G Bootsma
Immunotherapie

Immunotherapie:

18:00 – 18:25 uur	**Immunotherapie** Dr. Gerben Bootsma, longarts, Zuyderland MC
18:25 – 18:50 uur	**SCLC / mesothelioom** Dr. Ben van den Borne, longarts, Catharina ziekenhuis
18:50 – 19:15 uur	**RT en combinatie immunotherapie** Prof. dr. Dirk de Ruysscher, radiotherapeut-oncoloog MAASTRO Clinic

Immunotherapie:

18:00 – 18:25 uur **Immunotherapie**
Dr. Gerben Bo

18:25 – 18:

longarts, Catharina ziekenhuis

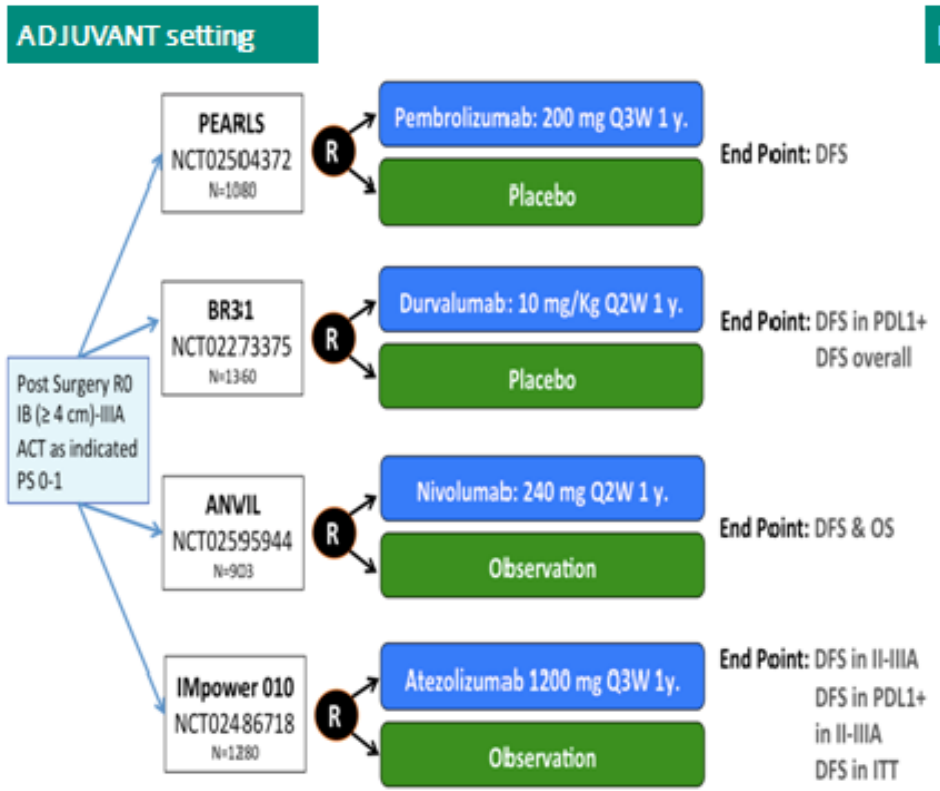
18.

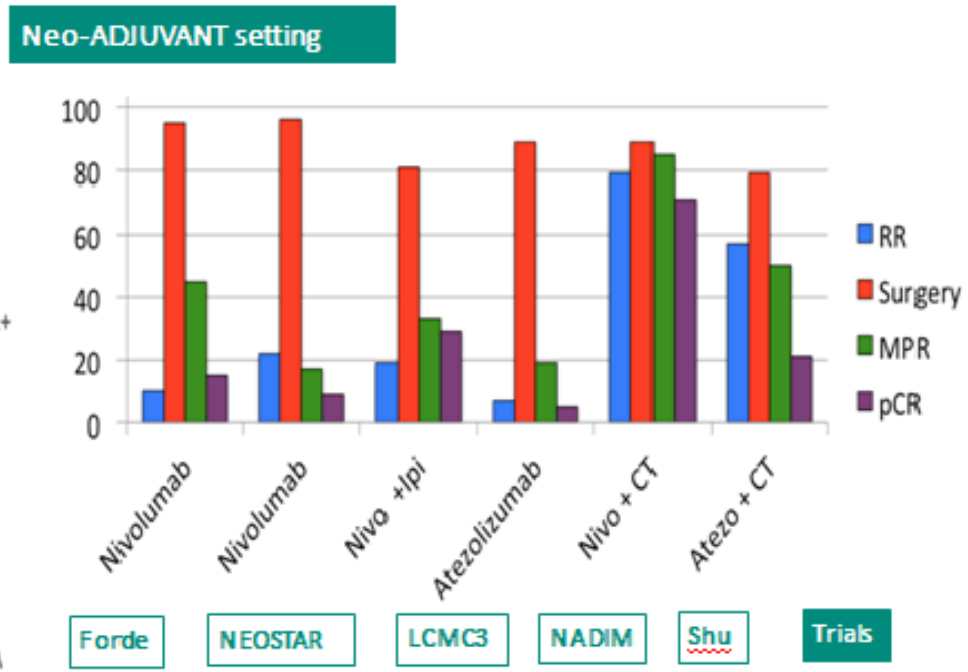
RT en combinatie immunotherapie
Prof. dr. Dirk de Ruysscher, radiotherapeut-oncoloog
MAASTRO Clinic

IMMUNOTHERAPIE !

Immunotherapie in vroege stadia

Waiting for.....IMMUNOTHERAPY in EARLY STAGE





TOP 1501 (NCT 02818920); **PRINCEPS** (NCT 02994576)
KN 617 (NCT 03425643), **CM 816** (NCT 02998528),
ImPOWER 130 (NCT 03456063); **AEGEAN** (NCT03800134)

Stadium III NSCLC adjuvant IT

Dirk..

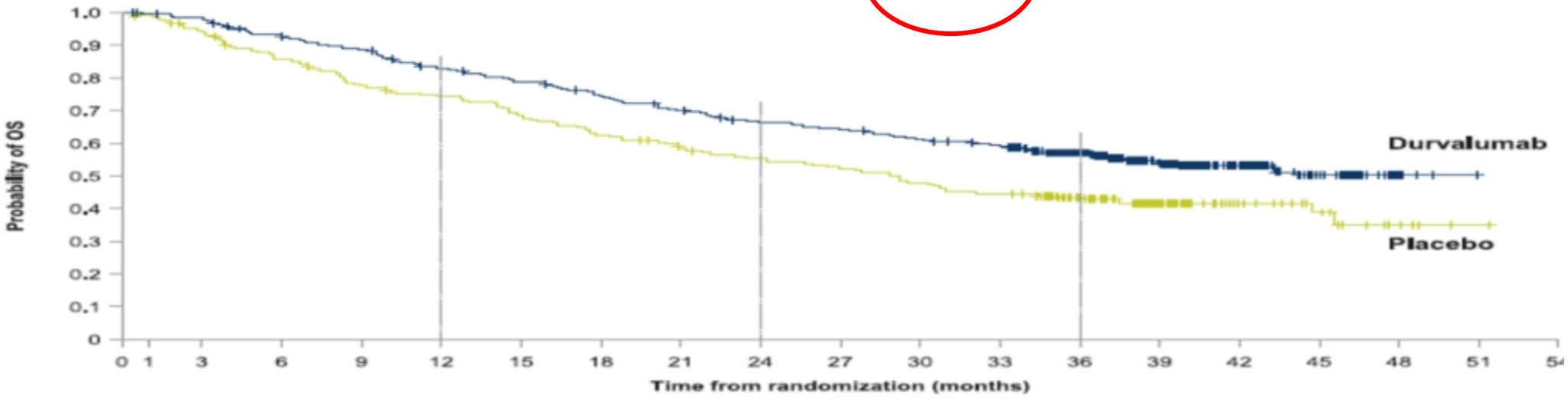
CURRENT SOC IN LA

PACIFIC SURVIVAL UPDATE ASCO 2019

Figure 3. Updated OS in the ITT population

	No. of events/ total no. of patients (%)	Median OS (95% CI) months	12-month OS rate (95% CI) %	24-month OS rate (95% CI) %	36-month OS rate (95% CI) %
Durvalumab	210/476 (44.1)	NR (38.4–NR)	83.1 (79.4–86.2)	66.3 (61.8–70.4)	57.0 (52.3–61.
Placebo	134/237 (56.5)	29.1 (22.1–35.1)	74.6 (68.5–79.7)	55.3 (48.6–61.4)	43.5 (37.0–49.

Stratified hazard ratio for death, 0.69 (95% CI, 0.55–0.86)
Stratified hazard ratio for death from the primary analysis,[9] 0.68 (95% CI, 0.53–0.87)



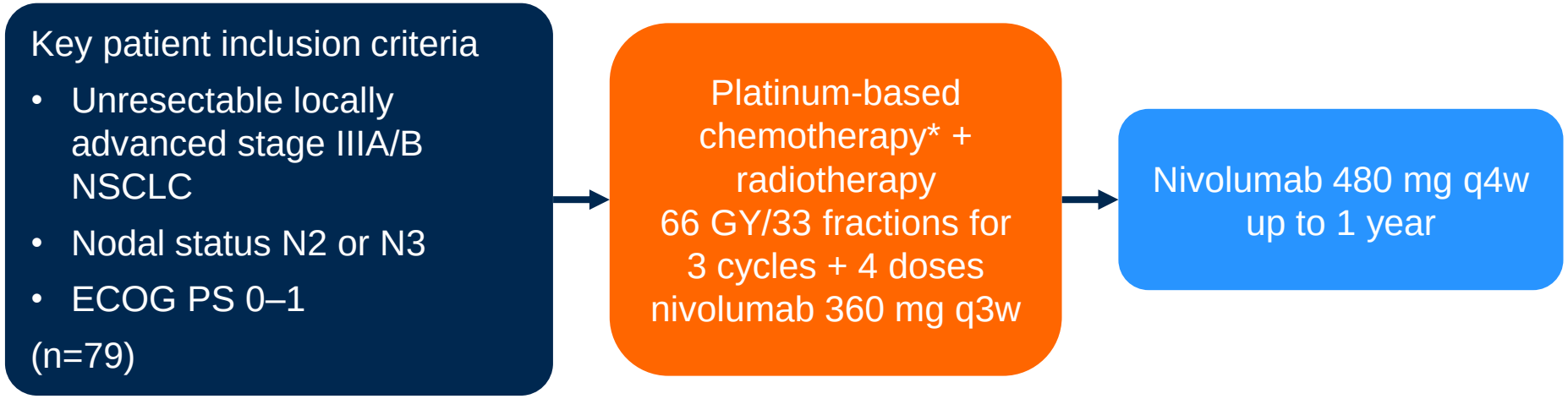
No. at risk																		
Durvalumab	476	464	431	415	385	364	343	319	298	289	274	263	205	132	73	33	7	0
Placebo	237	220	199	179	171	156	143	133	123	116	107	99	79	49	25	13	5	1

NR, not reached

- Updated subgroup analysis of OS is presented in **Figure 4** and was consistent with that reported at the time of the primary OS

1457PD: Efficacy evaluation of concurrent nivolumab addition to a first-line, concurrent chemo-radiotherapy regimen in unresectable locally advanced NSCLC – Results from the European Thoracic Oncology Platform (ETOP 6-14) NICOLAS phase II trial – Peters S, et al

- **Study objective**
  - To evaluate the efficacy of nivolumab combined with 1L concurrent chemoradiotherapy in patients with unresectable locally advanced NSCLC



Primary endpoints

- Grade ≥3 pneumonitis-free rate, 1-year PFS rate

Secondary endpoints

- Time to first grade ≥3 pneumonitis, ORR, OS, time-to-treatment failure, safety

*Cisplatin + vinorelbine/etoposide/pemetrexed

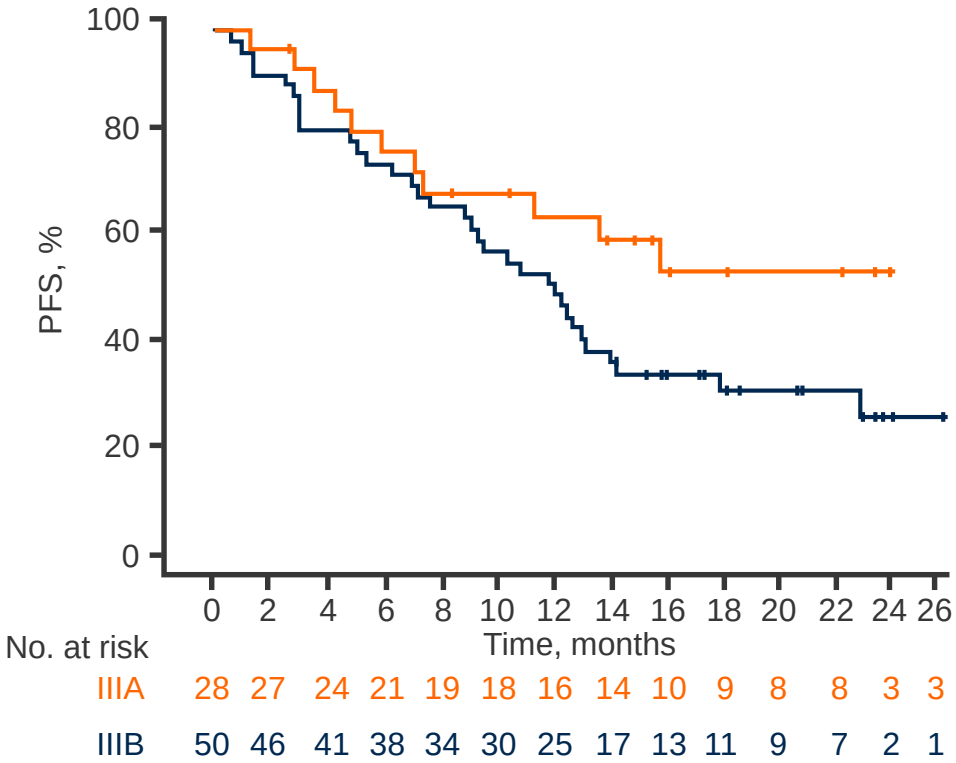
Peters S, et al. Ann Oncol 2019;30(suppl):Abstr 1457PD

1457PD: Efficacy evaluation of concurrent nivolumab addition to a first-line, concurrent chemo-radiotherapy regimen in unresectable locally advanced NSCLC – Results from the European Thoracic Oncology Platform (ETOP 6-14) NICOLAS phase II trial – Peters S, et al

- **Key results**

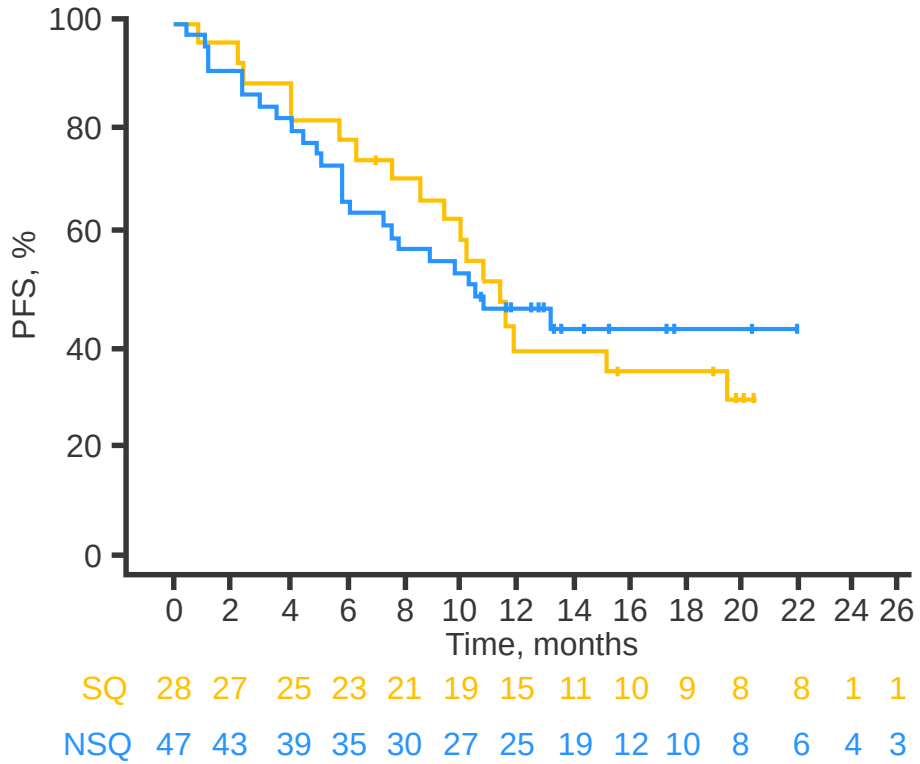
PFS: Stage

Stage	PFS events, n (%)	12-mo PFS, % (95%CI)	Median, months (95%CI)	Log-rank p-value
IIIA	13 (46.4)	66.3 (45.2, 88.9)	27.4 (7.3, NE)	0.11
IIIB	33 (66.0)	50.0 (35.6, 62.8)	12.1 (8.9, 17.8)	



PFS: Histology

Histology	PFS events, n (%)	12-mo PFS, % (95%CI)	Median, months (95%CI)	Log-rank p-value
SQ	19 (67.9)	56.3 (35.9, 72.3)	13.5 (10.1, 22.0)	0.68
NSQ	26 (55.3)	54.5 (39.1, 67.5)	12.9 (7.2, NE)	



Peters S, et al. Ann Oncol 2019;30(suppl):Abstr 1457PD

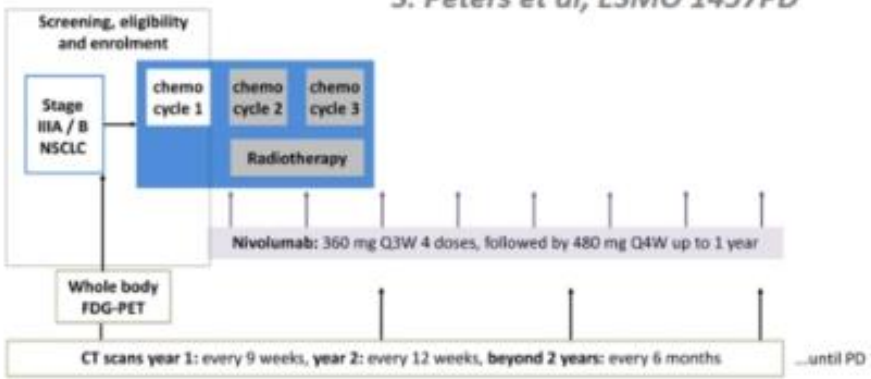
1457PD: Efficacy evaluation of concurrent nivolumab addition to a first-line, concurrent chemo-radiotherapy regimen in unresectable locally advanced NSCLC – Results from the European Thoracic Oncology Platform (ETOP 6-14) NICOLAS phase II trial – Peters S, et al

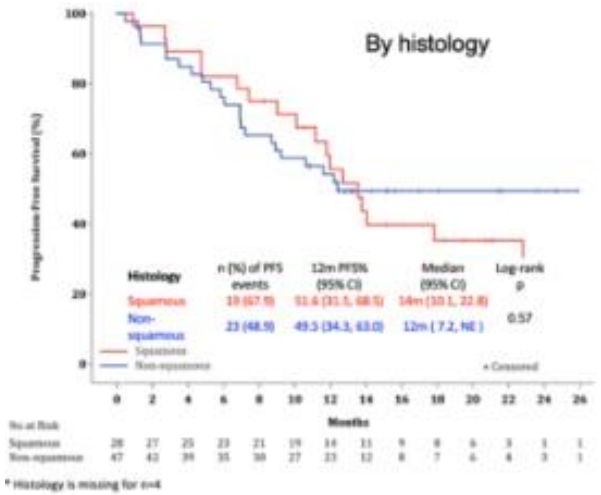
- **Key results (cont.)**
  - Overall, pneumonitis was reported by 34 patients (7 grade 3, 1 grade 5), oesophagitis by 24 patients (5 grade 3) and dyspnoea by 27 patients (2 grade 3)
  - In total, 240 nivolumab TRAEs were reported; 26 grade 3, 5 grade 4 and 4 grade 5 (colitis, pulmonary fibrosis, autoimmune disorder, pneumonitis). Of these, 7% (17/240 TRAEs) led to permanent discontinuation
- **Conclusions**
  - In patients with unresectable locally advanced NSCLC combining nivolumab with concurrent chemoradiation is feasible, without any unexpected safety signal
  - The PFS observed for combining nivolumab with concomitant definitive chemoradiation as 1L therapy compares favourably to other studies in the same patient population

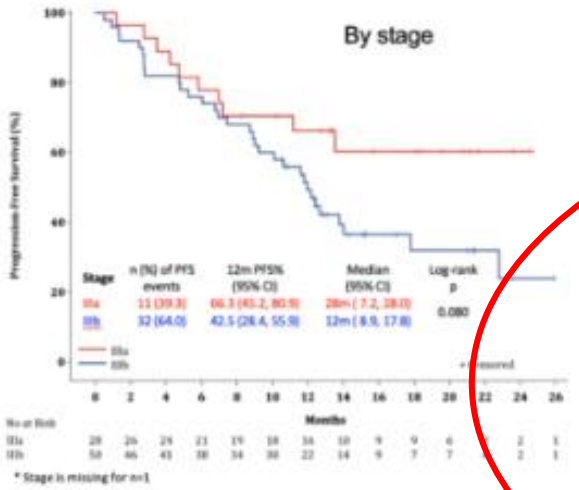
Peters S, et al. Ann Oncol 2019;30(suppl):Abstr 1457PD

Efficacy evaluation of concurrent nivolumab addition to a first-line, concurrent chemo-radiotherapy regimen in unresectable locally advanced NSCLC –NICOLAS phase II trial.

S. Peters et al, ESMO 1457PD







Primary endpoints:

- Pneumonitis-free rate of grade ≥ 3 (CTCAE V4.0) any time during 6 months post radiotherapy.
- Hierarchically tested: 1-year progression-free survival (PFS) (from chemotherapy start)

Hierarchical design: IF safety proven → Efficacy evaluation:

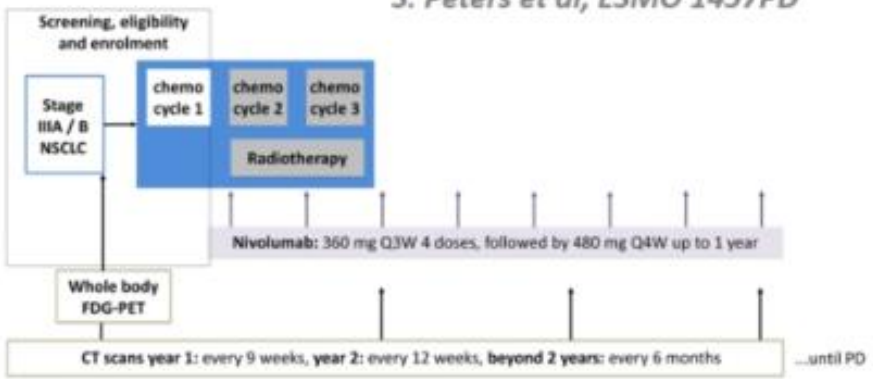
- **1-year PFS, sample size n=74**
- H_0: $PFS_0 \leq 45\%$ vs H_1: $PFS_1 > 60\%$ (1-sided alpha=5%, power=83%)
- *Success rule: at least 41 patients reach 1-year without PFS event (i.e., maximum 33 PFS events)*

Authors Conclusions

- Based on the formal hierarchical efficacy analysis, we cannot reject the null hypothesis of 1-year PFS rate ≤45% versus 60% (p=0.23).
- Overall (N=79 patients), the estimate of 1-year survival rate is 50.1% (95% CI: 38.3, 60.7%).
- NICOLAS PFS with a median of 12.7 months, compares favourably to studies in the same population, all reporting less than 12 months median.

Efficacy evaluation of concurrent nivolumab addition to a first-line, concurrent chemo-radiotherapy regimen in unresectable locally advanced NSCLC –NICOLAS phase II trial.

S. Peters et al, ESMO 1457PD



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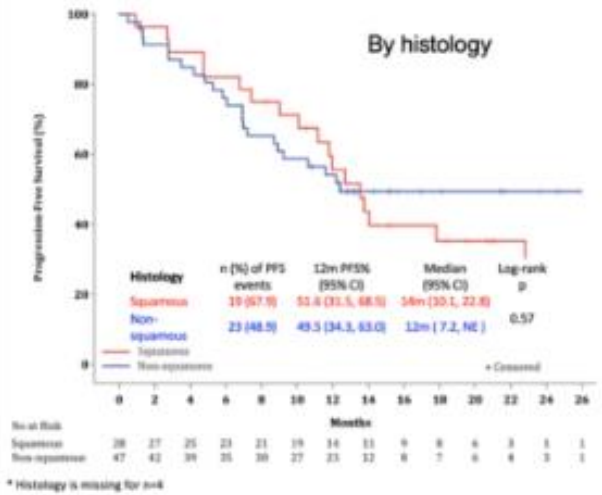
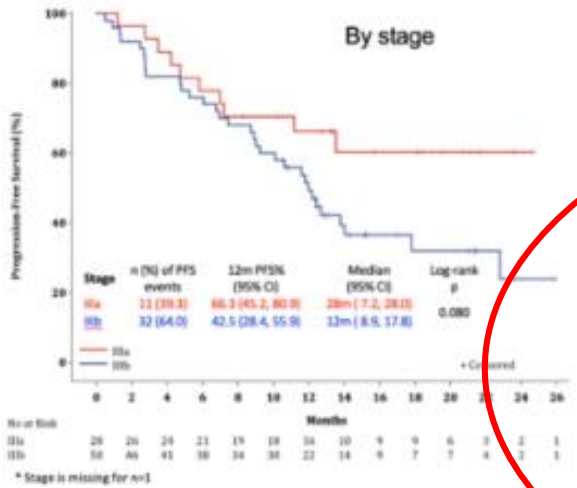




Discussant Conclusions

- **The study failed the formal planned hierarchical efficacy analysis and not exciting efficacy data**
- **Pneumonitis: 7/79 had grade 3 and 1 grade 5 AND overall toxicity was however not negligible**
- **In the future we need to strictly enforce exact T and N staging in all CT/RT trials this includes not only PET-CT but also EBUS/mediastinal staging**

St IV NSCLC

BARCELONA 2019 ESMO congress

LBA78

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

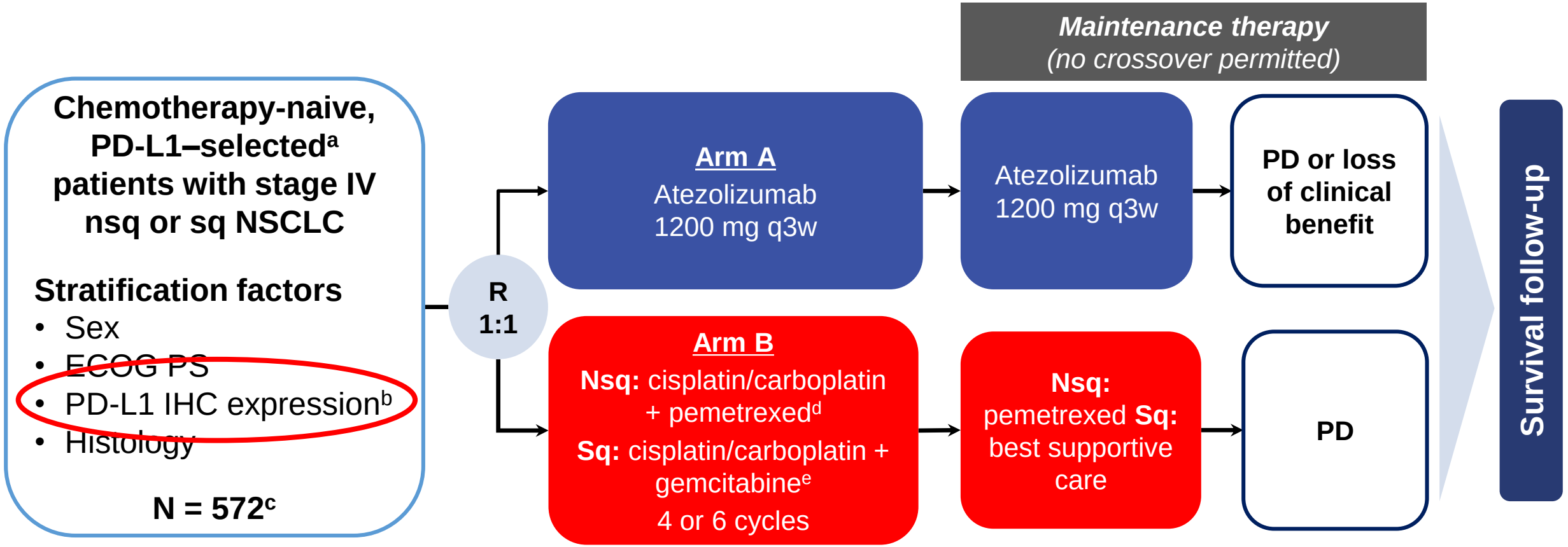
Background

- Anti–PD-1 monotherapy or PD-L1/PD-1 inhibitors in combination with platinum-based doublet chemotherapy, with or without bevacizumab, are 1L standards of care in metastatic NSCLC[1,2]
  - Tumour PD-L1 expression level and histology are used to determine treatment regimens
- In the Phase II BIRCH study, atezolizumab monotherapy demonstrated tolerability and efficacy in PD-L1–selected patients with advanced NSCLC across lines of therapy[3]
- The Phase III IMpower110 study (NCT02409342) evaluates atezolizumab monotherapy as 1L treatment in PD-L1–selected patients, independent of tumour histology
  - We report results of the interim OS analysis in IMpower110

1L, first-line.

1. NCCN Clinical Practice Guidelines. NSCLC. V7.2019; 2. Planchard D, et al. *Ann Oncol*. 2018;29(Suppl 4):iv192-iv237; 3. Peters S, et al. *J Clin Oncol*. 2017;35(24):2781-2789.

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.

PD-L1 analysis

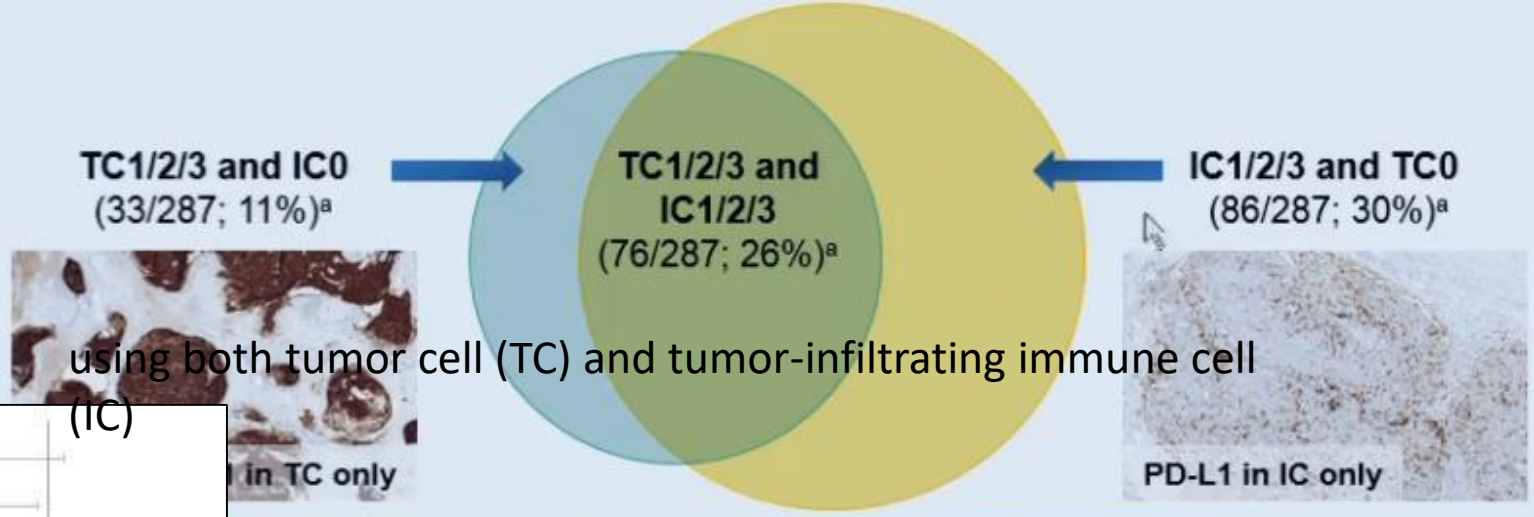
Agent	Assay	Analysis	Definition of positivity	PD-L1 expression
Nivolumab (anti-PD-1)[1–5]	Dako automated IHC assay (28-8 rabbit antibody) Analytically validated	• Original or new FFPE, tumor cells	• 1% and 5% cutoff among >100 evaluable tumor cells	Pretreated • 56%: 1% cutoff • 49%: 5% cutoff 1st line • 70%: 1% cutoff
Pembrolizumab (anti-PD-1)[6]	Dako automated IHC assay (22C3 mouse antibody)	• Contemporaneous tumor biopsy	• % of neoplastic cells with membranous PD-L1 staining at <1%, 1-49%, and ≥50%	• 23.2%: ≥50% • 37.6%: 1-49% • 39.2: <1%
Atezolizumab (anti-PD-L1)[7]	Ventana automated clinical research IHC assay	• Original or new FFPE, immune and tumor cells	• TC3 or IC3 = TC ≥50% or IC ≥10% PD-L1+ • TC2/3 or IC 2/3 = TC or IC ≥5% PD-L1+ • TC1/2/3 or IC 1/2/3 = TC or IC ≥1% PD-L1+ • TC0 and IC0 = <1% PD-L1+	• 16%: TC3 or IC3 • 37%: TC2/3 or IC 2/3 • 68%: TC1/2/3 or IC 1/2/3 • 32%: TC0 and IC0
Durvalumab (anti-PD-L1)[8,9]	First-generation or Ventana IHC Automated Assay (in development)	• Original or new FFPE, tumor cells	• Membranous staining in ≥25% of tumor cells at any intensity	• 48%
Avelum… (anti-PD				

using both tumor cell (TC) and
tumor-infiltrating immune cell (IC)

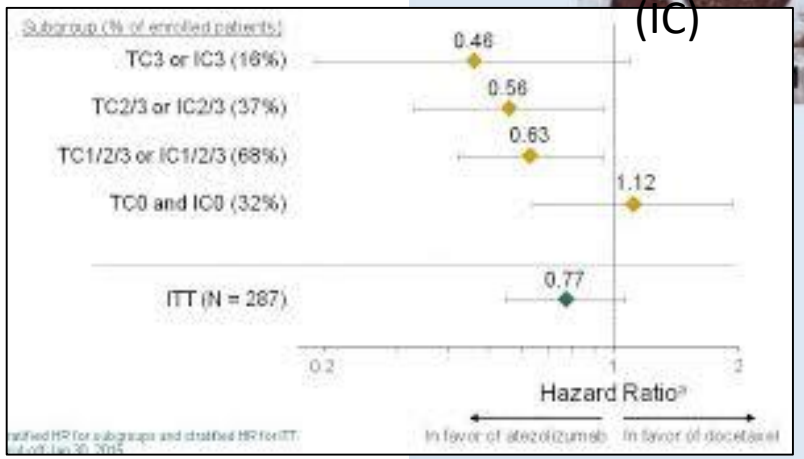
1. Antonia S, et al. Poster presented at WCLC 2013, Abstract P2.11-03. 2. Brahmer J, et al. Poster presented at ASCO 2014, Abstract 8112. 3. Gettinger S, et al. Poster presented at ASCO 2014, Abstract 8024. 4. Topalian S, et al. *N Engl J Med.* 2012;366:2443–2454. 5. Gettinger S, et al. Poster presented at ASCO 2015, Abstract 8025. 6. Garon EB, et al. *New Engl J Med* 2015; 372:2018-2028. 7. Spira AI, et al. Presentation at ASCO 2015. Abstract 80108. Brahmer J, et al. Poster presented at ASCO 2014, Abstract 8021. 9. Rizvi NA, et al. Poster presented at ASCO 2015. Abstract 8032. 10. Gulley LJ, et al. Poster presented at ASCO 2015, Abstract 8034.

ECC
2015

POPLAR: Both TC and IC are independent predictors of survival improvement



using both tumor cell (TC) and tumor-infiltrating immune cell (IC)

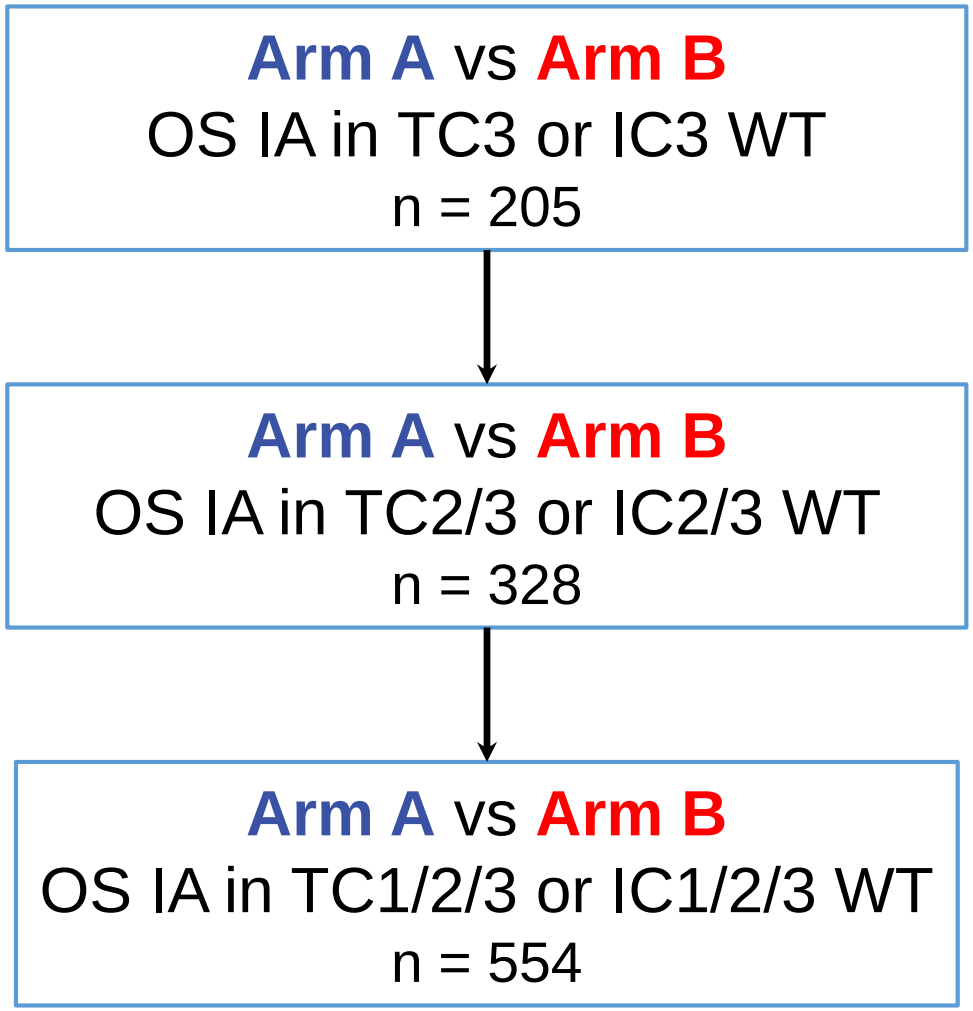


PD-L1 status	OS HR[b] (95% CI)
TC1/2/3 and IC0	0.37 (0.12,1.13)
IC1/2/3 and TC0	0.63 (0.36,1.12)
TC1/2/3 and IC1/2/3	0.60 (0.34, 1.08)
TC1/2/3 or IC1/2/3	0.59 (0.40, 0.85)

[a]Number of patients with both TC and IC cutoff levels ≥ 1 divided by the total number of patients in the study; Percentage of total study population.
[b]Unstratified HR.
Data cut-off May 8, 2015.

Vansteenkiste J. et al., atezolizumab in NSCLC (POPLAR)

Statistical Testing Plan

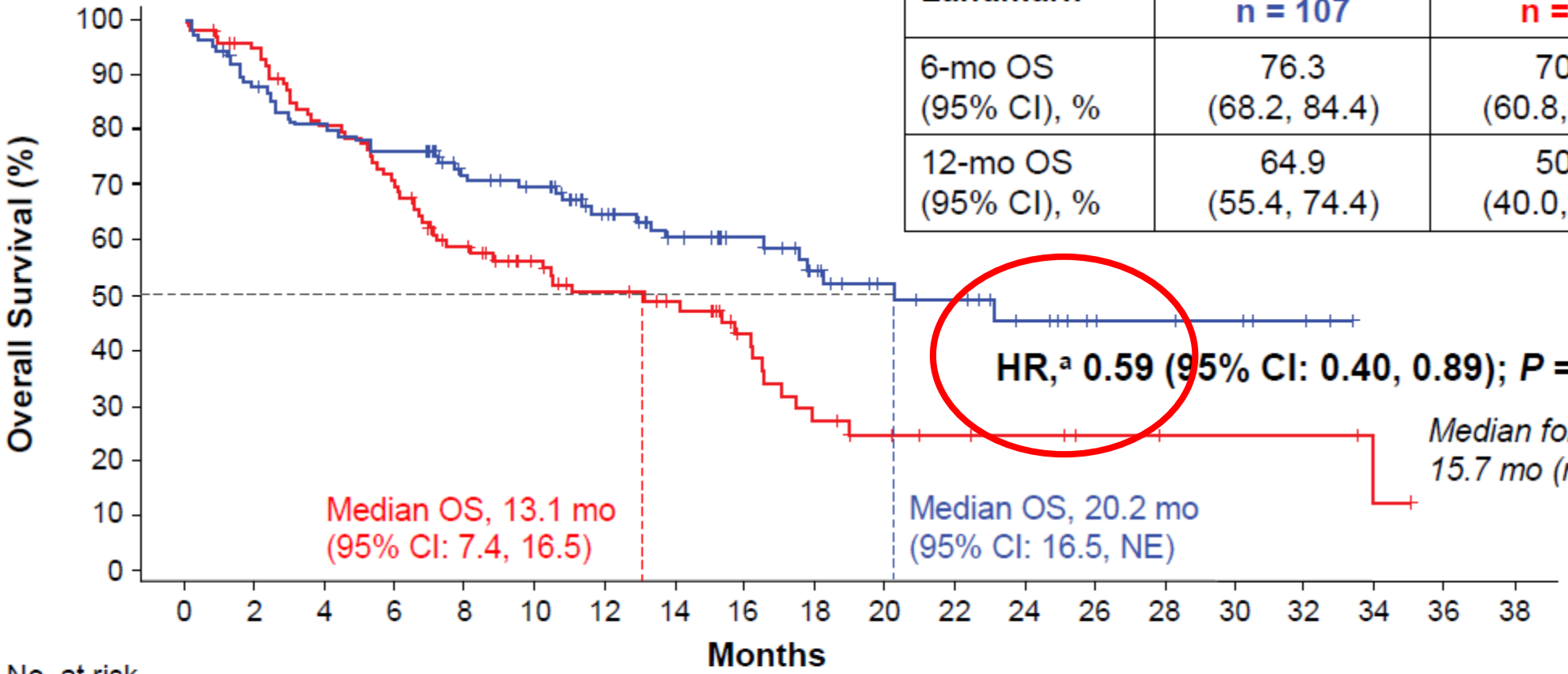


- The primary OS endpoint was tested hierarchically in the following order: TC3 or IC3 WT → TC2/3 or IC2/3 WT → TC1/2/3 or IC1/2/3 WT
- The secondary endpoint of PFS can be formally tested only when the primary endpoint is positive among all 3 populations

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

OS: TC3 or IC3 WT

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

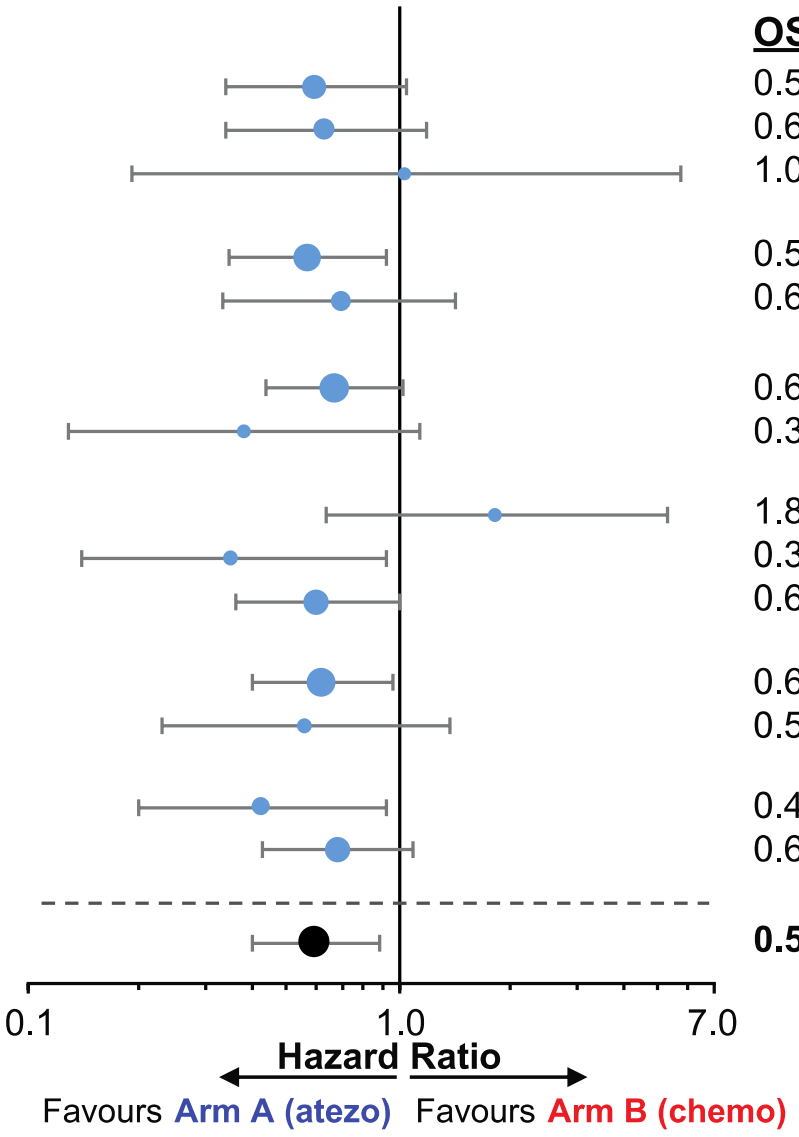
NE, not estimable. [a] Stratified. [b] Stratified log-rank.
Data cutoff: 10 September 2018.

Spigel ESMO 2019

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

TC3 or IC3 WT: OS in Key Subgroups

Subgroup[a]	n (%)	OS HR (95% CI)[b]	Median OS, mo	
			Arm A	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**

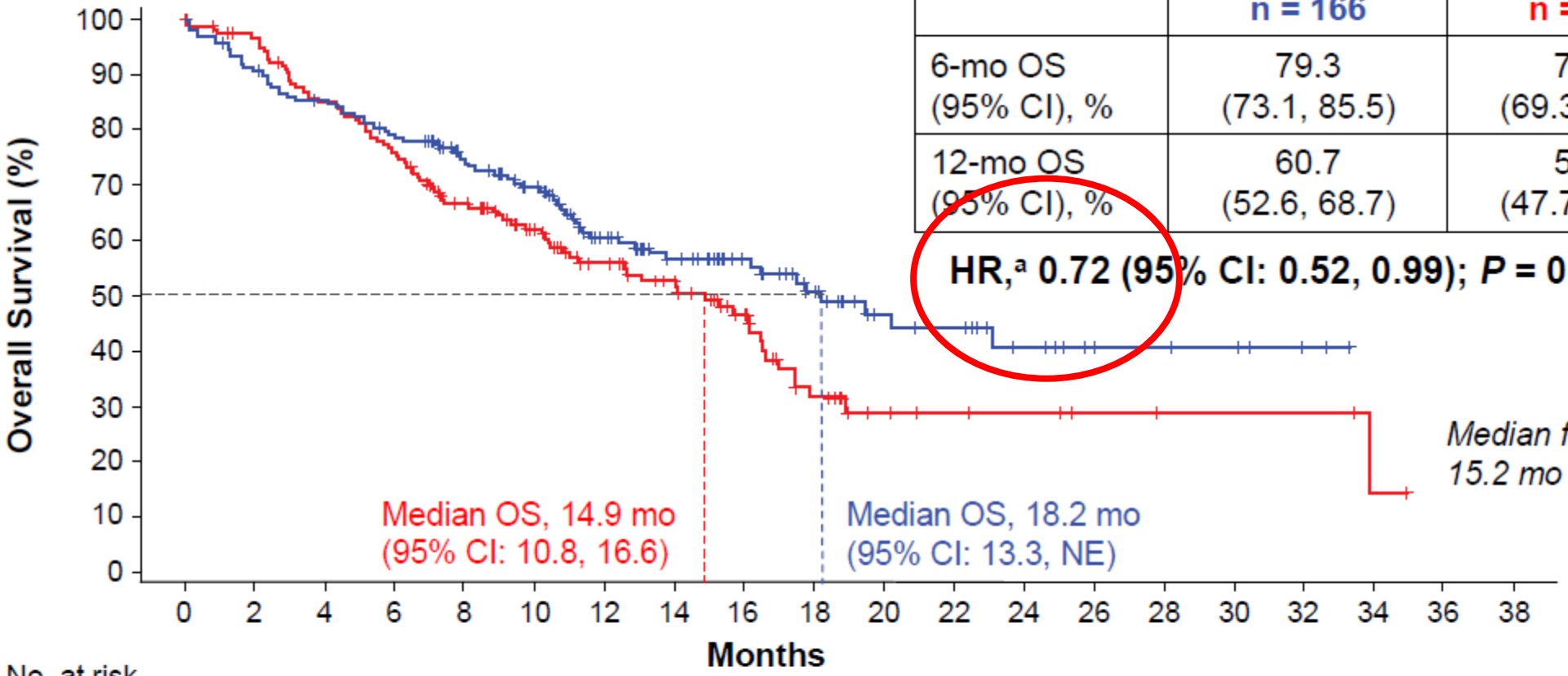


[a] The 1 patient in the ≥ 85 years subgroup is not included; 1 patient's race was unknown. [b] Unstratified. [c] Stratified.
Data cutoff: 10 September 2018.

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]



No. at risk

Atezolizumab	166	151	139	128	108	92	66	54	42	30	19	17	11	7	6	5	2
Chemotherapy	162	150	131	117	95	75	57	46	32	17	9	7	6	4	3	3	3	1

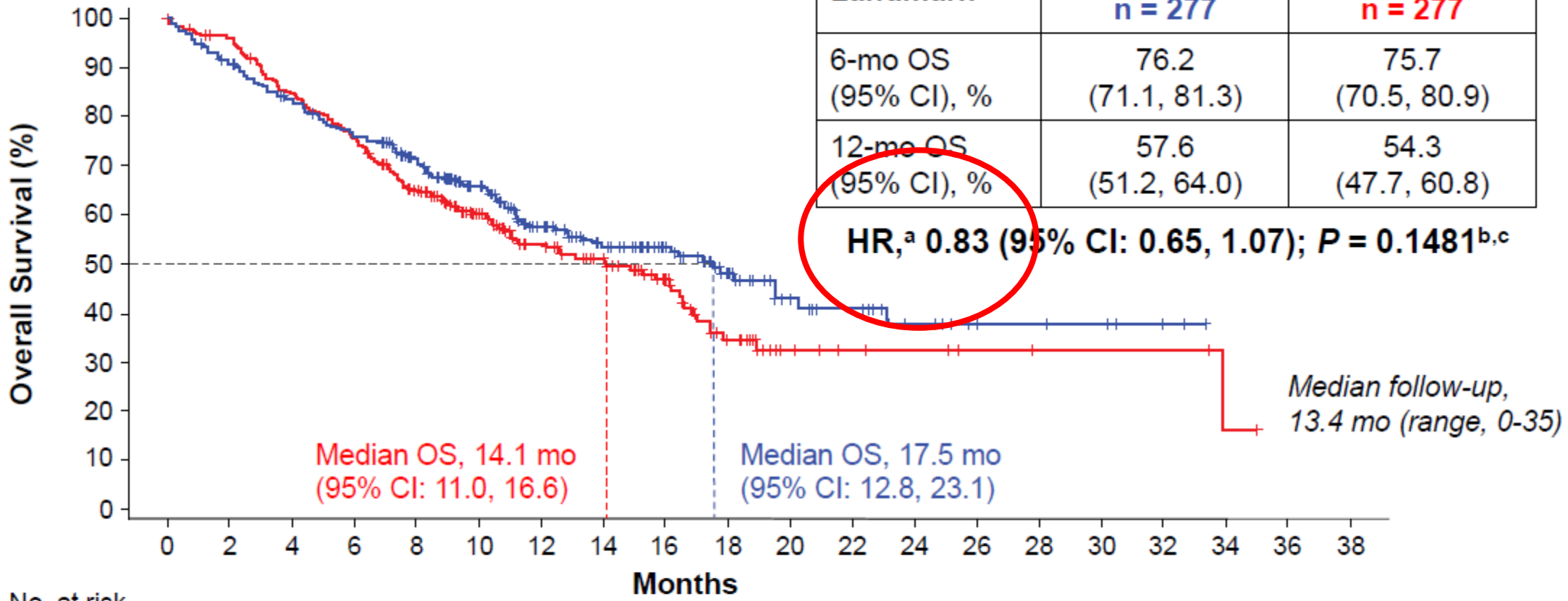
[a] Stratified. [b] Stratified log-rank. [c] Not crossing the pre-specified alpha boundary. Data cutoff: 10 September 2018.

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

OS: TC1/2/3 or IC1/2/3 WT

Landmark	Arm A (atezo) n = 277	Arm B (chemo) n = 277
6-mo OS (95% CI), %	76.2 (71.1, 81.3)	75.7 (70.5, 80.9)
12-mo OS (95% CI), %	57.6 (51.2, 64.0)	54.3 (47.7, 60.8)

HR,[a] 0.83 (95% CI: 0.65, 1.07); *P* = 0.1481[b,c]



No. at risk

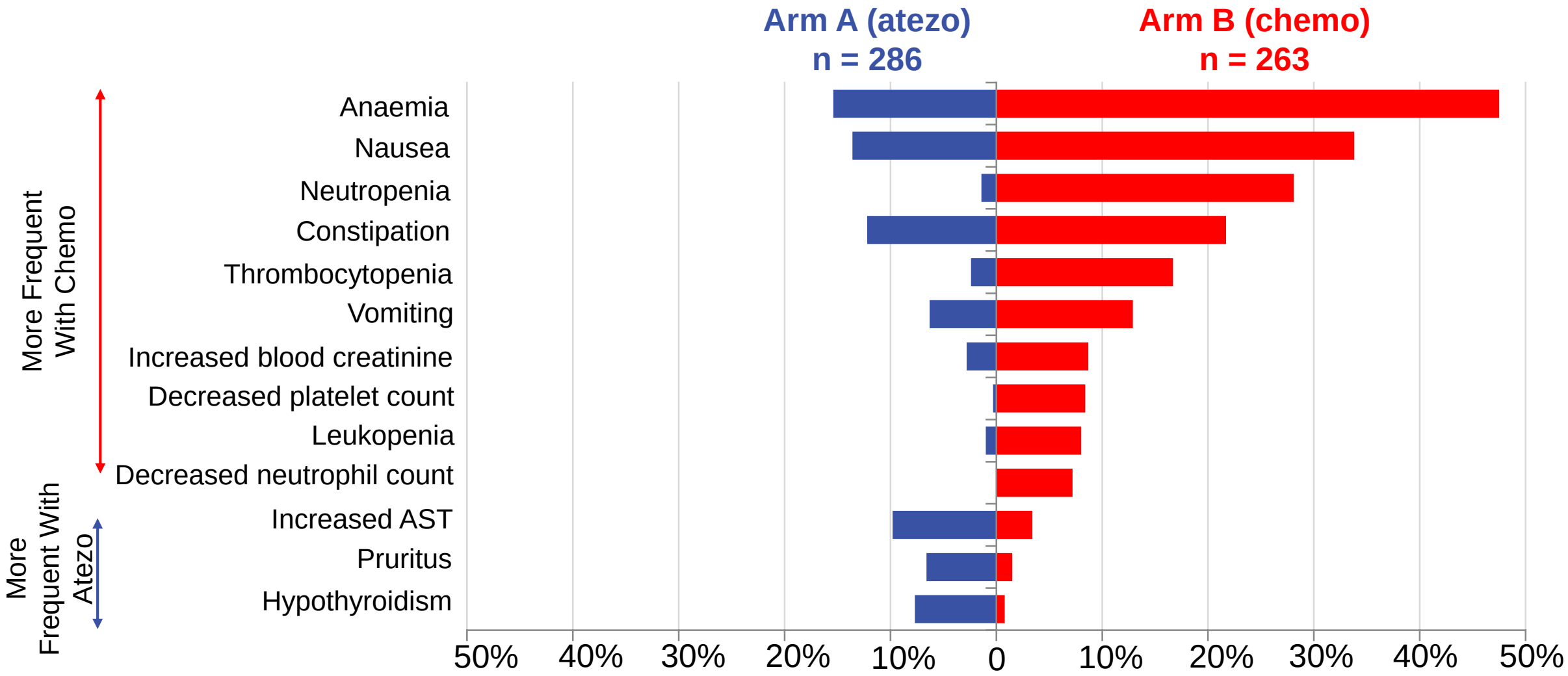
Atezolizumab	277	252	226	204	170	134	93	74	58	37	22	17	11	7	6	5	2
Chemotherapy	277	254	223	199	153	108	79	63	43	24	10	7	6	4	3	3	3	1

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

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

ALL-CAUSE AEs

> 5% difference between arms



AST, aspartate aminotransferase.

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)
- The OS testing boundary was not crossed in the TC2/3 or IC2/3 WT population. Therefore, the TC1/2/3 or IC1/2/3 WT population was not formally tested
  - IMpower110 will continue to the OS final analysis
- In the TC3 or IC3 WT population, atezolizumab showed meaningful improvement in PFS, ORR and DOR vs chemotherapy
- The safety profile of atezolizumab was consistent with prior observations; no new or unexpected safety signals were identified
- Additional biomarker analyses will be presented at a future congress
  - PD-L1 IHC by SP263 and 22C3, and bTMB
- Atezolizumab represents a promising 1L treatment option in patients with PD-L1–high NSCLC

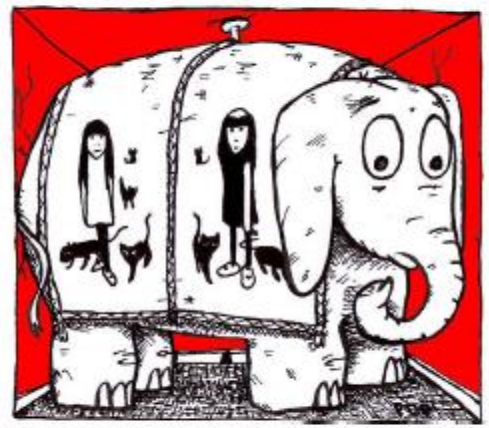
Conclusions (authors and discussant Dr. Naiyer Rizvi)

- 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?

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

Tumor Mutational Burden (TMB)

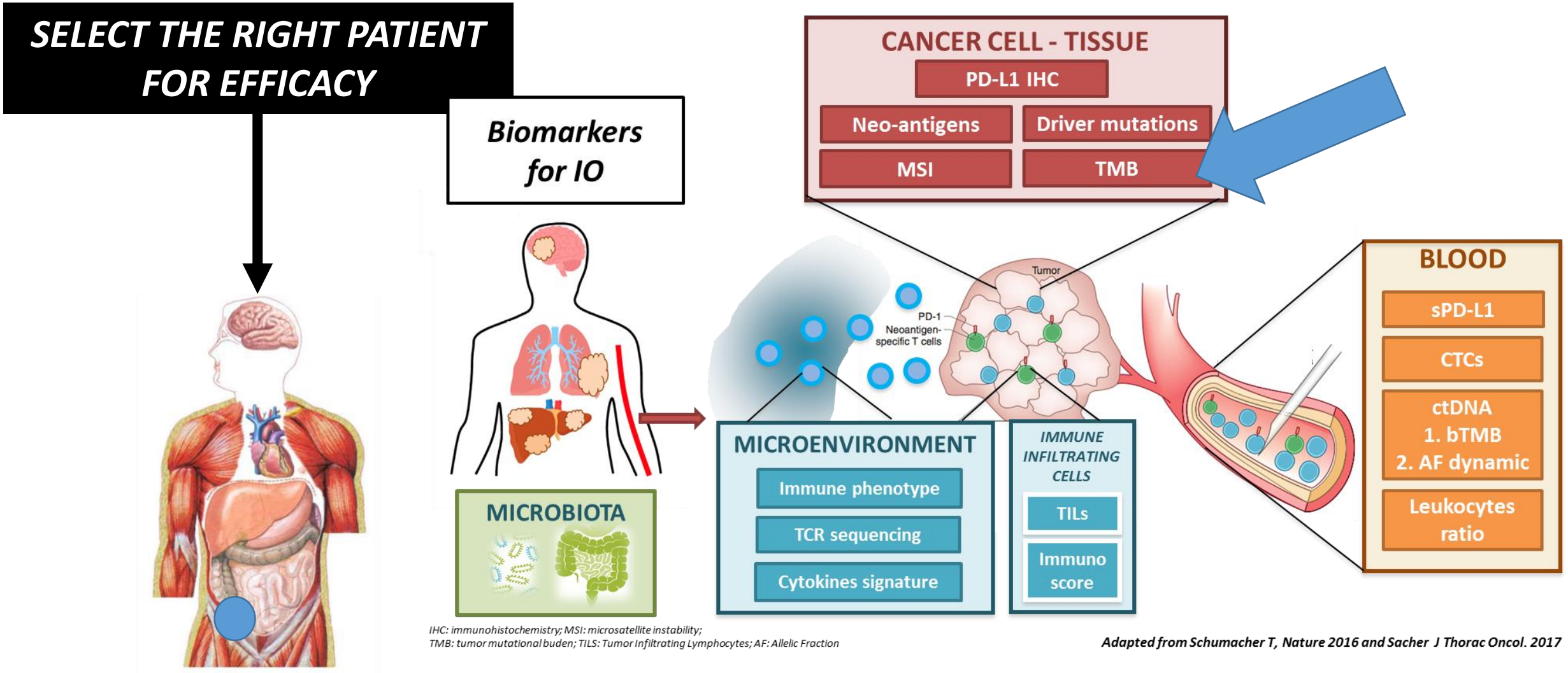
The elephant in the room



Dead **or** **Will it get you to the right place?**

Transports Metropolitans de Barcelona

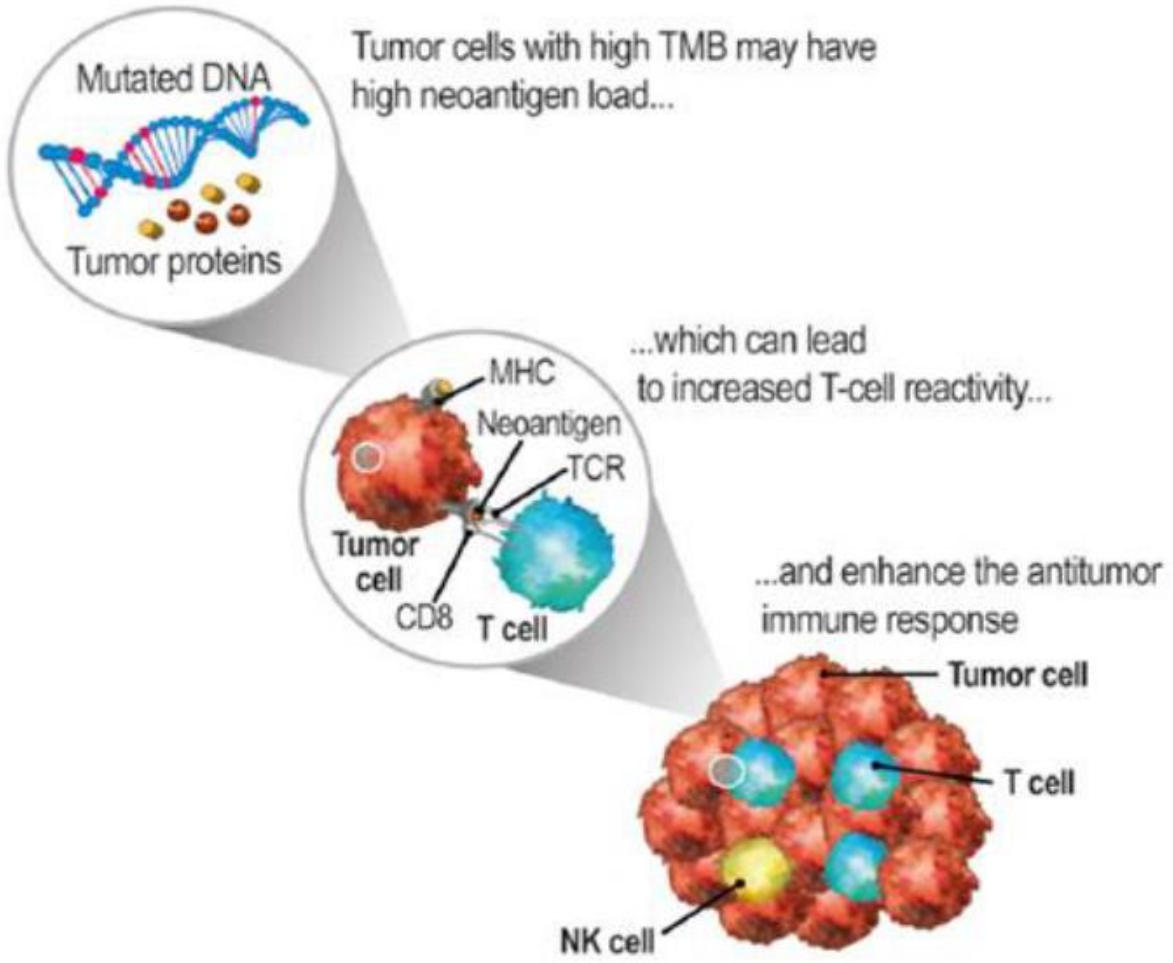
Immunotherapy - who to give?



Courtesy of A.Marabelle, adapted

Ferrara R, et al. WCLC 2017. Saâda-Bouzid E, et al. *Ann Oncol.* 2017;28(7):1605-1611; Champiat S, et al. *Clin Cancer Res.* 2017;23(8):1920-1928.

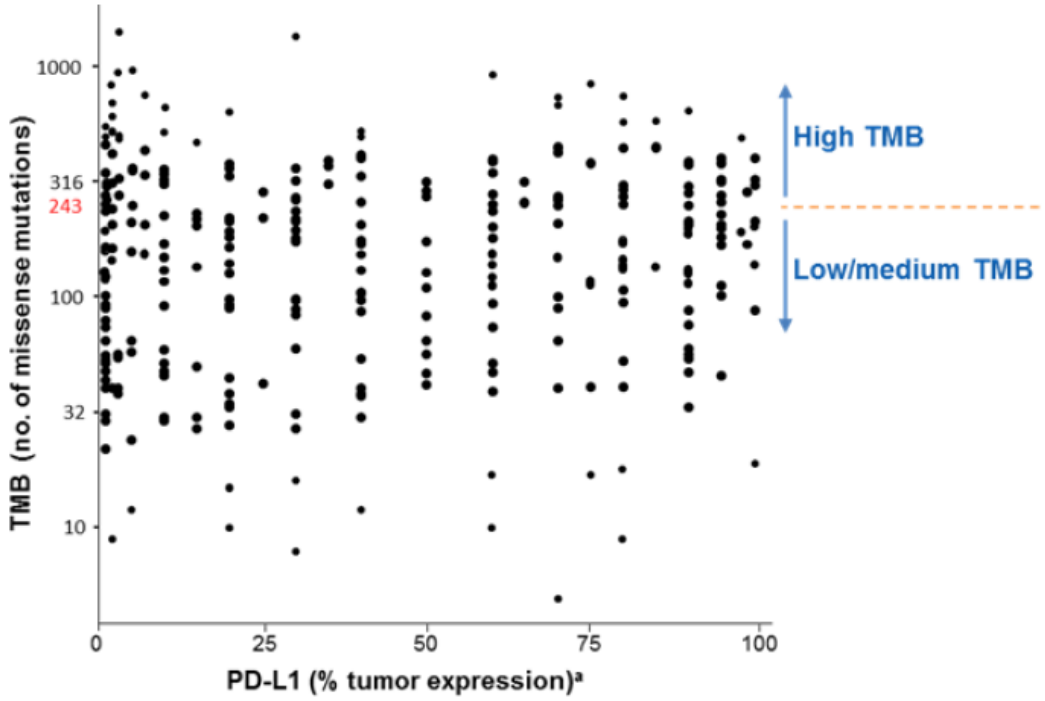
TMB and relevance in immunotherapy treatment



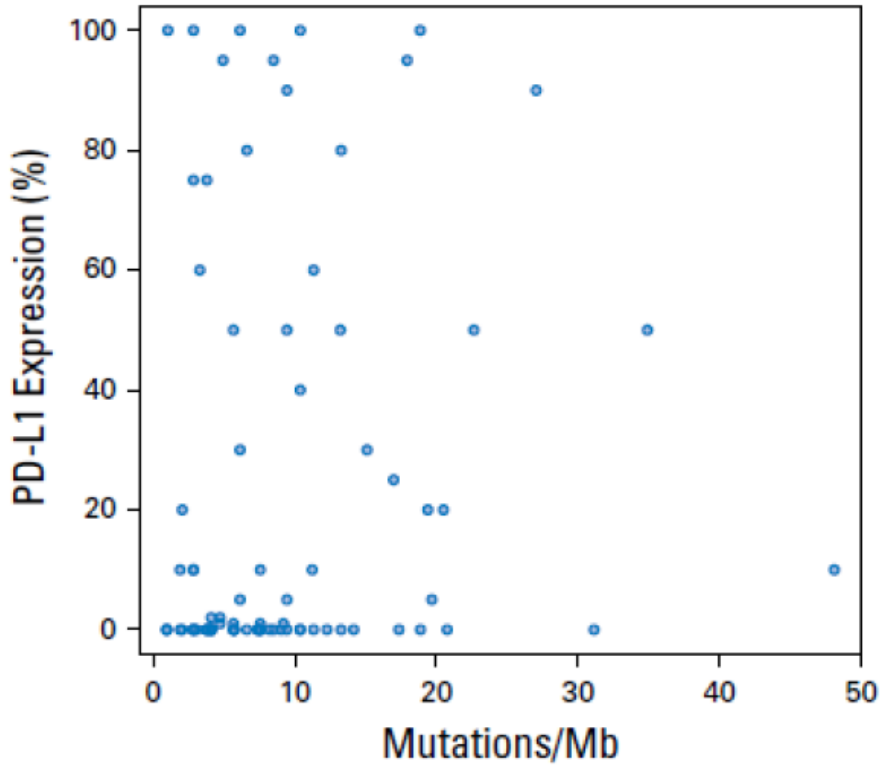
Stenzinger Genes Chromosomes Cancer 2019

TMB is independent of PD-L1 expression level

CM 26 - WES



MSK - IMPACT



Peters AACR 2017 * Rizvi JCO 2018

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

Background

- Pembrolizumab improved OS vs chemotherapy in patients with previously treated (KEYNOTE-010) and treatment-naive (KEYNOTE-042) PD-L1+ (TPS ≥1%), advanced NSCLC[1, 2]

1. Herbst RS et al. *Lancet* 2016; 387:1540-50. 2. Mok TSK et al. *Lancet 2019;* 393:1819-30.

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])

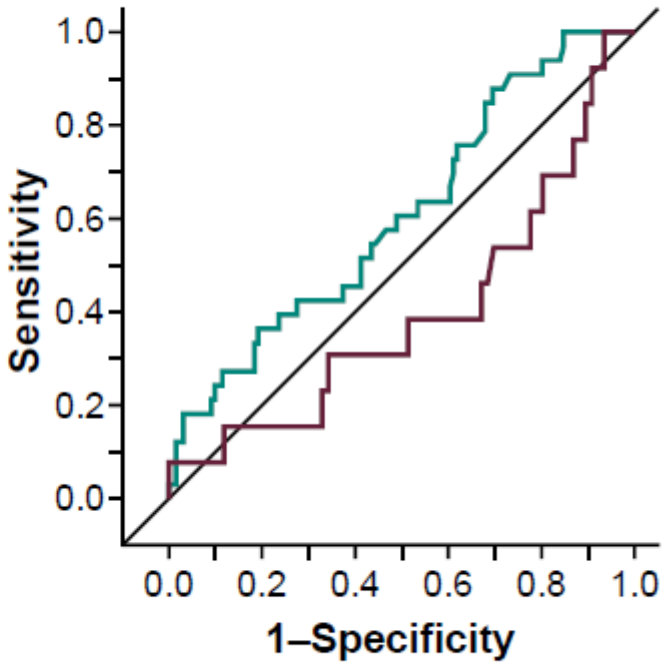
Nominal *P* Value[b]	Pembro (n = 164)	Chemo (n = 89)
OS	0.006 (one-sided)	0.410 (two-sided)
PFS	0.001 (one-sided)	0.579 (two-sided)
ORR	0.009 (one-sided)	0.330 (two-sided)

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

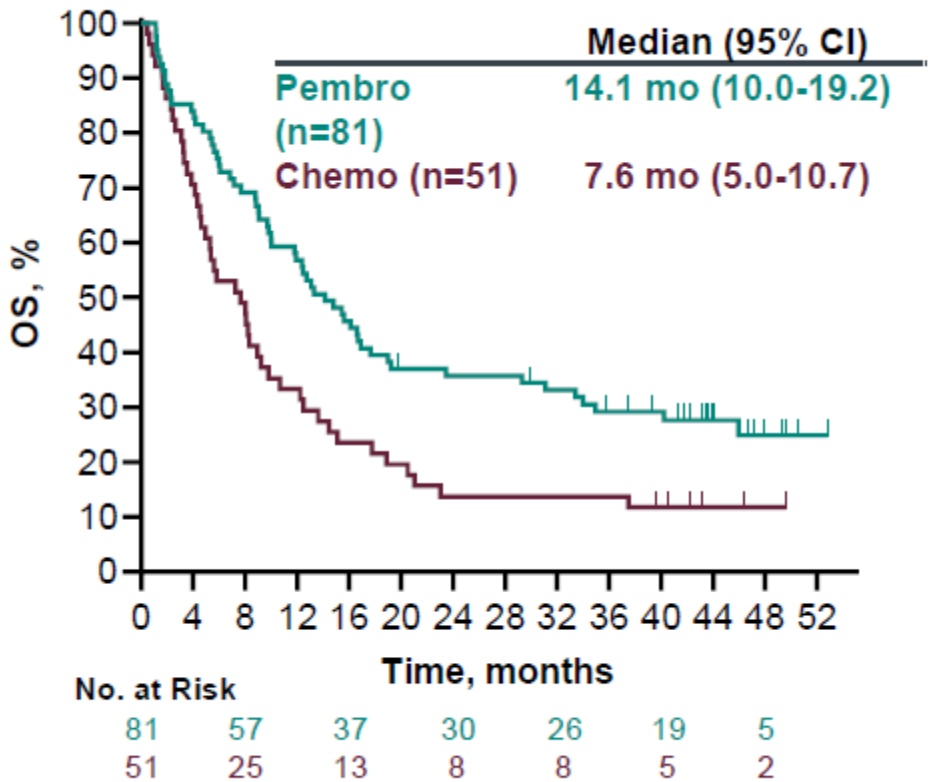
	AUROC (95% CI)
Pembro	0.61 (0.50-0.71)
Chemo	0.40 (0.21-0.58)



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

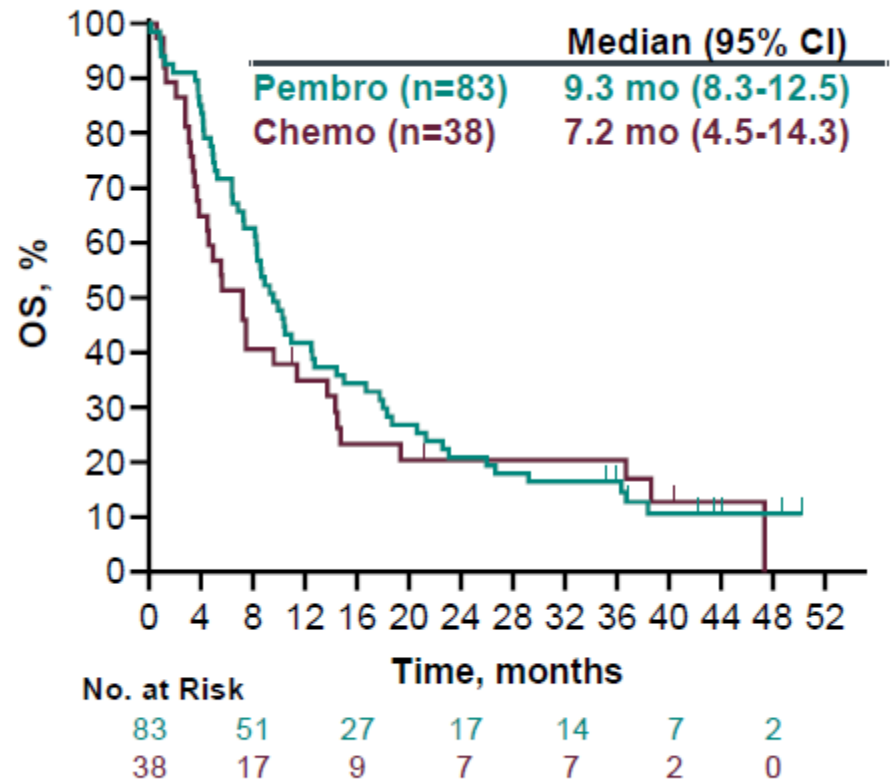
tTMB ≥175 mut/exome

HR 0.56 (95% CI 0.38-0.83)



tTMB <175 mut/exome

HR 0.85 (95% CI 0.56-1.30)



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

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

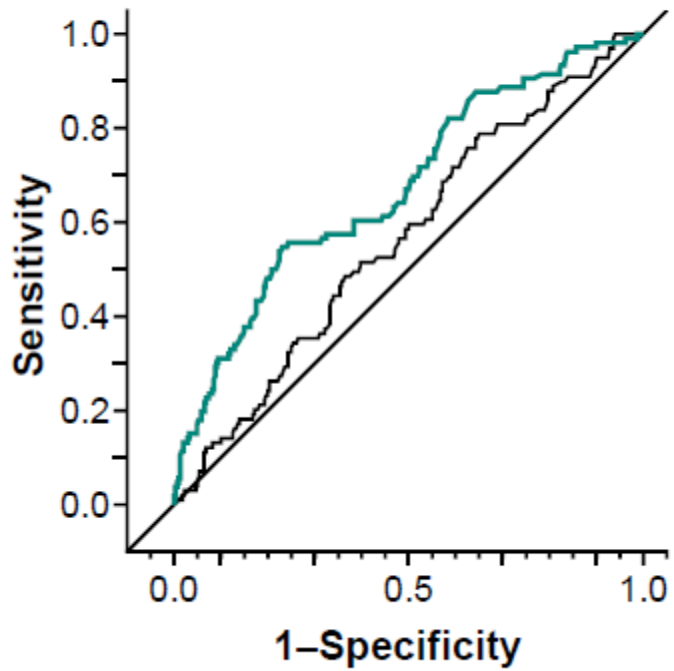
	Pembro (n = 414)	Chemo (n = 379)	Nominal *P* Value[b]
OS	<0.001 (one-sided)	0.060 (two-sided)[c]	
PFS	<0.001 (one-sided)	0.174 (two-sided)[c]	
ORR	<0.001 (one-sided)	0.035 (two-sided)	

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

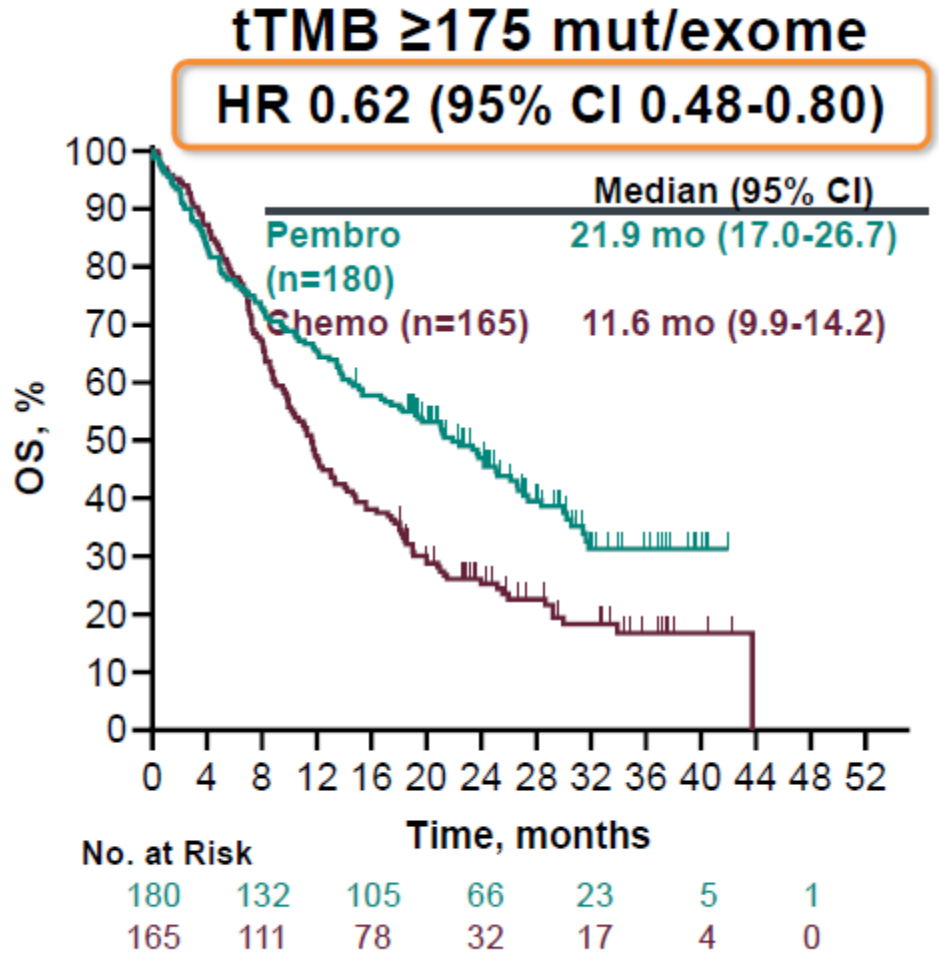
[a]All patients were PD-L1-positive (TPS ≥1%). [b]Wald test. *P* values are one-sided for pembro as the a priori hypothesis was that tTMB was positively associated with improved outcomes of pembro. *P* values are two-sided for placebo as there was no a priori hypothesis regarding the direction of association 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.

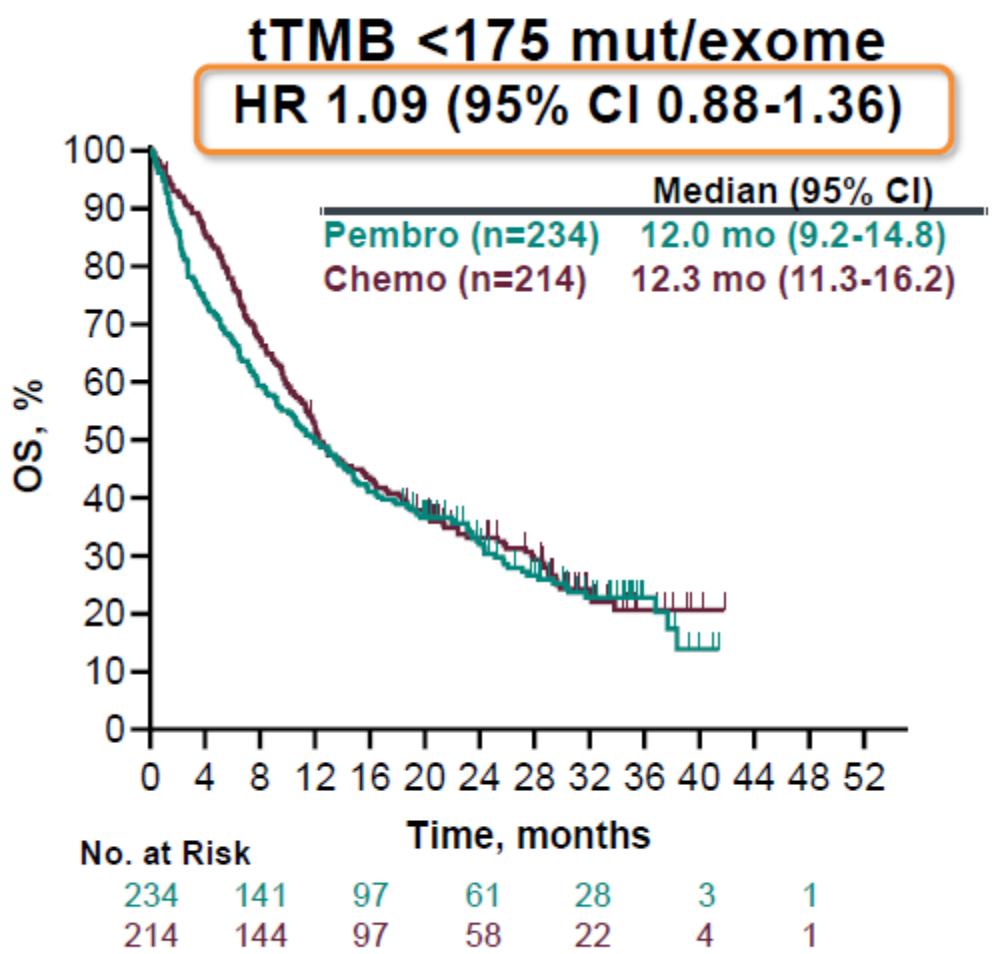
ROC Curves of ORR for tTMB

	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.

BARCELONA 2019 ESMO congress

LBA80

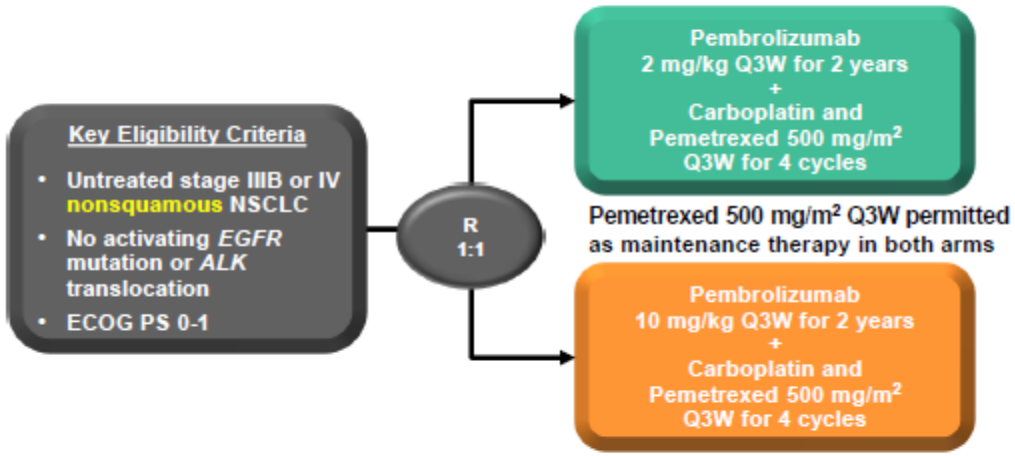
Pembrolizumab Plus Platinum-Based Chemotherapy for Metastatic NSCLC: Tissue TMB (tTMB) and Outcomes in KEYNOTE-021, 189, and 407

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]

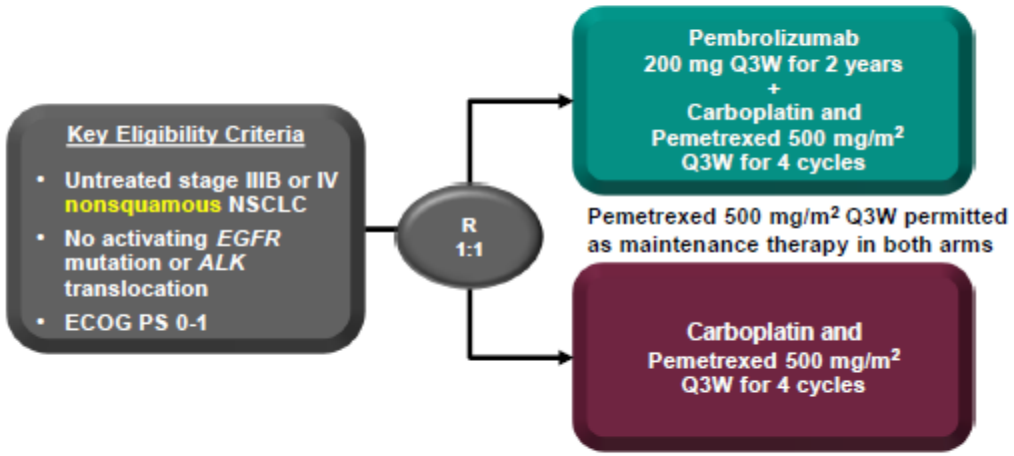
[1]Hospital Universitario 12 de Octubre, Spanish National Cancer Research Center, Universidad Complutense and Ciberonc, Madrid, Spain; [2]Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA, USA; [3]University of Turin, Orbassano, Italy; [4]Montefiore Medical Center/Albert Einstein 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

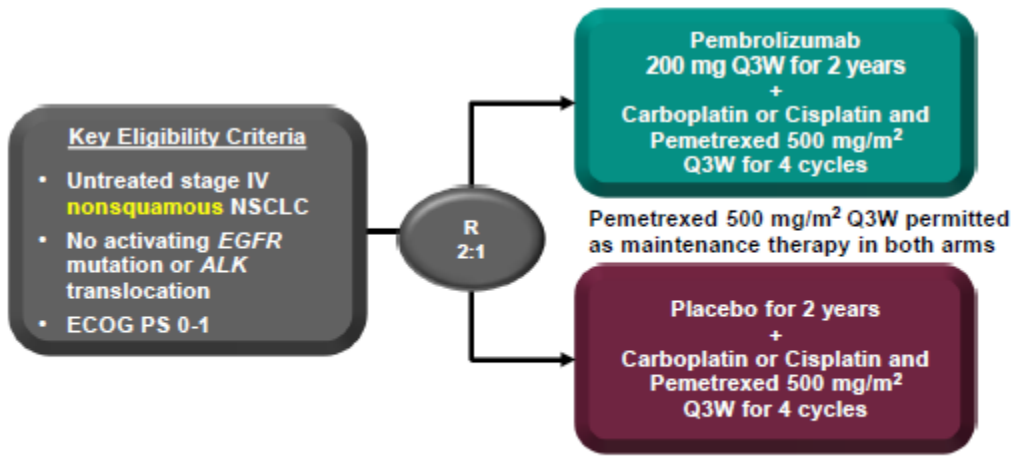
KEYNOTE-021 Cohort C (N = 24)[1]



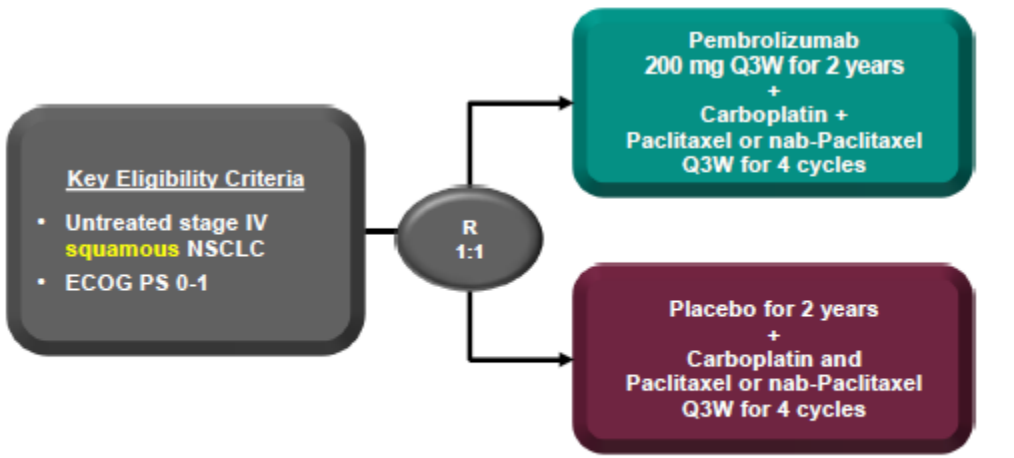
KEYNOTE-021 Cohort G (N = 123)[2,3]



KEYNOTE-189 (N = 616)[4]



KEYNOTE-407 (N = 559)[5]



1. *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).

Conclusions

- **Higher tTMB** levels as assessed by WES were associated with **improved clinical outcomes** for **pembrolizumab monotherapy** in patients with PD-L1-positive advanced NSCLC
- PD-L1 1-49% and TMB high may be appropriate for pembrolizumab monotherapy
- **Pembrolizumab/chemotherapy** combinations active in **both TMB high and low** tumors
- Limitations:
  - Exploratory analysis
  - Analysis in subsets of patients with available tTMB in these trials

- TMB high and PD-L1 <1% ?
- Different methods and definitions of TMB testing – harmonization needed

ERS

INTERNATIONAL CONGRESS 2019

MADRID Spain, 28 September – 2 October

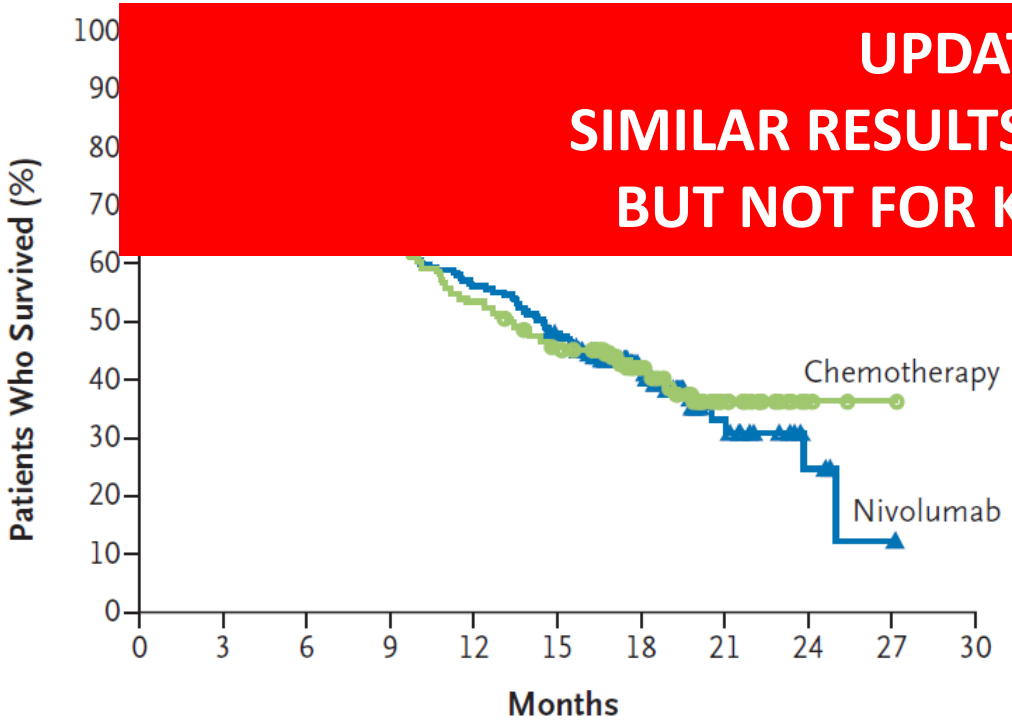
Next-generation sequencing and assessment of tumour mutational burden: are these tools ready for clinical routine use?

L. Hendriks, pulmonologist, MD, PhD

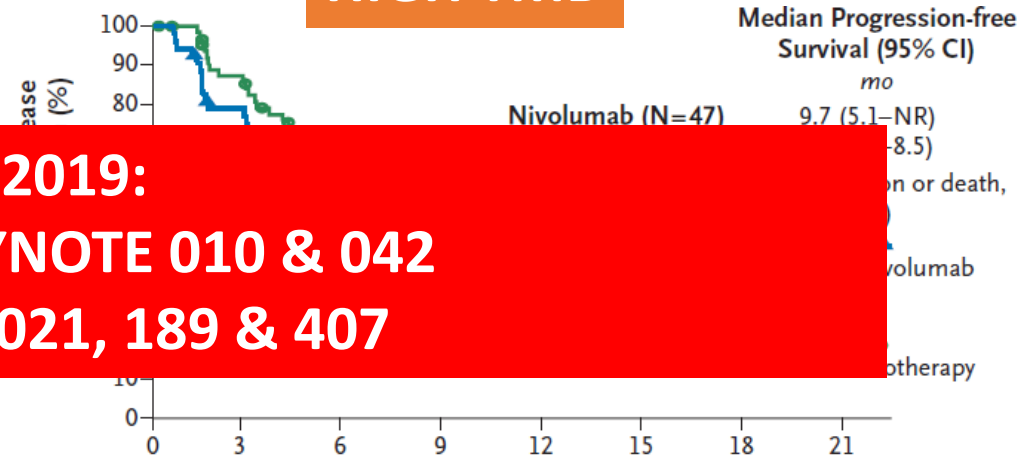
Maastricht UMC+, The Netherlands

Impact of TMB on anti-PD-1

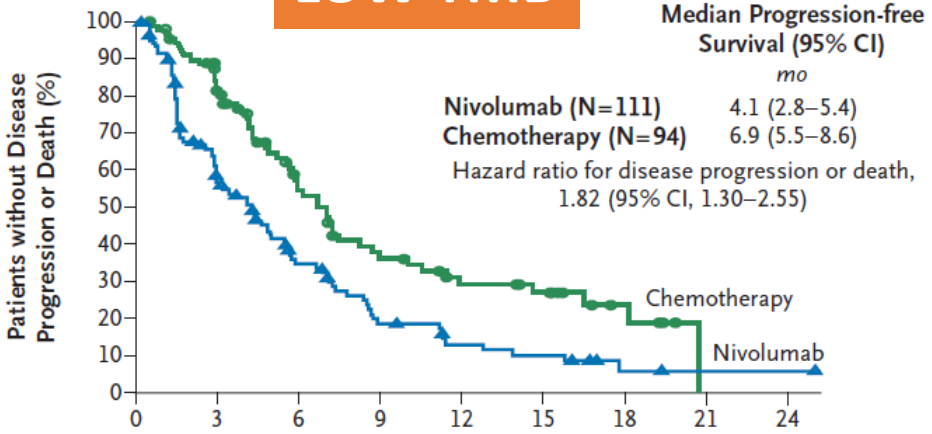
UPDATE ESMO 2019:
SIMILAR RESULTS FOR KEYNOTE 010 & 042
BUT NOT FOR KEYNOTE 021, 189 & 407



HIGH TMB

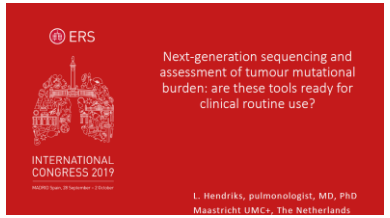


LOW TMB

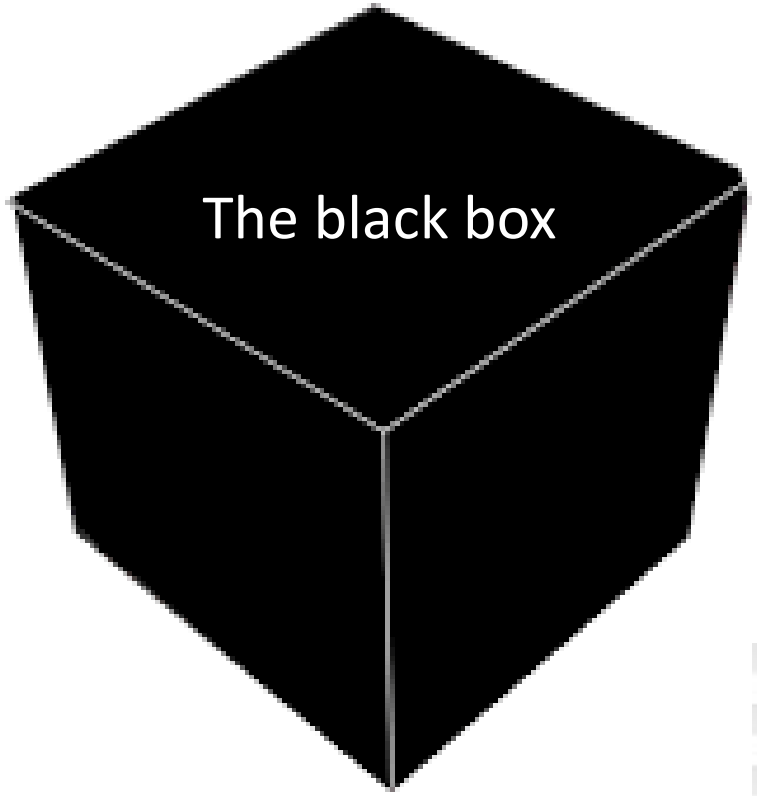


Carbone DP, N. Engl. J. Med. 2017; 376(25):2415–2426 * Herbst ESMO 2019 * Paz-Ares ESMO 2019

TMB definition



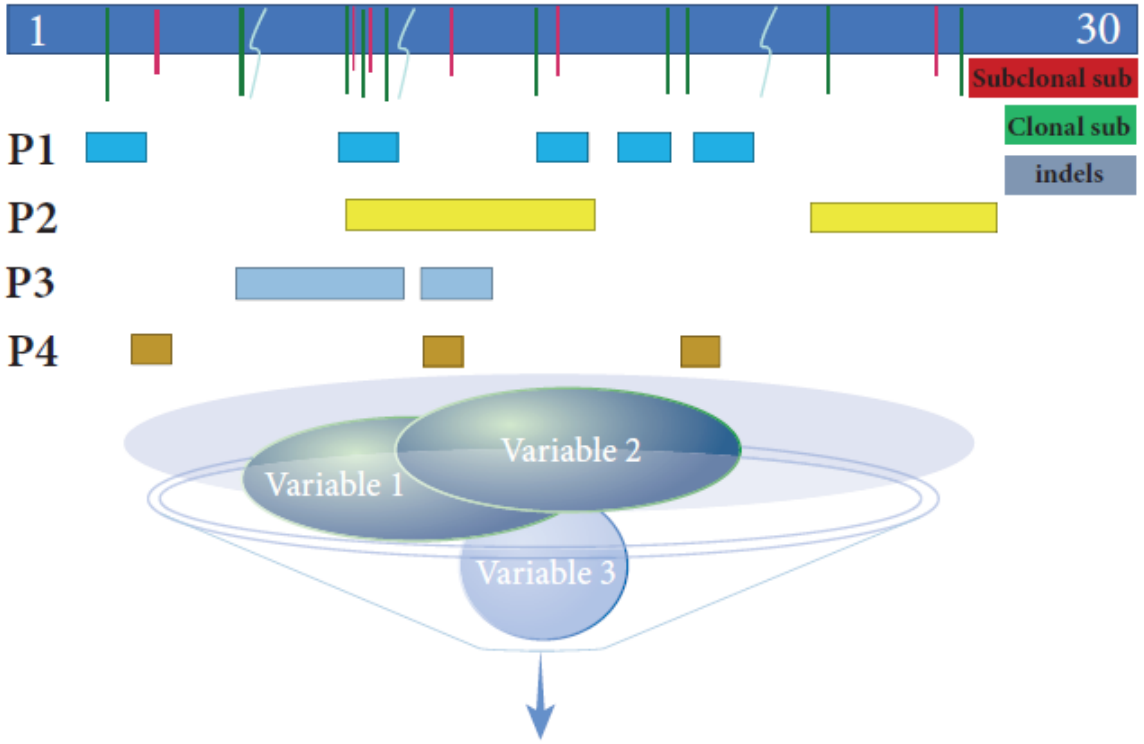
Number of mutations in genome……



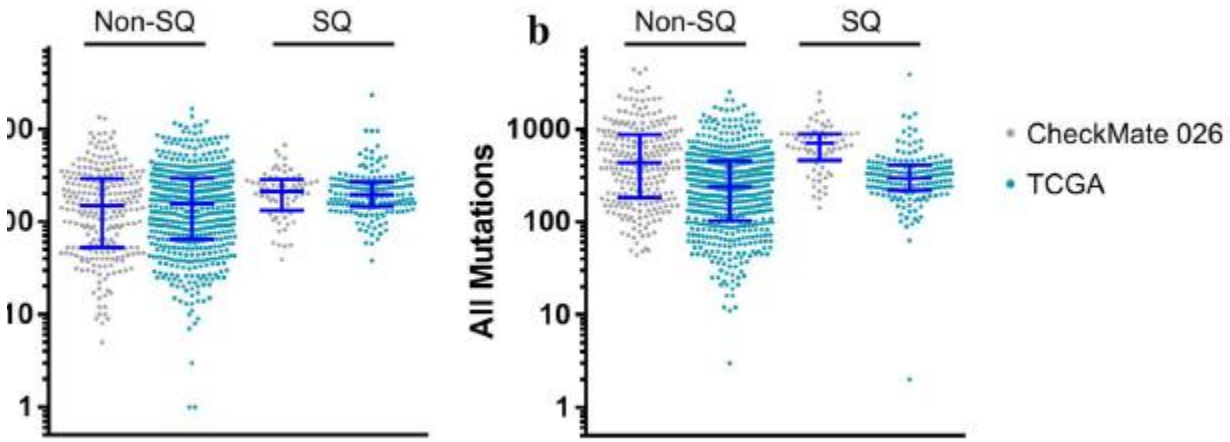
TMB pitfalls

Genes covered

Exome (coding region - approx. 1-2% of genome)-
1MB = 1 million nucleotides
→ Variability regarding definition

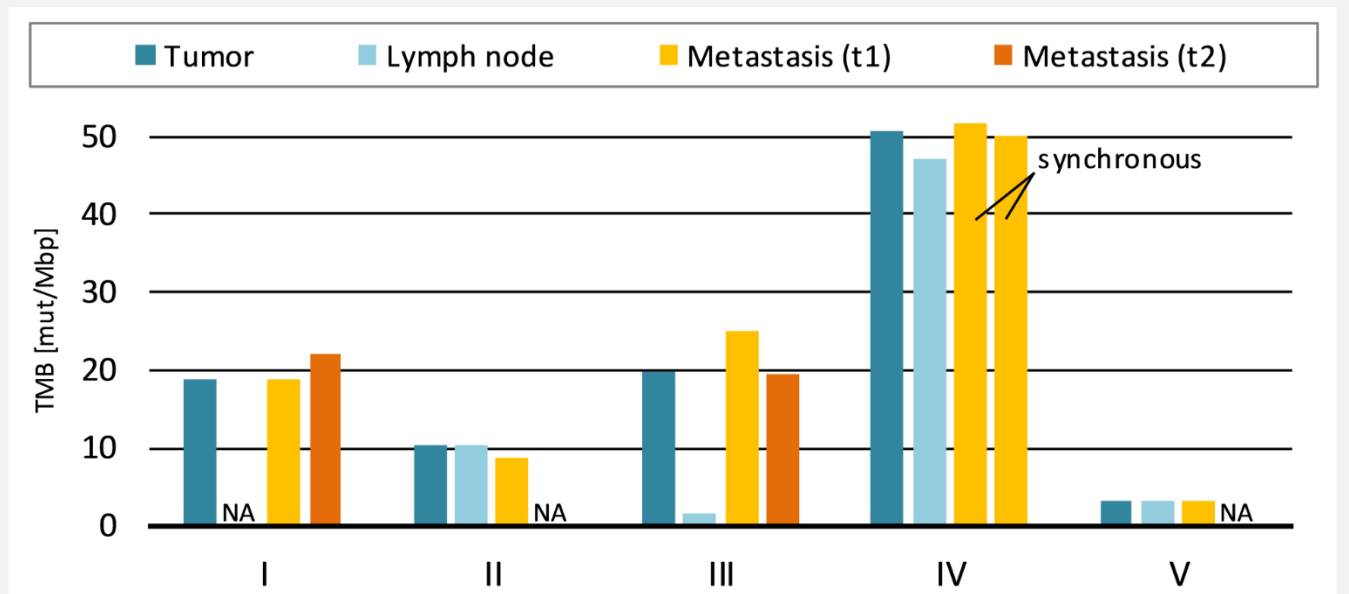


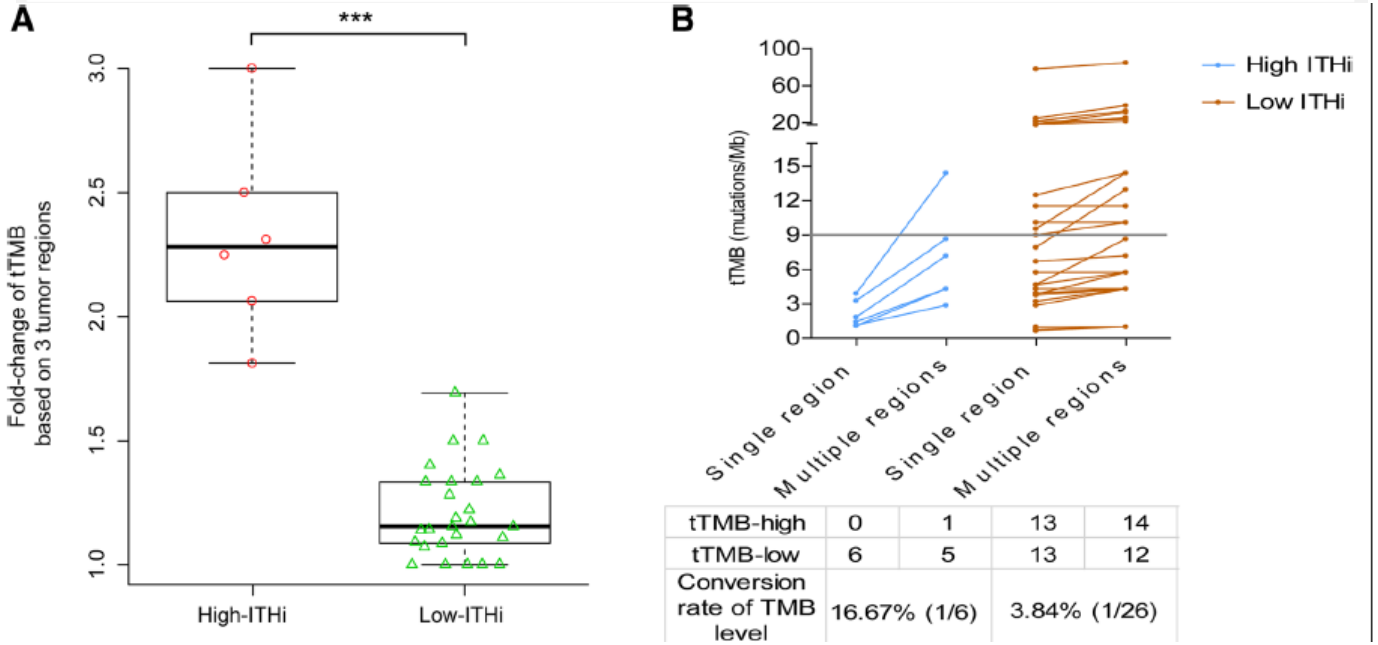
Missense vs "all" mutations



Chang mol diagnosis and therapy 2019 * Chan ann oncol 2018

TMB pitfalls





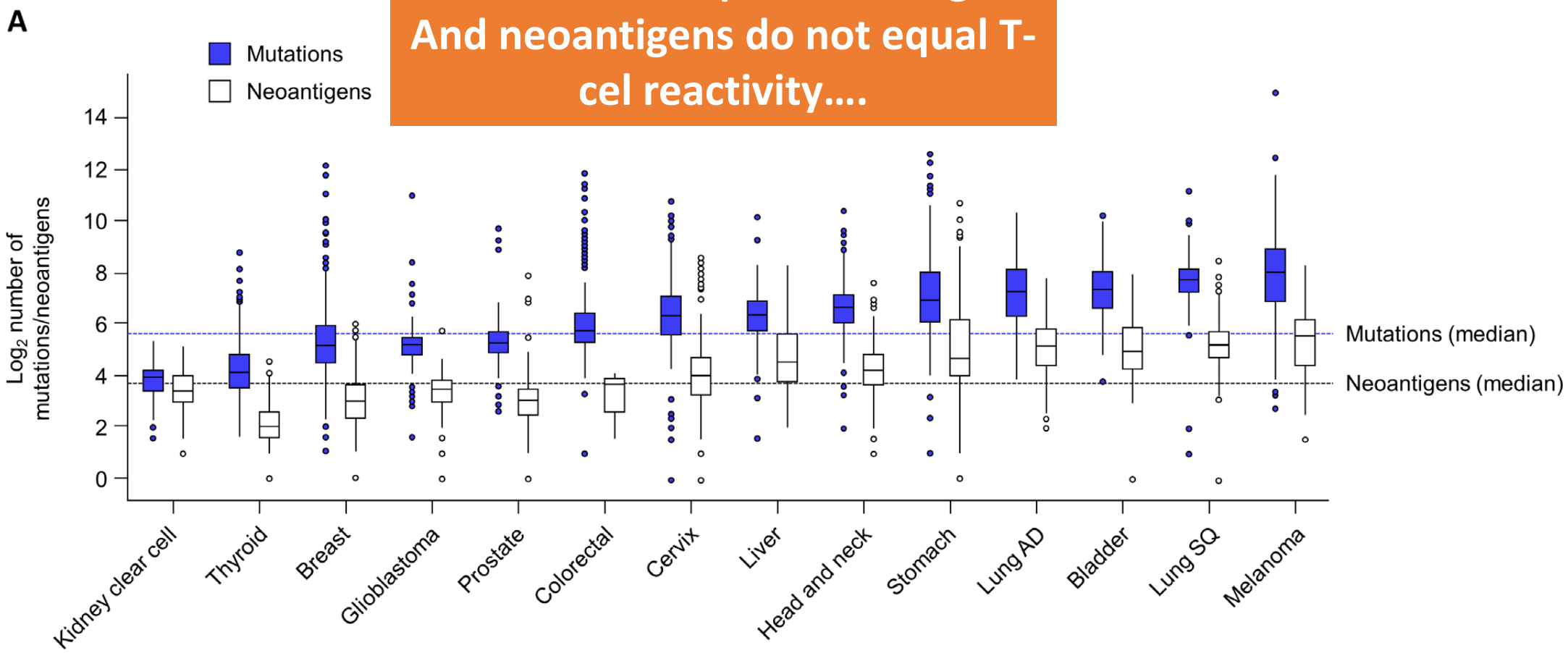
Heterogeneity primary – LN - metastasis

Intratumor heterogeneity 30%, up to 14 mut/Mb difference!

Kazdal JTO 2019 * Zhang JITC 2019

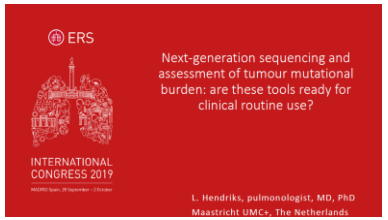
TMB pitfalls

TMB does not equal neoantigen
And neoantigens do not equal T-cel reactivity….

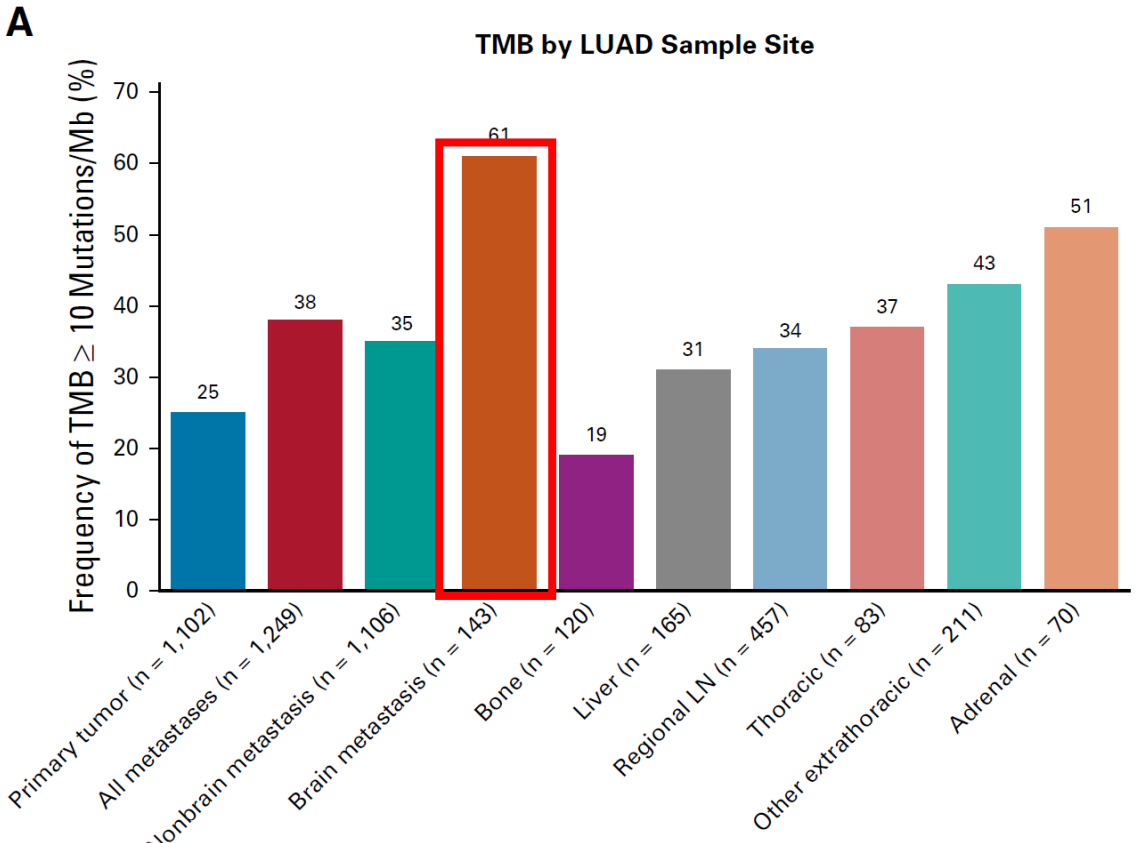


Buttner ESMO open 2019

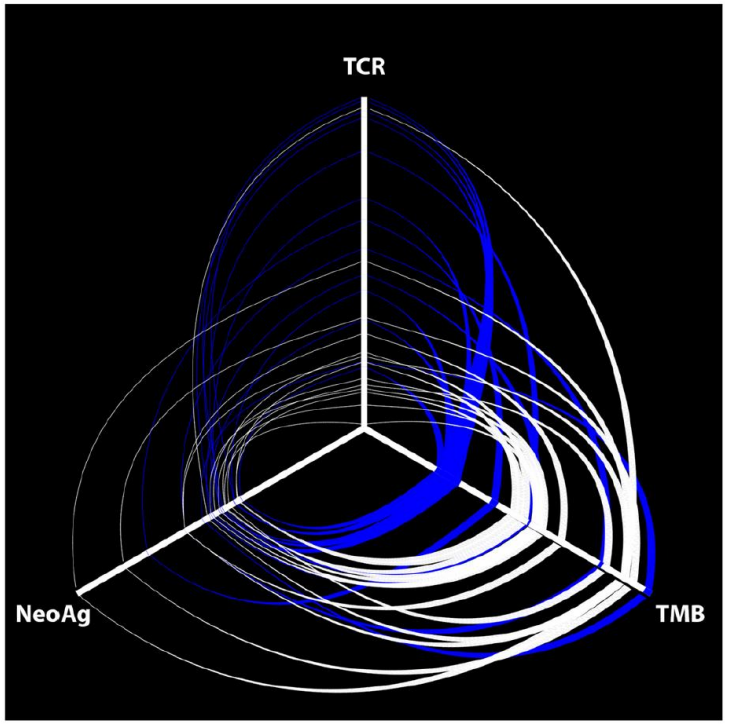
TMB pitfalls
tumor microenvironment matters



Brain mets often high TMB

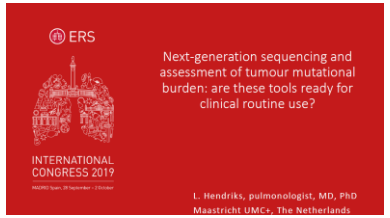


White = BM; Blue = lung



But less T-cell clonality in brain mets

Stein JCO precision oncology 2019 * Mansfield Sci Rep 2018



TMB summary

- ✓ Why?
  - ✓ Biological rationale
  - ✓ High TMB associated with long term outcome across tumor types

- ✓ Pitfalls - drawbacks
  - ✓ Heterogeneity++
  - ✓ Be aware of type of test (definition, coverage, genes sequenced, race)
  - ✓ TAT 2 weeks for tissue, < 1 week for blood

- ✓ **Implement?**
  - ✓ Interesting but not ready for clinical use yet

ERS

INTERNATIONAL CONGRESS 2019

MADRID Spain, 29 September – 2 October

Next-generation sequencing and assessment of tumour mutational burden: are these tools ready for clinical routine use?

L. Hendriks, pulmonologist, MD, PhD
Maastricht UMC+, The Netherlands

IO-IO combinations: more is better?

Nivolumab + Low-Dose Ipilimumab Versus Platinum-Doublet Chemotherapy as First-Line Treatment for Advanced Non-Small Cell Lung Cancer: CheckMate 227 Part 1 Final Analysis

Solange Peters,[1] Suresh Ramalingam,[2] Luis Paz-Ares,[3] Reyes Bernabe Caro,[4] Bogdan Zurawski,[5] Sang-We Kim,[6] Aurelia Alexandru,[7] Lorena Lupinacci,[8] Emmanuel de la Mora Jimenez,[9] Hiroshi Sakai,[10] István Albert,[11] Alain Vergnenegre,[12] Martin Reck,[13] Hossein Borghaei,[14] Julie R. Brahmer,[15] Kenneth O'Byrne,[16] William J. Geese,[17] Prabhu Bhagavatheeswaran,[17] Faith E. Nathan,[17] Matthew D. Hellmann[18]

[1]Centre hospitalier universitaire Vaudois (CHUV), Lausanne University, Lausanne, Switzerland; [2]Winship Cancer Institute, Emory University, Atlanta, GA, USA; [3]Hospital Universitario Doce de Octubre, CNIO, Universidad Complutense & CiberOnc, Madrid, Spain; [4]Hospital Universitario Virgen Del Rocio, Seville, Spain; [5]Ambulatorium Chemioterapii, Bydgoszcz, Poland; [6]Asan Medical Center, Seoul, Republic of Korea; [7]Institute Of Oncology "Prof. Dr. Alexandru Trestioreanu" Bucha, Bucharest, Romania; [8]Hospital Italiano De Buenos Aires, Buenos Aires, Argentina; [9]Instituto Jalisciense De Cancerología, Guadalajara, Jalisco, Mexico; [10]Saitama Cancer Center, Saitama, Japan; [11]Matrai Gyogyintezet, Matrahaza, Hungary; [12]Limoges University Hospital, Limoges, France; [13]Lung Clinic Grosshansdorf, German Center for Lung Research, Grosshansdorf, Germany; [14]Fox Chase Cancer Center, Philadelphia, PA, USA; [15]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA; [16]Princess Alexandra Hospital, Brisbane, Queensland, Australia; [17]Bristol-Myers Squibb, Princeton, NJ, USA; [18]Memorial Sloan-Kettering Cancer Center, New York, NY, USA

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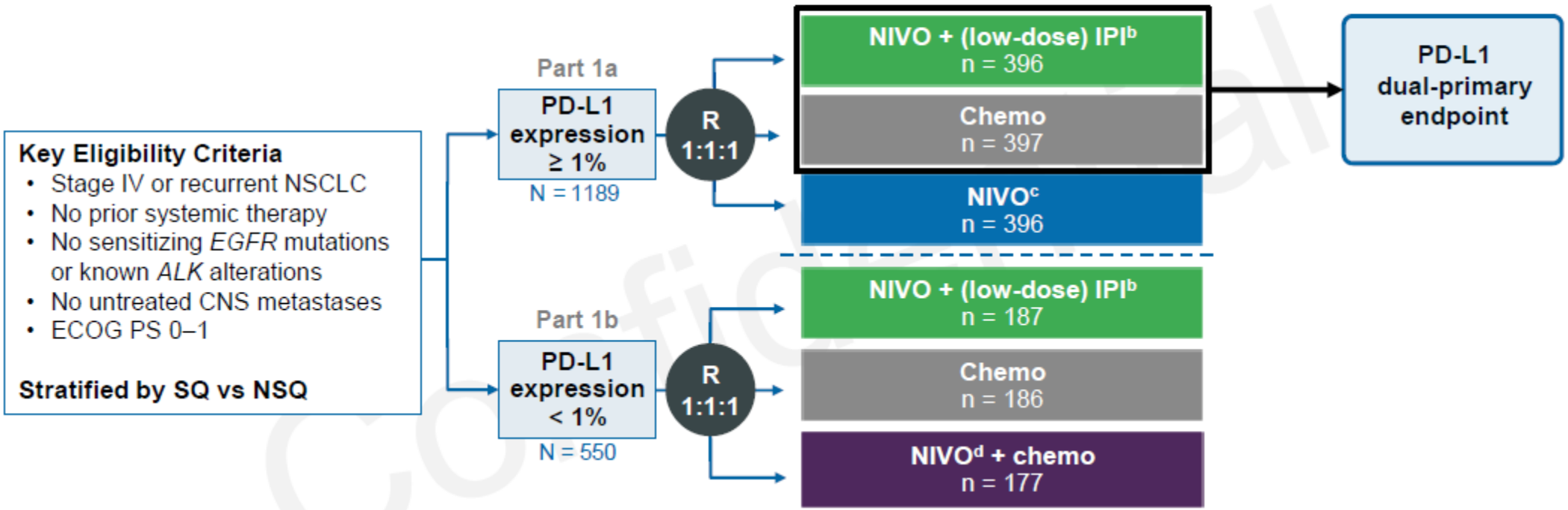
CheckMate 227 Part 1 Study Design[a]



Dual-primary endpoints: NIVO + IPI vs chemo

- PFS in high TMB populations[e]
- OS in PD-L1 ≥ 1% populations[f]

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

Study treatments continued until disease progression, unacceptable toxicity, or for 2 years for immunotherapy.

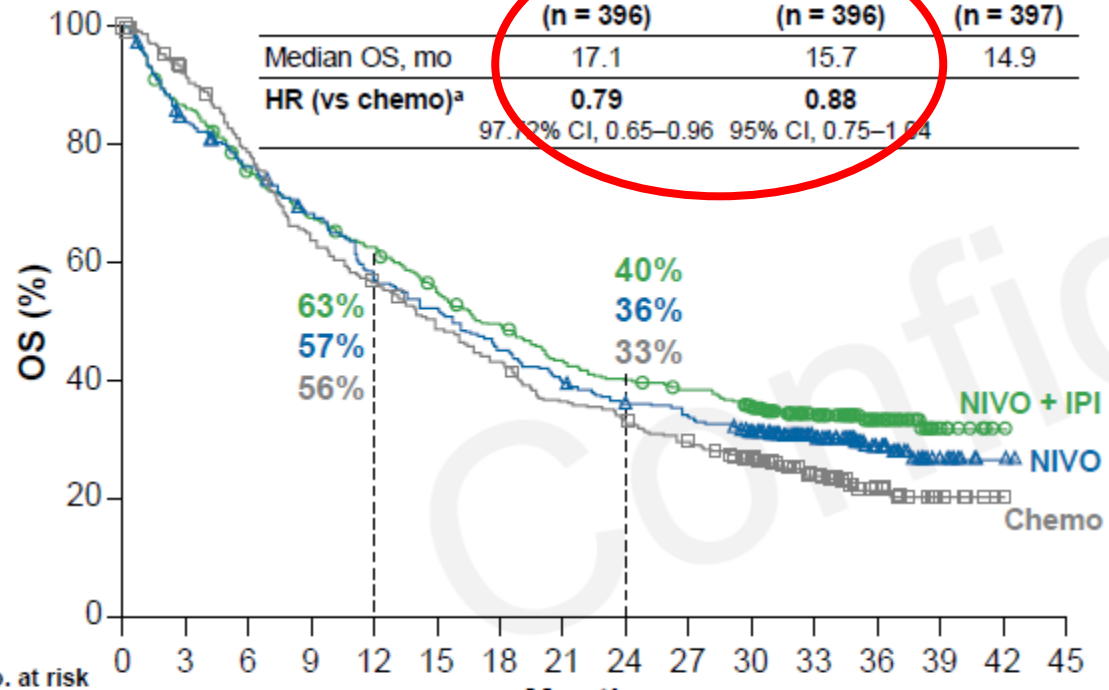
[a]NCT02477826; [b]NIVO (3 mg/kg Q2W) plus IPI (1 mg/kg Q6W); [c]NIVO (240 mg Q2W); [d]NIVO (360 mg Q3W); [e]TMB dual-primary endpoint analysis conducted at January 24, 2018 database lock in subset of patients randomized to NIVO + IPI or chemo; alpha allocated was 0.025; [f]Alpha allocated was 0.025 overall (0.023 for final analysis)

OS and PFS With NIVO + IPI vs NIVO vs Chemo in Patients With Tumor PD-L1 Expression ≥ 1%

Part 1a
NIVO + IPI
Chemo
NIVO

OS

	NIVO + IPI (n = 396)	NIVO (n = 396)	Chemo (n = 397)
Median OS, mo	17.1	15.7	14.9
HR (vs chemo)[a]	0.79	0.88	
	97.7[illegible]% CI, 0.65–0.96	95% CI, 0.75–1.04	

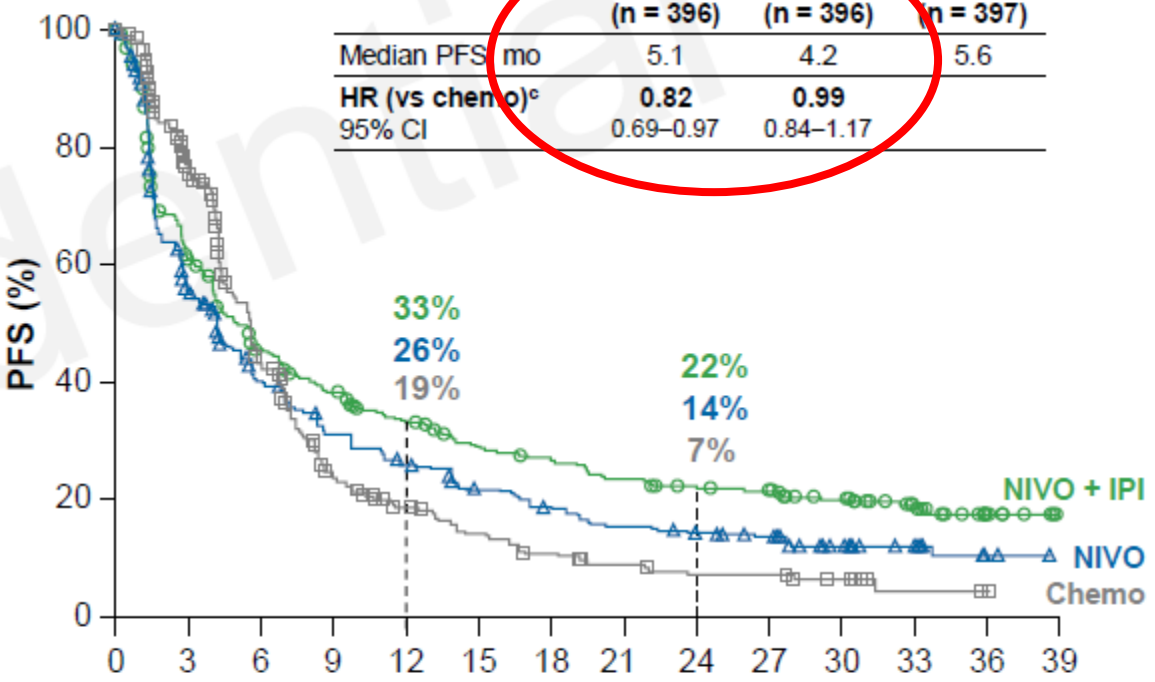


No. at risk

NIVO + IPI	396	341	295	264	244	212	190	165	153	145	129	91	41	9	1	0
NIVO	396	330	299	265	220	201	176	153	139	129	115	70	36	10	2	0
Chemo	397	358	306	250	218	190	166	141	126	112	93	57	22	6	1	0

PFS by BICR

	NIVO + IPI (n = 396)	NIVO (n = 396)	Chemo (n = 397)
Median PFS, mo	5.1	4.2	5.6
HR (vs chemo)[c]	0.82	0.99	
95% CI	0.69–0.97	0.84–1.17	



	396	221	158	130	108	91	83	73	65	62	47	31	7	0
	396	199	136	104	85	68	56	47	42	37	24	15	3	0
	397	253	130	63	44	32	23	17	12	12	8	2	1	0

Dosages were NIVO (3 mg/kg Q2W) plus IPI (1 mg/kg Q6W), and NIVO (240 mg Q2W). Subsequent systemic therapy was received by 35% of patients in the NIVO + IPI arm, 44% in the NIVO arm, and 54% of patients in the chemo arm; subsequent immunotherapy was received by 6%, 8%, and 43%, respectively.
[a]HR (95% CI) for NIVO + IPI vs NIVO, 0.90 (0.76–1.07); [b]HR (95% CI) for NIVO + IPI vs NIVO, 0.83 (0.71–0.97).

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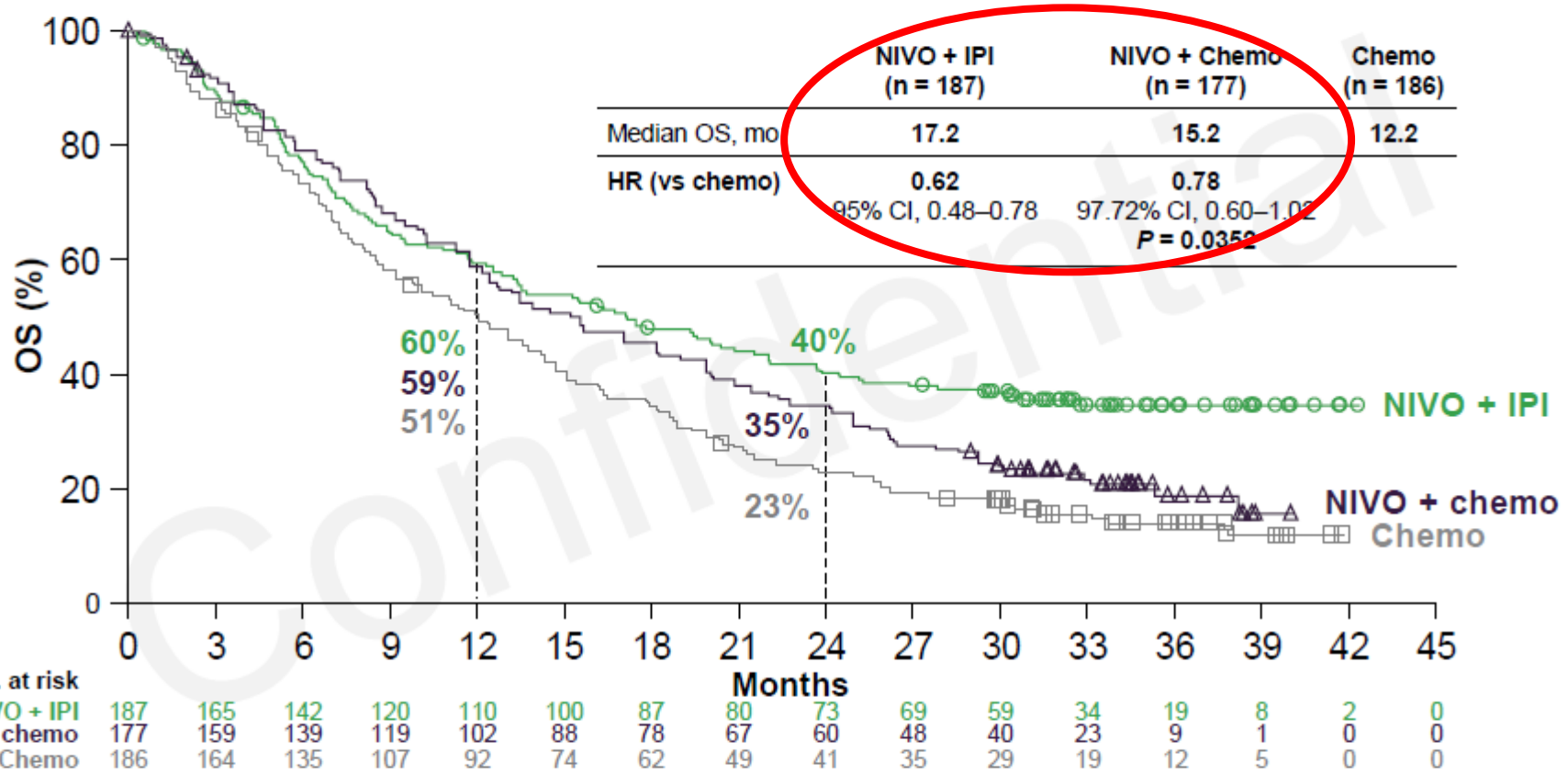
OS With NIVO + IPI and NIVO + Chemo vs Chemo in Patients With Tumor PD-L1 Expression < 1%

Part 1b
NIVO + IPI
Chemo
NIVO + chemo



- PFS for NIVO + chemo vs chemo (secondary endpoint) in PD-L1 < 1% was met (HR, 0.73; *P* = 0.0070)
- OS for NIVO + chemo vs chemo was not met; subsequent secondary endpoints in the hierarchy are descriptive

Dosages were NIVO (3 mg/kg Q2W) plus IPI (1 mg/kg Q6W), and NIVO (360 mg Q3W) plus chemo. Subsequent systemic therapy was received by 44% of patients in the NIVO + IPI arm, 41% in the NIVO + chemo arm, and 53% of patients in the chemo arm; subsequent immunotherapy was received by 4%, 4%, and 36%, respectively. Among patients with PD-L1 <1%, patients were randomized 1:1:1 across treatment arms.

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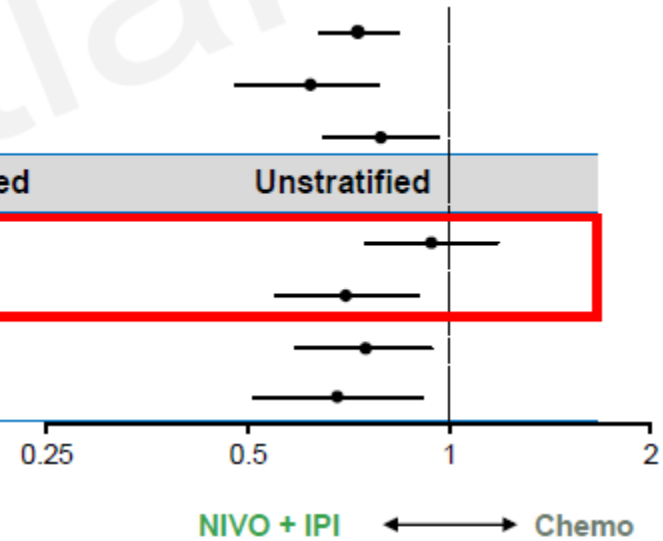
OS for NIVO + IPI vs Chemo By Tumor PD-L1 Expression, TMB Status, and Combined Subgroups in All Randomized Patients

		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 not controlled by randomization				**Unstratified**	**Unstratified**
PD-L1	1–49% (n = 396)	15.1	15.1	0.94	
	≥ 50% (n = 397)	21.2	14.0	0.70	
TMB[b] (mut/Mb)	low, < 10 (n = 380)	16.2	12.6	0.75	
	high, ≥ 10 (n = 299)	23.0	16.4	0.68	



(modified from Peters ESMO 2019)

[a]Stratified HR (97.72% CI); [b]Unstratified HR for NIVO + IPI vs chemo in TMB evaluable (n = 679) and non evaluable (n = 487) patients was 0.74 (95% CI, 0.61–0.88) and 0.74 (95% CI, 0.60–0.92), respectively.

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

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

- With 18 months more follow-up, safety was consiste
- Median duration of therapy (range) was 4.2 mo (0.03 2.6 mo (0.03–37.6+) with chemo

Event	KN-189 Pembrolizumab Combination (N=405)	
	Any Grade	Grade 3, 4, or 5
		number of p
Any event	404 (99.8)	272 (67.2)
Event leading to discontinuation of all treatment†	56 (13.8)	48 (11.9)

Dosages were NIVO (3 mg/kg Q2W) plus IPI (1 mg/kg Q6W), and NIVO (240 mg Q2W).
[a]Includes events reported between first dose and 30 days after last dose of study drug; [b]Study tr than NIVO occurred in 3% of patients; [d]Treatment-related deaths in the NIVO + IPI arm were pne the NIVO arm were pneumonitis, and critical neutropenia and sepsis; deaths in the chemo arm w disease, and thrombocytopenia.

1. Hellmann MD et al. *N Engl J Med* 2018;378:2093–2104.

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Conclusions Authors

- CheckMate 227 is the first phase 3 randomized trial to show **NIVO + IPI vs chemo** is **effective** in NSCLC
- **NIVO + IPI** represents a **first-line treatment option** for patients with NSCLC with the potential to provide a long-term OS benefit, and preserve chemo treatment options in the second-line setting

However (Discussant Dr Sanjay Popat):

- In PDL1+ OS benefit driven by ≥50% group, beware the trAEs & discontinuation rate for similar OS benefit with IO mono & less toxicity.
- A potential role in PDL1-negatives, but not seemingly better than chemo-pembro and with notable toxicities.
- Is nivo-ipi the preferred clinical option? This depends on other treatment options and balance of efficacy and safety (patient individualization).
- **Comment** (also pointed out by Dr. Popat): will nivo-ipi improve the "tail" of the OS curve due to an ipi effect maintaining long term survivors?

OUDEREN ?

PBS NEWS HOUR

Doctors want to give their cancer patients every chance. But are they pushing off hard talks too long?

By – Bob Tedeschi, STAT

The New York Times

The Problem With Miracle Cancer Cures

By Robert M. Wachter

KHN KAISER HEALTH NEWS

TREATING CANCER: HOPE VS. HYPE

Widespread Hype Gives False Hope To Many Cancer Patients

The ASCO Post

The Challenge of Prognostication in the Era of Immunotherapy

EDITORIAL | VOLUME 19, ISSUE 7, P845, JULY 01, 2018

Immunotherapy: hype and hope

The Lancet Oncology

Published: July, 2018 • DOI: https://doi.org/10.1016/S1470-2045(18)30317-6 •

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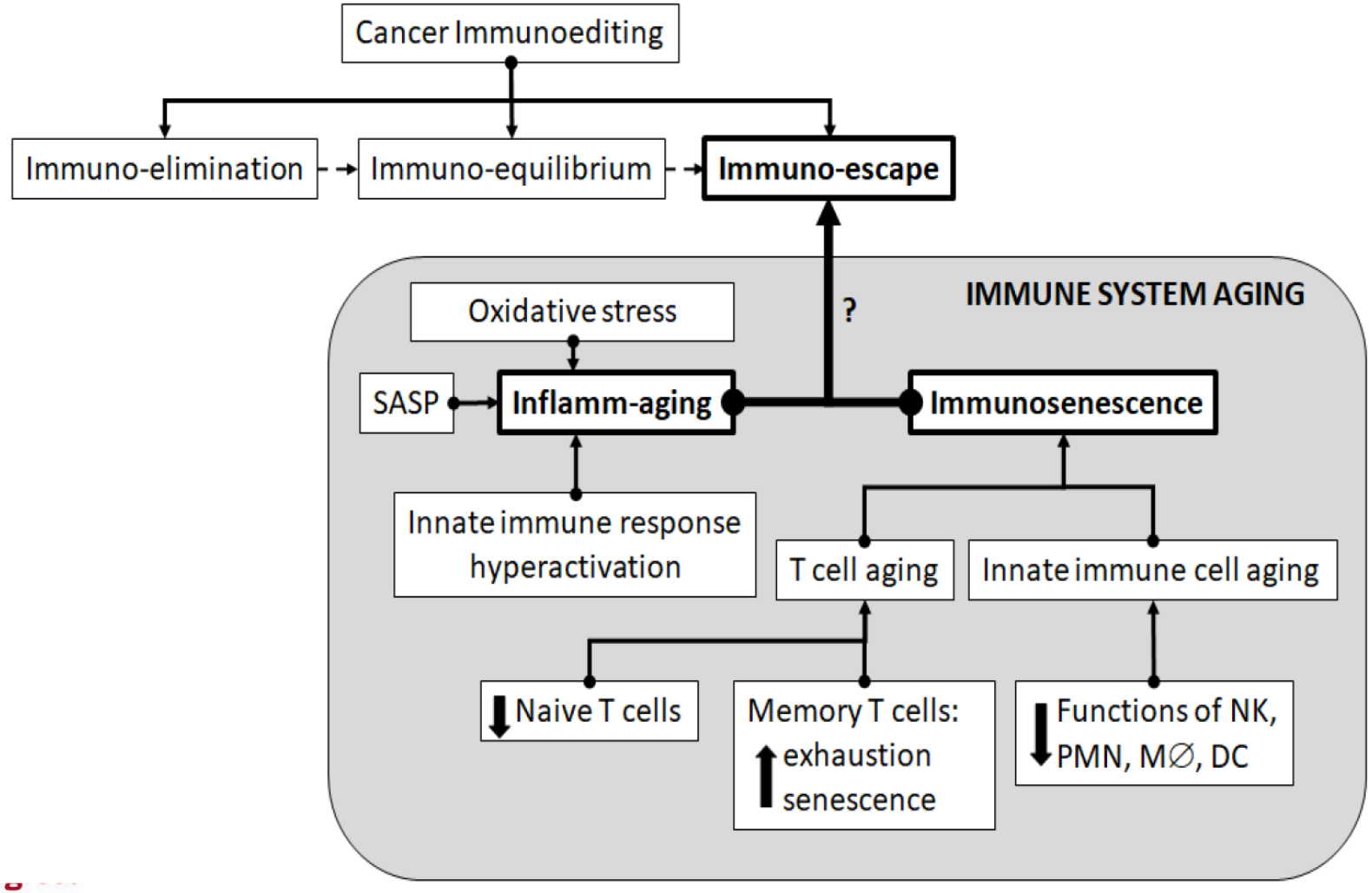
Verouderd immuunsysteem en kanker ontwikkeling



Slide witkowski esmo 2019 – basics in immunotherapy Springer 2019

Zijn er data bij oudere NSCLC patiënten en immunotherapie?

Safety and Efficacy of Pembrolizumab Monotherapy in Elderly Patients With PD-L1 Positive Advanced NSCLC: Pooled Analysis From KEYNOTE-010, KEYNOTE-024, and KEYNOTE-042

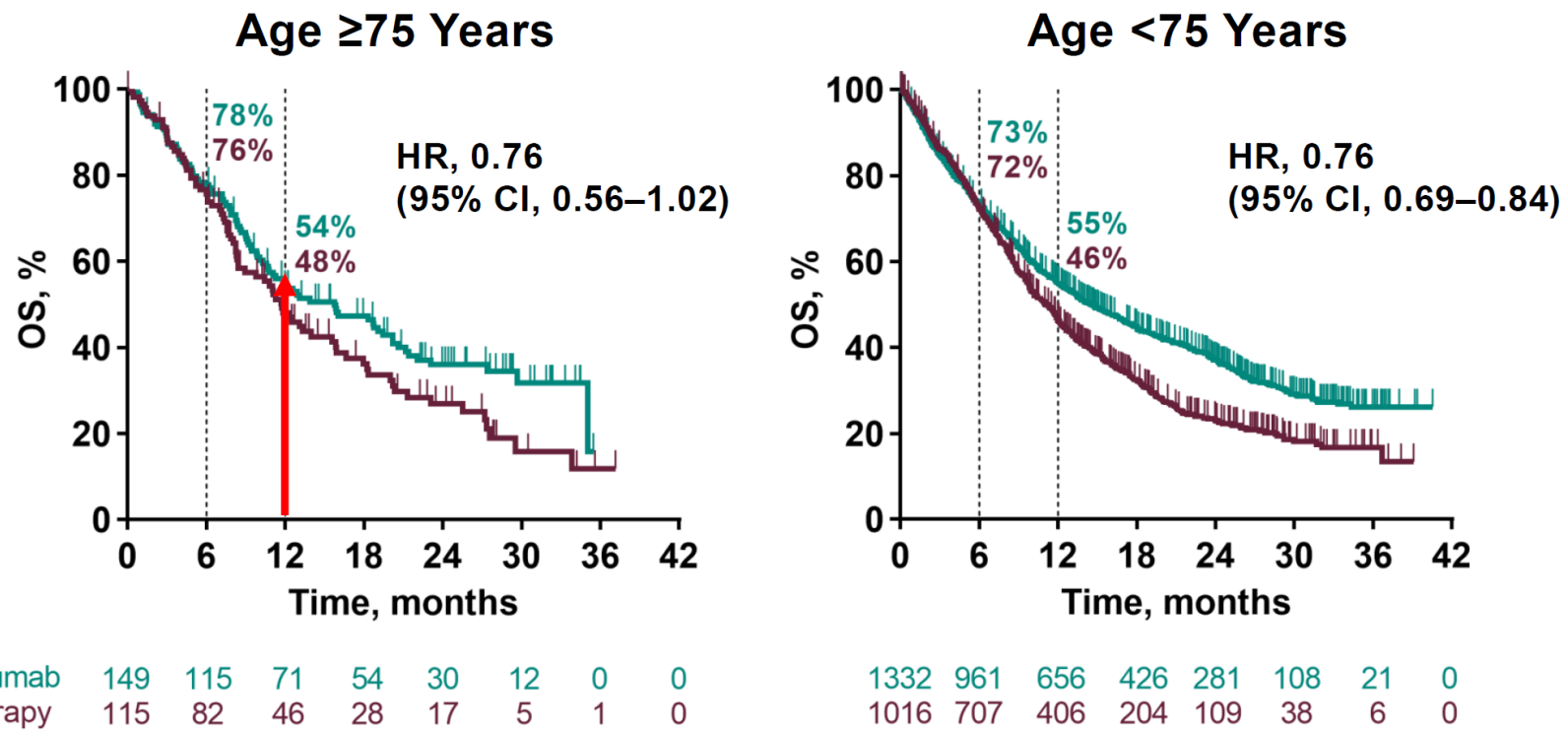
Kaname Nosaki[1]; Yukio Hosomi[2]; Hideo Saka[3]; Paul Baas[4]; Giberto de Castro Jr[5]; Martin Reck[6]; Yi-Long Wu[7]; Julie R. Brahmer[8]; Enriqueta Felip[9]; Takeshi Sawada[10]; Kazuo Noguchi[10]; Shi Rong Han[10]; Bilal Piperdi[11]; Debra A. Kush[11]; Gilberto Lopes[12]

264/2612 = 10% ouderen

Overleving ouderen versus jongeren

Kaplan-Meier Estimate of OS

PD-L1 TPS ≥1% (KN010, KN024, KN042)



No. at risk

Pembrolizumab	149	115	71	54	30	12	0	0
Chemotherapy	115	82	46	28	17	5	1	0

1332	961	656	426	281	108	21	0
1016	707	406	204	109	38	6	0

Data cutoff dates: KN010, March 24, 2017; KN024, May 9, 2016; KN042, February 26, 2018.

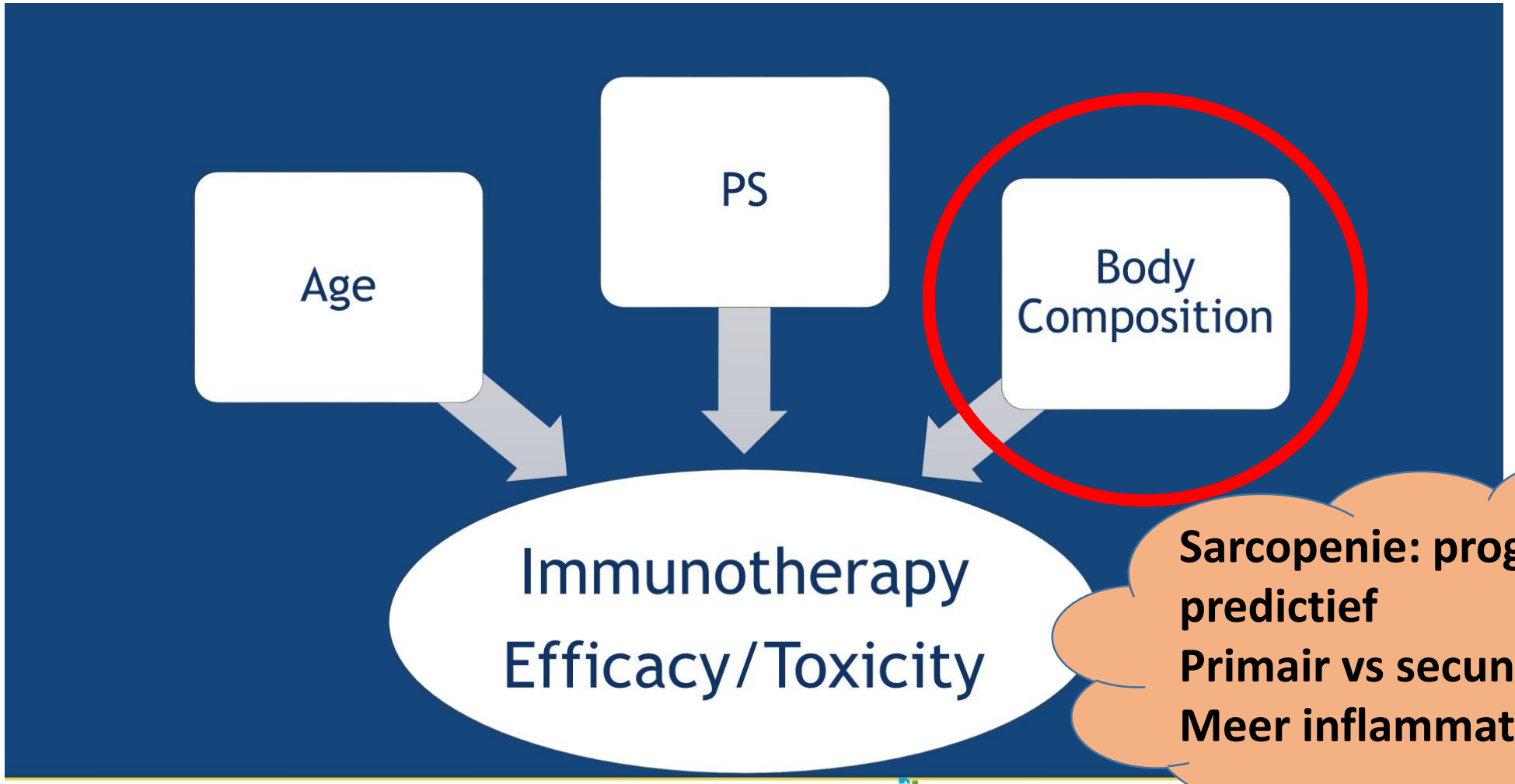
Geldt voor iedere PD-L1 subgroep

Geen relevante verschillen in bijwerkingen

Waar letten we bij ouderen nu op bij immunotherapie?

Presented By Rawad Elias at 2019 ASCO Annual Meeting

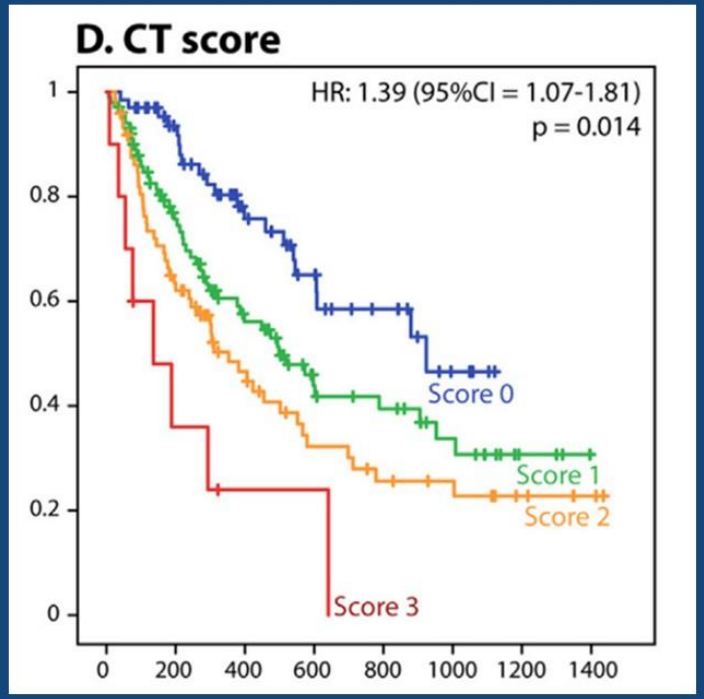
Wat heeft naast leeftijd en conditie invloed?



Sarcopenie: prognostisch en predictief
Primair vs secundair
Meer inflammatoire markers

Immunotherapy & Body Composition: Efficacy

- 251 Patients on Phase-1 Trials
- Prognostic Score: PS3-CT
- PS3-CT:
  - High Tumor Burden (> 9 cm)
  - Low Skeletal Muscle Index (< 53 cm^2 m^{-2})
  - Non-Pulmonary Visceral Metastases



Ook meer toxiciteit!

Dercle et al. Eur J Cancer 2016

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Stelling I

- Ouderen moeten in aanmerking komen voor immunotherapie voor longkanker
  - Ip JA maar…

Stelling II

- Immunotherapie is niet zo effectief bij ouderen als bij jongeren
  - Ip NEE maar..

Vragen ?

MPM

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

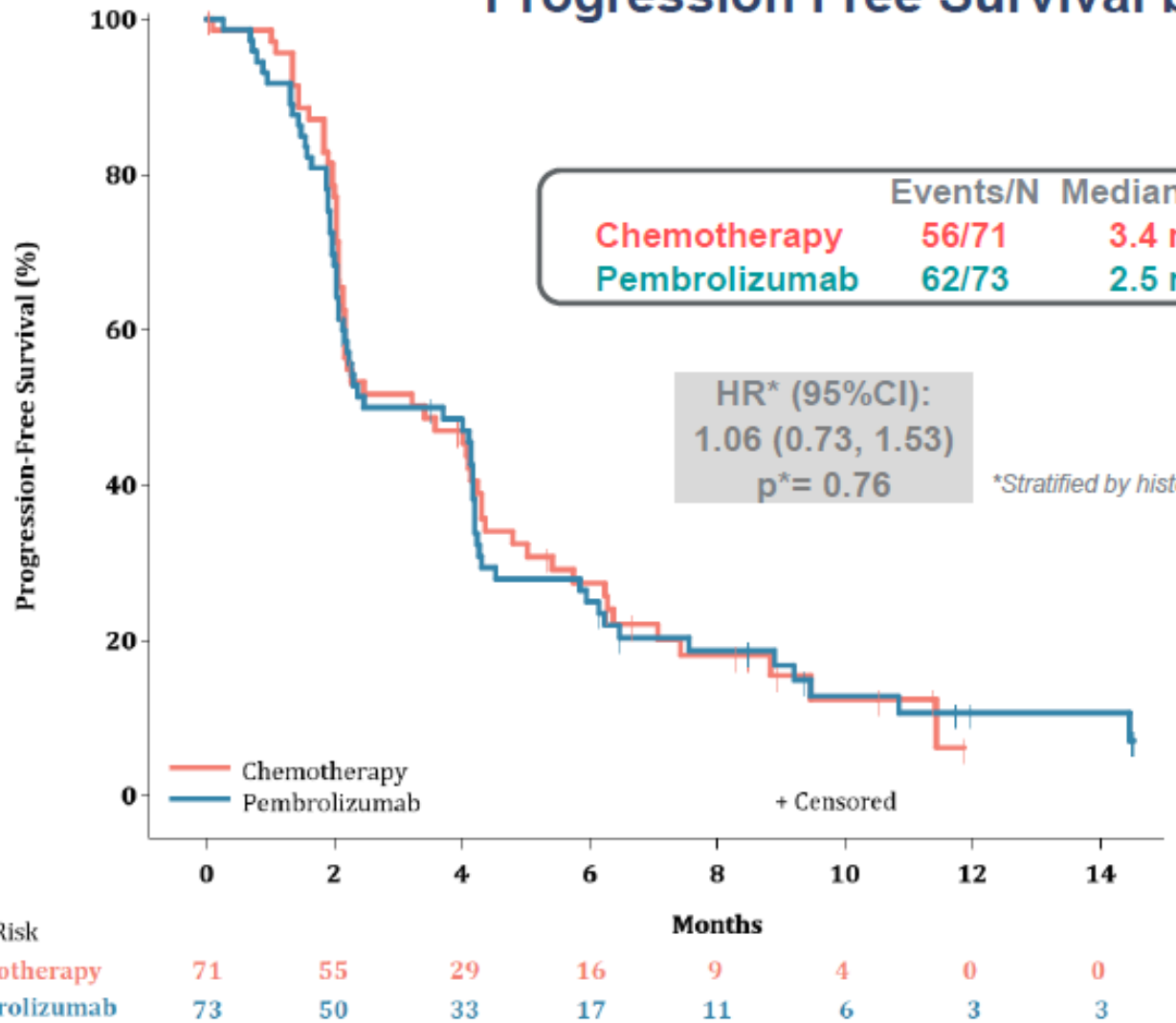
Primary endpoint:
Progression-free survival (PFS) assessed by independent radiology review (IRR)

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

Popat S et al, Abstract 1665, Proferred Paper 30 Sep

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

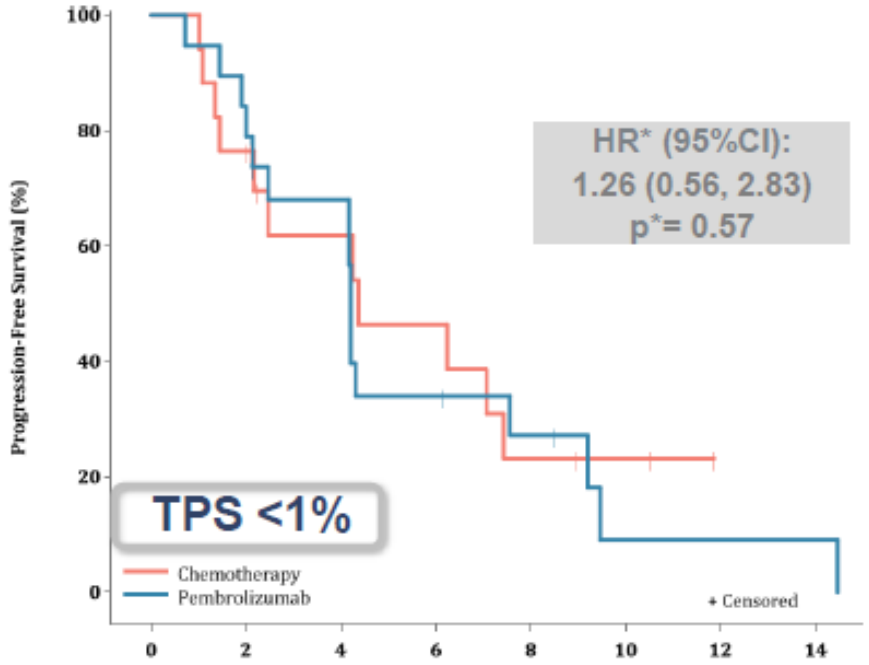
**Stratified by histological subtype*

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

Popat S et al, Abstract 1665

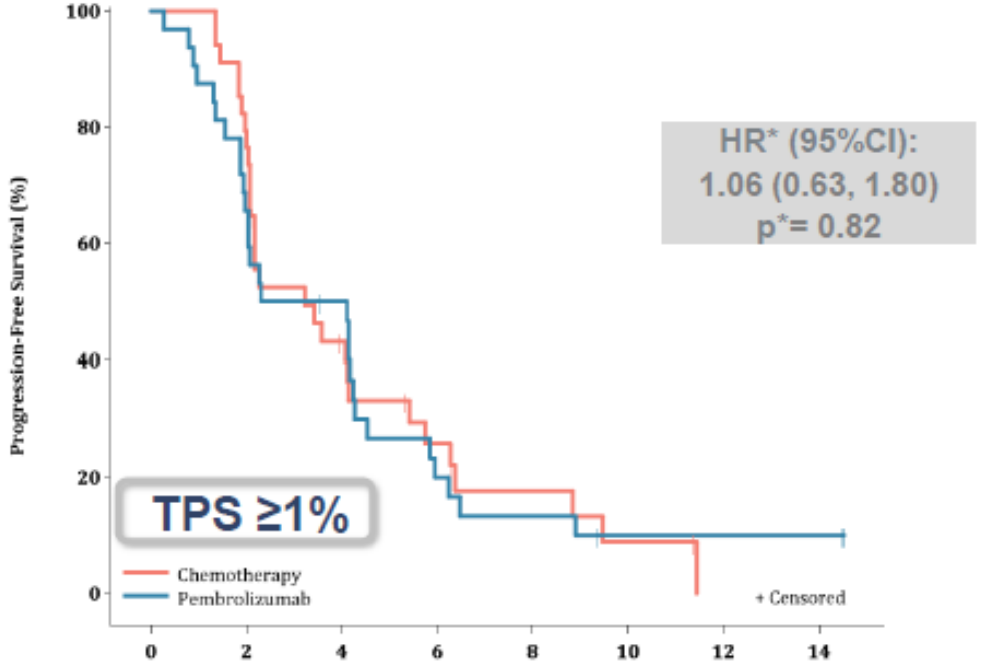
PFS (IRR) by PD-L1 status

	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)



No at Risk								
Chemotherapy	17	13	8	6	3	2	0	
Pembrolizumab	19	16	12	6	4	1	1	1

	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)



No at Risk								
Chemotherapy	34	27	13	7	4	2	0	
Pembrolizumab	32	21	15	6	4	2	2	2

*Stratified by histological subtype

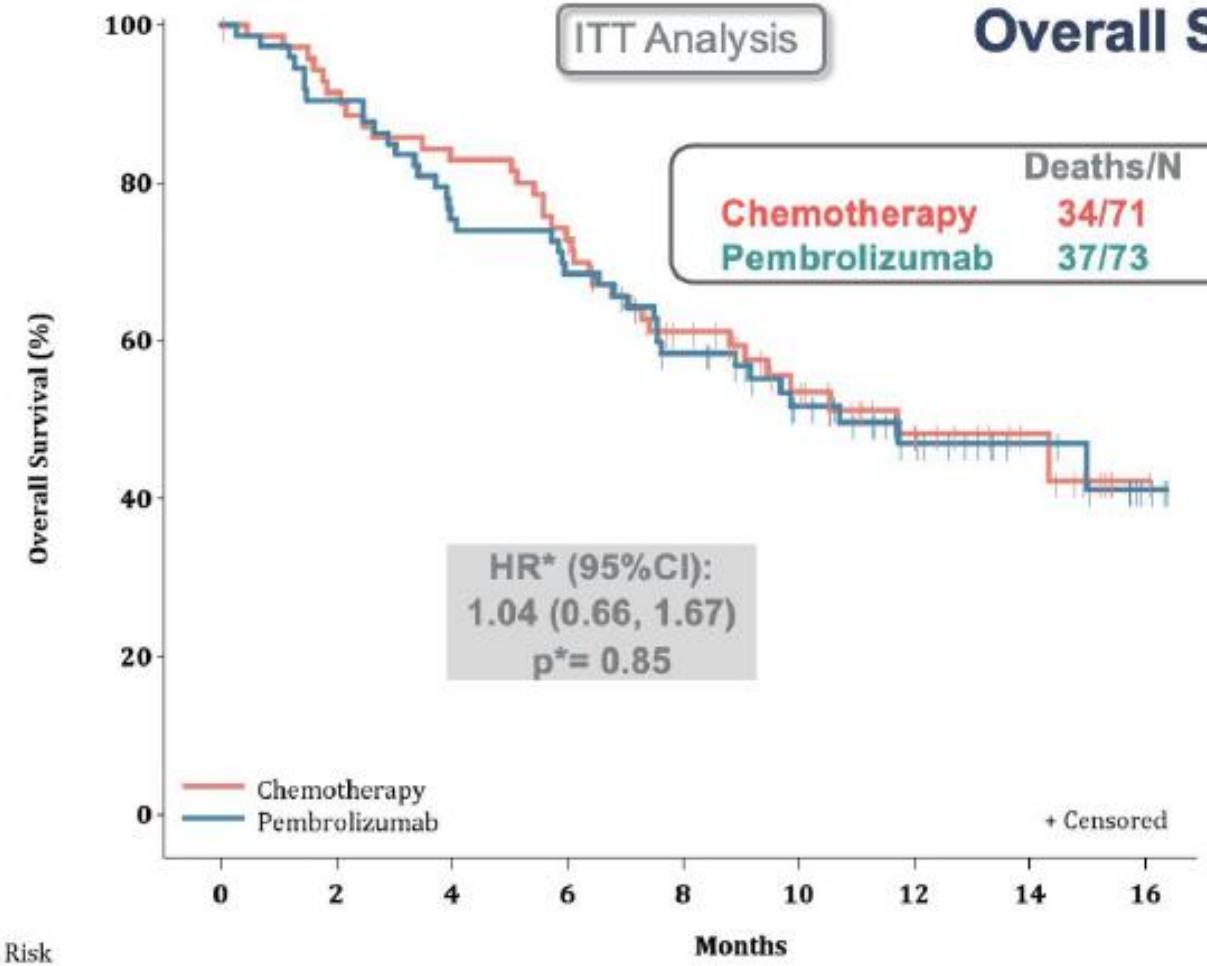
Popat S et al, Abstract 1665

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

Popat S et al, Abstract 1665

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

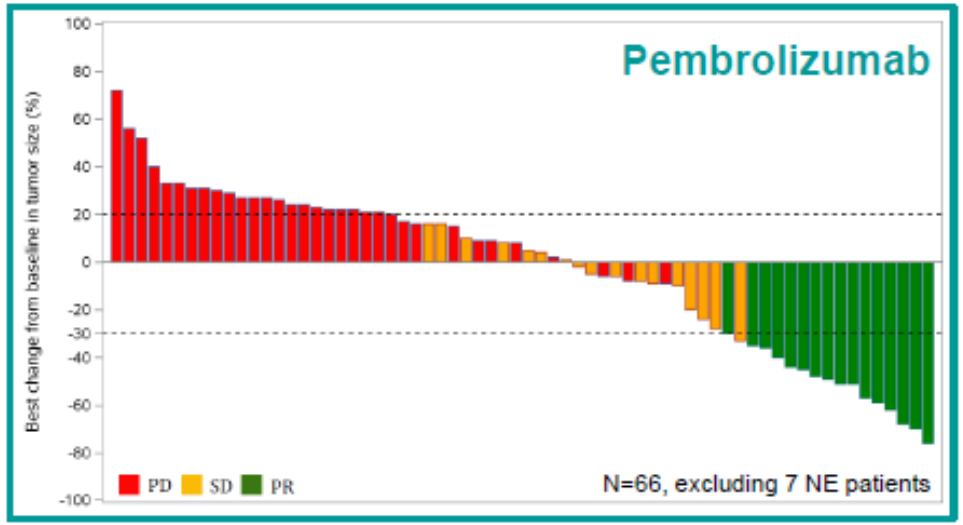
	Pembrolizumab N (%)	Chemotherapy N (%)
ORR (95% CI)	**22% (13%, 33%)**	**6% (2%, 14%)**
Partial response (PR)	16 (21.9)	4 (5.6)
Stable Disease (SD)	17 (23.3)	23 (32.4)
Progression of Disease (PD)	33 (45.2)	35 (49.3)
Not Evaluable (NE)	7 (9.6)	9 (12.7)
Median DOR* (95% CI)	**4.6 months (2.2, 10.3)**	**11.2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

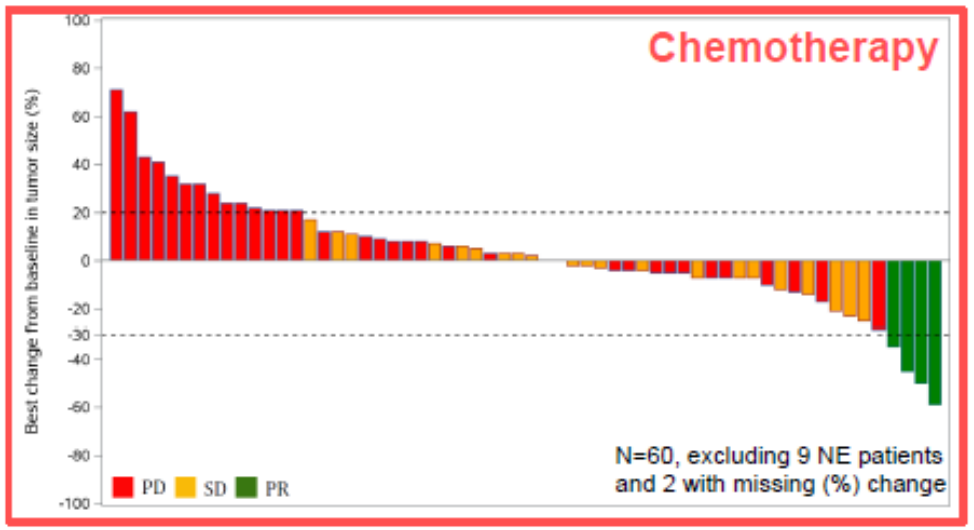
→ Stratified p=0.004

* Updated as of August 2019

16 responders
→ 7 PD and 4 deaths

4 responders
→ 3 PD





Popat S et al, Abstract 1665

etop
Information | Research

SCLC

IASLC
INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER
IASLC 19th World Conference on Lung Cancer
September 23–26, 2018 Toronto, Canada
WCLC2018.IASLC.ORG
#WCLC2018

IMpower133: Primary PFS, OS, and safety in a Ph1/3 study of 1L atezolizumab + carboplatin + etoposide in extensive-stage SCLC

S. V. Liu,[1] A. S. Mansfield,[2] A. Szczesna,[3] L. Havel,[4] M. Krzakowski,[5] M. J. Hochmair,[6] F. Huemer,[7] G. Losonczy,[8] M. L. Johnson,[9] M. Nishio,[10] M. Reck,[11] T. Mok,[12] S. Lam,[13] D. S. Shames,[13] J. Liu,[14] B. Ding,[13] F. Kabbinavar,[13] W. Lin,[13] A. Sandler,[13] L. Horn[15]

[1]Georgetown University, Washington DC, USA; [2]Mayo Clinic, Rochester, MN, USA; [3]Mazowieckie Centrum Leczenia Chorób Płuc i Gruźlicy, Otwock, Poland; [4] Thomayerova Nemocnice, Pneumologická Klinika 1.LF UK, Prague, Czech Republic; [5]Centrum Onkologii-Instytut im. M. Skłodowskiej-Curie w Warszawie, Warsaw, Poland; [6]Department of Respiratory and Critical Care Medicine & Ludwig Boltzmann Institute for COPD & Respiratory Epidemiology – Baumgartner Höhe, Otto-Wagner-Spital, Vienna, Austria; [7]2nd Department of Respiratory and Critical Care Medicine & Ludwig Boltzmann Institute for COPD & Respiratory Epidemiology – Baumgartner Höhe, Otto-Wagner-Spital, Vienna, Austria; [8]Semmelweis Egyetem ÁOK, Pulmonológiai Klinika, Budapest, Hungary; [9]Sarah Cannon Research Institute/Tennessee Oncology PLLC, Nashville, TN, USA; [10]The Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan; [11]LungClinic Grosshansdorf, Airway Research Center North (ARCN), German Center for Lung Research, Grosshansdorf, Germany; [12]State Key Laboratory of South China, The Chinese University of Hong Kong, Hong Kong, China; [13]Genentech, Inc., South San Francisco, CA, USA; [14]F. Hoffmann-La Roche, Ltd., Shanghai, China; [15]Vanderbilt University Medical Center, Nashville, TN, USA

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BARCELONA 2019 ESMO congress

IMPOWER133: UPDATED OVERALL SURVIVAL (OS) ANALYSIS OF FIRST-LINE (1L) ATEZOLIZUMAB (ATEZO) + CARBOPLATIN + ETOPOSIDE IN EXTENSIVE-STAGE SCLC (ES-SCLC)

Martin Reck,[1] Stephen V. Liu[2], Aaron S. Mansfield[3], Tony Mok[4], Arnaud Scherpereel[5], Niels Reinmuth[6], Marina Chiara Garassino[7], Javier De Castro Carpeno[8], Raffaele Califano[9], Makoto Nishio[10], Francisco Orlandi[11], Jorge Arturo Alatorre Alexander[12], Ticiana Leal[13], Ying Cheng[14], Jong-Seok Lee[15], Sivuonthanh Lam[16], Mark McCleland[16], Yu Deng[16], See Phan[16], Leora Horn[17]

[1]Lung Clinic Grosshansdorf, Airway Research Center North, German Center of Lung Research, Grosshansdorf, Germany; [2]Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC, USA; [3]Division of Medical Oncology, Mayo Clinic, Rochester, Minnesota, USA; [4]State Key Laboratory of South China, The Chinese University of Hong Kong, China; [5]University of Lille, CHU Lille, Inserm, U1189 - ONCO-THAI - F-59000 Lille, France; [6]Thoracic Oncology, Asklepios Clinics Munich-Gauting, Gauting, Germany; [7]Thoracic Oncology Unit, Instituto Nazionale dei Tumori, Milan, Italy; [8]Hospital Universitario La Paz, Madrid, Spain; [9]Department of Medical Oncology, Christie NHS Foundation Trust, Manchester, UK; [10]The Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan; [11]Instituto Nacional del Tórax, Prosalud Oncología, Santiago, Chile; [12]Health Pharma Professional Research, Mexico City, Mexico; [13]University of Wisconsin Carbone Cancer Center, Madison, WI; [14]Jilin Cancer Hospital, Jilin, China; [15]Seoul National University College of Medicine, Seoul National University Bundang Hospital, Seongnam, South Korea; [16]Genentech, Inc., South San Francisco, CA, USA; [17]Vanderbilt University Medical Center, Nashville, TN, USA

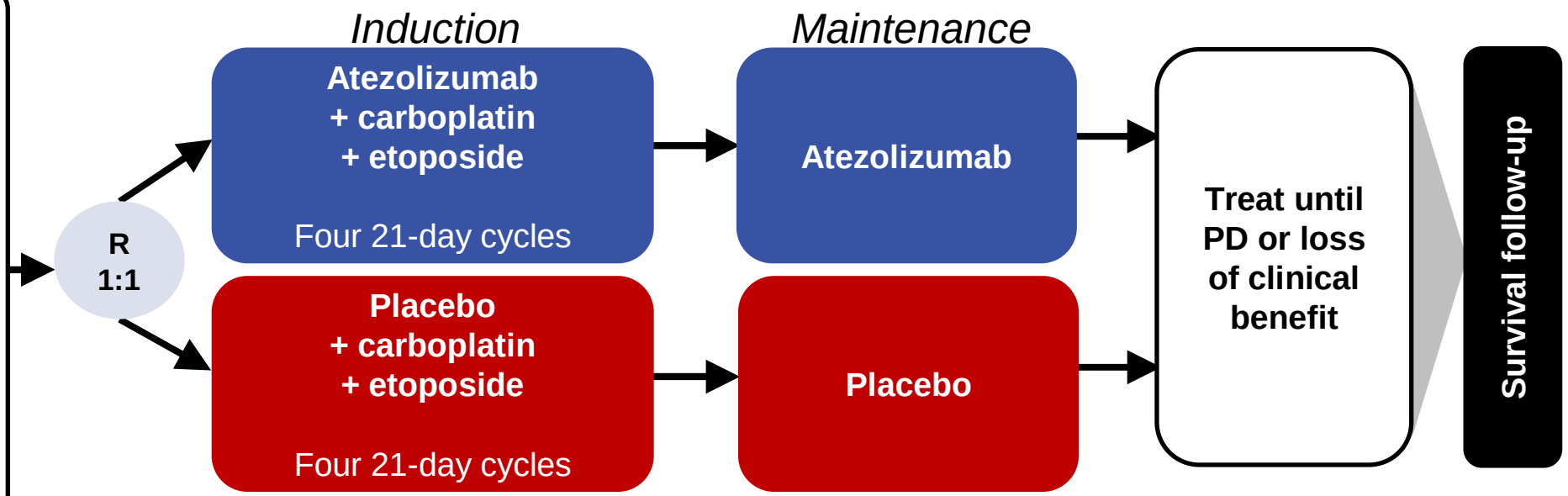
IMpower133 study design

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]



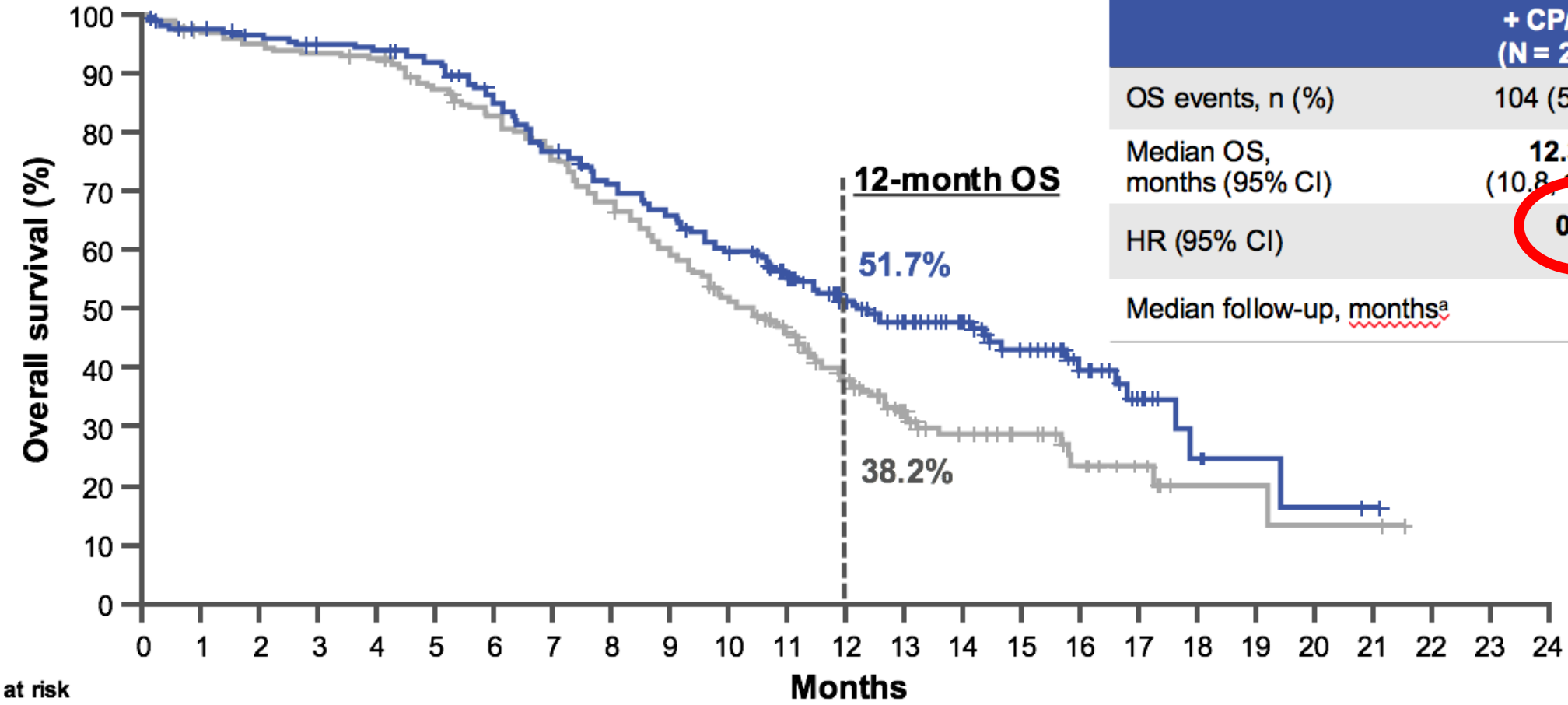
Co-primary end points
- Overall survival
- Investigator-assessed PFS

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.

Overall survival

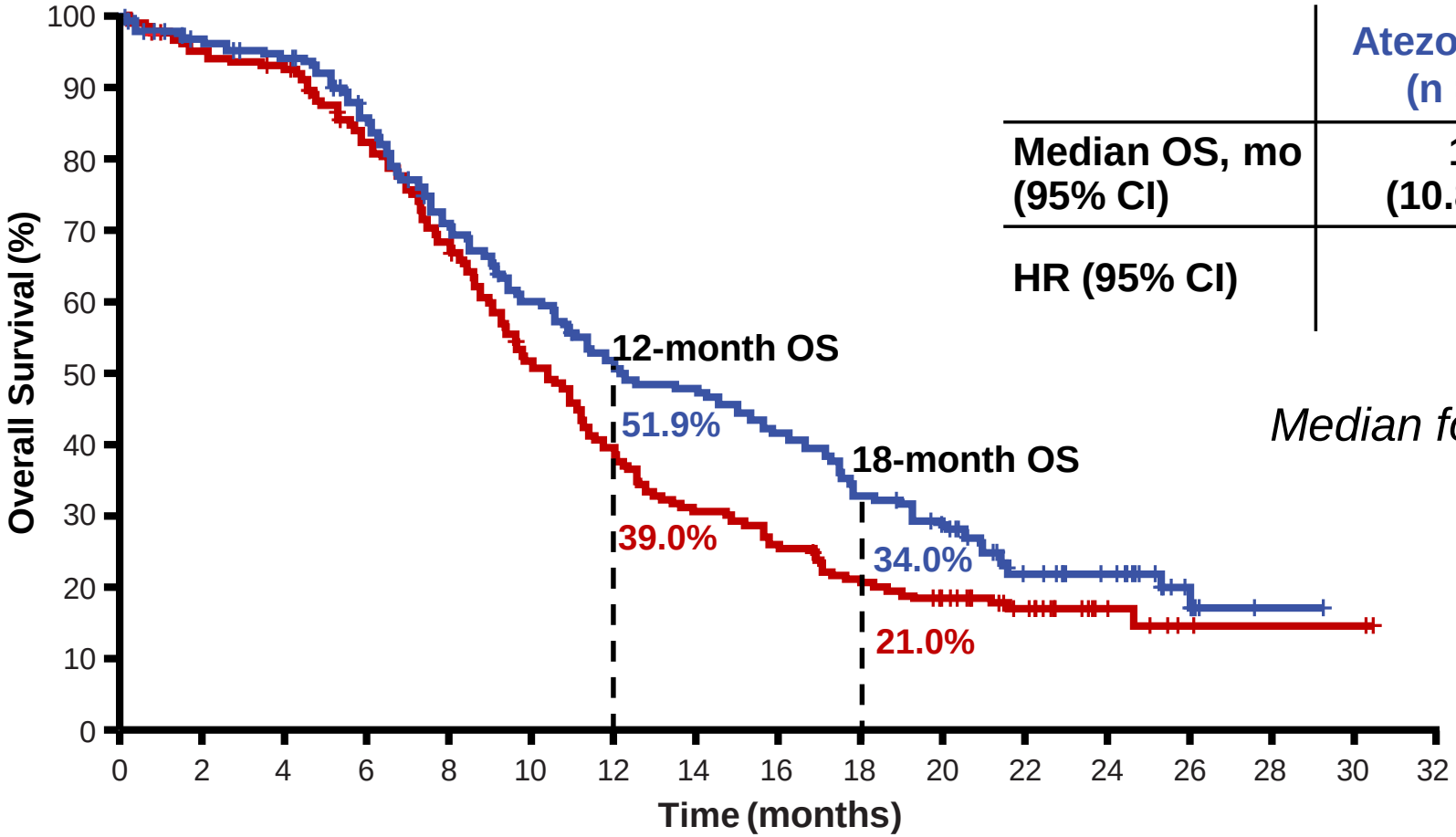


	Atezolizumab + CP/ET (N = 201)	Placebo + CP/ET (N = 202)
OS events, n (%)	104 (51.7)	134 (66.3)
Median OS, months (95% CI)	**12.3** (10.8, 15.9)	**10.3** (9.3, 11.3)
HR (95% CI)	**0.70** (0.54, 0.91) p = 0.0069	
Median follow-up, months[a]	13.9	

No. at risk																						
Atezolizumab	201	191	187	182	180	174	159	142	130	121	108	92	74	58	46	33	21	11	5	3	2	1
Placebo	202	194	189	186	183	171	160	146	131	114	96	81	59	36	27	21	13	8	3	3	2	2

[a] Clinical data cutoff date: April 24, 2018, 11 months after the last patient was enrolled. CI, confidence interval; HR, hazard ratio; CP/ET, carboplatin + etoposide.

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

Commissie BOM:

PASKWIL 2016 superioriteit

Palliatief, effectiviteit

• winst totale overleving	> 12 weken of HR < 0,7	+
• winst progressievrije overleving	> 12 weken of HR < 0,7	+

Gradering volgens ESMO-MCBS (inclusief bijdrage door QoL-analyse)

Bijwerkingen (verschil tussen de behandelarmen)

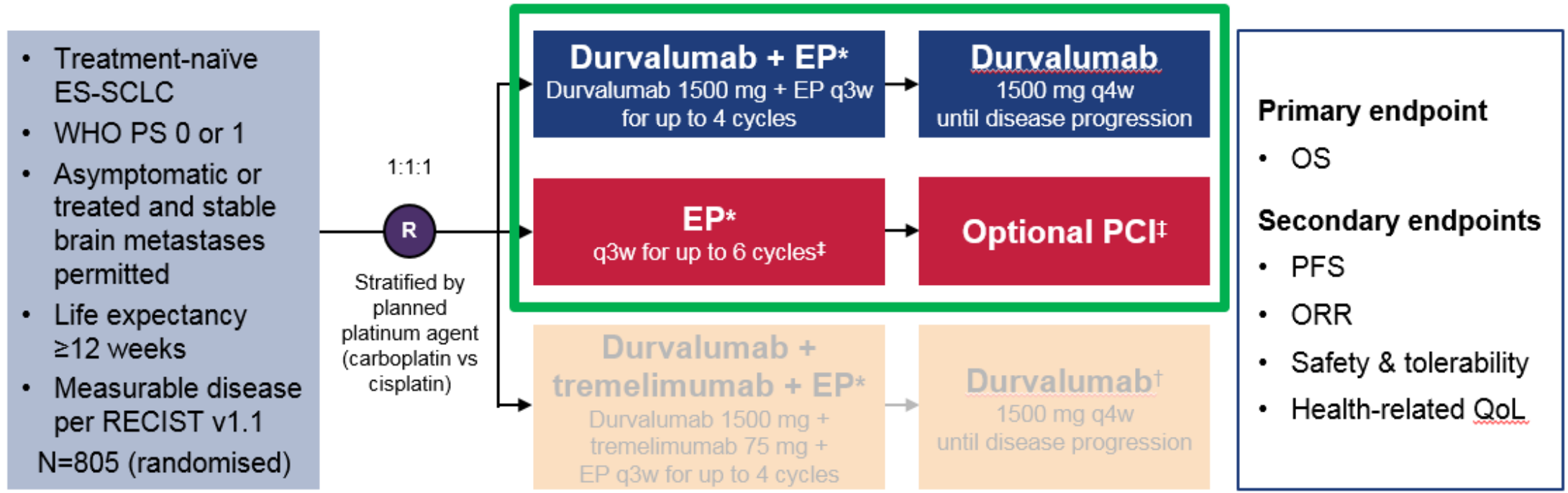
• lethaal (absoluut)	< 5%	+
• acuut, ernstig	< 25%	+
• chronisch beperkend		+

Conclusie

De toevoeging van atezolizumab aan standaard eerstelijns chemotherapie met carboplatine en etoposide bij patiënten met SCLC-ES leidt tot een 2,0 maanden langere OS (12,3 versus 10,3 maanden; HR: 0,70 [95%-BI: 0,54-0,90]; P = 0,007) en een verlenging van de PFS van 0,9 maanden (5,2 versus 4,3 maanden; HR: 0,77 [95%-BI: 0,62-0,96]; P = 0,02). Deze resultaten voldoen niet aan de criteria voor een positief advies volgens de PASKWIL-criteria voor palliatieve behandeling. ←

CASPIAN Study Design

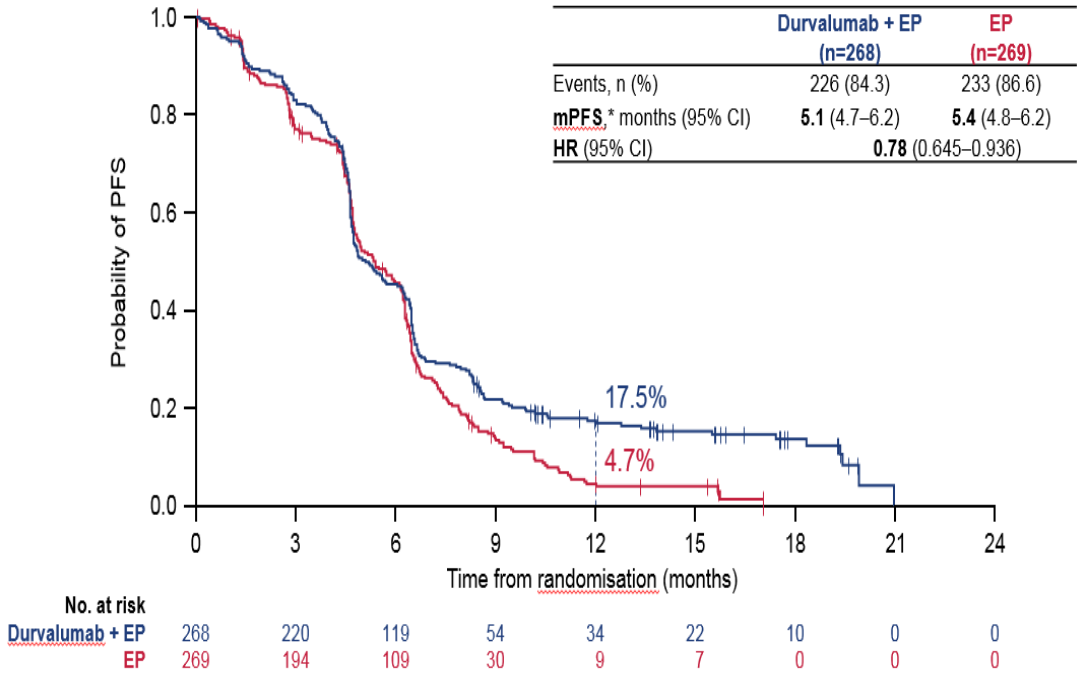
Phase 3, global, randomised, open-label, sponsor-blind multicentre study



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

CASPIAN Study

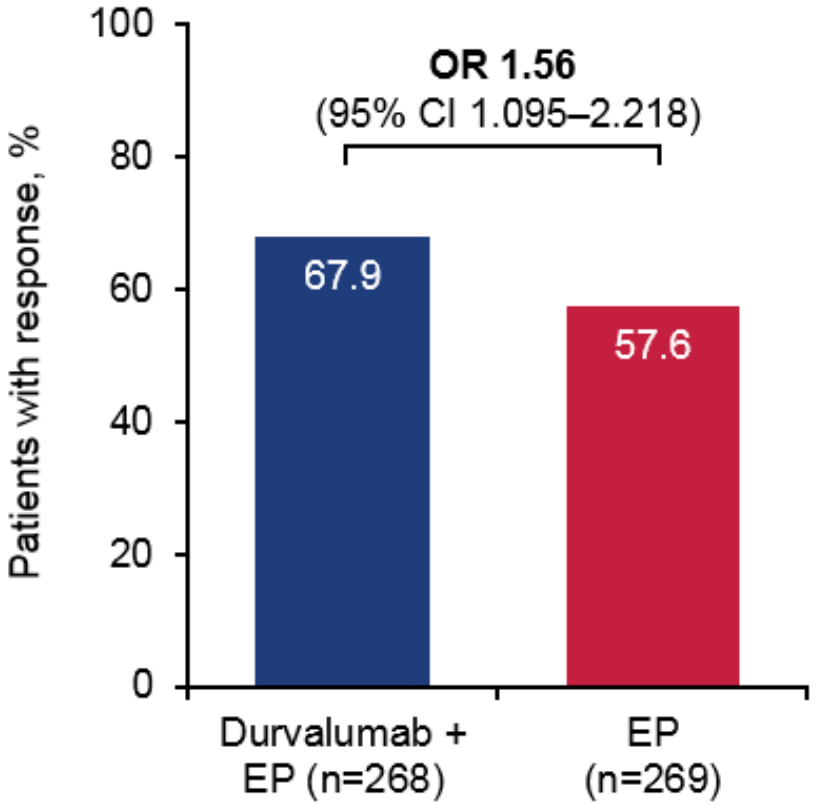
Progression-free Survival



	Durvalumab + EP (n=268)	EP (n=269)
Events, n (%)	226 (84.3)	233 (86.6)
mPFS,* months (95% CI)	**5.1** (4.7–6.2)	**5.4** (4.8–6.2)
HR (95% CI)	**0.78** (0.645–0.936)	

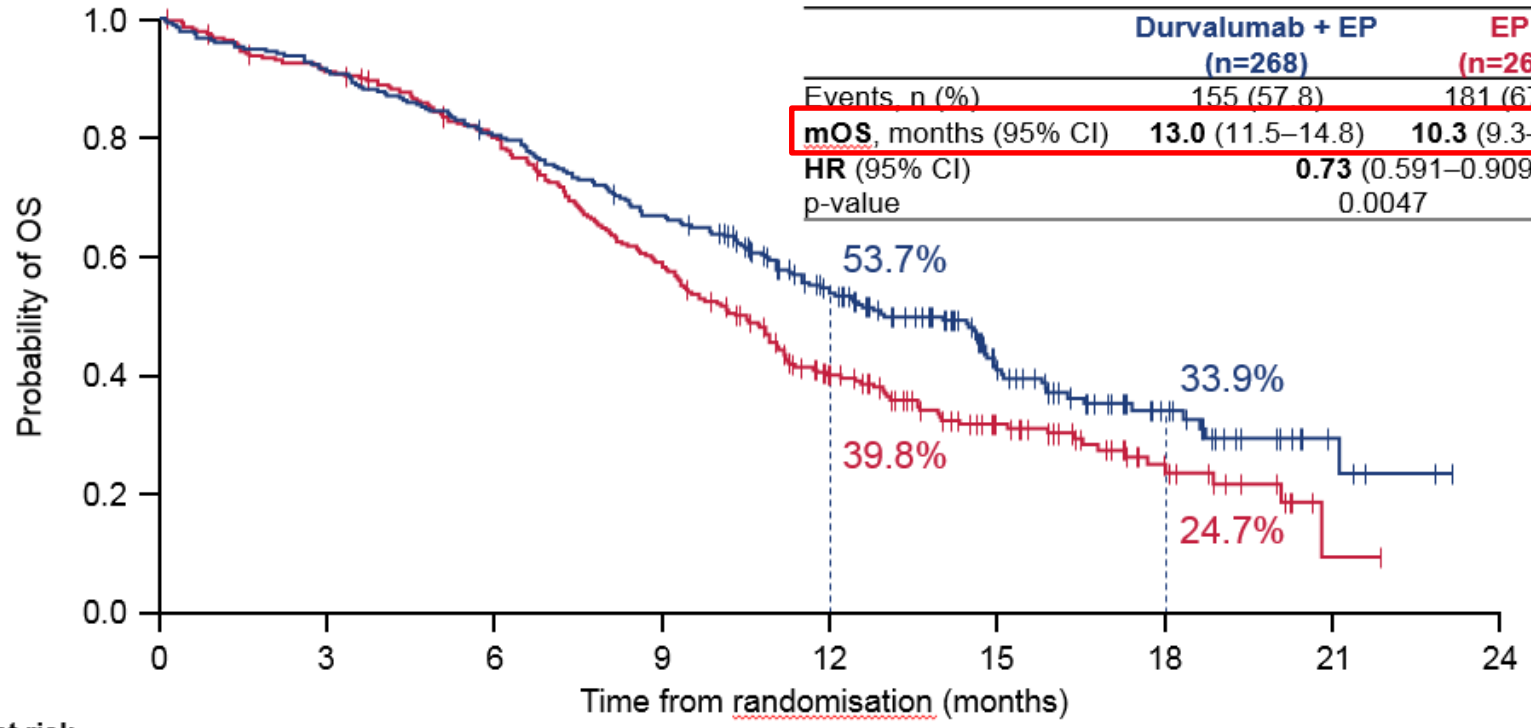
No. at risk									
Durvalumab + EP	268	220	119	54	34	22	10	0	0
EP	269	194	109	30	9	7	0	0	0

ORR*



CASPIAN Study

Overall Survival (Primary Endpoint)



	Durvalumab + EP (n=268)	EP (n=269)
Events, n (%)	155 (57.8)	181 (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

2.7 mnd. = 11.7 wkn

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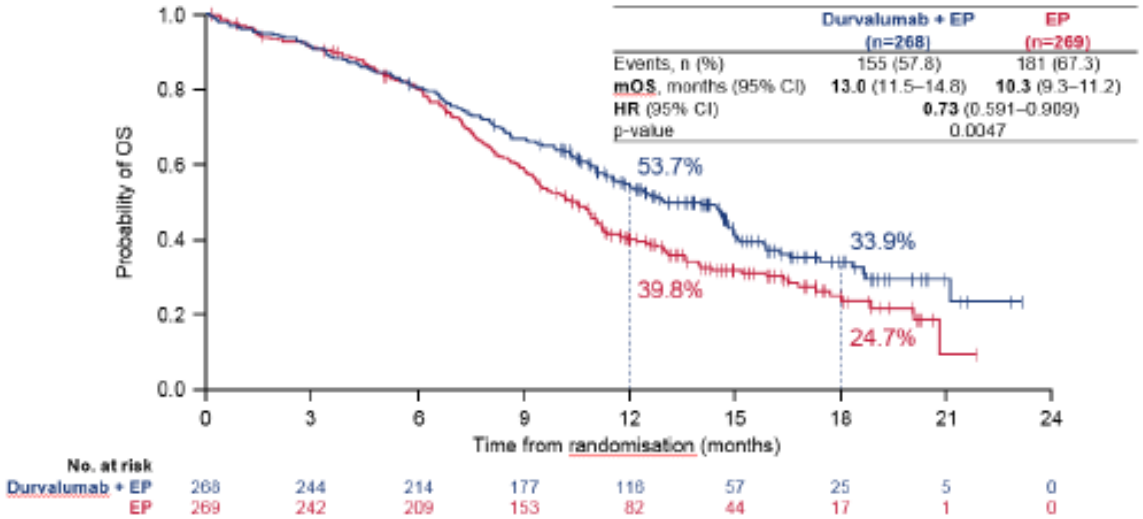
CASPIAN Trial - WCLC - PL02.11

Overall Survival (Primary Endpoint)



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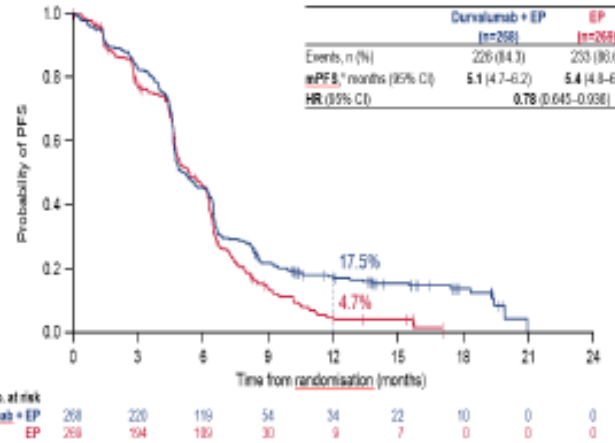
Progression-free Survival



	Durvalumab + EP (n=268)	EP (n=268)
Events, n (%)	226 (84.3)	253 (94.0)
mPFS,* months (95% CI)	**5.1** (4.7–6.2)	**5.4** (4.8–6.2)
HR (95% CI)	**0.78** (0.645–0.936)	

No. at risk									
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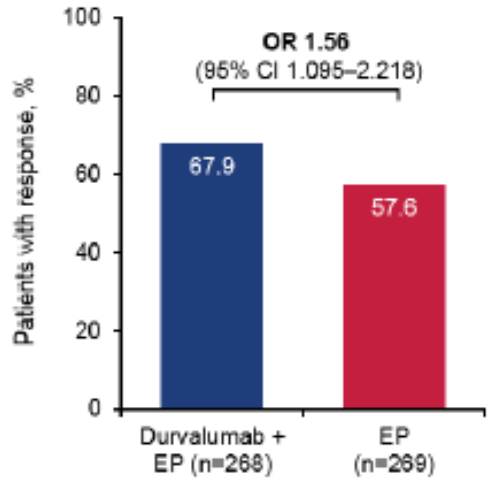
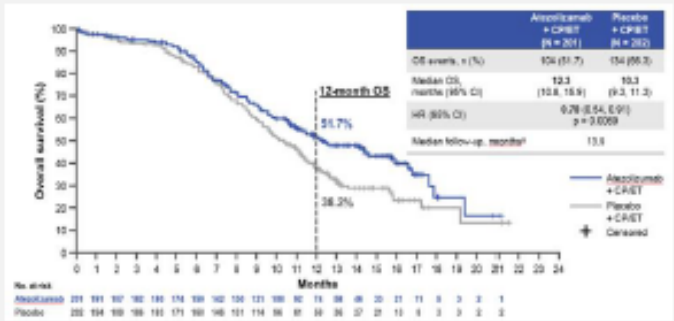
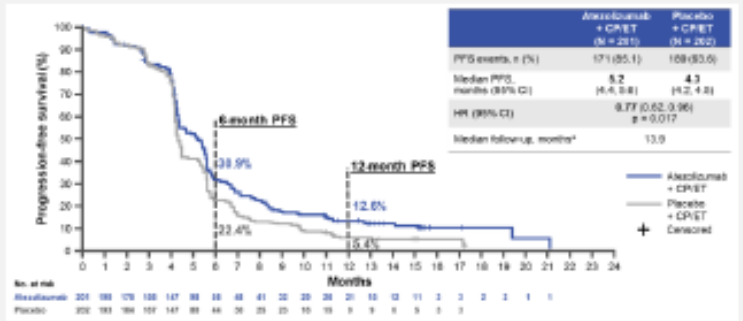
ORR*

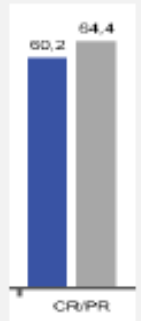


Paz-Ares L et al WCLC 2019

IMpower 133







Horn L et al NEJM 2018

CASPIAN vs IMpower 133

	CASPIAN		IMpower 133	
	Durvalumab+EP (n=268)	EP (n=269)	Atezolizumab +EC (n= 201)	EC + placebo (n=202)
Median age	62	63	64	64
Male,%	70.9	68.4	64	65
White/Asian,%	85.4/13.4	82.2/15.6	81/16	79/18
PS 0/1,%	36.9/63.1	33.5/66.5	36/64	33/67
Smoker,%	91.8	94.4	95.5	98.5
Brain meta,%	10.4	10.0	8	9
Liver meta,%	40.3	38.7	38	36
Study design	Open label	Open label	Placebo control	Placebo control
Carbo/cispla	78.5/24.5	78.2/25.2	100/-	100/-
No.chemo (med)	4	6	4	4
PCI,%	-	8	11	10

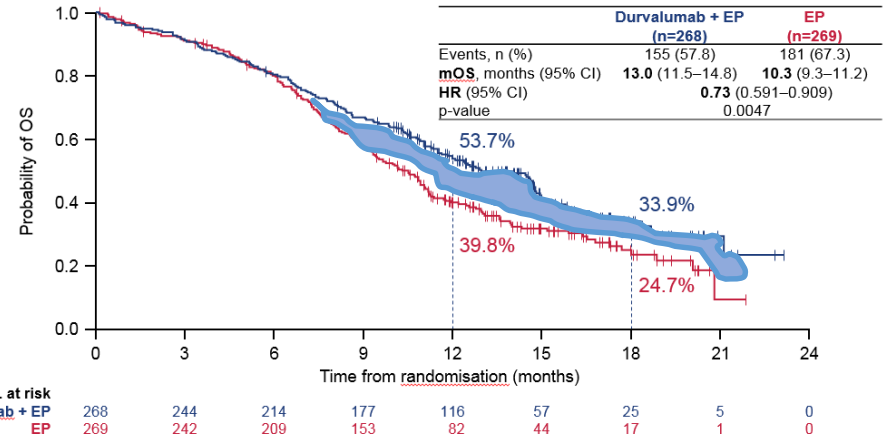
CASPIAN vs IMpower 133

	CASPIAN		IMpower 133	
	Durvalumab+EP (n=268)	EP (n=269)	Atezolizumab +EC (n= 201)	EC + placebo (n=202)
OS,m	13.0	10.3 HR=0.73	12.3	10.3 HR=0.7
OS at 12m,%	53.7	39.8	51.7	38.2
PFS, m	5.1	5.4 HR=0.78	5.2	4.3 HR=0.77
ORR, %	67.9	57.6	60.2	64.4
DOR, m	5.1	5.1	4.2	3.9
G 3/4 AEs	61.5	62.4	67.2	63.8
irAE	19.6	2.6	39.9	24.5
Biomarker	NA	NA	Only bTMB available	
Poststudy Tx	42	44	50/14/1/5	57/18/7

Predictive Biomarker to Select Patients Benefit from IO?

CASPIAN

OS



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p-value	0.0047	

No. at risk

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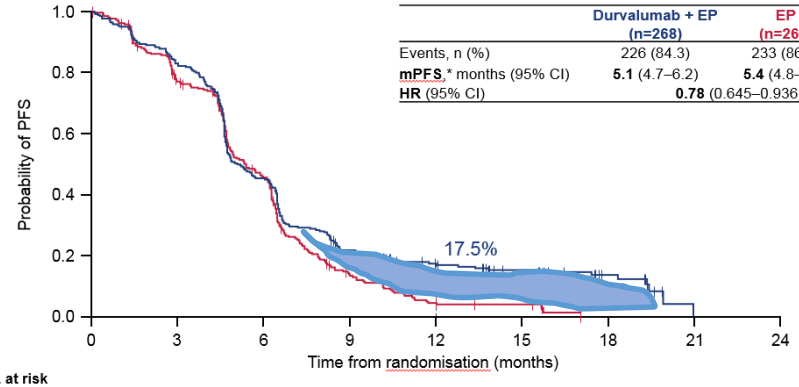
PFS



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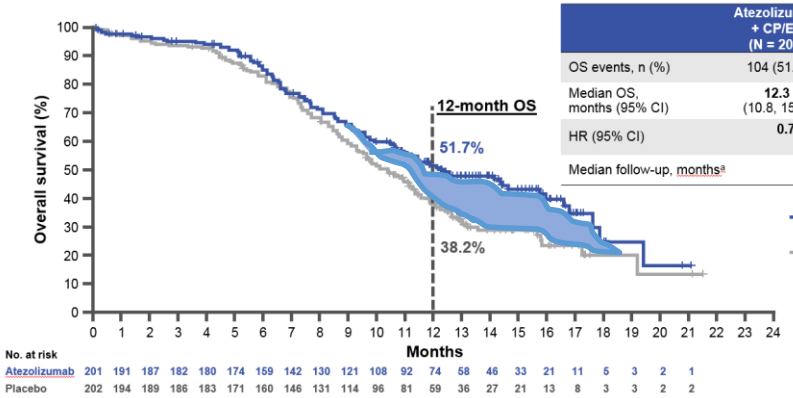
IMpower133

OS



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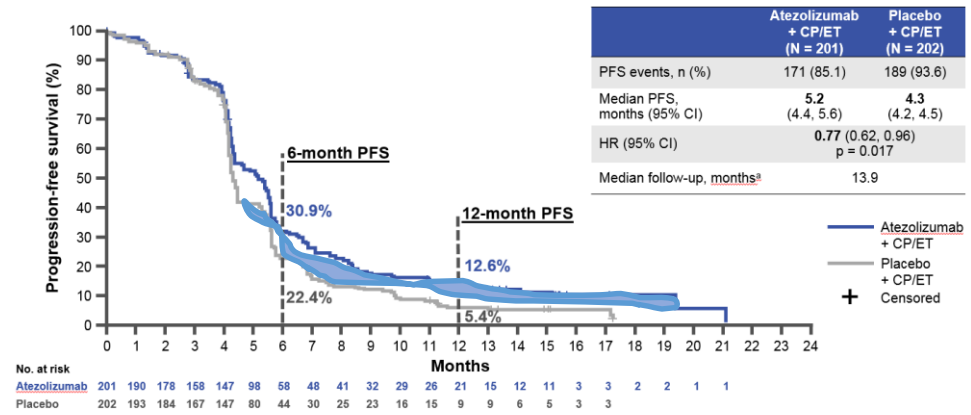
HR (95% CI)	**0.70** (0.54, 0.91) p = 0.0069	
Median follow-up, months[a]	13.9	

No. at risk

Atezolizumab	201	191	187	182	180	174	159	142	130	121	108	92	74	58	46	33	21	11	5	3	2	1
Placebo	202	194	189	186	183	171	160	146	131	114	96	81	59	36	27	21	13	8	3	3	2	2

PFS



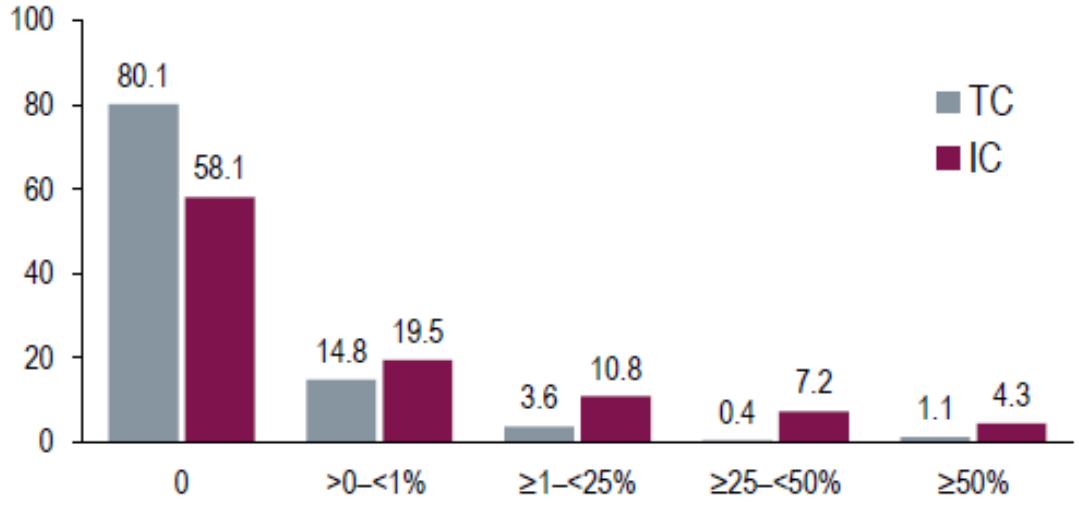
	Atezolizumab + CP/ET (N = 201)	Placebo + CP/ET (N = 202)
PFS events, n (%)	171 (85.1)	189 (93.6)
Median PFS, months (95% CI)	**5.2** (4.4, 5.6)	**4.3** (4.2, 4.5)
HR (95% CI)	**0.77** (0.62, 0.96) p = 0.017	
Median follow-up, months[a]	13.9	

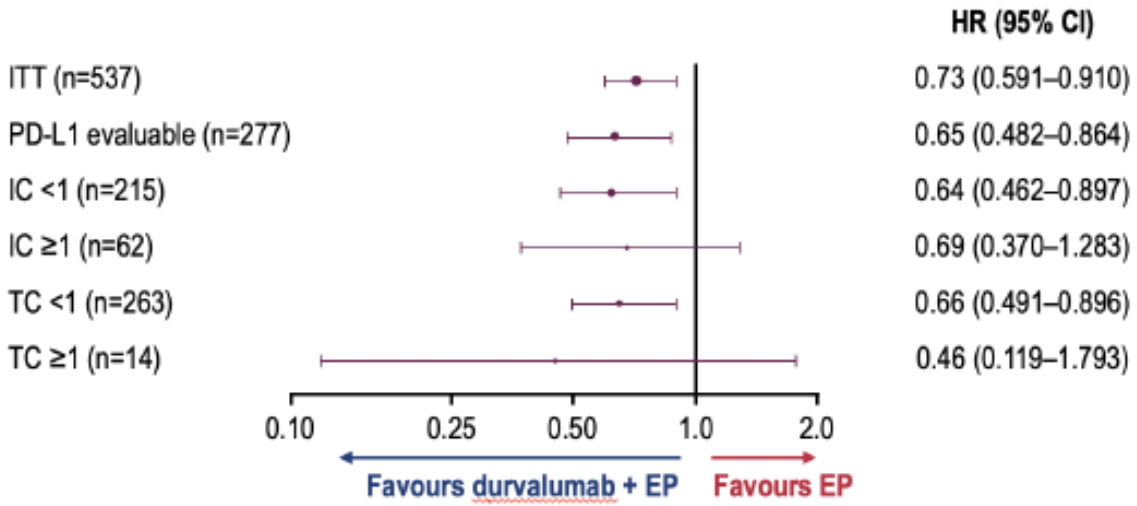
No. at risk

Atezolizumab	201	190	178	158	147	98	58	48	41	32	29	26	21	15	12	11	3	3	2	2	1	1
Placebo	202	193	184	167	147	80	44	30	25	23	16	15	9	9	6	5	3	3				

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

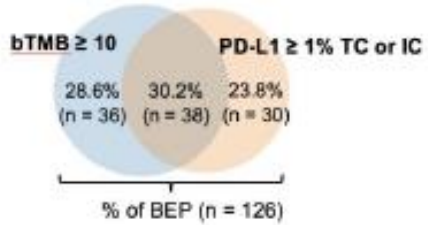
Paz Ares L et al, ESMO Proferred Paper 28Sep

IMpower 133-Update on biomarkers

- 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%

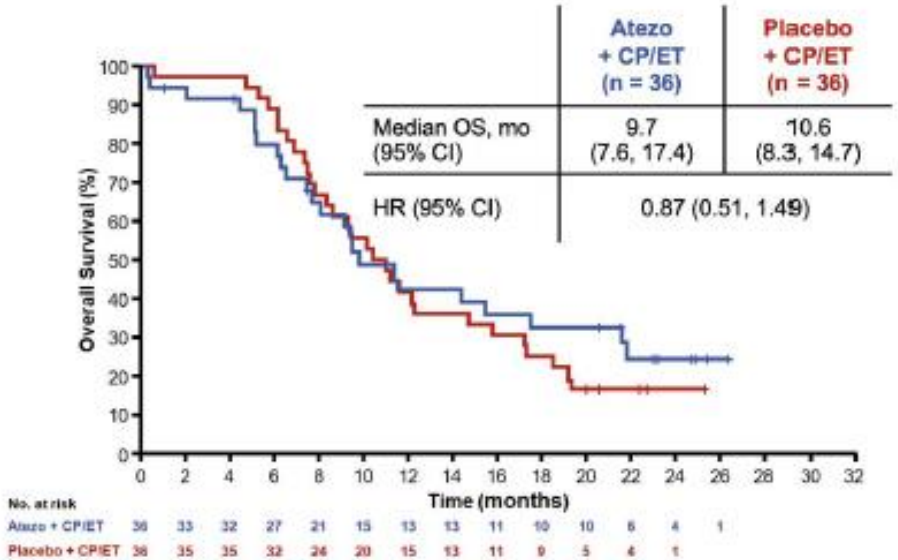
- PD-L1 analysis was based on a limited data set **(34%** of the ITT)

bTMB – PD-L1 IHC overlap



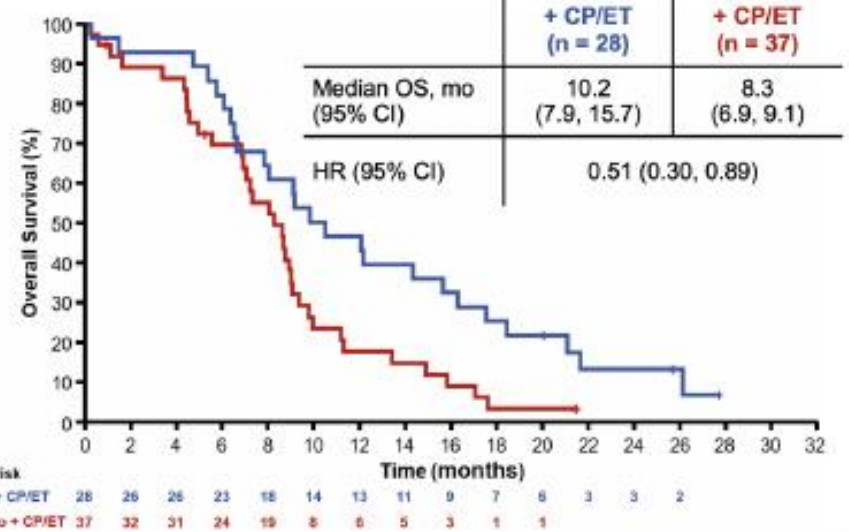
PD-L1 IHC expression in ES-SCLC (n = 137)			
IC	% BEP (n)	TC	% BEP (n)
< 1%	49.6% (68)	< 1%	94.2% (129)
≥ 1%	50.4% (69)	≥ 1%	5.8% (8)
≥ 5%	20.4% (28)	≥ 5%	1.5% (2)

PD-L1 Expression ≥ 1% TC or IC



	Atezo + CP/ET (n = 36)	Placebo + CP/ET (n = 36)
Median OS, mo (95% CI)	9.7 (7.6, 17.4)	10.6 (8.3, 14.7)
HR (95% CI)	0.87 (0.51, 1.49)	

PD-L1 Expression < 1% TC or IC

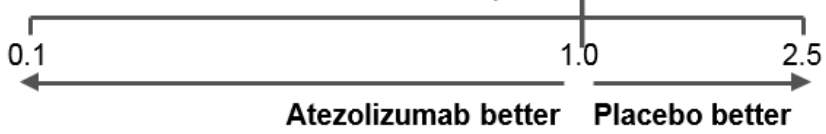


	Atezo + CP/ET (n = 28)	Placebo + CP/ET (n = 37)
Median OS, mo (95% CI)	10.2 (7.9, 15.7)	8.3 (6.9, 9.1)
HR (95% CI)	0.51 (0.30, 0.89)	

Median follow-up, 22.9 months

bTMB did not differentiate benefit of atezolizumab in IMpower133

Population	Median overall survival (months) Atezolizumab + CP/ET	Placebo + CP/ET	OS hazard ratio[a] (95% CI)
Male (n = 261)	12.3	10.9	0.74 (0.54, 1.02)
Female (n = 142)	12.5	9.5	0.65 (0.42, 1.00)
< 65 years (n = 217)	12.1	11.5	0.92 (0.64, 1.32)
≥ 65 years (n = 186)	12.5	9.6	0.53 (0.36, 0.77)
ECOG PS 0 (n = 140)	16.6	12.4	0.79 (0.49, 1.27)
No brain metastases (n = 368)	12.6	10.4	0.68 (0.52, 0.89)
Liver metastases (n = 149)	9.3	7.8	0.81 (0.55, 1.20)
No liver metastases (n = 254)	16.8	11.2	0.64 (0.45, 0.90)
bTMB < 10 mut/mb (n = 139)	11.8	9.2	0.70 (0.45, 1.07)
bTMB ≥ 10 mut/mb (n = 212)	14.6	11.2	0.68 (0.47, 0.97)
bTMB < 16 mut/mb (n = 271)	12.5	9.9	0.71 (0.52, 0.98)
bTMB ≥ 16 mut/mb (n = 80)	17.8	11.9	0.63 (0.35, 1.15)
ITT (N = 403)	12.3	10.3	0.70 (0.54, 0.91)



Biomarker study is not available in CASPIAN study !

Clinical data cutoff date: April 24, 2018. bTMB (blood tumor mutational burden) assessed as reported in Gandara DR, et al. *Nat Med,* 2018.

[a] Hazard ratios are unstratified for patient subgroups and stratified for the ITT.

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)

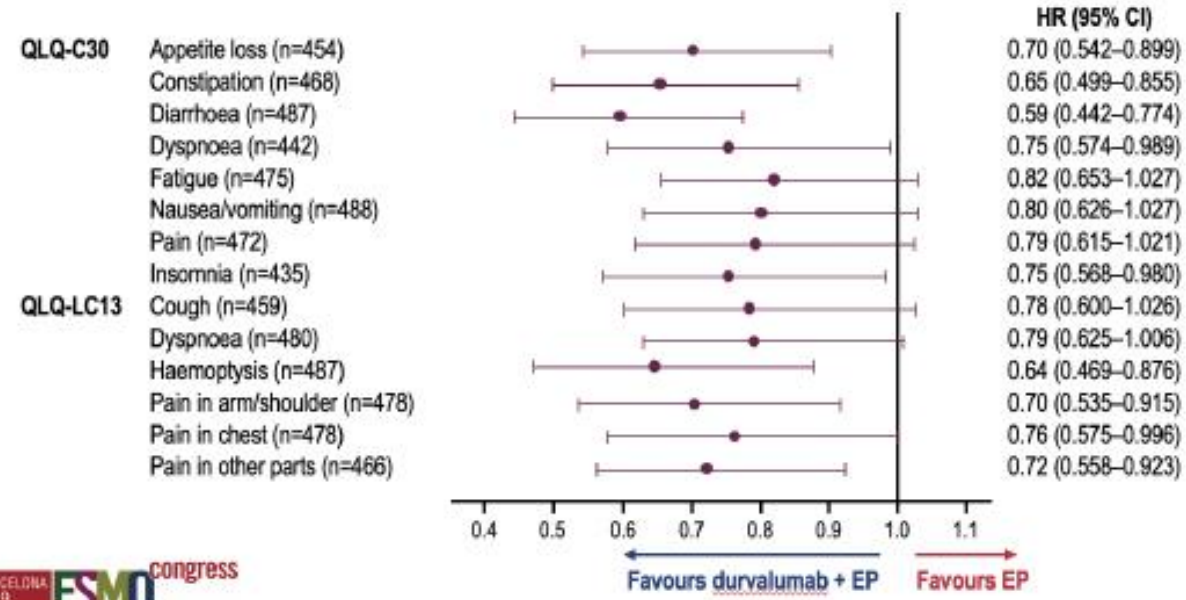
- Numerically fewer patients developed new lesions at first progression with durvalumab + EP versus EP
- No difference in the incidence of new brain/CNS lesions between arms

Paz Ares L et al, ESMO Proferred Paper 28Sep

CNS, central nervous system

CASPIAN – TIME TO DETERIORATION

- Durvalumab + EP was favoured across all symptoms



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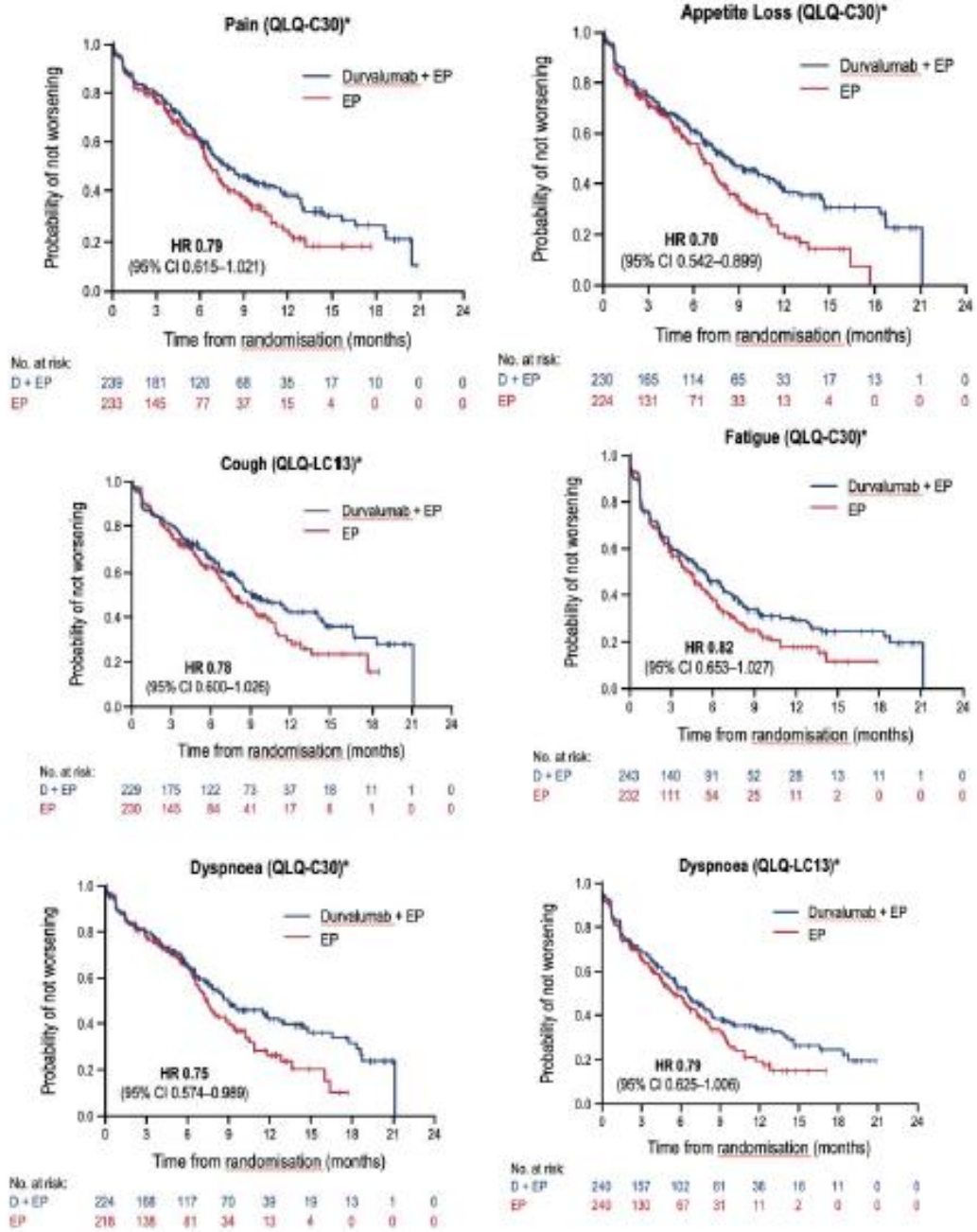

Vragen voor checkpoint inhibitie bij SCLC

- Caspian studie: immature data. Worden deze beter?
- Data arm: durva/tremilumumab + chemo?
- Identificeren van een subgroep die op immuuntherapie respondeert?
- Is een biomarker wel haalbaar in de dagelijkse praktijk?
- Wat zijn gevolgen als we in Nederland geen immuuntherapie geven bij SCLC?