies was similar across the PD-L1 subgroups

Conclusions (authors and discussant Dr. Naiyer Rizvi)

- The safety profile of atezolizumab was consistent with prior observations; no new or unexpected safety signals were identified
- Atezolizumab represents a promising 1L treatment option in patients with PD-L1–high NSCLC
- Outcomes with other PD-L1 diagnostic antibodies than SP142; 22C3 IHC? TC3 vs. IC3 ? TC2/IC2?

AGENDA

mNSCLC

ONCOGENE ADDICTED

- FLAURA OS
- FINAL OS AURA 3

IMMUNOTHERAPY

- TMB (PEMBRO TRIALS)
- IO-IO COMBO (CM 227)
- IO vs CHEMO /IMP 110)

Extended SCLC

- CHEMO-IMMUNO

Mesothelioma

- IMMUNO

Thymic carcinoma

- REMORA trial

TMB

- TMB quantifies the number of non-sinonimous mutations, related to neoantigens
- TMB is higher in smokers than in never smoker, suggesting smoking history to be a surrogate marker of TMB
- TMB can measure the number of non sinonimous mutation in WES o in a NGS panel, in blood or tissue
- TMB, as PDL-1, is a continous variable, so the cut off is important
- No correlation between TMB and PDL-1
- Role of TMB has still to be defined

ESMO 2019: data from KN studies with pembrolizumab alone or in combination with chemo

Camidge et al NRCO 2019

TMB

BARCELONA 2019 ESMO congress

LBA79

Association Between Tissue TMB and Clinical Outcomes with Pembrolizumab Monotherapy in PD-L1-Positive Advanced NSCLC in the KEYNOTE-010 and 042 Trials

Roy S. Herbst[1], Gilberto Lopes[2], Dariusz M. Kowalski[3], Makoto Nishio[4]; Yi-long Wu[5], Gilberto de Castro Jr[6], Paul Baas[7], Dong-Wan Kim[8], Matthew A. Gubens[9], Razvan Cristescu[10], Deepti Aurora-Garg[10], Andrew Albright[10], Mark Ayers[10], Andrey Loboda[10], Jared Lunceford[10], Julie Kobie[10], Gregory Lubiniecki[10], M. Catherine Pietanza[10], Bilal Piperdi[10], Tony SK Mok[11]

[1]Yale University School of Medicine, Yale Cancer Center, New Haven, CT, USA; [2]Sylvester Comprehensive Cancer Center at the University of Miami, Miami, FL, USA; [3]The Maria Sklodowska Curie Memorial Cancer Centre and Institute of Oncology, Warsaw, Poland; [4]Department of Thoracic Medical Oncology, The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan; [5]Guandong Lung Cancer Institute, Guangdong General Hospital, and Guangdong Academy of Medical Sciences, Guangdong, China; [6]Instituto do Cancer do Estado de Sao Paulo, Sao Paulo, Brazil; [7]Netherlands Cancer Institute, Amsterdam, Netherlands; [8]Seoul National, University Hospital, Seoul, Republic of Korea; [9]University of California, San Francisco, CA, USA; [10]Merck &Co., Inc, Kenilworth, NJ, USA; [11]State Key Laboratory of Translational Oncology, Chinese University of Hong Kong, Shatin, Hong Kong, China

Methods: Clinical Utility of TMB

Rationale for WES TMB cutpoint

- Exploratory TMB cutpoint was identified as a biologically optimal threshold across multiple tumor types in pembrolizumab studies using **WES** platform[1,2]
- WES platform:
  - Comprehensive, gold standard method of sequencing cancer genetics including somatic alterations[3]
  - Benchmark method in ongoing TMB assessment harmonization efforts[3,4]
  - Consistent analytical pipeline across the pembrolizumab translational program

Clinical Utility of tTMB

- Assessed using prespecified exploratory **cutpoint of 175 mut/exome**
  - Derived using GEP and WES TMB data from multiple tumor cohorts across the pembrolizumab clinical program[1,2,5]
  - Yields most statistically significant difference in distribution of an 18-gene GEP in a mixed-tumor dataset[1,2,5]
  - Most closely approximates 13 mut/Mb by FoundationOne CDx (legacy F1CDx, Foundation Medicine proprietary pipeline QSR_F1Dx_v1.03) and 10 mut/Mb (updated pipeline F1Dx_v3.2)

1. Cristescu R et al. *Science* 2018;362:pii:eaar3593. 2. Panda A et al. *JCO Precis Oncol* 2017;doi:10.1200/PO.17.00146. 3. Stenzinger A et al. *Genes Chromosomes Cancer* 2019; 58:578-588. 4. Fabrizio D et al. *J Immunotherapy Cancer* 2018;6:434. 5. Ayers M et al. *J Clin Invest* 2017;127:2930-40.

Association of tTMB (log_{10}) With Efficacy (KEYNOTE-010[a])

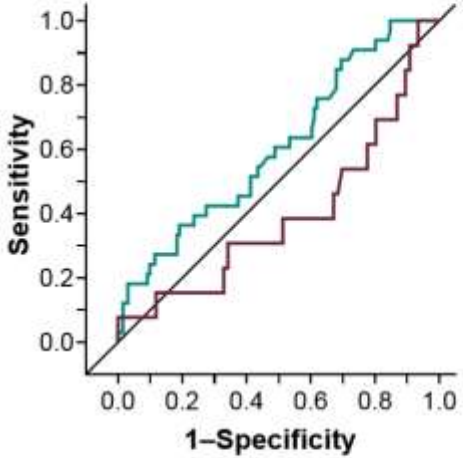
Nominal *P* Value[b]	Pembro (n = 164)	Chemo (n = 89)
OS	0.006 (one-sided)	0.410 (two-sided)
PFS	0.001 (one-sided)	0.579 (two-sided)
ORR	0.009 (one-sided)	0.330 (two-sided)

tTMB was associated with outcomes for pembro as a continuous variable but not with chemo based on α = 0.05 significance level and AUROC analysis

[a]All patients were PD-L1-positive (TPS ≥1%). [b]Wald test. *P* values are one-sided for pembro as the a priori hypothesis was that tTMB was positively associated with improved outcomes of pembro. *P* values are two-sided for placebo because there was no a priori hypothesis regarding the direction of the association between tTMB and outcomes of chemo. TMB was assessed as a continuous, log_{10}-transformed variable.
Data cutoff date: Mar 16, 2018.

ROC Curves of ORR for tTMB

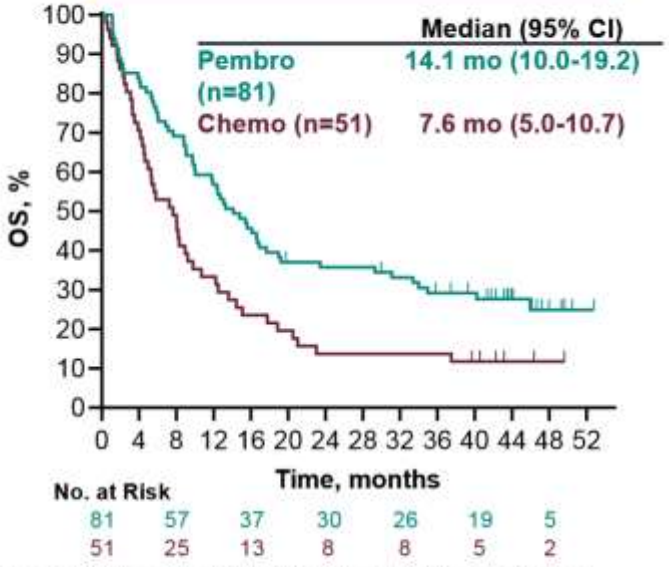
	AUROC (95% CI)
Pembro	0.61 (0.50-0.71)
Chemo	0.40 (0.21-0.58)



Clinical Utility for OS (KEYNOTE-010[a]): tTMB Cutpoint of 175 mut/exome

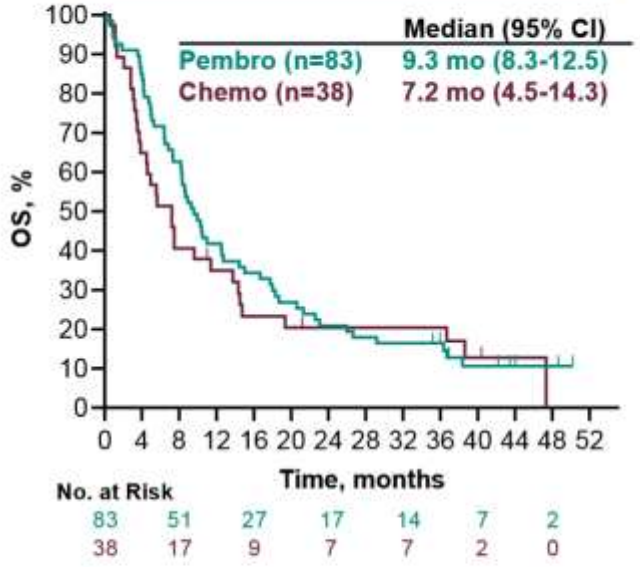
tTMB ≥175 mut/exome

HR 0.56 (95% CI 0.38-0.83)



tTMB <175 mut/exome

HR 0.85 (95% CI 0.56-1.30)



All patients were PD-L1-positive (TPS ≥1%). Data cutoff date: Mar 16, 2018.

Association of tTMB (log_{10}) With Efficacy (KEYNOTE-042[a])

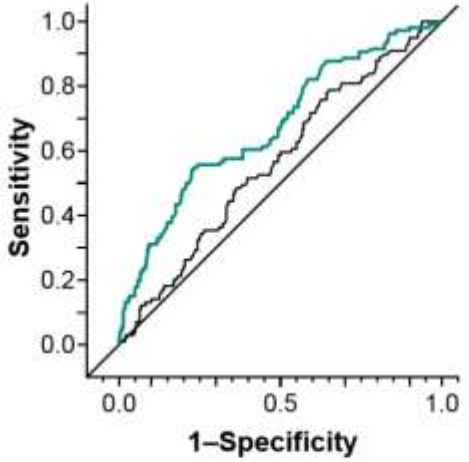
	Pembro (n = 414)	Chemo (n = 379)
Nominal *P* Value[b]		
OS	<0.001 (one-sided)	0.060 (two-sided)[c]
PFS	<0.001 (one-sided)	0.174 (two-sided)[c]
ORR	<0.001 (one-sided)	0.035 (two-sided)

tTMB was associated with outcomes for pembro as a continuous variable but not chemo in general, based on α = 0.05 significance level and AUROC

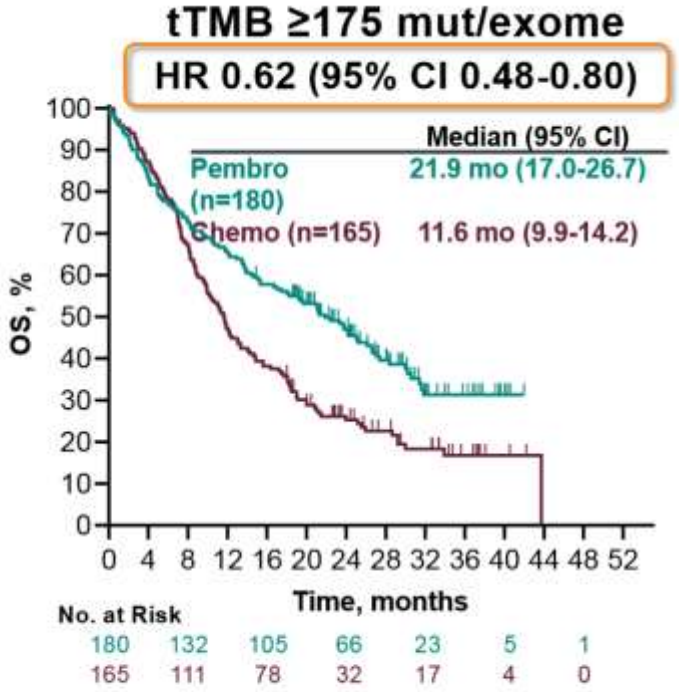
[a]All patients were PD-L1-positive (TPS ≥1%). [b]Wald test. *P* values are one-sided for pembro as the a priori hypothesis was that tTMB was positively associated with improved outcomes of pembro. *P* values are two-sided for placebo as there was no a priori hypothesis regarding the direction of association between tTMB and outcomes of chemo. TMB was assessed as a continuous, log_{10}-transformed variable. [c]tTMB showed negative directions of association with OS and PFS in the chemo arm.
Data cutoff date: Sep 4, 2018.

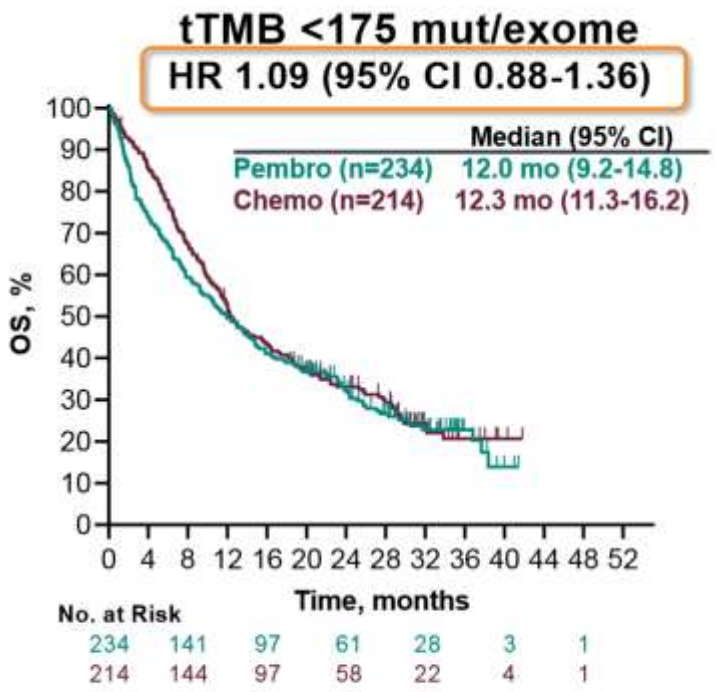
ROC Curves of ORR for tTMB

	AUROC (95% CI)
Pembro	0.67 (0.61-0.73)
Chemo	0.57 (0.50-0.63)



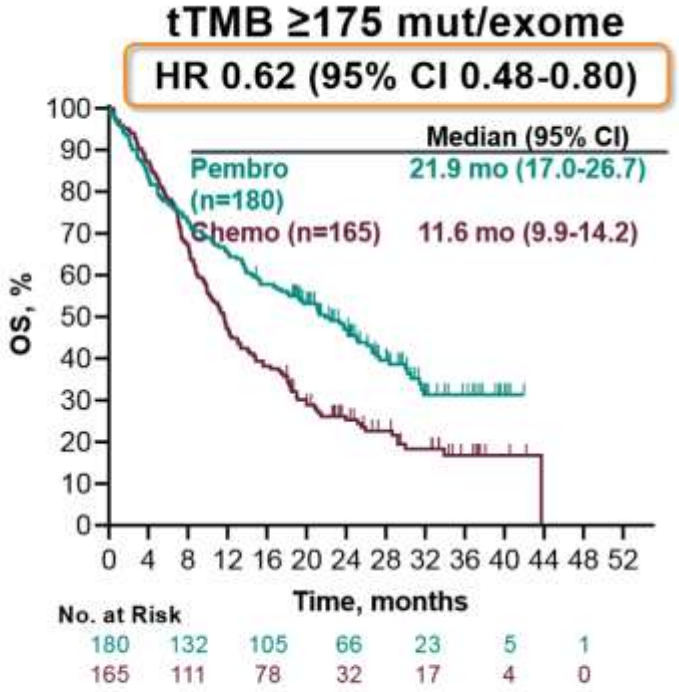
Clinical Utility for OS (KEYNOTE-042[a]): tTMB Cutpoint of 175 mut/exome

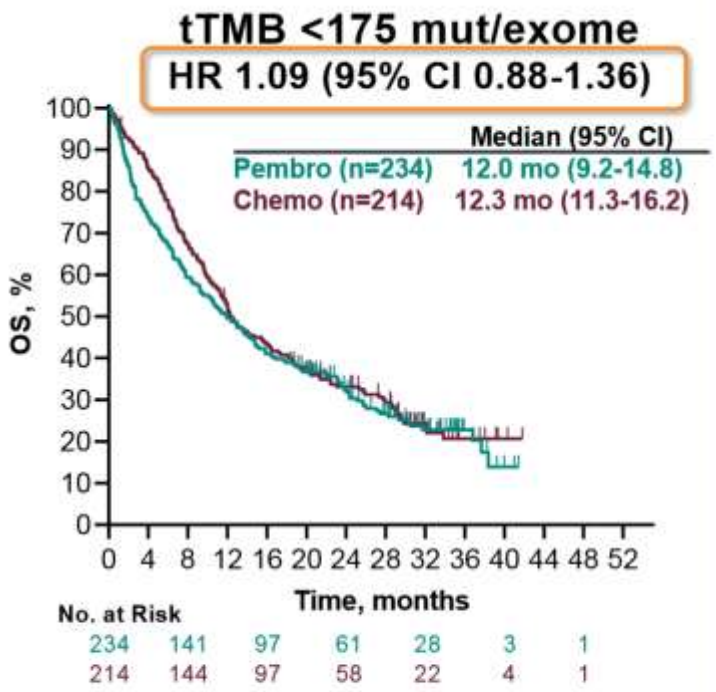




[a]All patients were PD-L1-positive (TPS ≥1%). Data cutoff date: Sep 4, 2018.

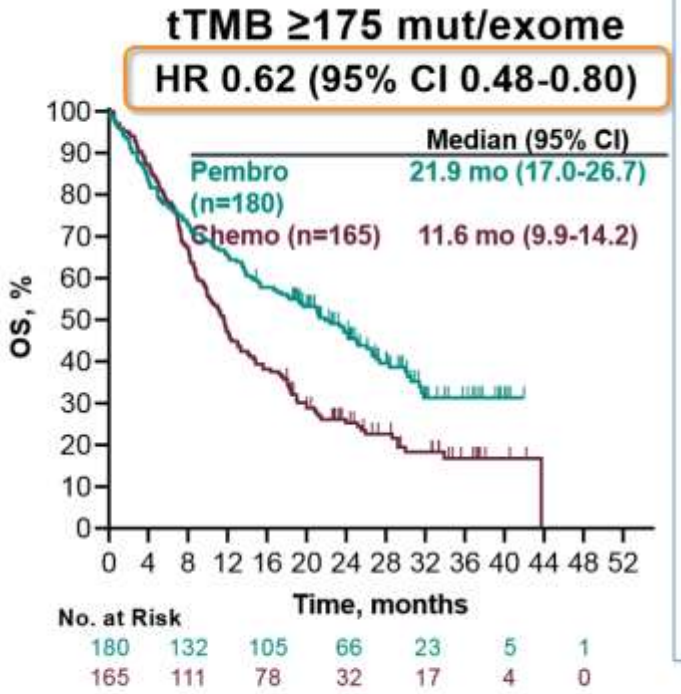
Clinical Utility for OS (KEYNOTE-042[a]): tTMB Cutpoint of 175 mut/exome

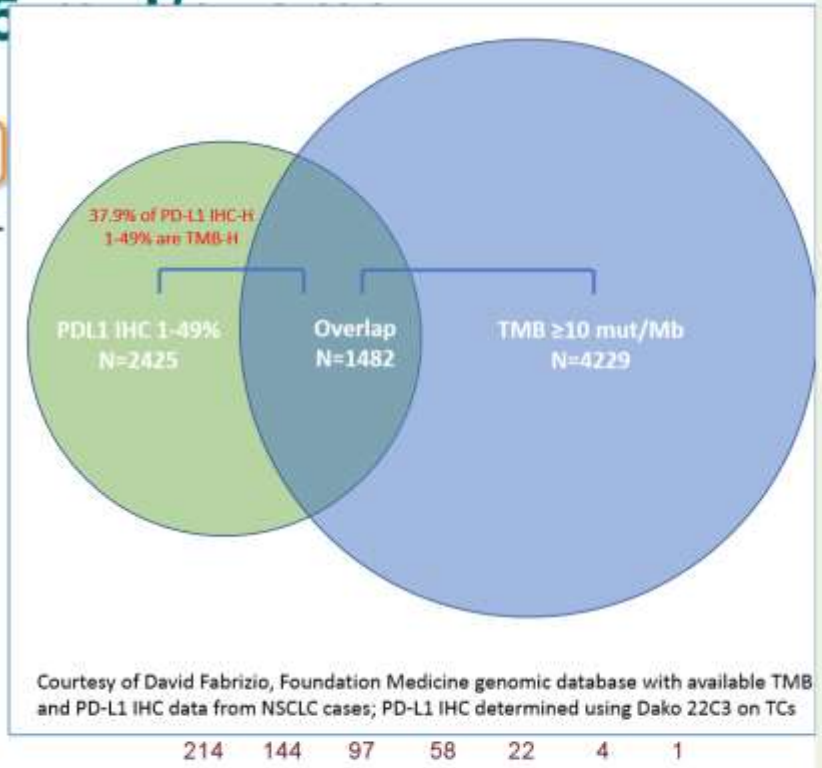




[a]All patients were PD-L1-positive (TPS ≥1%). Data cutoff date: Sep 4, 2018.

Clinical Utility for OS (KEYNOTE-042[a]): tTMB Cutpoint of 175





Courtesy of David Fabrizio, Foundation Medicine genomic database with available TMB and PD-L1 IHC data from NSCLC cases; PD-L1 IHC determined using Dako 22C3 on TCs

[a]All patients were PD-L1-positive (TPS ≥1%). Data cutoff date: Sep 4, 2018.

BARCELONA 2019 ESMO congress

LBA80

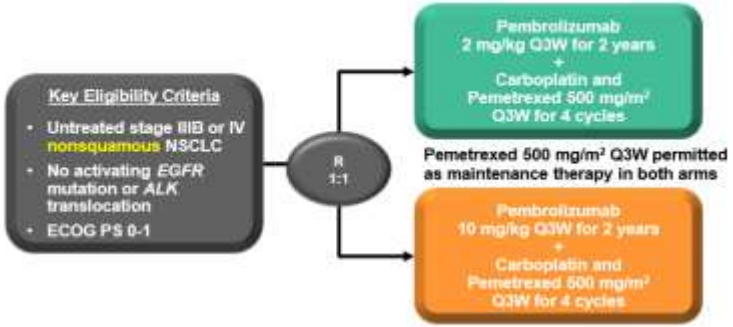
Pembrolizumab Plus Platinum-Based Chemotherapy for Metastatic NSCLC: Tissue TMB (tTMB) and Outcomes in KEYNOTE-021, 189, and 407

Luis Paz-Ares,[1] Corey J. Langer,[2] Silvia Novello,[3] Balazs Halmos,[4] Ying Cheng,[5] Shirish M. Gadgeel,[6] Rina Hui,[7] Shunichi Sugawara,[8] Hossein Borghaei,[9] Razvan Cristescu,[10] Deepti Aurora-Garg,[10] Andrew Albright,[10] Andrey Loboda,[10] Julie Kobie,[10] Jared Lunceford,[10] Mark Ayers,[10] Gregory M. Lubiniecki,[10] M. Catherine Pietanza,[10] Bilal Piperdi,[10] Marina C. Garassino[11]

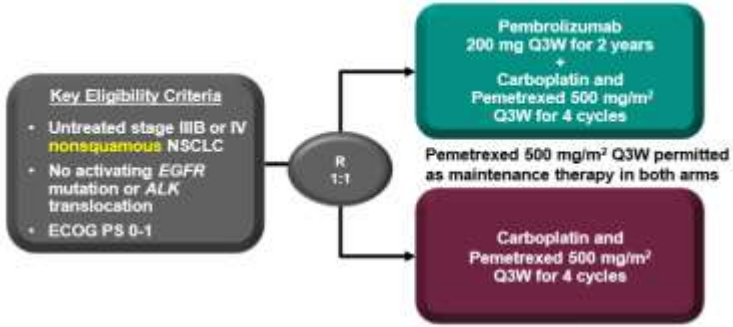
[1]Hospital Universitario 12 de Octubre, Spanish National Cancer Research Center, Universidad Complutense and Ciberonc, Madrid, Spain; [2]Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA, USA; [3]University of Turin, Orbassano, Italy; [4]Montefiore Medical Center/Albert Einstein College of Medicine, Bronx, NY, USA; [5]Jilin Cancer Hospital, Changchun, China; [6]Karmanos Cancer Institute, Detroit, MI, USA (currently at University of Michigan, Ann Arbor, MI, USA); [7]Westmead Hospital and University of Sydney, Sydney, NSW, Australia; [8]Sendai Kousei Hospital, Miyagi, Japan; [9]Fox Chase Cancer Center, Philadelphia, PA, USA; [10]Merck & Co., Inc., Kenilworth, NJ, USA; [11]Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Study Designs

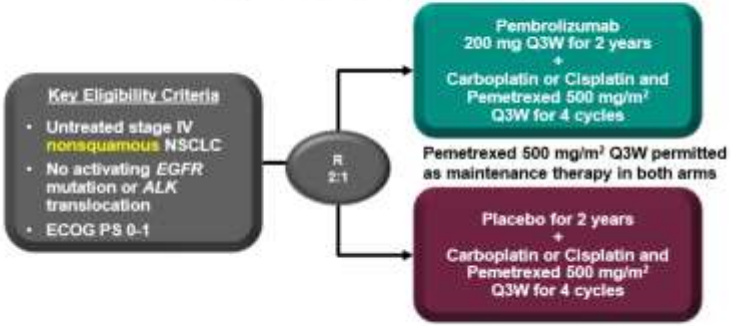
KEYNOTE-021 Cohort C (N = 24)[1]



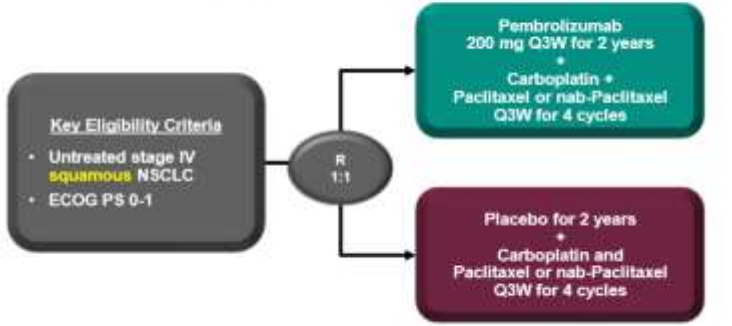
KEYNOTE-021 Cohort G (N = 123)[2,3]



KEYNOTE-189 (N = 616)[4]



KEYNOTE-407 (N = 559)[5]



Lung Cancer 2018;125:273-81. 2. *Lancet Oncol* 2016;17:1497-508. 3. *J Thorac Oncol* 2019;14:124-9. 4. *N Engl J Med* 2018;378:2078-92. 5. *N Engl J Med* 2018;379:2040-51.

Association of tTMB (log_{10}) With Efficacy

Nominal *P* Value[a]	KEYNOTE-021 C and G		KEYNOTE-189		KEYNOTE-407	
	Pembro + Chemo (n = 44)	Chemo Alone (n = 26)	Pembro + Chemo (n = 207)	Placebo + Chemo (n = 86)	Pembro + Chemo (n = 143)	Placebo + Chemo (n = 169)
ORR	0.180	0.279	0.072	0.434	0.393	0.086
PFS	0.187	0.409	0.075	0.055	0.052	0.560
OS	0.081	0.475	0.174	0.856	0.160	0.818

No association between tTMB (continuous, log_{10}-transformed) and efficacy for pembrolizumab + chemotherapy or chemotherapy ± placebo in any study based on α = 0.05 significance level

[a]*P* were values calculated using the Wald test and are one-sided for pembro + chemo (a priori hypothesis that tTMB was positively associated with improved outcomes for pembro + chemo) and two-sided for chemo alone and placebo + chemo (no a priori hypothesis regarding direction of the association between tTMB and outcomes).
Data cutoff dates: Dec 1, 2017 (KEYNOTE-021); Sep 21, 2018 (KEYNOTE-189); May 9, 2019 (KEYNOTE-407).

TMB IN FIRST LINE STUDIES

STUDIO	N TESTATI/ TOTALI (%)	CUT OFF	POSITIVI	HR (VS CT) OS
CM227 (coprimary endpoint)	1004/1739 (58%)	T NGS ≥10 mut/Mb	444 (44.2%)	0.48 PFS (95%CI 0.27-0.85)
MYSTIC (esploratorio prepianificato)	809/1118 (72.4%)	B Guardant OMNI TMB ≥20 mut/Mb	319 (40%)	0.62 (95% CI 0.451–0.855) D/T vs CHT
KN 189 (esploratoria)	293/601 (47.6%)	T WES ≥175mut/ exome (10 mut/Mb)	134 (45%)	HR 0.64 (95% CI 0.38-1.07)
KN042 (esploratoria)	793/1070 (74%)	T WES ≥175mut/ exome (10 mut/Mb)	345 (43%)	HR 0.62 (95% CI 0.48-0.80)

T: tissue, B: blood

TMB TAKE HOME MESSAGE

- TMB threshold of 175 muts by WES and 10 muts/mb is a consistent threshold
- TMB not associated with PDL-1
- TMB in general not associated with response
- TMB associated with OS and PFS in pembro arm vs chemo
- TMB high may be useful for pembrolizumab monotherapy in PDL-1<50
- Pembrolizumab plus chemo active in both TMB high and low→TMB not useful

Challenges:

Harmonization needed to define TMB (see N. Vokes, JCO Nov 2019)

RARE THORACIC MALIGNANCIES

AGENDA

mNSCLC

ONCOGENE ADDICTED

- FLAURA OS
- FINAL OS AURA 3

IMMUNOTHERAPY

- IO-IO COMBO (CM 227)
- IO vs CHEMO /IMP 110)
- TMB (PEMBRO TRIALS)

Extended SCLC

- CHEMO-IMMUNO

Mesothelioma

- IMMUNO

Thymic carcinoma

- REMORA trial

MESO

ETOP 9-15 PROMISE-meso – Study Design & Objectives

Key eligibility criteria

- **Malignant pleural mesothelioma (all histologies)**
- **Progression after previous platinum-based chemotherapy**
- ECOG PS 0-1
- Measurable or evaluable disease according to RECIST 1.1 criteria
- Adequate haematological, renal, and liver function
- Availability of tumour tissue for translational research

R* 1:1

Pembrolizumab
200 mg fixed dose *i.v.* day1 of each 3 week cycle (q3w)

Institutional choice Chemotherapy
Gemcitabine 1000 mg/m² d1/8 q3w *i.v.* **or**
Vinorelbine 30 mg/m² d1/8 q3w *i.v.* **or**
Vinorelbine 60/80 mg/m² d1/8 q3w *p.o.*

Treatment until progression by RECIST 1.1, max 2 years*
**beyond PD allowed in case of clinical benefit*

RECIST 1.1 Assessment:
Every 9 weeks for the first 6 months and 12 weeks thereafter

*Cross-over to **pembrolizumab** allowed at progression*

***Stratification factor**
Histological subtype:
Epithelioid vs. Non-epithelioid

Primary endpoint:
Progression-free survival (PFS) assessed by independent radiology review (IRR)

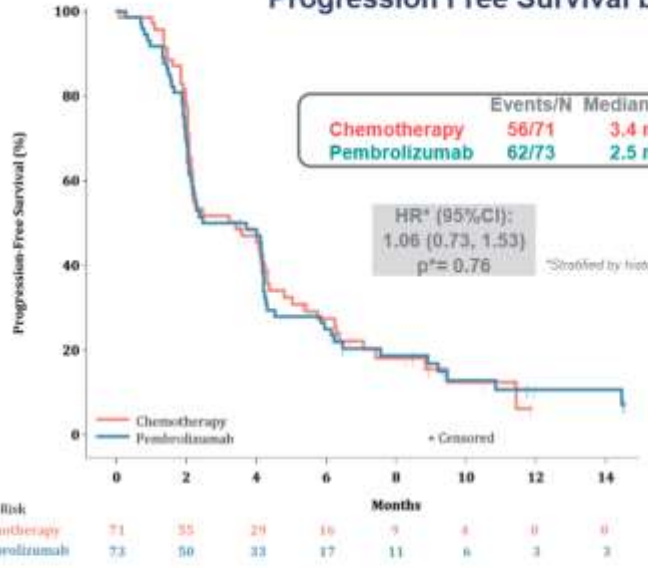
Secondary endpoints:
- Objective response rate (ORR)
- Time to treatment failure (TTF)
- Overall survival (OS)
- Investigator assessed (IA) PFS
- Adverse events

Correlative endpoints:
- Outcome by PD-L1 status

Ponat S et al. Abstract 1665. Proffered Paper 30 Sep

MESO

Progression Free Survival by IRR



	Events/N	Median PFS (95%CI)	6m PFS%(95%CI)
Chemotherapy	56/71	3.4 m (2.2, 4.3)	27.4% (17.1, 38.7)
Pembrolizumab	62/73	2.5 m (2.1, 4.2)	25.0% (15.5, 35.6)

HR* (95%CI): 1.06 (0.73, 1.53)
p*= 0.76

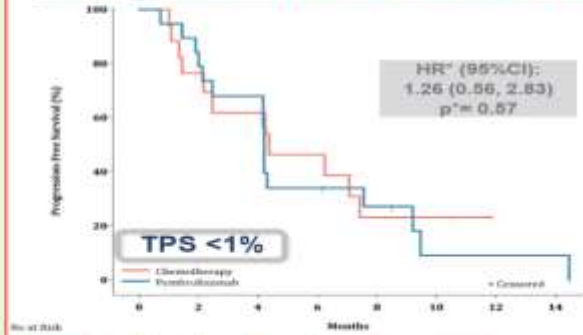
*Stratified by histological subtype

92% (91/99) IRR PDs were identified also by IA

Papat S et al, Abstract 1665

PFS (IRR) by PD-L1 status

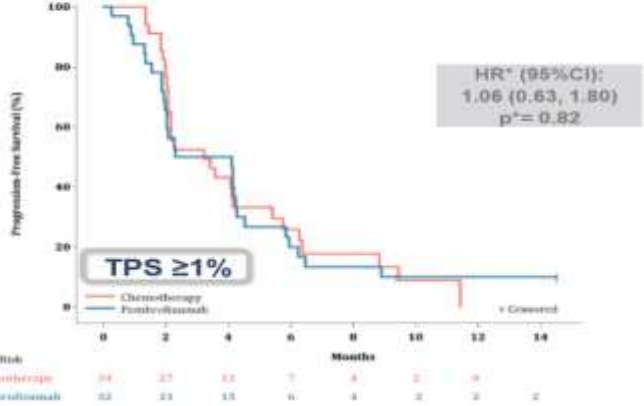
	Events/N	Median PFS (95%CI)	6m PFS (95%CI)
Chemo.	11/17	4.4 m (1.4, 7.4)	46.3% (20.2, 69.1)
Pembro.	16/19	4.2 m (2.1, 7.6)	34.0% (14.0, 55.3)



HR* (95%CI): 1.26 (0.56, 2.83)
p*= 0.57

*Stratified by histolo

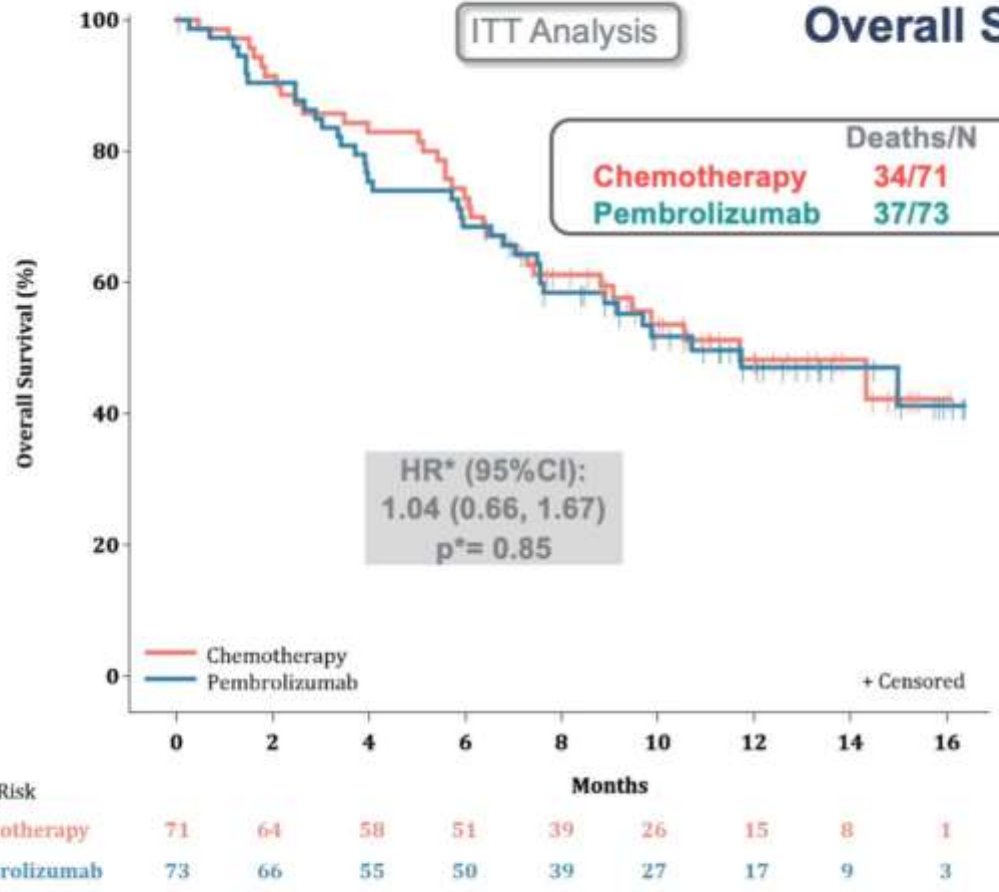
	Events/N	Median PFS (95%CI)	6m PFS (95%CI)
Chemo.	29/34	3.2 m (2.1, 4.1)	25.8% (12.1, 42.0)
Pembro.	28/32	3.2m (1.9, 4.2)	20.0% (8.2, 35.5)



HR* (95%CI): 1.06 (0.63, 1.80)
p*= 0.82

Overall Survival

ITT Analysis



	Deaths/N	Median OS (95%CI)	6m OS%(95%CI)
Chemotherapy	34/71	11.7 m (7.4, NE)	72.9% (60.8, 81.7)
Pembrolizumab	37/73	10.7 m (7.6, NE)	68.5% (56.5, 77.8)

NE: Not estimable

Adjusting for Cross-over

Analysis	HR* (95% CI)	p*
Censored	1.44 (0.77, 2.67)	0.25
Inverse probability weighting (IPW)	1.07 (0.67, 1.71)	0.79

**Stratified by histological subtype*

etop

Best Overall Response – Duration of Response (DOR) by IRR

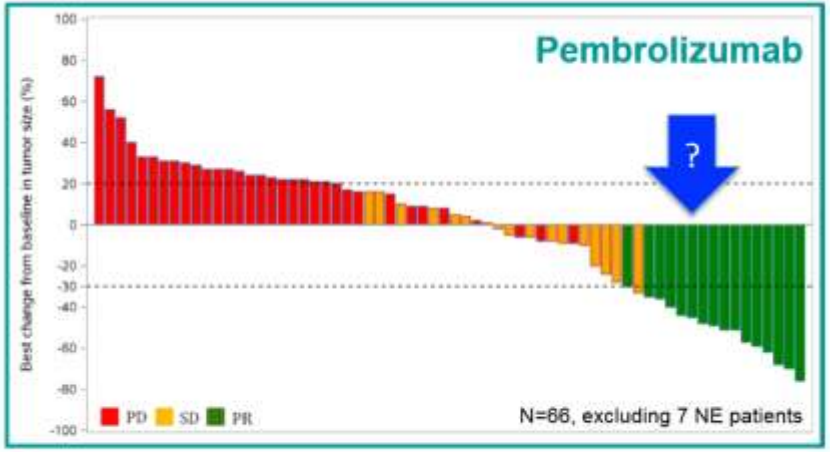
	Pembrolizumab N (%)	Chemotherapy N (%)
ORR (95% CI)	**22% (13%, 33%)**	**6% (2%, 14%)**
Partial response (PR)	16 (21.9)	4 (5.6)
Stable Disease (SD)	17 (23.3)	23 (32.4)
Progression of Disease (PD)	33 (45.2)	35 (49.3)
Not Evaluable (NE)	7 (9.6)	9 (12.7)
Median DOR* (95% CI)	**4.6 months (2.2, 10.3)**	**11.2 months (6.2, 15.3)**

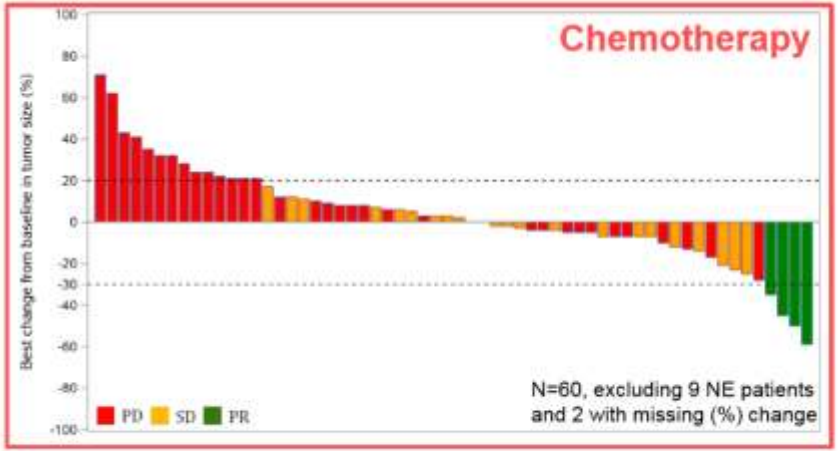
→ Stratified p=0.004

* Updated as of August 2019

16 responders
→ 7 PD and 4 deaths

4 responders
→ 3 PD





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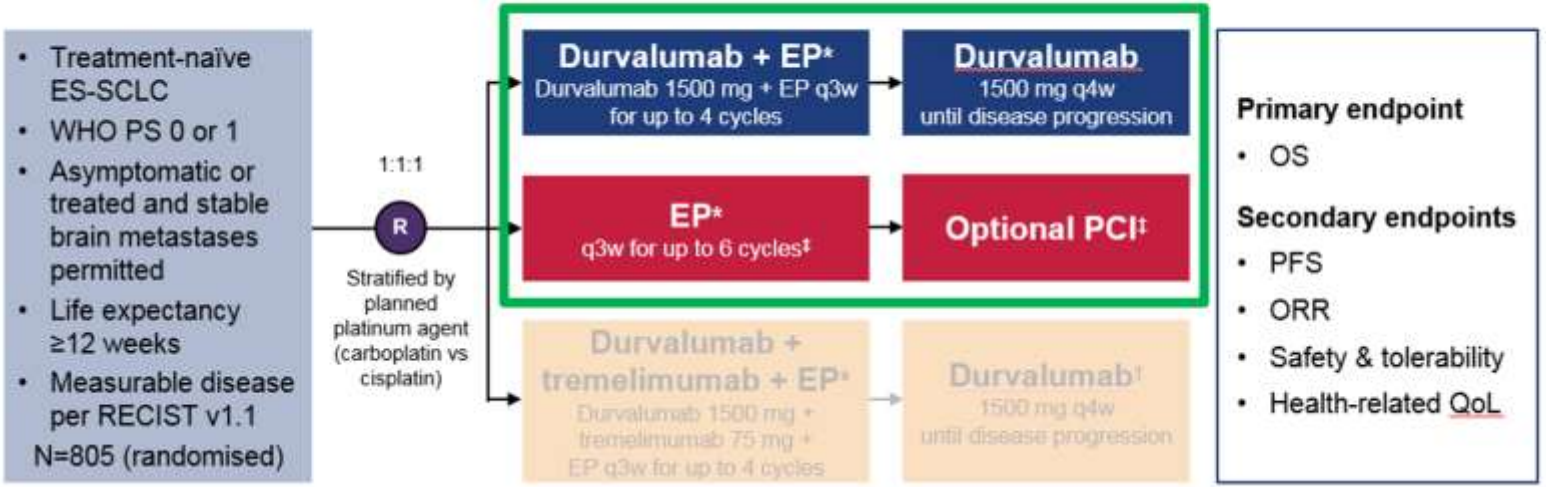
- IMMUNO

Thymic carcinoma

- REMORA trial

CASPIAN Study Design

Phase 3, global, randomised, open-label, sponsor-blind multicentre study



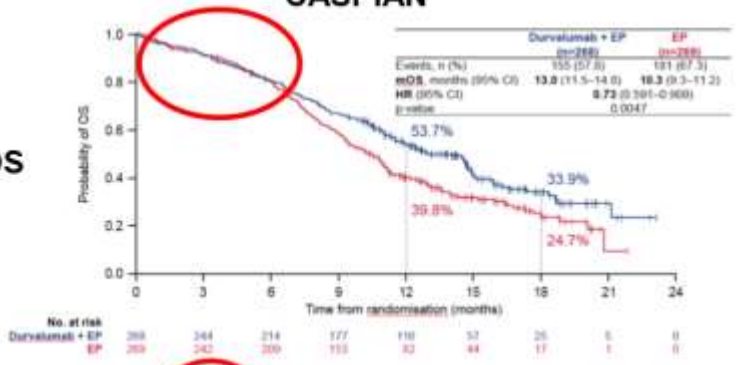
Following preplanned interim analysis by the IDMC, the durvalumab + tremelimumab + EP versus EP comparison continues to final analysis

Paz-Ares L et al WCLC 2019

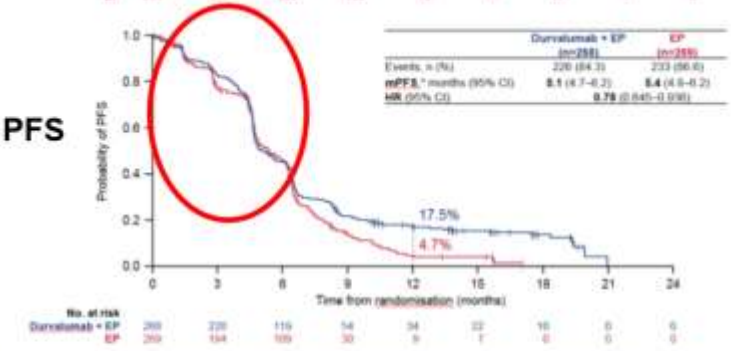
SCLC

CASPIAN

OS

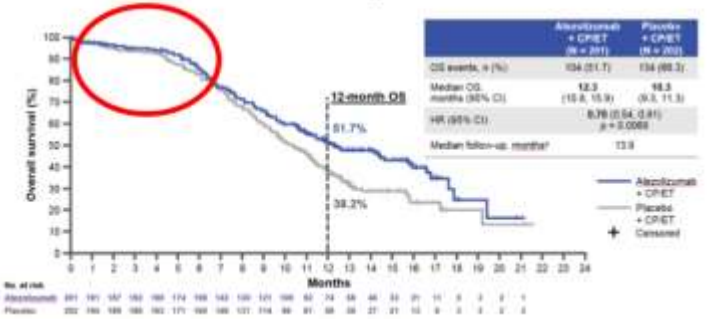


PFS

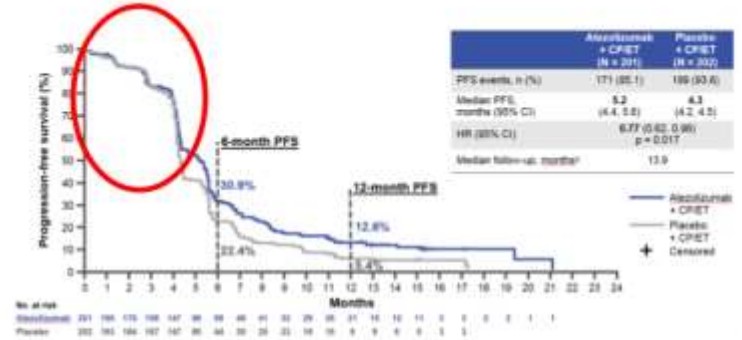


IMpower133

OS



PFS



CASPIAN - PATTERNS OF FIRST PROGRESSION

Types of progression

	Durvalumab + EP (N=268)	EP (N=269)
Total progression events, n (%)	226 (84.3)	233 (86.6)
RECIST-defined progression, n (%)	192 (71.6)	194 (72.1)
Target lesions	115 (42.9)	106 (39.4)
Non-target lesions	66 (24.6)	61 (22.7)
New lesions	111 (41.4)	127 (47.2)
Death in absence of progression, n (%)	34 (12.7)	39 (14.5)

Sites of new lesions (>5% patients)

	Durvalumab + EP (N=268)	EP (N=269)
New lesions, n (%)	111 (41.4)	127 (47.2)
Lung	23 (8.6)	41 (15.2)
Brain/CNS	31 (11.6)	31 (11.5)
Liver	15 (5.6)	24 (8.9)
Bone	12 (4.5)	19 (7.1)
Regional lymph nodes	15 (5.6)	12 (4.5)

- Numerically fewer patients developed new lesions at first progression with durvalumab + EP versus EP
- No difference in the incidence of new brain/CNS lesions between arms

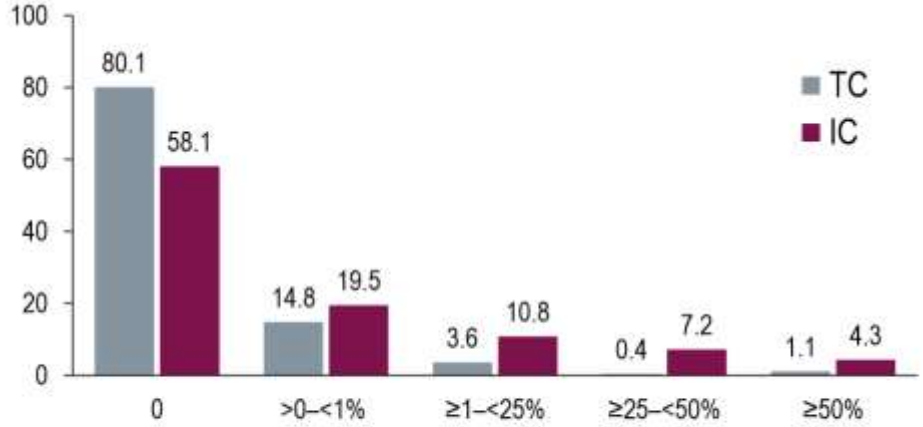
Paz Ares L et al, ESMO Proferred Paper 28Sep

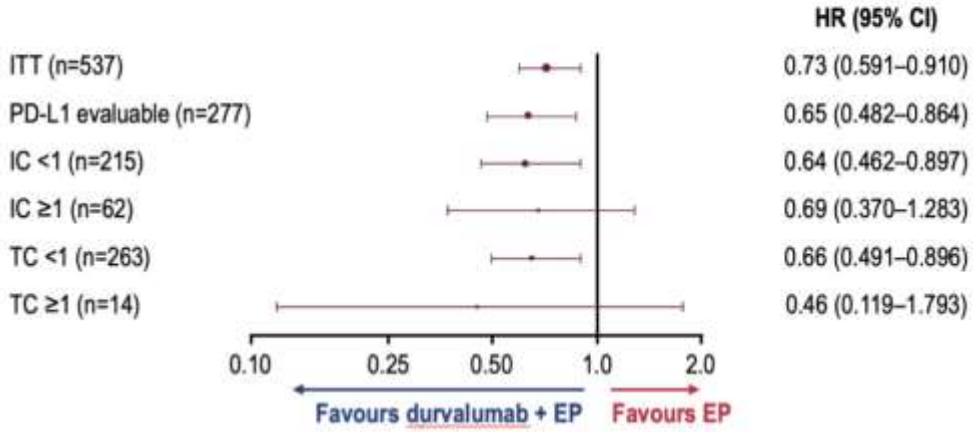
CNS, central nervous system

SCLC

CASPIAN - EXPLORATORY PD-L1 ANALYSIS

- 94.9% and 77.6% of patients had PD-L1 expression <1% on TCs and ICs, respectively
- Due to low PD-L1 expression, a 1% cut-off was used in post-hoc analyses





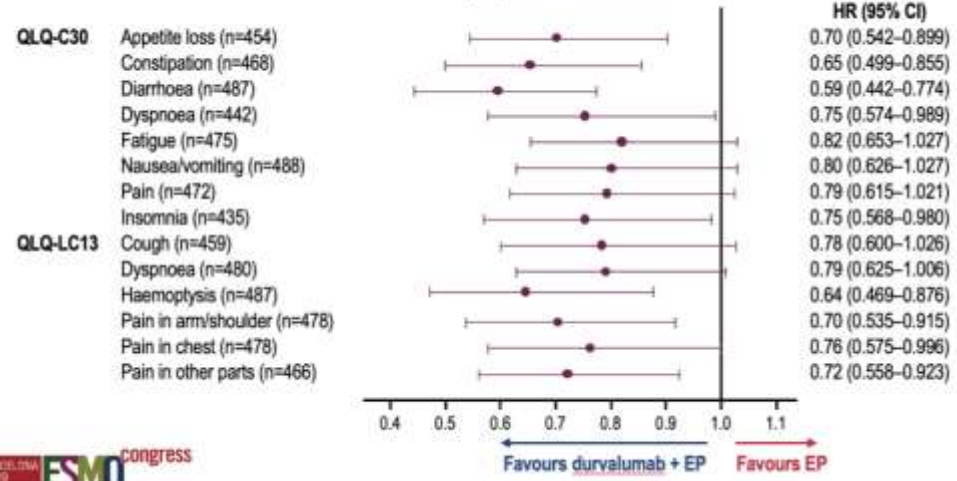
- Durvalumab + EP was associated with improved OS vs EP, regardless of PD-L1 expression with a 1% cut-off
- No significant interaction was observed with OS based on PD-L1 expression as a continuous variable (TC, p=0.54; IC, p=0.23); similar results were observed with PFS and ORR

Paz Ares L et al, ESMO Proferred Paper 28Sep

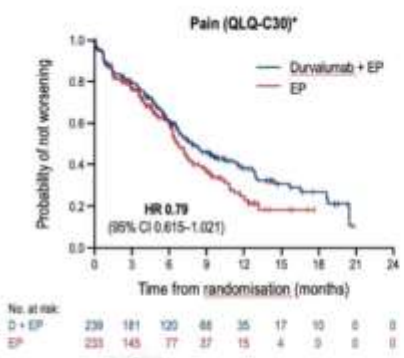
SCLC

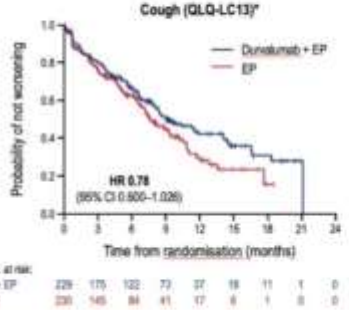
CASPIAN – TIME TO DETERIORATION

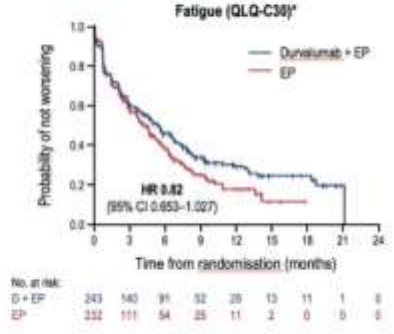
- Durvalumab + EP was favoured across all symptoms

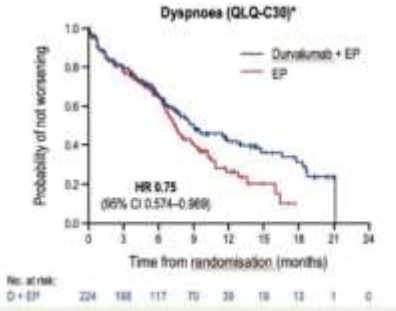


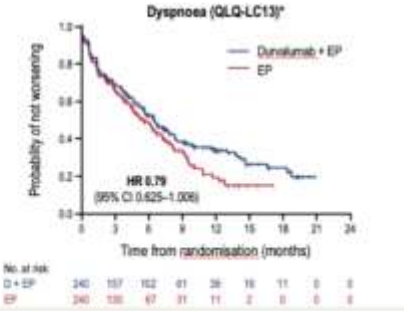
BARCELONA 2019 ESMO congress





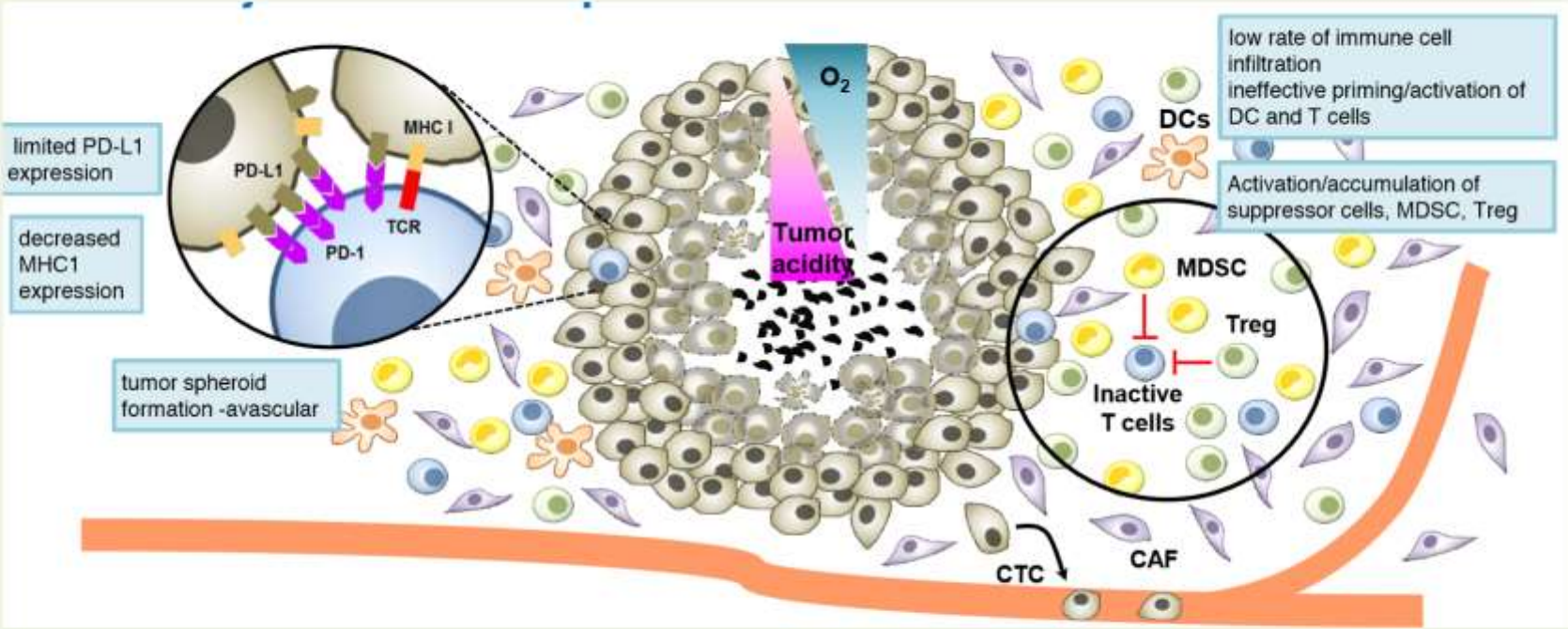






Paz Ares L et al, ESMO Proferred Paper 28Sep

WHY IMMUNOTHERAPY DOESN'T WORK WELL IN SCLC



Hamilton et al Expert Opin Biol 2019

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Mesothelioma

- IMMUNO

Thymic carcinoma

- REMORA trial

Durable anti-tumor activity of the multi-targeted inhibitor lenvatinib in patients with advanced or metastatic thymic carcinoma; Preliminary results from a multicenter phase II (REMORA) trial.

Shoichi Itoh et al, ESMO 1844O

Patients with advanced or metastatic Thymic carcinoma (Any histology; n=42) → Lenvatinib 24 mg QD → Until PD, unacceptable toxicity or loss of clinical benefit

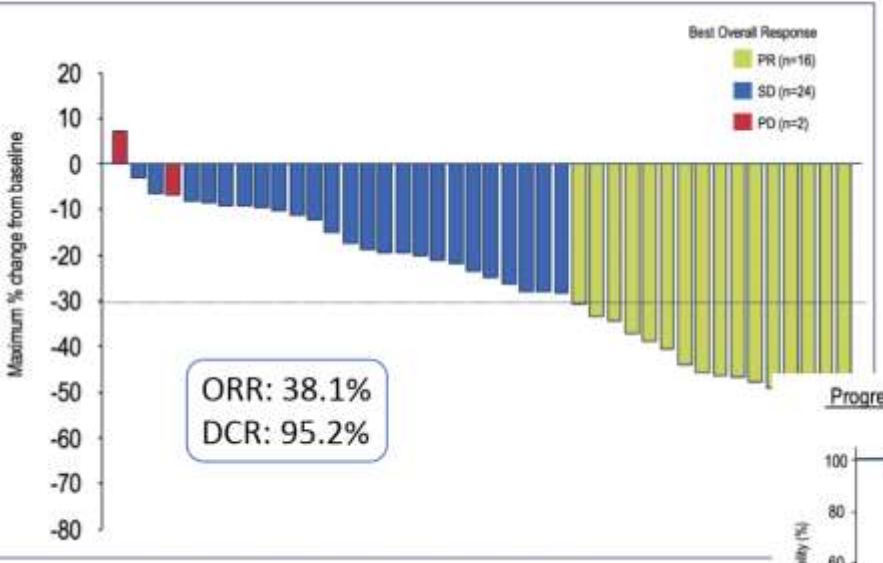
Inclusion Criteria
- Pathologically confirmed thymic carcinoma
- Measureable disease per RECIST v1.1
- ECOG PS of 0 or 1
- Disease progression after at least one previous line of platinum-based chemotherapy

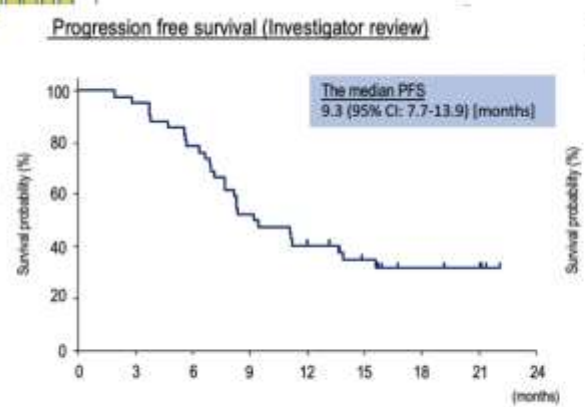
Exclusion Criteria
- Uncontrolled hypertension
- Treatment history of TKIs targeted for VEGFR
- Active brain metastases requiring treatment

Primary endpoint
- Objective response rate (ORR) by independent radiological review

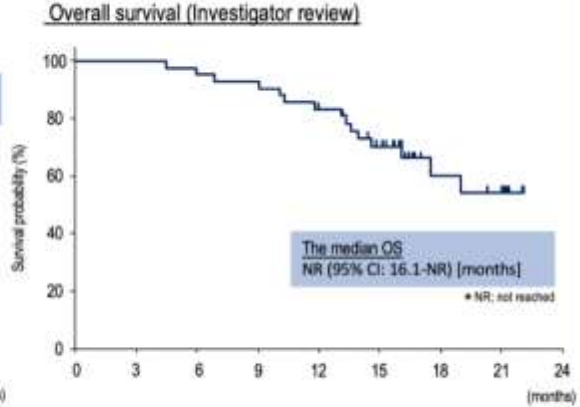
Secondary endpoints
- Efficacy endpoints: Progression-free survival (PFS), Over all survival (OS) and disease control rate (DCR)
- Safety endpoints: Treatment-related adverse events

Sample size consideration
- As per the SWOG two-stage design, the sample size of 40 had 80% power with one-sided alpha error of 5%; threshold ORR, 10%; and expected ORR, 25%





- The median follow up period was 15.5 months (IQR 13.1-17.5).



- the median 12-month OS probability were 83.3% (95%CI; 68.2%-91.7%)

THYMIC CARCINOMA

Key messages from ESMO 2019

- **OSIMERTINIB** SoC first line EGFR mut-NSCLC
- **IPI-NIVO** new potential option for PDL-1≥1% NSCLC-non oncogene addicted→URGENT DEFINITION OF PATIENT **SELECTION CRITERIA**
- **TMB** MAYbe has a role, but we don't yet know where
- **Atezolizumab** alone effective in TC3/IC3 NSCLC →confirmation of PDL-1 as predictive biomarker→IMPORTANCE OF CORRECT **TESTING**


550,000 patients treated
in trials presented at the ESMO Congress over the last 10 years
| Translating science into better cancer patient care

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REGINA ELENA

GRAZIE!!!

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