Recent Advances and Unmet Needs in Cancer Immunotherapy

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Disclosure

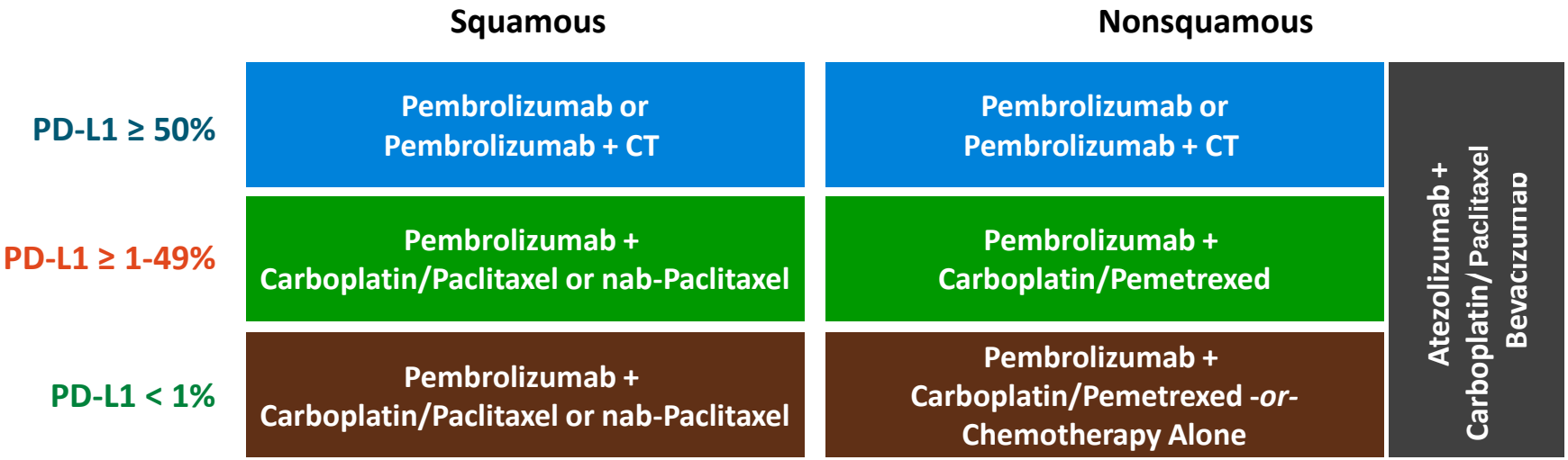
speaking honoraria from AstraZeneca, Roche, Boehringer Ingelheim, Eli Lilly, Pfizer, Novartis, Merck Sharp & Dohme, Ono Pharmaceutical, Chugai, AbbVie, and Bristol-Myers Squibb

expenses for travel and accommodations from Roche, Boehringer Ingelheim, Pfizer, Merck Sharp & Dohme, and Bristol-Myers Squibb.

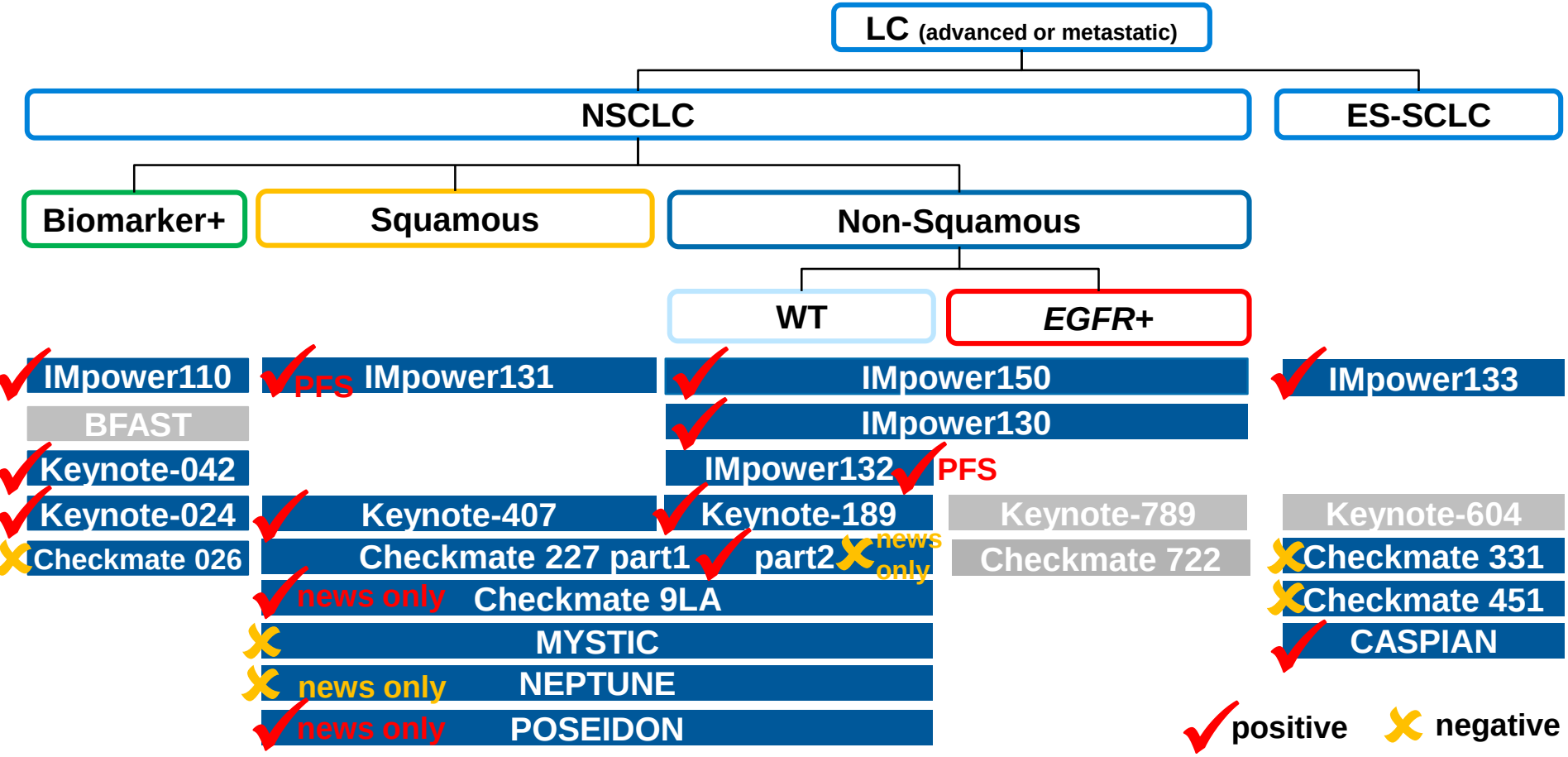
Disclaimer

This presentation contains off-label information which is presented only for purposes of providing an overview of clinical data and should not be construed as a recommendation for use of any product for unapproved uses. There are currently no published head-to-head studies between therapeutics such as checkpoint inhibitors or TKIs, and slides summarising studies together are provided only for scientific discussion purposes.

Immunotherapy Treatment Algorithm for NSCLC in 2018



Overview of 2019 key phase III trials for IO



IMpower110 (2019 ESMO)

BARCELONA 2019 ESMO congress

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

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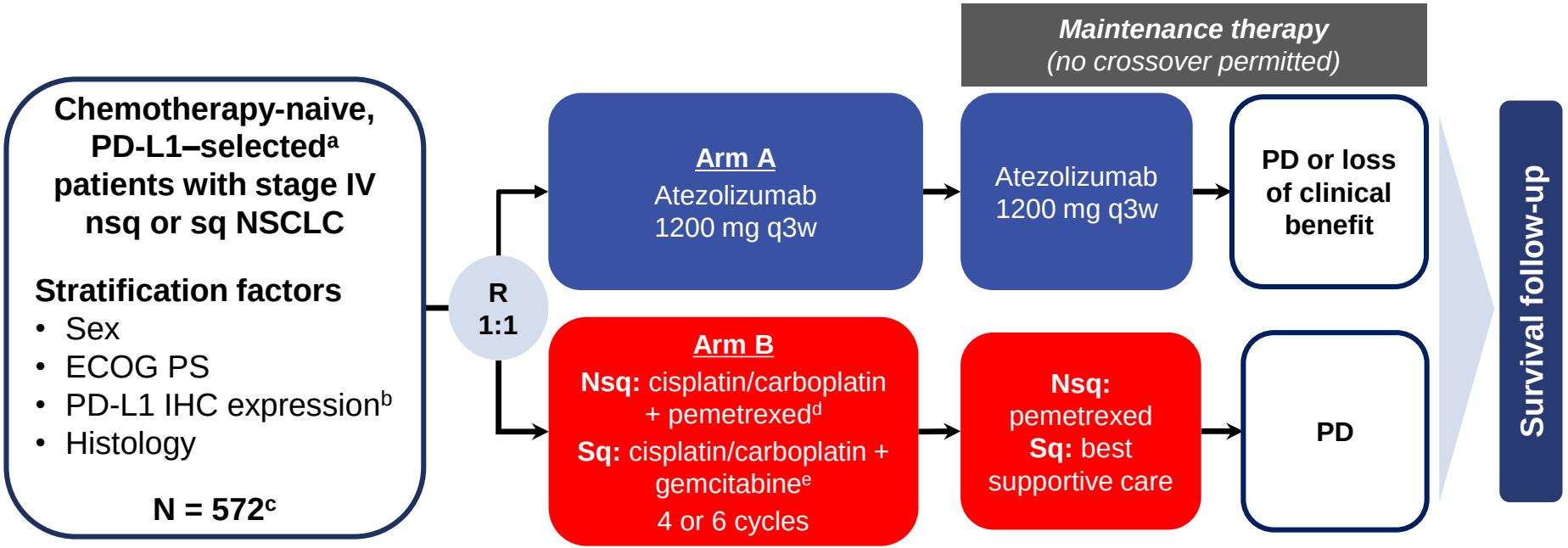
IMpower110 Study Design

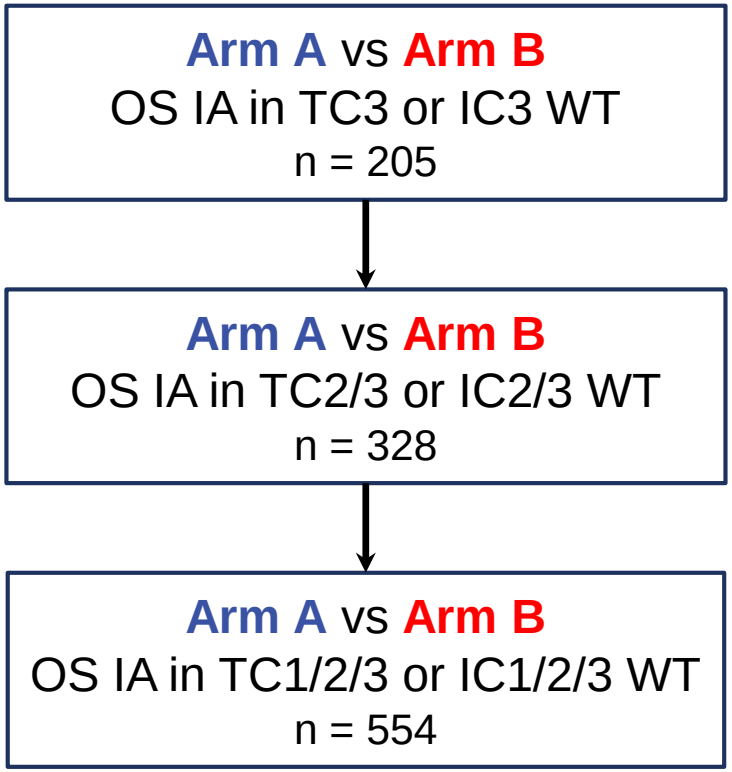


- Primary endpoint: OS in WT population (TC3 or IC3 → TC2/3 or IC2/3 → TC1/2/3 or IC1/2/3)[f]
- Key secondary endpoints: investigator-assessed PFS, ORR and DOR (per RECIST version 1.1)

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

Statistical Testing Plan



- 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

IA, interim analysis. WT, wild-type (excluding patients with *EGFR*+ and/or *ALK*+ NSCLC).
Data cutoff: 10 September 2018.

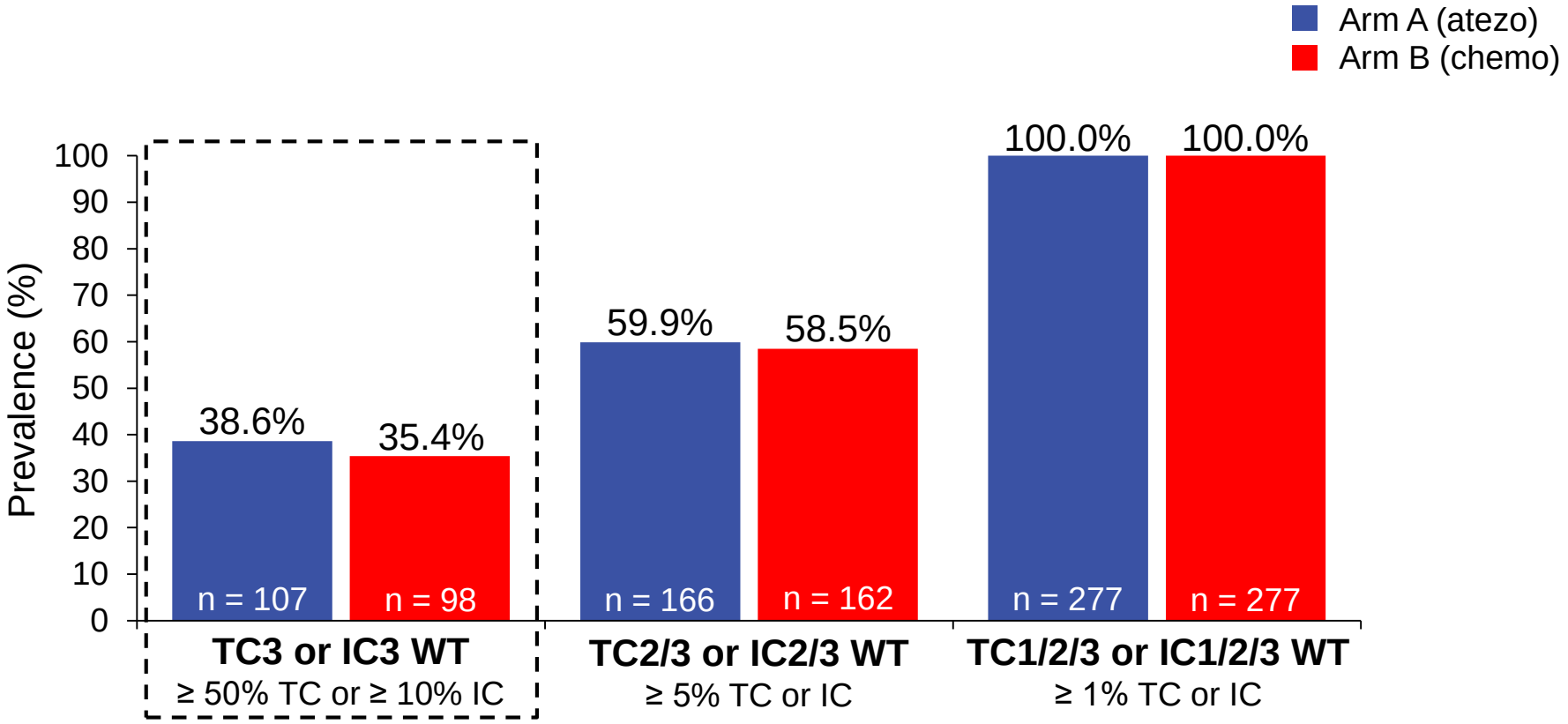
Baseline Characteristics

Characteristic	TC1/2/3 or IC1/2/3 WT		TC3 or IC3 WT	
n (%)	Arm A (atezo) n = 277	Arm B (chemo) n = 277	Arm A (atezo) n = 107	Arm B (chemo) n = 98
Age < 65 y	143 (51.6)	134 (48.4)	59 (55.1)	43 (43.9)
Male	196 (70.8)	193 (69.7)	79 (73.8)	64 (65.3)
White	227 (81.9)	240 (86.6)	87 (81.3)	82 (83.7)
Asian	45 (16.2)	30 (10.8)	20 (18.7)	15 (15.3)
Never used tobacco	37 (13.4)	35 (12.6)	9 (8.4)	15 (15.3)
Non-squamous histology	192 (69.3)	193 (69.7)	80 (74.8)	75 (76.5)
ECOG PS 0	97 (35.0)	102 (36.8)	35 (32.7)	38 (38.8)

Data cutoff: 10 September 2018.

Spigel et al. IMpower110 Interim OS Analysis

Prevalence of PD-L1 Expression[a]

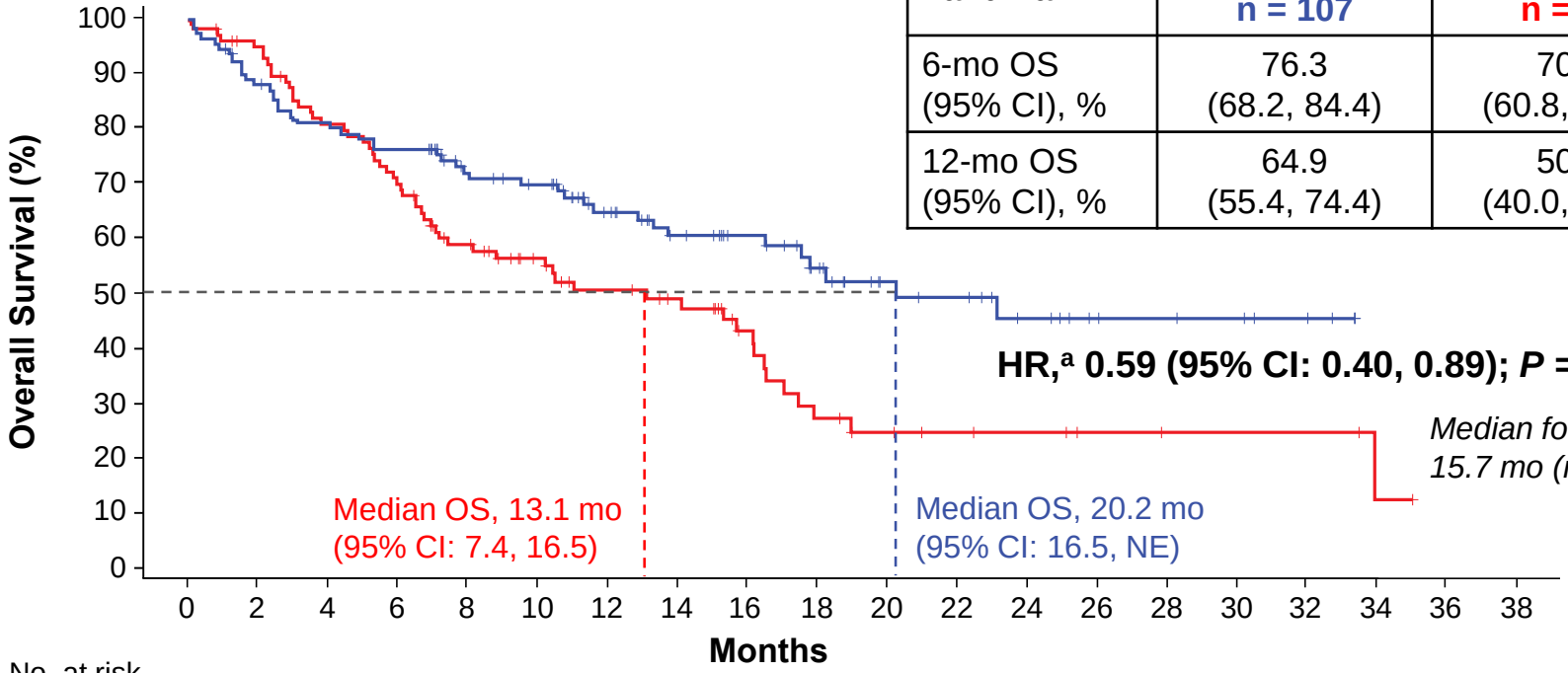


[a] PD-L1 status determined using the SP142 PD-L1 IHC assay.
Data cutoff: 10 September 2018.

Spigel et al. IMpower110 Interim OS Analysis

Primary endpoint TC3 or IC3 WT OS

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

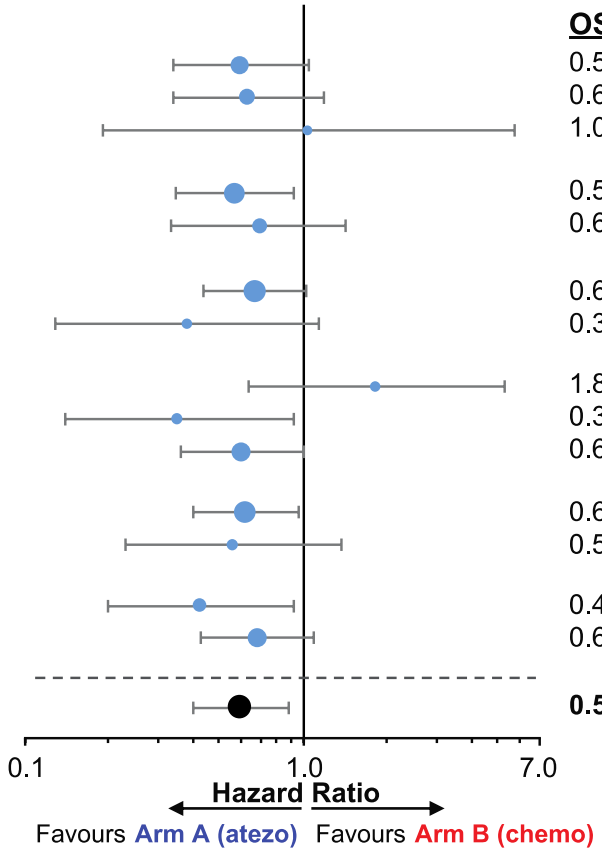
Atezolizumab	107	94	85	80	66	61	48	40	34	25	18	16	11	7	6	5	2	
Chemotherapy	98	89	75	65	50	40	33	28	19	12	9	7	6	4	3	3	3	1

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

Spigel et al. IMpower110 Interim OS Analysis

TC3 or IC3 WT: OS in Key Subgroups

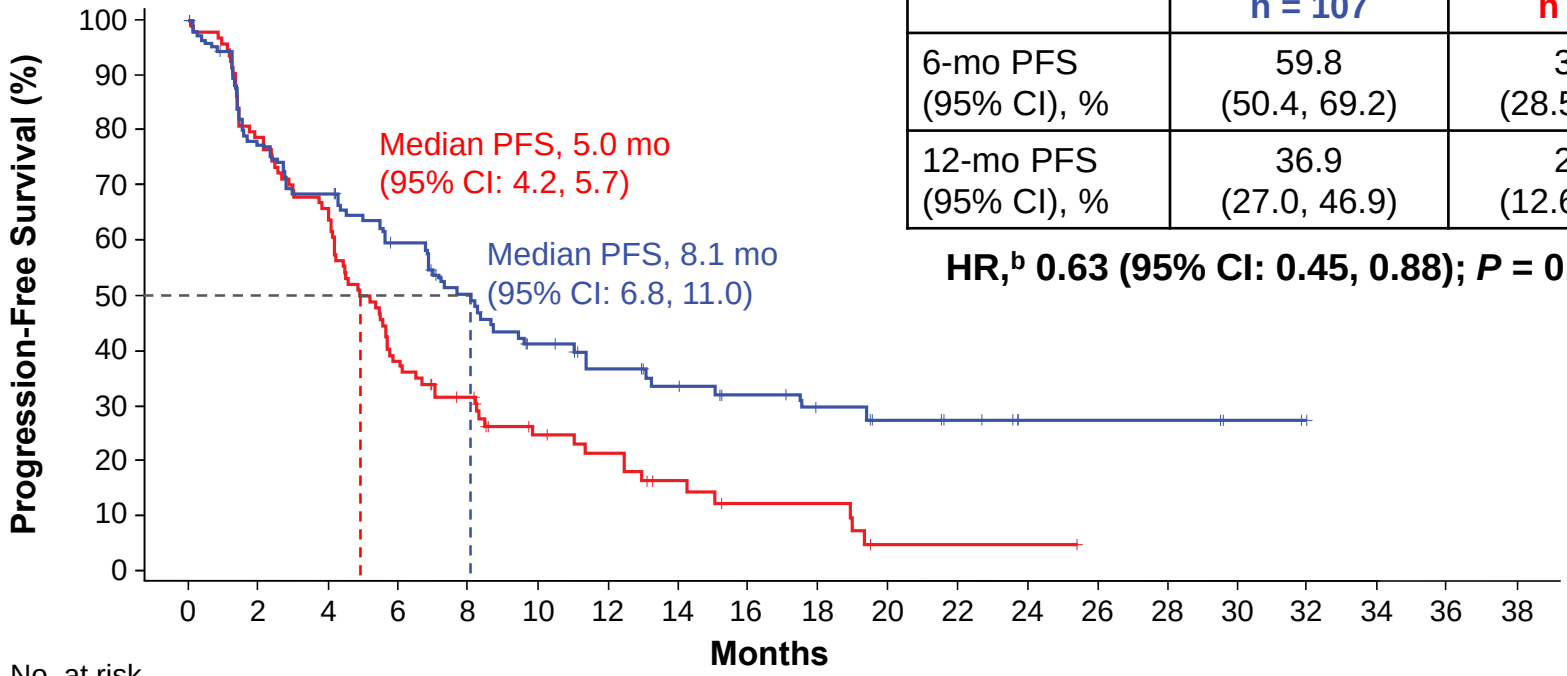
Subgroup[a]	n (%)	OS HR (95% CI)[b]	Median OS, mo: Arm A	Median OS, mo: Arm B
< 65 years	102 (49.8)	0.59 (0.34, 1.04)	NE	13.1
65-74 years	80 (39.0)	0.63 (0.34, 1.19)	17.8	10.4
75-84 years	22 (10.7)	1.04 (0.19, 5.70)	NE	16.2
Male	143 (69.8)	0.57 (0.35, 0.93)	23.1	13.1
Female	62 (30.2)	0.69 (0.34, 1.39)	17.8	14.1
White	169 (82.4)	0.67 (0.44, 1.03)	17.8	13.1
Asian	35 (17.1)	0.38 (0.13, 1.13)	NE	14.1
Never used tobacco	24 (11.7)	1.83 (0.63, 5.31)	8.0	15.9
Current tobacco user	49 (23.9)	0.35 (0.14, 0.88)	NE	10.2
Previous tobacco user	132 (64.4)	0.60 (0.36, 1.00)	23.1	13.1
Non-squamous histology	155 (75.6)	0.62 (0.40, 0.96)	20.2	10.5
Squamous histology	50 (24.4)	0.56 (0.23, 1.37)	NE	15.3
ECOG PS 0	73 (35.6)	0.42 (0.20, 0.92)	NE	15.7
ECOG PS 1	132 (64.4)	0.69 (0.43, 1.10)	16.5	13.1
All TC3 or IC3 WT patients	**205 (100)**	**0.59 (0.40, 0.89)[c]**	**20.2**	**13.1**



[a] The 1 patient in the ≥ 85 years subgroup is not included; 1 patient's race was unknown. [b] Unstratified. [c] Stratified.
Data cutoff: 10 September 2018.

Spigel et al. IMpower110 Interim OS Analysis

PFS[a]: TC3 or IC3 WT



Landmark	Arm A (atezo) n = 107	Arm B (chemo) n = 98
6-mo PFS (95% CI), %	59.8 (50.4, 69.2)	38.3 (28.5, 48.1)
12-mo PFS (95% CI), %	36.9 (27.0, 46.9)	21.6 (12.6, 30.6)

HR,[b] 0.63 (95% CI: 0.45, 0.88); *P* = 0.0070[c,d]

No. at risk

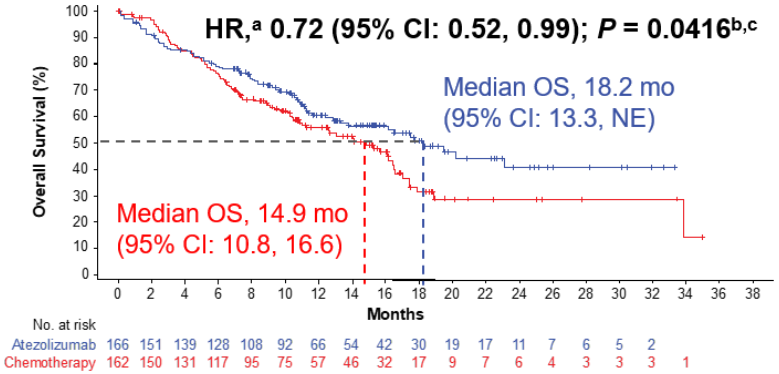
Atezolizumab	107	82	72	60	45	31	25	21	16	13	10	8	4	4	4	2
Chemotherapy	98	74	62	36	26	16	13	8	5	5	1	1	1			

[a] Investigator assessed per RECIST 1.1. [b] Stratified. [c] Stratified log-rank.
[d] For descriptive purposes only. Data cutoff: 10 September 2018.

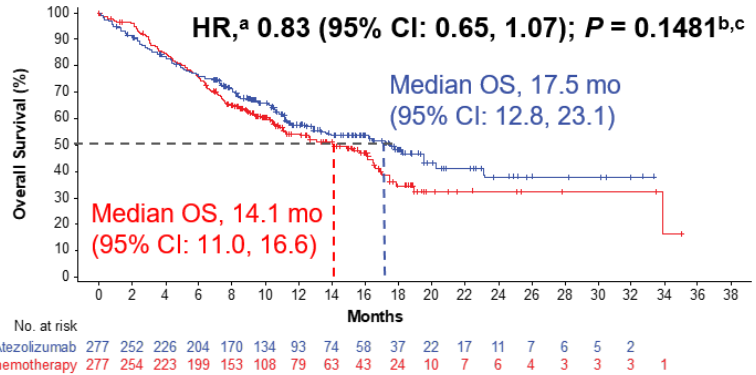
Spigel et al. IMpower110 Interim OS Analysis

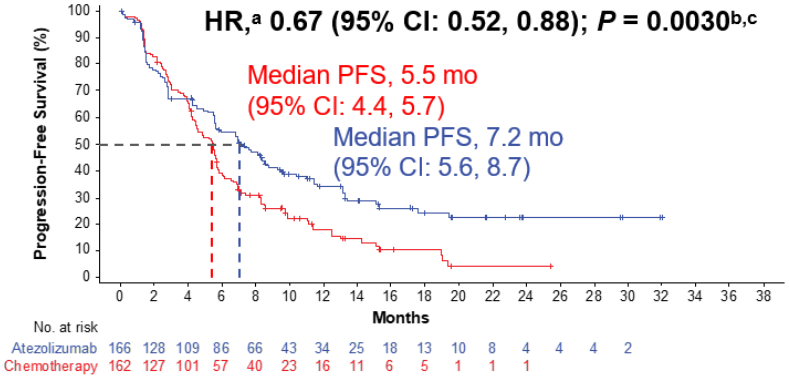
OS&PFS: TC2/3 or IC2/3 and TC1/2/3 or IC1/2/3

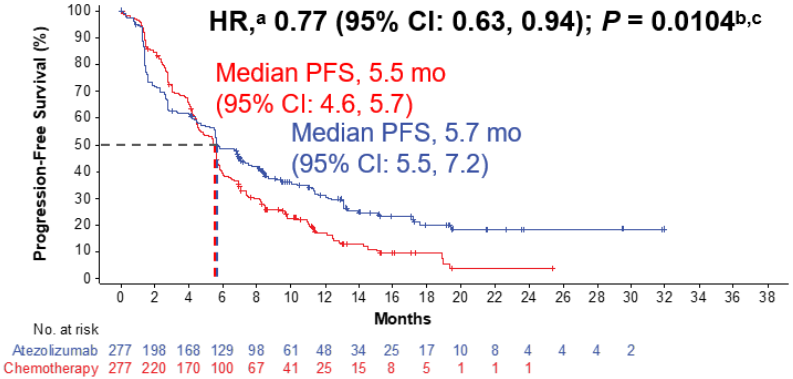
TC2/3 or IC2/3 WT



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



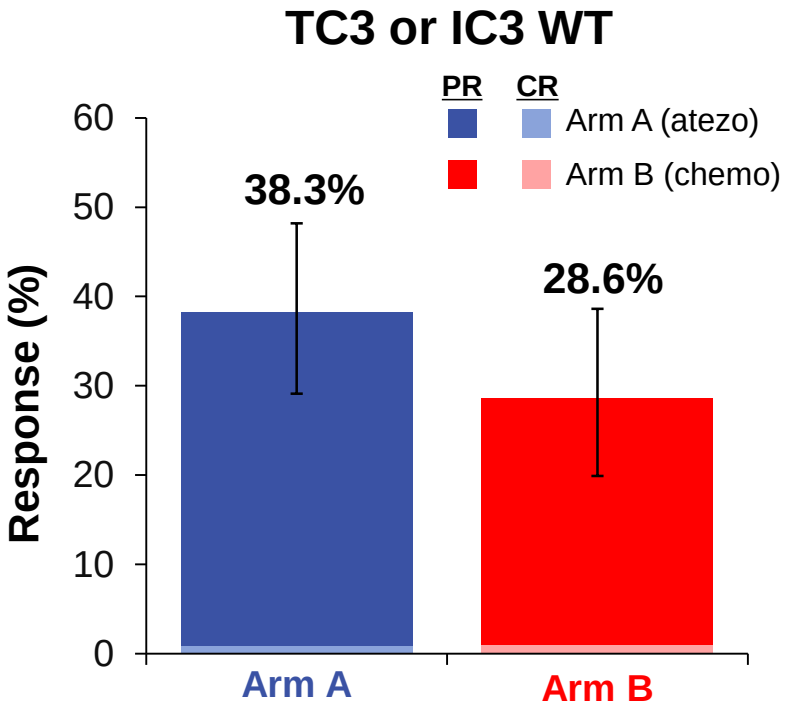




[a] Stratified. [b] Stratified log-rank.
[c] For descriptive purposes only. Data cutoff: 10 September 2018.

courtesy to Spigel et al., 2019 ESMO

Confirmed ORR and DOR



	Arm A (atezo)	Arm B (chemo)
TC2/3 or IC2/3 WT	**n = 166**	**n = 162**
ORR (95% CI), %	30.7 (23.8, 38.3)	32.1 (25.0, 39.9)
Median DOR (range), mo	NE (1.8+ to 29.3+)	5.8 (2.6 to 23.9+)
TC1/2/3 or IC1/2/3 WT	**n = 277**	**n = 277**
ORR (95% CI), %	29.2 (24.0, 35.0)	31.8 (26.3, 37.6)
Median DOR (range), mo	NE (1.8+ to 29.3+)	5.7 (2.4 to 23.9+)

CR, complete response; PR, partial response.
+, censored. Data cutoff: 10 September 2018.

Spigel et al. IMpower110 Interim OS Analysis

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 2018.

Spigel et al. IMpower110 Interim OS Analysis

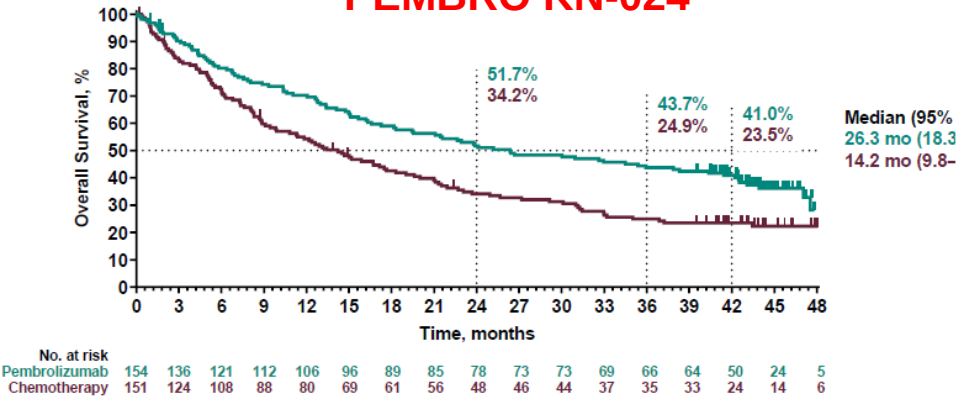
IMpower110 Conclusions

- Atezolizumab monotherapy showed statistically significant and clinically meaningful OS improvement in the TC3 or IC3 WT population vs platinum-based chemotherapy (HR, 0.59 [95% CI: 0.40, 0.89]; *P* = 0.0106)
- In the TC3 or IC3 WT population, atezolizumab showed meaningful improvement in PFS, ORR and DOR vs chemotherapy
- Atezolizumab represents a promising 1L treatment option in patients with PD-L1–high NSCLC

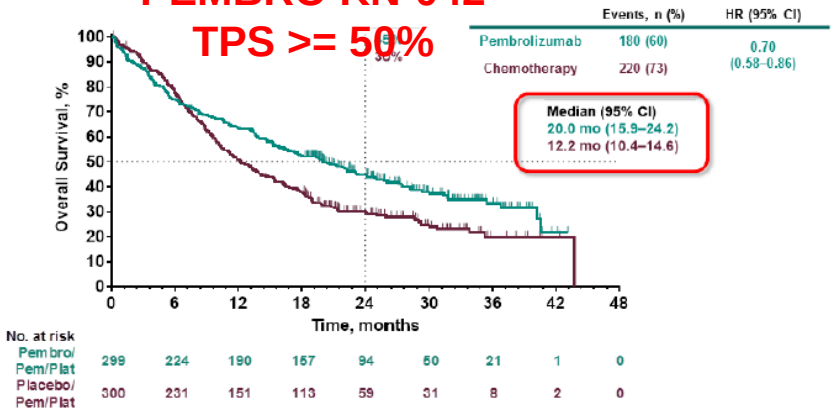
Spigel et al. IMpower110 Interim OS Analysis

Do they look so different?

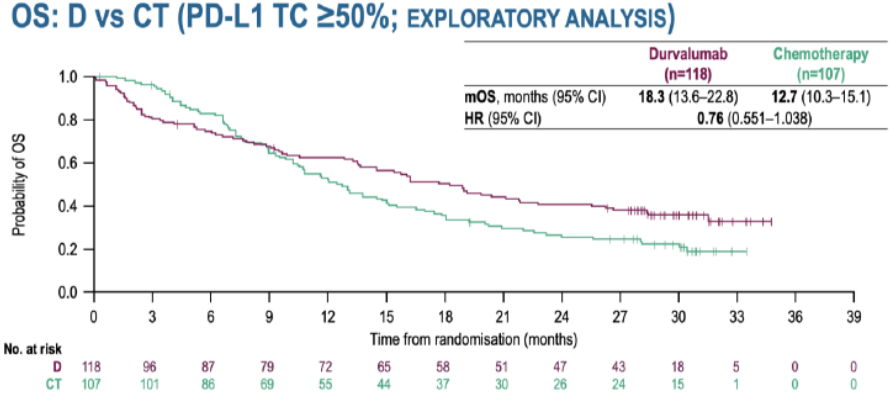
PEMBRO KN-024



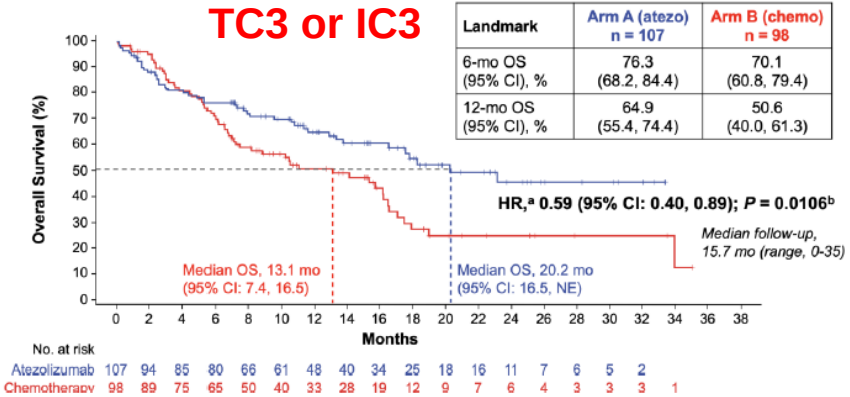
PEMBRO KN-042
TPS >= 50%



DURVA MYSTIC



ATEZO IMpower110
TC3 or IC3



Unanswered questions and unmet needs

1. Clinical benefits in individual TC3 and IC3 subgroups separately?

IMpower110 (TC3 or IC3)

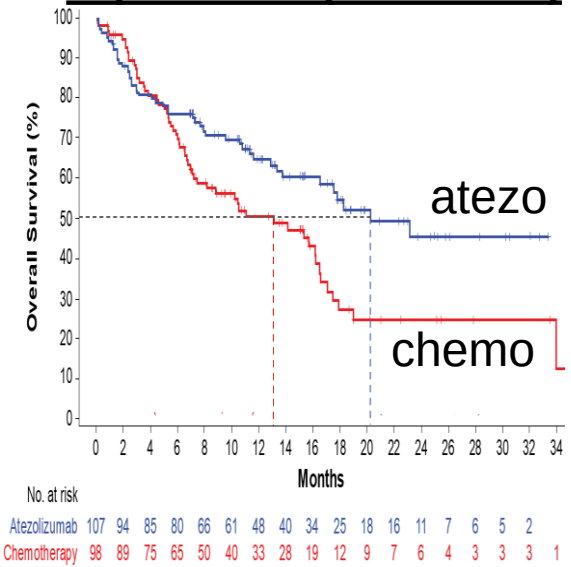


Table 1. PD-L1 IHC Scoring Criteria on TC and IC in NSCLC Using the SP142 Assay

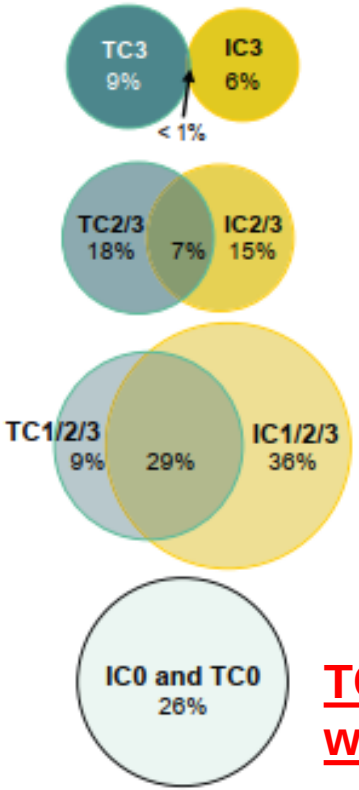
PD-L1 TC Scoring		PD-L1 IC Scoring	
TC Score	% of PD-L1–Expressing TC	IC Score	% of PD-L1–Expressing IC
TC3	≥ 50%	IC3	≥ 10%
TC2	≥ 5% and < 50%	IC2	≥ 5% and < 10%
TC1	≥ 1% and < 5%	IC1	≥ 1% and < 5%
TC0	< 1%	IC0	< 1%

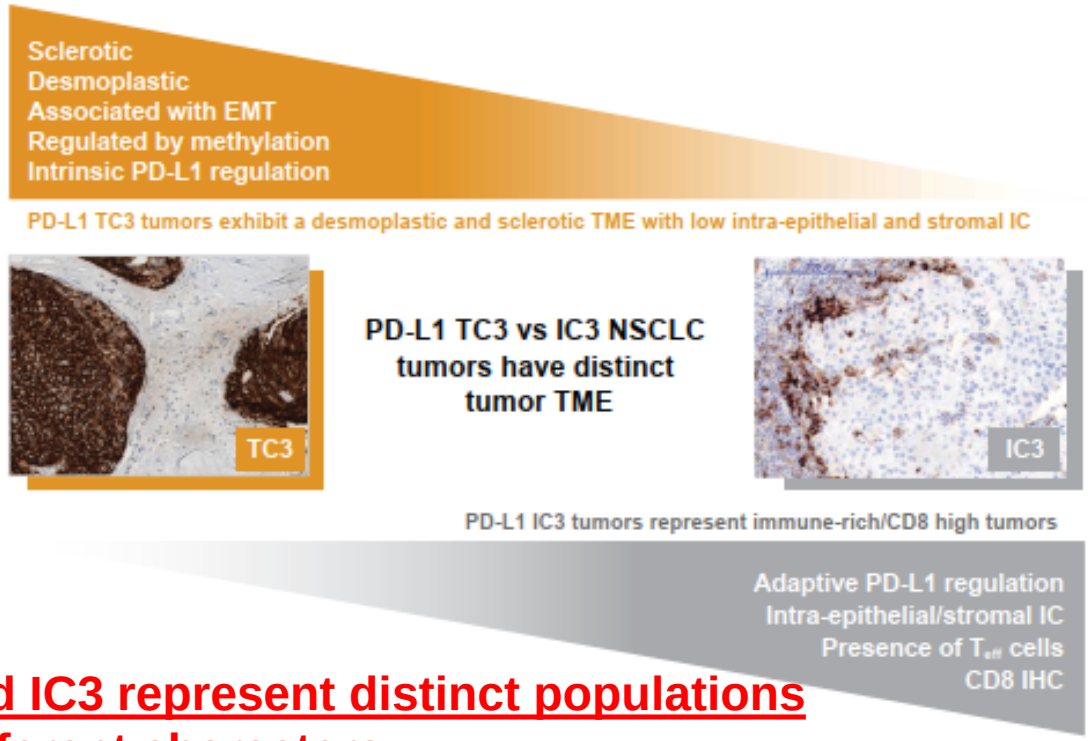
TC scored as percentage of tumor cells and IC scored as percentage of tumor area.

courtesy to Spigel et al., 2019 ESMO; Schmid et al., 2015 ECC

Unanswered questions and unmet needs

1. Clinical benefits in individual TC3 and IC3 subgroups separately?





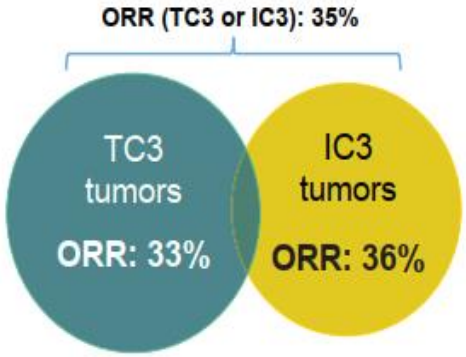
TC3 and IC3 represent distinct populations with different characters

Schmid et al., 2015 ECC

Unanswered questions and unmet needs

1. Clinical benefits in individual TC3 and IC3 subgroups separately? **YES**

Data from pooled ORR analysis in 2L+ NSCLC PCD4989g (data cutoff, Dec 2, 2014), FIR (cohort 2; data cutoff, Jan 7, 2015) and POPLAR (data cutoff, Jan 30, 2015) trials



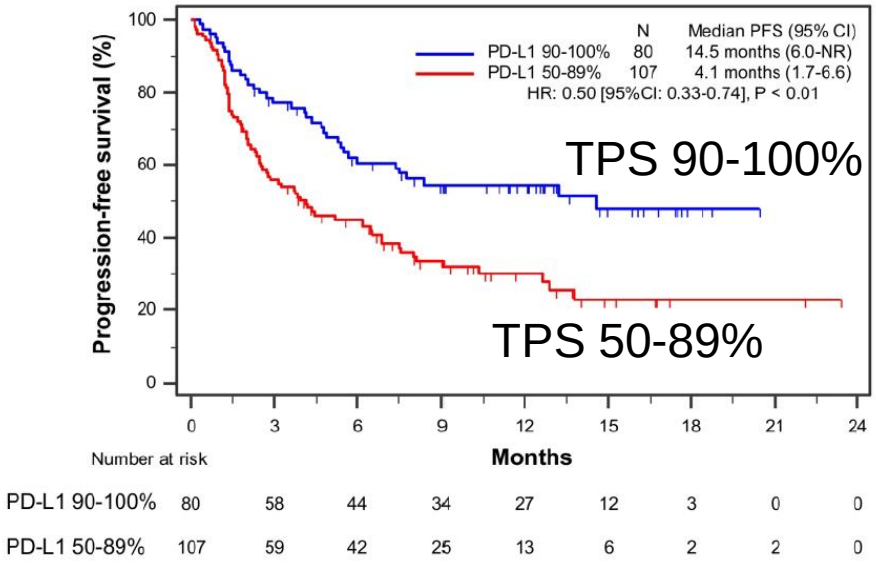
PD-L1 Status	ORR (RECIST v1.1) Pooled Analysis From Phase I and II NSCLC Atezolizumab Trials	
	n	% (95% CI)
TC3 (TC High)	45	33% (20, 49)
IC3 (IC High)	42	36% (22, 52)
TC3 or IC3	81	35% (24, 56)
TC0 and IC0	69	9% (3, 18)

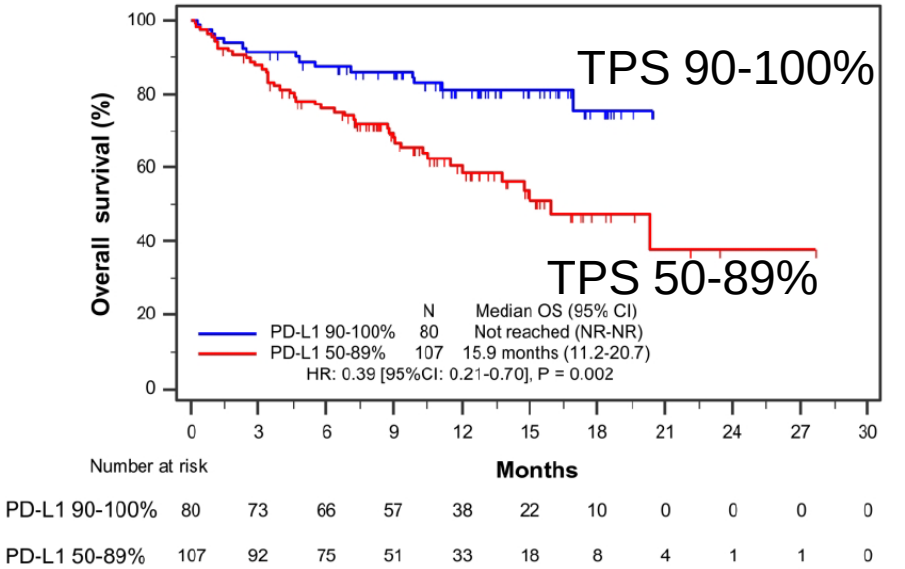
Schmid et al., 2015 ECC

Unanswered questions and unmet needs

2. PD-L1 IHC score 50% as the best threshold for monotherapy of IO?

Higher is better, but how high is high?





overall ORR **90-100%** vs **50-89%** (TPS)

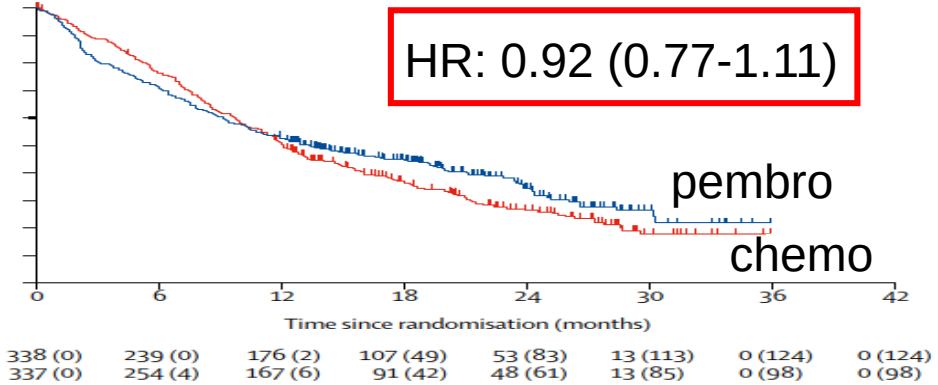
44% **60%** vs **32.7%** (ORR)

EJ Aguilar et al., 2019

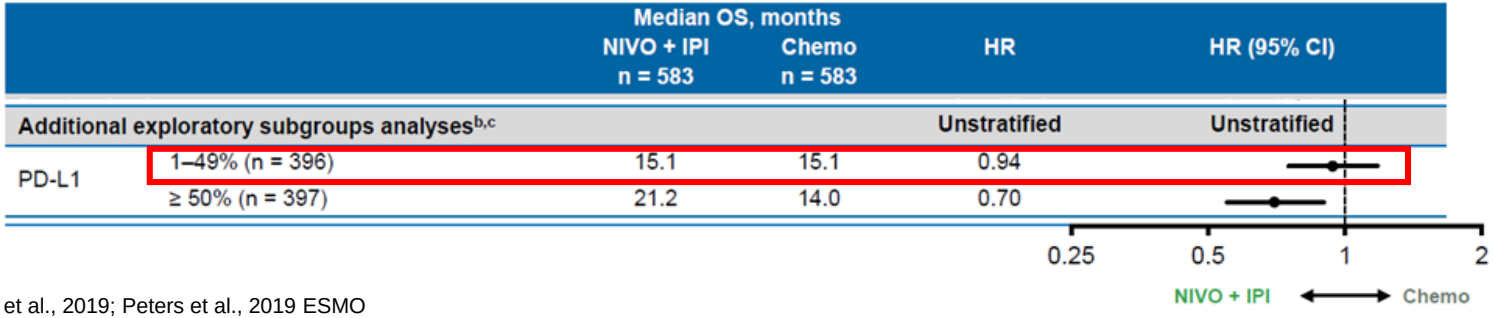
Unanswered questions and unmet needs

3. PD-L1 IHC score 1-49% or < 1% for IO monotherapy? **1-49% no efficacy?**

Keynote-042 (TPS 1-49%)



Checkmate 227 (IO + IO)

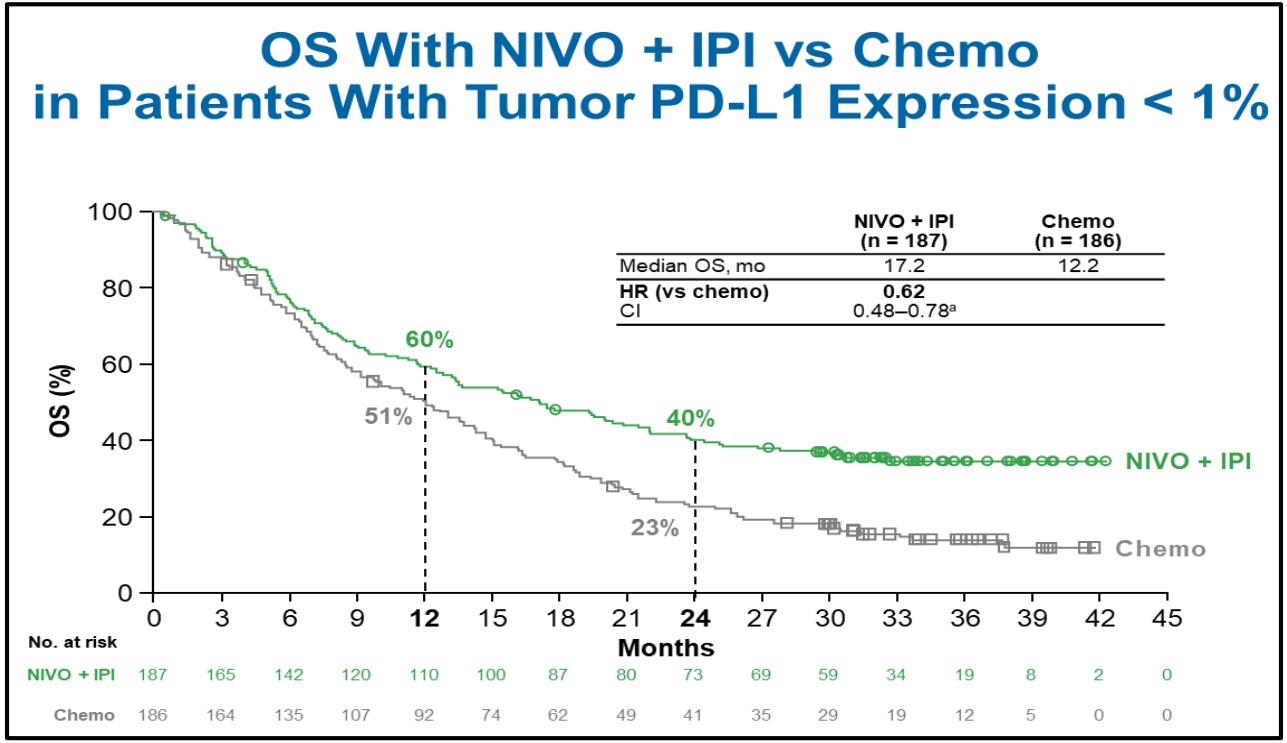


courtesy to Mok et al., 2019; Peters et al., 2019 ESMO

Unanswered questions and unmet needs

3. PD-L1 IHC score 1-49% or < 1% for IO monotherapy?

< 1% mono unknown, but Nivo + Ipi might bring benefits



Peters et al., 2019 ESMO

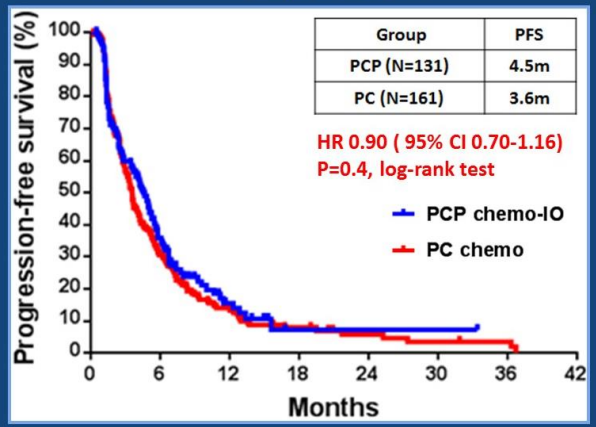
Unanswered questions and unmet needs

4. Other biomarkers beyond PD-L1 IHC for IO?

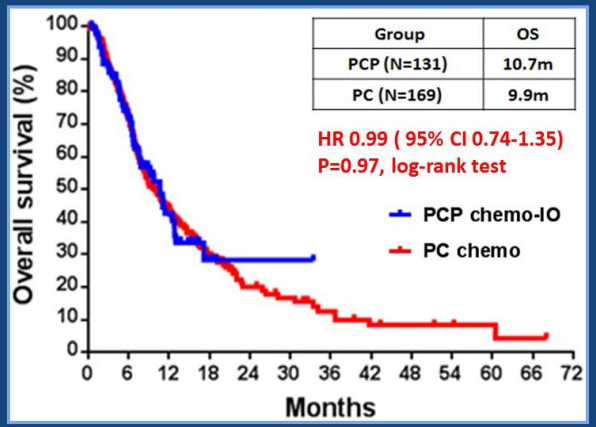
***STK11/KEAP1* as negative selection biomarker for IO (mono and combo)**

Lack of benefit from addition of pembrolizumab to CP chemotherapy in *STK11* and/or *KEAP1*-mutant non-squamous NSCLC

STK11^{MUT} and/or *KEAP1*^{MUT}



STK11^{MUT} and/or *KEAP1*^{MUT}



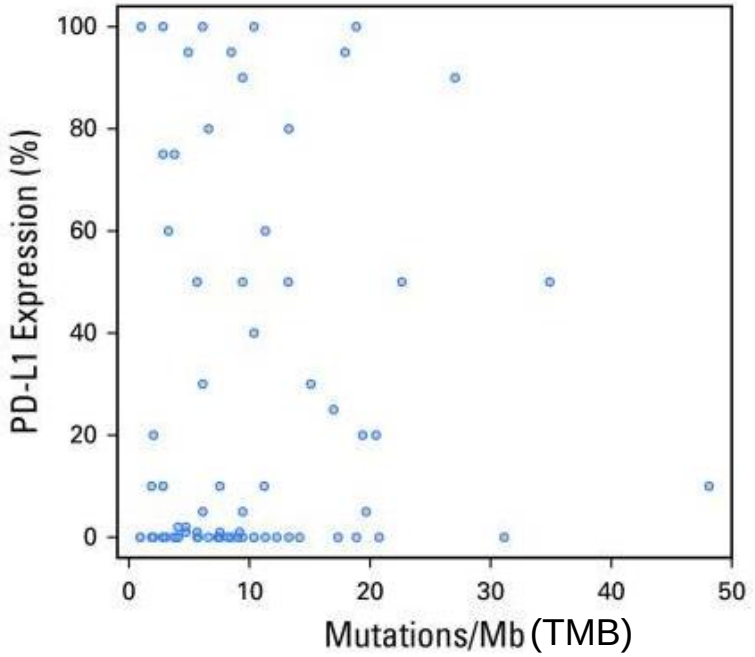
Skoulidis et al., 2019 ASCO

Unanswered questions and unmet needs

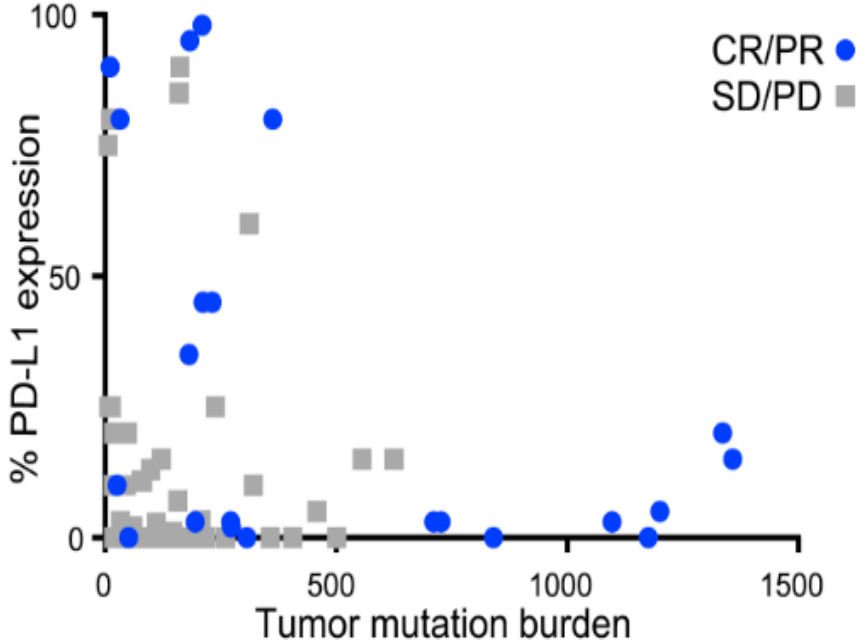
4. Other biomarkers beyond PD-L1 IHC for IO?

How about TMB? PD-L1 IHC and TMB represent independent groups

Retrospective study 1

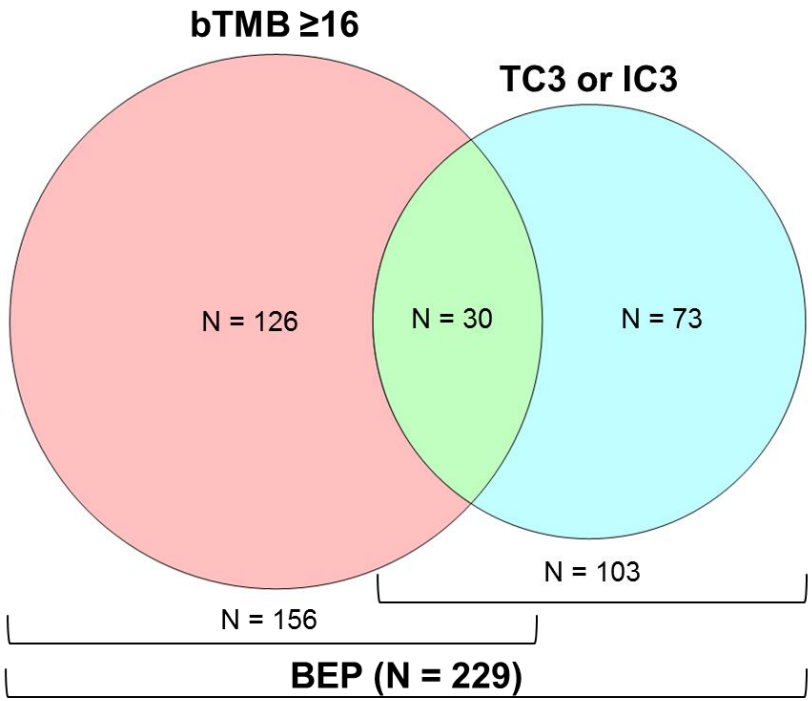


Retrospective study 2



Rizvi et al., 2018; Hellmann et al., 2018

Limited overlap between bTMB high and PD-L1 high (retrospective analysis of OAK)



- Non-significant overlap between the bTMB ≥16 and TC3 or IC3 subgroups (Fisher exact test, *P* = 0.62)
  - **19.2%** of tumors with bTMB ≥16 were also TC3 or IC3
  - **29.1%** of tumors with TC3 or IC3 also had bTMB ≥16

	PFS HR (95% CI)	OS HR (95% CI)
bTMB ≥16	0.64 (0.46, 0.91)	0.64 (0.44, 0.93)
TC3 or IC3	0.62 (0.41, 0.93)	0.44 (0.27, 0.71)
bTMB ≥16 and TC3 or IC3	0.38 (0.17, 0.85)	0.23 (0.09, 0.58)

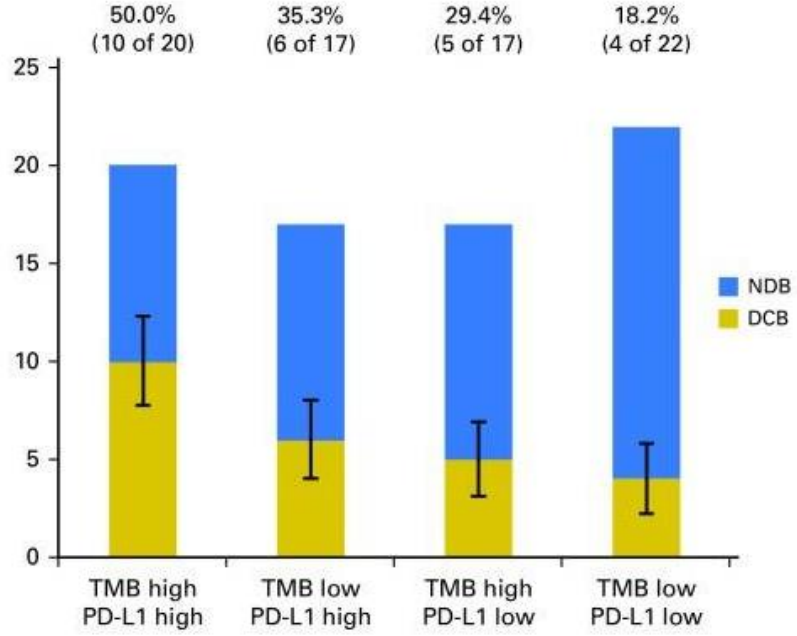
[a] PD-L1 expression was evaluated by immunohistochemistry (IHC) using the VENTANA SP142 assay; TC3 or IC3, ≥50% of TC or ≥10% of IC express PD-L1.
BEP, biomarker-evaluable population; IC, tumor-infiltrating immune cell; TC, tumor cell.

Gandara DR, et al. bTMB in POPLAR & OAK

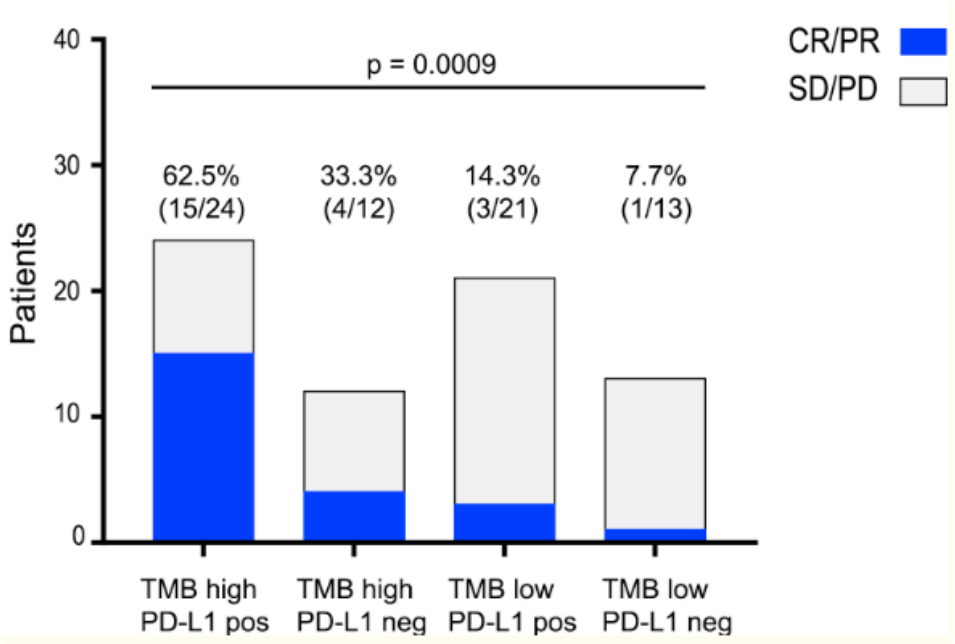
Unanswered questions and unmet needs

4. Other biomarkers beyond PD-L1 IHC for IO?

Retrospective study 1



Retrospective study 2

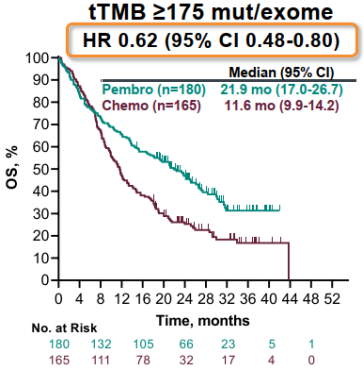


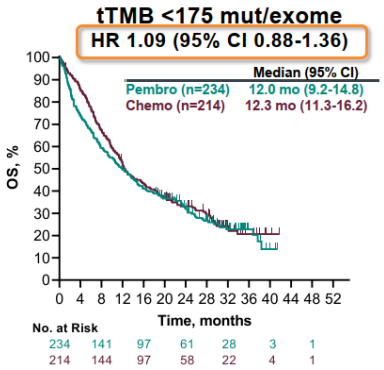
Rizvi et al., 2018; Hellmann et al., 2018

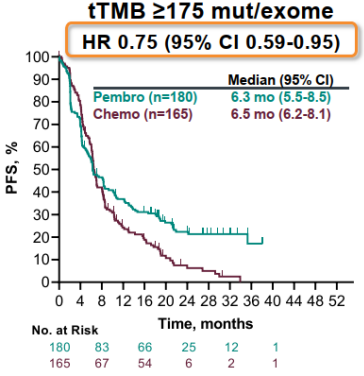
Unanswered questions and unmet needs

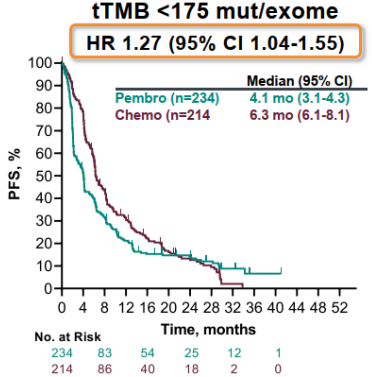
4. Other biomarkers beyond PD-L1 IHC for IO? **TMB might work for IO mono but not for IO combo? Need further prospective trial validation**

Keynote-042

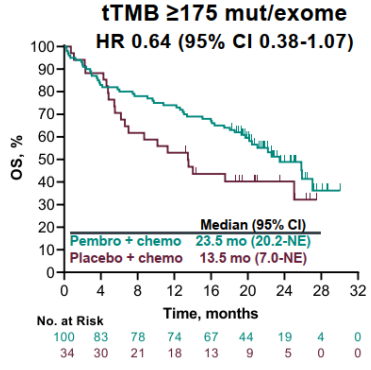


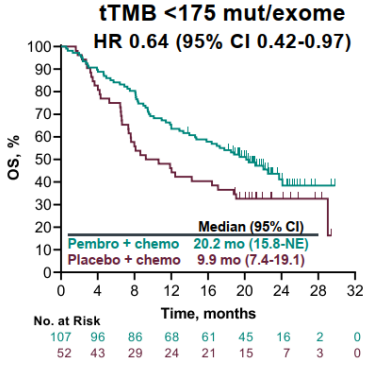


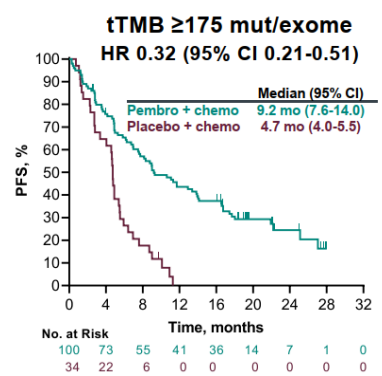


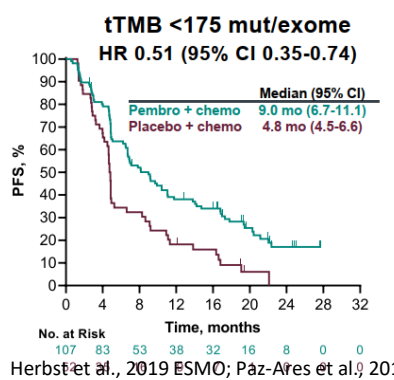


Keynote-189









Herbst et al., 2019 ESMO; Paz-Ares et al., 2019 ESMO

Final analysis from B-F1RST, a prospective phase II trial to evaluate bTMB as a biomarker for first-line atezo in NSCLC

Stage IIIB-IVB[a] locally advanced or metastatic NSCLC (any histology; N = 152[b]) → **Atezolizumab 1200 mg IV q3w** → **Until PD, unacceptable toxicity or loss of clinical benefit**

Inclusion criteria
- Measurable disease per RECIST 1.1
- ECOG PS of 0 or 1
- Immunotherapy naive
- PD-L1 unselected
- Provision of blood[c]

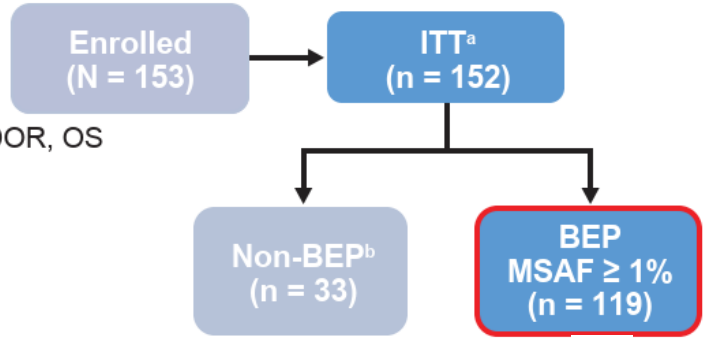
Exclusion criteria
- Sensitizing *EGFR* mutations or *ALK* rearrangements
- Active brain metastases requiring treatment

Final analysis
- All enrolled patients with ≥ 18 months of follow-up

Co-primary endpoints
- Efficacy endpoint: INV-assessed ORR per RECIST 1.1
- Biomarker endpoint: INV-assessed PFS per RECIST 1.1 at the prespecified bTMB cutoff of 16

Secondary objectives
- Safety and assessment of efficacy by INV-assessed DOR, OS

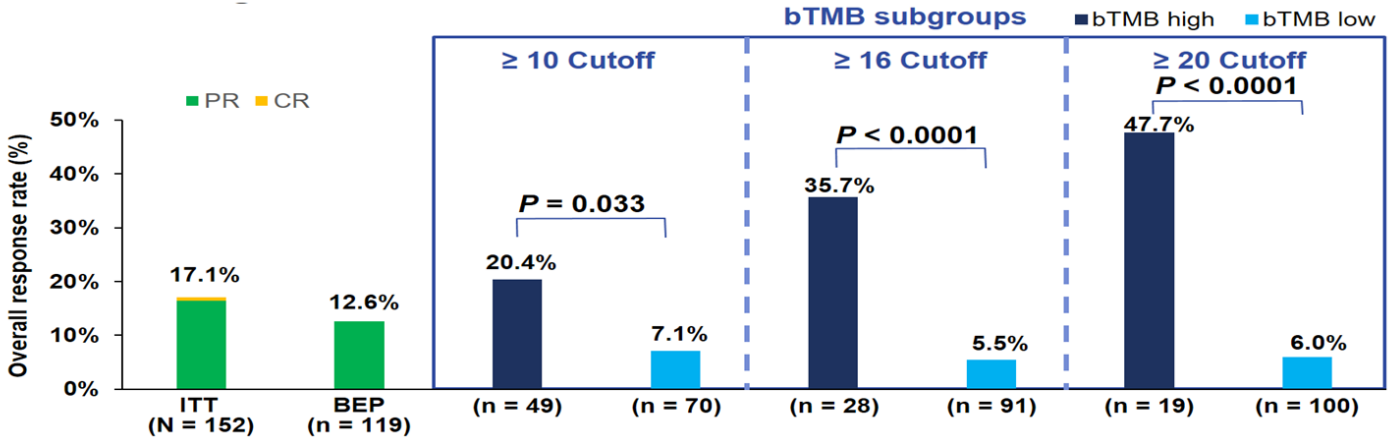
Exploratory endpoint
- OS at various bTMB cutoffs
- OS according to CRP ratio

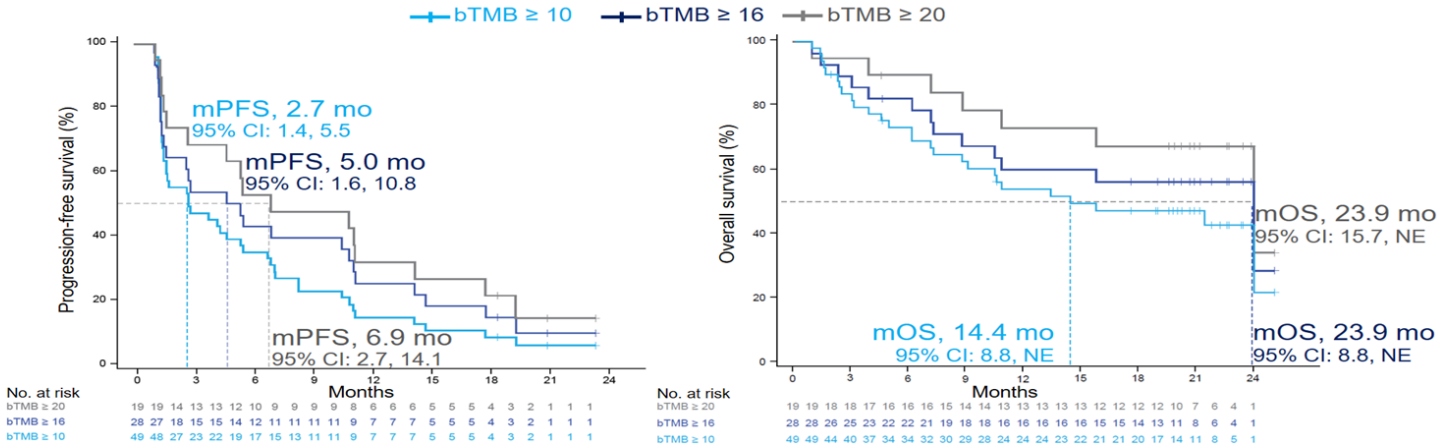


biomarker-evaluable population: maximum somatic allele frequency [MSAF] ≥ 1%)

Socinski et al., 2019 ESMO

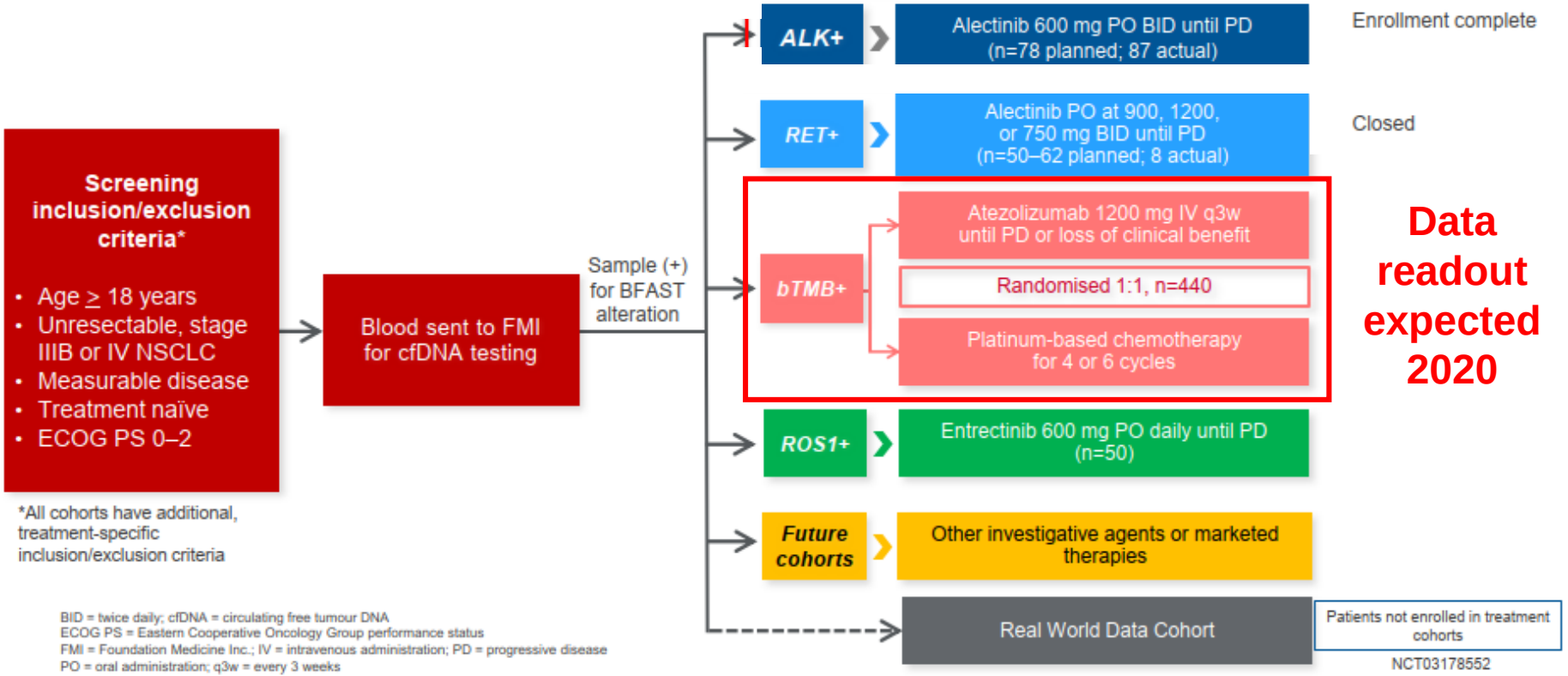
B-F1RST: ORR(top), PFS and OS(bottom)





Socinski et al., 2019 ESMO

Ongoing BFAST phase III trial to prospectively evaluate bTMB predictive role for atezo as first-line in NSCLC

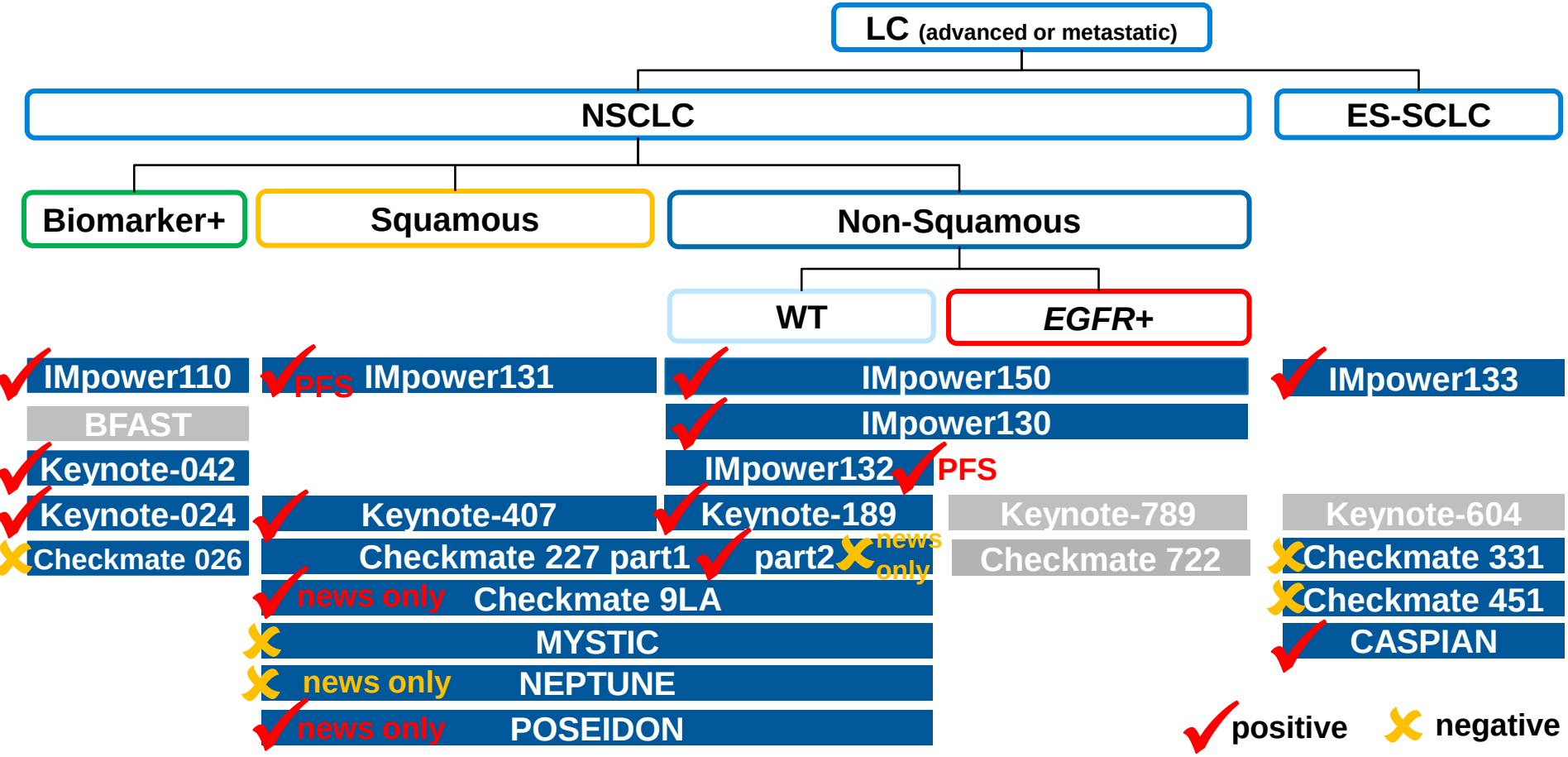


Unanswered questions and unmet needs

5. IO mono vs IO combo? **Tradeoff between ORR and DoR**

	Trial	ORR (study vs control)	DoR (study vs control)
Monotherapy	Keynote-042 (TPS >= 1%)	27% vs 26.5%	20.2 mo vs 8.3 mo
	IMpower110 (TC1/2/3 or IC1/2/3)	29% vs 32%	NE vs 5.7 mo
Combination therapy	Keynote-189	48% vs 19.4%	12.4 mo vs 7.1 mo
	IMpower150	64% vs 48%	9 mo vs 5.7 mo

Overview of 2019 key phase III trials for IO



IMpower133 study design

Patients with (N = 403)

- Measurable ES-SCLC (RECIST version 1.1)
- ECOG PS 0 or 1
- No prior systemic treatment for ES-SCLC
- Patients with treated asymptomatic brain metastases were eligible

Stratification

- Sex (male vs female)
- ECOG PS (0 vs 1)
- Brain metastases (yes vs no)[a]

R 1:1

Induction

Atezolizumab + carboplatin + etoposide
Four 21-day cycles

Placebo + carboplatin + etoposide
Four 21-day cycles

Maintenance

Atezolizumab

Placebo

Treat until PD or loss of clinical benefit

Survival follow-up

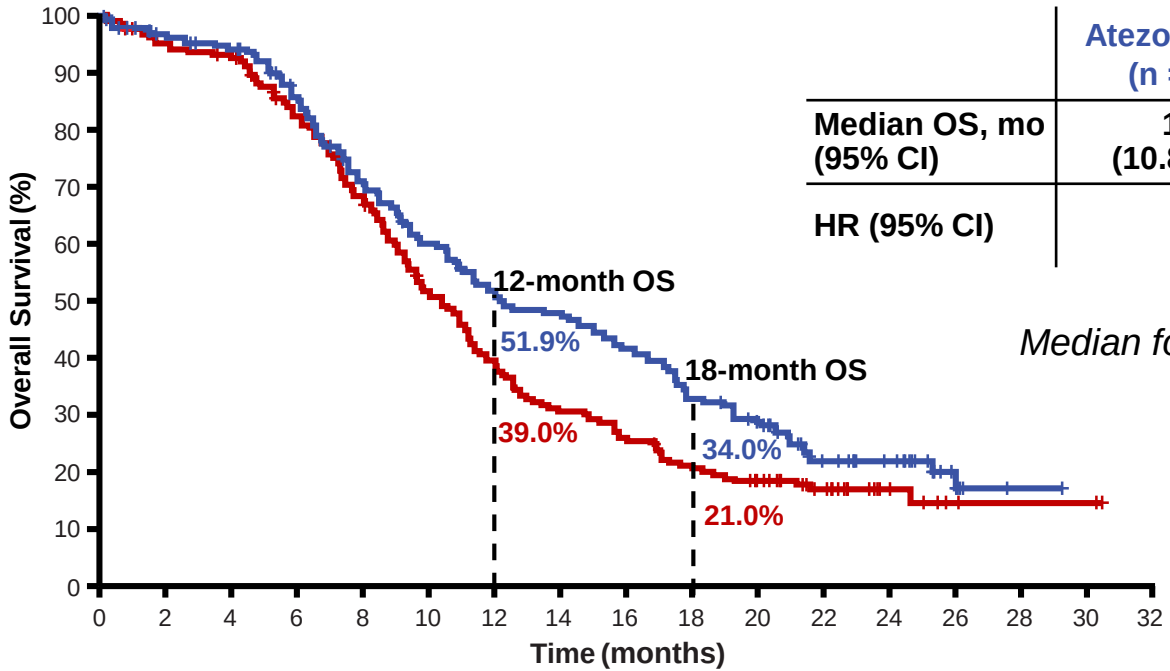
Co-primary end points
- ✓ Overall survival
- ✓ Investigator-assessed PFS

Key secondary end points
- ✓ Objective response rate
- ✓ Duration of response
- ✓ Safety

- ❑ **Updated OS in ITT and by PD-L1 subgroups**
- ❑ **Updated DOR/ORR in ITT**
- ❑ **Updated Safety**

Atezolizumab, 1200 mg IV, Day 1; Carboplatin, AUC 5 mg/mL/min IV, Day 1; Etoposide, 100 mg/m^2 IV, Days 1–3.
[a] Only patients with treated brain metastases were eligible.

Updated OS in ITT



	Atezo + CP/ET (n = 201)	Placebo + CP/ET (n = 202)
Median OS, mo (95% CI)	12.3 (10.8, 15.8)	10.3 (9.3, 11.3)
HR (95% CI)	0.76 (0.60, 0.95) p = 0.0154[a]	

Median follow-up, 22.9 months

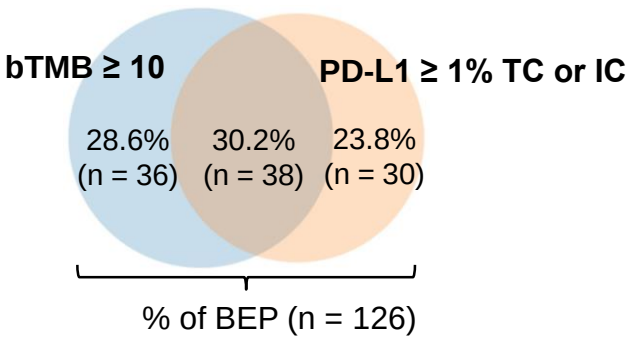
No. at risk																
Atezo + CP/ET	201	187	180	159	130	109	93	86	75	61	51	28	21	8	1	
Placebo + CP/ET	202	189	183	160	131	97	74	58	49	39	33	20	8	3	2	2

[a]p-value is provided for descriptive purpose.
CCOD 24 January 2019

Biomarker analysis: bTMB and PD-L1 expression

- PD-L1 and bTMB biomarkers identify distinct patient populations in ES-SCLC
- Post-hoc exploratory analysis conducted for OS by PD-L1 expression
  - The PD-L1 IHC biomarker evaluable population (BEP) comprised 34% of the ITT population
  - VENTANA SP263 assay was used to determine PD-L1 status on slide sections ≤ 1 year old
  - PD-L1 expression was observed mostly on immune cells (IC), with limited expression on tumour cells (TC)
  - Efficacy analyses were conducted using PD-L1 expression cut-offs of 1% and 5%

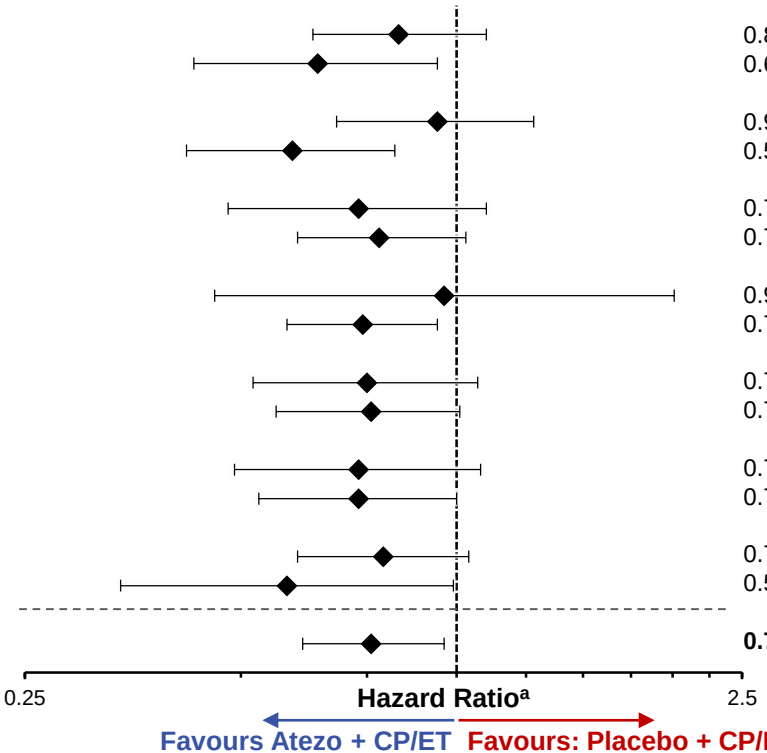
bTMB – PD-L1 IHC overlap



PD-L1 IHC expression in ES-SCLC (n = 137)			
IC	**% BEP (n)**	**TC**	**% BEP (n)**
< 1%	49.6% (68)	< 1%	94.2% (129)
≥ 1%	50.4% (69)	≥ 1%	5.8% (8)
≥ 5%	20.4% (28)	≥ 5%	1.5% (2)

Updated OS in subgroups

Subgroup	Median OS (months) Atezo + CP/ET	Median OS (months) Placebo + CP/ET	OS Hazard Ratio[a] (95% CI)
Male (n = 261)	12.2	10.9	0.83 (0.63, 1.10)
Female (n = 142)	13.6	9.5	0.64 (0.43, 0.94)
< 65 years (n = 217)	12.1	11.5	0.94 (0.68, 1.28)
≥ 65 years (n = 186)	14.4	9.6	0.59 (0.42, 0.82)
ECOG PS 0 (n = 140)	16.8	12.6	0.73 (0.48, 1.10)
ECOG PS 1 (n = 263)	11.3	9.3	0.78 (0.60, 1.03)
Brain metastases (n = 35)	8.5	9.7	0.96 (0.46, 2.01)
No brain metastases (n = 368)	12.6	10.4	0.74 (0.58, 0.94)
Liver metastases (n = 149)	9.3	7.8	0.75 (0.52, 1.07)
No liver metastases (n = 254)	16.3	11.2	0.76 (0.56, 1.01)
bTMB < 10 (n = 134)	11.8	9.4	0.73 (0.49, 1.08)
bTMB ≥ 10 (n = 212)	14.9	11.2	0.73 (0.53, 1.00)
bTMB < 16 (n = 266)	12.5	10.0	0.79 (0.60, 1.04)
bTMB ≥ 16 (n = 80)	17.1	11.9	0.58 (0.34, 0.99)
ITT (N = 403)	**12.3**	**10.3**	**0.76 (0.61, 0.96)**



A total of 57 patients had unknown bTMB score.
bTMB, blood tumour mutational burden.
[a] Hazard ratios are unstratified for patient subgroups and stratified for the ITT.
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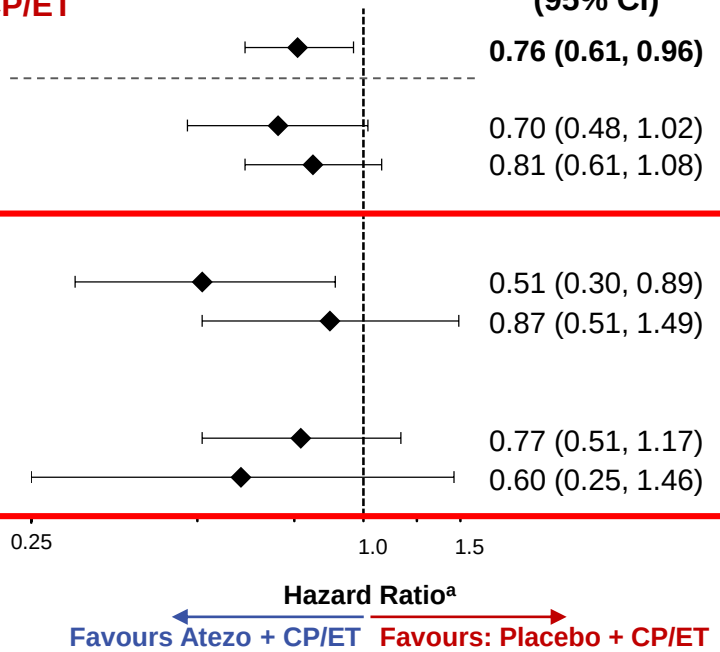
Updated OS in PD-L1 expression subgroups

Subgroup	Median OS (months) Atezo + CP/ET	Median OS (months) Placebo + CP/ET	OS Hazard Ratio[a] (95% CI)
ITT (N = 403)	**12.3**	**10.3**	**0.76 (0.61, 0.96)**
ITT-BEP (n = 137)	9.9	8.9	0.70 (0.48, 1.02)
Non-BEP (n = 266)	14.6	11.2	0.81 (0.61, 1.08)
PD-L1 expression 1% TC or IC			
< 1% PD-L1 (n = 65)	10.2	8.3	0.51 (0.30, 0.89)
≥ 1% PD-L1 (n = 72)	9.7	10.6	0.87 (0.51, 1.49)
PD-L1 expression 5% TC or IC			
< 5% PD-L1 (n = 108)	9.2	8.9	0.77 (0.51, 1.17)
≥ 5% PD-L1 (n = 29)	21.6	9.2	0.60 (0.25, 1.46)



[a] Hazard ratios are unstratified for patient subgroups and stratified for the ITT.
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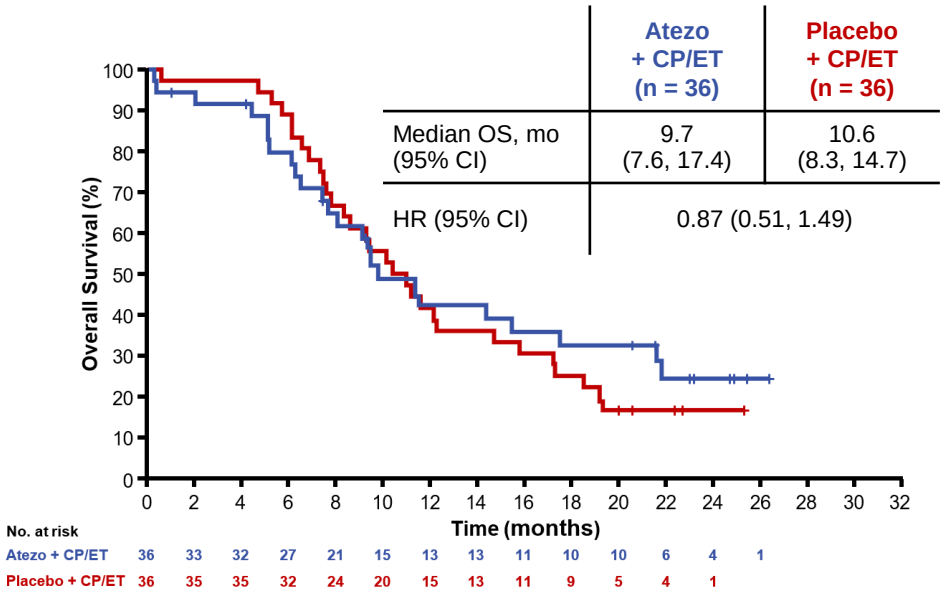
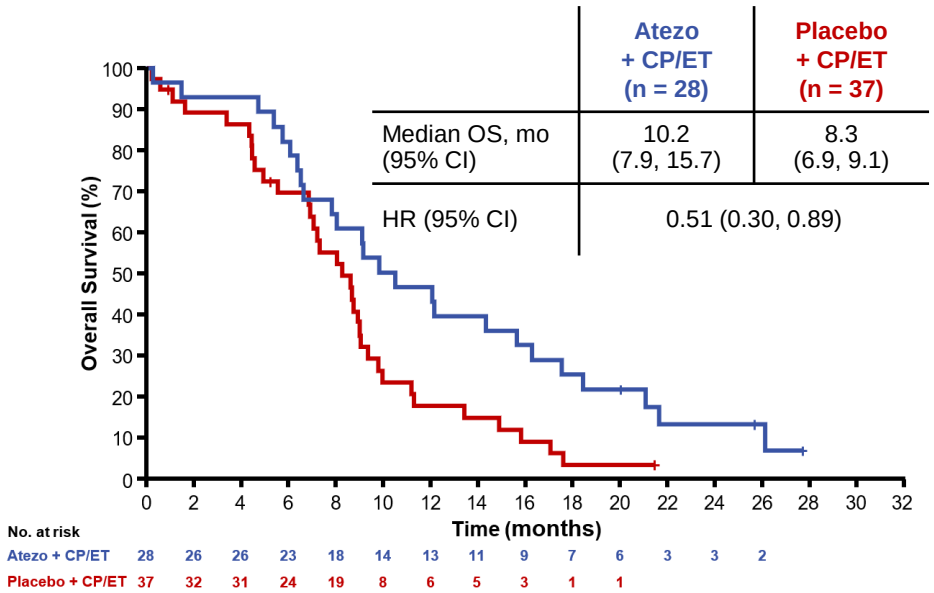
Updated OS in PD-L1 expression subgroups

PD-L1 Expression ≥ 1% TC or IC



PD-L1 Expression < 1% TC or IC



Median follow-up, 22.9 months

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IMpower133 Updated OS Analysis: presented by Dr Martin Reck

http://bit.ly/2Z32WhW

Safety summary

Patients, n (%)	Atezo + CP/ET (n = 198)	Placebo + CP/ET (n = 196)
Patients with ≥ 1 AE	198 (100)	189 (96.4)
Grade 3–4 AEs	134 (67.7)	124 (63.3)
Treatment-related AEs	188 (94.9)	181 (92.3)
Serious AEs	77 (38.9)	69 (35.2)
Immune-related AEs	82 (41.4)	48 (24.5)
Treated with steroids or hormone replacement therapy[a]	40 (20.2)	11 (5.6)
AEs leading to withdrawal from any treatment[b]	24 (12.1)	6 (3.1)
AEs leading to withdrawal from atezolizumab/placebo	23 (11.6)	5 (2.6)
AEs leading to withdrawal from carboplatin	5 (2.5)	1 (0.5)
AEs leading to withdrawal from etoposide	8 (4.0)	2 (1.0)
Treatment-related Grade 5 AEs	3 (1.5)	3 (1.5)

- Median duration of treatment with atezolizumab was 4.7 months (range: 0 to 29)
- Median number of doses received:
  - Atezolizumab: 7 (range: 1 to 39)
  - Chemotherapy: 4 for carboplatin; 12 doses etoposide (for both arms)

[a] An event consistent with an immune-mediated mechanism of action requiring treatment with systemic corticosteroids or hormone replacement therapy.
[b] Incidence of treatment-related AEs and AEs leading to withdrawal from any treatment are for any treatment component.
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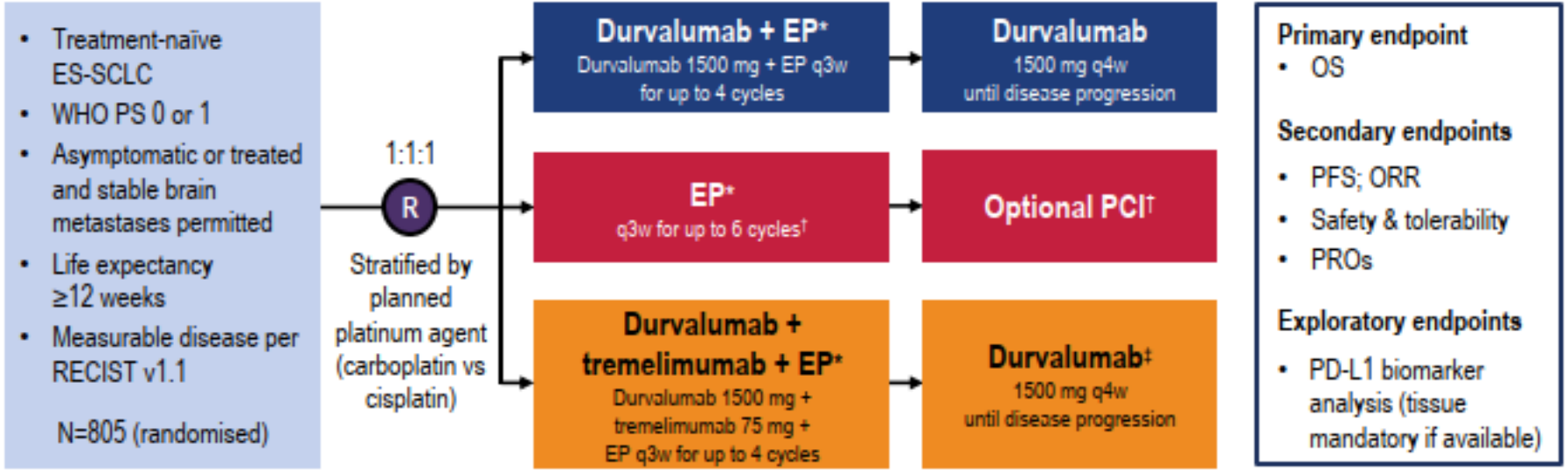
CASPIAN STUDY DESIGN

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



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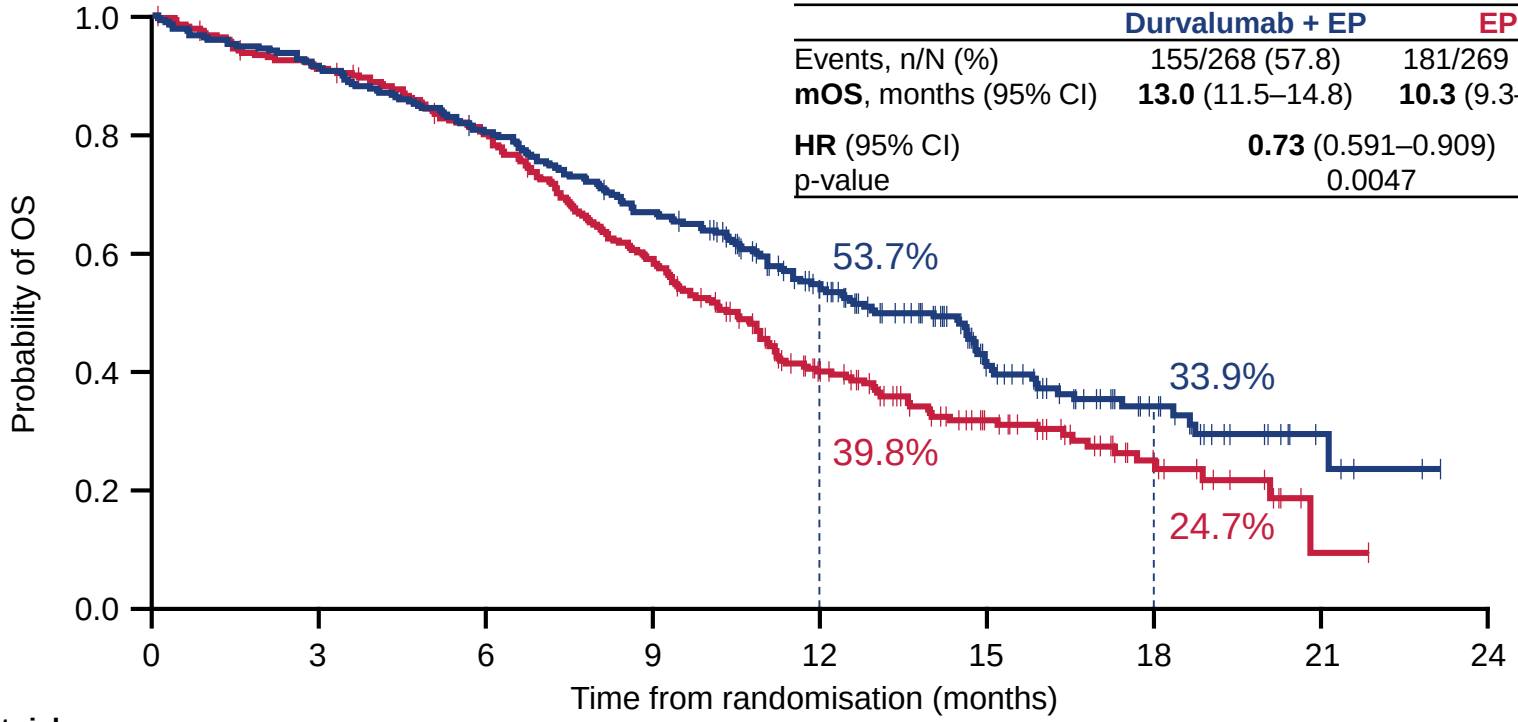
*EP consists of etoposide 80–100 mg/m^2 with either carboplatin AUC 5–6 or cisplatin 75–80 mg/m^2; †Patients could receive an additional 2 cycles of EP (up to 6 cycles total) and PCI at the investigator's discretion; ‡Patients received an additional dose of tremelimumab post-EP

AUC, area under the curve; IDMC, Independent Data Monitoring Committee; ORR, objective response rate; PCI, prophylactic cranial irradiation; PFS, progression-free survival; PS, performance status; q3w, every 3 weeks; q4w, every 4 weeks; RECIST, Response Evaluation Criteria in Solid Tumors version 1.1; WHO, World Health Organization

CASPIAN OS (Primary Endpoint)

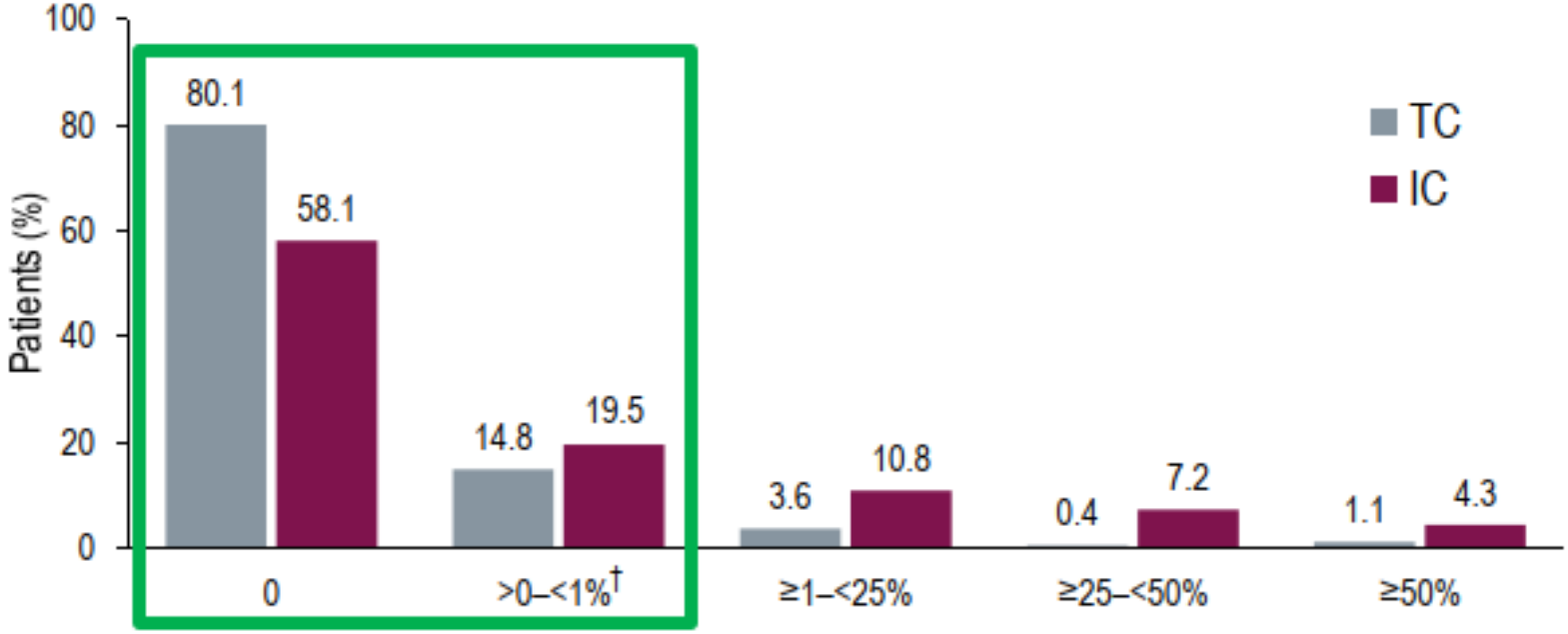


	Durvalumab + EP	EP
Events, n/N (%)	155/268 (57.8)	181/269 (67.3)
mOS, months (95% CI)	**13.0** (11.5–14.8)	**10.3** (9.3–11.2)
HR (95% CI)	**0.73** (0.591–0.909)	
p-value	0.0047	

No. at risk									
Durvalumab + EP	268	244	214	177	116	57	25	5	0
EP	269	242	209	153	82	44	17	1	0

Paz Ares et al., 2019 WCLC

PREVALENCE OF PD-L1 EXPRESSION ON TCs OR ICs*



- 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

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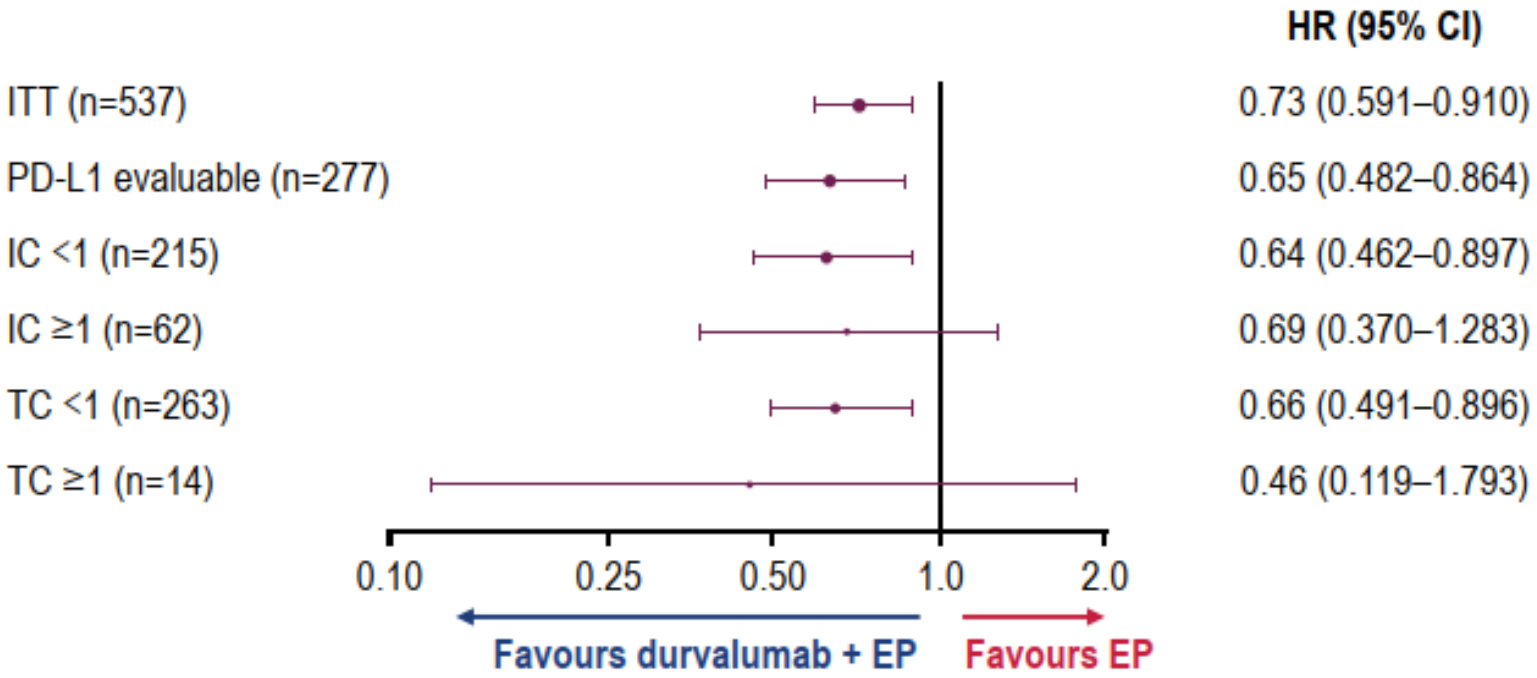
*Based on 277 PD-L1-evaluable patients in the durvalumab + EP and EP arms
†Includes patients whose tumours had <1% PD-L1 expression on TCs or ICs, but not absolute 0

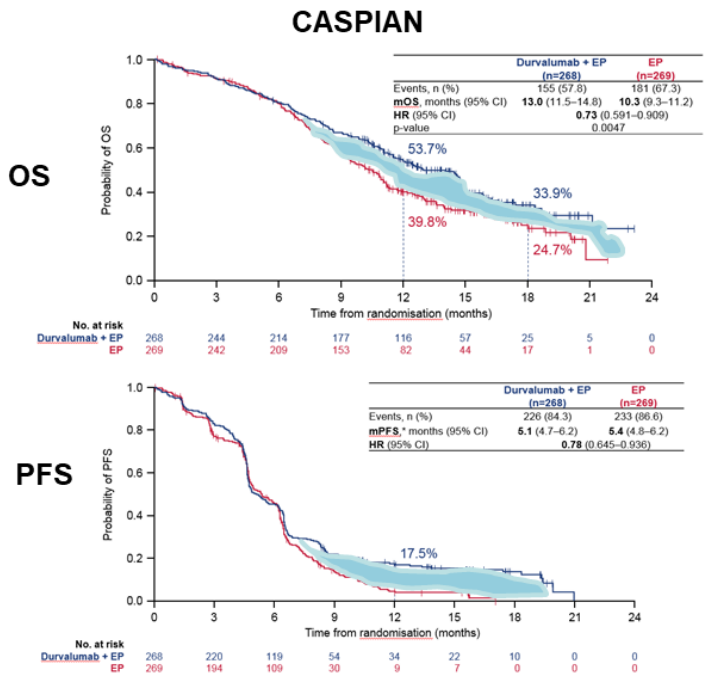
CASPIAN: OS based on PD-L1 expression

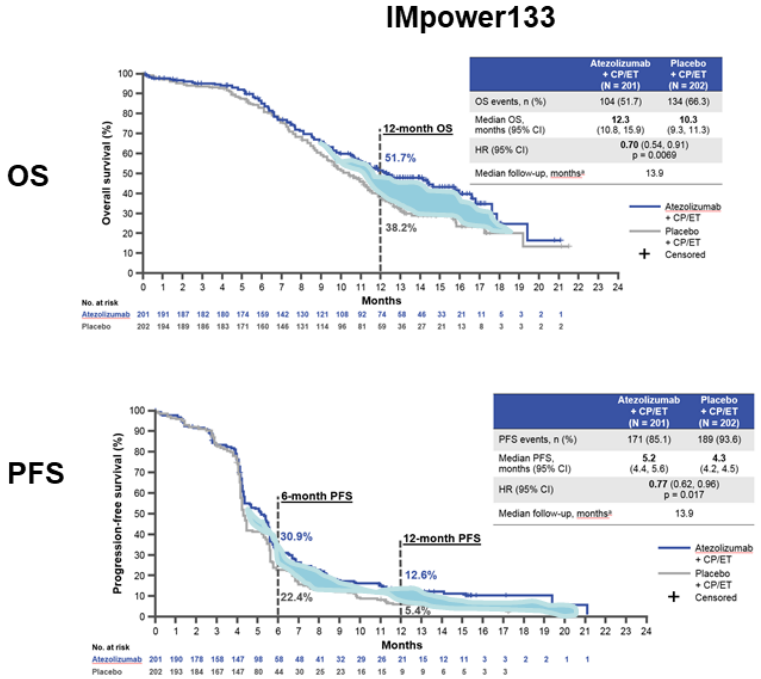


Garassino et al., 2019 ESMO

Clinical implication

Data from IMpower133 and CASPIAN conclude clinical benefits in ES-SCLC patients when treated with atezolizumab or durvalumab combined with EP as first-line, regardless of PD-L1 expression.





courtesy to Ahn., 2019 WCLC

Thank you for your attention