Welcome & Introduction

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Speaker’s Bureau, Advisory Board, Consultant	Amgen, AstraZeneca, Boehringer Ingelheim, BeiGene, Eli Lilly, Pfizer, Roche, MSD, Janssen, Thermo Fisher, Novartis, Pierre Fabre, Takeda
Advisory Board, Consultant	Sanofi

COI, conflict of interest.

Chairs and Speakers

Prof. Silvia Novello (Co-chair)
San Luigi Hospital (part of University of Turin),
Orbassano, Italy

Prof. Tony Mok (Co-chair)
Li Shu Fan Medical Foundation
Professor of Clinical Oncology
The Chinese University of Hong Kong

Dr. Mariano Provencio
Hospital Universitario Puerta de Hierro Majadahonda,
Autonomous University Madrid, Spain

Dr. Luis Paz-Ares
Hospital Universitario “12 de Octubre”
Universidad Complutense de Madrid
Lung Cancer Unit at National Oncology
Research Center

Prof. Martin Reck
Lung Clinic Grosshansdorf,
Grosshansdorf, Germany

A new comprehensive approach to lung cancer treatment

Agenda		Co-Chairs & Speakers
13.00	Welcome and introduction	Silvia Novello (Co-chair)
13.05	Resectable NSCLC – neo-adjuvant / adjuvant	Mariano Provencio
13.20	Debate: Single agent IO is the only treatment option for NSCLC with PD-L1 high expression	PRO – Martin Reck CON – Tony Mok
13.50	What to do in NSCLC with low PD-1 expression?	Luis Paz-Ares
14.05	1L SCLC	Silvia Novello
14.20	General panel discussion / audience Q&A	All
14.29	Take-home message and farewell	Tony Mok (Co-chair)

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Resectable NSCLC – neo-adjuvant/adjuvant (RATIONALE-315)

Mariano Provencio, MD, PhD

Hospital Universitario Puerta de Hierro Majadahonda,

Autonomous University Madrid, Spain

Disclosures

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Honoraria	BMS, AstraZeneca, MSD, Roche, Takeda, Eli Lilly, F. Hoffmann-La Roche, Janssen, Pfizer, Amgen
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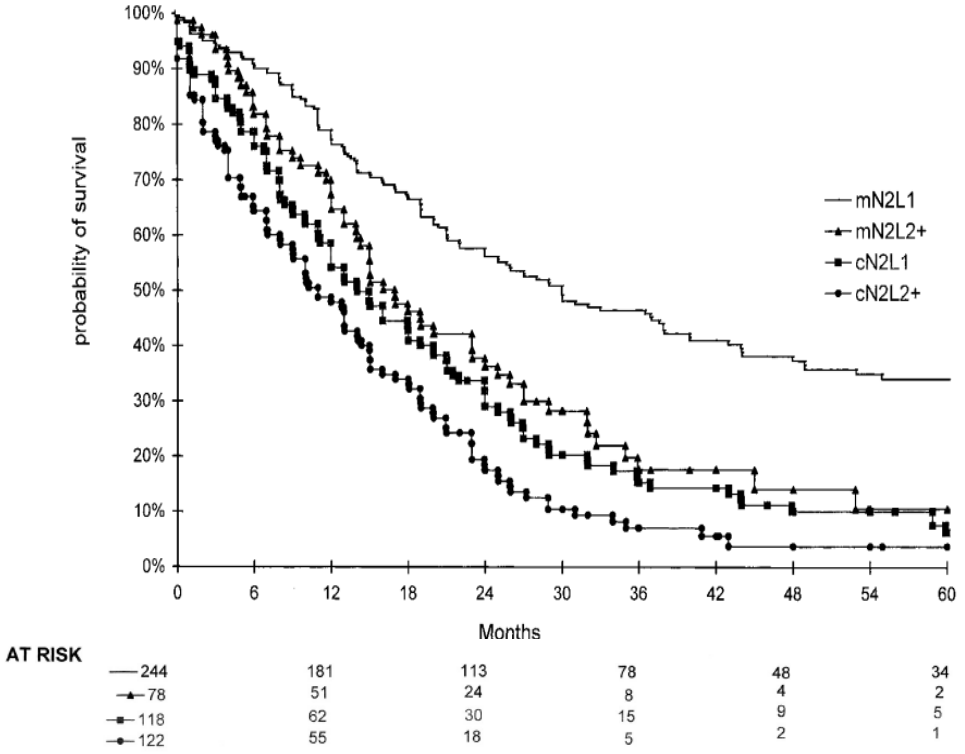
Surgery gives the best chance to cure early-stage NSCLC but recurrence is common

- 5-year tumor recurrence rate up to 67% (depending on disease stage)[1-7]

Overall survival by clinical stage[6]

Stage	Events / N	MST	24 Month	60 Month
IA1	139 / 1389	NR	97%	90%
IA2	823 / 5633	NR	94%	85%
IA3	875 / 4401	NR	92%	80%
IB	1618 / 6095	NR	89%	73%
IIA	556 / 1638	NR	82%	65%
IIB	2175 / 5226	NR	76%	56%
IIIA	3219 / 5756	41.9	65%	41%
IIIB	1215 / 1729	22.0	47%	24%
IIIC	55 / 69	11.0	30%	12%

Survival of patients with N2 disease treated with primary surgery according to N2 status and number of levels involved[7]



cN2, clinical ipsilateral mediastinal lymph node involvement; mN2, minimal N2; MST, median survival time; NR, not reached; NSCLC, non-small cell lung cancer.

Extracted from 1) Uramoto H and Tanaka F. Transl Lung Cancer Res. 2014;3(4):242-249; 2) Kelsey CR et al. Cancer 2009;115(22):5218-5227; 3) Gourcerol D et al. Eur Respir J. 2013;42(5):1357-1364; 4) NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Non-Small Cell Lung Cancer: Version 5 2023. nscl.pdf (nccn.org); 5) West H et al. Clin Lung Cancer. 2023;24(3):260-268; 6) Goldstraw P et al. J Thorac Oncol. 2016;11(1):39-51; 7) André F et al. J Clin Oncol. 2000;18(16):2981-9.

Induction treatment in the pre-IO era

- Quite small trials
- Many patients not considered Stage IIIA now
- Survival differences were significant
- Ideal approach: induction Chemo vs concurrent Chemo-RT?

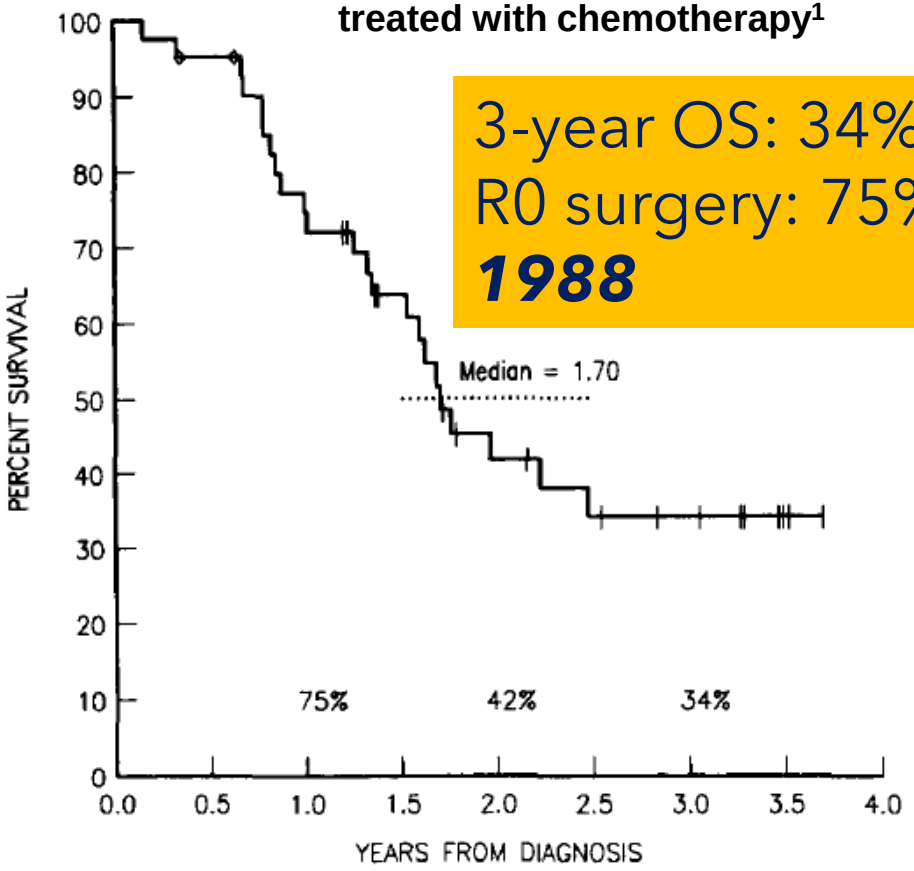
Table 2
Randomized trials comparing induction chemotherapy alone with surgery

				% 5-y Survival	
Author, Year	**n**	**% Confirmed N2**	**Induction Therapy**	**Induction Therapy**	**Surgery**
Roth et al,[13] 1994	60	85	CEP	36	15
Rosell et al,[14] 1994	60	73	MIP	17	9
Depierre et al,[35] 2002	167	N/R	MIP	30	22
Nagai et al,[36] 2003	62	100	PV	23	22

CEP, cyclophosphamide + etoposide + cisplatin; Chemo, chemotherapy; IO, immuno-oncology; MIP, mitomycin + ifosphamide + cisplatin; N/R, not reported; PV, vindesine + cisplatin; RT, radiotherapy.
Extracted from Donington JS, Pass HI. Thorac Surg Clin. 2014; 24(4):449-456.

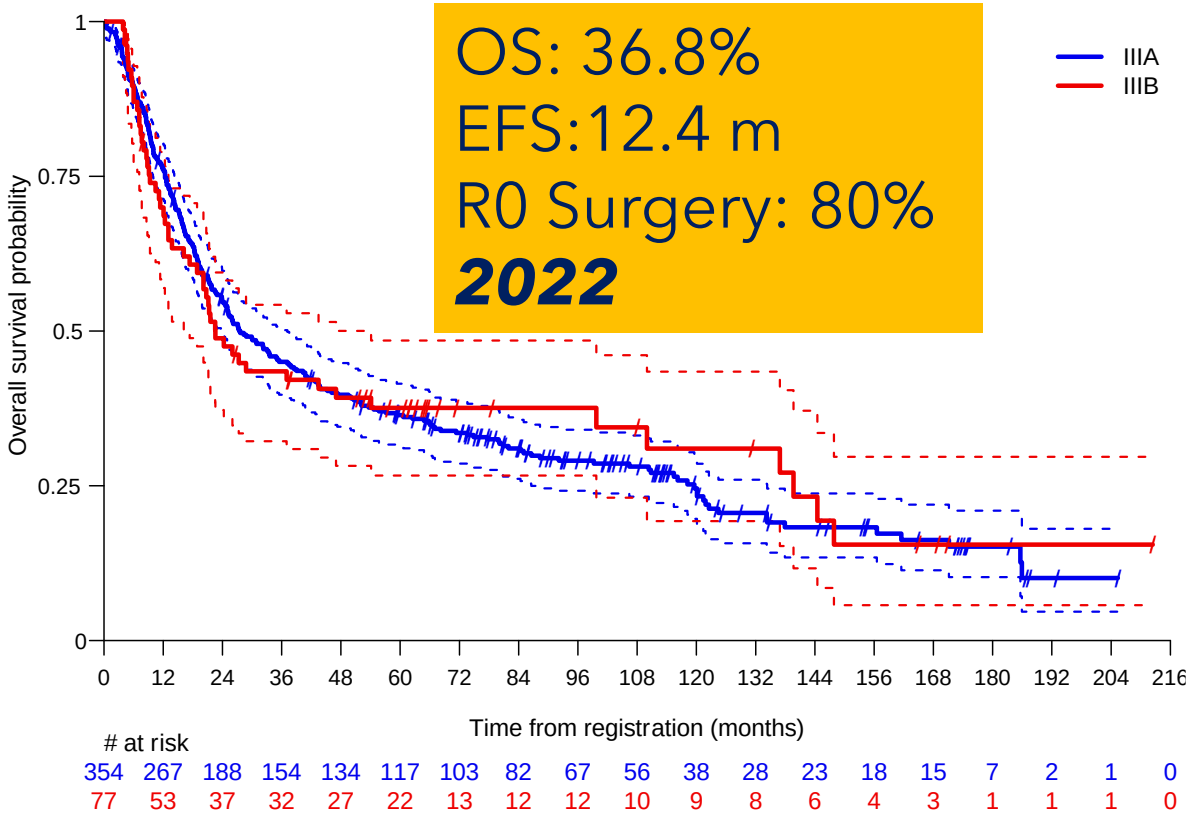
Little progress in outcomes in 30 years pre-IO

Survival from diagnosis for 41 patients treated with chemotherapy[1]



3-year OS: 34%
R0 surgery: 75%
1988

OS probability for patients with stage III NSCLC[2]



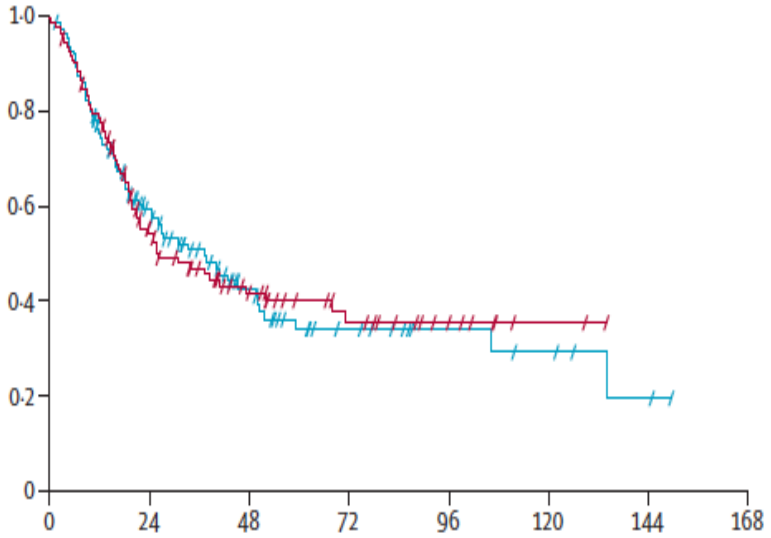
OS: 36.8%
EFS:12.4 m
R0 Surgery: 80%
2022

EFS, event-free survival; IO, immuno-oncology; OS, overall survival.
Extracted from 1) Martini N et al. Ann Thorac Surg. 1988;45(4):370-9; 2) König D et al. ESMO Open. 2022;7(2):100455 (supplementary appendix).

Radiotherapy did not add benefit to induction chemotherapy and surgery

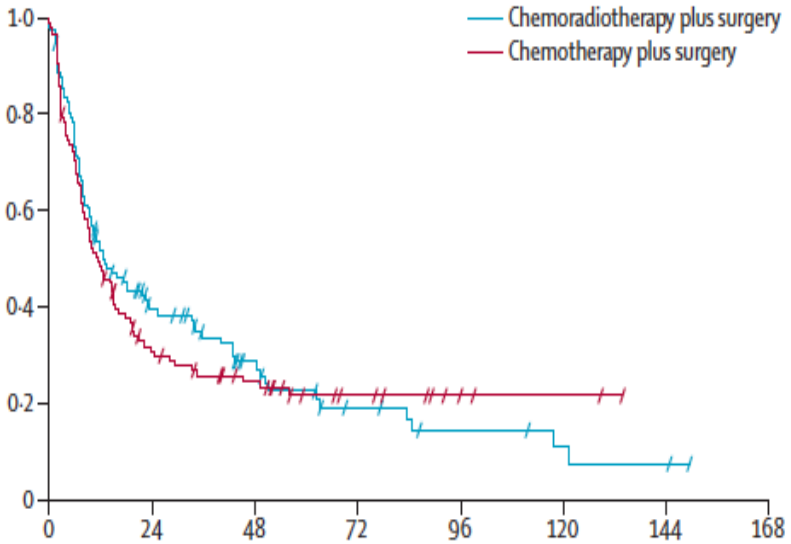
Interpretation: Radiotherapy did not add any benefit to induction chemotherapy followed by surgery. We suggest that one definitive local treatment modality combined with neoadjuvant chemotherapy is adequate to treat resectable stage IIIA/N2 non-small-cell lung cancer

OS



Number at risk								
Chemoradiotherapy group	117	57	27	13	7	5	2	0
Chemotherapy group	115	53	28	15	7	2	0	0

EFS



Number at risk								
Chemoradiotherapy group	117	37	19	9	5	3	2	0
Chemotherapy group	115	31	19	9	3	2	0	0

Ch-RT, chemoradiotherapy; EFS, event-free survival; NSCLC, non-small cell lung cancer; OS, overall survival.
Extracted from Pless M et al. Lancet. 2015;386(9998):1049-56.

Neoadjuvant chemoradiotherapy does not improve survival compared with neoadjuvant chemotherapy alone

TABLE 1. Trial Characteristics

First Author	Accrual Years	Group	Treatment	Number of Patients	Median OS	3-y OS	*P*	Median DFS/PFS	3y-DFS/ PFS	*P*
Albain et al[12]	1994–2001	S	Neo-ChRT + S	202	23.6	37.9	0.24	12.8	27.3	0.017
		ChRT	ChRT alone	194	22.2	33.9		10.5	17.3	
Johnstone et al[13]	1990–1994	S	Neo-ChT + S	29	19.4	33	0.46	-	-	-
		ChRT	ChT + RT	32	17.4	22		-	-	
Van Meerbeeck et al[14]	1994–2002	S	Neo-ChT + S	167	16.4	24.9	0.596	9	17.2	0.605
		ChRT	ChT + RT	165	17.5	27.8		11.3	15.8	
Shepherd et al[15]	––	S	Neo-ChT + S	16	18.7	-	>0.05	-	-	-
		RT	RT alone	15	16.2	-		-	-	
Katakami et al[16]	2000–2006	ChRT	Neo-ChRT + S	29	39.6	51.7	0.397	12.4	34.5	0.187
		ChT	Neo-ChT + S	29	29.9	39.3		9.7	17.9	
Thomas et al[7]	1995–2003	ChRT	Neo-ChRT + S	55	19	31	0.21	9	-	0.69
		ChT	Neo-ChT + S	70	17	18		10	-	
Girard et al[17]	2003–2007	ChRT	Neo-ChRT + S	32	-	51.8	-	17.2	25	-
		ChT	Neo-ChT + S	14	24.2	25.4		12.5	38.5	

ChT, chemotherapy; ChRT, chemoradiotherapy; DFS, disease-free survival; Neo, neoadjuvant; OS, overall survival; PFS, progression-free survival; S, surgery.
Extracted from Xu Y-P et al. Medicine (Baltimore) 2015;94(23):e879.

New data?

Where do the data come from?

PAST

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5.4% Adjuvant benefit[1]

4-8% pCR[2]

3-year OS: 34%[3]

RT did not add any benefit[4]

GECP
EFS: 9.9 m[5]
3-year OS: 36.8%[5]

EFS: 12.4 m[6]
5-year OS: 36.8%[6]

Beva/erlonitib No[7]

30% treated With Ch-RT[8]

Ch-RT, chemoradiotherapy; EFS, event-free survival; OS, overall survival; pCR, pathologic complete response; RT, radiotherapy.

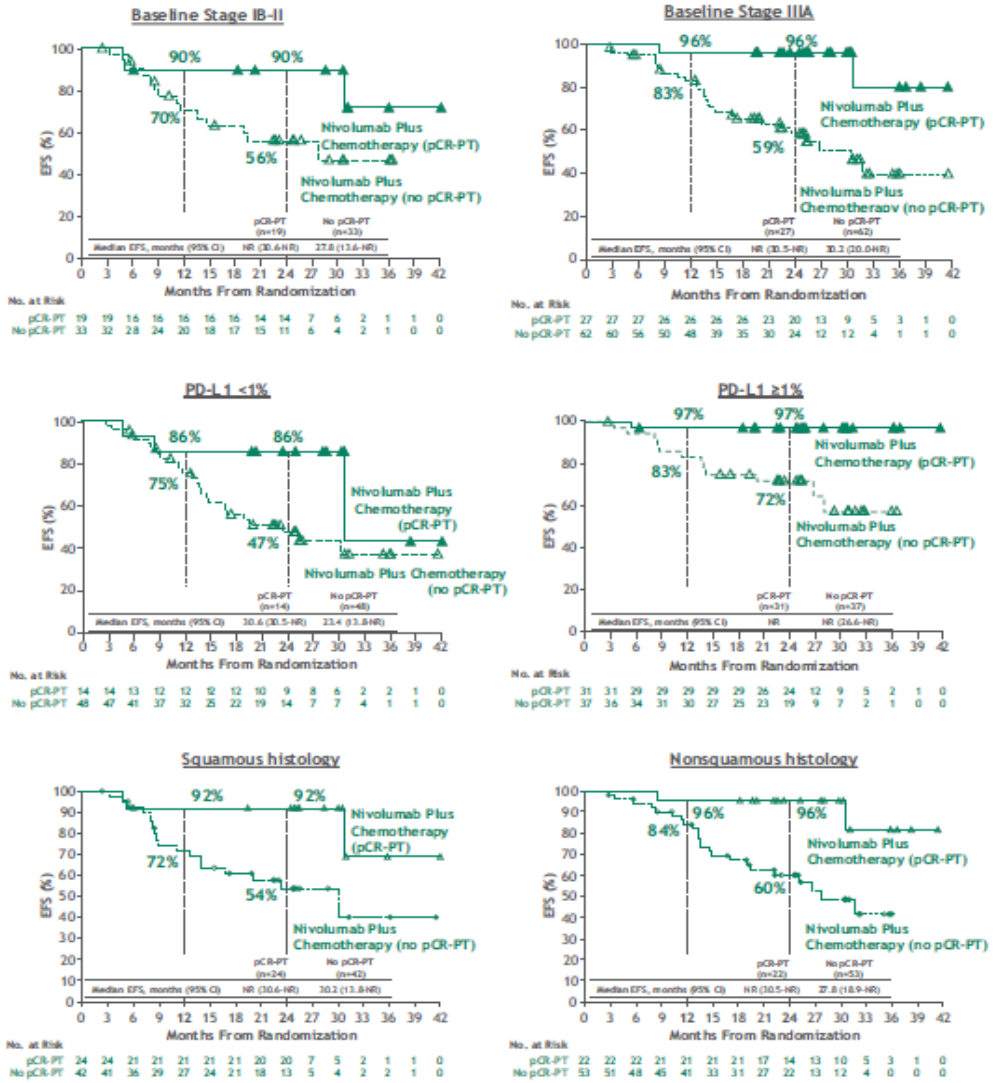
Extracted from 1) Pignon J et al. J Clin Oncol. 2008;26(21):3552-9; 2) Hellmann MD et al. Lancet Oncol. 2014;15(1):e42-50; 3) Martini N et al. Ann Thorac Surg. 1988;45(4):370-9; 4) Xu Y-P et al. Medicine (Baltimore) 2015;94(23):e879; 5) Garrido P et al. J Clin Oncol. 2007;25(30):4736-42; 6) König D et al. ESMO Open. 2022;7(2):100455; 7) Socinski MA et al. J Clin Oncol. 2012;30(32):3953-9; 8) Provencio M et al. Transl Lung Cancer Res. 2023;12(10):2113-2128; 9) Provencio M et al. Lancet Oncol. 2020;21(11):1413-1422; 10) Provencio M et al. N Engl J Med. 2023;389(6):504-513; 11) Forde PM et al. N Engl J Med. 2022;386(21):1973-1985; 12) Wakelee H et al. N Engl J Med. 2023;389(6):491-503; 13) Cascone T et al. N Engl J Med. 2024;390:1756-1769; 14) Heymach JV et al. N Engl J Med 2023;389:1672-1684; 15) Lu S et al. JAMA. 2024;331(3):201-211; 16) Yue D et al. Presented at the ESMO Virtual Plenary with AACR Expert Commentary; February 15&16, 2024 (Accessed 17 July 2024). Available at: Yue_BGB-A317-315_ESMO-VP_Presentation_2024.pdf.

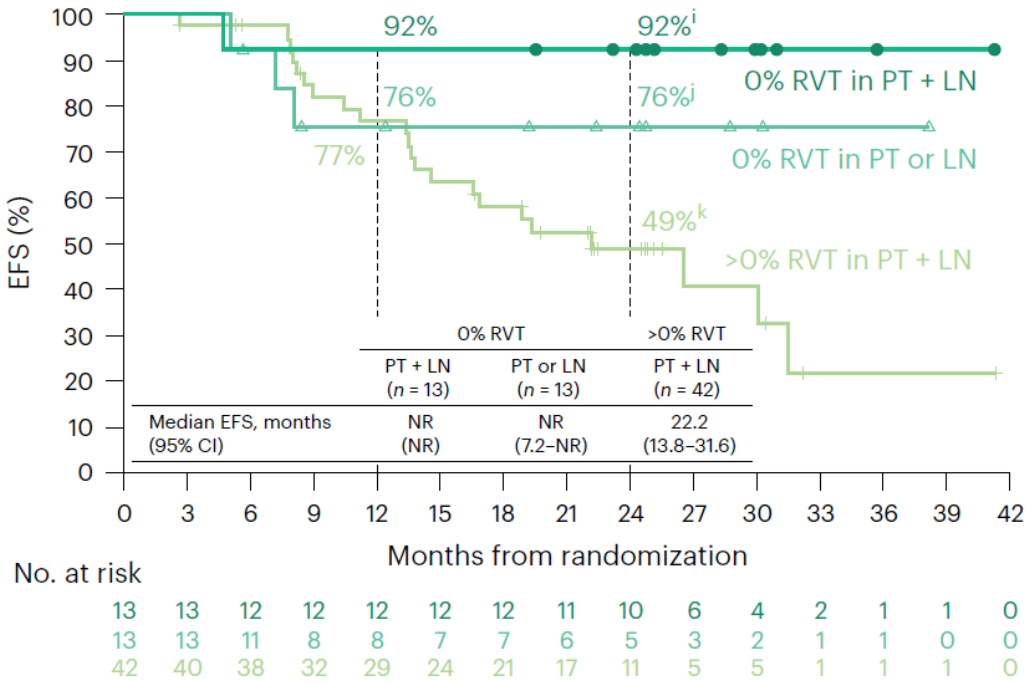
Neoadjuvant/perioperative chemo-IO treatment

- New key aspects
  - Pathologic response
  - Surgical aspects
  - Survival

IO, immuno-oncology.

Pathologic response may be a surrogate for survival after neoadjuvant chemoimmunotherapy





CI, confidence interval; EFS, event-free survival; LN, lymph node; NR, not reached; pCR, pathologic complete response; PD-L1, programmed death ligand 1; PT, primary tumor; RVT, residual viable tumor.
Extracted from Deutsch JS et al. Nature Medicine. 2024;30:218–228.

ESMO VIRTUAL PLENARY

WITH AACR EXPERT COMMENTARY

Presented here at ESMO on Friday 13 September (VP1-2024): Dr Yue

RATIONALE-315: Event-Free Survival (EFS) and Overall Survival (OS) of Neoadjuvant Tislelizumab (TIS) plus Chemotherapy (CT) with Adjuvant TIS in Resectable Non-Small Cell Lung Cancer (NSCLC)

Dongsheng Yue,[1] Wenxiang Wang,[2] Hongxu Liu,[3] Qixun Chen,[4] Chun Chen,[5] Lunxu Liu,[6] Peng Zhang,[7] Guofang Zhao,[8] Fan Yang,[9] Guang Han,[10] Ying Cheng,[11] Bentong Yu,[12] Yue Yang,[13] Haiquan Chen,[14] Jie Jiang,[15] Bin Yao,[16] Shengfei Wang,[17] Ruihua Wang,[17] Wenjuan Zheng,[16] Changli Wang[1] on behalf of the RATIONALE-315 Investigators

[1]Tianjin Medical University Cancer Institute and Hospital, Tianjin, China; [2]Hunan Cancer Hospital, Hunan, China; [3]Liaoning Cancer Hospital and Institute, Shenyang, China; [4]Zhejiang Cancer Hospital, Hangzhou, China; [5]Fujian Medical University Union Hospital, Fuzhou, China; [6]West China Hospital, Sichuan University, Chengdu, China; [7]Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, China; [8]Ningbo No.2 Hospital, Ningbo, China; [9]Peking University People's Hospital, Beijing, China; [10]Hubei Cancer Hospital, Wuhan, China; [11]Jilin Cancer Hospital, Changchun, China; [12]The First Affiliated Hospital of Nanchang University, Nanchang, China; [13]Beijing Cancer Hospital, Beijing, China; [14]Fudan University Shanghai Cancer Center, Shanghai, China; [15]The First Affiliated Hospital of Xiamen University, Xiamen, China; [16]BeiGene (Beijing) Co., Ltd, Beijing, China; [17]BeiGene (Shanghai) Co., Ltd, Shanghai, China

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Extracted from Yue D, Wang W, Liu H, Chen Q, Chen C, Liu L, Zhang P et al. RATIONALE-315: Event-Free Survival (EFS) and Overall Survival (OS) of Neoadjuvant Tislelizumab (TIS) plus Chemotherapy (CT) with Adjuvant TIS in Resectable Non-Small Cell Lung Cancer (NSCLC). Presented at the ESMO Virtual Plenary with AACR Expert Commentary; February 15&16, 2024 (Accessed 17 July 2024). Available at: Yue_BGB-A317-315_ESMO-VP_Presentation_2024.pdf.

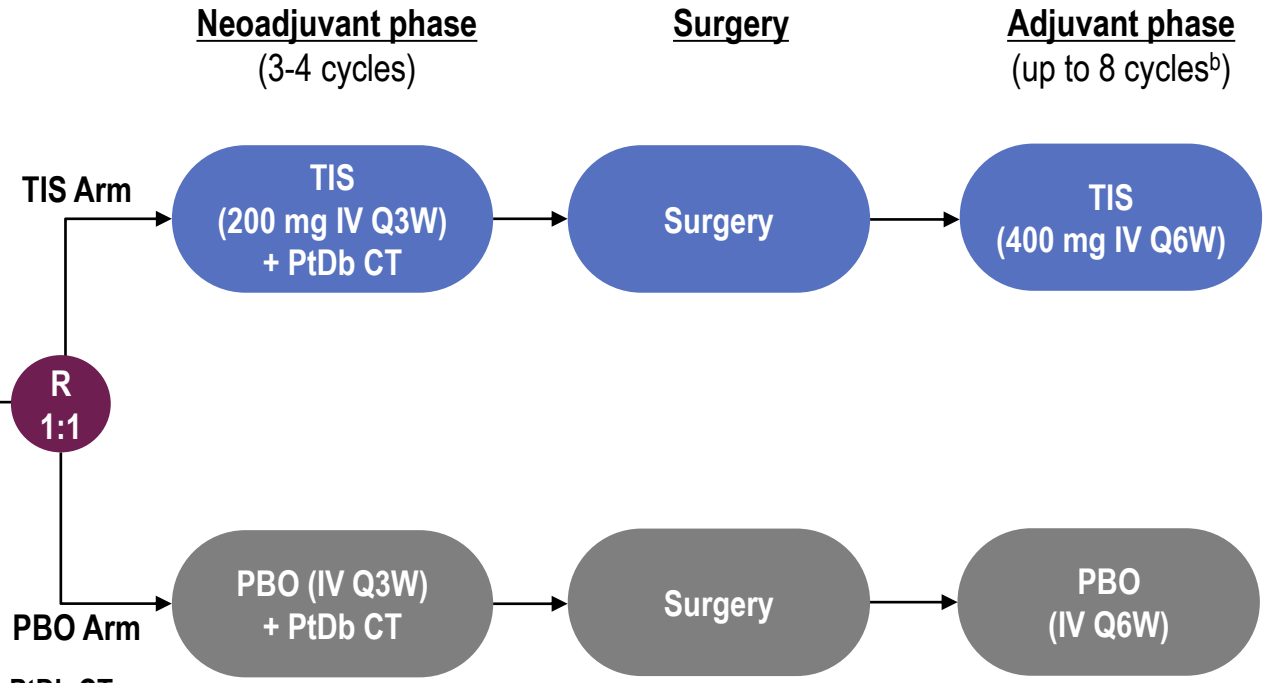
RATIONALE-315 Study Design

Key eligibility criteria

- Resectable stage II-IIIA NSCLC per AJCC 8th edition (eligible for R0 resection)
- ECOG PS 0 or 1
- *EGFR/ALK* WT[a]

Stratification

- Histology (squamous vs non-squamous)
- Disease stage (II vs IIIA)
- PD-L1 expression (≥1% vs <1%/not evaluable/indeterminate)



PtDb CT

- Squamous: cisplatin/carboplatin + paclitaxel
- Non-squamous: cisplatin/carboplatin + pemetrexed

Primary endpoints:

- MPR rate by BIPR and EFS by BICR

Key secondary endpoint:

- pCR rate by BIPR

Other secondary endpoints:

- OS, EFS by investigator, safety (and others not reported here)

Data cut-off: August 21, 2023 (median study follow-up: 22.0 months [range: 0.1, 38.4]).

ClinicalTrials.gov Identifier: NCT04379635.

[a] EGFR testing was mandatory for non-squamous NSCLC. [b] Adjuvant treatment was only received by patients with an ECOG PS of 0 or 1 and adequate organ function for ≤8 cycles or until disease recurrence/progression, unacceptable adverse events, or death occurs, or if the patient and/or investigator decided to discontinue study treatment.

Abbreviations: ALK, anaplastic large-cell lymphoma kinase; BICR, blinded independent central review; BIPR, blinded independent pathology review; ECOG PS, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; EGFR, epidermal growth factor receptor; IV, intravenously; MPR, major pathological response; NSCLC, non-small cell lung cancer; OS, overall survival; PBO, placebo; pCR, pathological complete response; PD-L1, programmed death-ligand 1; PtDb CT, platinum-based doublet chemotherapy; Q3W, once every 3 weeks; Q6W, once every 6 weeks; R, randomised; R0, pathological complete resection of the primary tumour; TIS, tislelizumab; WT, wild-type.

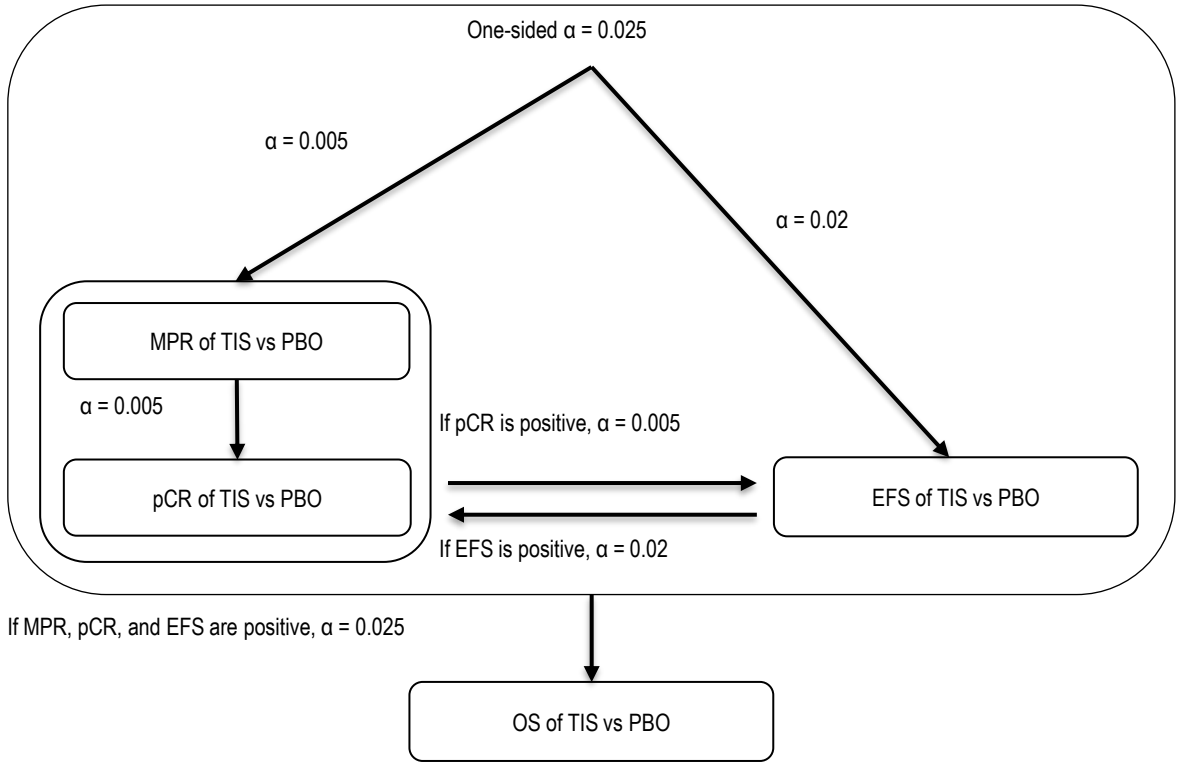
ESMO VIRTUAL PLENARY
WITH AACR EXPERT COMMENTARY

Extracted from Yue D, Wang W, Liu H, Chen Q, Chen C, Liu L, Zhang P et al. RATIONALE-315: Event-Free Survival (EFS) and Overall Survival (OS) of Neoadjuvant Tislelizumab (TIS) plus Chemotherapy (CT) with Adjuvant TIS in Resectable Non-Small Cell Lung Cancer (NSCLC). Presented at the ESMO Virtual Plenary with AACR Expert Commentary; February 15&16, 2024 (Accessed 17 July 2024). Available at: Yue_BGB-A317-315_ESMO-VP_Presentation_2024.pdf

Statistical Considerations

- Overall type I error was strongly controlled at a one-sided alpha of 0.025
- The interim analysis for EFS was planned for when ~75% of the targeted EFS events (184 EFS events) had occurred, with Lan-DeMets α spending function approximation to the O'Brien–Fleming boundary
- The OS interim analysis was to be tested with Haybittle–Peto *P*-value boundary at 0.0001 at this interim analysis

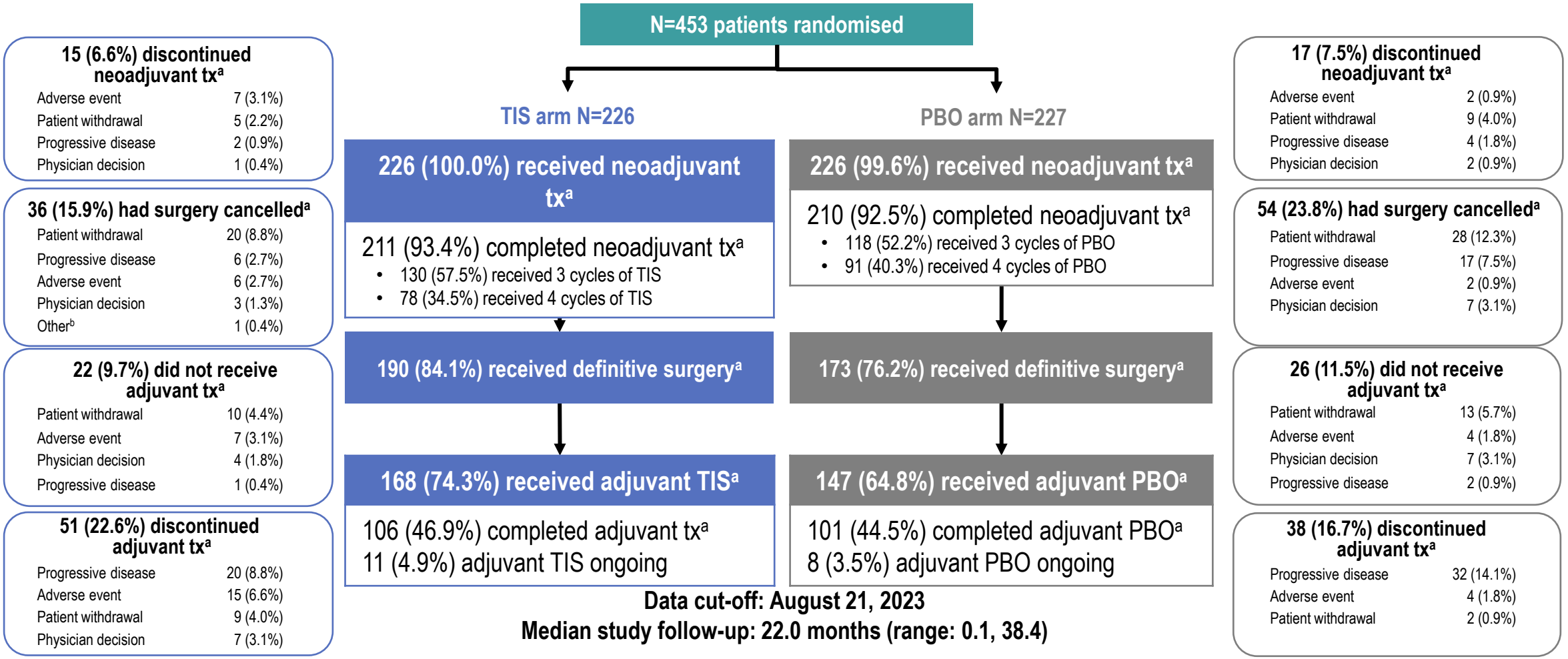
Type I Error Control Scheme



Abbreviations: EFS, event-free survival; MPR, major pathological response; OS, overall survival; PBO, placebo; pCR, pathological complete response; TIS, tislelizumab.

Extracted from Yue D, Wang W, Liu H, Chen Q, Chen C, Liu L, Zhang P et al. RATIONALE-315: Event-Free Survival (EFS) and Overall Survival (OS) of Neoadjuvant Tislelizumab (TIS) plus Chemotherapy (CT) with Adjuvant TIS in Resectable Non-Small Cell Lung Cancer (NSCLC). Presented at the ESMO Virtual Plenary with AACR Expert Commentary; February 15&16, 2024 (Accessed 17 July 2024). Available at: Yue_BGB-A317-315_ESMO-VP_Presentation_2024.pdf

Patient Disposition (ITT Analysis Set)



The ITT analysis set included all randomised patients. [a] Denominator based on randomised patients. [b] Patient was reported to cancel surgery due to lost to follow-up.
Abbreviations: ITT, intention-to-treat; PBO, placebo; TIS, tislelizumab; tx, treatment.

ESMO VIRTUAL PLENARY
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Extracted from Yue D, Wang W, Liu H, Chen Q, Chen C, Liu L, Zhang P et al. RATIONALE-315: Event-Free Survival (EFS) and Overall Survival (OS) of Neoadjuvant Tislelizumab (TIS) plus Chemotherapy (CT) with Adjuvant TIS in Resectable Non-Small Cell Lung Cancer (NSCLC). Presented at the ESMO Virtual Plenary with AACR Expert Commentary; February 15&16, 2024 (Accessed 17 July 2024). Available at: Yue_BGB-A317-315_ESMO-VP_Presentation_2024.pdf

Demographics and Baseline Characteristics

ITT Analysis Set

	TIS arm (N=226)	PBO arm (N=227)
Age, median (IQR), years	62.0 (57.0, 67.0)	63.0 (56.0, 68.0)
Male sex, n (%)	205 (90.7)	205 (90.3)
Asian race, n (%)	226 (100.0)	227 (100.0)
ECOG PS, n (%)[a]		
0	142 (62.8)	154 (67.8)
1	83 (36.7)	73 (32.2)
Smoking status, n (%)		
Current/former	193 (85.4)	190 (83.7)
Never	33 (14.6)	37 (16.3)
Histology, n (%)[b]		
Squamous	179 (79.2)	175 (77.1)
Non-squamous	45 (19.9)	50 (22.0)
Disease stage, n (%)		
II	92 (40.7)	91 (40.1)
IIIA	132 (58.4)	133 (58.6)
cN status, n (%)[c]		
N0	60 (26.5)	54 (23.8)
N1	84 (37.2)	93 (41)
N2	82 (36.3)	79 (34.8)
PD-L1 expression, n (%)[d]		
<1%	89 (39.4)	84 (37.0)
≥1%	130 (57.5)	132 (58.1)
Not evaluable/indeterminate	7 (3.1)	11 (4.8)

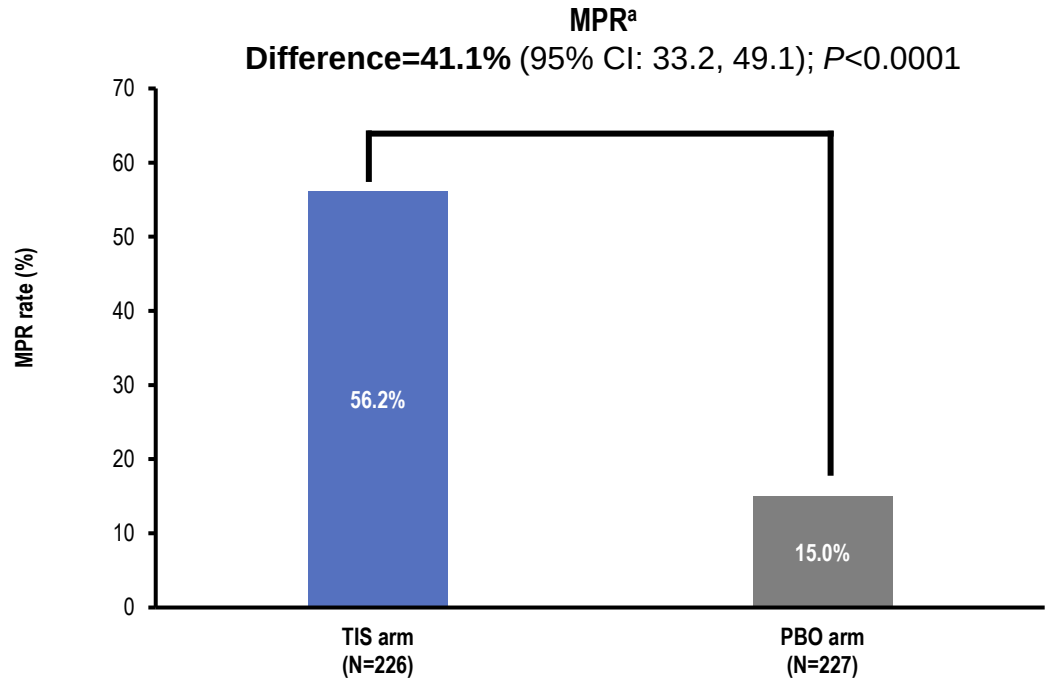
[a] One patient in the TIS arm had a missing ECOG PS. [b] Histology by CRF; patients with mixed histology were categorised as 'Other' (n=2 [0.9%] in each arm). [c] One patient was enrolled (PBO arm) with N3. [d] PD-L1 expression from Central Lab.

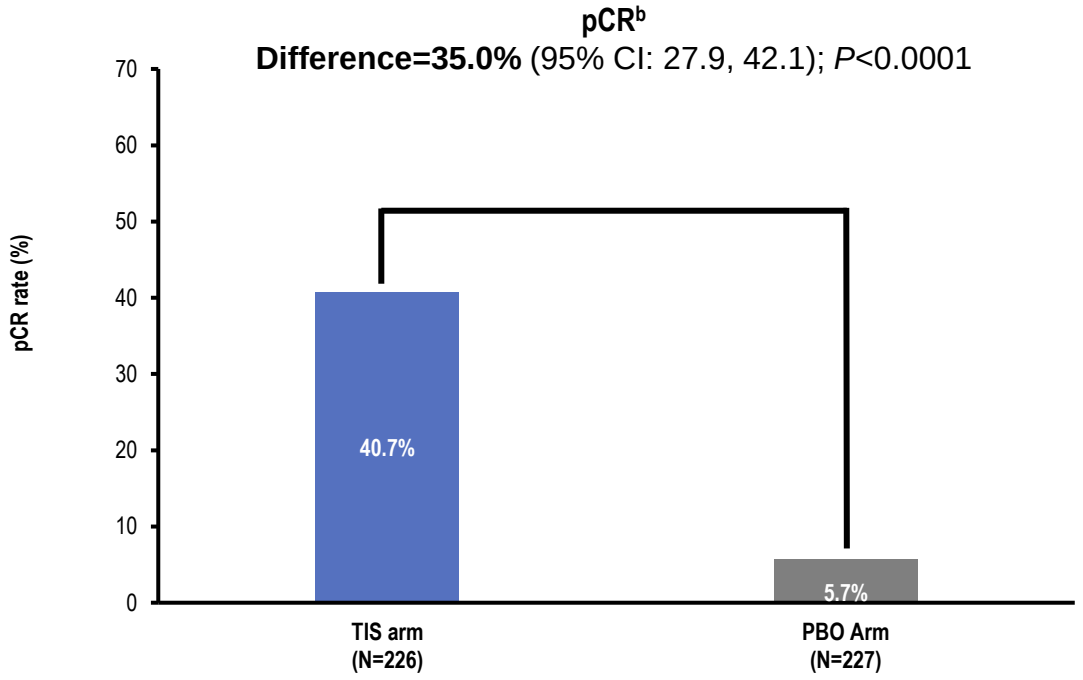
Abbreviations: CRF, case report form; ECOG PS, Eastern Cooperative Oncology Group performance status; IQR, interquartile range; ITT, intention-to-treat; PBO, placebo; PD-L1, programmed death-ligand 1; TIS, tislelizumab; cN, clinical N.

Extracted from Yue D, Wang W, Liu H, Chen Q, Chen C, Liu L, Zhang P et al. RATIONALE-315: Event-Free Survival (EFS) and Overall Survival (OS) of Neoadjuvant Tislelizumab (TIS) plus Chemotherapy (CT) with Adjuvant TIS in Resectable Non-Small Cell Lung Cancer (NSCLC). Presented at the ESMO Virtual Plenary with AACR Expert Commentary; February 15&16, 2024 (Accessed 17 July 2024). Available at: Yue_BGB-A317-315_ESMO-VP_Presentation_2024.pdf

Major Pathological and Pathological Complete Responses

Per BIPR (ITT Analysis Set)





- **Neoadjuvant TIS + PtDb CT showed a statistically significant and clinically meaningful improvement in MPR and pCR rates vs neoadjuvant PBO + PtDb CT**

Final MPR and pCR analysis at the February 20, 2023, cut-off. Patients who did not receive surgical resection were considered non-responders. [a] MPR was defined as the proportion of patients with ≤10% residual viable tumour in the resected primary tumour and resected lymph nodes after completion. [b] pCR was defined as the proportion of patients absent of residual viable tumour in the resected primary tumour and resected lymph nodes after treatment.

Abbreviations: BIPR, blinded independent pathology review; CI, confidence interval; CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ITT, intention-to-treat; MPR, major pathological response; NSCLC, non-small cell lung cancer; OR, odds ratio; PBO, placebo; PD-L1, programmed-death ligand 1; pCR, pathological complete response; PtDb, platinum-based doublet; TIS, tislelizumab. Yue D, et al. Presented at ESMO, Madrid, Spain; October 23, 2023.

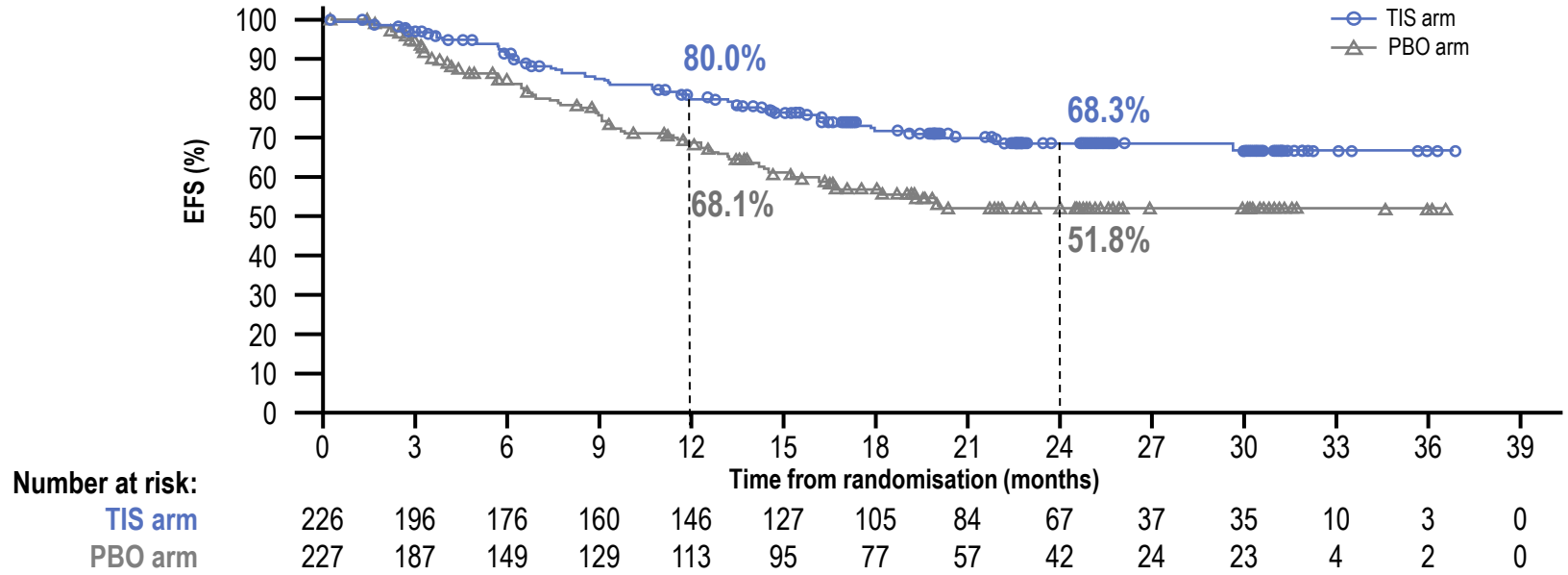
ESMO VIRTUAL PLENARY
WITH AACR EXPERT COMMENTARY

Extracted from Yue D, Wang W, Liu H, Chen Q, Chen C, Liu L, Zhang P et al. RATIONALE-315: Event-Free Survival (EFS) and Overall Survival (OS) of Neoadjuvant Tislelizumab (TIS) plus Chemotherapy (CT) with Adjuvant TIS in Resectable Non-Small Cell Lung Cancer (NSCLC). Presented at the ESMO Virtual Plenary with AACR Expert Commentary; February 15&16, 2024 (Accessed 17 July 2024). Available at: Yue_BGB-A317-315_ESMO-VP_Presentation_2024.pdf

Event-Free Survival

Per BICR (ITT Analysis Set)

	Events (%)	Median (95% CI), months	HR (95% CI)	*P*-value
TIS arm	58 (25.7)	NR (NE, NE)	**0.56 (0.40, 0.79)**	0.0003
PBO arm	83 (36.6)	NR (16.6, NE)		



Number at risk:														
TIS arm	226	196	176	160	146	127	105	84	67	37	35	10	3	0
PBO arm	227	187	149	129	113	95	77	57	42	24	23	4	2	0

- **A statistically significant and clinically meaningful improvement in EFS (HR=0.56 [95% CI: 0.40, 0.79]; one-sided *P*=0.0003) was observed favouring perioperative TIS**
- A clinically meaningful improvement in EFS per investigator (HR=0.55 [95% CI: 0.39, 0.77]) was also observed

Analysis occurred at the August 21, 2023, cut-off. EFS was defined as the time from randomisation until any of the following, whichever occurred first: disease progression precluding surgery, local or distant recurrence, or death due to any cause. The significance boundary of the EFS interim analysis was 0.0105 (calculated based on 141 actual EFS events).

Abbreviations: CI, confidence interval; BICR, blinded independent central review; EFS, event-free survival; HR, hazard ratio; ITT, intention-to-treat; NE, not evaluable; NR, not reached; PBO, placebo; TIS, tislelizumab.

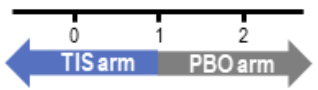
ESMO VIRTUAL PLENARY
WITH AACR EXPERT COMMENTARY

Extracted from Yue D, Wang W, Liu H, Chen Q, Chen C, Liu L, Zhang P et al. RATIONALE-315: Event-Free Survival (EFS) and Overall Survival (OS) of Neoadjuvant Tislelizumab (TIS) plus Chemotherapy (CT) with Adjuvant TIS in Resectable Non-Small Cell Lung Cancer (NSCLC). Presented at the ESMO Virtual Plenary with AACR Expert Commentary; February 15&16, 2024 (Accessed 17 July 2024). Available at: Yue_BGB-A317-315_ESMO-VP_Presentation_2024.pdf

Event-Free Survival By Subgroups

ITT Analysis Set

Subgroup	TIS arm, n/N	PBO arm, n/N	HR (95% CI)
Overall	58/226	83/227	0.57 (0.41, 0.80)
Age group			
<65 years	38/143	47/129	0.61 (0.40, 0.94)
≥65 years	20/83	36/98	0.51 (0.30, 0.89)
Sex			
Male	53/205	78/205	0.57 (0.40, 0.80)
Female	5/21	5/22	0.68 (0.19, 2.40)
ECOG performance status			
0	35/142	54/154	0.57 (0.37, 0.87)
1	23/83	29/73	0.58 (0.33, 1.00)
Disease stage at baseline			
II	16/92	29/91	0.47 (0.26, 0.87)
IIIA	42/132	54/133	0.62 (0.42, 0.94)
Histologic type of tumour			
Squamous	43/179	63/175	0.56 (0.38, 0.83)
Non-squamous	15/45	19/50	0.64 (0.32, 1.26)
PD-L1 expression			
<1% [excluding not evaluable/indeterminate]	26/89	27/84	0.80 (0.47, 1.38)
≥1%	31/130	51/132	0.50 (0.32, 0.78)
1-49%	12/59	31/70	0.34 (0.17, 0.66)
≥50%	19/71	20/62	0.71 (0.38, 1.34)
Smoking status			
Current	10/43	16/52	0.61 (0.28, 1.34)
Former	40/150	56/138	0.54 (0.36, 0.81)
Never	8/33	11/37	0.60 (0.24, 1.51)



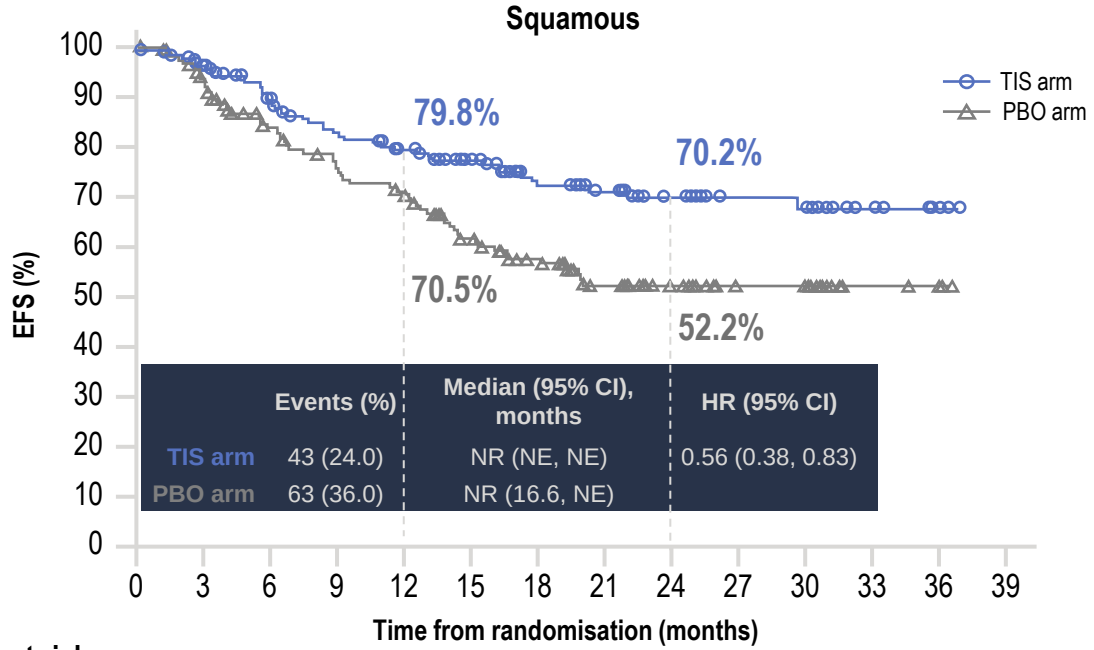
EFS was defined as the time from randomisation until any of the following, whichever occurred first: disease progression precluding surgery, local or distant recurrence, or death due to any cause.
Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; HR, hazard ratio; ITT, intention-to-treat; PD-L1, programmed death-ligand 1;

The EFS benefit with perioperative TIS over PBO was generally consistent across prespecified subgroups

Extracted from Yue D, Wang W, Liu H, Chen Q, Chen C, Liu L, Zhang P et al. RATIONALE-315: Event-Free Survival (EFS) and Overall Survival (OS) of Neoadjuvant Tislelizumab (TIS) plus Chemotherapy (CT) with Adjuvant TIS in Resectable Non-Small Cell Lung Cancer (NSCLC). Presented at the ESMO Virtual Plenary with AACR Expert Commentary; February 15&16, 2024 (Accessed 17 July 2024). Available at: Yue_BGB-A317-315_ESMO-VP_Presentation_2024.pdf

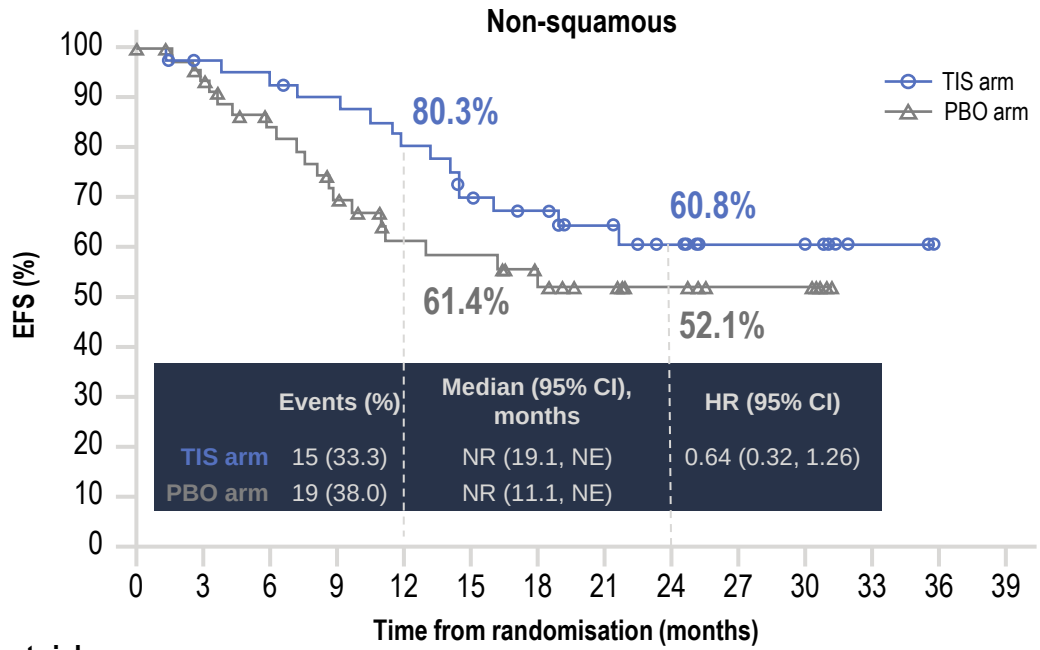
Event-Free Survival By Histology

ITT Analysis Set



Number at risk:

TIS arm	179	154	135	122	112	99	80	65	53	29	27	8	3	0
PBO arm	175	143	114	101	92	75	61	45	33	18	17	4	2	0



Number at risk:

TIS arm	45	40	39	36	32	27	24	18	13	8	8	2	0	0
PBO arm	50	43	35	28	21	20	16	12	9	6	6	0	0	0

The EFS improvement with perioperative TIS over PBO was consistently observed in patients with squamous and non-squamous NSCLC

EFS was defined as the time from randomisation until any of the following, whichever occurred first: disease progression precluding surgery, local or distant recurrence, or death due to any cause.

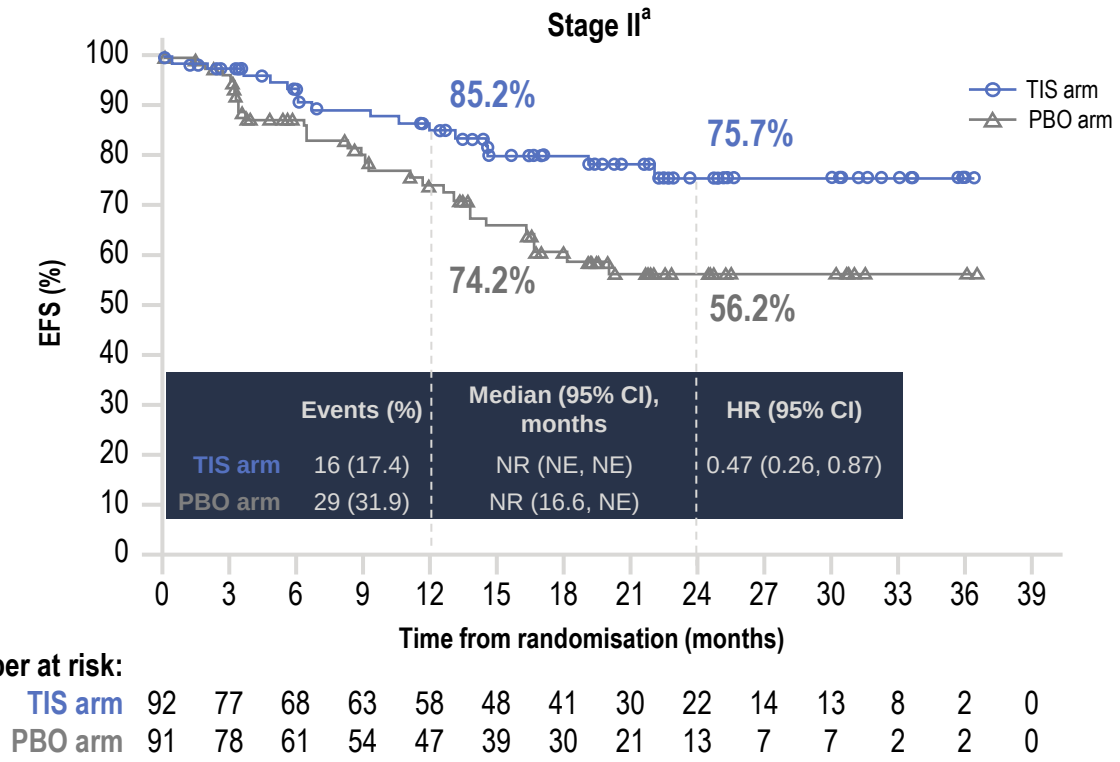
Abbreviations: CI, confidence interval; EFS, event-free survival; HR, hazard ratio; ITT, intention-to-treat; NE, not evaluable; NR, not reached; NSCLC, non-small cell lung cancer; PBO, placebo; TIS, tislelizumab.

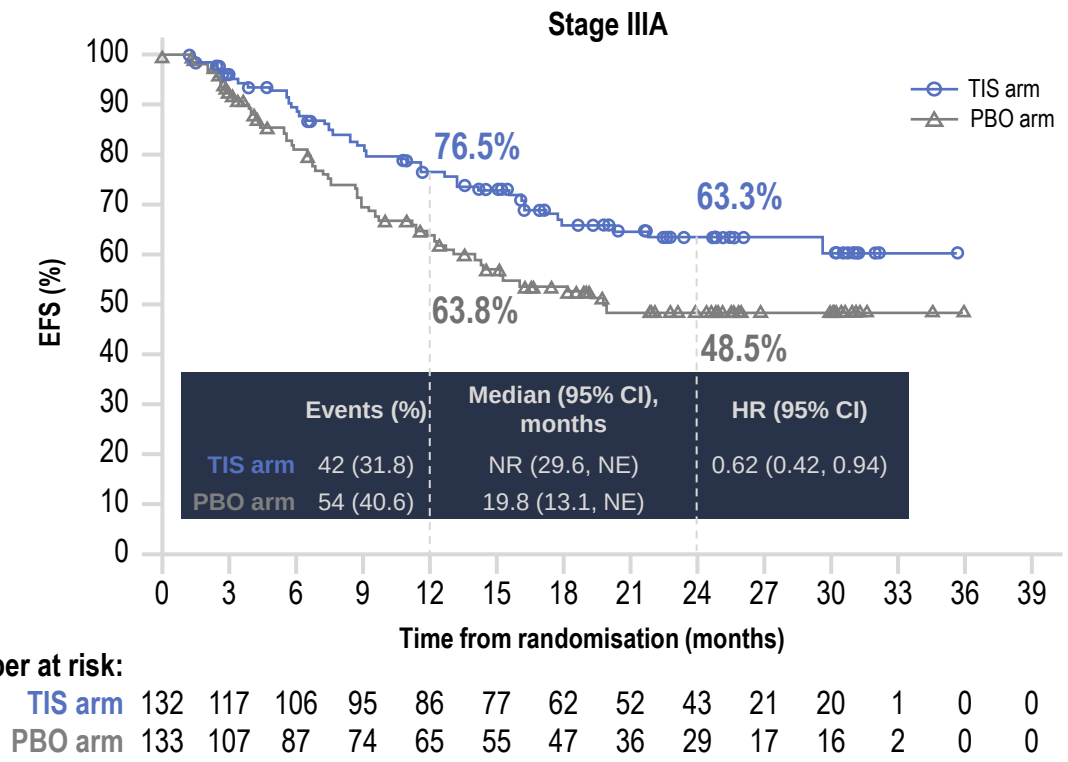
ESMO VIRTUAL PLENARY
WITH AACR EXPERT COMMENTARY

Extracted from Yue D, Wang W, Liu H, Chen Q, Chen C, Liu L, Zhang P et al. RATIONALE-315: Event-Free Survival (EFS) and Overall Survival (OS) of Neoadjuvant Tislelizumab (TIS) plus Chemotherapy (CT) with Adjuvant TIS in Resectable Non-Small Cell Lung Cancer (NSCLC). Presented at the ESMO Virtual Plenary with AACR Expert Commentary; February 15&16, 2024 (Accessed 17 July 2024). Available at: Yue_BGB-A317-315_ESMO-VP_Presentation_2024.pdf

Event-Free Survival By Disease Stage

ITT Analysis Set





The EFS benefit with perioperative TIS over PBO was confirmed in patients with stage II and IIIA NSCLC

[a] Stage IIA, IIB: 6.2% and 34.5% in TIS arm, 4.8% and 35.2% in PBO arm. EFS was defined as the time from randomisation until any of the following, whichever occurred first: disease progression precluding surgery, local or distant recurrence, or death due to any cause.
Abbreviations: CI, confidence interval; EFS, event-free survival; HR, hazard ratio; ITT, intention-to-treat; NE, not evaluable; NR, not reached; NSCLC, non-small cell lung cancer; PBO, placebo; TIS, tislelizumab.

ESMO VIRTUAL PLENARY
WITH AACR EXPERT COMMENTARY

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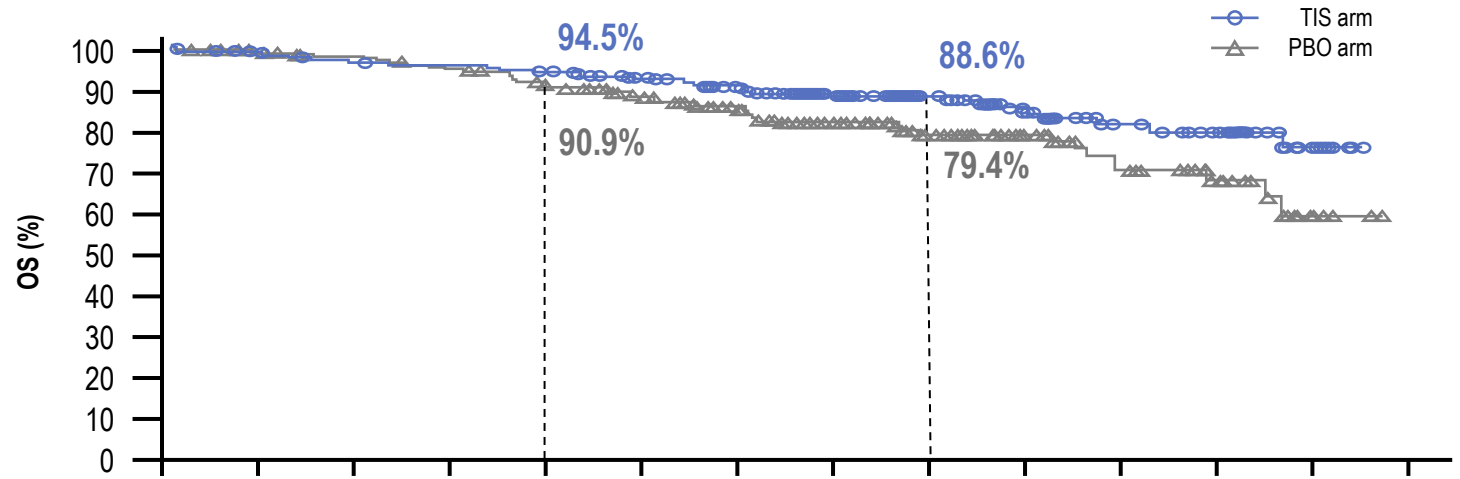
Overall Survival

ITT Analysis Set

	Events (%)	Median (95% CI), months	HR (95% CI)	*P*-value
TIS arm	31 (13.7)	NR (NE, NE)	**0.62 (0.39, 0.98)**	0.0193
PBO arm	45 (19.8)	NR (35.0, NE)		



Number at risk:														
TIS arm	226	218	211	208	204	184	160	131	103	72	47	35	11	0
PBO arm	227	214	207	199	182	157	136	112	84	55	40	26	7	0

An OS benefit trend (HR=0.62 [95% CI: 0.39, 0.98]; one-sided *P*=0.0193) was observed favouring perioperative TIS

OS was defined as the time from the date of randomisation to the date of death due to any cause.

Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; NE, not evaluable; NR, not reached; OS, overall survival; PBO, placebo; TIS, tislelizumab.

Extracted from Yue D, Wang W, Liu H, Chen Q, Chen C, Liu L, Zhang P et al. RATIONALE-315: Event-Free Survival (EFS) and Overall Survival (OS) of Neoadjuvant Tislelizumab (TIS) plus Chemotherapy (CT) with Adjuvant TIS in Resectable Non-Small Cell Lung Cancer (NSCLC). Presented at the ESMO Virtual Plenary with AACR Expert Commentary; February 15&16, 2024 (Accessed 17 July 2024). Available at: Yue_BGB-A317-315_ESMO-VP_Presentation_2024.pdf

Safety Summary

Safety Analysis Set

n (%)	TIS arm (N=226)	PBO arm (N=226)
Patients with ≥1 TRAE	224 (99.1)	225 (99.6)
Grade ≥3	163 (72.1)	150 (66.4)
Serious	35 (15.5)	18 (8.0)
Leading to death[a]	4 (1.8)	2 (0.9)
Leading to discontinuation	29 (12.8)	21 (9.3)
Leading to dose modification[b]	88 (38.9)	73 (32.3)
Leading to surgery delay[c]	12 (5.3)	4 (1.8)
Leading to surgery cancellation	1 (0.4)	1 (0.4)
Patients with ≥1 immune-mediated AE	90 (39.8)	40 (17.7)
Grade ≥3	21 (9.3)	6 (2.7)
Serious	23 (10.2)	5 (2.2)
Leading to death	2 (0.9)[d]	0
Leading to discontinuation	15 (6.6)	0
Leading to dose modification	30 (13.3)	6 (2.7)

[a] TIS arm (n=1 each): infection, pneumonia, pneumonitis, immune-mediated lung disease. PBO arm: respiratory haemorrhage, cardiac failure. [b] Including temporary discontinuation of TIS/PBO in neoadjuvant phase, chemotherapy dose reduction, dose interruption, dose delay, and infusion rate decrease. [c] Defined as when date of surgery is beyond 6 weeks after last neoadjuvant treatment dose. [d] (n=1 each): pneumonitis, immune-mediated lung disease.
The safety analysis set included all randomised patients who received ≥1 dose of any study drug. AEs were classified based on MedDRA v26.0. AEs were graded for severity using Common Terminology Criteria for AEs v5.0.
Abbreviations: AE, adverse event; PBO, placebo; MedDRA, Medical Dictionary for Regulatory Activities; TIS, tislelizumab; TRAE, treatment-related adverse event.

Extracted from Yue D, Wang W, Liu H, Chen Q, Chen C, Liu L, Zhang P et al. RATIONALE-315: Event-Free Survival (EFS) and Overall Survival (OS) of Neoadjuvant Tislelizumab (TIS) plus Chemotherapy (CT) with Adjuvant TIS in Resectable Non-Small Cell Lung Cancer (NSCLC). Presented at the ESMO Virtual Plenary with AACR Expert Commentary; February 15&16, 2024 (Accessed 17 July 2024). Available at: Yue_BGB-A317-315_ESMO-VP_Presentation_2024.pdf

Most Frequently Reported TRAEs

≥20% of Patients; Safety Analysis Set

	TIS arm (N=226)		PBO arm (N=226)	
n (%)	Any grade	Grade ≥3	Any grade	Grade ≥3
Neutrophil count decreased	177 (78.3)	138 (61.1)	176 (77.9)	134 (59.3)
White blood cell count decreased	143 (63.3)	38 (16.8)	152 (67.3)	32 (14.2)
Alopecia	106 (46.9)	1 (0.4)	118 (52.2)	1 (0.4)
Anaemia	91 (40.3)	11 (4.9)	96 (42.5)	15 (6.6)
ALT increased	65 (28.8)	2 (0.9)	48 (21.2)	1 (0.4)
Nausea	60 (26.5)	1 (0.4)	59 (26.1)	0 (0.0)
AST increased	53 (23.5)	2 (0.9)	38 (16.8)	0 (0.0)
Platelet count decreased	47 (20.8)	5 (2.2)	49 (21.7)	6 (2.7)
Hypoaesthesia	44 (19.5)	0 (0.0)	47 (20.8)	0 (0.0)
Decreased appetite	40 (17.7)	1 (0.4)	47 (20.8)	0 (0.0)

AEs were classified based on MedDRA v26.0 and were graded for severity using Common Terminology Criteria for Adverse Events v5.0.
Abbreviations: AE, adverse event; ALT, alanine transaminase; AST, aspartate transaminase; PBO, placebo; MedDRA, Medical Dictionary for Regulatory Activities; TIS, tislelizumab; TRAE, treatment-related adverse event.

ESMO VIRTUAL PLENARY
WITH AACR EXPERT COMMENTARY

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Most Frequently Reported Immune-Mediated AEs

≥1% of Patients; Safety Analysis Set

	TIS arm (N=226)		PBO arm (N=226)	
n (%)	Any grade	Grade ≥3	Any grade	Grade ≥3
Immune-mediated skin adverse reaction	39 (17.3)	5 (2.2)	24 (10.6)	0 (0.0)
Immune-mediated pneumonitis	18 (8.0)	7 (3.1)	4 (1.8)	0 (0.0)
Immune-mediated hepatitis	5 (2.2)	4 (1.8)	5 (2.2)	5 (2.2)
Immune-mediated endocrinopathies				
Hypothyroidism	33 (14.6)	2 (0.9)	6 (2.7)	0 (0.0)
Hyperthyroidism	16 (7.1)	1 (0.4)	7 (3.1)	0 (0.0)
Thyroiditis	5 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)
Adrenal insufficiency	3 (1.3)	1 (0.4)	0 (0.0)	0 (0.0)

AEs were classified based on MedDRA v26.0 and were graded for severity using Common Terminology Criteria for Adverse Events v5.0.
Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; PBO, placebo; TIS, tislelizumab.

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Patient-reported outcomes in the RATIONALE-315 trial

Presented at ESMO 2024 poster #1213P on Saturday, 14 September: Cappuzzo et al. 2024 PROs in R-315

Patients in the tislelizumab + CT arm experienced better HRQoL outcomes than those in the placebo + CT arm in this population of patients with resectable NSCLC, with improvements in coughing and lower risk of chest pain

HRQoL endpoint	Least Squares Mean (95% CI)			
	Cycle 3: adjuvant phase		Cycle 7: adjuvant phase	
	TIS	PBO	TIS	PBO
QLQ-C30				
GHS/QoL	-1.14 (-3.79, 1.52)	-1.97 (-4.77, 0.83)	1.09 (-1.34, 3.53)	1.90 (-0.66, 4.46)
Physical functioning	-3.57 (-5.10, -2.05)	-3.61 (-5.22, -2.01)	-2.60 (-4.20, 1.00)	-2.23 (-3.92, -0.54)
Fatigue	2.52 (0.23, 4.81)	2.97 (0.57, 5.37)	2.54 (0.09, 4.99	2.87 (0.30, 5.45)
QLQ-LC13				
Coughing	-4.58 (-7.75, -1.42)	-5.63 (-8.97, -2.29)	-12.15 (-15.60, -8.71)	-7.52 (-11.16, -3.89)
Chest pain	0.43 (-2.42, 3.28)	5.42 (2.39, 8.44)	0.36 (-2.34, 3.05)	1.89 (-0.96, 4.75)
Dyspnea	4.62 (2.57, 6.67)	6.57 (4.41, 8.74)	3.18 (0.82, 5.55)	4.56 (2.07, 7.06)

CI, confidence interval; CT, chemotherapy; GHS, global health status; HRQoL, health-related quality of life; NSCLC, non-small cell lung cancer; PBO, placebo; PRO, patient-reported outcomes; QLQ, quality of life questionnaire; TIS, tislelizumab.
Extracted from Cappuzzo F et al. ESMO 2024; Abstract 1213P.

Conclusions

- RATIONALE-315 demonstrated a clinically meaningful and statistically significant benefit in EFS with perioperative TIS plus PtDb CT vs PBO plus neoadjuvant PtDb CT at this interim analysis
    - HR=0.56 [95% CI: 0.40, 0.79]; one-sided P=0.0003
    - EFS benefit was generally consistent across predefined subgroups
- MPR and pCR rate were significantly improved: 56.2% vs 15.0% (*P*<.0001) and 40.7% vs 5.7% (*P*<.0001), respectively
- An OS benefit trend favouring perioperative TIS (HR=0.62 [95% CI: 0.39, 0.98]; one-sided *P*=0.0193) was observed at this interim analysis. The trial will continue to assess OS with longer follow-up
- The safety profile of perioperative TIS plus PtDb CT was manageable and consistent with the known risks of the individual therapies
- Taken together, the statistically and clinically significant EFS, MPR, and pCR benefits, alongside manageable safety, support the use of perioperative TIS plus neoadjuvant PtDb CT for patients with resectable stage II-IIIA NSCLC

Abbreviations: CI, confidence interval; EFS, event-free survival; HR, hazard ratio; MPR, major pathological response; NSCLC, non-small cell lung cancer; OS, overall survival; PBO, placebo; PtDb CT, platinum-based doublet chemotherapy; TIS, tislelizumab.

Extracted from Yue D, Wang W, Liu H, Chen Q, Chen C, Liu L, Zhang P et al. RATIONALE-315: Event-Free Survival (EFS) and Overall Survival (OS) of Neoadjuvant Tislelizumab (TIS) plus Chemotherapy (CT) with Adjuvant TIS in Resectable Non-Small Cell Lung Cancer (NSCLC). Presented at the ESMO Virtual Plenary with AACR Expert Commentary; February 15&16, 2024 (Accessed 17 July 2024). Available at: Yue_BGB-A317-315_ESMO-VP_Presentation_2024.pdf

Single agent IO is the only treatment option for NSCLC with high PD-L1 expression

Debate: PRO – CON

Single agent IO is the only treatment option for NSCLC with high PD-L1 expression

Debate: PRO

Martin Reck, MD, PhD

Lung Clinic Grosshansdorf,
Grosshansdorf, Germany

Disclosures

COI	Sponsor
Honoraria for lectures and consultancy from:	Amgen, AstraZeneca, BeiGene, Boehringer-Ingelheim, Daiichi-Sankyo, Lilly, Mirati, Merck, MSD, Novartis, Pfizer, Roche, Sanofi, Samsung Bioepis
Compensated Membership in Study Steering Committees:	Amgen, AstraZeneca, BeiGene, Daiichi-Sankyo, Mirati, Merck, MSD, Novartis, Pfizer, Roche, Sanofi
Compensated Membership in Data Safety Monitoring Committees:	Daiichi-Sankyo, Sanofi

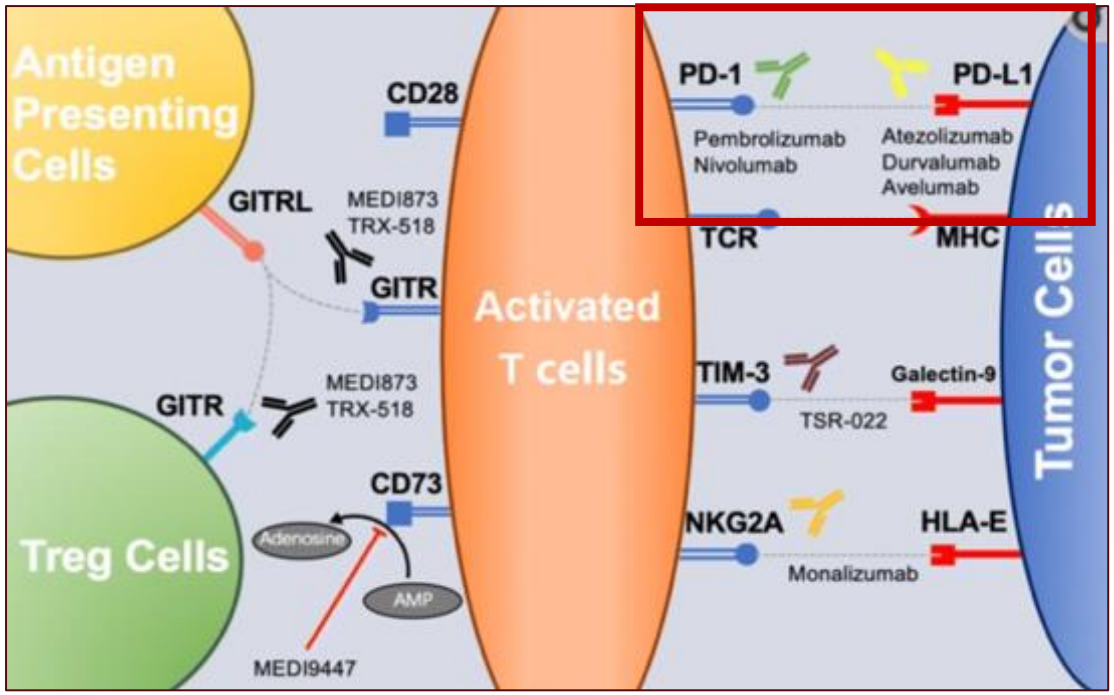
COI, conflict of interest.

The major challenge: Not the debate, but the debate “against“ a colleague with a long history of friendship!

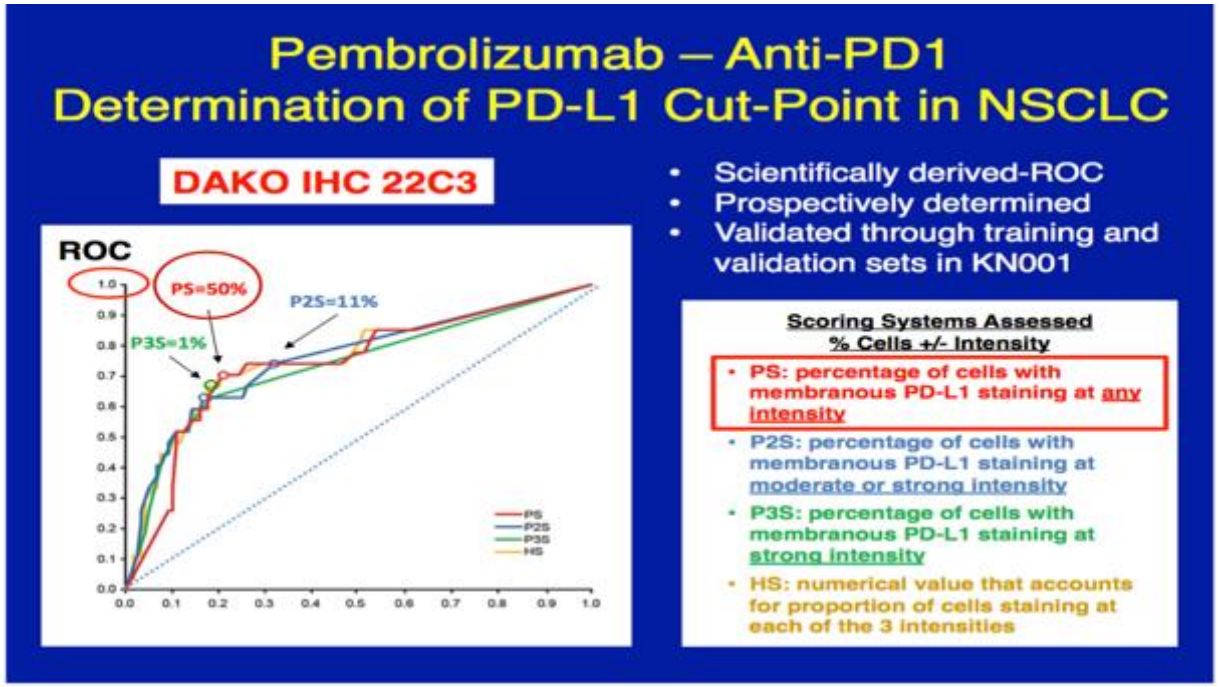
And by the way one of the inventors of targeted monotherapies in oncogenic-driven LC!!

Immunotherapy with anti-PD(L)1 checkpoint inhibitors – the breakthrough in non-oncogenic-driven NSCLC

The concept



The therapeutic cut-off of 50% PD-L1 expression (TPS)



CD28 or 73, cluster of differentiation 28 or 73; GITR, glucocorticoidinduced tumor necrosis factor receptor–related protein; HLA-E, human leukocyte antigen-E; MHC, major histocompatibility complex; NKG2A, natural killer cell receptor group 2 member A; NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1; ROC, receiver operating characteristic; TCR, T cell receptor; TIM-3, cell immunoglobulin and mucin domain-containing protein 3; TPS, tumor proportion score.
Extracted from 1) Qiu Z et al. Exp Hematol Oncol. 2019:8:19; 2) Garon E et al N Engl J Med. 2015;372(21):2018-28 (supplementary appendix).

Single agent IO – an attractive concept!

2

Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial

Tony S K Mok, Yi-Long Wu, Iveta Kudaba, Dariusz M Kowalski, Byoung Chul Cho, Hande Z Turna, Gilberto Castro Jr, Vichien Srimuninnimit, Konstantin K Laktionov, Igor Bondarenko, Kaoru Kubota, Gregory M Lubiniecki, Jin Zhang, Debra Kush, Gilberto Lopes, for the KEYNOTE-042 Investigators*

1

ORIGINAL ARTICLE

Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer

Martin Reck, M.D., Ph.D., Delvys Rodríguez-Abreu, M.D., Andrew G. Robinson, M.D., Rina Hui, M.B., B.S., Ph.D., Tibor Csőszi, M.D., Andrea Fülöp, M.D., Maya Gottfried, M.D., Nir Peled, M.D., Ph.D., Ali Tafreshi, M.D., Sinead Cuffe, M.D., Mary O'Brien, M.D., Suman Rao, M.D., Katsuyuki Hotta, M.D., Ph.D., Melanie A. Leiby, Ph.D., Gregory M. Lubiniecki, M.D., Yue Shentu, Ph.D., Reshma Rangwala, M.D., Ph.D., and Julie R. Brahmer, M.D., for the KEYNOTE-024 Investigators*

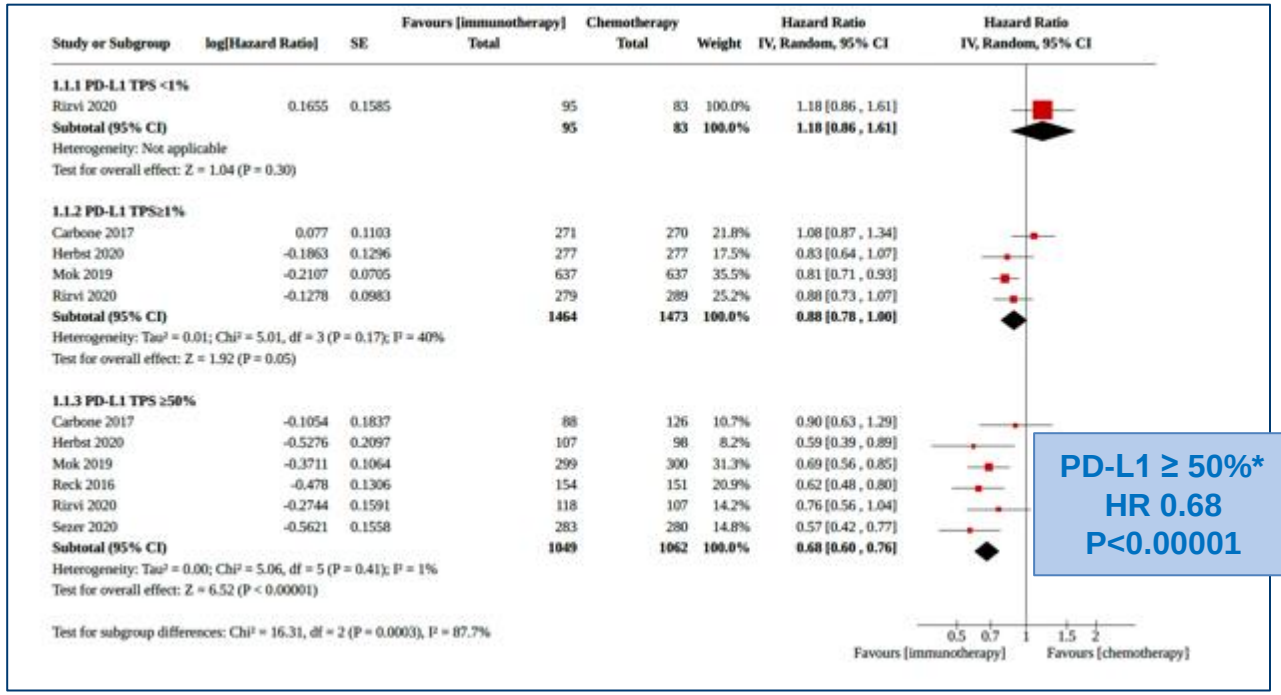
IO, immuno-oncology; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death-ligand 1.

1) Reck M et al. N Engl J Med. 2016;375(19):1823-1833; 2) Mok TSK et al. Lancet. 2019;393(10183):1819-1830.

IO monotherapy vs chemotherapy
What do we know?

Better efficacy

Overall survival

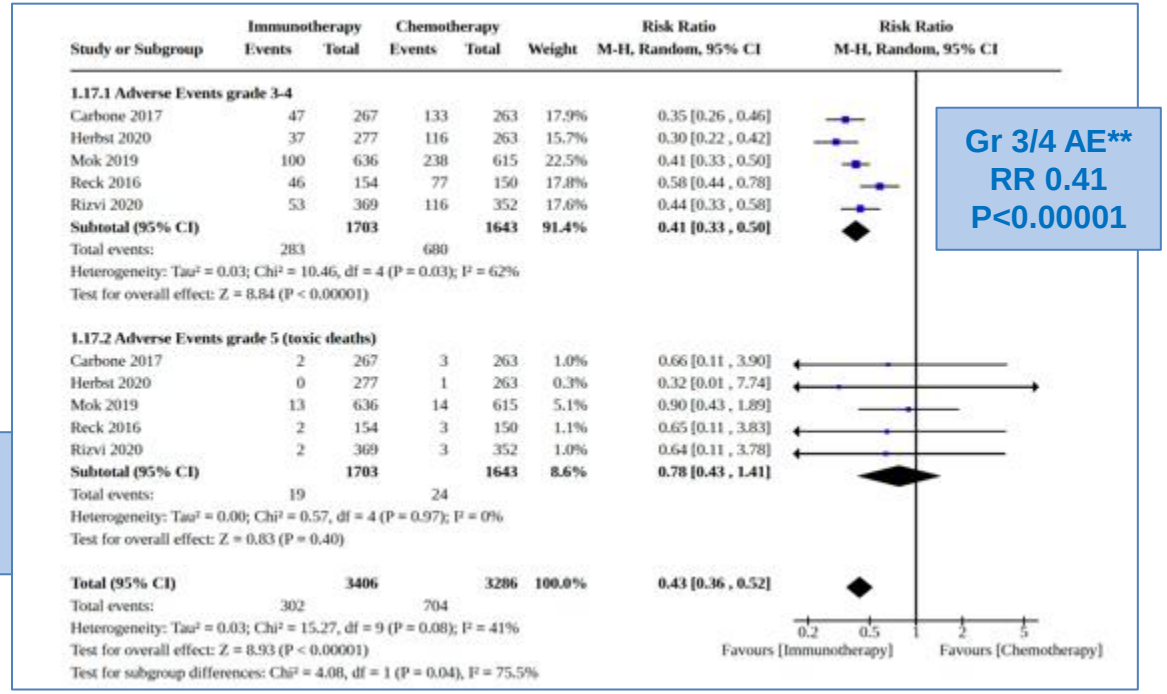


PD-L1 ≥ 50%*
HR 0.68
P<0.00001

* Moderate certainty of evidence

Better tolerability

Adverse events



Gr 3/4 AE**
RR 0.41
P<0.00001

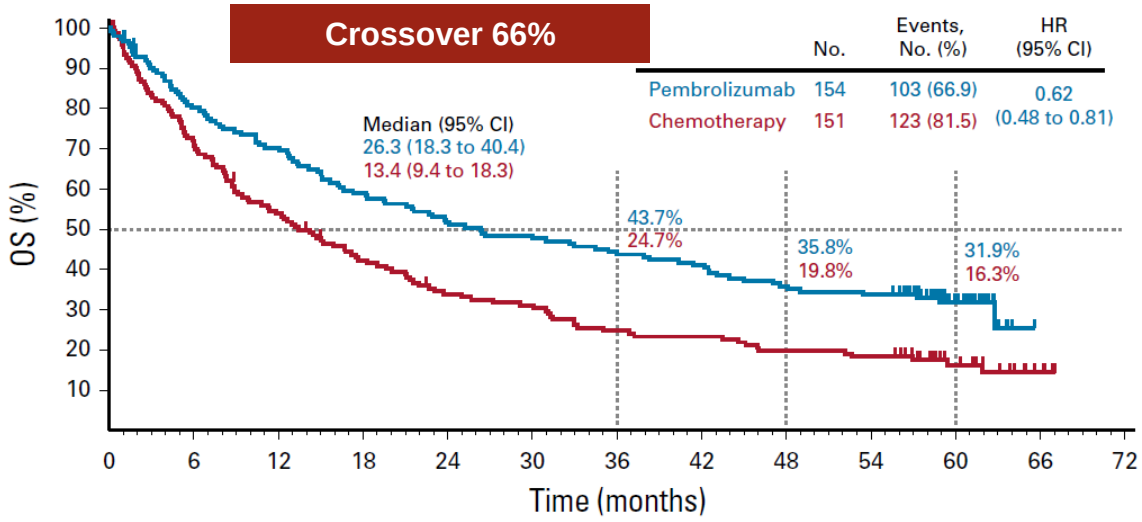
** Low certainty of evidence

Single-agent IO vs platinum-based chemotherapy

AE, adverse event; CI, confidence interval; Gr, grade; HR, hazard ratio; IO, immuno-oncology; PD-L1, programmed cell death-ligand 1; RR, risk ratio.
Extracted from Ferrara R et al. Cochrane Database Syst Rev. 2021;4(4):CD013257.

IO monotherapy – the miracle of long-term survival
Example: Keynote-024 trial

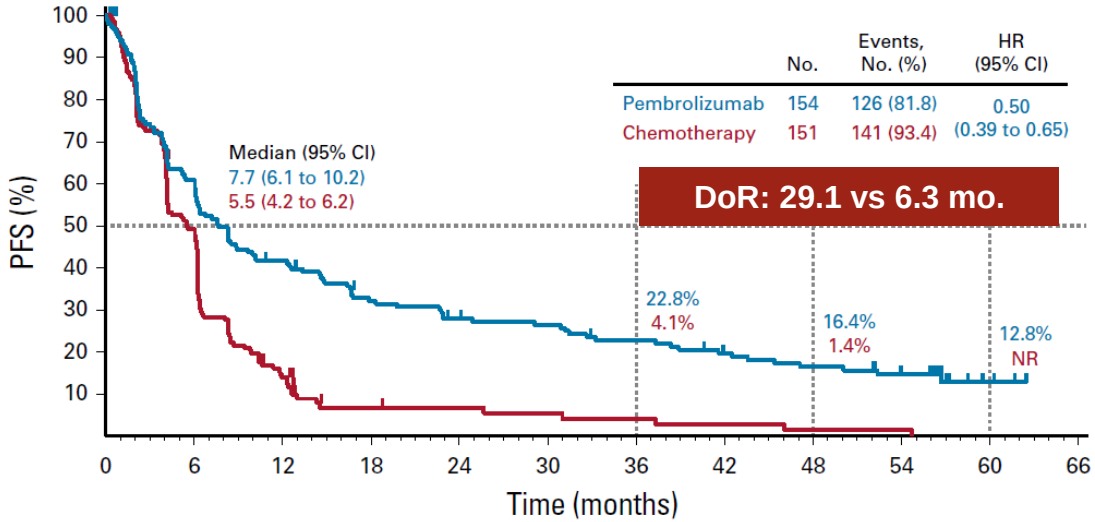
OS



No. at risk:

Pembrolizumab	154	121	106	89	78	73	66	62	54	51	20	0	0
Chemotherapy	151	108	80	61	48	44	35	33	28	26	13	3	0

PFS



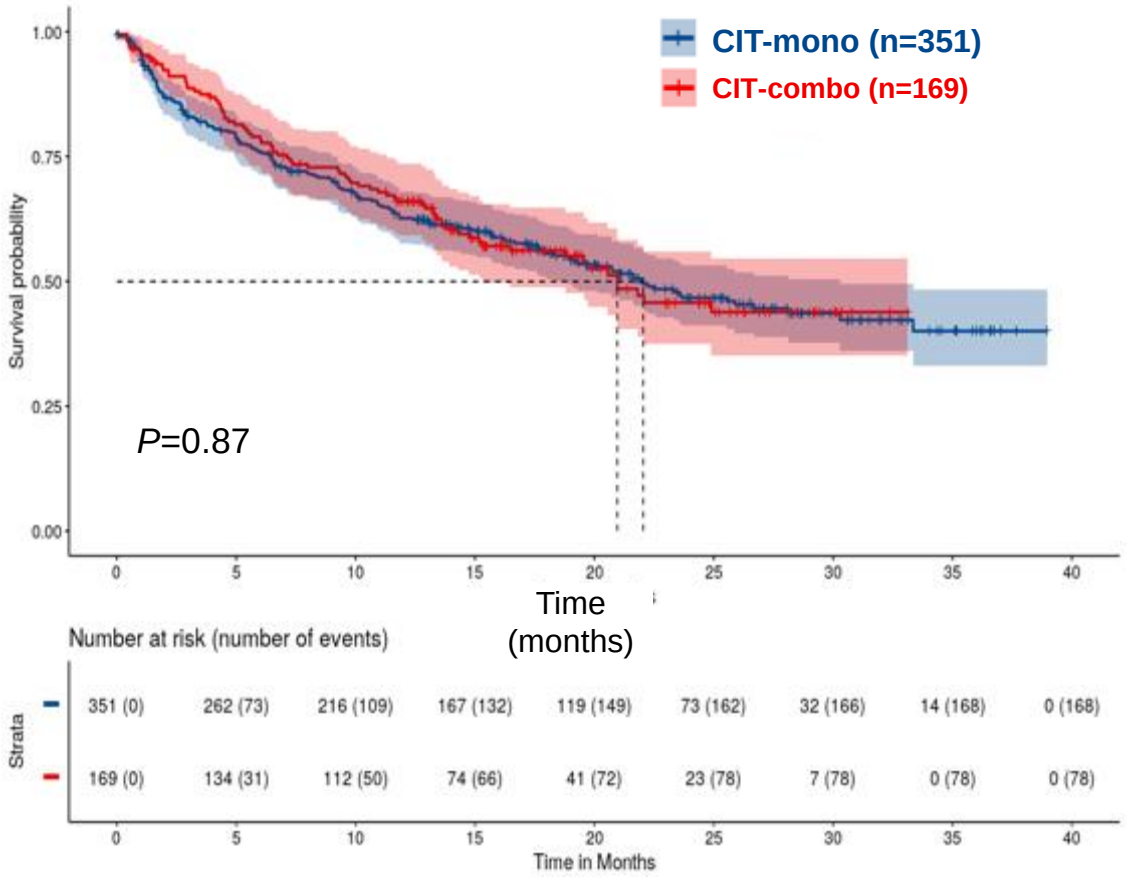
No. at risk:

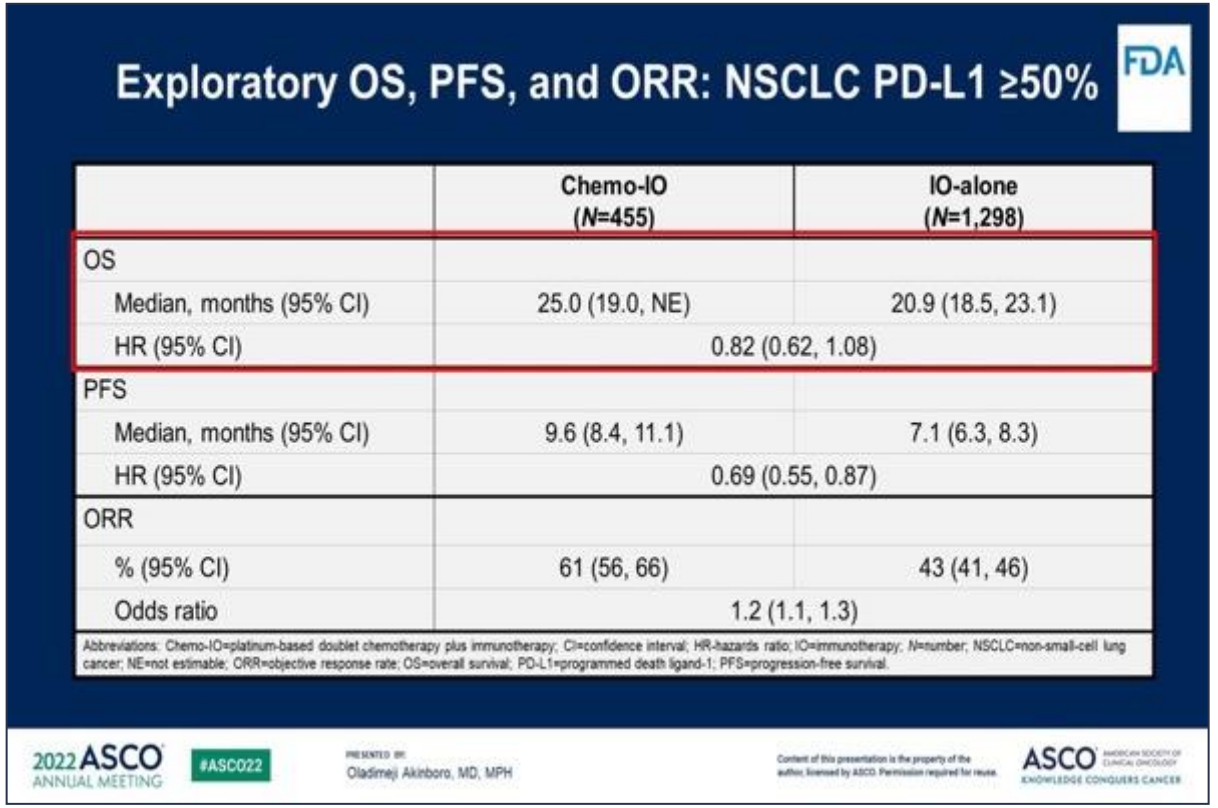
Pembrolizumab	154	92	62	46	38	36	30	24	20	15	3	0	
Chemotherapy	151	73	20	6	5	4	3	2	1	1	0	0	

5-year OS: 31.9% vs 16.3%
Crossover: 66%

CI, confidence interval; DoR, duration of response; HR, hazard ratio; IO, immuno-oncology; mo., months; OS, overall survival; PFS, progression-free survival.
Extracted from Reck M et al. J Clin Oncol. 2021;39(21):2339-2349.

IO vs IO + chemotherapy in PD-L1 ≥ 50%
Any benefit of combination? : No clear data





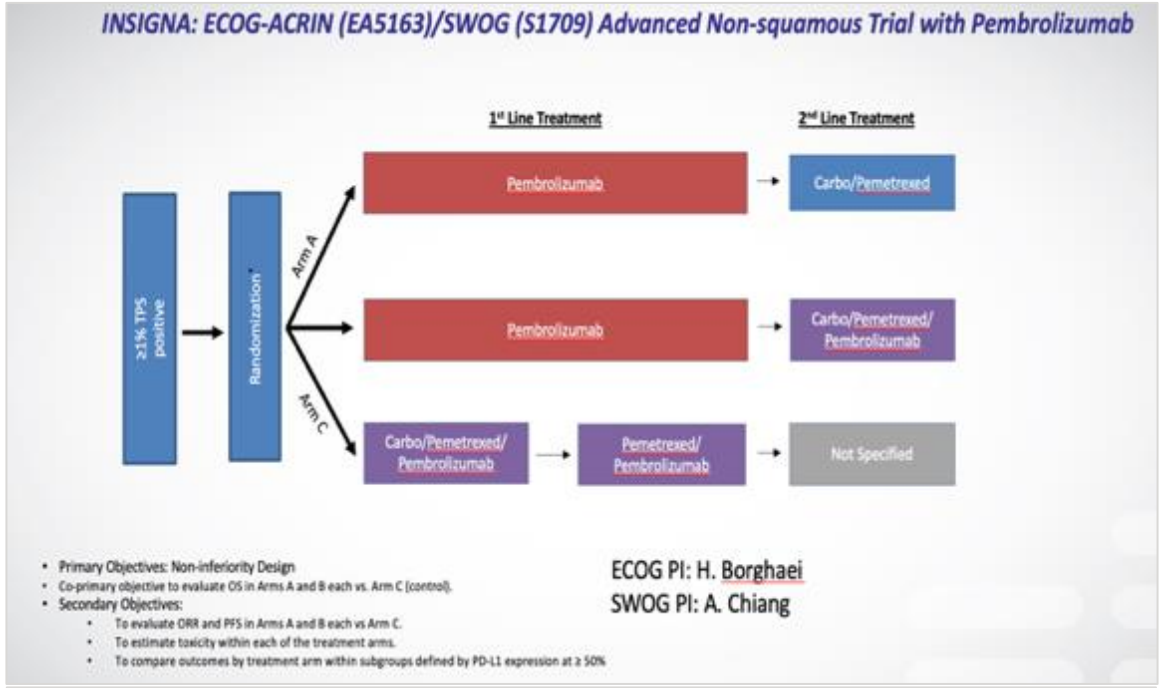
- Benefit for IO/CT vs IO in PFS
- No significant difference in OS
- IO monotherapy beneficial in elderly patients (≥ 75 years)

Chemo or CT, chemotherapy; CI, confidence interval; CIT, chemoimmunotherapy; HR, hazard ratio; IO, immuno-oncology; NE, not estimable; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival.

Extracted from Reck M et al. Presented at the ASCO 2024 Annual Meeting; May 31-June 04, 2024; Chicago, IL (Accessed 31 July 2024). Available at: https://meetings.asco.org/2024-asco-annual-meeting/15686?presentation=228375#228375.

Ongoing prospective trials

Insigna Trial[1]

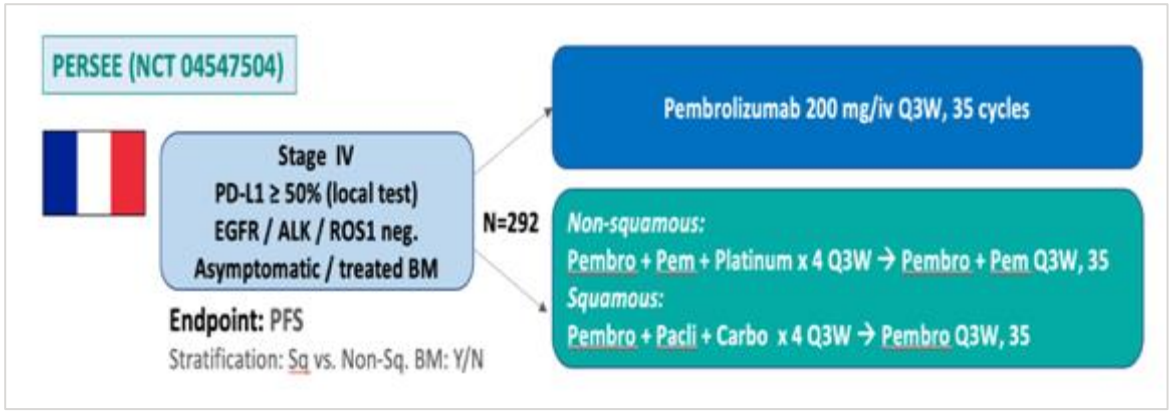


Integrated Biomarker Objective:

- To establish a ***predictive signature*** for clinical benefit (OS), to treatment with chemo combined with pembrolizumab versus pembrolizumab alone in patients with PD-L1 expressing tumors (>=1%, 1-49%, >=50%).
- To establish a ***prognostic signature*** associated with better outcome (OS) to 1st line treatment with pembrolizumab alone in patients with PD-L1 expressing tumors (>=1%, 1-49%, >=50% TPS).

Persee Trial[2]

GFPC 01-2020



Primary endpoint: PFS
Exploratory endpoints: Early progression rate, QoL, translational analysis of blood and tissue based biomarkers

OS, overall survival; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; QoL, quality of life; Q3W, every 3 weeks; TPS, tumor proportion score.
1) Provided courtesy of Hoss Borghaei and David Carbone; 2) Provided courtesy of R Descourt and C Decroisette.

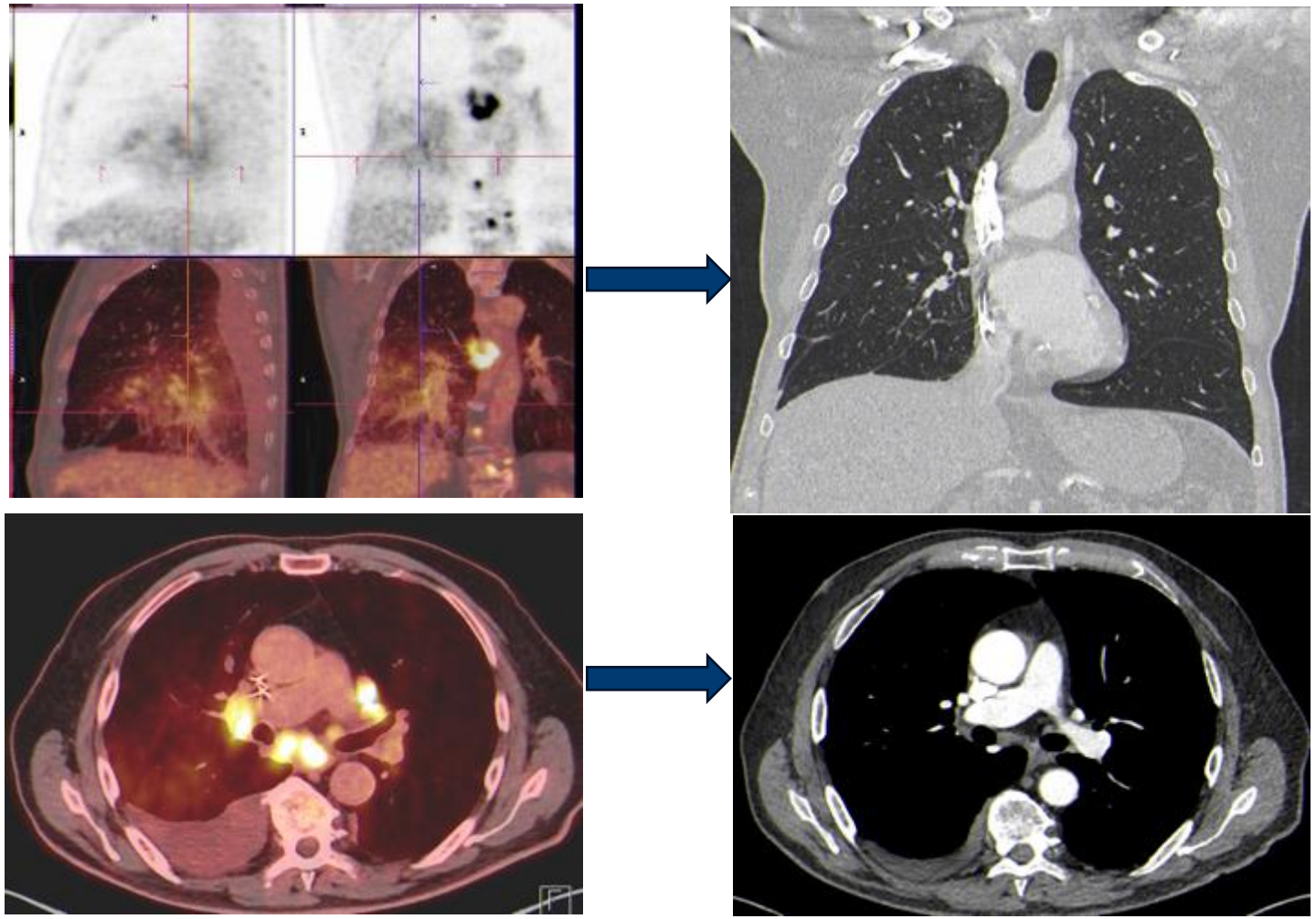
So, how to proceed in clinical practice?

- Let´s ask the patients!

Patient A

04/23

IO Monotherapy
08/24



85-year-old male patient

- 03/23 Admission for diagnosis of stroke
- „By accident“ diagnosis of metastatic adenocarcinoma
- No actionable mutation
- PD-L1 Expression: 80% TPS
- Treatment recommendation?

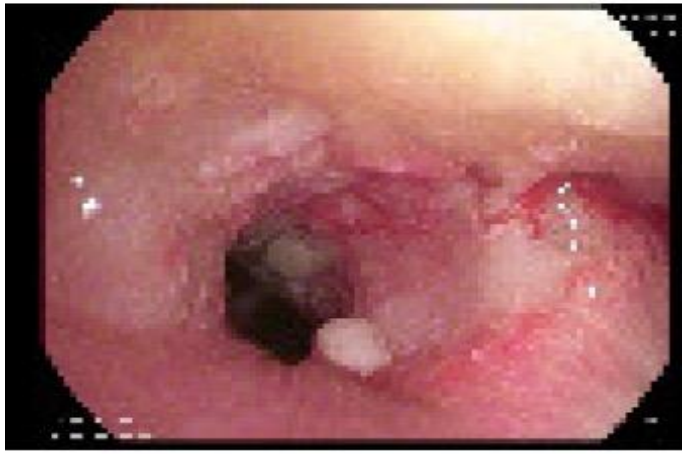
- Improvement of cough
- Improvement of dyspnea
- Improvement of fatigue
- “I am feeling fine“!

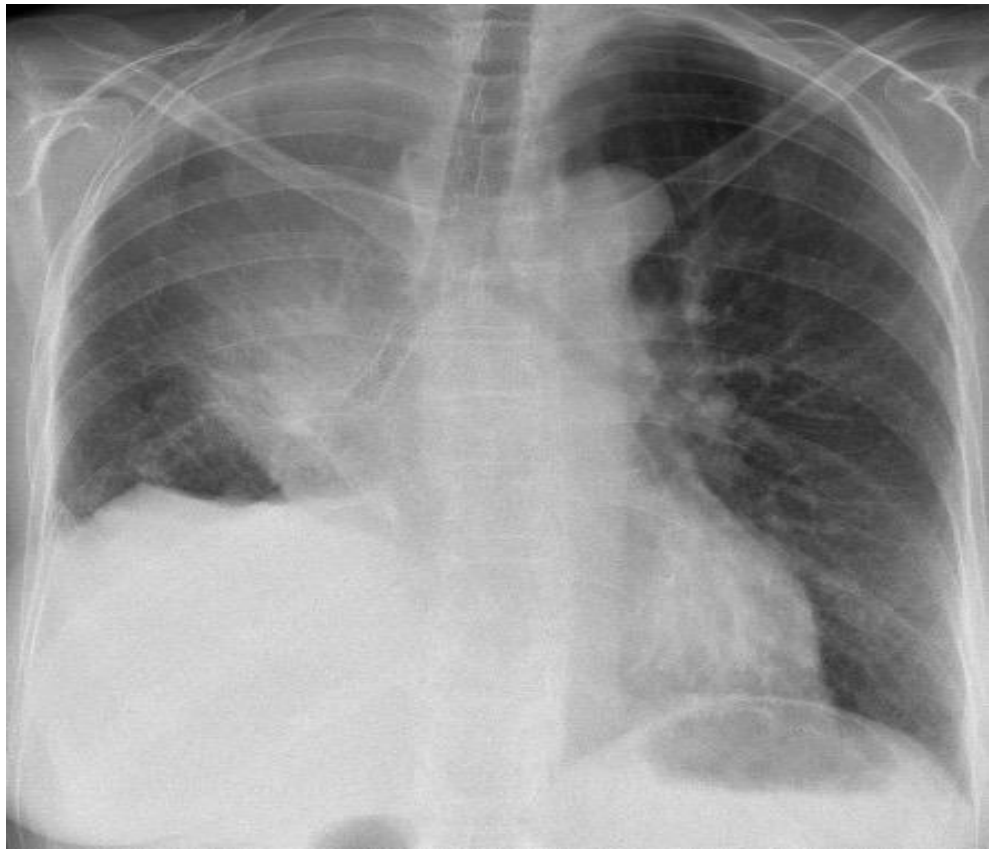
PD-L1, programmed cell death-ligand 1; TPS, tumor proportion score.
Provided by the Speaker for educational purposes only.

Patient B

55-year-old female patient

- Central lung cancer (infiltration of trachea and main bronchi)
- High tumor burden (mediastinal lymph nodes, liver and brain metastases)
- Histology: Low differentiated adenocarcinoma (TTF-1 negative)
- No actionable oncogenic alterations
- PD-L1 55%TPS
- Treatment recommendation?

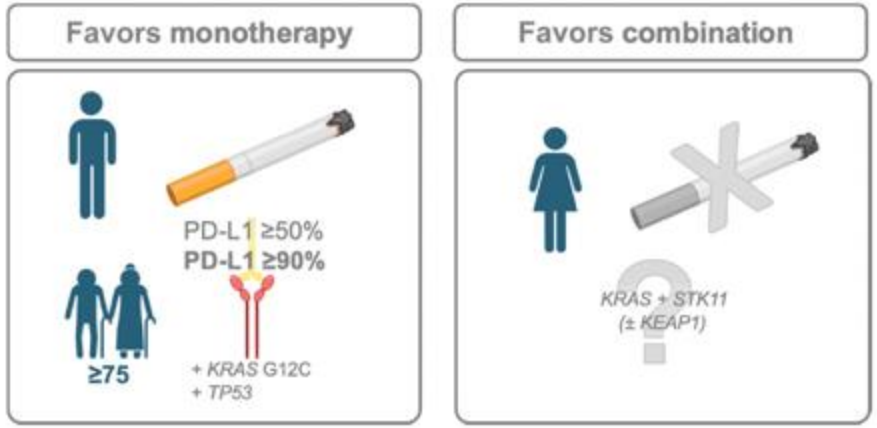




PD-L1, programmed cell death-ligand 1; TPS, tumor proportion score; TTF-1, hyroid transcription factor 1.

Until we get trial results – some guidance for making decisions…

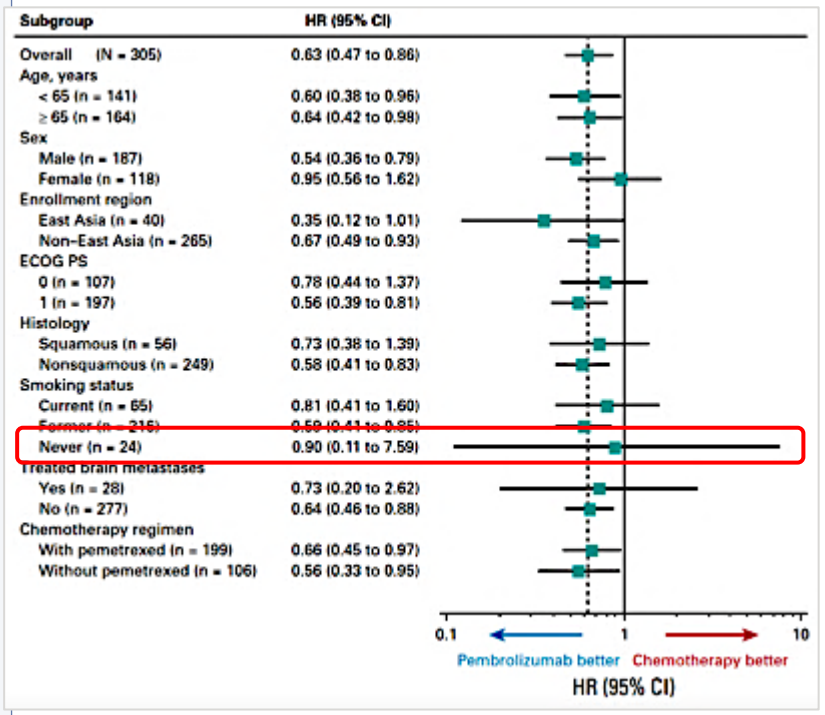
Favors Monotherapy (IO)	Favors Combination (IO+CT)
Elderly patients (≥ 75 y)	Tumor burden
Smoking	Never smoking
PD-L1 ≥ 90% • Improved PFS/OS • Different microenvironment	PD-L1 < 50%
Male	Female (Enhanced efficacy of IO-CT combination)
Molecular profile (*KRAS* G12c + *TP53*) • Immunogenic microenvironment	



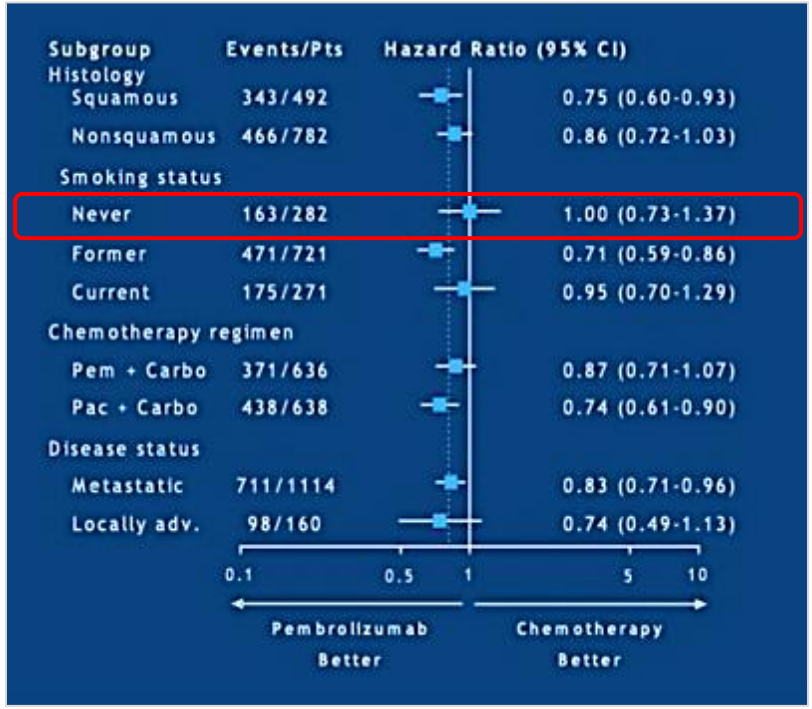
CT, chemotherapy; IO, immuno-oncology; *KRAS*, Kirsten rat sarcoma virus; OS, overall survival; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; *TP53*, tumor protein p53.
Extracted from Frost N and Reck M. Am Soc Clin Oncol Educ Book. 2024;44(3):e432524.

IO monotherapy – no doubt in smokers, but in never-smokers?

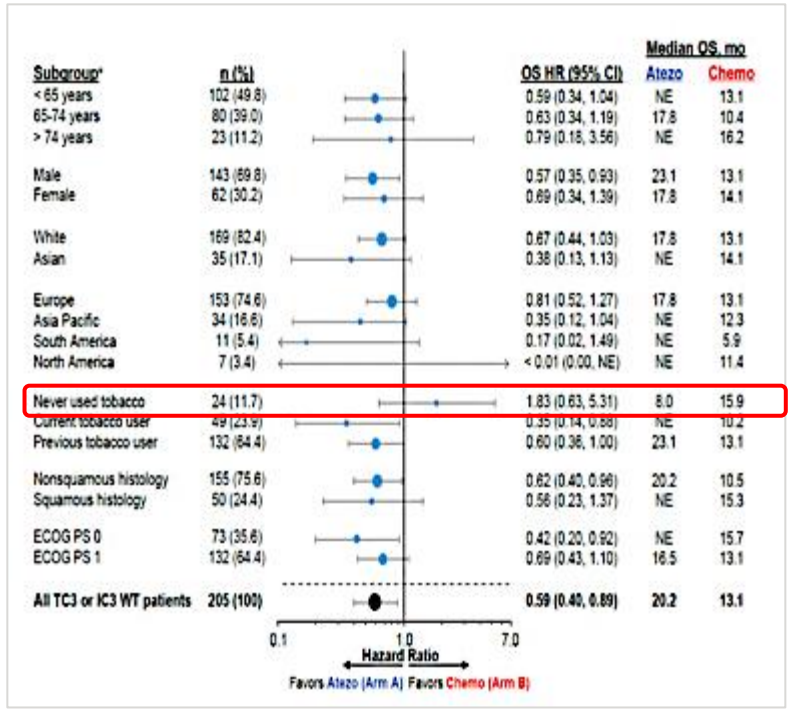
Keynote-024 (TPS ≥50%)[1]



Keynote-042 (TPS ≥1%)[2]



IMpower 110 (TC3/IC3)[3]



HR, 0.9 (95%CI: 0.11–7.59)

HR, 1.00 (95%CI: 0.73–1.37)

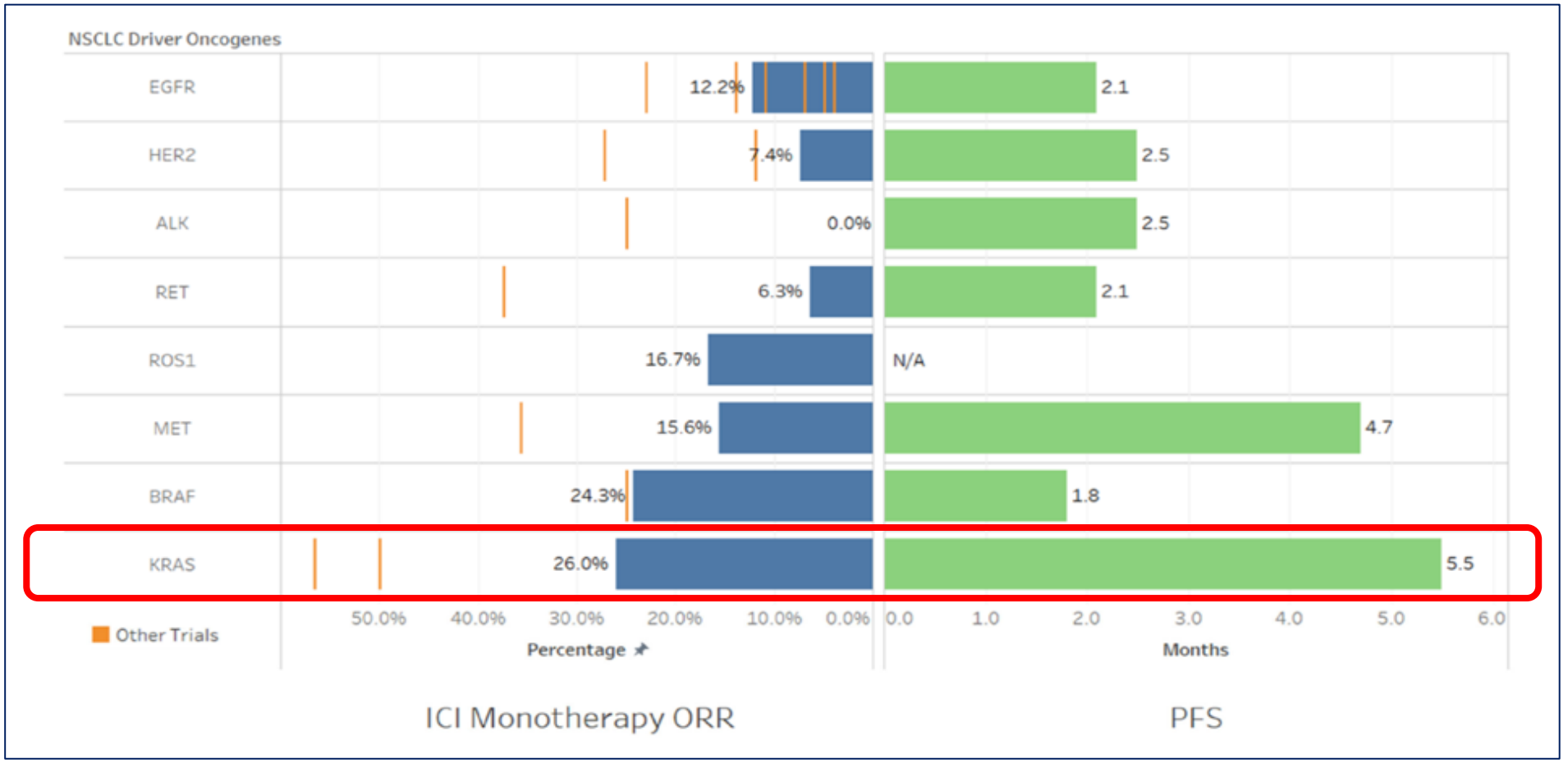
HR, 1.83 (95%CI: 0.63–5.31)

Hazard ratios (95% CIs) in never-smokers

CI, confidence interval; HR, hazard ratio; IC, immune cell; IO, immuno-oncology; TC, tumor cell; TPS, tumor proportion score.

Extracted from 1) Reck M et al. J Clin Oncol. 2019;37(7):537-546; 2) Lopes G et al. Presented at ASCO Annual Meeting; June 1-5, 2018. Abstract LBA4 (Accessed 05 August 2024). Available at: https://psmo.org.ph/wp-content/uploads/2019/04/Non-Small-Cell-Lung-Carcinoma-Abstract-Presentation-C.pdf; 3) Herbst R et al N Engl J Med. 2020;383(14):1328-1339 (supplementary appendix).

Immunotherapy in oncogene-addicted NSCLC



ORR: 0-24.3%, mPFS: 1.8-4.7 months (IMMUNOTARGET study)

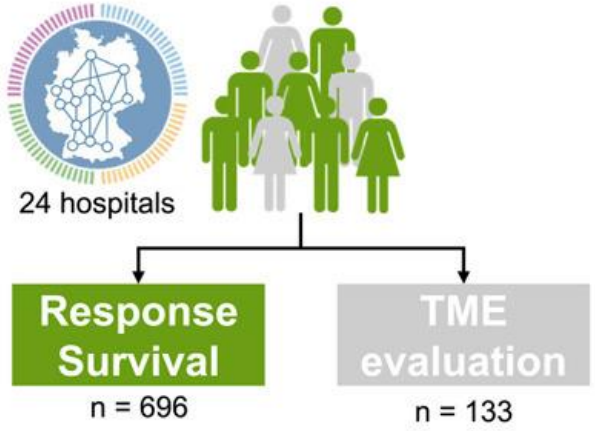
ICI, immune checkpoint inhibitor; mPFS, median progression-free survival; NSCLC, non-small cell lung cancer; ORR, overall response rate.
Extracted from Vokes N et al. Ther Adv Med Oncol. 2023;15:17588359231161409.

German Network Data on *KRAS/TP53* + PD-L1 ≥ 50% and IO monotherapy

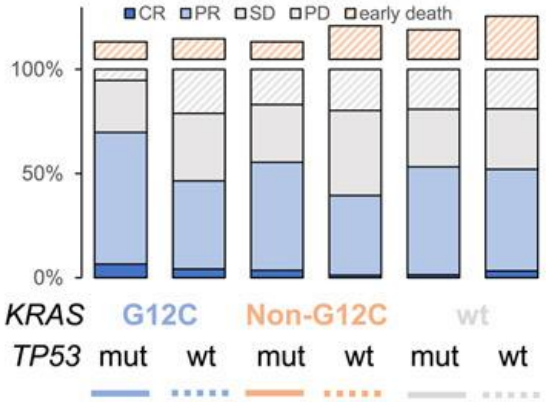
Clinical question

Value of co-occurring *KRAS/TP53* mutations predicting response to ICI monotherapy in PD-L1 high patients

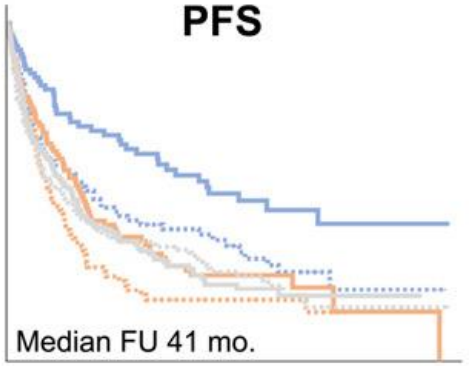
Nsq NSCLC PD-L1 ≥50%



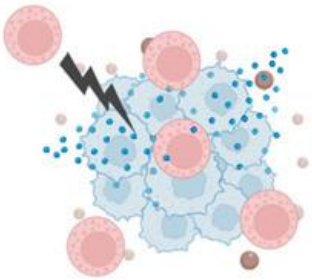
ORR

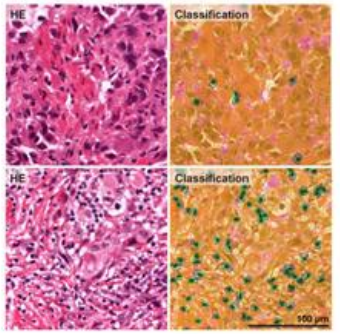


PFS

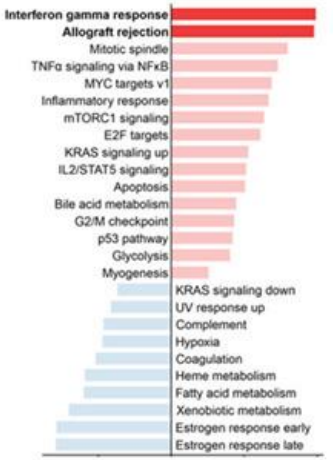


Histology





TCGA gene expression

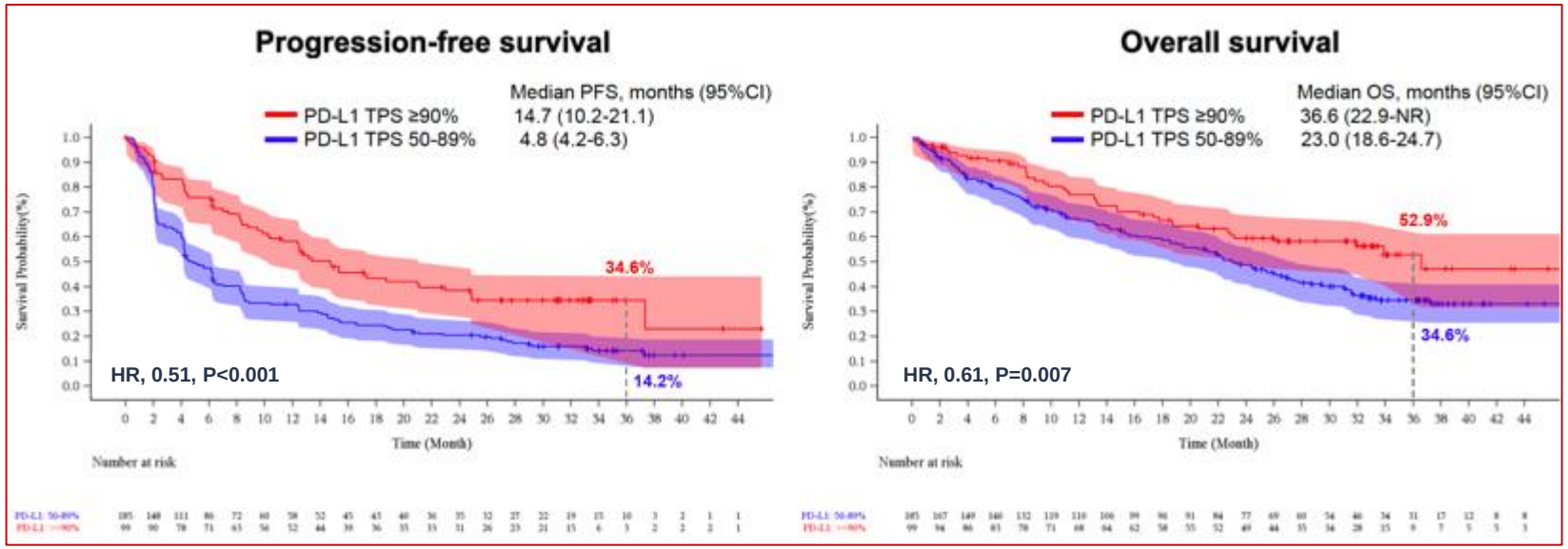


CONCLUSION: G12C/*TP53* co-mutations identify a subset of patients with a very favorable long-term survival with ICI monotherapy, mediated by highly active IFNγ signaling in a pro-inflammatory TME

ICI, immune checkpoint inhibitor; IFNγ, interferon gamma; IO, immuno-oncology; *KRAS*, Kirsten rat sarcoma virus; ORR, overall response rate; PD-L1, programmed cell death-ligand 1; PFS, progression-free suvival; TCGA, The Cancer Genome Atlas; TME, tumor microenvironment; *TP53*, tumor protein p53.

Extracted from Bischoff P et al. J Thorac Oncol. 2024;19(5):803-817.

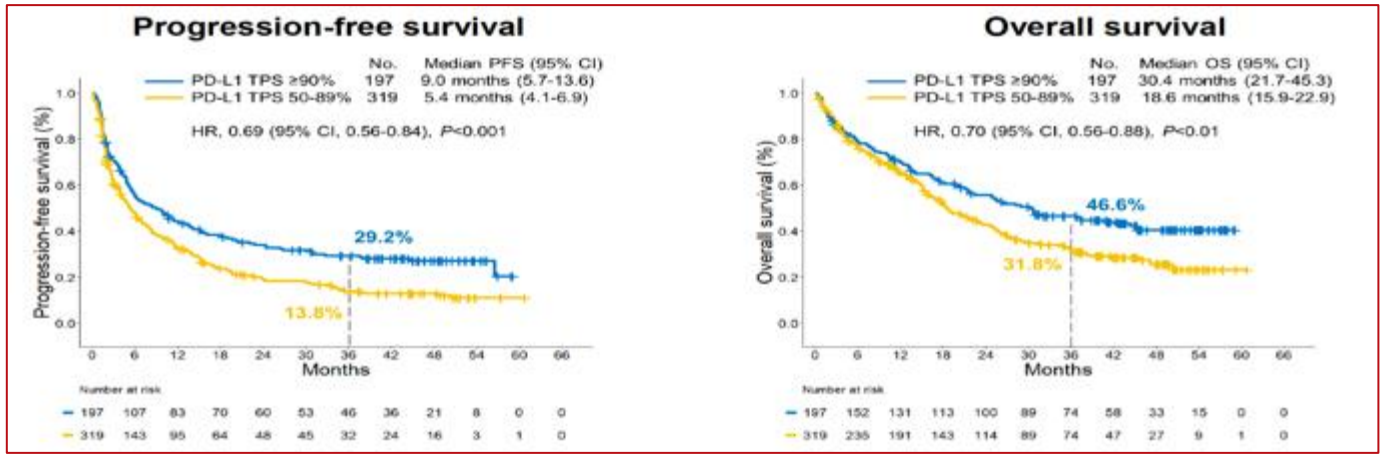
Impact of very high PD-L1 expression (≥ 90%) on IO monotherapy



EMpower-Lung 01

mPFS: 14.7 vs 4.8 m
3-y PFS: 34.6% vs 14.2%
HR 0.51, p<0.001

mOS: 36.6 vs 23.0 m
3-y OS: 52.9% vs 34.6%
HR 0.61, p=0.007



Academic Cohort

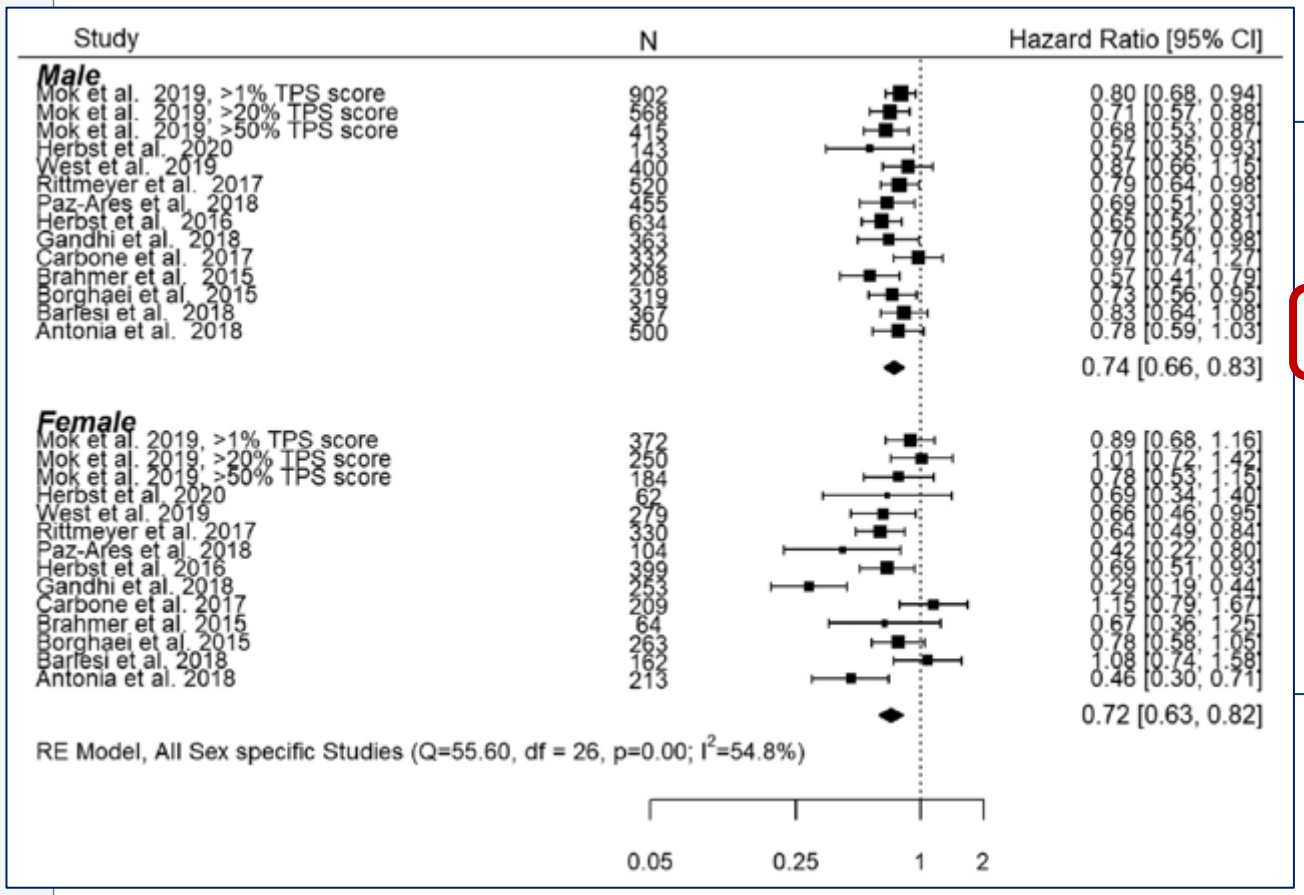
mPFS: 9.0 vs 5.4 m
3-y PFS: 29.2% vs 13.8%
HR 0.69, p<0.001

mOS: 30.4 vs 18.6 m
3-y OS: 46.6% vs 31.8%
HR 0.7, p<0.01

ICI, immune checkpoint inhibitor; IFNγ, interferon gamma; IO, immuno-oncology; *KRAS*, Kirsten rat sarcoma virus; ORR, overall response rate; PD-L1, programmed cell death-ligand 1; PFS, progression-free suvival; TCGA, The Cancer Genome Atlas; TME, tumor microenvironment; *TP53*, tumor protein p53.
Extracted from Ricciuti B et al. JTO Clinical and Research Reports. 2024; doi: https://doi.org/10.1016/j.jtocrr.2024.100675 (pre-proof).

So far no consistent gender-specific survival differences for lung cancer treated with IO: Prospective results required

Overall Survival



Pooled hazard ratios of immunotherapy treatment on overall survival and progression-free survival outcomes

Group	Overall survival			Progression-free survival		
	Pooled hazard ratio (95% CI)	*P*	*P* for moderator	Pooled hazard ratio (95% CI)	*P*	*P* for Moderator
Overall	0.72 (0.65–0.81)	<0.001		0.62 (0.54–0.72)	<0.001	
Gender			0.709			0.3718
Female	0.72 (0.63–0.82)	<0.001		0.72 (0.58–0.88)	0.001	
Male	0.74 (0.66–0.83)	<0.001		0.63 (0.53–0.75)	<0.001	
Treatment			0.021			<0.001
Immunotherapy alone	0.78 (0.71–0.86)	<0.001		0.91 (0.79–1.04)	0.17	
Immunotherapy/chemotherapy combination	0.62 (0.52–0.74)	<0.001		0.57 (0.5–0.64)	<0.001	
Checkpoint inhibitor			0.85			0.063
PD-1	0.73 (0.65–0.81)	<0.001		0.73 (0.63–0.86)	<0.001	
PD-L1	0.74 (0.64–0.86)	<0.001		0.57 (0.47–0.70)	<0.001	
First-line therapy			0.669			0.197
Immunotherapy as first line	0.74 (0.66–0.83)	<0.001		0.62 (0.53–0.73)	<0.001	
Failed chemotherapy at first line	0.72 (0.63–0.81)	<0.001		0.74 (0.60–0.93)	0.008	

CI, confidence interval; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1.

HR 0.74 (Male) and 0.72 (Female)

CI, confidence interval; ; HR, hazard ratio; IO, immuno-oncology; PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1.
Extracted from Madala S et al. Clin Oncol (R Coll Radiol). 2022;34(12):799-809.

Single agent IO is the *favorable* treatment option for NSCLC with high PD-L1 expression (Speaker's own)

- In principle yes, based on:
  - Efficacy
  - Impact on long-term overall survival (= chronification)
  - Tolerability
  - Symptom control and quality of life
- Clinical treatment decision should be based on individual patient factors
- The additional value of chemotherapy in patients with high PD-L1 expression needs to be shown prospectively
- The potential value of chemotherapy needs to be weighed against the harm to patients by toxicity

IO, immuno-oncology; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death-ligand 1.

Single agent IO is the only treatment option for NSCLC with high PD-L1 expression

Debate: CON

Professor Tony Mok

Li Shu Fan Medical Foundation
Professor of Clinical Oncology

The Chinese University of Hong Kong

Disclosures

COI	Sponsor
Grant/Research Support	AstraZeneca, Boehringer Ingelheim, Pfizer, Novartis, SFJ Pharmaceuticals, Roche, Merck Sharp & Dohme, Bristol-Myers Squibb, Eisai, Taiho
Speaker's Fees	BeiGene, AstraZeneca, Roche/Genentech, Pfizer, Eli Lilly, Boehringer Ingelheim, Merck Sharp & Dohme, Novartis, Bristol-Myers Squibb, Taiho
Major Stock Shareholder	Prenetics Ltd
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Board of Directors	AstraZeneca Ltd, HutchMed Ltd, Insighta Ltd.

COI, conflict of interest.

ONLY is a serious word

Adjective:

1. Being the single one or the relatively few of the kind
2. Single in superiority or distinction; unique; the best

Is single agent IO the ONLY option?

NCCN Guidelines for Metastatic NSCLC 2024

ESMO Guideline for Metastatic NSCLC 2023

ESMO, European Society for Medical Oncology; IO, immuno-oncology; NCCN, National Comprehensive Cancer Network; NSCLC, non-small cell lung cancer.

NCCN Guidelines for Patients Metastatic NSCLC, 2024

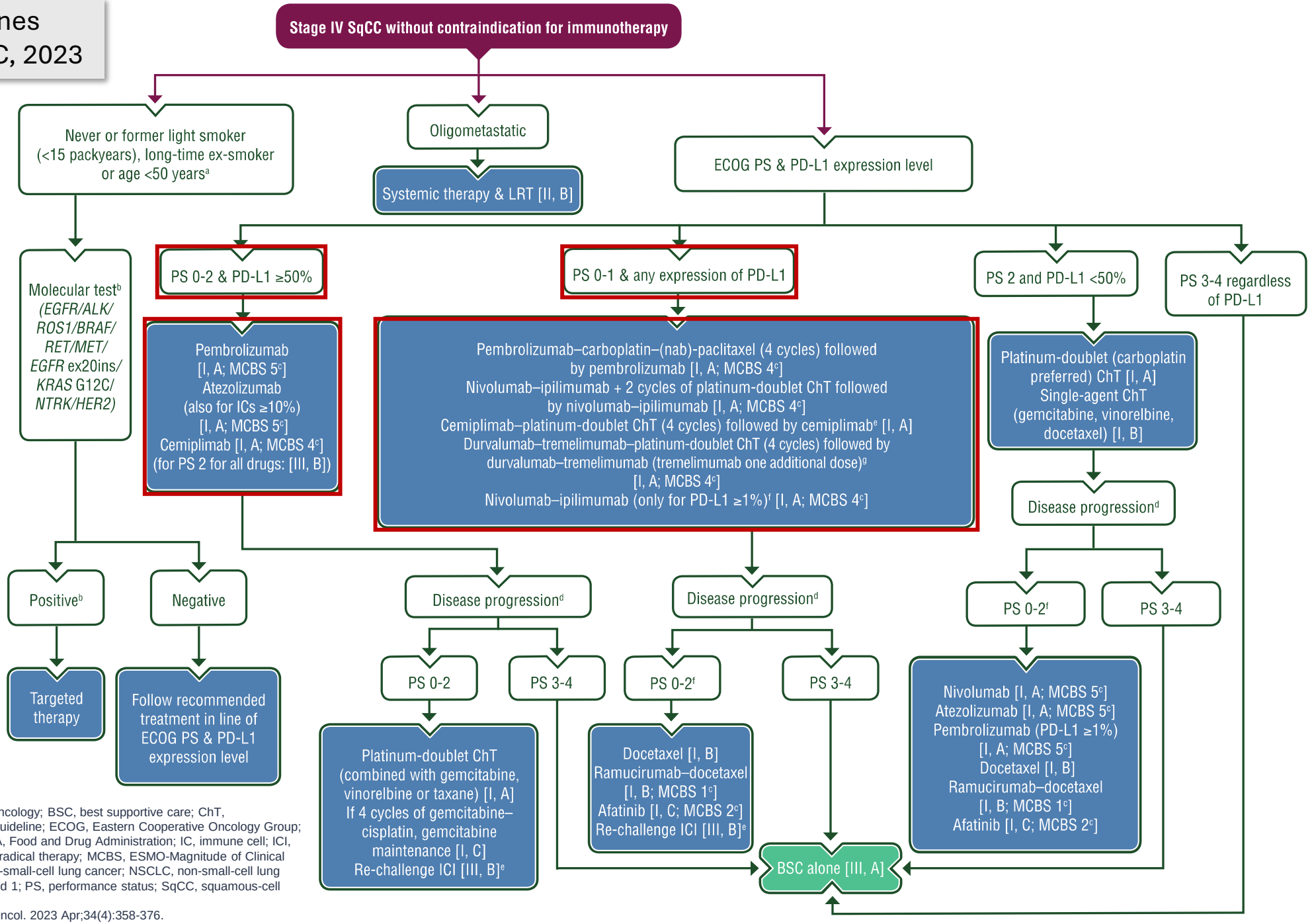
Guide 7
Treatment of metastatic NSCLC with low or high PD-L1: Adenocarcinoma, large cell carcinoma, and rare cell types

Regimens	Low PD-L1	High PD-L1
Atezolizumab		●
Cemiplimab-rwlc		●
Pembrolizumab	●	●
Pembrolizumab, carboplatin, pemetrexed	●	●
Pembrolizumab, cisplatin, pemetrexed	●	●
Cemiplimab-rwlc, carboplatin, pemetrexed	●	●
Cemiplimab-rwlc, cisplatin, pemetrexed	●	●
Atezolizumab, carboplatin, paclitaxel, bevacizumab	●	●
Atezolizumab, carboplatin, albumin-bound paclitaxel	●	●
Nivolumab, ipilimumab, carboplatin, pemetrexed	●	●
Nivolumab, ipilimumab, cisplatin, pemetrexed	●	●
Cemiplimab-rwlc, carboplatin, paclitaxel	●	●
Cemiplimab-rwlc, cisplatin, paclitaxel	●	●
Tremelimumab-actl, durvalumab, carboplatin, albumin-bound paclitaxel	●	●
Tremelimumab-actl, durvalumab, carboplatin, pemetrexed	●	●
Tremelimumab-actl, durvalumab, cisplatin, pemetrexed	●	●
Nivolumab, ipilimumab	●	●

● Preferred regimen because it works better, is safer, or costs less than other options or there are better data supporting its use

NCCN, National Comprehensive Cancer Network; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death-ligand 1.
Extracted from NCCN Guidelines for Patients®, Metastatic NSCLC, 2024.

ESMO Guidelines Metastatic NSCLC, 2023

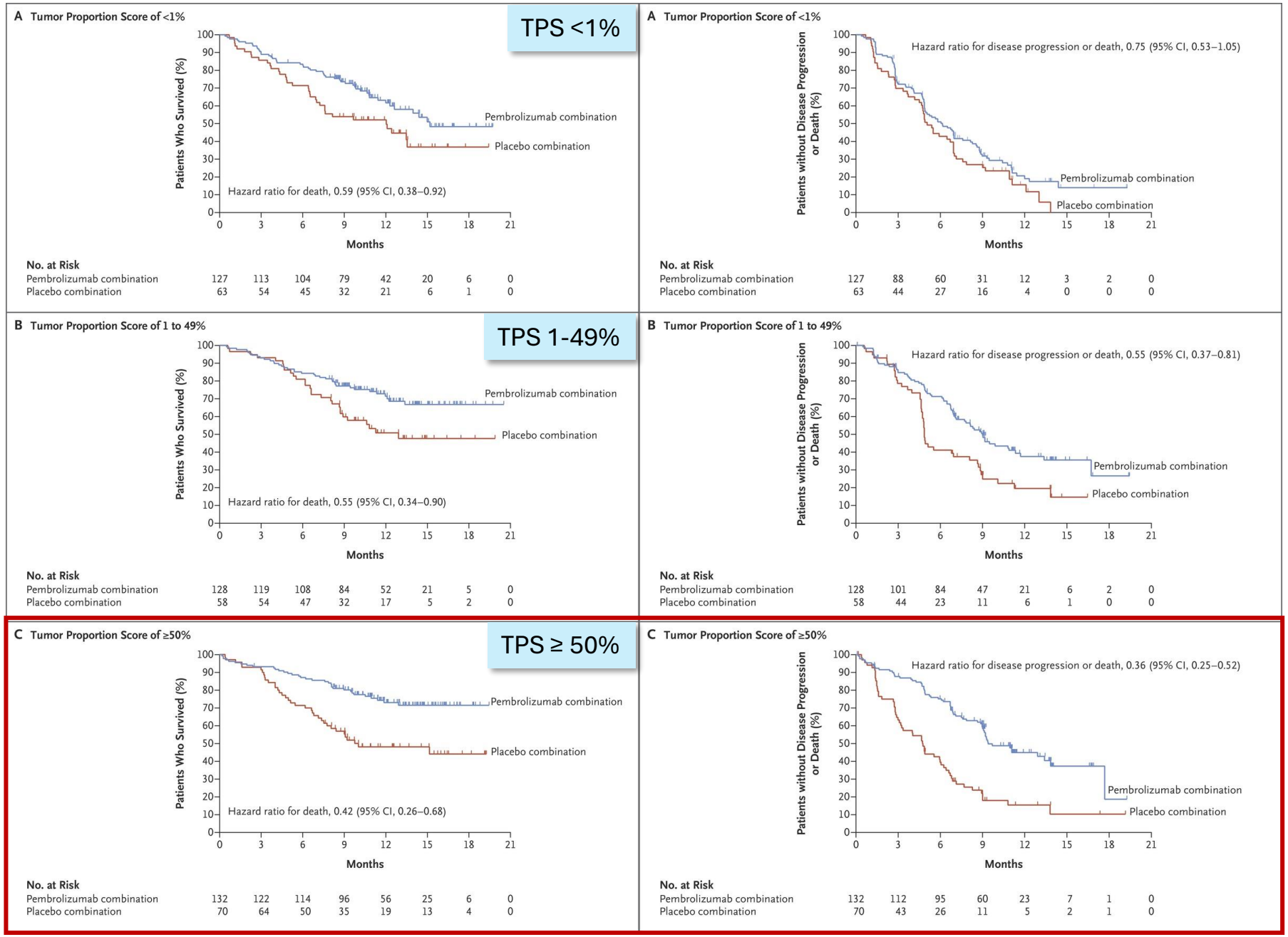


ESMO, European Society for Medical Oncology; BSC, best supportive care; ChT, chemotherapy; CPG, Clinical Practice Guideline; ECOG, Eastern Cooperative Oncology Group; EMA, European Medicines Agency; FDA, Food and Drug Administration; IC, immune cell; ICI, immune checkpoint inhibitor; LRT, local radical therapy; MCBS, ESMO-Magnitude of Clinical Benefit Scale; mNSCLC, metastatic non-small-cell lung cancer; NSCLC, non-small-cell lung cancer; PD-L1, programmed death-ligand 1; PS, performance status; SqCC, squamous-cell carcinoma.

Extracted from Hendriks LE et al. Ann Oncol. 2023 Apr;34(4):358-376.

KEYNOTE189

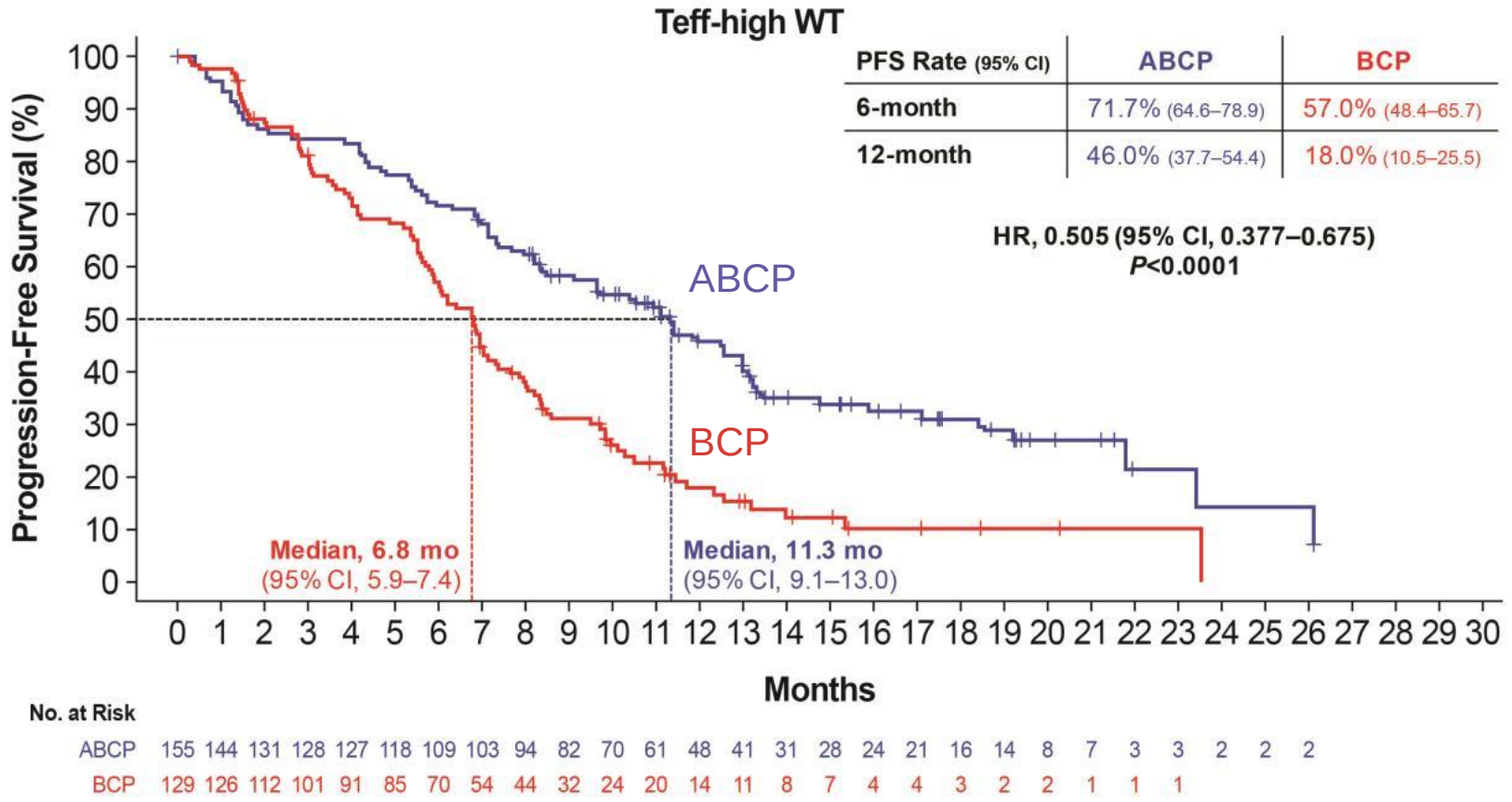
Pembro + CT
vs CT



CT, chemotherapy; Pembro, pembrolizumab; TPS, tumor proportion score.
Extracted from Gandhi L et al. N Engl J Med. 2018;378(22):2078-2092.

IMpower150: High expression

Atezolizumab (A) + CP
vs
Bevacizumab (B) + CP
vs
ABCP



ABCP, atezolizumab + bevacizumab + carboplatin + paclitaxel; BCP, bevacizumab + carboplatin + paclitaxel; CI, confidence interval; HR, hazard ratio; mo, months; PFS, progression-free survival; Teff, effector T-cell; WT, wild type.
Extracted from Socinski MA et al. N Engl J Med. 2018;378(24):2288-2301 (supplemental appendix).

Difference in toxicity profile

KEYNOTE-189 (Pembro + CT, any PD-L1)[1]

Table 2. Adverse Events of Any Cause in the As-Treated Population.*

Event	Pembrolizumab Combination (N=405)		Placebo Combination (N=202)	
	Any Grade	Grade 3, 4, or 5	Any Grade	Grade 3, 4, or 5
	number of patients (percent)			
Any event	404 (99.8)	272 (67.2)	200 (99.0)	133 (65.8)
Event leading to discontinuation of all treatment†	56 (13.8)	48 (11.9)	16 (7.9)	14 (6.9)
Event leading to discontinuation of any treatment component‡	112 (27.7)	81 (20.0)	30 (14.9)	22 (10.9)
Discontinuation of pembrolizumab or placebo	82 (20.2)	64 (15.8)	21 (10.4)	17 (8.4)
Discontinuation of pemetrexed	93 (23.0)	69 (17.0)	23 (11.4)	17 (8.4)
Discontinuation of platinum-based drug	31 (7.7)	27 (6.7)	12 (5.9)	10 (5.0)
Event leading to death§	27 (6.7)	27 (6.7)	12 (5.9)	12 (5.9)
Event occurring in ≥15% of patients in either group¶				
Nausea	225 (55.6)	14 (3.5)	105 (52.0)	7 (3.5)
Anemia	187 (46.2)	66 (16.3)	94 (46.5)	31 (15.3)
Fatigue	165 (40.7)	23 (5.7)	77 (38.1)	5 (2.5)
Constipation	141 (34.8)	4 (1.0)	64 (31.7)	1 (0.5)
Diarrhea	125 (30.9)	21 (5.2)	43 (21.3)	6 (3.0)
Decreased appetite	114 (28.1)	6 (1.5)	61 (30.2)	1 (0.5)
Neutropenia	110 (27.2)	64 (15.8)	49 (24.3)	24 (11.9)
Vomiting	98 (24.2)	15 (3.7)	47 (23.3)	6 (3.0)
Cough	87 (21.5)	0	57 (28.2)	0
Dyspnea	86 (21.2)	15 (3.7)	52 (25.7)	11 (5.4)
Asthenia	83 (20.5)	25 (6.2)	49 (24.3)	7 (3.5)
Rash	82 (20.2)	7 (1.7)	23 (11.4)	3 (1.5)
Pyrexia	79 (19.5)	1 (0.2)	30 (14.9)	0
Peripheral edema	78 (19.3)	1 (0.2)	26 (12.9)	0
Thrombocytopenia	73 (18.0)	32 (7.9)	29 (14.4)	14 (6.9)
Increased lacrimation	69 (17.0)	0	22 (10.9)	0

KEYNOTE-024 (Pembro vs CT, PD-L1 ≥50%)[2]

Table 3. Adverse Events in the As-Treated Population.*

Adverse Event	Pembrolizumab Group (N=154)		Chemotherapy Group (N=150)	
	Any Grade	Grade 3, 4, or 5	Any Grade	Grade 3, 4, or 5
	number of patients (percent)			
Treatment-related†				
Any	113 (73.4)	41 (26.6)	135 (90.0)	80 (53.3)
Serious	33 (21.4)	29 (18.8)	31 (20.7)	29 (19.3)
Led to discontinuation	11 (7.1)	8 (5.2)	16 (10.7)	9 (6.0)
Led to death	1 (0.6)	1 (0.6)	3 (2.0)	3 (2.0)
Occurred in ≥10% of patients in either group‡				
Nausea	15 (9.7)	0	65 (43.3)	3 (2.0)
Anemia	8 (5.2)	3 (1.9)	66 (44.0)	29 (19.3)
Fatigue	16 (10.4)	2 (1.3)	43 (28.7)	5 (3.3)
Decreased appetite	14 (9.1)	0	39 (26.0)	4 (2.7)
Diarrhea	22 (14.3)	6 (3.9)	20 (13.3)	2 (1.3)
Neutropenia	1 (0.6)	0	34 (22.7)	20 (13.3)
Vomiting	4 (2.6)	1 (0.6)	30 (20.0)	1 (0.7)
Pyrexia	16 (10.4)	0	8 (5.3)	0
Constipation	6 (3.9)	0	17 (11.3)	0
Stomatitis	4 (2.6)	0	18 (12.0)	2 (1.3)
Decreased neutrophil count	0	0	20 (13.3)	6 (4.0)
Increased blood creatinine level	3 (1.9)	0	15 (10.0)	1 (0.7)
Decreased platelet count	0	0	18 (12.0)	9 (6.0)
Thrombocytopenia	0	0	17 (11.3)	8 (5.3)
Decreased white-cell count	1 (0.6)	0	16 (10.7)	3 (2.0)
Dysgeusia	1 (0.6)	0	15 (10.0)	0
Immune-mediated§				
Any	45 (29.2)	15 (9.7)	7 (4.7)	1 (0.7)
Hypothyroidism	14 (9.1)	0	2 (1.3)	0
Hyperthyroidism	12 (7.8)	0	2 (1.3)	0
Pneumonitis	9 (5.8)	4 (2.6)	1 (0.7)	1 (0.7)
Infusion reaction	7 (4.5)	0	2 (1.3)	0
Severe skin reaction	6 (3.9)	6 (3.9)	0	0
Thyroiditis	4 (2.6)	0	0	0
Colitis	3 (1.9)	2 (1.3)	0	0
Myositis	3 (1.9)	0	0	0
Hypophysitis	1 (0.6)	1 (0.6)	0	0
Nephritis	1 (0.6)	1 (0.6)	0	0
Pancreatitis	1 (0.6)	1 (0.6)	0	0
Type 1 diabetes mellitus	1 (0.6)	1 (0.6)	0	0

CT, chemotherapy; Pembro, pembrolizumab; PD-L1, programmed cell death-ligand 1; TPS, tumor proportion score.
Extracted from 1) Gandhi L et al. N Engl J Med. 2018;378(22):2078-20; 2) Reck M et al. N Engl J Med. 2016;375(19):1823-1833.

PREFERRED ≠ ONLY

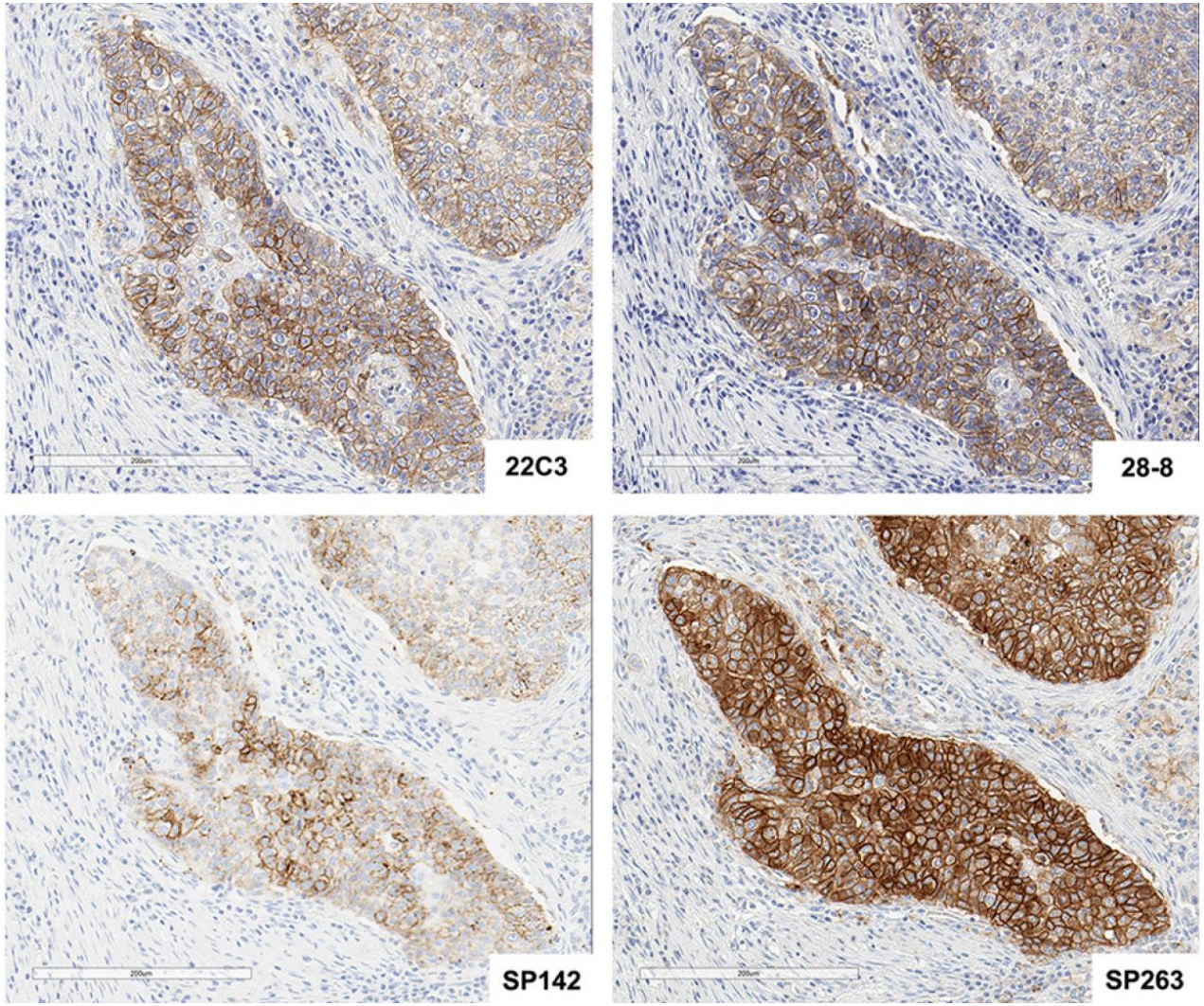
Single agent IO is preferred but certainly NOT the ONLY treatment for PD-L1 >50%

IO, immuno-oncology; PD-L1, programmed cell death-ligand 1.

High PD-L1 is not a single entity?

PD-L1, programmed cell death-ligand 1.

PD-L1 protein expression is a semi-quantitative biomarker that varies with different antibodies

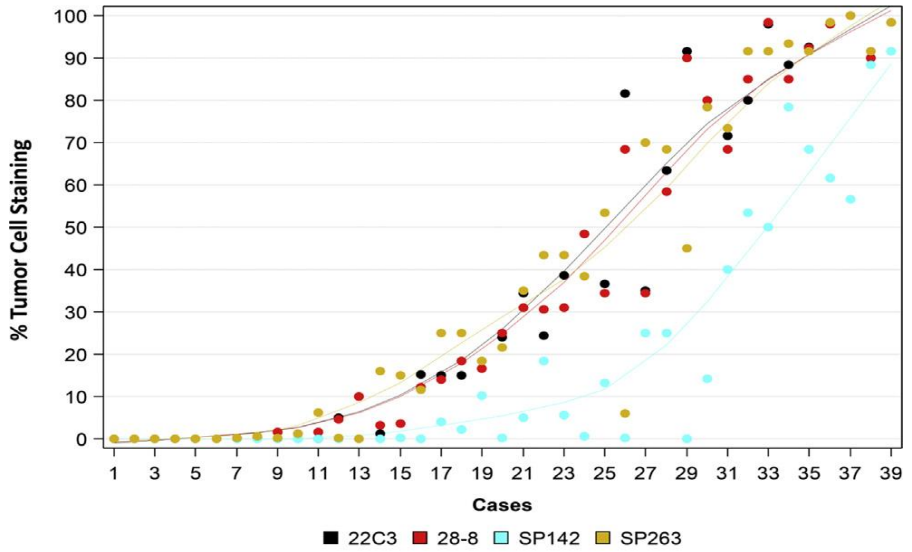


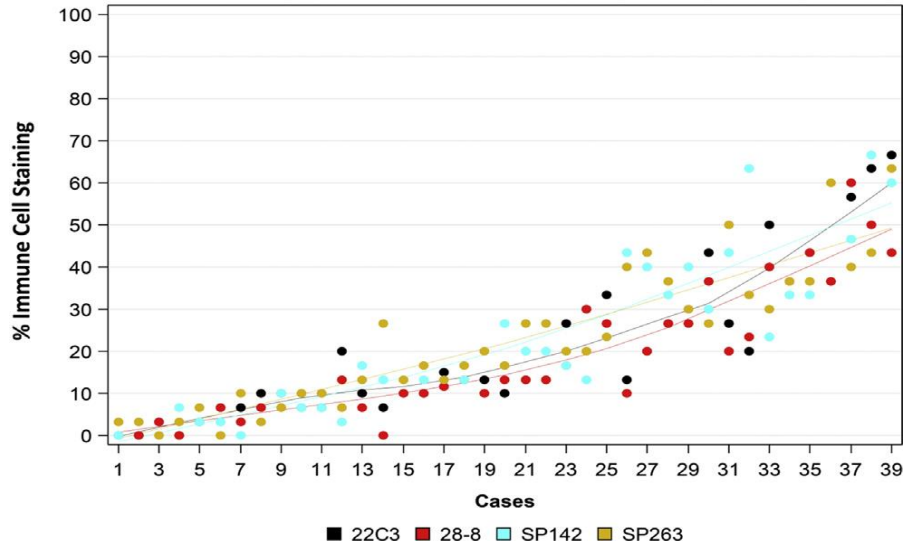
We need standardization of antibody and a validated cut-off

PD-L1, programmed cell death-ligand 1.
Extracted from Hirsch FR et al. J Thorac Oncol. 2017;12(2):208-222.

Standardized test: Blueprint PD-L1 IHC assay comparison project

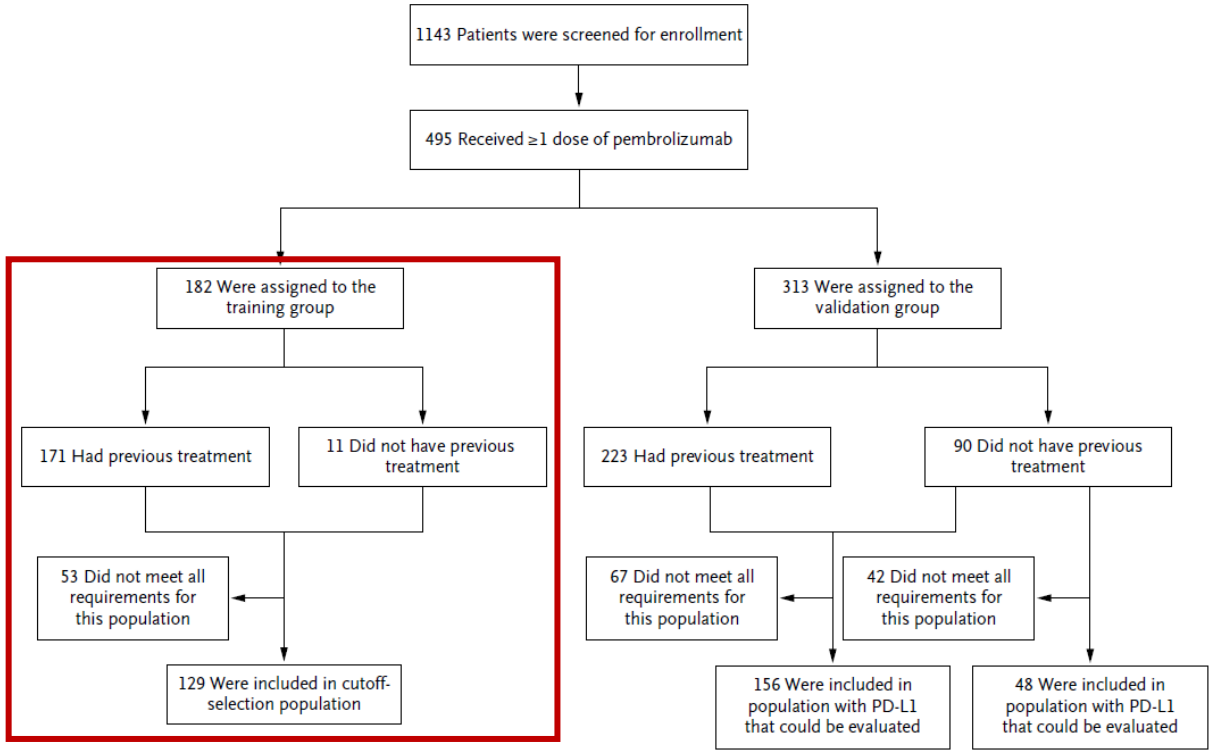
- Multiple companies
- Multiple platforms
  - Ventana vs Dako
- Multiple antibodies
  - 22C3
  - 28-8
  - SP142
- Multiple cut-off
  - >1%, >25%, >50%



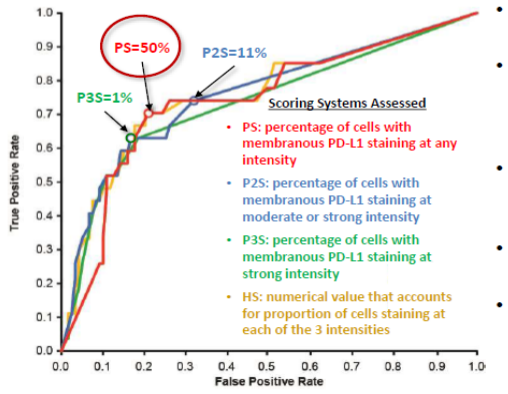


PD-L1, programmed cell death-ligand 1.
Extracted from Hirsch FR et al. J Thorac Oncol. 2017;12(2):208-222.

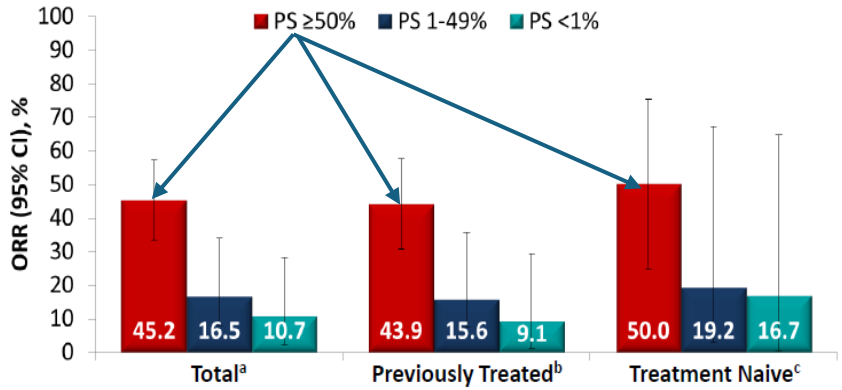
KEYNOTE-001: First study that validated PD-L1 expression cut-off at 50%



Training Set: Selection of PD-L1 Cutpoint and Scoring System Using a Clinical Trial IHC Assay



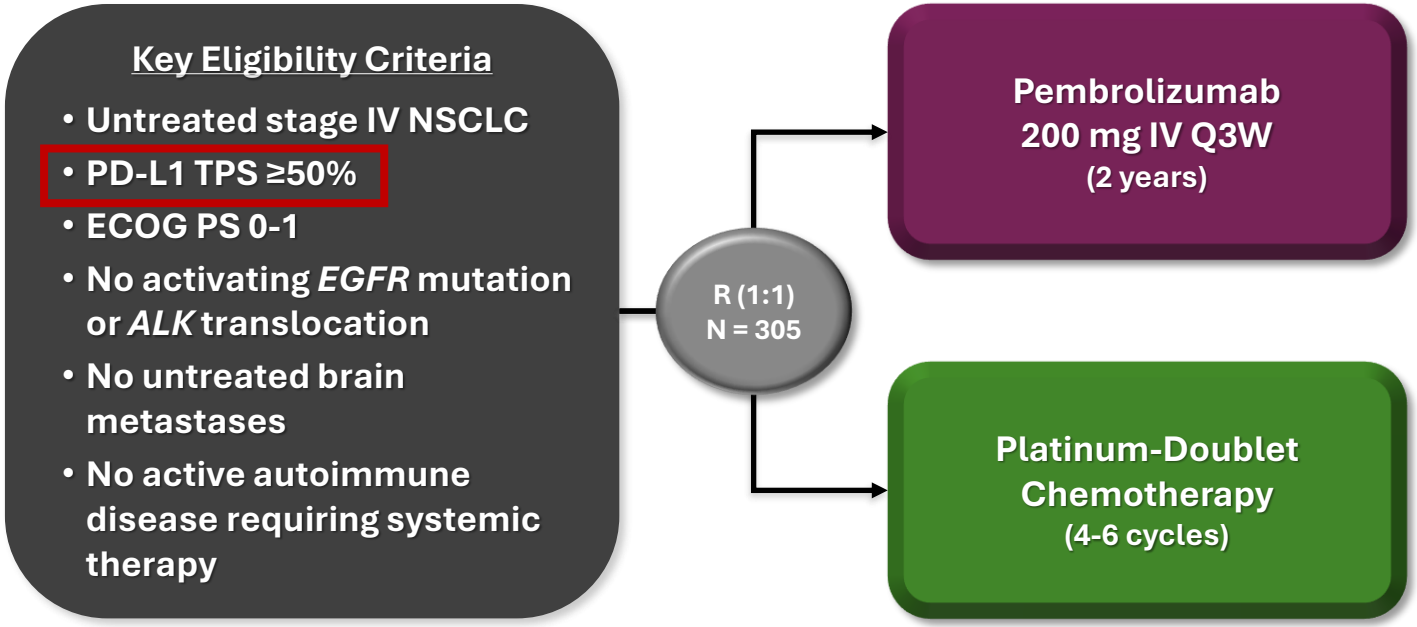
- Clinical trial assay (CTA) used same 22C3 antibody as prototype assay
- Cutpoint selection based on irRC by investigator review
  - Results confirmed using RECIST v1.1 by central review
- Choice of PS ≥50% based on:
  - Correlation with the Youden index
  - Ease of use
- Predictive value not improved by incorporating inflammatory T cells
- At time of cutpoint selection, 30.1% had PS ≥50%
  - 45.5% ORR per investigator irRC
  - 36.6% ORR per central RECIST v1.1



When measurable disease is NOT required, the ORR (95% CI) in the PS ≥50% subgroups are: **42.3%, 41.0%, and 47.1%** in the total, previously treated, and treatment-naive populations[d]

CI, confidence interval; IHC, immunohistochemistry; ORR, overall response rate; PD-L1, programmed cell death-ligand 1; PS, performance status.
Extracted from Garon EB et al. N Engl J Med. 2015;372(21):2018-28.

KEYNOTE-024



Martin Reck

Key End Points

Primary: PFS (RECIST v1.1 per blinded, independent central review)

Secondary: OS, ORR, safety

Exploratory: DOR

ALK, anaplastic lymphoma kinase; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, estimated glomerular filtration rate; IV, intravenous; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; Q3W, every 3 weeks; R, randomized; TPS, tumor proportion score.
Extracted from Reck M et al. N Engl J Med. 2016;375(19):1823-1833.

KEYNOTE-042

Key Eligibility Criteria

- Untreated locally advanced or metastatic NSCLC of any histology
- PD-L1 TPS ≥1%[a]
- No sensitizing *EGFR* or *ALK* alterations
- ECOG PS 0 or 1
- No untreated or unstable CNS metastases
- No history of pneumonitis that required systemic corticosteroids

Stratification Factors

- Region (east Asia vs rest of the world)
- ECOG PS (0 vs 1)
- Histology (squamous vs nonsquamous)
- PD-L1 TPS (≥50% vs 1-49%)

R (1:1)
N=1274

Pembrolizumab
200 mg Q3W
for up to 35 cycles

Carboplatin AUC 5 or 6 Q3W + Paclitaxel 200 mg/m^2 Q3W[b]
OR
Carboplatin AUC 5 or 6 Q3W + Pemetrexed 500 mg/m^2 Q3W[b]
for up to 6 cycles

Key End Points

Primary: OS

Secondary: PFS, ORR, safety

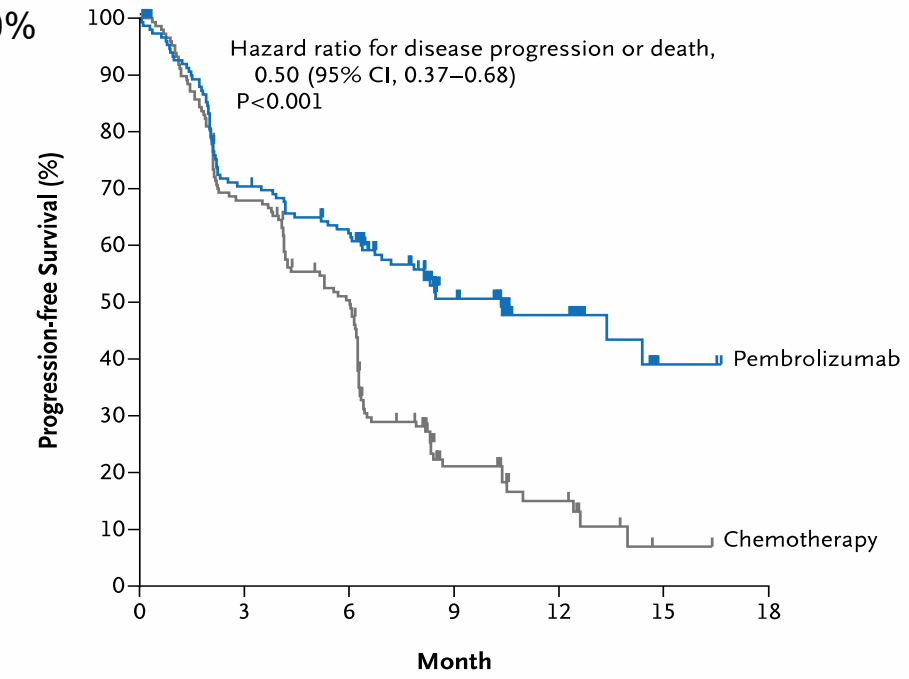
Exploratory: DOR

Tony Mok

ALK, anaplastic lymphoma kinase; AUC, area under the curve; CNS, central nervous system; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, estimated glomerular filtration rate; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; Q3W, every 3 weeks; R, randomized; TPS, tumor proportion score.
Extracted from Mok TSK et al. Lancet. 2019;393(10183):1819-1830.

PFS outcomes of KEYNOTE-024 and -042 are different despite the similar high PD-L1 expression

PD-L1 ≥50%

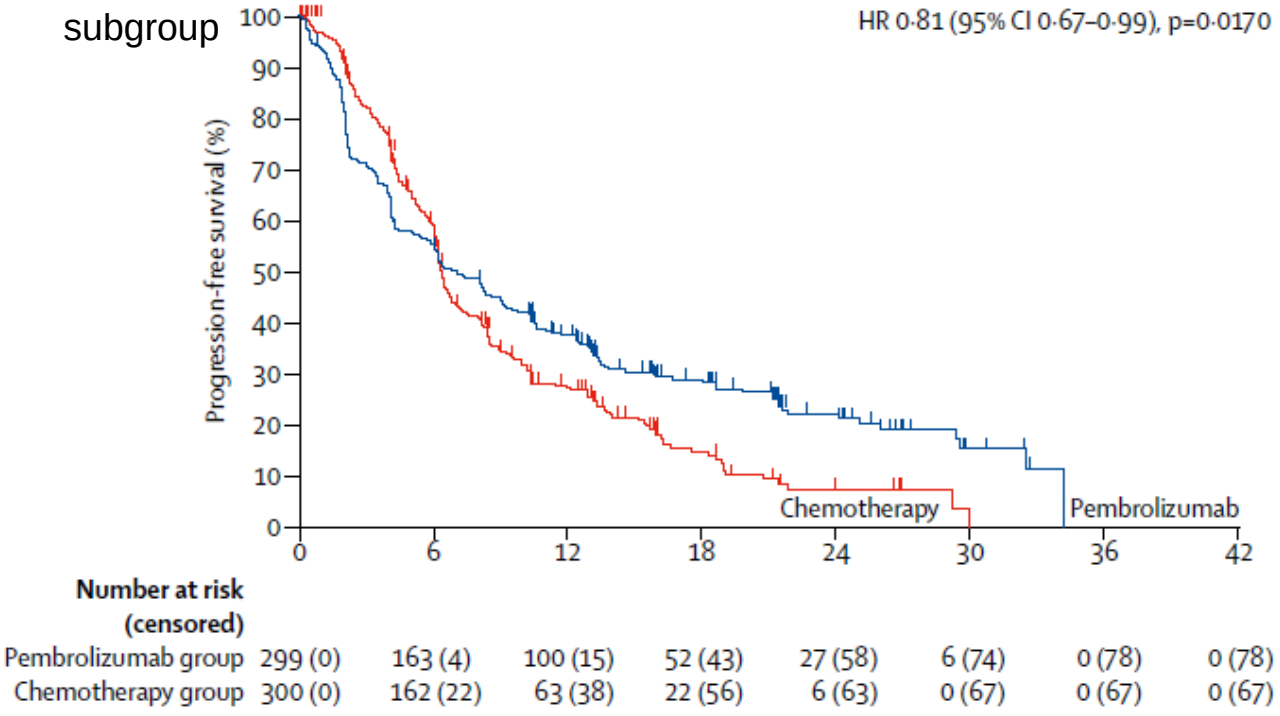


KN-024 PFS HR 0.50[1]

CI, confidence interval; HR, hazard ratio; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival.
Extracted from 1) Reck M et al. N Engl J Med. 2016;375(19):1823-1833; 2) Mok TSK et al. Lancet. 2019;393(10183):1819-1830.

PFS outcomes of KEYNOTE-024 and -042 are different despite the similar high PD-L1 expression

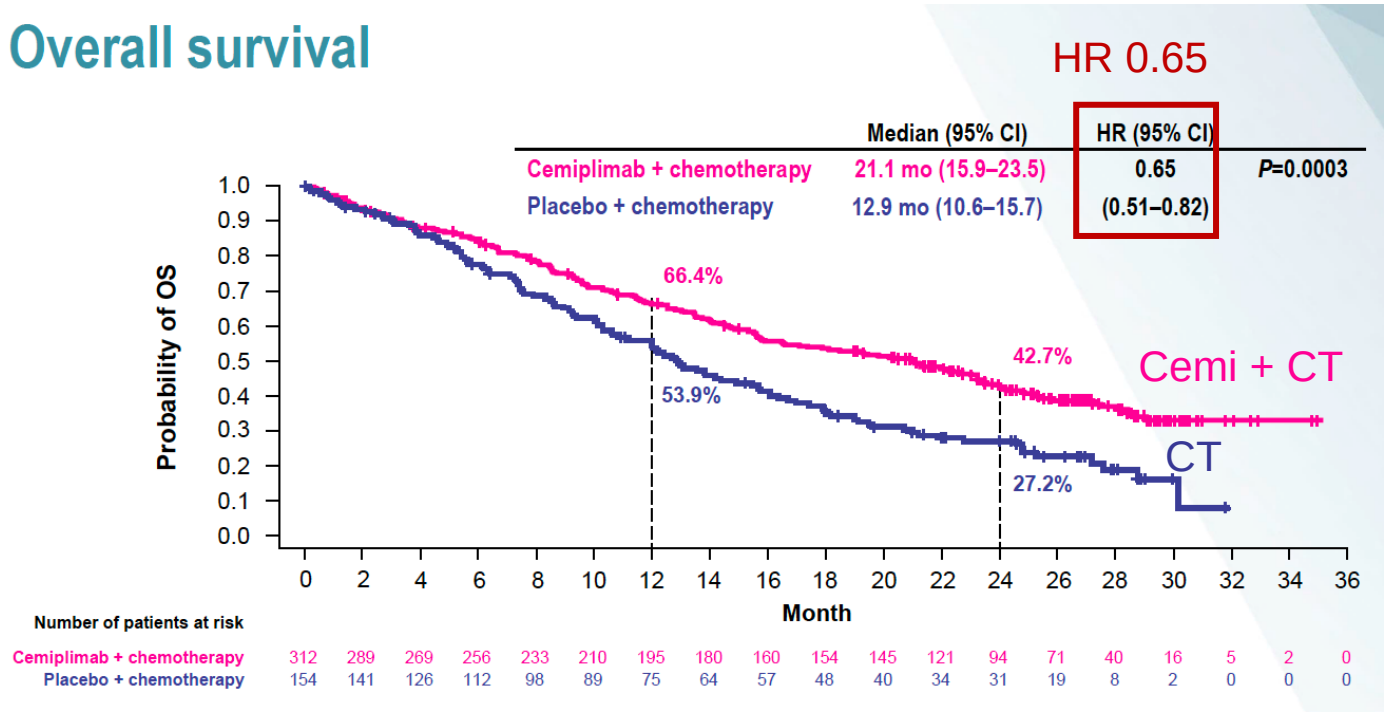
PD-L1 ≥50% subgroup



KN-042 PFS HR 0.81[2]

CI, confidence interval; HR, hazard ratio; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival.
Extracted from 1) Reck M et al. N Engl J Med. 2016;375(19):1823-1833; 2) Mok TSK et al. Lancet. 2019;393(10183):1819-1830.

EMPOWER-Lung 3: Chemo/cemiplimab combination is highly effective in PDL1>50% population



OS

Median (95% CI), months

PD-L1 expression	Cemiplimab + chemotherapy (n=312)	Placebo + chemotherapy (n=154)	HR (95% CI)
≥50%	23.5 (17.9–NE)	14.4 (9.3–19.5)	0.56 (0.36–0.86)
1–49%	23.2 (18.1–27.2)	12.0 (8.3–15.7)	0.50 (0.34–0.74)
<1%	12.8 (9.6–15.6)	14.2 (9.1–18.0)	0.94 (0.62–1.42)

HR 0.56

CI, confidence interrval; HR, hazard ratio; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival.
Extracted from Makharadze T et al. Cemiplimab plus chemotherapy versus chemotherapy alone in advanced non small cell lung cancer: 2 year follow up results from the Phase 3 EMPOWER Lung 3 Part 2 trial. Presented at ELCC; October 20-24, 2023; Madrid, Spain. Available at: https://oncologypro.esmo.org/meeting-resources/european-lung-cancer-congress-2023/cemiplimab-plus-chemotherapy-versus-chemotherapy-alone-in-non-small-cell-lung-cancer-longer-follow-up-results-from-the-phase-iii-empower-lung-3-trial.

RATIONALE-304: Chemo/tislelizumab is highly effective in the PD-L1 >50% population

Overall survival

[1]

Table 2. OS Analyses (ITT Analysis Set)

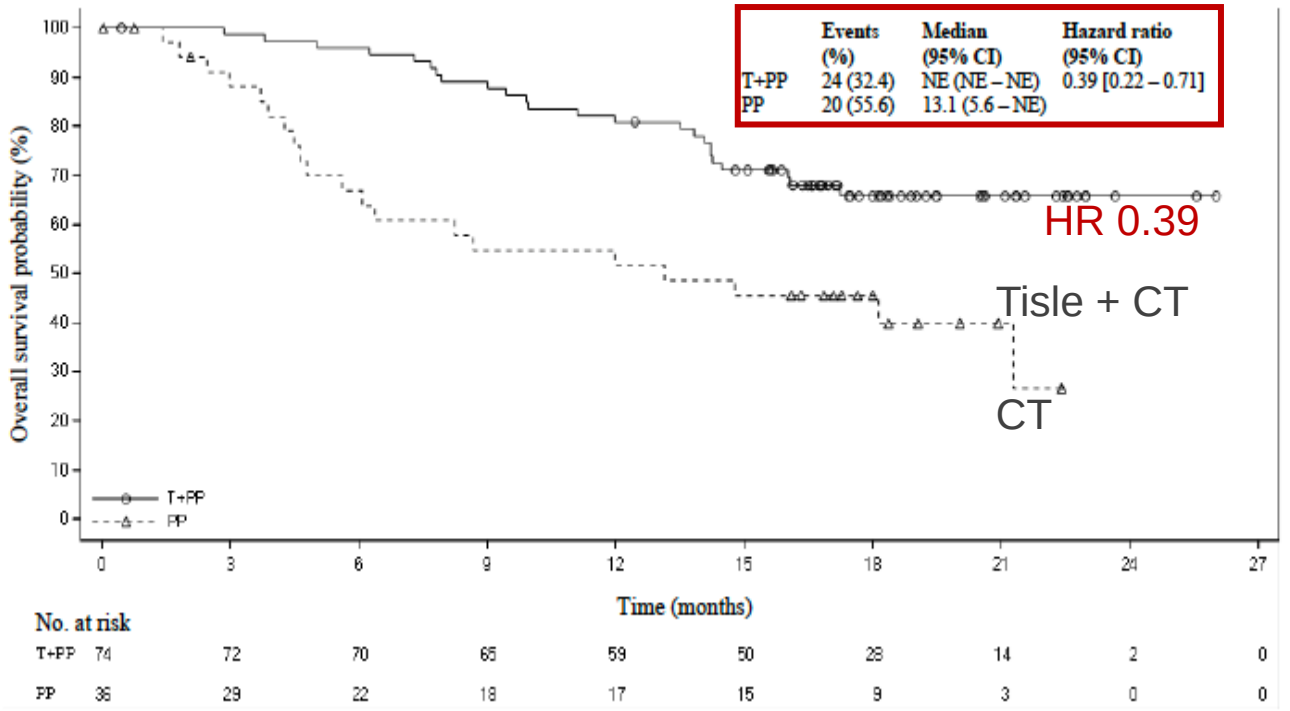
	Median OS, months (95% CI)		HR (95% CI)
	Arm A	Arm B	Arm A vs B
ITT analysis[a]	21.6 (17.9, 26.0)	20.1 (14.9, 28.1)	0.85 (0.63, 1.14)
Two-stage model[a,b]	21.6 (17.9, 26.0)	14.9 (13.3, 21.1)	0.68 (0.50, 0.92)

Data cutoff: July 15, 2022 (ad-hoc analysis). Arm A: Tislelizumab plus platinum-based chemotherapy and pemetrexed; Arm B: Platinum-based chemotherapy and pemetrexed. ITT analysis set included all randomized patients. [a]Median (95% CI) follow-up: Arm A, 38.8 (38.1, 40.1) months; Arm B, 38.6 (36.0, 40.6) months. [b]Median (95% CI) follow-up: Arm A, 38.8 (38.1, 40.1) months; Arm B, 20.0 (14.2, 36.0) months. **Abbreviations:** CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival.

HR 0.68
(two-stage model)

[2]

Figure 2 Kaplan-Meier plot of OS in BGB-A317-304 in patients with PD-L1 ≥50%



CI, confidence interval; chemo or CT, chemotherapy; HR, hazard ratio; ITT, intent-to-treat; NE, not estimable; NSCLC, non-small cell lung cancer; OS, overall survival; PD-L1, programmed cell death-ligand 1; Tisle, tislelizumab.

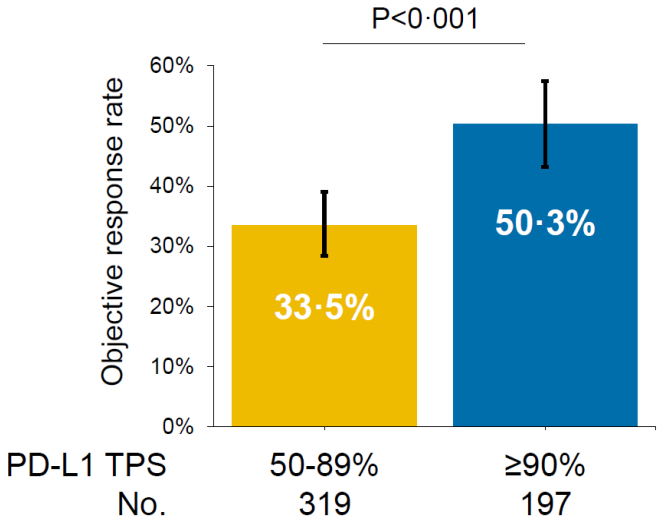
1) Extracted from Lu S et al. Randomized Phase 3 Study of Tislelizumab Plus Chemotherapy Versus Chemotherapy Alone as First-Line Treatment for Advanced Nonsquamous Non-Small Cell Lung Cancer: RATIONALE-304 Updated Analysis. Poster 138P. Presented at ESMO IO; December 2022; Geneva, Switzerland. Available at: Lu_BGB-A317-304_ESMO_IO_Poster_2022.pdf; 2) Tevimbra SmPC, July 2024.

PD-L1 >50% is a heterogenous population!

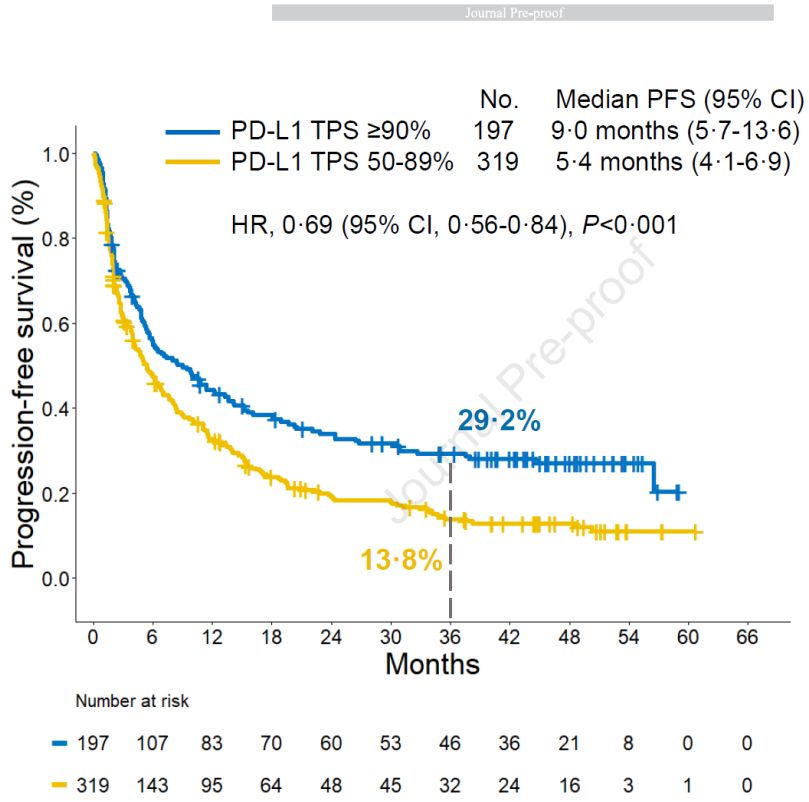
PD-L1, programmed cell death-ligand 1.

PD-1 inhibitors monotherapy for PD-L1 50-89% vs PD-L1 ≥90%

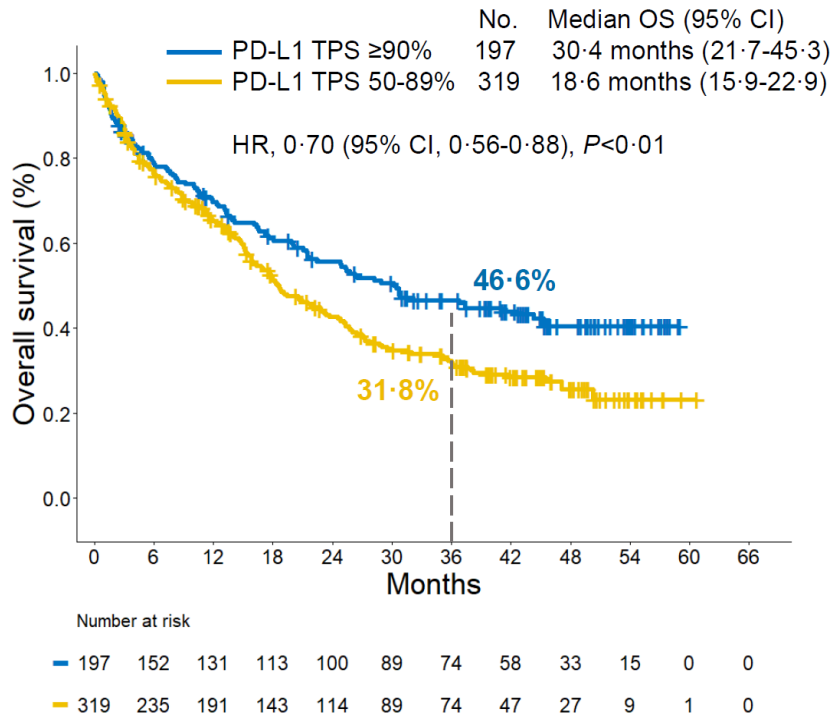
A



B

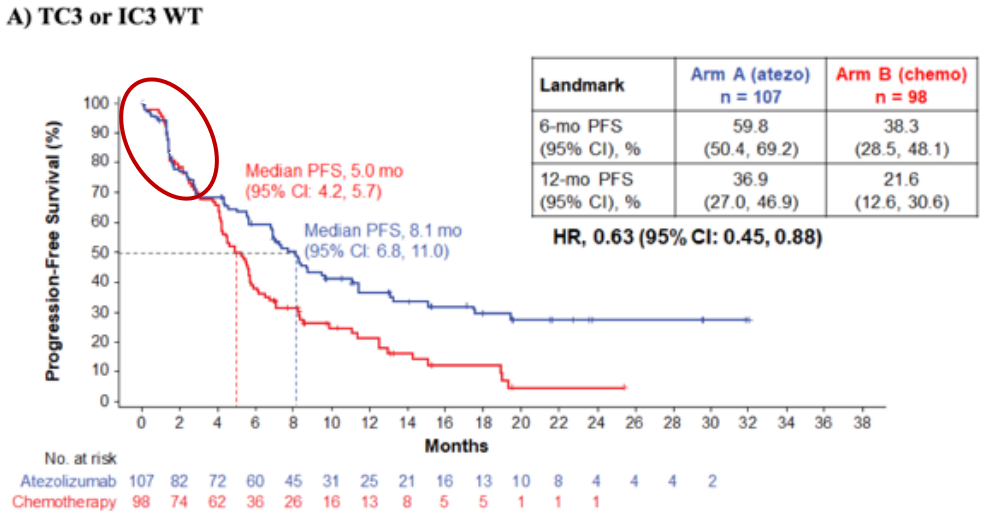


C



CI, confidence interval; HR, hazard ratio; PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; TPS, tumor proportion score.
Extracted from Ricciuti B et al. JTO Clinical and Research Reports. 2024; doi: https://doi.org/10.1016/j.jtocrr.2024.100675 (pre-proof).

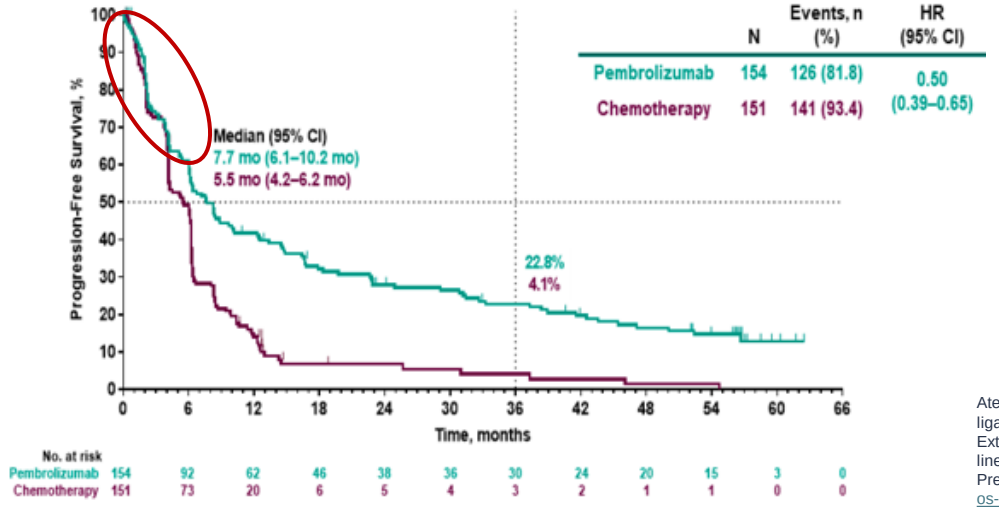
Some patients don’t do well with single-agent IO despite high PD-L1 expression



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, 0.63 (95% CI: 0.45, 0.88)

Atezolizumab (IMpower110)[1]



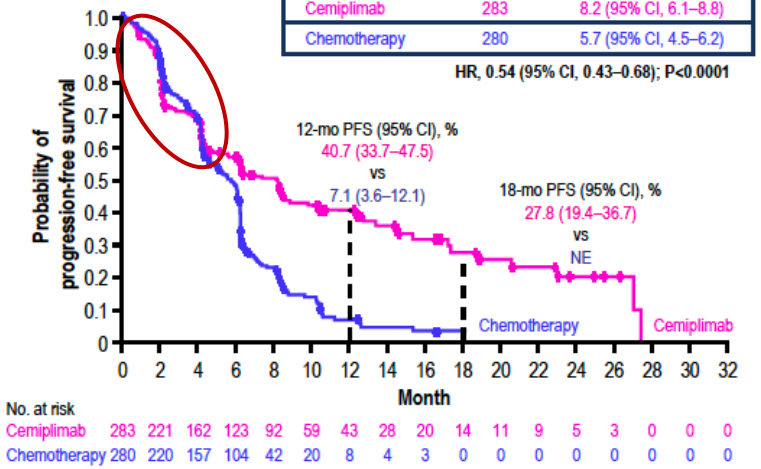
	N	Events, n (%)	HR (95% CI)
Pembrolizumab	154	126 (81.8)	0.50 (0.39–0.65)
Chemotherapy	151	141 (93.4)	

Pembrolizumab (KN-024)[2] PD-L1 ≥50%

PD-L1 ≥50% ITT

	No. of Patients	Median PFS (95% CI) *mo*
Cemiplimab	283	8.2 (95% CI, 6.1–8.8)
Chemotherapy	280	5.7 (95% CI, 4.5–6.2)

HR, 0.54 (95% CI, 0.43–0.68); P<0.0001



Cemiplimab (EMPOWER-Lung1)

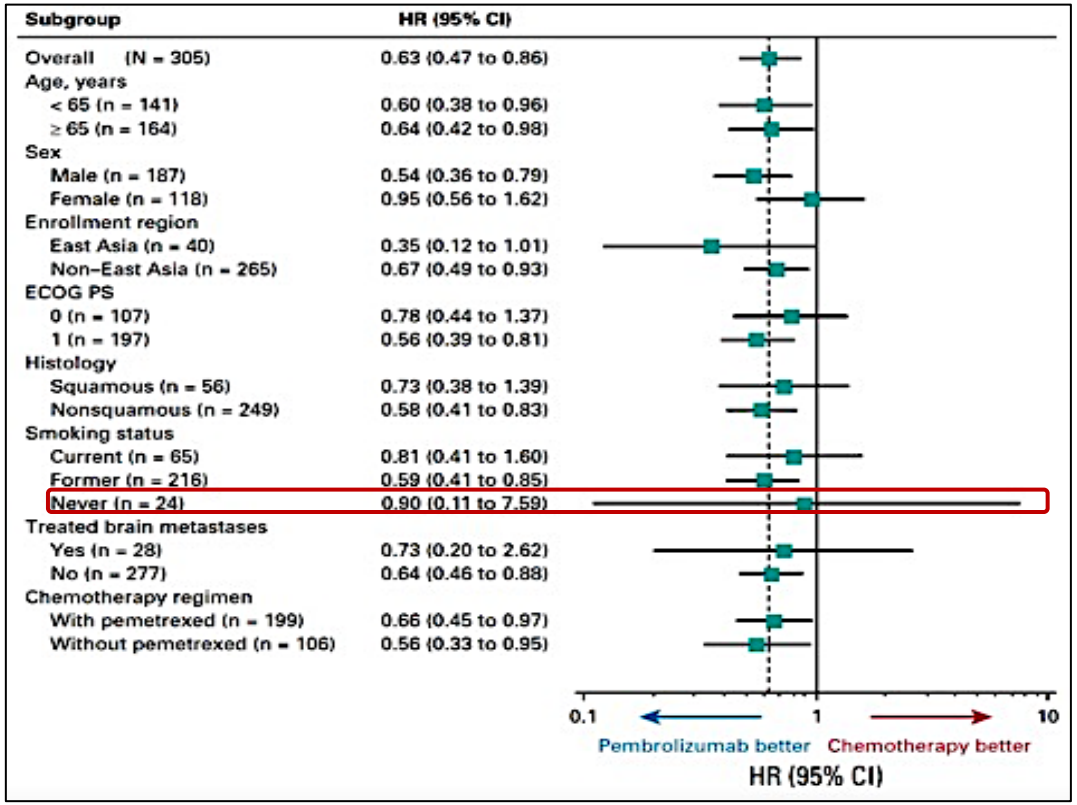
*Dako 22C3; past history of smoking

Atezo, atezolizumab; chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; IO, immuno-oncology; ITT, intent-to-treat; mo, months; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; TC, tumor cell, PD-LI expression on ≥50% of tumor cells; WT, wild type.

Extracted from 1) Herbst RS et al. N Engl J Med. 2020;383(14):1328-1339 (supplementary appendix); 2) Brahmer JR et al. LBA51 - KEYNOTE-024 5-year OS update: First-line (1L) pembrolizumab (pembro) vs platinum-based chemotherapy (chemo) in patients (pts) with metastatic NSCLC and PD-L1 tumour proportion score (TPS) ≥50%. Presented at ESMO Virtual Congress; September 19-21, 2020. Available at: https://oncologypro.esmo.org/meeting-resources/esmo-virtual-congress-2020/keynote-024-5-year-os-update-first-line-1l-pembrolizumab-pembro-vs-platinum-based-chemotherapy-chemo-in-patients-pts-with-metastatic-nsclc; 3) Sezer A et al. LBA52 - EMPOWER-Lung 1: Phase III first-line (1L) cemiplimab monotherapy vs platinum-doublet chemotherapy (chemo) in advanced non-small cell lung cancer (NSCLC) with programmed cell death-ligand 1 (PD-L1) ≥50%. Presented at ESMO Virtual Congress; September 19-21, 2020. Available at: https://oncologypro.esmo.org/meeting-resources/esmo-virtual-congress-2020/empower-lung-1-phase-iii-first-line-1l-cemiplimab-monotherapy-vs-platinum-doublet-chemotherapy-chemo-in-advanced-non-small-cell-lung-cancer-n.

Never-smokers may not do well with single-agent IO

Keynote-024 (TPS ≥50%)[1]

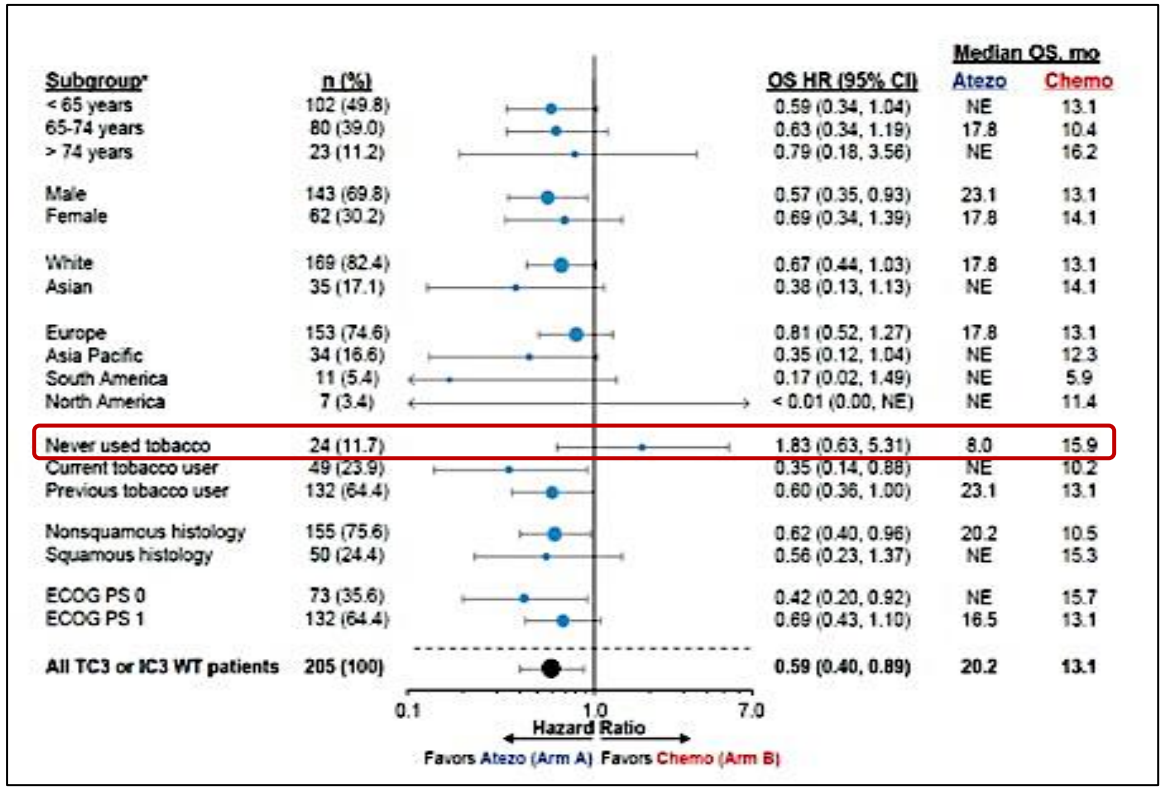


Never-smoker: HR, 0.9 (95%CI: 0.11–7.59)

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; IC, immune cell; IO, immuno-oncology; TPS, tumor proportion score.
Extracted from 1) Reck M et al. J Clin Oncol. 2019;37(7):537-546; 2) Herbst RS et al. N Engl J Med. 2020;383(14):1328-1339 (supplementary appendix).

Never-smokers may not do well with single-agent IO

IMpower 110 (TC3/IC3)[2]



Never-smoker: HR, 1.83 (95%CI: 0.63–5.31)

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; IC, immune cell; IO, immuno-oncology; TPS, tumor proportion score.
Extracted from 1) Reck M et al. J Clin Oncol. 2019;37(7):537-546; 2) Herbst RS et al. N Engl J Med. 2020;383(14):1328-1339 (supplementary appendix).

Subgroup of patients with high PD-L1 don’t respond as well to single agent IO, thus certainly NOT the ONLY treatment

IO, immuno-oncology; PD-L1, programmed cell death-ligand 1.

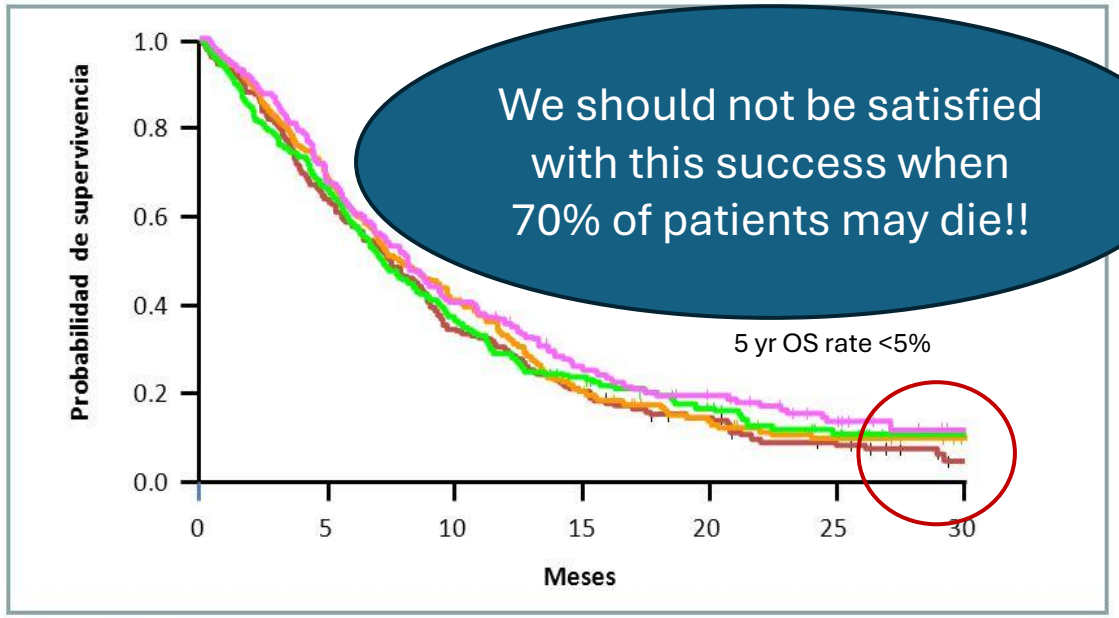
Why do we give immunotherapy to patients?

To help patient living a full and colorful life

Image provided courtesy of Tony Mok.

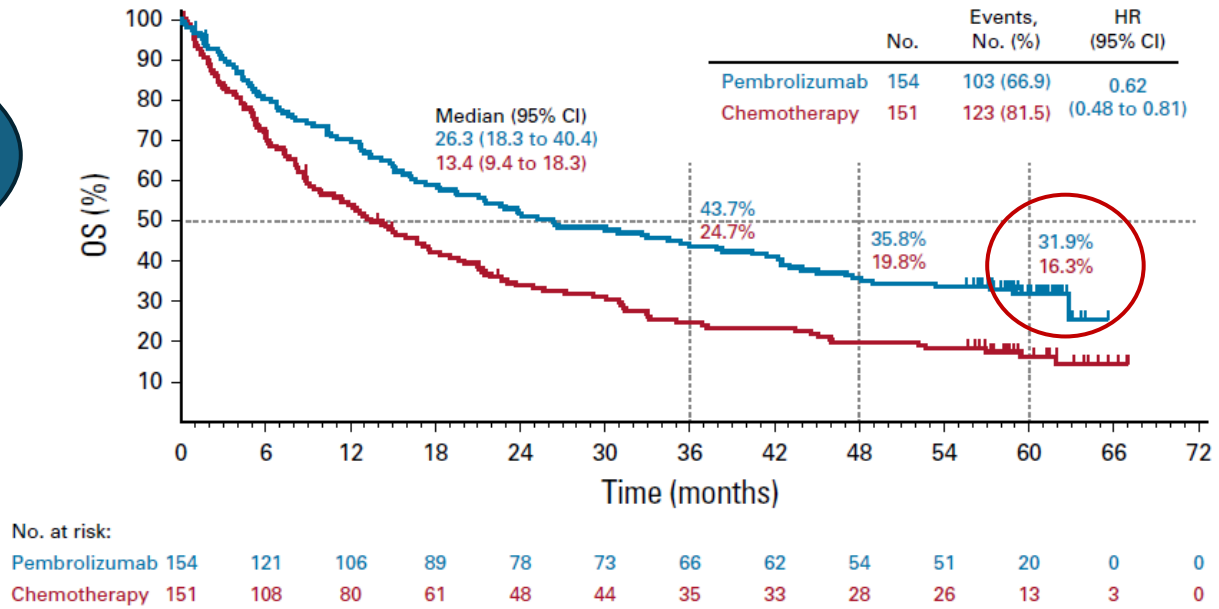
Single-agent IO has improved the 5-year OS rate of patients with advanced NSCLC

Platinum-based doublets in advanced NSCLC[1]



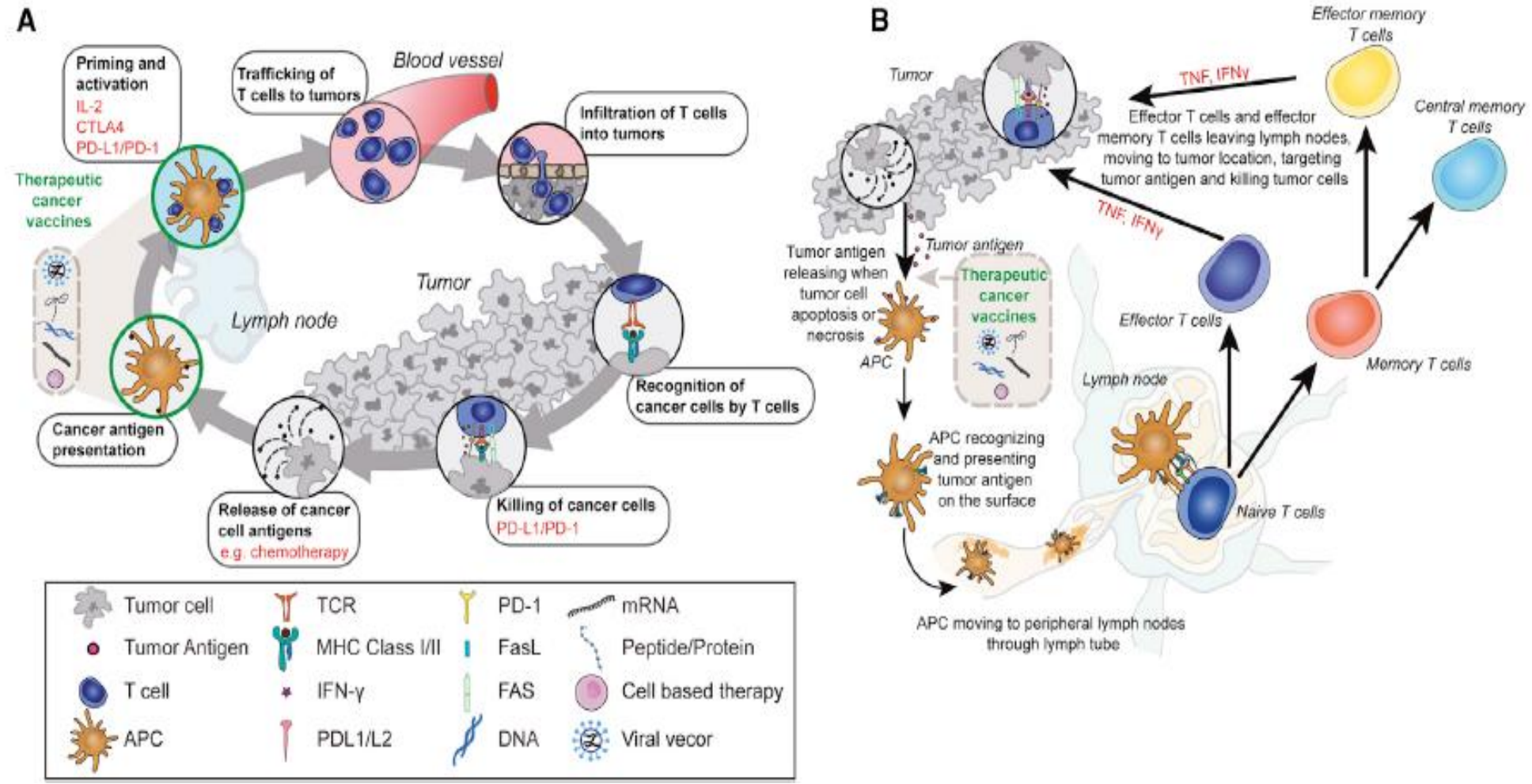
ECOG trial 1594
ECOG, Eastern Cooperative Oncology Group
Schiller et al. N Engl J Med 346:92, 2002

Single agent IO for PD-L1 ≥50% advanced NSCLC[2]



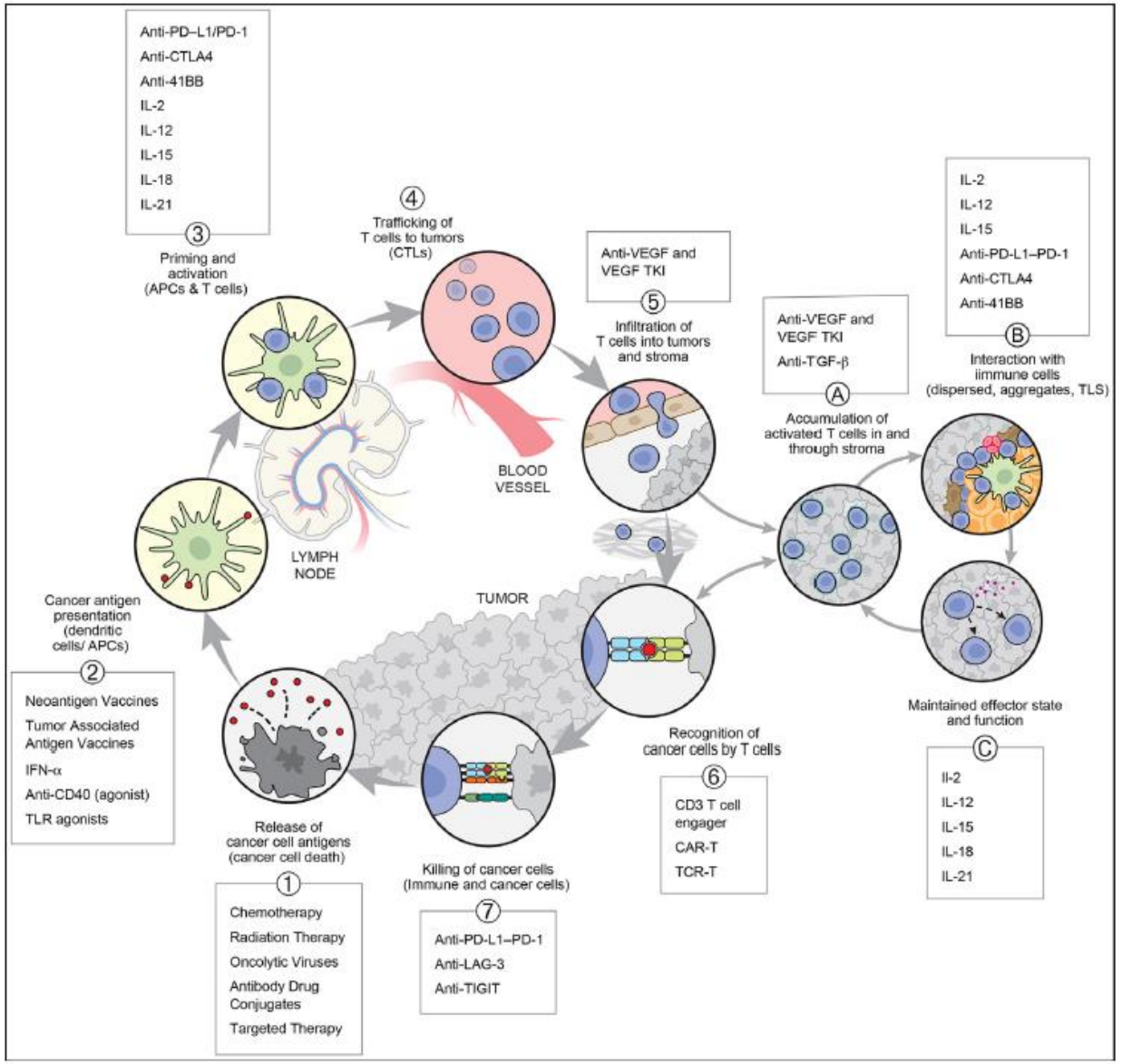
CI, confidence interval; HR, hazard ratio; IO, immuno-oncology; NSCLC, non-small cell lung cancer; OS, overall survival; PD-L1, programmed cell death-ligand 1.
Extracted from 1) Schiller JH et al. N Engl J Med. 2002 Jan 10;346(2):92-8; 2) Reck M et al. J Clin Oncol. 2021;39(21):2339-2349.

PD-L1 is only one piece of a complex puzzle



APC, antigen-presenting cell; CTLA4, cytotoxic T-lymphocyte-associated protein 4; IFNγ, interferon gamma; IL-2, interleukin-2; MHC, major histocompatibility complex; PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1; TCR, T cell receptor; TNF, tumor necrosis factor.
Extracted from Katopodi T et al. Pharmaceutics. 2024;16(4):455.

Multiple potential partners



APC, antigen-presenting cell; CAR-T, chimeric antigen receptor T cells; CD, cluster of differentiation; CTLA4, cytotoxic T-lymphocyte-associated protein 4; IFN, interferon; IL, interleukin; LAG-3, lymphocyte-activation gene 3 protein; PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1; TCR, T cell receptor; TIGIT, T cell immunoreceptor with Ig and ITIM domains; TLR, toll-like receptor; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.
Extracted from Mellman I et al. Immunity. 2023;56(10):2188-2205.

CTLA-4 inhibitor as partner: POSEIDON

Stage IV NSCLC

N=1013 (randomised)

- *EGFR*/*ALK*wt
- ECOG PS 0 or 1
- Treatment-naïve for metastatic disease
- Tumour biopsy* and baseline plasma sample (for ctDNA)

Stratification factors

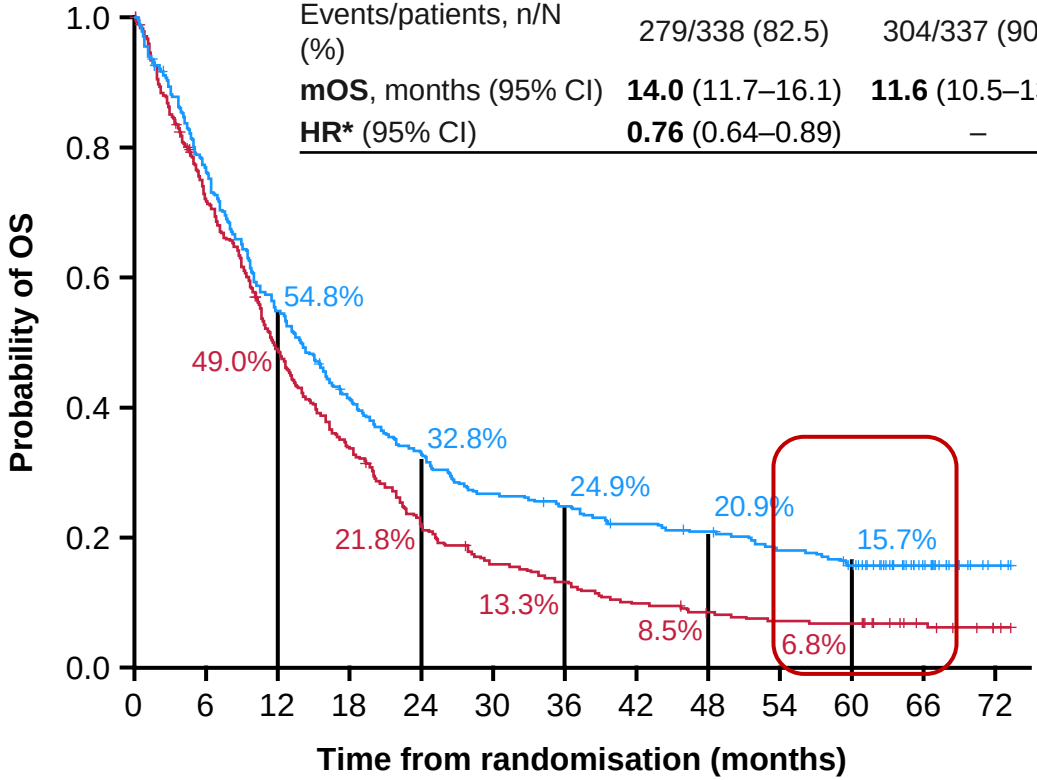
- PD-L1 expression (TC ≥50% vs <50%)
- Disease stage (IVA vs IVB)
- Histology (NSQ vs SQ)

R 1:1:1

- **T+D+CT† q3w 4 cycles** → **T (week 16 only) + D q4w until PD**
- **D+CT† q3w 4 cycles** → **D q4w until PD**
- **Platinum-based CT† q3w up to 6 cycles**

T+D+CT vs CT

	T+D+CT	CT
Events/patients, n/N (%)	279/338 (82.5)	304/337 (90.2)
mOS, months (95% CI)	**14.0** (11.7–16.1)	**11.6** (10.5–13.1)
HR* (95% CI)	**0.76** (0.64–0.89)	–



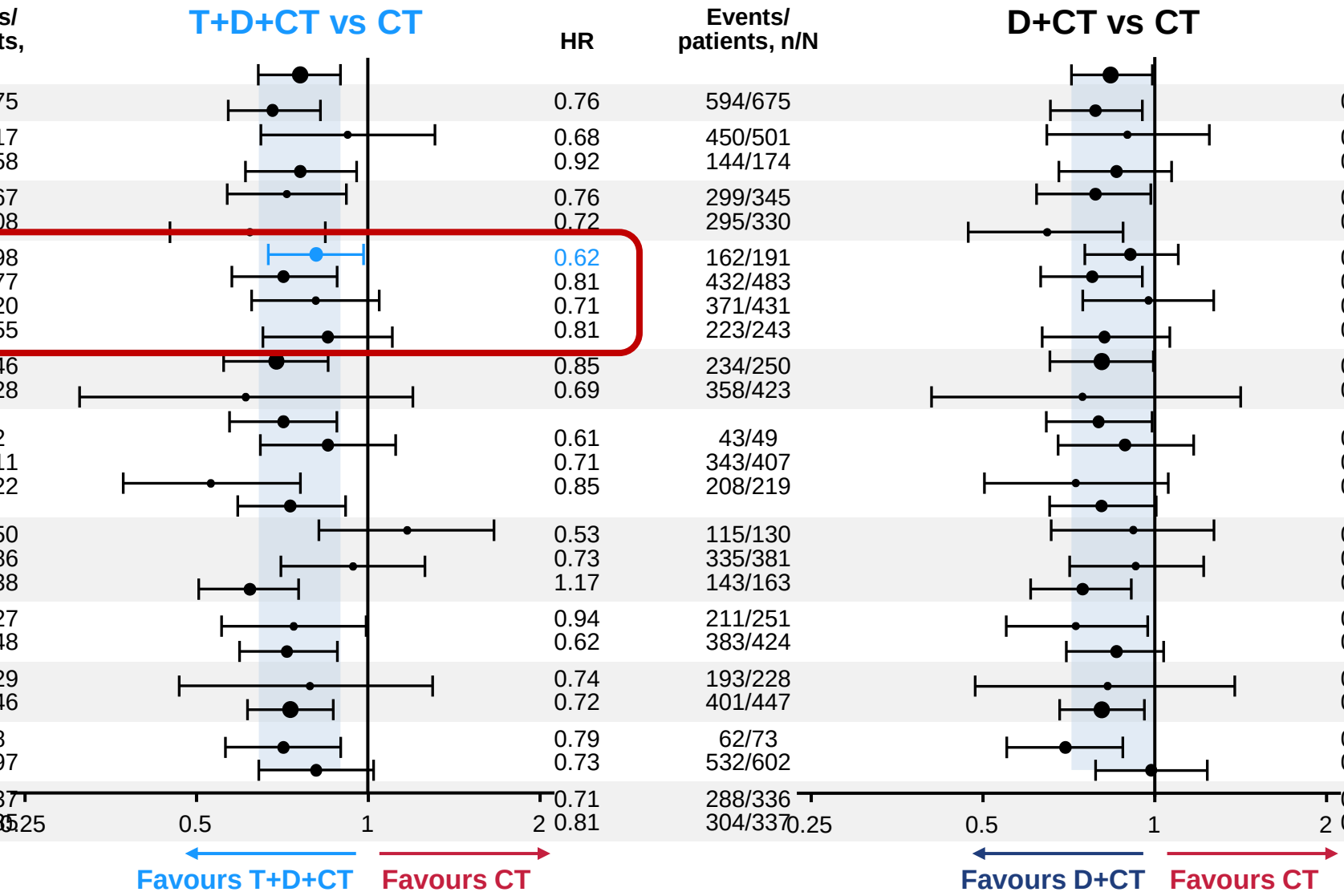
No. at risk

T+D+CT	338	256	183	136	108	88	81	71	66	56	47	21	3
CT	337	235	159	110	70	50	42	31	25	21	20	10	2

ALK, anaplastic lymphoma kinase; CI, confidence interval; CT, chemotherapy; ctDNA, circulating tumor DNA; CTLA4, cytotoxic T-lymphocyte-associated protein 4; D, durvalumab; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, estimated glomerular filtration rate; HR, hazard ratio; mOS, median overall survival; NSQ, non-squamous; PD, progressive disease; PD-L1, programmed cell death ligand 1; q3w, every 3 weeks; q4w, every 4 weeks; SQ, squamous; T, tremelimumab; TC, tumor cell; WT, wild type.
Extracted from Peters S et al. LBA3 - Durvalumab (D) ± tremelimumab (T) + chemotherapy (CT) in first-line metastatic (m) NSCLC: 5-year overall survival (OS) update from the POSEIDON study. Presented at ESMO Immuno-Oncology Congress; December 06-08, 2023; Geneva, Switzerland. Available at: https://oncologypro.esmo.org/meeting-resources/esmo-immuno-oncology-congress-2023/durvalumab-d-tremelimumab-t-chemotherapy-ct-in-first-line-metastatic-m-nsclc-5-year-overall-survival-os-update-from-the-poseidon-study.

More impressive HR in patients with high PD-L1

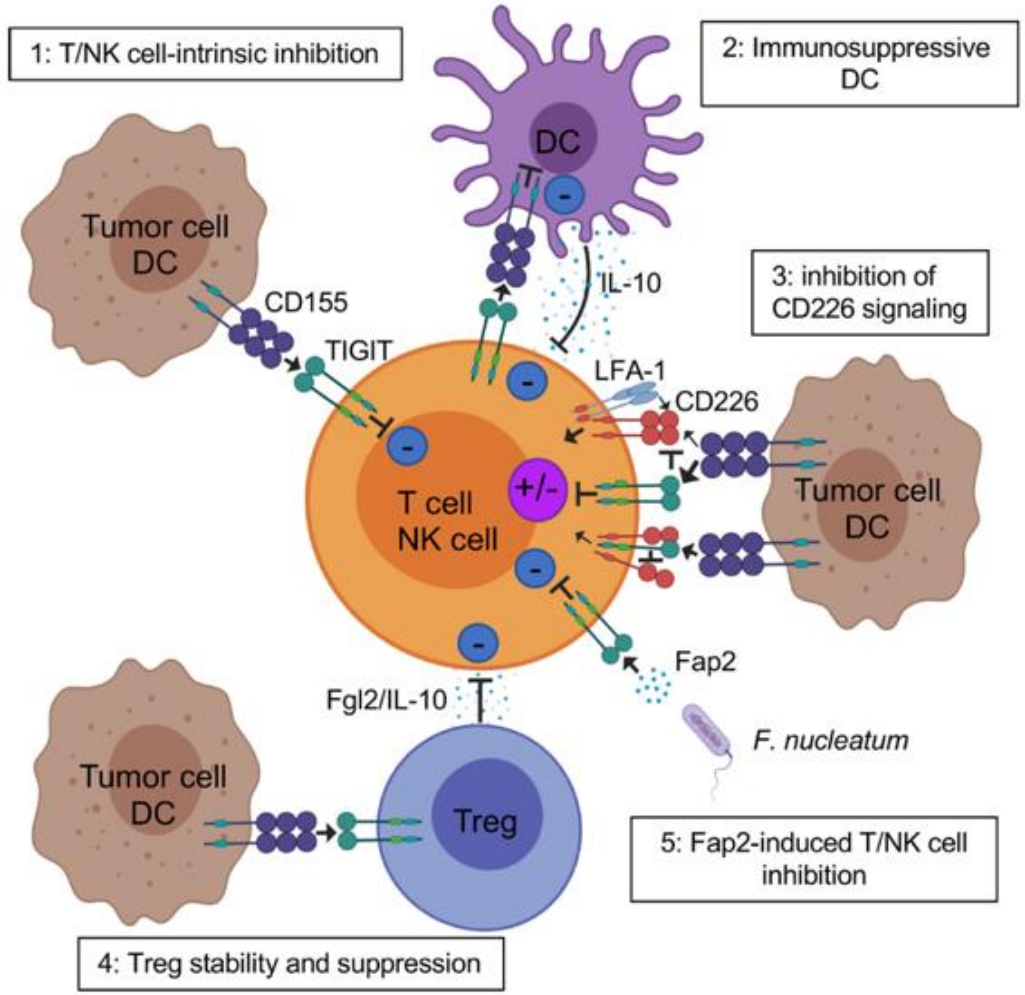
		Events/ patients, n/N	T+D+CT vs CT HR	Events/ patients, n/N	D+CT vs CT HR
All patients		583/675	0.76	594/675	0.84
Sex	Male	455/517	0.68	450/501	0.79
	Female	128/158	0.92	144/174	0.90
Age	<65 years	308/367	0.76	299/345	0.86
	≥65 years	275/308	0.72	295/330	0.79
PD-L1 expression	TC ≥50%	161/198	0.62	162/191	0.65
	TC <50%	422/477	0.81	432/483	0.91
	TC ≥1%	350/420	0.71	371/431	0.78
	TC <1%	233/255	0.81	223/243	0.98
Histology	SQ	229/246	0.85	234/250	0.82
	NSQ	353/428	0.69	358/423	0.81
Planned CT	Nab-paclitaxel doublet	36/42	0.61	43/49	0.75
	Pemetrexed doublet	338/411	0.71	343/407	0.80
	Gemcitabine doublet	209/222	0.85	208/219	0.89
Smoking history	Current	125/150	0.53	115/130	0.73
	Former	331/386	0.73	335/381	0.81
	Never	126/138	1.17	143/163	0.92
Race	Asian	189/227	0.94	211/251	0.93
	Non-Asian	394/448	0.62	383/424	0.75
ECOG PS	0	187/229	0.74	193/228	0.73
	1	396/446	0.72	401/447	0.86
Brain metastases	Yes	64/78	0.79	62/73	0.83
	No	519/597	0.73	532/602	0.81
AJCC disease stage	IVA	290/337	0.71	288/336	0.70
	IVB	292/335	0.81	304/337	0.99



AJCC, American Joint Committee on Cancer
HR <1 favours D(±T)+CT vs CT (all patients analysis stratified, subgroup analysis unstratified); size of circle is proportional to the number of events across both treatment groups; DCO, 24 Aug 2023.
CT, chemotherapy; D, durvalumab; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; NSQ, non-squamous; PD-L1, programmed cell death ligand 1; SQ, squamous; T, tremelimumab; TC, tumor cell.
Extracted from Peters S et al. LBA3 - Durvalumab (D) ± tremelimumab (T) + chemotherapy (CT) in first-line metastatic (m) NSCLC: 5-year overall survival (OS) update from the POSEIDON study. Presented at ESMO Immuno-Oncology Congress; December 06-08, 2023; Geneva, Switzerland. Available at: https://oncologypro.esmo.org/meeting-resources/esmo-immuno-oncology-congress-2023/durvalumab-d-tremelimumab-t-chemotherapy-ct-in-first-line-metastatic-m-nsclc-5-year-overall-survival-os-update-from-the-poseidon-study

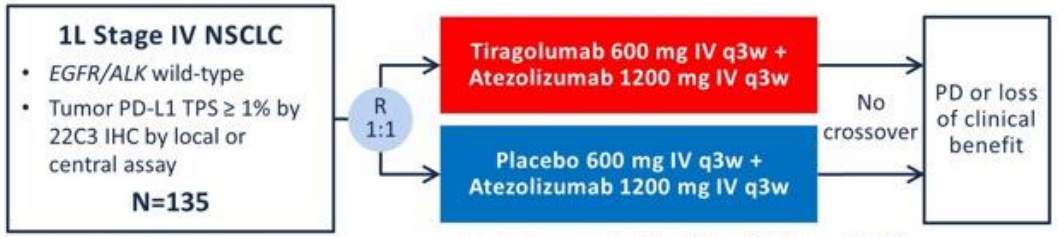
TIGIT

T cell immunoreceptor with immunoglobulin and ITIM domain



APCs, antigen-presenting cells; IL, interleukin; ITIM, immunoreceptor tyrosine-based inhibitory motif; TIGIT, T cell immunoreceptor with immunoglobulin and ITIM domain; Tregs, regulatory T cells.
Extracted from Chauvin J-M and Zarour HM. J Immunother Cancer. 2020 Sep;8(2):e000957.

CITYSCAPE: TIGIT-PD-L1 in NSCLC

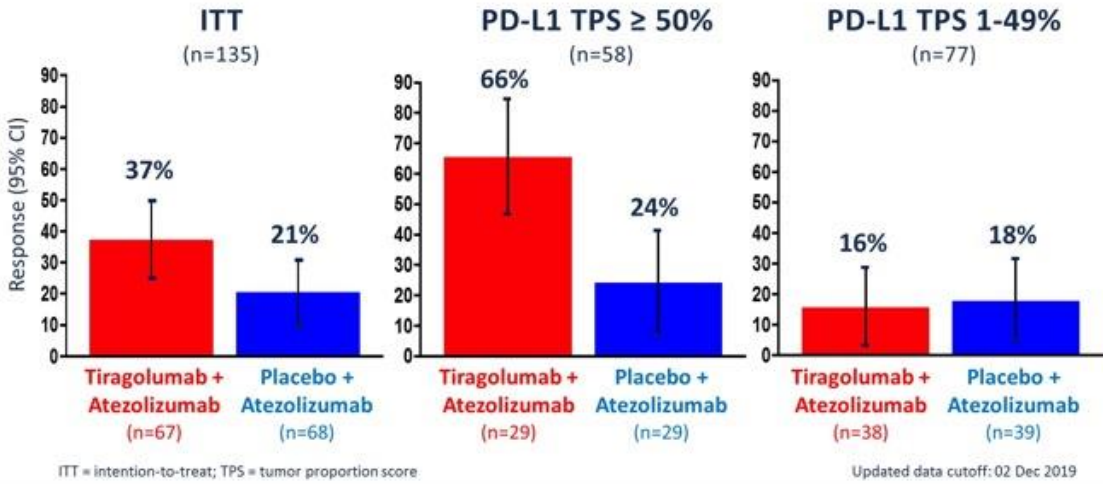


Stratification Factors:

- PD-L1 TPS (1-49% vs ≥ 50%)
- Histology (Non-Squamous vs Squamous)
- Tobacco use (yes vs no)

- **Co-Primary Endpoints: ORR** and **PFS**
- **Key Secondary Endpoints: Safety,** DOR, OS, Patient-reported outcomes (PROs)
- **Exploratory Endpoints:** Efficacy analysis by PD-L1 status

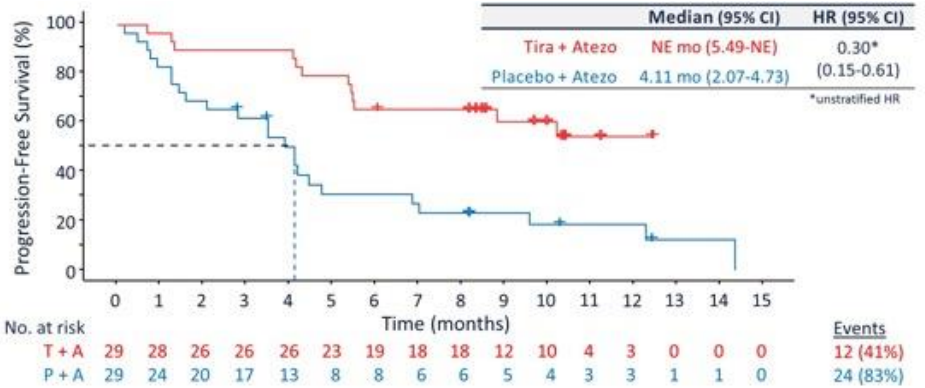
Updated Confirmed Overall Response Rate (ORR)



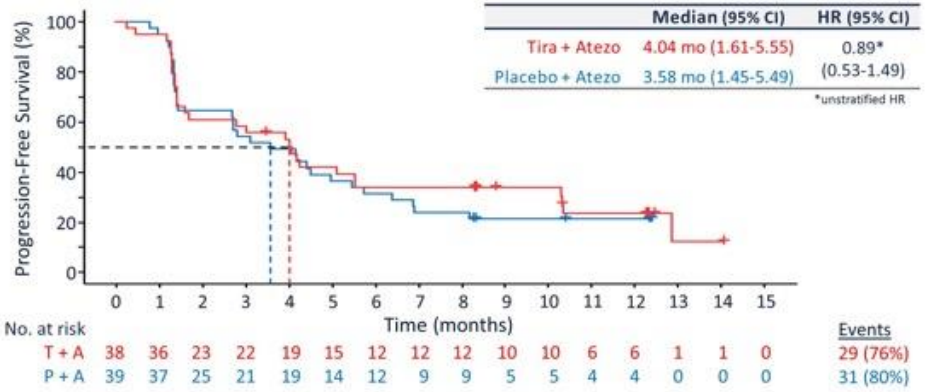
ITT = intention-to-treat; TPS = tumor proportion score

Updated data cutoff: 02 Dec 2019

PD-L1 TPS ≥ 50%



PD-L1 TPS 1-49%



Atezo, atezolizumab; CI, confidence interval; DOR, duration of response; HR, hazard ratio; IHC, immunohistochemistry; ITT, intent-to-treat; NSCLC, non-small cell lung cancer; ORR, confirmed overall response rate; OS, overall survival; PD, progressive disease; PD-L1, programmed cell death-ligand 1; PFS, progression free survival; q3w, every 3 weeks; R, randomized; TIGIT, T cell immunoreceptor with immunoglobulin and ITIM domain; Tira, tiragolumab; TPS, tumor proportion score.

Extracted from Rodriguez-Abreu D et al. CITYSCAPE: Primary Analysis of a Randomized, Double-Blind, Phase II Study of the Anti-TIGIT Antibody Tiragolumab plus Atezolizumab versus Placebo plus Atezolizumab as 1L Treatment in Patients with PD-L1-Selected NSCLC. Presented at the ASCO Annual Meeting; May 29-June 02, 2020; Chicago, IL. Available at: https://medically.roche.com/content/dam/pdmahub/non-restricted/oncology/asco-2020/ASCO-2020-presentation-rodriguez-abreu-primary-analysis-of-a-randomized-double-blind-phase-II-study-of-the-anti-TIGIT-antibody-tiragolumab-tira-plus-atezolizumab-atezo.pdf.

SKYSCRAPER-01 (GO41717): tiragolumab + atezolizumab in PD-L1-high 1L NSCLC

Phase III, double-blind study in 1L PD-L1-high patients with metastatic NSCLC

1L Stage IV NSCLC

- *EGFR/ALK* WT
- PD-L1 TPS ≥50% (PD-L1 IHC 22C3 pharmDx assay) **OR** TC3 or IC3 (VENTANA PD-L1 SP142 assay) **OR** TC ≥50% (VENTANA PD-L1 SP263 assay)

N=500

May 11 2022
SKYSCRAPER-1 Trial does not meet primary endpoint of PFS with tiragolumab plus atezolizumab in PDL1 high population

Treat until PD or loss of clinical benefit

Stratification factors

- ECOG (0 vs 1)
- Histology (NSQ vs SQ)
- Geographic region (Asian vs non-Asian)

- OS in ITT
- PFS in ITT

Secondary endpoints:

- ORR
- DOR
- PFS & OS landmarks
- PK/ADA
- PRO
- Safety

1L, first-line; ALK, anaplastic lymphoma kinase; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; IHC, immunohistochemistry; ITT, intention-to-treat; IV, intravenously; NSQ, nonsquamous; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PK/ADA, pharmacokinetic/anti-drug antibodies; PRO, patient-reported outcome; Q3W, every 3 weeks; SQ, squamous; TC, tumour cell; TPS, tumour proportion score; WT, wild-type.
https://clinicaltrials.gov/study/NCT04294810.

“Data leak” in August 2023

- The interim results for the primary endpoint of overall survival were not mature at the time of the second interim analysis, with median overall survival estimates of 22.9 months [95% CI: 17.5, NE] in the tiragolumab plus Tecentriq arm, and 16.7 months [95% CI: 14.6, 20.2] in the Tecentriq monotherapy arm, yielding a hazard ratio of 0.81 [95% CI: 0.63, 1.03].

July 24, 2024

Roche announced on Thursday that it will discontinue the Phase II/III SKYSCRAPER-06 study due to disappointing results from its investigational anti-TIGIT antibody, tiragolumab. The drug failed to significantly improve survival rates in patients with non-small cell lung cancer (NSCLC).

CI, confidence interval; NE, not estimable; TIGIT, T cell immunoreceptor with immunoglobulin and ITIM domain.

With more approaches to come…

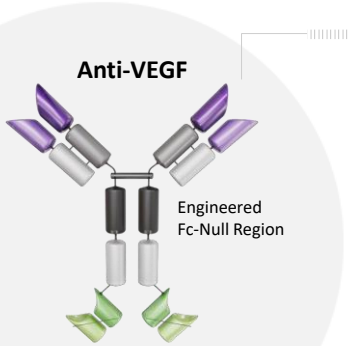
Dual Checkpoint inhibitor combinations					
LAG3 based combinations					
NCT04618393	I/II	EMB-02	Anti-PD-1/LAG-3 bispecific mAb	Pretreated	Recruiting
NCT04140500	I	RO72747669	Anti-PD-1/LAG-3 bispecific mAb	Pretreated	Recruiting
NCT03849469	I	XmAb22841+- Pembrolizumab	Anti-CTLA-4/LAG-3 bispecific mAb	Pretreated	Active, not recruiting
NCT03250832	I	TSR-033 +- Dostarlimab	Anti-LAG3 mAb	Pretreated	Active, not recruiting
TIGIT based combinations					
NCT04672369	I	IBI939	Anti-TIGIT mAb	Pretreated	Recruiting
NCT04995523	II	AZD2936	Anti-PD-1/TIGIT bispecific mAb	Pretreated	Recruiting
NCT05102214	I/II	HLX301	Anti-PD-1/TIGIT bispecific mAb	Pretreated	Recruiting
NCT04761198	I/II	Etigilimab + Nivolumab	Anti-TIGIT mAb	Pretreated	Recruiting
NCT04738487 (KEYVIBE-003)	III	MK-7684A (Vibostolimab)/Pembrolizumab vs. Pembrolizumab	Anti-TIGIT mAb	First-Line	Recruiting
NCT04746924	III	Ociperliamab/Tislelizumab vs. Pembrolizumab	Anti-TIGIT mAb	First-Line	Recruiting
NCT04736173 (ARC-10)	III	Zimberelimab + Domvanalimab vs. Zimberelimab vs. Chemotherapy	Anti-TIGIT mAb	First-Line	Recruiting
NCT05502237 (STAR-121)	III	Zimberelimab + Domvanalimab + Chemotherapy vs. Pembrolizumab + Chemotherapy	Anti-TIGIT mAb	First-Line	Recruiting
TIM3 based combinations					
NCT02817633	I	TSR-022 + nivolumab or TSR-042 or TSR-033	Anti-TIM3 mAb	Pretreated	Recruiting
NCT03708328	I	RO7121661	Anti-PD-1/TIM-3 bispecific mAb	Pretreated	Active, not recruiting
GITR based combinations					
NCT03126110	I/II	INCAGN01876 + Anti-PD-1 mAb/Anti-PD-1 + Anti-CTLA-4 mAb	GITR agonist mAb	Pretreated	Completed
NKG2A based combinations					
NCT05221840	III	Durvalumab + Monalizumab vs. Durvalumab + Placebo	Anti-NKG2A mAb	Stage III unresectable	Recruiting

CTLA4, cytotoxic T-lymphocyte-associated protein 4; GITR, glucocorticoid-induced tumor necrosis factor receptor family-related receptor; LAG-3, lymphocyte-activation gene 3 protein; mAB, monoclonal antibody; PD-L1, programmed cell death-ligand 1; TIGIT, T cell immunoreceptor with immunoglobulin and ITIM domain; IM-3, T cell immunoglobulin domain and mucin domain-3.
https://clinicaltrials.gov/.

Ivonescimab

Ivonescimab

Designed to Potentially Improve the Balance of Anti-tumor Activity & Safety[1,2]



First in Class* PD-1/VEGF

Brings two validated oncologic mechanisms into ONE novel tetravalent molecule[1,4,5]

Only Phase III PD-1/VEGF Bispecific

In clinical development in the United States, Canada, Europe & Japan

Cooperative Binding

Simultaneous blocking of PD-1 & VEGF[1,2,3]

Increased:
Avidity in TME[6]
Activity of T Cells[6,7]

*There are no known PD-1-based bispecific antibodies approved by the U.S. Food and Drug Administration ("FDA") or the European Medicines Agency ("EMA").

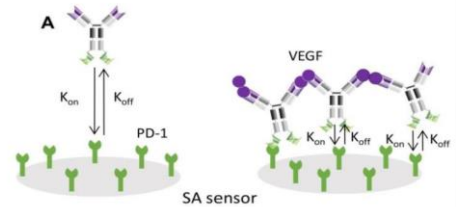
1. Manegold C, et al. J Thorac Oncol 2017;12(2):194-207, 2. Zhao Y, et al. eClinicalMedicine. 2023; 3(62): 102106., 3. Data on File. [14, 15] Summit Therapeutics Inc., 4. Pardoll, D. Nat Rev Cancer 2012;12(4):252-64, 5. Tamura R, et al. Med Oncol 2020;37(1):2, 6. Zhong T, et al. AACR-NCI-EORTC International Conference 2023.Poster #B123, Abstract #35333, Boston, MA, USA, 7. Zhong T, et al. JITC 2022;10(2):S21., 8. Zhou C, et al. J Clin Oncol. 2022;40:16_suppl, 9040., 9. Zhang L, et al. ASCO 2023 poster #9087.

Ivonescimab is an investigational therapy that is not approved by any regulatory authority.
Ivonescimab is currently being investigated in Phase III clinical studies

Ivonescimab

Cooperative Binding Enhances Ivonescimab Affinity[1]

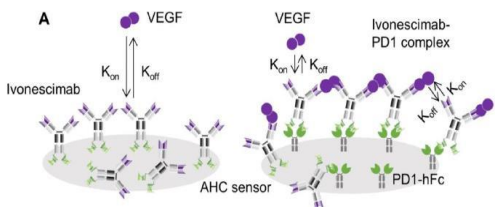
VEGF promotes cooperative binding of ivonescimab to human PD-1[1]



Fixed antigen	Antibody	VEGFA-his (nM)	K_D (M)	k_{on} (1/ms)	k_{dis} (1/s)
PD1-his, 200 nM	Ivonescimab	0	7.15E-10	2.94E+05	2.10E-04
	Ivonescimab + VEGF	50-1.56	3.83E-11	2.51E+05	9.62E-05

Note: A. Diagram to represent the binding profile of Ivonescimab to PD-1 in the presence/absence of VEGF

PD-1 enhances binding avidity of ivonescimab to human VEGF[1]



Fixed antigen	Analyte	K_D (M)	k_{on} (1/ms)	k_{dis} (1/s)
Ivonescimab	VEGFA-his[b]	1.96E-09	2.04E+05	4.01E-04
Ivonescimab+ PD1-hFc[a]		4.11E-10	1.60E+05	6.58E-05

Note: A. Diagram to represent the binding profile of Ivonescimab to VEGF with or without PD-1.

1. Zhong T, et al. AACR-NCI-EORTC International Conference 2023.Poster #B123,Abstract #35333, Boston, MA, USA

Ivonescimab is an investigational therapy that is not approved by any regulatory authority.
Ivonescimab is currently being investigated in Phase III clinical studies

May 31 2024

First-line treatment with ivonescimab (AK112; SMT112) monotherapy led to a statistically significant and clinically meaningful improvement in progression-free survival (PFS) compared with pembrolizumab (Keytruda) monotherapy in patients with locally advanced or metastatic, PD-L1–positive non–small cell lung cancer (NSCLC), meeting the primary end point of the phase 3 HARMONi-2 trial (NCT05499390).[1]

PD-L1, programmed cell death ligand 1; VEGF, vascular endothelial growth factor.

Extracted from Zhong T et al. Mechanism of Action of Ivonescimab (AK112/SMT112): A First-in-Class Tetravalent Bispecific Antibody with Dual Blockade of PD-1 and VEGF that Promotes Cooperative Biological Effects. Abstract 35333. Presented at AACR-NCI-EORTC; October 11-15, 2023; Boston, MA. Available at: https://www.smmttx.com/publications/.

Single agent is NOT the ONLY treatment

- Single agent IO may be preferred for patient with high PD-L1 expression but is NOT the ONLY treatment option[1]
- PD-L1 >50% represents a heterogenous population and some patients don't respond well to single-agent IO, thus certainly NOT the ONLY treatment[2-7]
- Objective of immunotherapy is to help patients to live a long and normal life, but current 5-year OS rate is only 30%, thus we must declare single-agent IO NOT the ONLY treatment[8,9]

IO, immuno-oncology; OS, overall survival; PD-L1, programmed cell death ligand 1.

1) Speaker's own; 2) Ricciuti B et al. JTO Clinical and Research Reports. 2024; doi: https://doi.org/10.1016/j.jtocrr.2024.100675 (pre-proof); 3) Herbst RS et al. N Engl J Med. 2020;383(14):1328-1339 (supplementary appendix); 4) Brahmer JR et al. LBA51 - KEYNOTE-024 5-year OS update: First-line (1L) pembrolizumab (pembro) vs platinum-based chemotherapy (chemo) in patients (pts) with metastatic NSCLC and PD-L1 tumour proportion score (TPS) ≥50%. Presented at ESMO Virtual Congress; September 19-21, 2020. Available at: https://oncologypro.esmo.org/meeting-resources/esmo-virtual-congress-2020/keynote-024-5-year-os-update-first-line-1l-pembrolizumab-pembro-vs-platinum-based-chemotherapy-chemo-in-patients-pts-with-metastatic-nsclc; 5) Sezer A et al. LBA52 - EMPOWER-Lung 1: Phase III first-line (1L) cemiplimab monotherapy vs platinum-doublet chemotherapy (chemo) in advanced non-small cell lung cancer (NSCLC) with programmed cell death-ligand 1 (PD-L1) ≥50%. Presented at ESMO Virtual Congress; September 19-21, 2020. Available at: https://oncologypro.esmo.org/meeting-resources/esmo-virtual-congress-2020/empower-lung-1-phase-iii-first-line-1l-cemiplimab-monotherapy-vs-platinum-doublet-chemotherapy-chemo-in-advanced-non-small-cell-lung-cancer-n; 6) Reck M et al. J Clin Oncol. 2019;37(7):537-546; 7) Herbst RS et al. N Engl J Med. 2020;383(14):1328-1339; 8) Schiller JH et al. N Engl J Med. 2002 Jan 10;346(2):92-8; 9) Reck M et al. J Clin Oncol. 2021;39(21):2339-2349.

Single tapa is good but combination may be better

Instituto de Investigación
Hospital 12 de Octubre

SPANISH NATIONAL CANCER RESEARCH CENTRE

UNIVERSIDAD COMPLUTENSE MADRID

What to do in NSCLC with low PD-L1 expression?

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Disclosures

COI	Sponsor
Leadership	Altum Sequencing (founding partner and member of the board), Stab therapeutics (founding partner and member of the board), Genomica (external member of the board),
Travel, accommodation, expenses	AstraZeneca, AstraZeneca Spain, Bristol-Myers Squibb, Lilly, MSD, Pfizer, Roche
Honoraria (Scientific advice, speaker)	Amgen, Astellas, AstraZeneca, Bayer, BeiGene, BioNTech, BMS, Boehringer, Esteve, GSK, Hutchmed, iTM, Lilly, Merck, MSD, Novartis, Pierre-Fabre, Pfizer, Pharmamar, Regeneron, Roche, Sanofi, Servier, Takeda
Research grants to Institution	MSD, BMS, AstraZeneca, Pfizer, Pharmamar

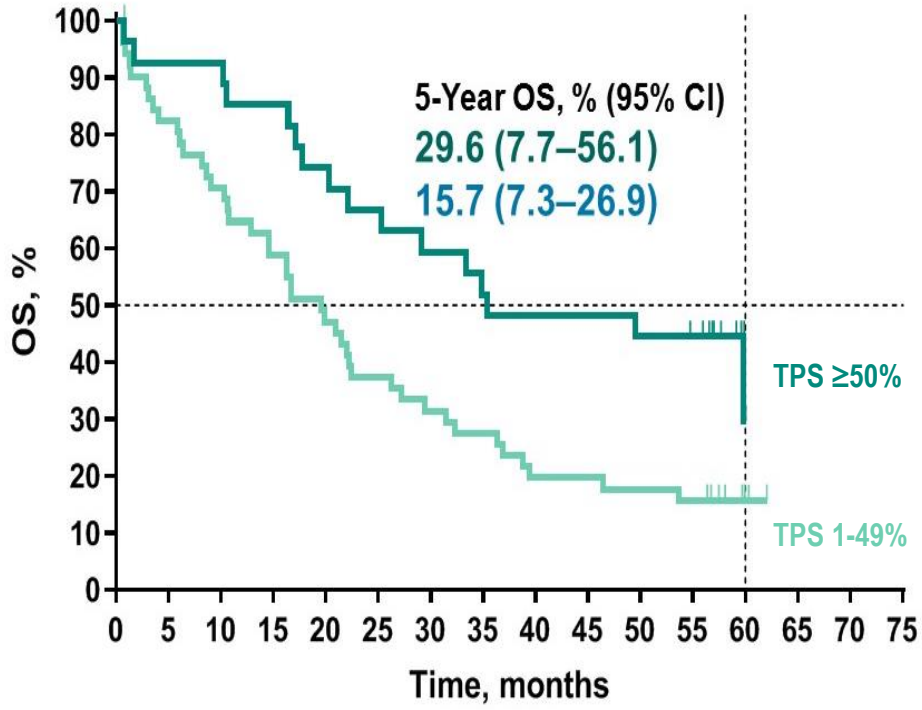
COI, conflict of interest.

KEYNOTE-001
Phase 1b
Pembro
PD-L1 ≥1%
5-year OS

PD-1/PD-L1 inhibitors benefit a relevant subset of patients

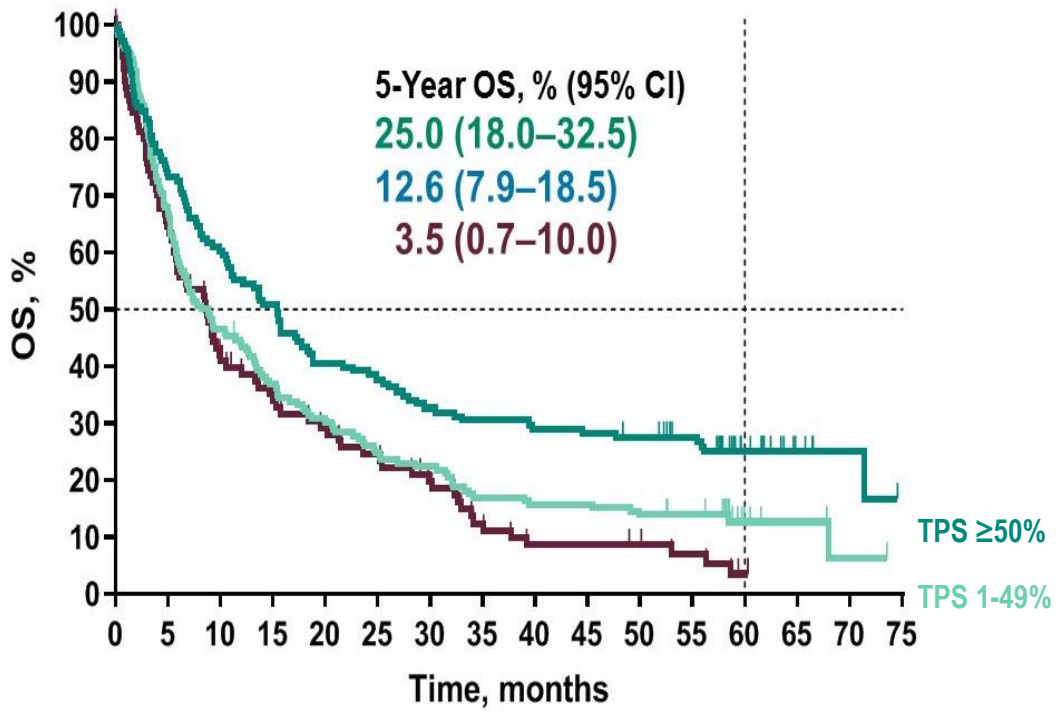
Treatment-Naive Patients

PD-L1 TPS	Events, n/N	Median (95% CI) OS, mo
TPS ≥50%	17/27	35.4 (20.3–63.5)
TPS 1%–49%	43/52	19.5 (10.7–26.3)



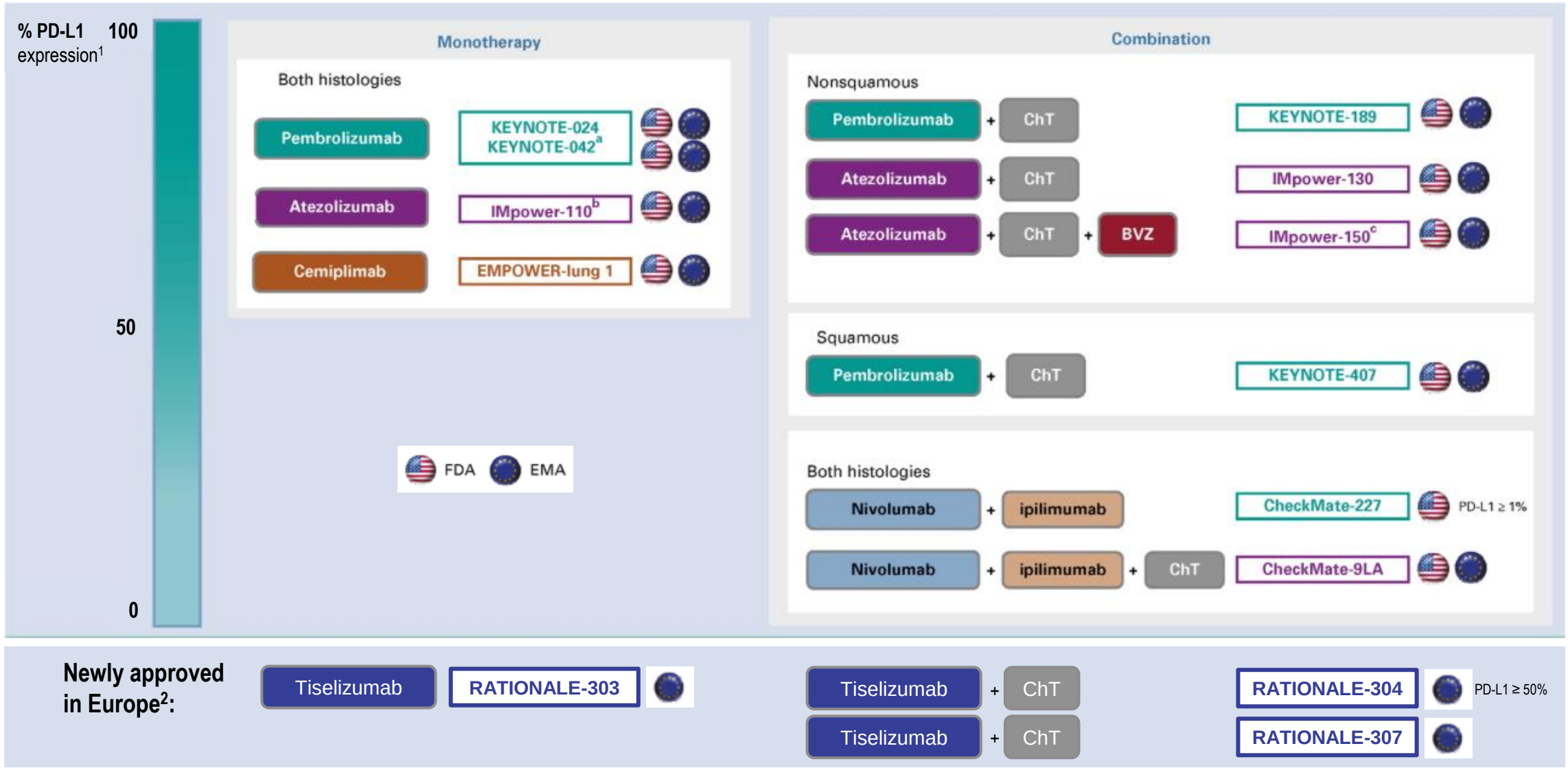
Previously Treated Patients

PD-L1 TPS	Events, n/N	Median (95% CI) OS, mo
TPS ≥50%	104/138	15.4 (10.6–18.8)
TPS 1%–49%	146/168	8.5 (6.0–12.6)
TPS <1%	83/90	8.6 (5.5–10.6)



CI, confidence interval; mo, months; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1; Pembro, pembrolizumab; TPS, tumor proportion score.
Extracted from Garon EB et al. J Clin Oncol. 2019;37(28):2518-2527.

IO strategy in first-line setting NSCLC



BVZ, bevacizumab; ChT, chemotherapy; IO, immuno-oncology; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death-ligand 1.
1) Extracted from Reck M et al. J Clin Oncol. 2022;40(6):586-597; 2) Available from: press release.

Advanced NSCLC: IO Selection

- IO Monotherapy
- Chemo plus IO
- IO plus IO combos

Tumor

- **PD-L1**
- Aggressiveness
- Tumor burden
- Genomics/TMB

Patient

- Performance status
- Smoking
- Gender
- Comorbidities
- Convenience
- Expectations

Chemo, chemotherapy; IO, immuno-oncology; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death-ligand 1; TMB, tumor mutational burden.

Agenda

- IO Monotherapy
- Chemo plus IO
- IO plus IO combos

Chemo, chemotherapy; IO, immuno-oncology; TMB, tumor mutational burden.

Agenda

- IO Monotherapy
- Chemo plus IO
- IO plus IO combos

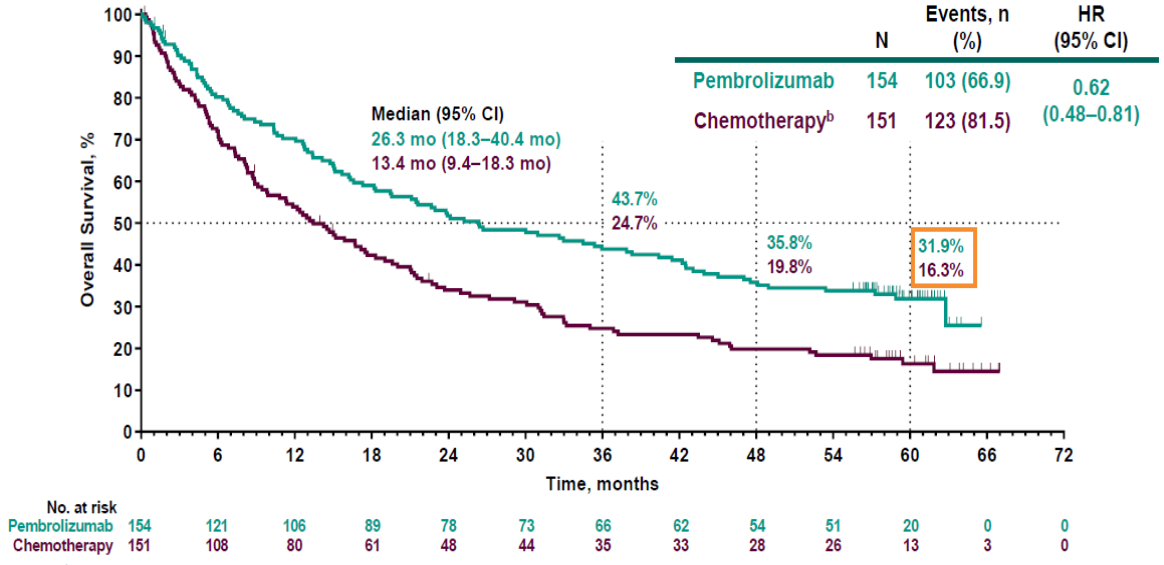
Chemo, chemotherapy; IO, immuno-oncology; TMB, tumor mutational burden.

KEYNOTE-024
Phase 3
Pembro vs CT
PD-L1 ≥50%
5-year OS

KEYNOTE-024 (PD-L1 ≥50%) – 5 year update

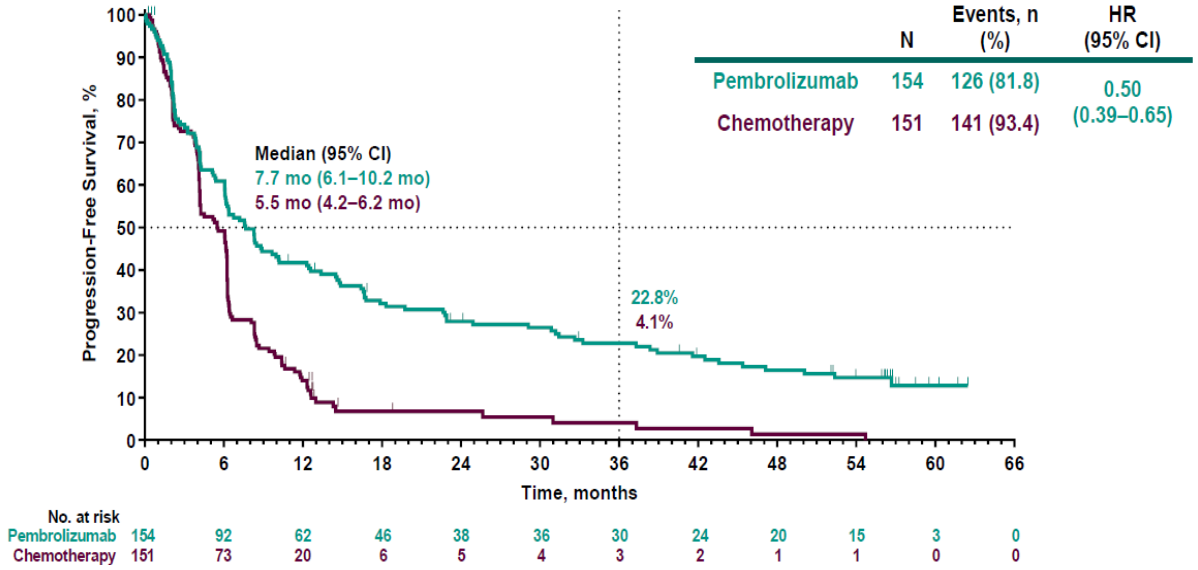
Median follow up: 59.9 months (range: 55.5–68.4)

Overall Survival[a]



Progression-Free Survival[a]

By RECIST v1.1 per Investigator Review[c]



[a]ITT population.
[b]Effective crossover rate from chemotherapy to anti–PD-L1 therapy, 66.0% (99 patients in total crossed over to anti-PD-L1 therapy: 83 patients crossed over to pembrolizumab during the study, and 16 patients received subsequent anti–PD-[L]1 therapy outside of crossover; patients may have received >1 subsequent anti–PD-[L]1 therapy).
[c]Secondary end point; primary endpoint was PFS assessed per blinded, independent, central radiology review.
CI, confidence interval; CT, chemotherapy; HR, hazard ratio; mo, months; OS, overall survival; PD-L1, programmed cell death-ligand 1; Pembro, pembrolizumab.
Extracted from Brahmer JR et al. LBA51 KEYNOTE-024 5-year OS update: First-line (1L) pembrolizumab (pembro) vs platinum-based chemotherapy (chemo) in patients (pts) with metastatic NSCLC and PD-L1 tumour proportion score (TPS)≥ 50%. Presented at: European Society of Medical Oncology; September 19-21, 2020; virtual. Abstract LBA51. Available at: https://doi.org/10.1016/j.annonc.2020.08.2284.

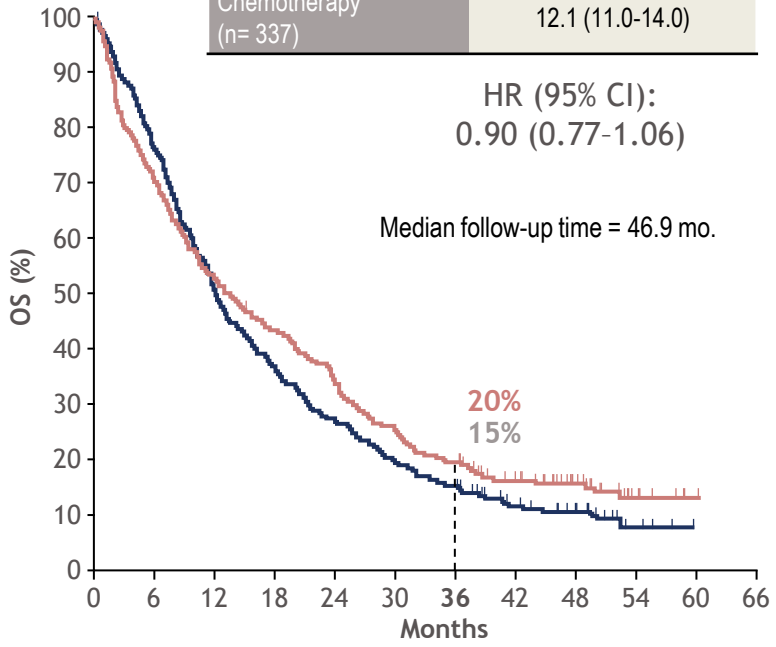
Benefit from IO monotherapy is limited in PD-L1 low or intermediate expressors

KEYNOTE-042: PD-L1 1-49%[1]

	Median OS (95% CI), mo
Pembrolizumab (n=338)	13.4 (10.7-16.9)
Chemotherapy (n= 337)	12.1 (11.0-14.0)

HR (95% CI): 0.90 (0.77–1.06)

Median follow-up time = 46.9 mo.

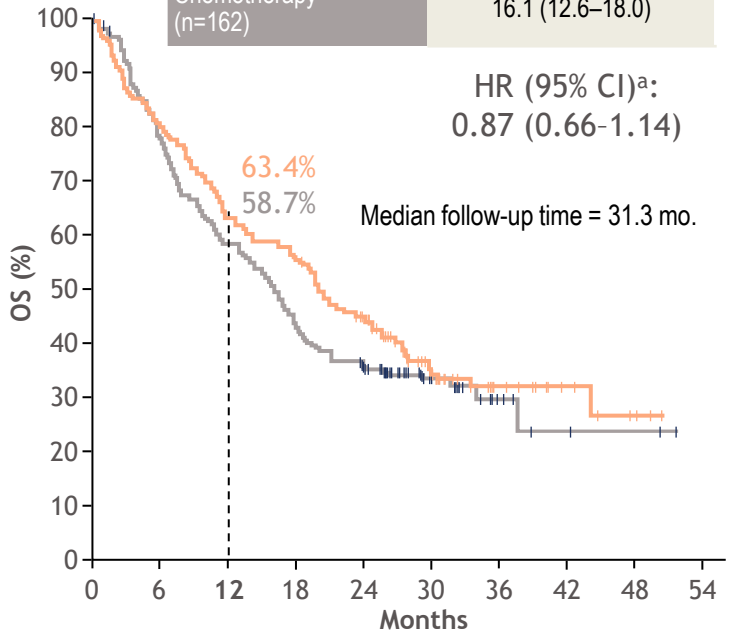


Impower110: PD-L1 TC2/3 or IC2/3[2] (PD-L1 ≥5%)

	Median OS (95% CI), mo
Atezolizumab (n=166)	19.9 (17.2–25.3)
Chemotherapy (n=162)	16.1 (12.6–18.0)

HR (95% CI)[a]: 0.87 (0.66–1.14)

Median follow-up time = 31.3 mo.

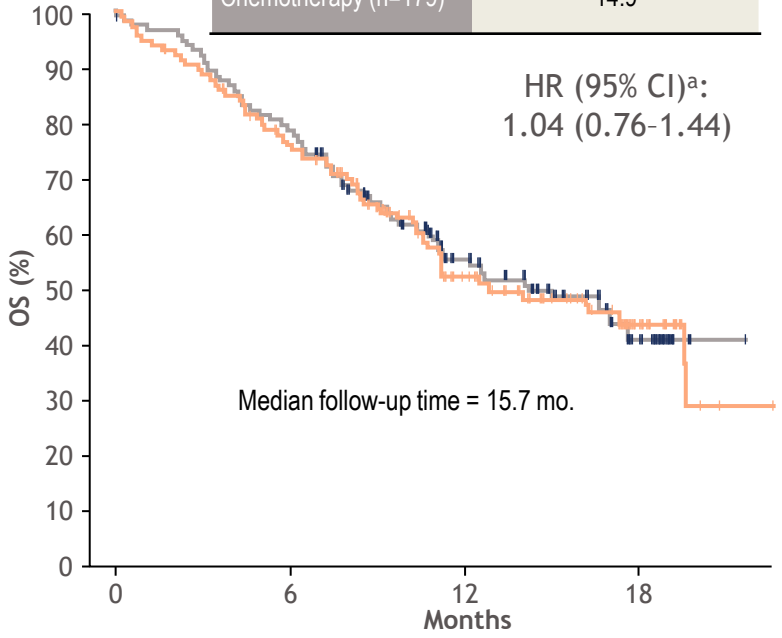


IMpower110: PD-L1 TC1/2 or IC1/2[3] (PD-L1 1-49%)

	Median OS, mo
Atezolizumab (n=170)	12.9
Chemotherapy (n=179)	14.9

HR (95% CI)[a]: 1.04 (0.76–1.44)

Median follow-up time = 15.7 mo.



Slide intended for educational purposes only. Cross-study comparisons are not intended.

[a] stratified.

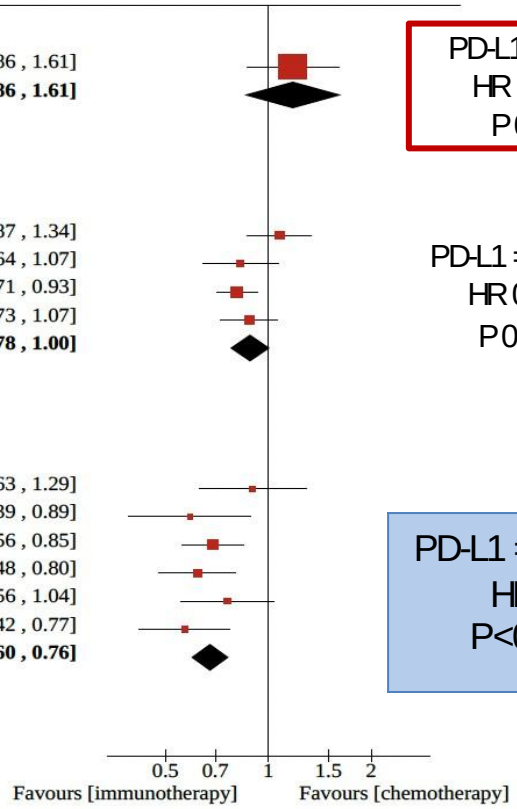
CI, confidence interval; HR, hazard ratio; IO, immuno-oncology; mo, months; OS, overall survival; PD-L1, programmed cell death-ligand 1.

TC1/2 denotes PD-L1 expression on ≥1% and <50% of tumor cells or ≥1% and <10% tumor-infiltrating cells, respectively. TC2/3 or IC2/3 denotes PD-L1 expression on ≥5% of tumor or tumor-infiltrating cells respectively.

Extracted from 1) Cho BC et al. KEYNOTE-042 3-Year Survival Update: 1L Pembrolizumab vs Platinum-Based Chemotherapy for PD-L1+ Locally Advanced/Metastatic NSCLC. Presented at 2020 WCLC; Singapore; January 28-31, 2021. Abstract FP13.04. Available at: https://wclc2020.iaslc.org/; 2) Herbst RS et al. IMpower110: updated OS analysis of atezolizumab vs platinum-based hemotherapy as first-line treatment in PD-L1–selected NSCLC. Presented at: 2020 World Conference on Lung Cancer Singapore. January 28-31, 2021. Abstract FP13.03. Available at: https://wclc2021.iaslc.org/; 3) Herbst RS et al. Clinical efficacy of atezolizumab (atezo) in biomarker subgroups by SP142, SP263 and 22C3 PD-L1 immunohistochemistry (IHC) assays and by blood tumour mutational burden (bTMB): Results from the IMpower110 study. Abstract LBA1. Presented at the ESMO IO Congress; December 11-14, 2019; Geneva, Switzerland. Available at: https://medically.gene.com/content/dam/pdmahub/restricted/oncology/esmo-io-2019/ESMO-IO-2019-presentation-herbst-clinical-efficacy-of-atezolizumab-in-biomarker-subgroups.pdf.

Cochrane-Analysis
Overall survival IO vs CT by PD-L1 expression

Study or Subgroup	log[Hazard Ratio]	SE	Favours [immunotherapy] Total	Chemotherapy Total	Weight	Hazard Ratio IV, Random, 95% CI
1.1.1 PD-L1 TPS <1%						
Rizvi 2020	0.1655	0.1585	95	83	100.0%	1.18 [0.86 , 1.61]
Subtotal (95% CI)			**95**	**83**	**100.0%**	**1.18 [0.86 , 1.61]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.04 (P = 0.30)						
1.1.2 PD-L1 TPS≥1%						
Carbone 2017	0.077	0.1103	271	270	21.8%	1.08 [0.87 , 1.34]
Herbst 2020	-0.1863	0.1296	277	277	17.5%	0.83 [0.64 , 1.07]
Mok 2019	-0.2107	0.0705	637	637	35.5%	0.81 [0.71 , 0.93]
Rizvi 2020	-0.1278	0.0983	279	289	25.2%	0.88 [0.73 , 1.07]
Subtotal (95% CI)			**1464**	**1473**	**100.0%**	**0.88 [0.78 , 1.00]**
Heterogeneity: Tau² = 0.01; Chi² = 5.01, df = 3 (P = 0.17); I² = 40%						
Test for overall effect: Z = 1.92 (P = 0.05)						
1.1.3 PD-L1 TPS ≥50%						
Carbone 2017	-0.1054	0.1837	88	126	10.7%	0.90 [0.63 , 1.29]
Herbst 2020	-0.5276	0.2097	107	98	8.2%	0.59 [0.39 , 0.89]
Mok 2019	-0.3711	0.1064	299	300	31.3%	0.69 [0.56 , 0.85]
Reck 2016	-0.478	0.1306	154	151	20.9%	0.62 [0.48 , 0.80]
Rizvi 2020	-0.2744	0.1591	118	107	14.2%	0.76 [0.56 , 1.04]
Sezer 2020	-0.5621	0.1558	283	280	14.8%	0.57 [0.42 , 0.77]
Subtotal (95% CI)			**1049**	**1062**	**100.0%**	**0.68 [0.60 , 0.76]**
Heterogeneity: Tau² = 0.00; Chi² = 5.06, df = 5 (P = 0.41); I² = 1%						
Test for overall effect: Z = 6.52 (P < 0.00001)						
Test for subgroup differences: Chi² = 16.31, df = 2 (P = 0.0003), I² = 87.7%						



PD-L1 < 1%
HR 1.18
P 0.3

PD-L1 =/> 1%
HR 0.88
P 0.05

PD-L1 =/> 50%*
HR 0.68
P<0.00001

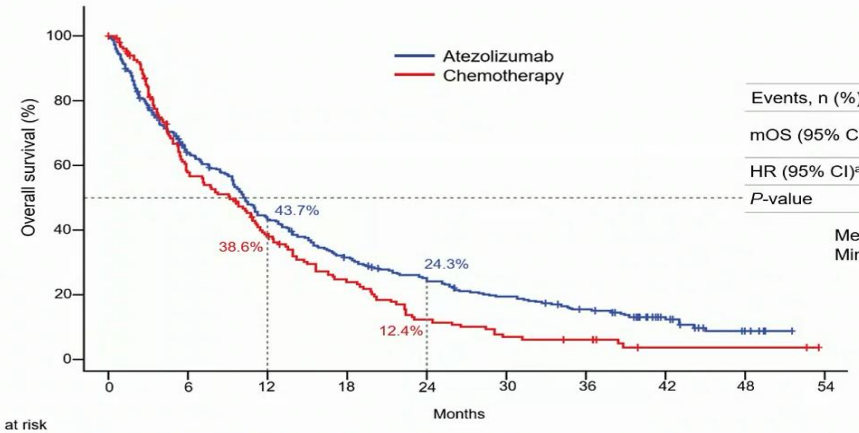
* Moderate certainty of evidence

Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; IO, immuno-oncology; PD-L1, programmed cell death-ligand 1; TPS, tumor proportion score.
Extracted from Ferrara R et al. Cochrane Database Syst Rev. 2020;12(12):CD013257.

IPSOS
Phase 3
Atezo vs CT
PD-L1 all %
mFU 41 mo.

IPSOS trial: Atezo 1L in PS 2-3 patients/elderly PS 1

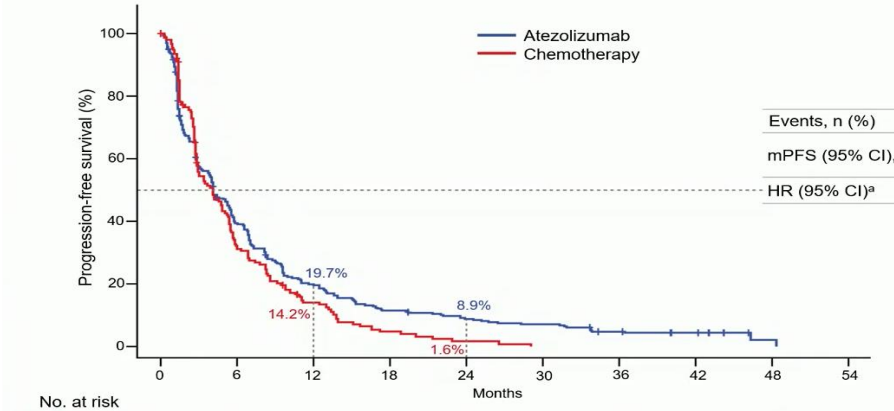
Primary Endpoint: OS



	Atezo (n=302)	Chemo (n=151)
Events, n (%)	249 (82.5)	130 (86.1)
mOS (95% CI), mo	10.3 (9.4, 11.9)	9.2 (5.9, 11.2)
HR (95% CI)[a]	**0.78 (0.63, 0.97)**	
P-value	0.028[b]	

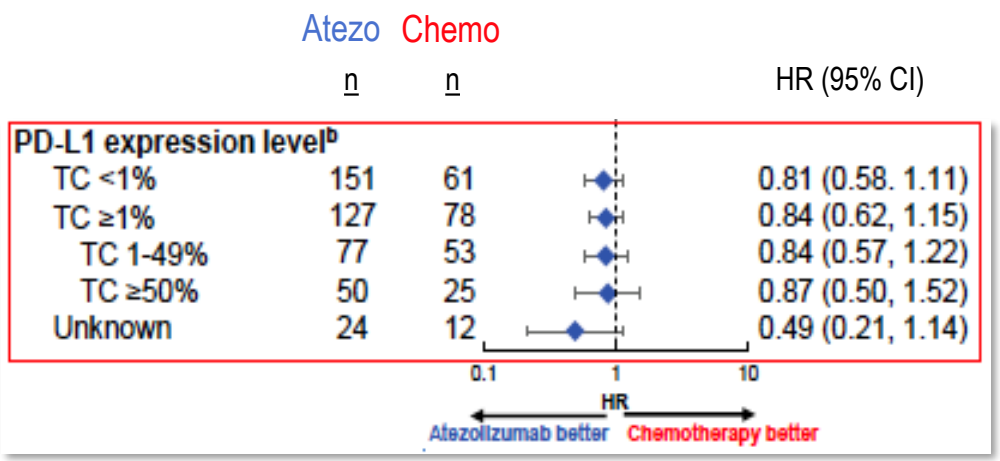
Median follow-up: 41.0 months
Minimum follow-up: 32.0 months

Secondary Endpoints: PFS



	Atezo (n=302)	Chemo (n=151)
Events, n (%)	276 (91.4)	138 (91.4)
mPFS (95% CI), mo	4.2 (3.7, 5.5)	4.0 (2.9, 5.4)
HR (95% CI)[a]	0.87 (0.70, 1.07)	

OS



Author's conclusion:
1L treatment with atezolizumab improved OS in this poor-prognosis NSCLC population with no *EGFR* and *ALK* alterations regardless of histology, PD-L1 status and ECOG PS with no new safety signals identified, while maintaining QoL

1L, first line; ALK, anaplastic lymphoma kinase; Atezo, atezolizumab; Chemo, chemotherapy; CI, confidence interval; EGFR, estimated glomerular filtration rate; HR, hazard ratio; mFU, median follow-up; mo, months; NSCLC, non-small cell lung cancer; OS, overall survival; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; PS, performance status; QoL, quality of life.

Extracted from Lee SM et al. IPSOS: Results from a Phase 3 study of first-line (1L) atezolizumab (atezo) vs single-agent chemotherapy (chemo) in patients (pts) with NSCLC not eligible for a platinum-containing regimen. Presented at the ESMO Congress; September, 09-13; 2022; Paris France. Abstract LBA11. Available at: http://medically.roche.com/global/.

Agenda

- IO Monotherapy
- Chemo plus IO
- IO plus IO combos

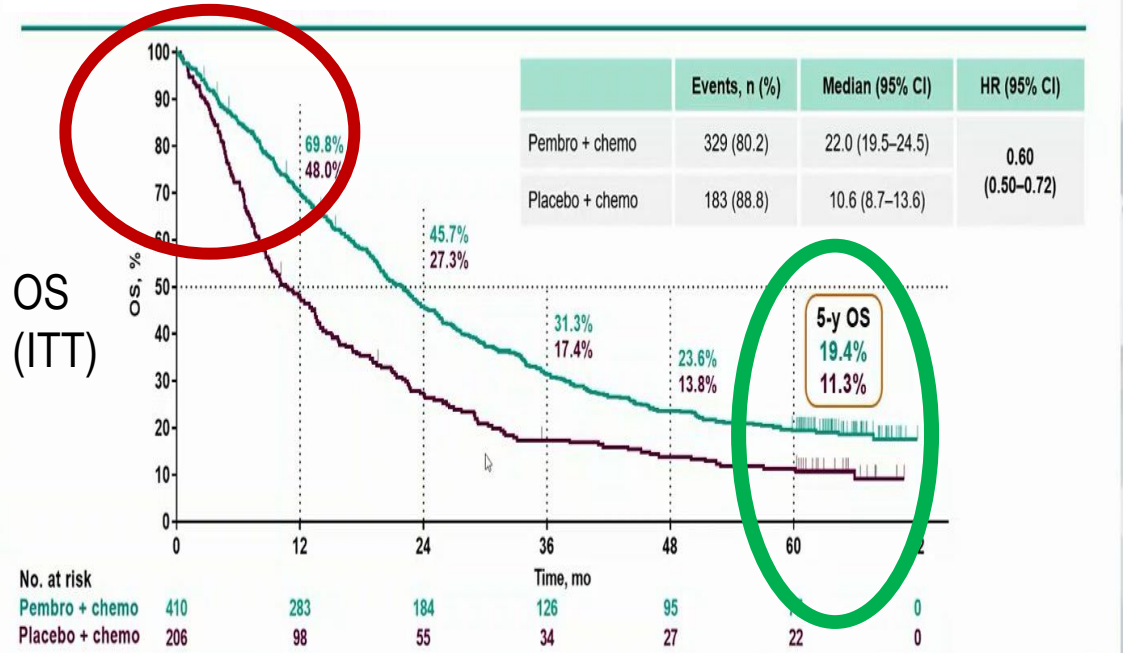
Chemo, chemotherapy; IO, immuno-oncology; TMB, tumor mutational burden.

PD-1/PD-L1 + CT combos may enlarge the benefit

KEYNOTE-189
Phase 3
Non-squamous
Pembro + CT vs CT
PD-L1 all %
5-year OS

KEYNOTE-407
Phase 3
Squamous
Pembro + CT vs CT
PD-L1 all %
5-year OS

KEYNOTE-189 (Non-Squamous)[1]

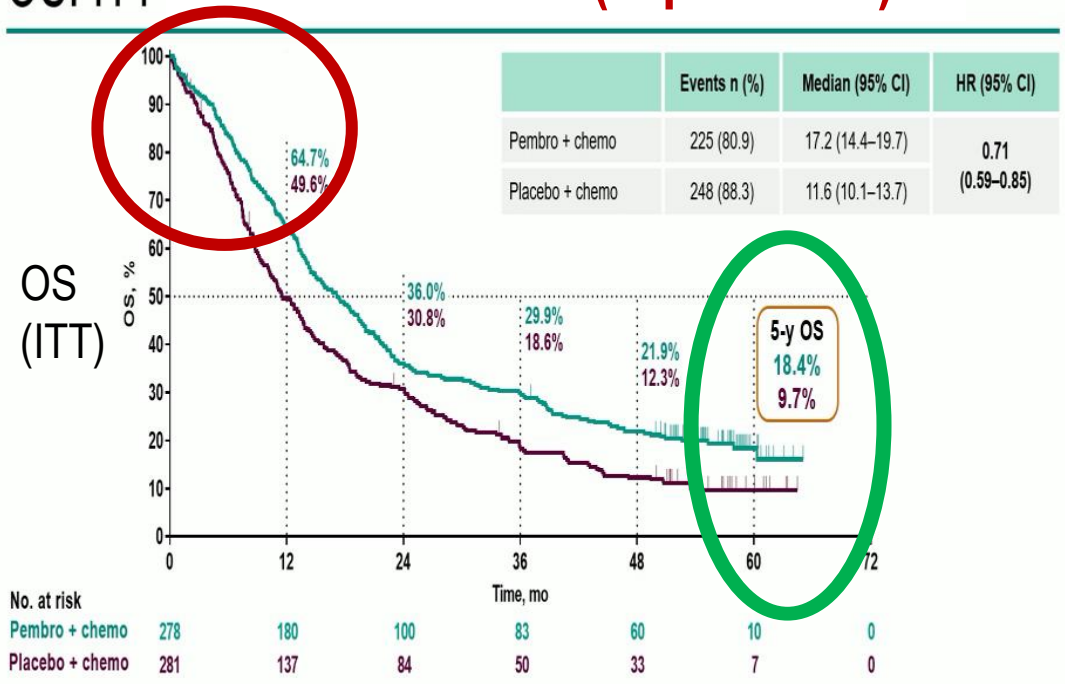


	Events, n (%)	Median (95% CI)	HR (95% CI)
Pembro + chemo	329 (80.2)	22.0 (19.5–24.5)	0.60 (0.50–0.72)
Placebo + chemo	183 (88.8)	10.6 (8.7–13.6)	

	PD-L1 TPS ≥50%		PD-L1 TPS 1%–49%		PD-L1 TPS <1%	
	Pembro + chemo (n = 132)	Placebo + chemo (n = 70)	Pembro + chemo (n = 128)	Placebo + chemo (n = 58)	Pembro + chemo (n = 127)	Placebo + chemo (n = 63)
OS HR (95% CI)	0.68 (0.49–0.96)		0.65 (0.46–0.90)		0.55 (0.39–0.76)	
5-y OS rate,[a] %	29.6	21.4	19.8	7.7	9.6	5.3

[a]Kaplan-Meier estimate. Data cutoff date: March 8, 2022.

OS: ITT KEYNOTE-407 (Squamous)[2]



	Events n (%)	Median (95% CI)	HR (95% CI)
Pembro + chemo	225 (80.9)	17.2 (14.4–19.7)	0.71 (0.59–0.85)
Placebo + chemo	248 (88.3)	11.6 (10.1–13.7)	

	PD-L1 TPS ≥50%		PD-L1 TPS 1%–49%		PD-L1 TPS <1%	
	Pembro + chemo (n = 73)	Placebo + chemo (n = 73)	Pembro + chemo (n = 103)	Placebo + chemo (n = 104)	Pembro + chemo (n = 95)	Placebo + chemo (n = 99)
OS HR (95% CI)	0.68 (0.47–0.97)		0.61 (0.45–0.83)		0.83 (0.61–1.13)	
5-y OS rate,[a] %	23.3	8.3	20.6	7.6	10.7	13.1

CI, confidence interval; CT, chemotherapy; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1; Pembro, pembrolizumab; TPS, tumor proportion score.

Extracted from Garassino MC et al. 973MO - KEYNOTE-189 5-year update: First-line pembrolizumab (pembro) + pemetrexed (pem) and platinum vs placebo (pbo) + pem and platinum for metastatic nonsquamous NSCLC. Presented at ESMO Congress; September, 09-13; 2022; Paris France. Abstract 973MO. Available at: https://oncologypro.esmo.org/973MO; 2) Novello S et al. 5-Year Update From KEYNOTE 407: Pembrolizumab Plus Chemotherapy in Squamous Non–Small Cell Lung Cancer. Presented at ESMO Congress; September, 09-13; 2022; Paris, France. Abstract 974MO. Available at: https://oncologypro.esmo.org/974MO.

Phase III trials with PD-1/PD-L1 inhibitors in advanced NSCLC

Trial	PD-(L)1 Inhibitor	Design	Population	PFS HR (95% CI) Median (mo)	OS HR (95% CI) Median (mo)
EMPOWER-Lung 3[1]	Cemiplimab	Plat doublet +/- cemiplimab	All histologies	0.56 (0.44-0.70) 8.2 vs. 5.0	0.71 (0.53-0.93) 21.9 vs. 13.0
Gemstone-302[2]	Sugemalimab	Carbo/pac or pem +/- sugemalimab	All histologies	0.50 (0.39-0.64) 7.8 vs. 4.9	0.65 (0.50-0.84) 25.4 vs. 16.9
CHOICE-01[3]	Toripalimab	Plat doublet +/- toripalimab	All histologies	0.49 (0.39-0.61) 8,4 vs. 5.6	0.69 (0.53-0.92) NR vs. 17.1
Keynote 407[4,5]	Pembrolizumab	Plus 7 additional phase III studies comparing chemoIO vs chemo in non-squamous NSCLC		57 (0.47-0.69) 0 vs. 5.1	0.71 (0.58-0.88) 17.1 vs. 11.6
IMpower131[6]	Atezolizumab			71 (0.60-0.85) 3 vs. 5.6	0.88 (0.73-1.05) 14.2 vs. 13.5
RATIONALE307[7]	Tislelizumab	Carbo/pac or nab-pac + tisle vs. carbo/pac	Squamous	0.48 (0.34-0.70) 7.6 vs. 5.5	Not reported
CameL-Sq[8]	Camrelizumab	Carbo/pac +/- camrelizumab	Squamous	0.37 (0.29-0.47) 8.5 vs. 4.9	0.55 (0.40-0.75) NR-14.5
Orient-12[9]	Sintilimab	Plat/gem +/- sintilimab	Squamous	0.54 (0.42-0.68) 5.5 vs. 4.9	0.57 (0.35-0.91) Not reported
ASTRUM-004[10]	**Serplulimab**	**Carbo/nab-pac +/- serplulimab**	**Squamous**	**0.55 (0.43-0.69) 8.3 vs. 5.7**	**0.73 (0.58-0.93) 22.7 vs. 18.2**

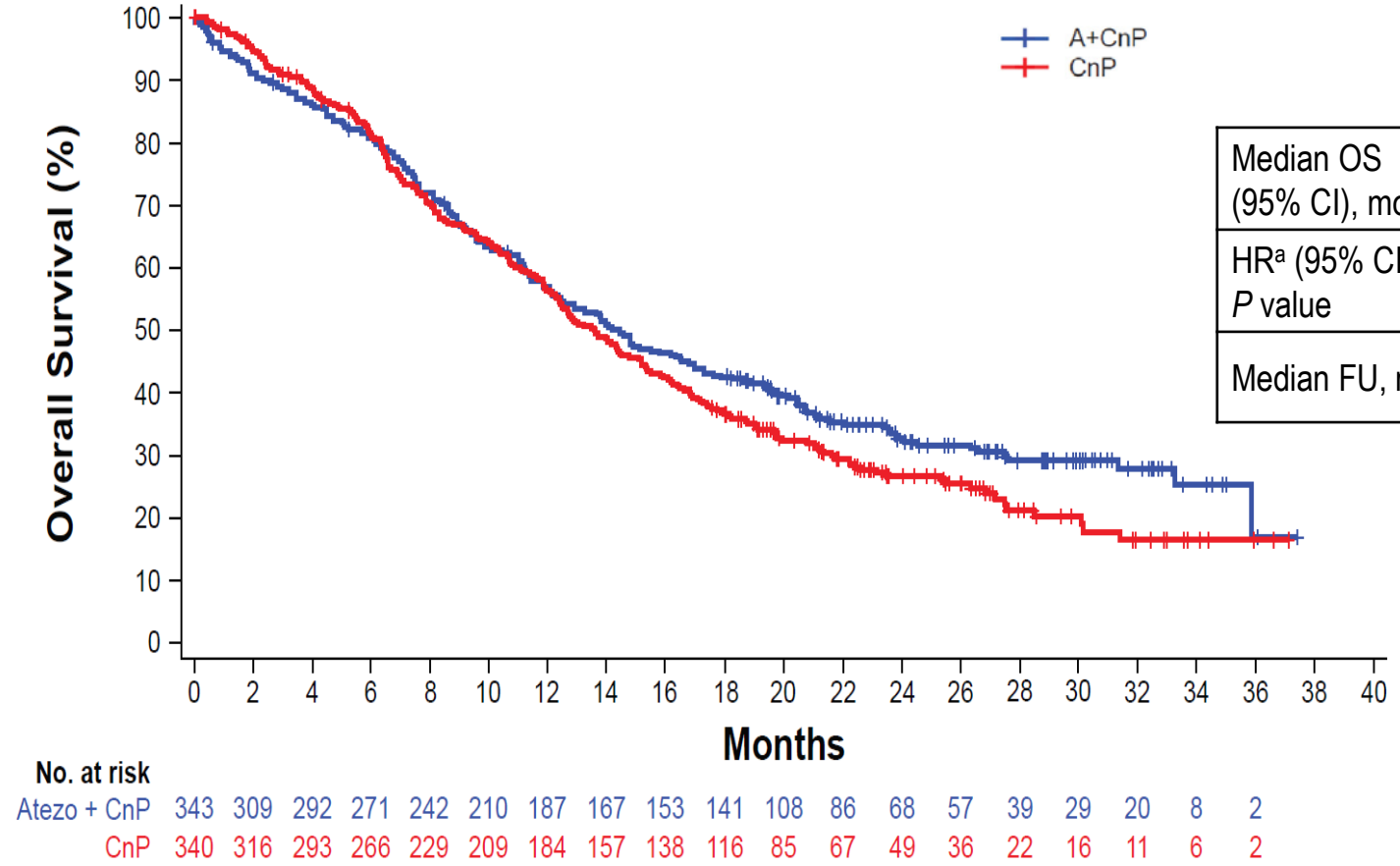
1. Gogishvili M, et al. Nat Med 2022; 2. Zhou C, et al. Lancet Oncol 2022; 3. Wang Z, et al. J Clin Oncol 2023; 4. Paz-Ares L, et al. NEJM 2018; 5. Novello S, et al. J Clin Oncol 2023; 6. Jotte R, et al. J Thorac Oncol 2020; 7. Wang J, et al. JAMA Oncol 2021; 8. Ren S, et al. J Thorac Oncol 2021; Zhou C, et al. J Thorac Oncol 2021; 10. Zhou C, et al. WCLC 2023

Gainor; Massachusetts General Hospital; Boston, MA

ChemoIO, chemoimmunotherapy; CI, confidence interval; HR, hazard ratio; mo, months; NSCLC, non-small cell lung cancer; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival.
Slide provided courtesy of Dr Paz-Ares.

IMpower131
Phase 3
Squamous
Atezo + CT vs CT
PD-L1 % all
Final OS

IMpower131 – CnP + atezolizumab
Final OS in the ITT population (Arm B vs Arm C)



	Arm B: Atezo + CnP	Arm C: CnP
Median OS (95% CI), mo	14.2 (12.3, 16.8)	13.5 (12.2, 15.1)
HR[a] (95% CI) *P* value	0.88 (0.73, 1.05) 0.1581	
Median FU, mo	26.8	24.8

- Although PFS was improved, OS was similar between arms
- OS improvement seen in PD-L1 ≥50% though not formally tested

A or Atezo, atezolizumab; CnP, carboplatin + nab-paclitaxel; CI, confidence interval; CT, chemotherapy; FU, follow-up; HR, hazard ratio; ITT, intent-to-treat; mo, months; OS, overall survival; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival.
Extracted from Jotte R et al. J Thorac Oncol. 2020 Aug;15(8):1351-1360.

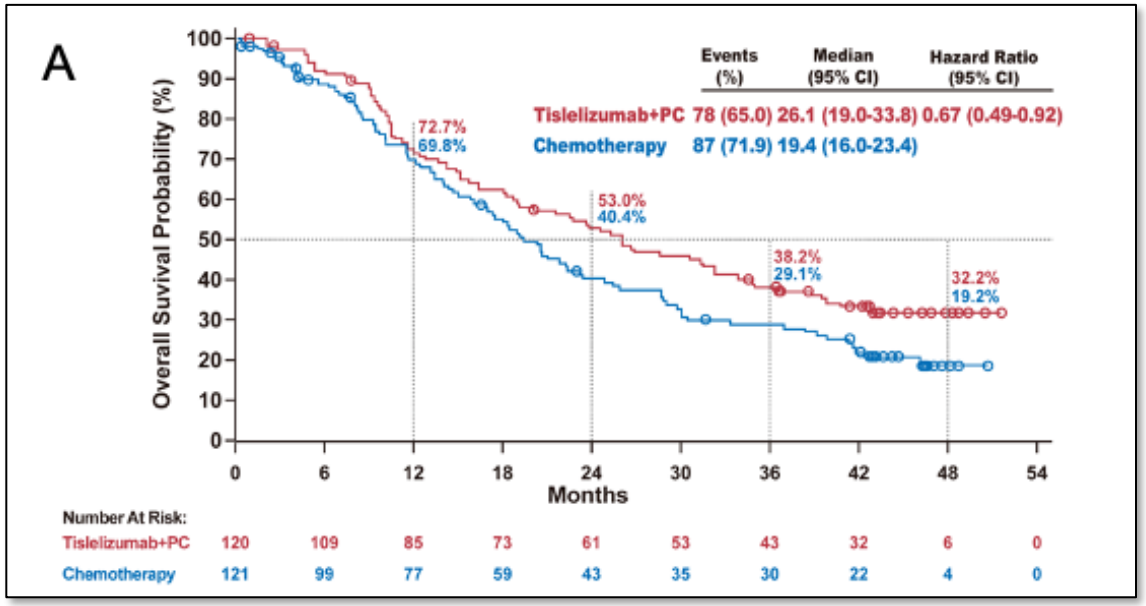
Chemo + tislelizumab trials in 1L NSCLC

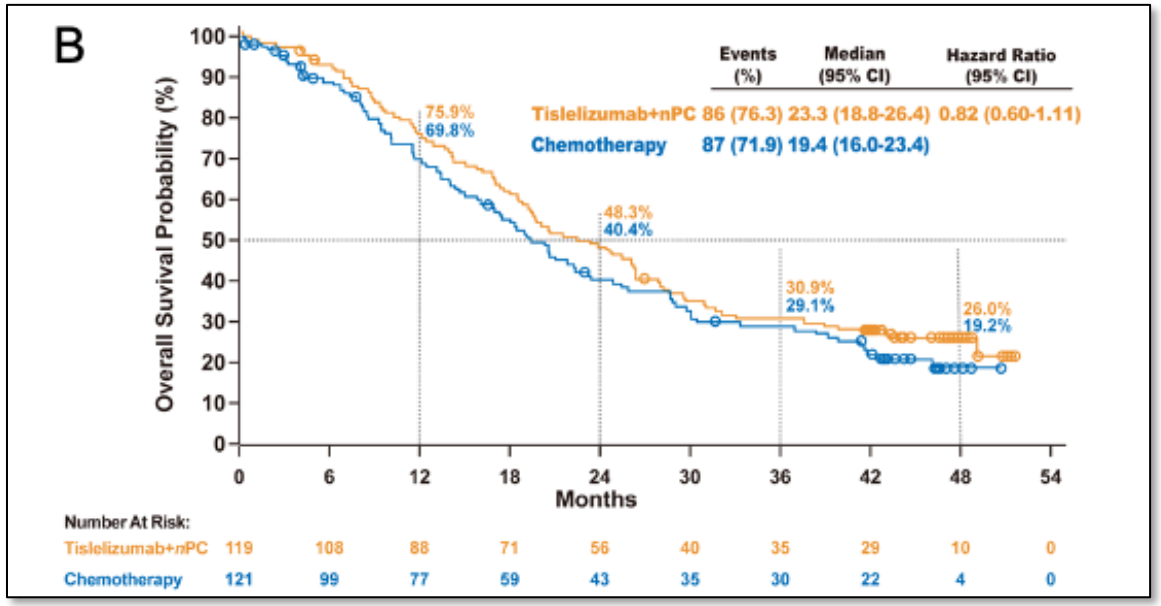
Presented here at ESMO 2024
Abstract #2876
(Wang et al. 2024):
4-year OS data

RATIONALE-307
Phase 3
Squamous, 1L
Tisle + CT vs CT
PD-L1 % all
mFU 50.3 mo.

RATIONALE-307 – Squamous
Long-term OS outcomes (mFU 50.3 mo.), ITT population

OS (secondary endpoint)





1L, first line; Chemo, chemotherapy; CI, confidence interval; ITT, intent-to-treat; mFU, median follow-up; mo, months; NSCLC, non-small cell lung cancer; OS, overall survival; PD-L1, programmed cell death-ligand 1; Tisle, tislelizumab.
Extracted from Wang Z et al. RATIONALE-307 Long-term Outcomes : First-line Tislelizumab (TIS) Plus Chemotherapy (chemo) vs Chemo Alone for Advanced Squamous (sq) NSCLC. Abstract 2876. ESMO 2024; September 13-17, 2024; Barcelona, Spain.

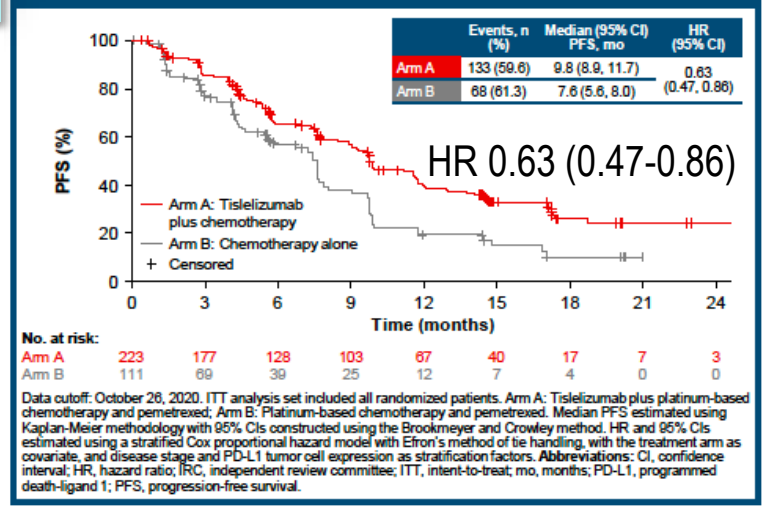
Chemo + tislelizumab trials in 1L NSCLC (2/2)

RATIONALE-304
Phase 3
Non-squamous, 1L
Tisle + CT vs CT
PD-L1 % all
mFU 16.1 mo.

RATIONALE-304 – Non-Squamous Updated analysis (mFU 16.1 mo.)

PFS
(primary endpoint)

Figure 1. IRC-Assessed PFS (ITT Analysis Set)



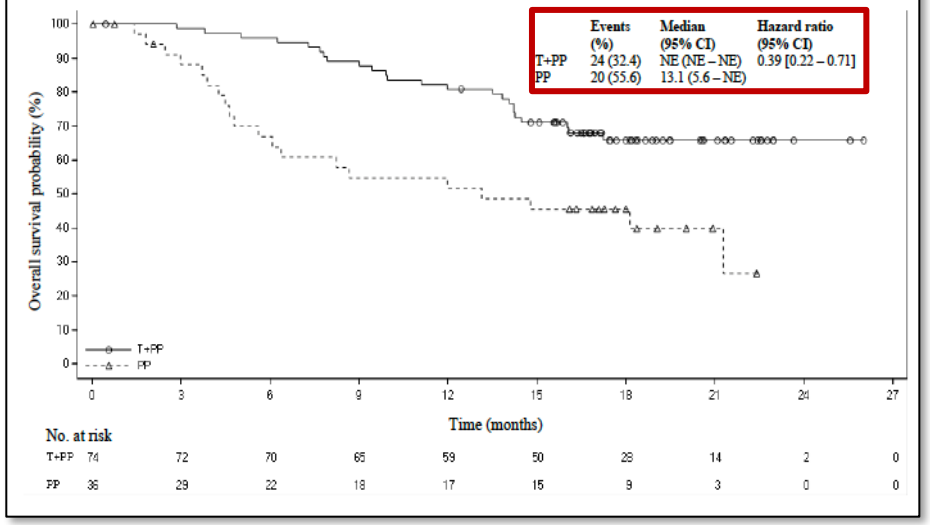
Data cutoff: October 26, 2020. ITT analysis set included all randomized patients. Arm A: Tislelizumab plus platinum-based chemotherapy and pemetrexed; Arm B: Platinum-based chemotherapy and pemetrexed. Median PFS estimated using Kaplan-Meier methodology with 95% CIs constructed using the Brookmeyer and Crowley method. HR and 95% CIs estimated using a stratified Cox proportional hazard model with Efron's method of tie handling, with the treatment arm as covariate, and disease stage and PD-L1 tumor cell expression as stratification factors. **Abbreviations:** CI, confidence interval; HR, hazard ratio; IRC, independent review committee; ITT, intent-to-treat; mo, months; PD-L1, programmed death-ligand 1; PFS, progression-free survival.

1

	Arm A	Arm B	HR (95% CI) Arm A vs B
Median PFS, months (95% CI)			
PD-L1 <1%	7.6 (5.4, 9.7)	7.6 (4.3, 7.9)	0.81 (0.52, 1.25)
PD-L1 1-49%	9.7 (6.9, 11.7)	9.7 (5.6, 16.8)	0.90 (0.49, 1.63)
PD-L1 ≥50%	14.6 (11.5, NE)	4.6 (3.5, 9.7)	0.29 (0.16, 0.50)

OS
(secondary endpoint)

Figure 2 Kaplan-Meier plot of OS in BGB-A317-304 in patients with PD-L1 ≥50%



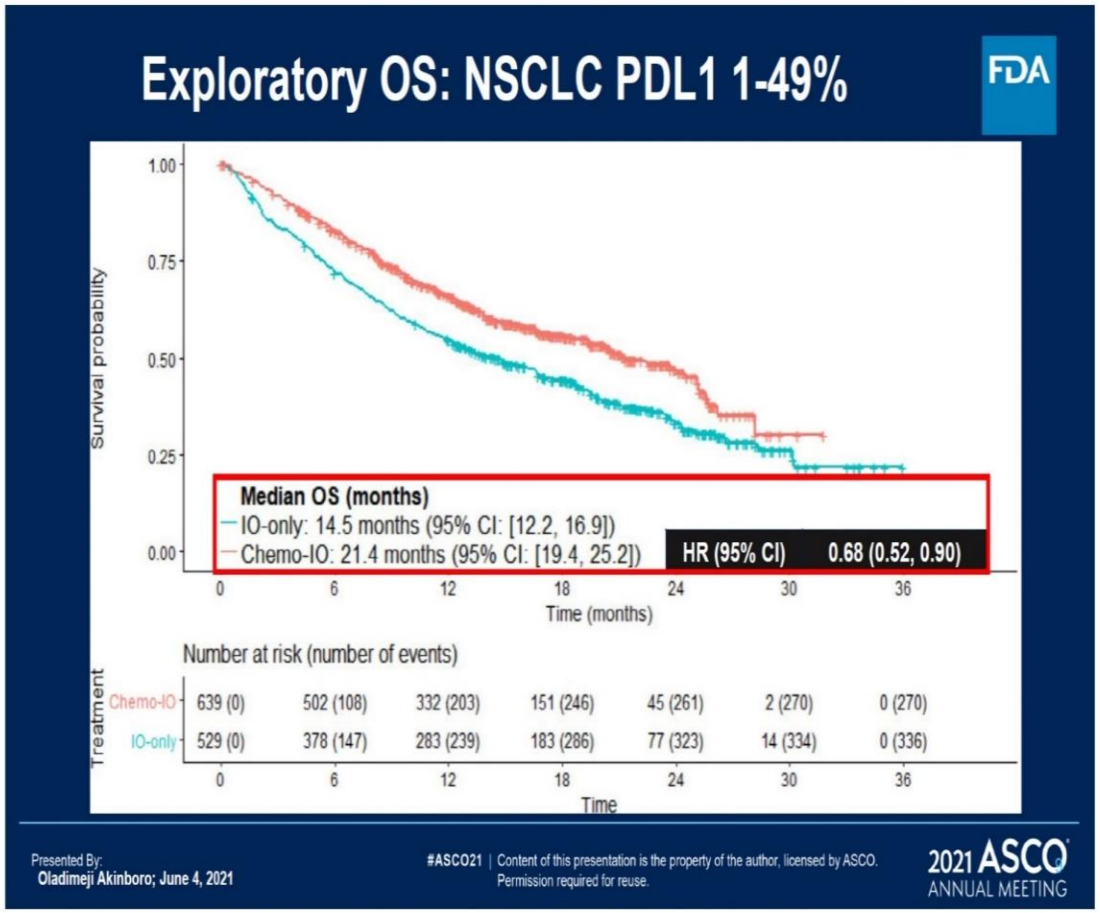
2

Data cutoff: October 26, 2020

1L, first line; CI, confidence interval; Chemo or CT, chemotherapy; HR, hazard ratio; ITT, intent-to-treat; mFU, median follow-up; mo, months; NSCLC, non-small cell lung cancer; OS, overall survival; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; Tisle, tislelizumab.

1) Extracted from Lu S et al. Randomized Phase 3 Study of Tislelizumab Plus Chemotherapy Versus Chemotherapy Alone as First-Line Treatment for Advanced Nonsquamous Non-Small Cell Lung Cancer: RATIONALE-304 Updated Analysis. Poster 138P. Presented at ESMO IO; December 2022; Geneva, Switzerland. Available at: Lu_BGB-A317-304_ESMO_IO_Poster_2022.pdf; 2) Tevimbra SmPC, July 2024.

IO alone v Chemo-IO in tumors with PD-L1 1-49%

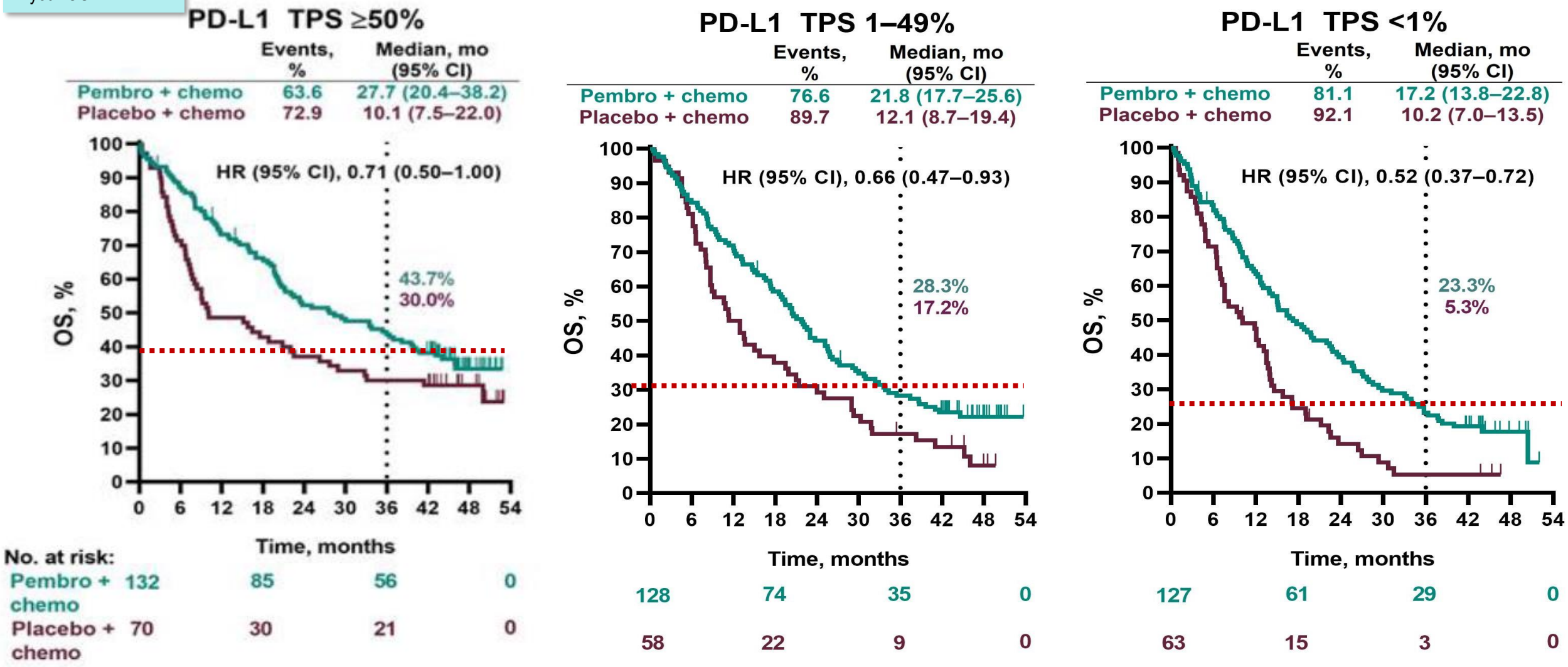


Study	Investigational Treatment	Histology	PD-L1 1-49% OS HR (95% CI)
Keynote 042	Pembrolizumab alone	All NSCLC	0.92 (0.77-1.11)
Checkmate 227	NIVO/IPI	All NSCLC	0.94 (0.75-1.18)
Keynote 189	Pembro-Chemo	Non-squamous	0.55 (0.34-0.90)
Keynote 407	Pembro-Chemo	Squamous	0.57 (0.36-0.90)
Checkmate 9LA	NIVO/IPI + Chemo	All NSCLC	0.61 (0.44-0.84) (published) 0.70 (not included) (update)

Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; IO, immuno-oncology; IPI, ipilimumab; Nivo, nivolumab; NSCLC, non-small cell lung cancer; OS, overall survival; PD-L1, programmed cell death-ligand 1.
Extracted from Redman M. Optimizing effective and safe deployment of immune checkpoint inhibitors for patients with NSCLC. Presented at the ASCO Annual Meeting (virtual); June 04-08, 2021. Available at: https://meetings.asco.org/abstracts-presentations/200362/slides.

KEYNOTE-189
Phase 3
Non-squamous
Pembro + CT vs CT
PD-L1 all %
4-year OS

KN-189 update (4 y): PD-L1 expression does not predict overall OS benefit but long-term outcome



Chemo or CT, chemotherapy; CI, confidence interval; HR, hazard ratio; OS, overall survival; PD-L1, programmed cell death-ligand 1; Pembro, pembrolizumab; TPS, tumor proportion score.

Extracted from Gray JE et al. Pembrolizumab + pemetrexed-platinum for metastatic NSCLC: 4-year follow-up from KEYNOTE-189. Presented at: 2020 WCLC Singapore. January 27-31, 2021. Abstract FP13.02. Available at: https://wclc2020.iaslc.org/

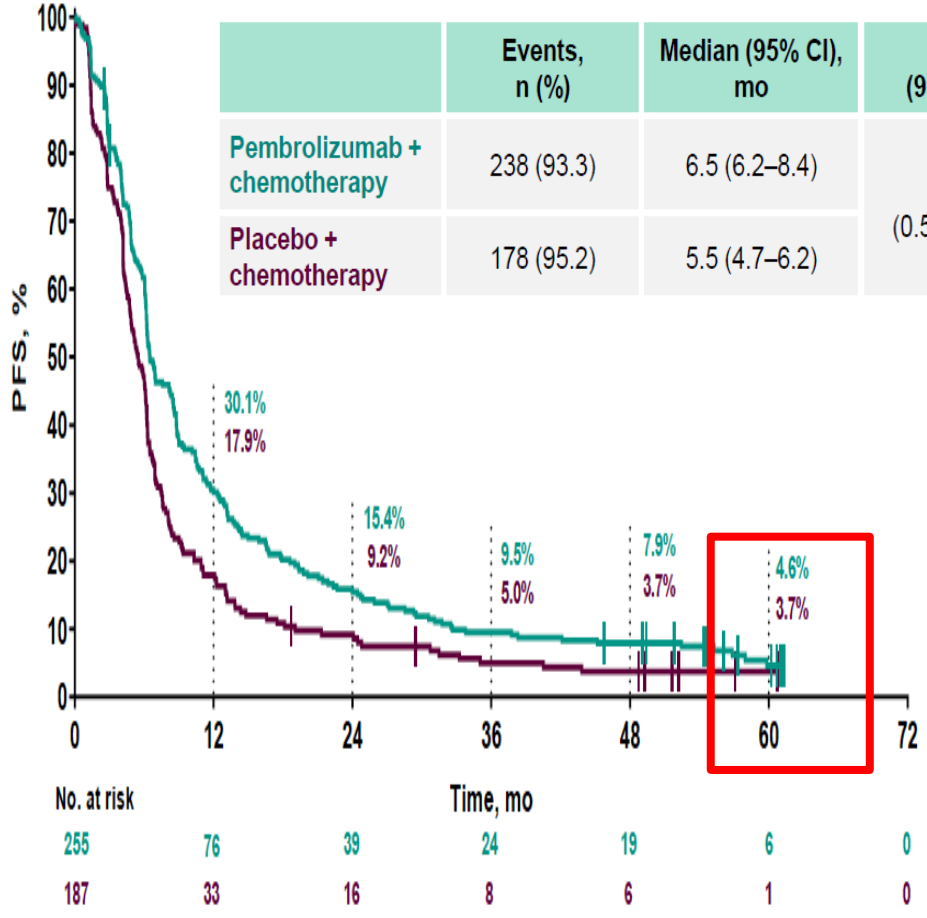
KEYNOTE-189
Phase 3
Non-squamous
Pembro + CT vs CT
PD-L1 all %
5-year PFS/OS

Pembro + CT in PD-L1 negative NSCLC
Update of KN-189/KN-407 trials

KEYNOTE-407
Phase 3
Squamous
Pembro + CT vs CT
PD-L1 all %
5-year PFS/OS

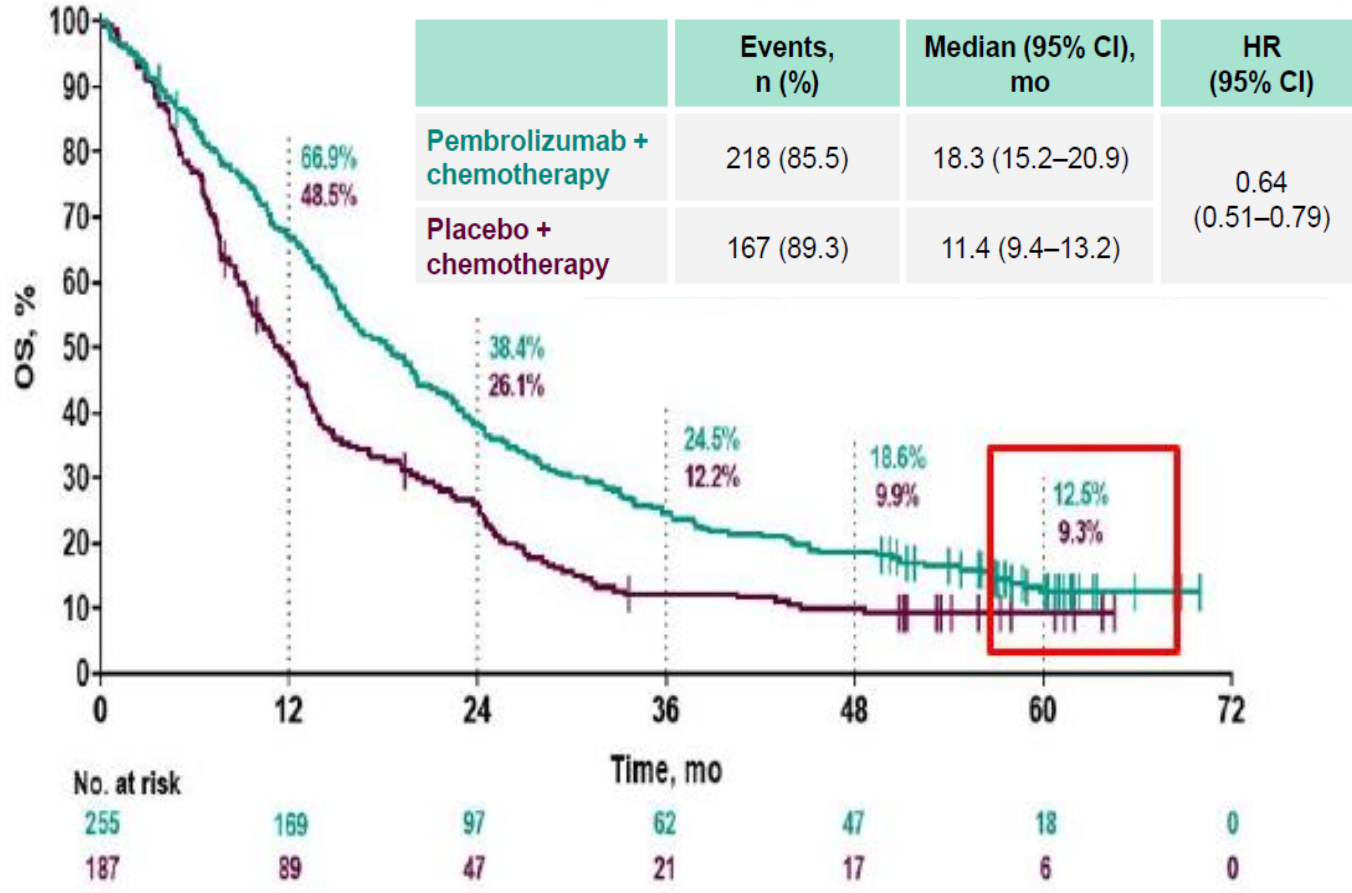
Progression-Free Survival

	Events, n (%)	Median (95% CI), mo	HR (95% CI)
Pembrolizumab + chemotherapy	238 (93.3)	6.5 (6.2–8.4)	0.66 (0.54–0.81)
Placebo + chemotherapy	178 (95.2)	5.5 (4.7–6.2)	



Pooled analysis KN189 global/Japan extension, KN407 global/China extension trials

	Events, n (%)	Median (95% CI), mo	HR (95% CI)
Pembrolizumab + chemotherapy	218 (85.5)	18.3 (15.2–20.9)	0.64 (0.51–0.79)
Placebo + chemotherapy	167 (89.3)	11.4 (9.4–13.2)	

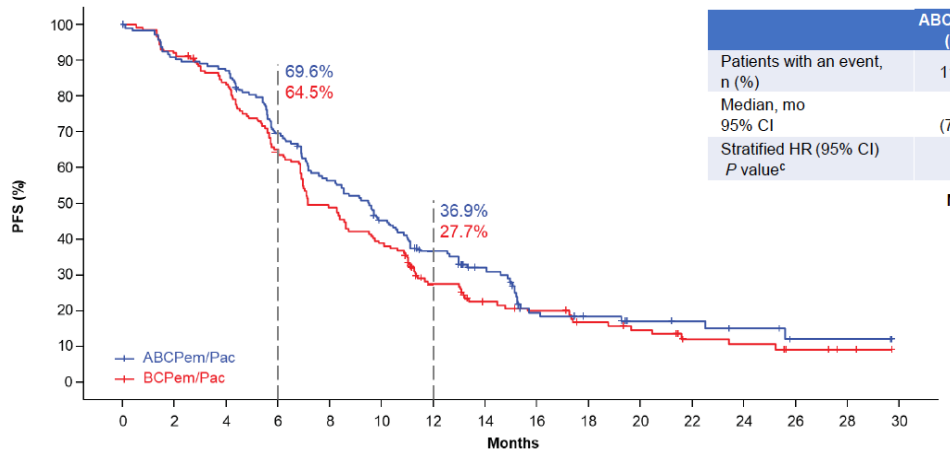


CT, chemotherapy; CI, confidence interval; HR, hazard ratio; NSCLC, non-small cell lung cancer; OS, overall survival; PD-L1, programmed cell death-ligand 1; Pembro, pembrolizumab; PFS, progression-free survival; TPS, tumor proportion score.
Extracted from Gadgeel S et al. OA14. 05 5-year survival of pembrolizumab plus chemotherapy for metastatic NSCLC with PD-L1 tumor proportion score< 1%. Presented at: WCLC; September 9-12, 2023; Singapore. Available at: https://wclc2023.iaslc.org/.

Impower151 Phase 3
Non-squamous, 1L
Atezo + Beva + CT vs Beva + CT
PD-L1 % all
mFU 14.0 mo.

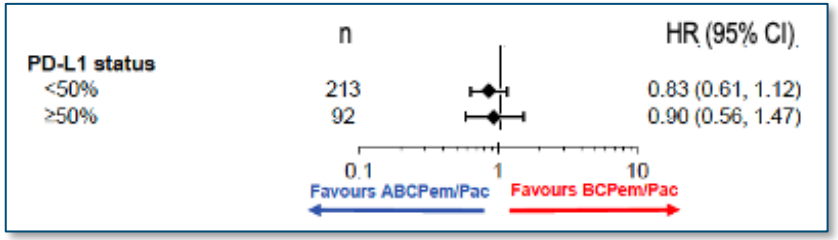
IMpower151 – primary endpoint missed

Primary Endpoint: INV-PFS in the ITT population

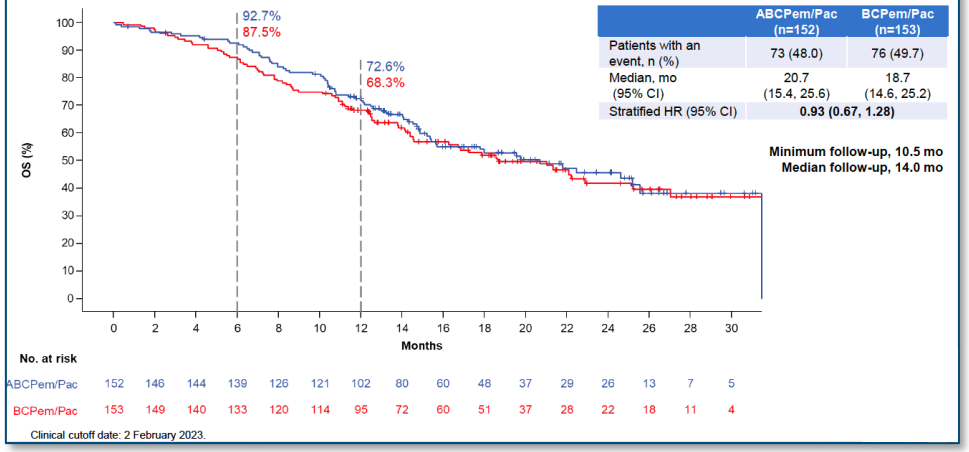


	ABCPem/Pac[b] (n=152)	BCPem/Pac[b] (n=153)
Patients with an event, n (%)	114 (75.0)	125 (81.7)
Median, mo 95% CI	9.5 (7.6, 10.6)	7.1 (6.9, 9.5)
Stratified HR (95% CI)	**0.84 (0.65, 1.09)**	
P value[c]	0.18	

Minimum follow-up, 10.5 mo
Median follow-up, 14.0 mo



OS in the ITT population



	ABCPem/Pac (n=152)	BCPem/Pac (n=153)
Patients with an event, n (%)	73 (48.0)	76 (49.7)
Median, mo (95% CI)	20.7 (15.4, 25.6)	18.7 (14.6, 25.2)
Stratified HR (95% CI)	**0.93 (0.67, 1.28)**	

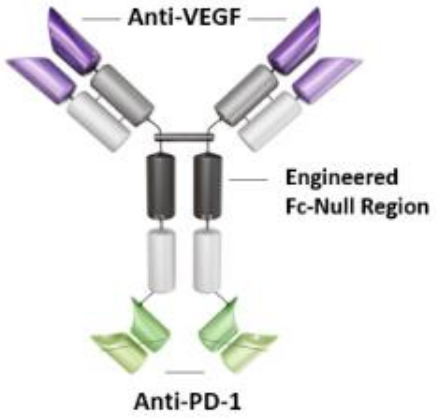
Minimum follow-up, 10.5 mo
Median follow-up, 14.0 mo

- **IMpower151 did not meet its primary endpoint** though numerical PFS improvements seen
- **53% of patients were *EGFR*/*ALK*+** and no incremental PFS benefit was seen in this subgroup
- **No PD-L1–dependent PFS differences** observed
- No clinically meaningful OS improvement
- ABCPem/Pac was generally well-tolerated, no new safety signals identified
- These results are inconsistent with the PFS and OS improvements seen with ABCPac in IMpower1501

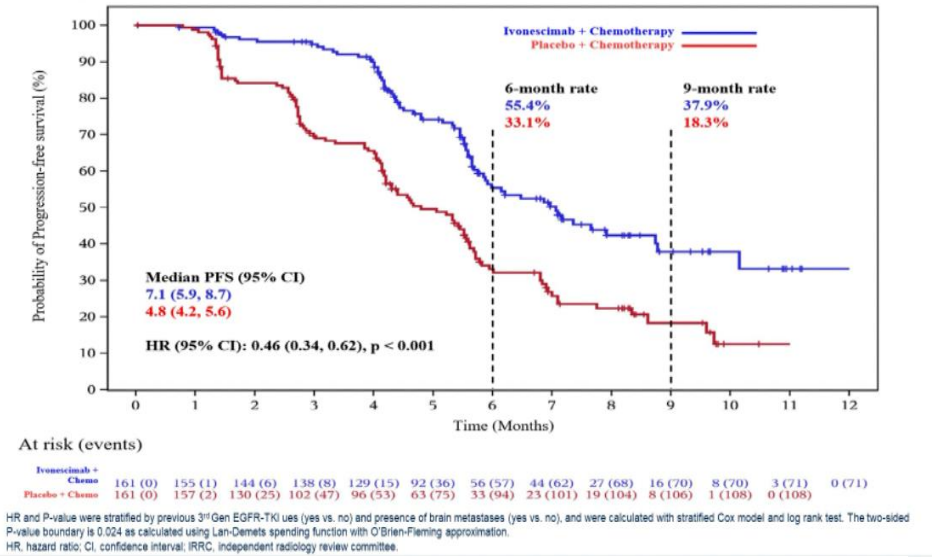
ABCPem, atezolizumab+bevacizumab+carboplatin+pemetrexed; ALK, anaplastic lymphoma kinase; Atezo, atezolizumab; Beva, bevacizumab; CT, chemotherapy; CI, confidence interval; EGFR, estimated glomerular filtration rate; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival; Pac, paclitaxel; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival.
Extracted from Zhou C et al. IMpower151: Phase III study of atezolizumab + bevacizumab + chemotherapy in first-line metastatic nonsquamous NSCLC. Presented at the WCLC; September 09-12 2023; Singapore. Available at: https://medically.roche.com/global/en/oncology/wclc-2023/medical-material/WCLC-2023-presentation-zhou-IMpower151-phase-study-of-atezolizumab-pdf.html.

HARMONi-A Phase 3
ivonescimab + CT vs CT in EGFR-mutant NSQ NSCLC

Bispecific Ab



PFS

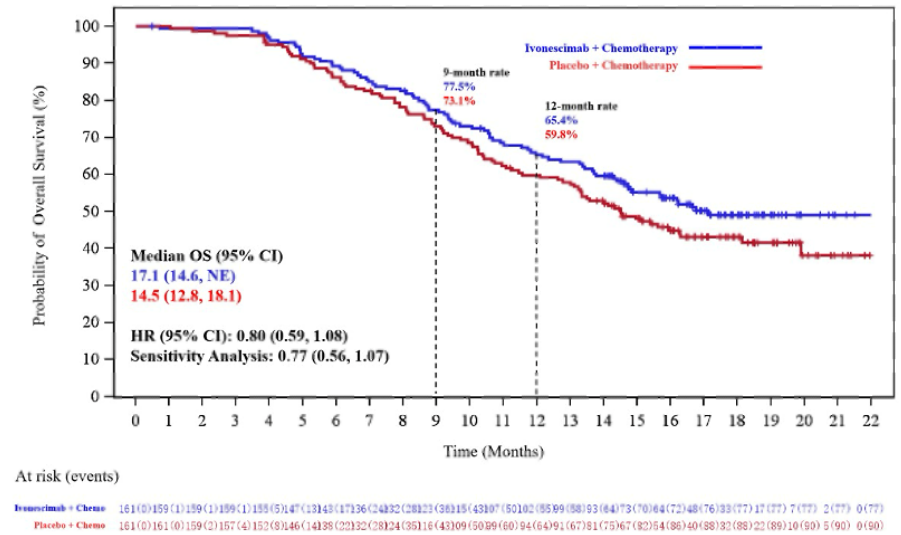


HR and P-value were stratified by previous 3rd Gen EGFR-TKI ues (yes vs. no) and presence of brain metastases (yes vs. no), and were calculated with stratified Cox model and log rank test. The two-sided P-value boundary is 0.024 as calculated using Lan-Demets spending function with O'Brien-Fleming approximation.
HR, hazard ratio; CI, confidence interval; IRRC, independent radiology review committee.

Met primary endpoint of PFS per IRRC
HR 0.46 (0.34-0.62)

mFU 7.89 mo.

OS



OS at 52% of data maturity
HR 0.80 (0.59-1.08)

Ab, antibody; CT, chemotherapy; CI, confidence interval;
HR, hazard ratio; IRRC, independent radiology review committee; OS, overall survival; PD-L1, programmed cell death-ligand 1; VEGF, vascular endothelial growth factor.
Extracted from Zhang L et al. Ivonescimab combined with chemotherapy in patients with EGFR-mutant non-squamous non-small cell lung cancer who progressed on EGFR-TKIs treatment: a randomized, double-blind, multi-center, phase 3 trial (HARMONi-A study). Presented at the ASCO Annual Meeting; May 31-June 04, 2024 ; Chicago, IL. Available at: https://www.akesobio.com/media/2203/ak112-301_2024-asco_oral-final-0530.pdf.

Agenda

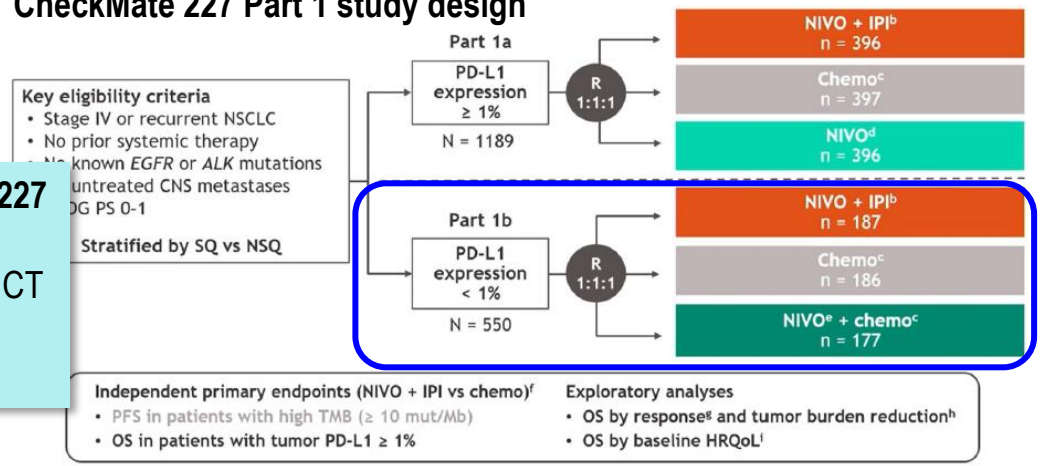
- IO Monotherapy
- Chemo plus IO
- IO plus IO combos

Chemo, chemotherapy; IO, immuno-oncology; TMB, tumor mutational burden.

CheckMate 227 – 6-year update

CheckMate 227
Phase 3
Nivo + Ipi vs CT
PD-L1 % all
6-year OS

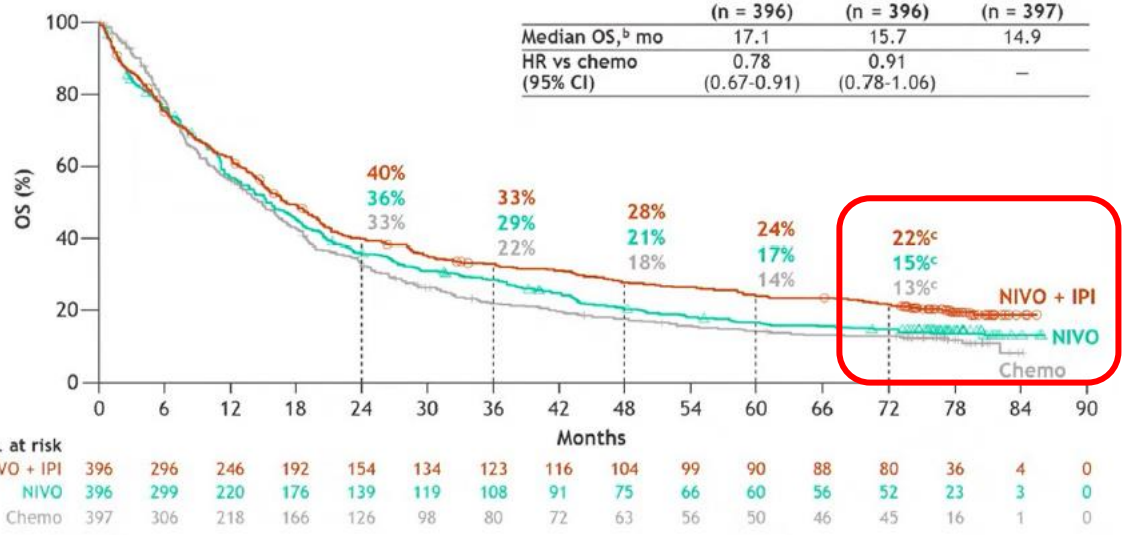
CheckMate 227 Part 1 study design



	PD-L1 ≥ 1%			PD-L1 < 1%		
	NIVO + IPI (n = 80)	NIVO (n = 52)	Chemo (n = 45)	NIVO + IPI (n = 27)	NIVO + chemo (n = 16)	Chemo (n = 9)
PFS						
Median PFS, mo (95% CI)	60.6 (33.2-NR)	71.8 (27.6-NR)	9.5 (7.0-23.6)	NR (19.4-NR)	30.6 (16.8-NR)	24.9 (1.6-NR)
6-year PFS rate, % (95% CI)	47 (34-59)	49 (33-63)	15 (5-31)	50 (28-69)	38 (14-61)	NA[b]
Response						
ORR, n (%) (95% CI)	64 (80) (70-88)	39 (75) (61-86)	23 (51) (36-66)	24 (89) (71-98)	13 (81) (54-96)	6 (67) (30-92)
Median DOR, mo (95% CI)	NR (52.6-NR)	NR (49.5-NR)	12.4 (5.6-31.6)	NR (18.0-NR)	29.1 (11.3-NR)	15.2 (2.7-NR)
6-year DOR rate, % (95% CI)	55 (41-67)	60 (40-75)	21 (5-43)	55 (31-74)	38 (14-63)	NA[b]

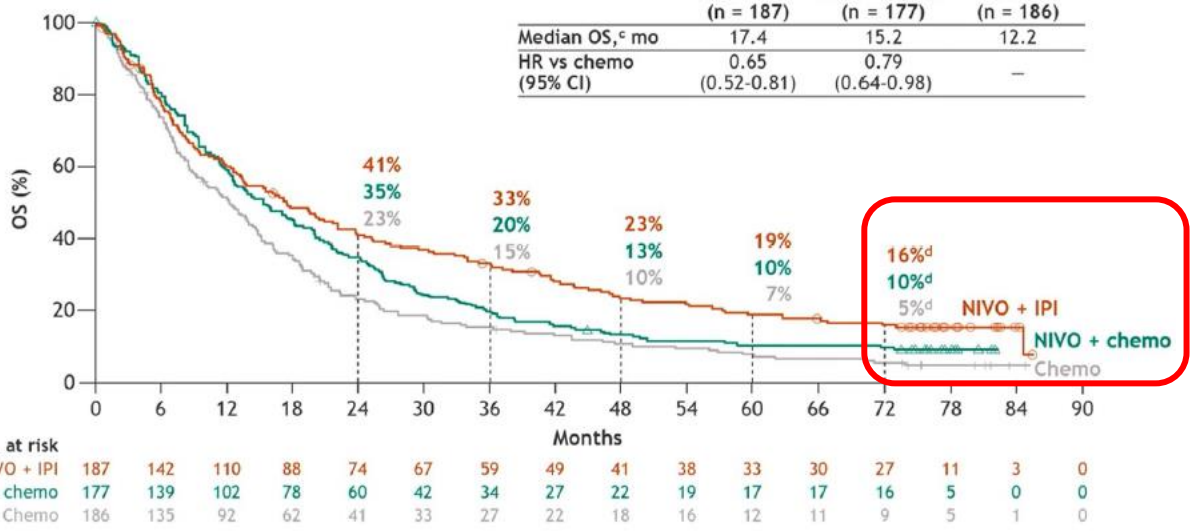
PD-L1 ≥ 1%

	NIVO + IPI[a] (n = 396)	NIVO (n = 396)	Chemo (n = 397)
Median OS,[b] mo	17.1	15.7	14.9
HR vs chemo (95% CI)	0.78 (0.67-0.91)	0.91 (0.78-1.06)	–



PD-L1 < 1%

	NIVO + IPI[b] (n = 187)	NIVO + chemo (n = 177)	Chemo (n = 186)
Median OS,[c] mo	17.4	15.2	12.2
HR vs chemo (95% CI)	0.65 (0.52-0.81)	0.79 (0.64-0.98)	–

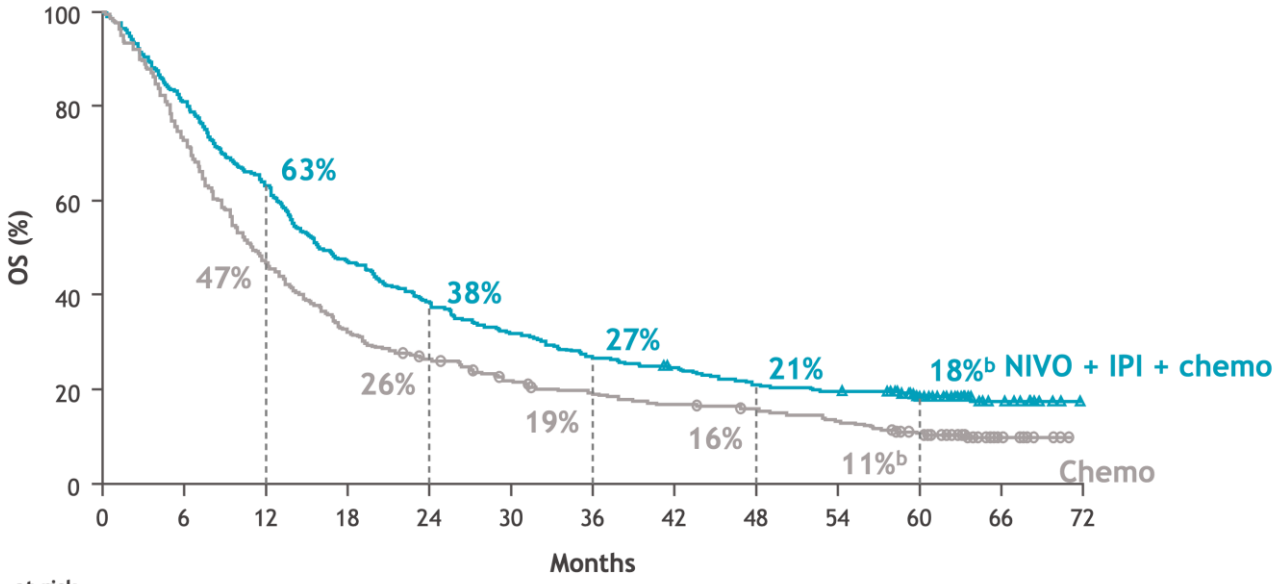


Chemo, chemotherapy; CI, confidence interval; DOR, duration of response; Ipi, ipilimumab; mo, months; Nivo, nivolumab; ORR, overall response rate; OS, overall survival; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival.

Ramalingam SS et al. Six-year survival and HRQoL outcomes with 1L Nivolumab+ Ipilimumab in patients with metastatic NSCLC from CheckMate227. Presented at: WCLC; September 9-12, 2023; Singapore. OA14.03 (Accessed 23 August 2024). Available at: https://wclc2023.iaslc.org/.

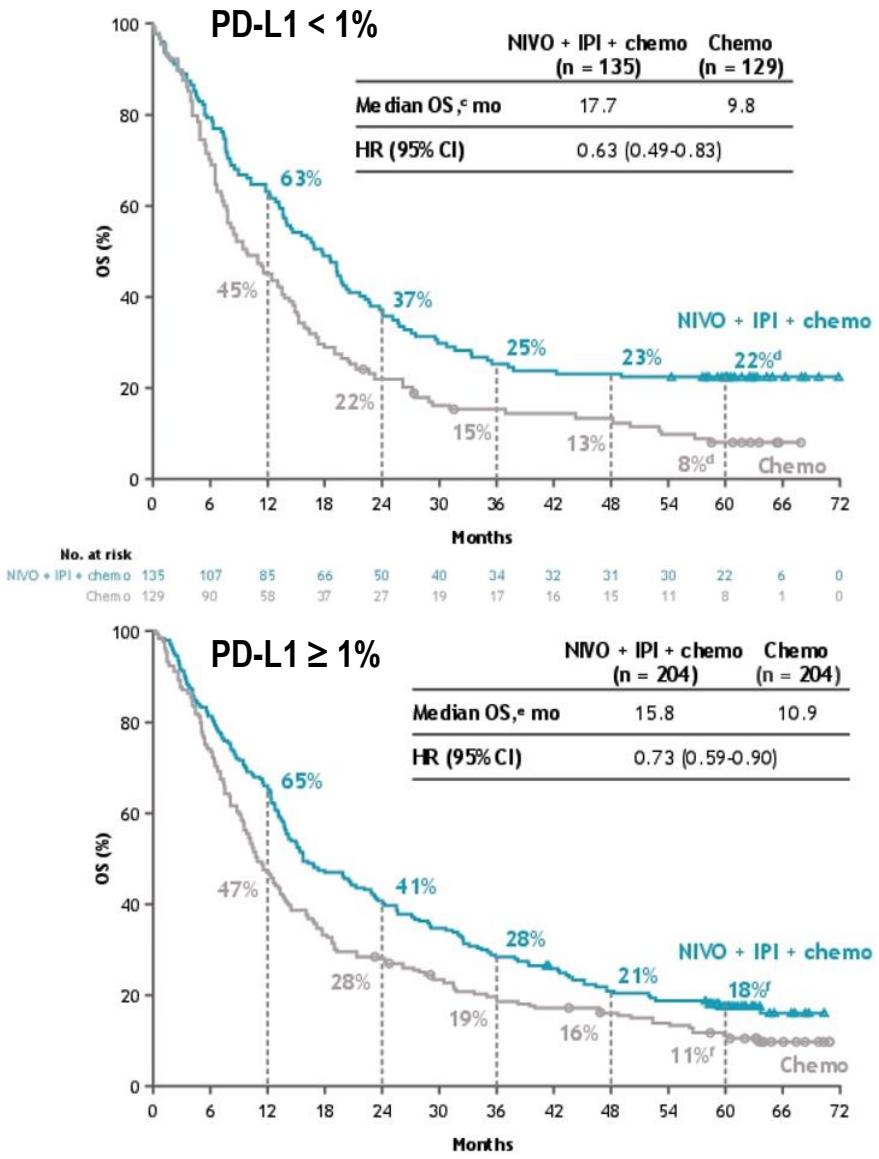
CheckMate 9LA
Phase 3
Nivo + Ipi + CT vs CT
PD-L1 % all
5-year OS update

CheckMate 9LA trial 5-year OS (all randomized patients)



No. at risk

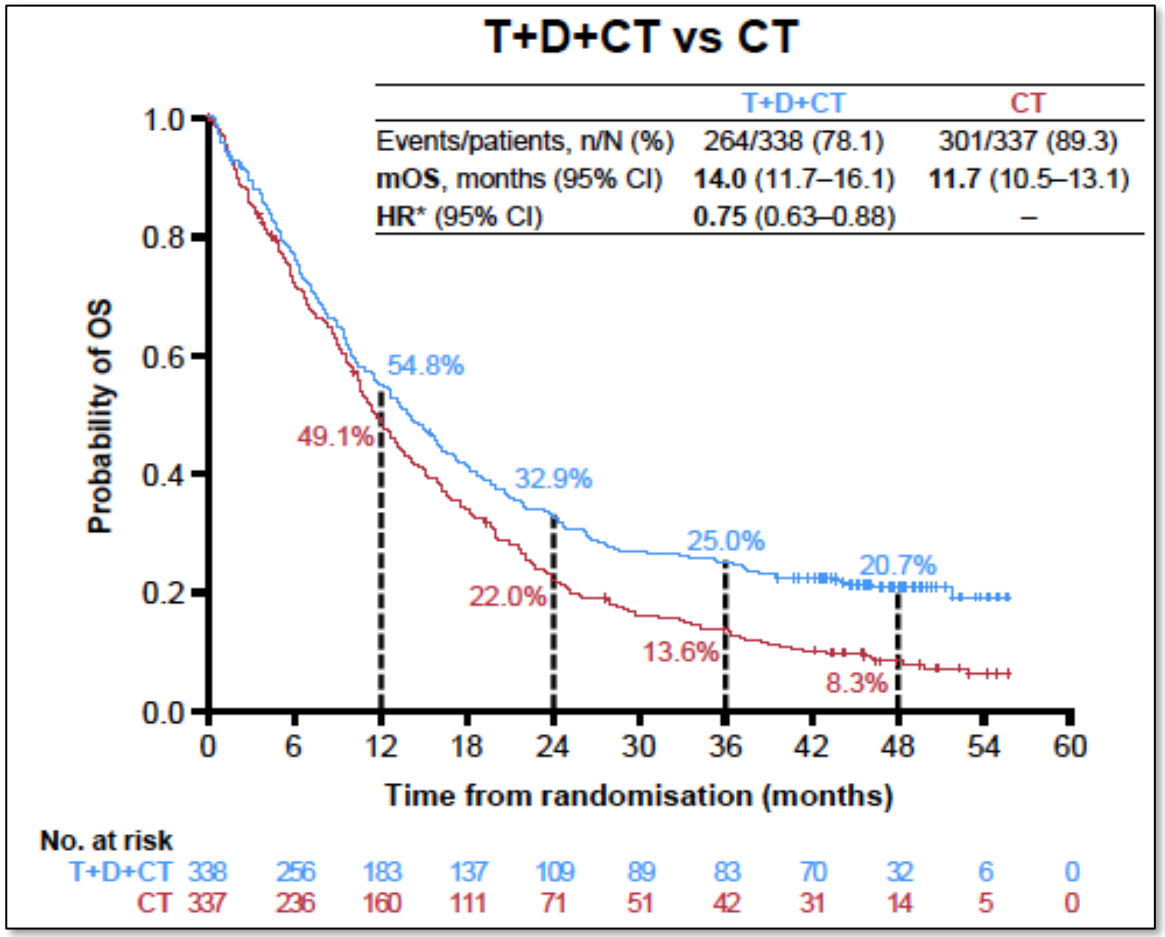
NIVO + IPI + chemo	361	292	227	170	138	115	96	87	74	69	48	13	0
Chemo	358	260	168	115	93	74	63	55	50	42	30	9	0

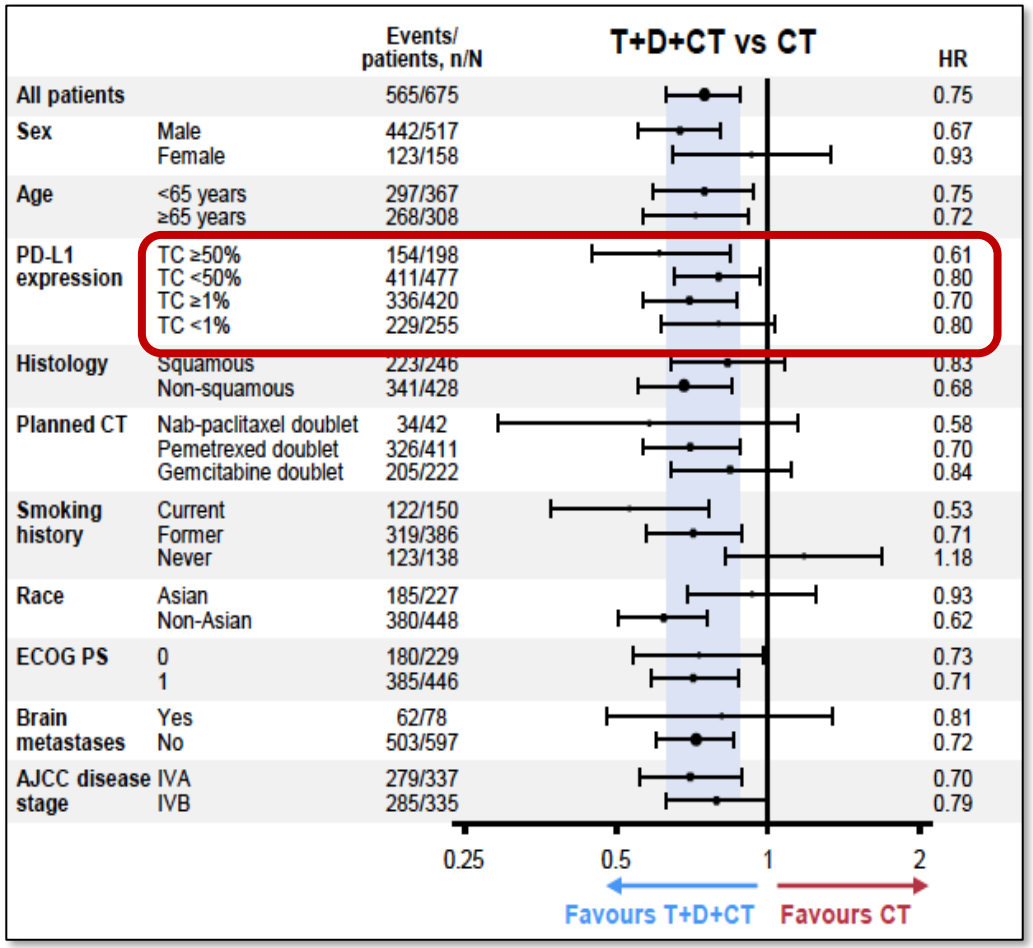


CT or chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; Ipi, ipilimumab; Nivo, nivolumab; OS, overall survival; PD-L1, programmed cell death-ligand 1
Extracted from Reck M et al. Five-year outcomes with first-line nivolumab plus ipilimumab with chemotherapy vs chemotherapy in patients with metastatic NSCLC in CheckMate 9LA. Poster 8560. Presented at the ASCO Annual Meeting; May 31-June 04, 2024; Chicago, IL.

POSEIDON
Phase 3
Durva + Trem + CT vs CT
PD-L1 % all
mFU 46.5 mo.

POSEIDON – 4-year OS update





Median follow-up: 46.5 months

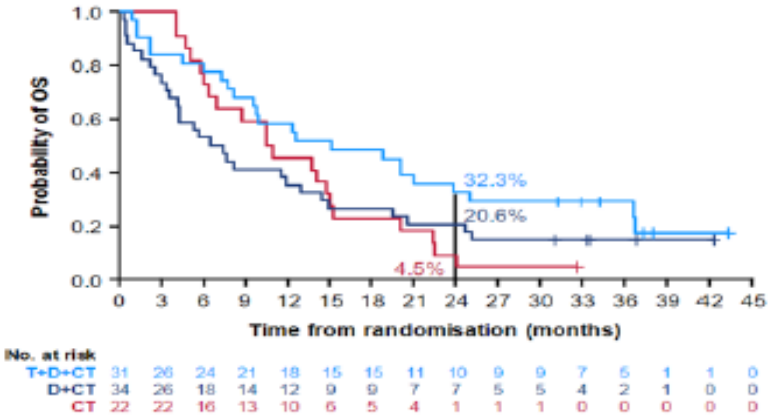
CT, chemotherapy; CI, confidence interval; D or Durva, durvalumab; HR, hazard ratio; mFU, median follow-up; OS, overall survival; PD-L1, programmed cell death-ligand 1; T or Trem, tremelimumab
Extracted from Johnson ML et al. Durvalumab ± Tremelimumab + Chemotherapy in 1L Metastatic NSCLC: Overall Survival Update from POSEIDON After Median Follow-Up of Approximately 4 Years. Abstract LBA59. Presented at the ESMO Congress; September, 09-13; 2022; Paris, France. Available at: https://oncologypro.esmo.org/meeting-resources/esmo-congress-2022/durvalumab-d-tremelimumab-t-chemotherapy-ct-in-1l-metastatic-m-nsclc-overall-survival-os-update-from-poseidon-after-median-follow-up.

Patients with LKB1 and/or KEAP1 mutations may particularly benefit from IO-IO combos

POSEIDON

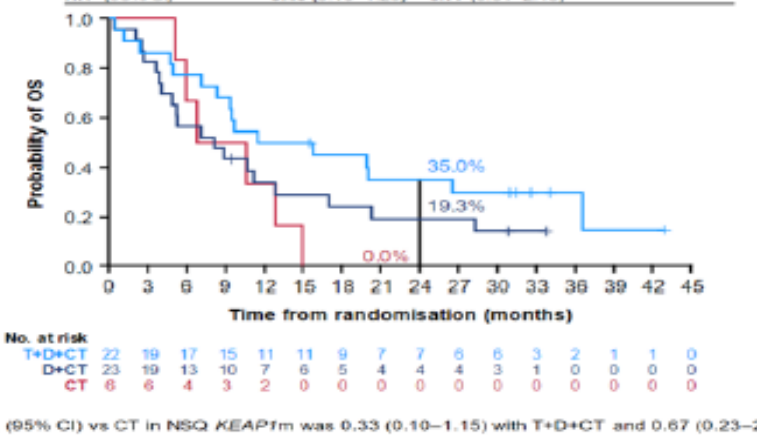
STK11-mut

	T+D+CT	D+CT	CT
Events, n/N	24/31	29/34	21/22
mOS, mo (95% CI)	**15.0** (8.2–23.8)	**6.9** (3.6–12.9)	**10.7** (5.0–14.9)
HR* (95% CI)	**0.56** (0.30–1.03)	**1.03** (0.59–1.84)	–



KEAP1-mut

	T+D+CT	D+CT	CT
Events, n/N	16/22	19/23	8/8
mOS, mo (95% CI)	**13.7** (7.2–26.5)	**8.1** (4.0–12.9)	**8.7** (5.1–NE)
HR* (95% CI)	**0.43** (0.16–1.25)	**0.77** (0.31–2.15)	–

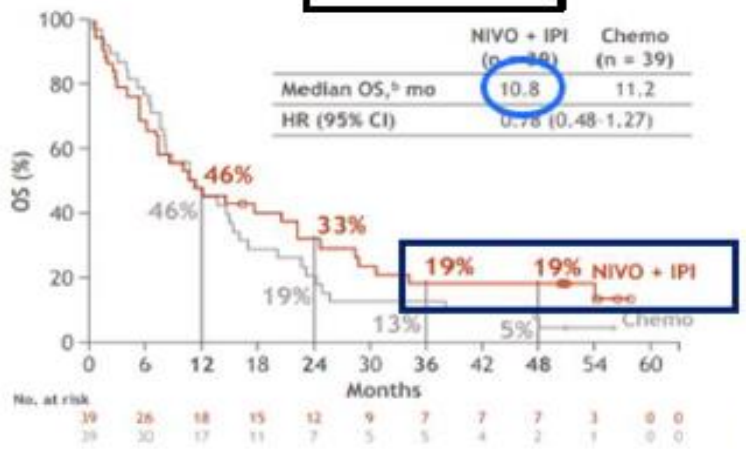


HR (95% CI) vs CT in NSQ *KEAP1*m was 0.33 (0.10–1.15) with T+D+CT and 0.67 (0.23–2.17) with D+CT

CM227

STK11-mut

	NIVO + IPI (n = 39)	Chemo (n = 39)
Median OS,[b] mo	10.8	11.2
HR (95% CI)	0.78 (0.48–1.27)	

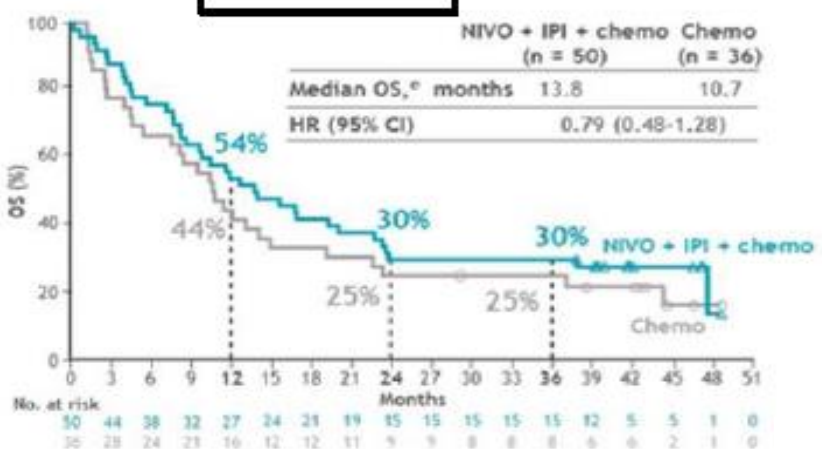


KEAP1^{MUT}(N=38)
Ipi/Nivo: mOS 24.4m
Chemo: mOS 8.9m

9-LA

STK11-mut

	NIVO + IPI + chemo (n = 50)	Chemo (n = 36)
Median OS,[e] months	13.8	10.7
HR (95% CI)	0.79 (0.48–1.28)	



CI, confidence interval; CT, chemotherapy; D, durvalumab; HR, hazard ratio; IO, immuno-oncology; mOS, median overall survival; T, tremelimumab.

Extracted from Peters S et al. Association Between KRAS STK11 KEAP1 Mutations and Outcomes in POSEIDON: Durvalumab Tremelimumab + Chemotherapy in mNSCLC. Abstract OA15.05. Presented at the WCLC; August 06-09, 2022; Vienna, Austria. Available at: https://wclc2022.iaslc.org/.

Take-home messages (Speaker's own)

- Novel immunotherapy strategies have improved the natural history of advanced NSCLC
- PD-1/PD-L1 monotherapy mainly benefits patients with PD-L1 ≥50%
- However, patients with **low/negative PD-L1 expression** still have good options, e.g.:
  - Chemo-IO combos
  - IO/IO combos
- Different treatment alternatives and combos should be considered according to tumor characteristics and patient health and expectations
- Multiparametric predictive biomarkers are required for personalized IO approaches

Chemo, chemotherapy; IO, immuno-oncology; NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1.

Gracias

lpazaresr@seom.org

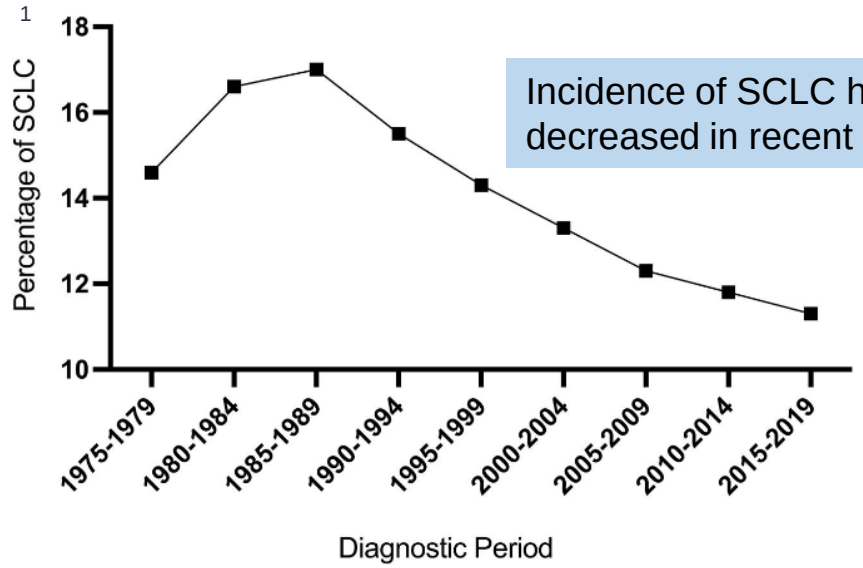
First-line small cell lung cancer

Silvia Novello, MD, PhD

San Luigi Hospital (part of University of Turin), Orbassano, Italy

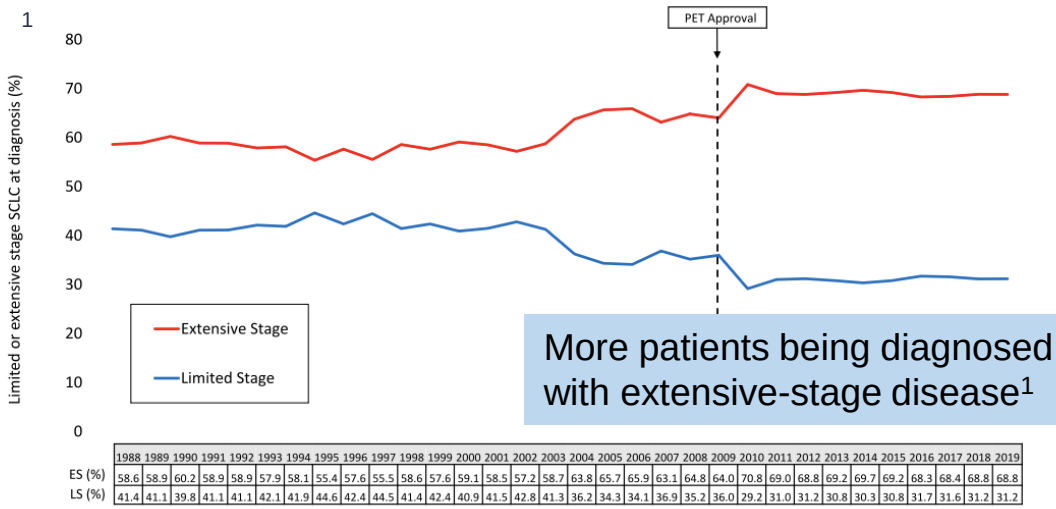
Small Cell Lung Cancer: Epidemiology

1



Incidence of SCLC has decreased in recent decades[2]

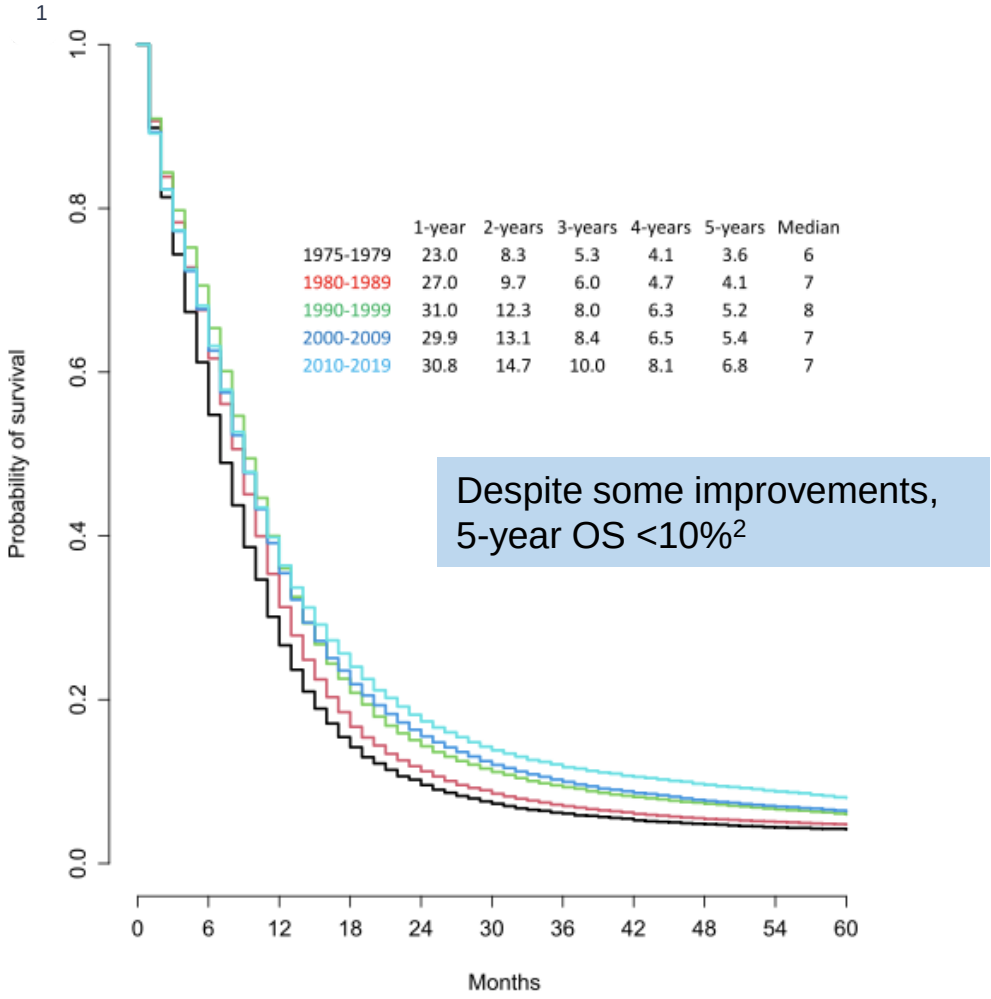
1



	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
ES (%)	58.6	58.9	60.2	58.9	58.9	57.9	58.1	55.4	57.6	55.5	58.6	57.6	59.1	58.5	57.2	58.7	63.8	65.7	65.9	63.1	64.8	64.0	70.8	69.0	68.8	69.2	69.7	69.2	68.3	68.4	68.8	68.8
LS (%)	41.4	41.1	39.8	41.1	41.1	42.1	41.9	44.6	42.4	44.5	41.4	42.4	40.9	41.5	42.8	41.3	36.2	34.3	34.1	36.9	35.2	36.0	29.2	31.0	31.2	30.8	30.3	30.8	31.7	31.6	31.2	31.2

More patients being diagnosed with extensive-stage disease[1]

1



	1-year	2-years	3-years	4-years	5-years	Median
1975-1979	23.0	8.3	5.3	4.1	3.6	6
1980-1989	27.0	9.7	6.0	4.7	4.1	7
1990-1999	31.0	12.3	8.0	6.3	5.2	8
2000-2009	29.9	13.1	8.4	6.5	5.4	7
2010-2019	30.8	14.7	10.0	8.1	6.8	7

Despite some improvements, 5-year OS <10%[2]

OS, overall survival; SCLC, small-cell lung cancer.

Extracted from 1) Cittolin-Santos GF et al. Cancer. 2024; 130(14): 2453-2461; 2) Dingemans A et al. Ann Oncol. 2021;32:839–853.

Small Cell Lung Cancer: Some Characteristics

SCLC is a very aggressive, poorly differentiated, and high-grade neuroendocrine carcinoma and accounts for ~15% of all lung cancers[1–6]

- **Most patients with SCLC have extensive-stage disease**[1,5]

In many instances this is a disease of the elderly

44% SCLC occurs in the 70+ years ago group[6]; 10% SCLC occurs in the 80+[7]

Decreasing survival from SCLC is observed with increasing age[5]

The 5-year survival rate for extensive-stage SCLC is ~3%[8]

Median OS is approximately 6–12 months[4–6]

Lack of significant drug therapy progress over the last 40 years

Current SoC 1L treatment for **extensive-stage SCLC** is systemic chemotherapy and immunotherapy (with or without consolidation RT)[6]

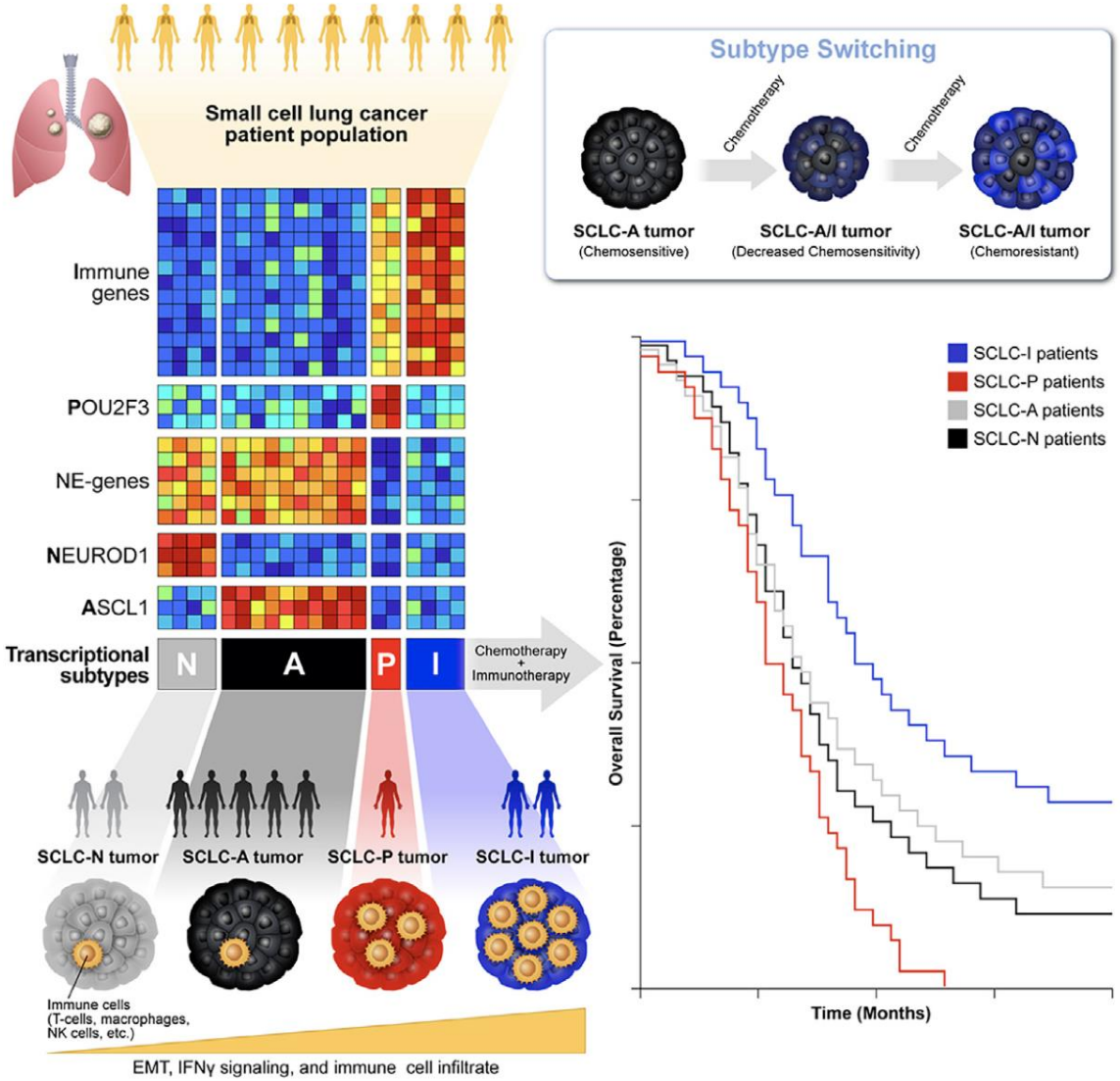
- **Targeting the PD-1/PD-L1 pathway has been shown to improve patient outcomes**, in combination with chemotherapy, in the first line setting[6,9]

NSCLC, non-small cell lung cancer; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; SCLC, small cell lung cancer; SoC, standard of care.

Extracted from 1) Meijer J-J et al. Semin Cancer Biol. 2022;86(Pt 2):376-385; 2) NCCN SCLC V3.2023; 3) Raso MG et al. Cancers (Basel). 2021;13(4):820; 4) Herzog BH et al. J Thorac Oncol. 2021;16(12):2002-2015; 5) National Cancer Institute. Small-cell lung cancer treatment PDQ. Available at: https://www.cancer.gov/types/lung/hp/small-cell-lung-treatment-pdq#_6_toc (Accessed 30 Aug 2023; 6) Dingemans A et al. Ann Oncol. 2021;32:839–853; 7) Pallis AG et al. Cancer. 2010;116(5):1192-200; 8) American Cancer Society Small-cell lung cancer. Available at: https://www.cancer.org/cancer/types/lung-cancer/detection-diagnosis-staging/survival-rates.html (Accessed 16 Jun 2024); 9) Horn L et al. N Engl J Med. 2018;379(23):2220-2229.

The other face(s) of SCLC…..

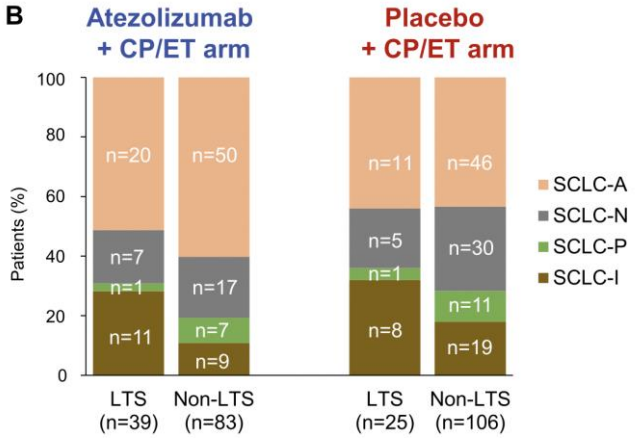
Despite a wealth of data on SCLC, treatment options are still limited

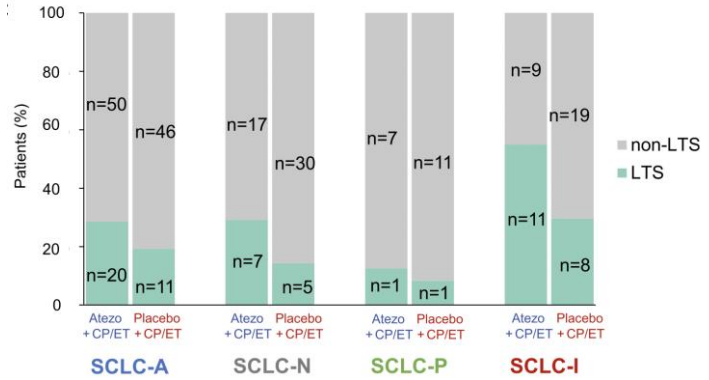


1

2

Subtype, n (%)	Atezolizumab + CP/ET		Placebo + CP/ET	
	LTS n=39	Non-LTS n=83	LTS n=25	Non-LTS n=106
SCLC-A	20 (51)	50 (60)	11 (44)	46 (43)
SCLC-N	7 (18)	17 (20)	5 (20)	30 (28)
SCLC-P	1 (2)	7 (8)	1 (4)	11 (10)
SCLC-I	11 (28)	9 (11)	8 (32)	19 (18)





CP/ET, carboplatin and etoposide; EMT, epithelial–mesenchymal transition; IFN-γ, interferon-gamma; LTS, long-term survivors; non-LTS, non–long-term survivors; SCLC, small-cell lung cancer; SCLC-A, ASCL1 driven; SCLC-I, SCLC inflamed; SCLC-N, NEUROD1 driven; SCLC-P, POU2F3 driven.

Extracted from 1) Gay CM et al. Cancer Cell. 2021;39(3):346-360.e7; 2) Liu SV et al. Lung Cancer. 2023:186:107418.

….and faces of SCLC patients

ASCO Educational Book (2024)[1]

«…..I have people in my support group who say, 'Don't even ask about prognosis, because it's just the average' I don't agree with that. ***You have SCLC- that's a huge thing introduced in your life****, the probability of dying just went way up. You have the opportunity to do what's necessary to prepare yourself and your loved ones. But sometimes people are so in denial that they just assume things are going to be fine»*

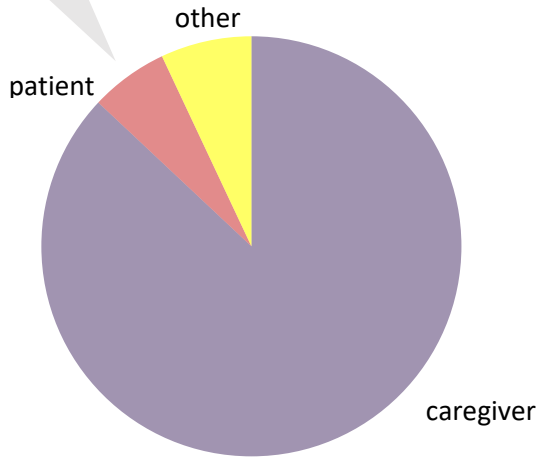
«……In hindsight, I feel like my medical oncologist was perhaps overly pessimistic about my case and my radiation oncologist was overly optimistic. ***I needed to get my affairs in order, to be prepared to die****, but I'm glad I didn't give away all of my money»*

1) Extracted from Wang X and Chiang AC. Am Soc Clin Oncol Educ Book. 2024 ;44(3):e432520;
2) Provided courtesy of Prof. Novello.

Pts, patients; SCLC, small-cell lung cancer

Network Listening (Jan 2017- Dec 2018)[2]

Only 6% of messages come from pts who describe their experience: a sign of a highly trying condition that leaves no room for the desire to share



-70% of messages express emotional needs and when they talk about chemo or radiotherapy users refer to them as *palliatives*
-Loneliness and anger emerge as the most prevalent feelings that caregivers talk about

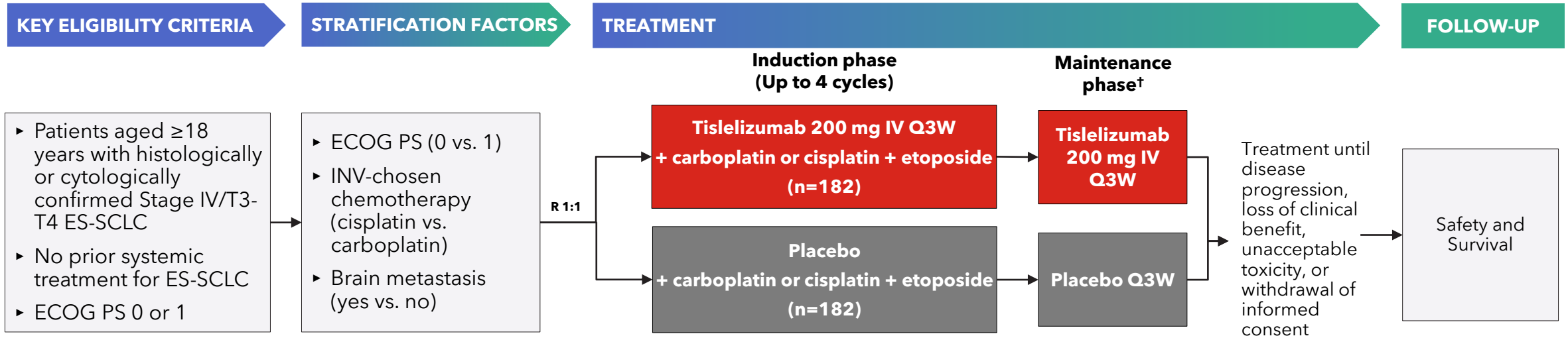
Tislelizumab and ES-SCLC: Trial Design[1,2]

RATIONALE-312

Phase 3

Study Identifier: RATIONALE-312, BGB-A317-312, NCT04005716

Primary Endpoint: OS
Key Secondary Endpoints: PFS, ORR, DoR, DCR (INV-assessed); Safety and tolerability; HRQoL.



Statistical methods

- Planned to enroll 455 pts; 80% power to detect HR 0.74 with 353 OS events
- Hierarchical testing on PFS: only when OS demonstrates significance*

*Under 1-sided P-value of 0.025.
Tislelizumab no está comercializado aún en España.
AUC, area under the curve, D, day, DCR, disease control rate, DoR, duration of response, ECOG, Eastern Cooperative Oncology Group, ES-SCLC, extensive stage small cell lung cancer, PS, performance status, HR, hazard ratio, HRQoL, health-related quality of life, INV, investigator, ITT, intention-to-treat, ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; R, randomized
1) Extracted from Cheng Y et al. J Thorac Oncol. 2024;19(7):1073-1085; 2) ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT04005716. Accessed September 2023.

Tislelizumab and ES-SCLC: Baseline Characteristics

RATIONALE-312

		Tislelizumab + chemo (n=227)	Placebo + chemo (n =230)
Age (years), median (IQR)		63 (56-66)	62 (56-67)
≥65 years, n (%)		89 (39)	81 (35)
Male, n (%)		186 (82)	186 (81)
ECOG PS, n (%)	0 1	35 (15) 192 (85)	34 (15) 196 (85)
Smoking status, n (%)	Never Current Former	53 (23) 151 (67) 23 (10)	59 (26) 135 (59) 36 (16)
AJCC stage at study entry (date of randomization), n (%)	IIIA IIIB IV	4 (2) 16 (7) 207 (91)	2 (1) 27 (12) 201 (87)
≥3 metastatic sites, n (%)		183 (81)	164 (71)
Distant metastatic site, n (%)	Liver Brain	64 (28) 1 (<1)	59 (26) 4 (2)
Baseline LDH	≤ULN >ULN	114 (50) 113 (50)	109 (47) 121 (53)
Choice of platinum	Carboplatin Cisplatin	180 (79) 47 (21)	181 (79) 49 (21)

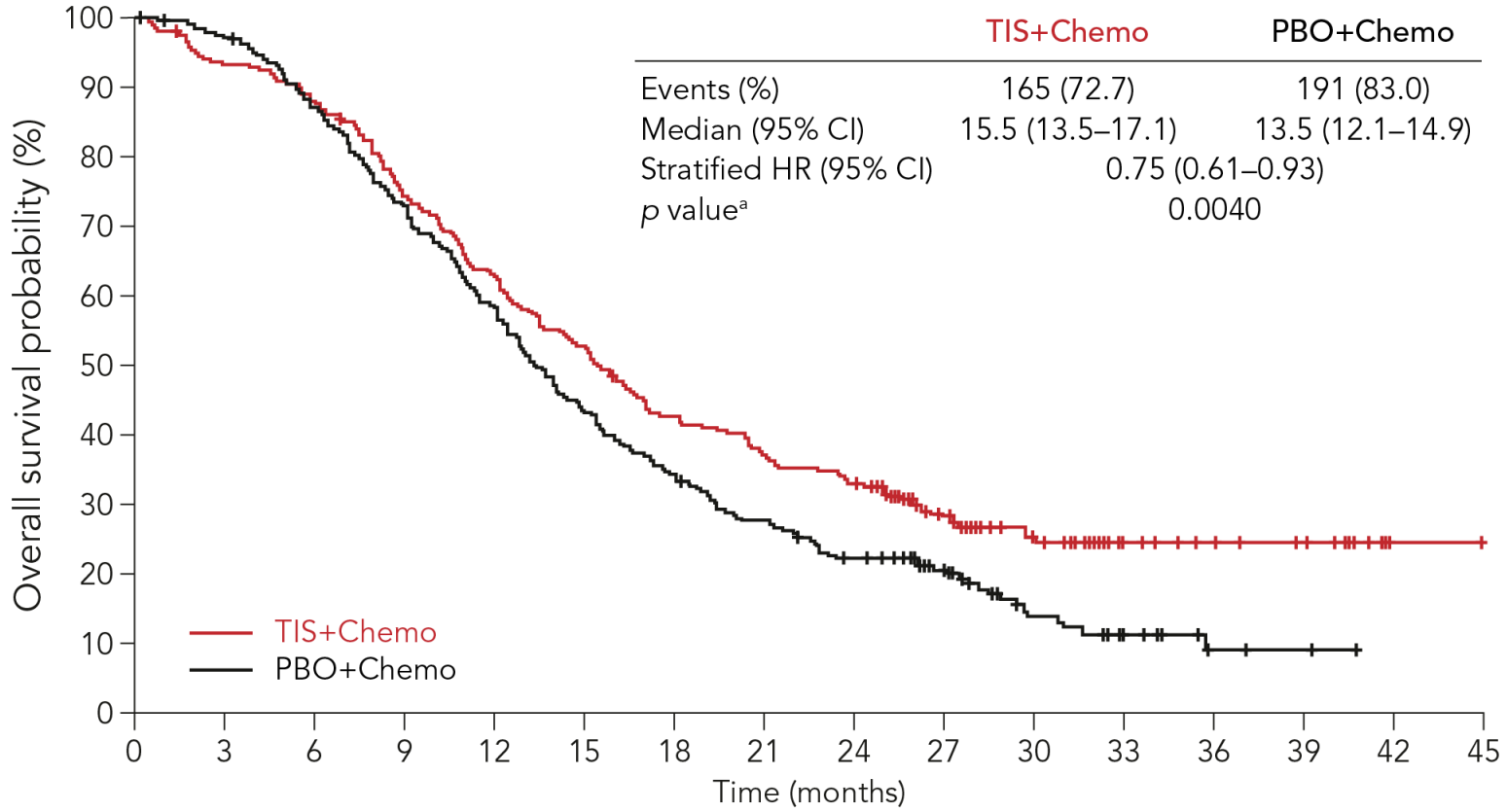
Data cut-off: April 19, 2023

AJCC, American Joint Committee on Cancer; chemo, chemotherapy; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; PS, performance status; ULN, upper limit of normal.

Extracted from Cheng Y et al. J Thorac Oncol. 2024;19(7):1073-1085.

Tislelizumab and ES-SCLC: Overall Survival

RATIONALE-312



	TIS+Chemo	PBO+Chemo
Events (%)	165 (72.7)	191 (83.0)
Median (95% CI)	15.5 (13.5–17.1)	13.5 (12.1–14.9)
Stratified HR (95% CI)	0.75 (0.61–0.93)	
p value[a]	0.0040	

No at Risk

TIS+Chemo	227	211	198	166	141	119	96	83	74	50	33	17	13	10	1	0
PBO+Chemo	230	221	197	165	132	98	78	62	48	34	17	9	3	2	0	0

Data cut-off: April 19, 2023

[a] One-sided p-value from stratified log-rank test; superiority threshold: 0.0211.

HRs and 95% CIs for the primary analysis of OS and the analysis of PFS were estimated using a stratified Cox regression model with the treatment arm as a factor and stratified by the actual value of the stratification factors.

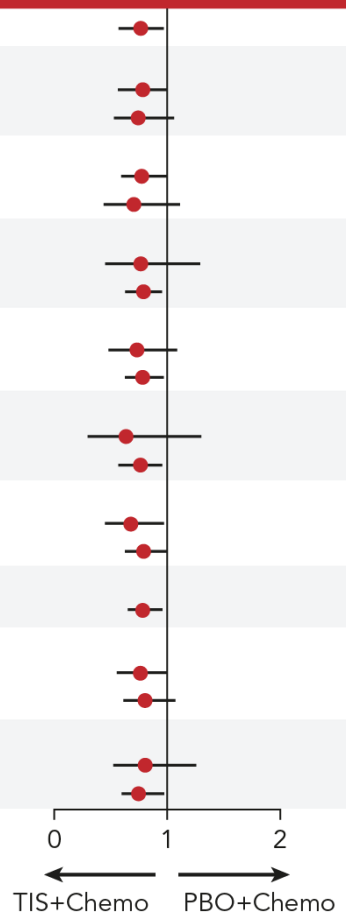
Chemo, chemotherapy; CI, confidence interval; mo, months; OS, overall survival.

Extracted from Cheng Y et al. J Thorac Oncol. 2024;19(7):1073-1085.

Tislelizumab and ES-SCLC: Overall Survival Subgroup Analyses

RATIONALE-312

Subgroup	Event/total TIS+Chemo	Event/total PBO+Chemo	HR (95% CI)[a]
Overall	165/227	191/230	0.75 (0.61–0.93)
Age			
< 65 years	98/138	122/149	0.76 (0.58–0.99)
≥ 65 years	67/89	69/81	0.74 (0.53–1.03)
Sex			
Male	136/186	153/186	0.76 (0.61–0.96)
Female	29/41	38/44	0.69 (0.42–1.12)
ECOG performance status			
0	23/35	27/34	0.74 (0.42–1.29)
1	142/192	164/196	0.76 (0.60–0.95)
Smoking status			
Never	36/53	48/59	0.70 (0.45–1.08)
Smoker	129/174	143/171	0.77 (0.60–0.97)
AJCC staging at study entry			
III	11/20	21/29	0.62 (0.30–1.29)
IV	154/207	170/201	0.75 (0.60–0.93)
Liver metastasis			
Yes	54/64	56/59	0.65 (0.44–0.95)
No	111/163	135/171	0.76 (0.59–0.98)
Brain metastasis			
No	164/226	187/226	0.76 (0.61–0.94)
Baseline LDH			
≤ULN	79/114	88/109	0.73 (0.54–0.99)
>ULN	86/113	103/121	0.80 (0.60–1.06)
Choice of platinum			
Cisplatin	35/47	42/49	0.81 (0.51–1.26)
Carboplatin	130/180	149/181	0.74 (0.59–0.94)



Data cut-off: April 19, 2023

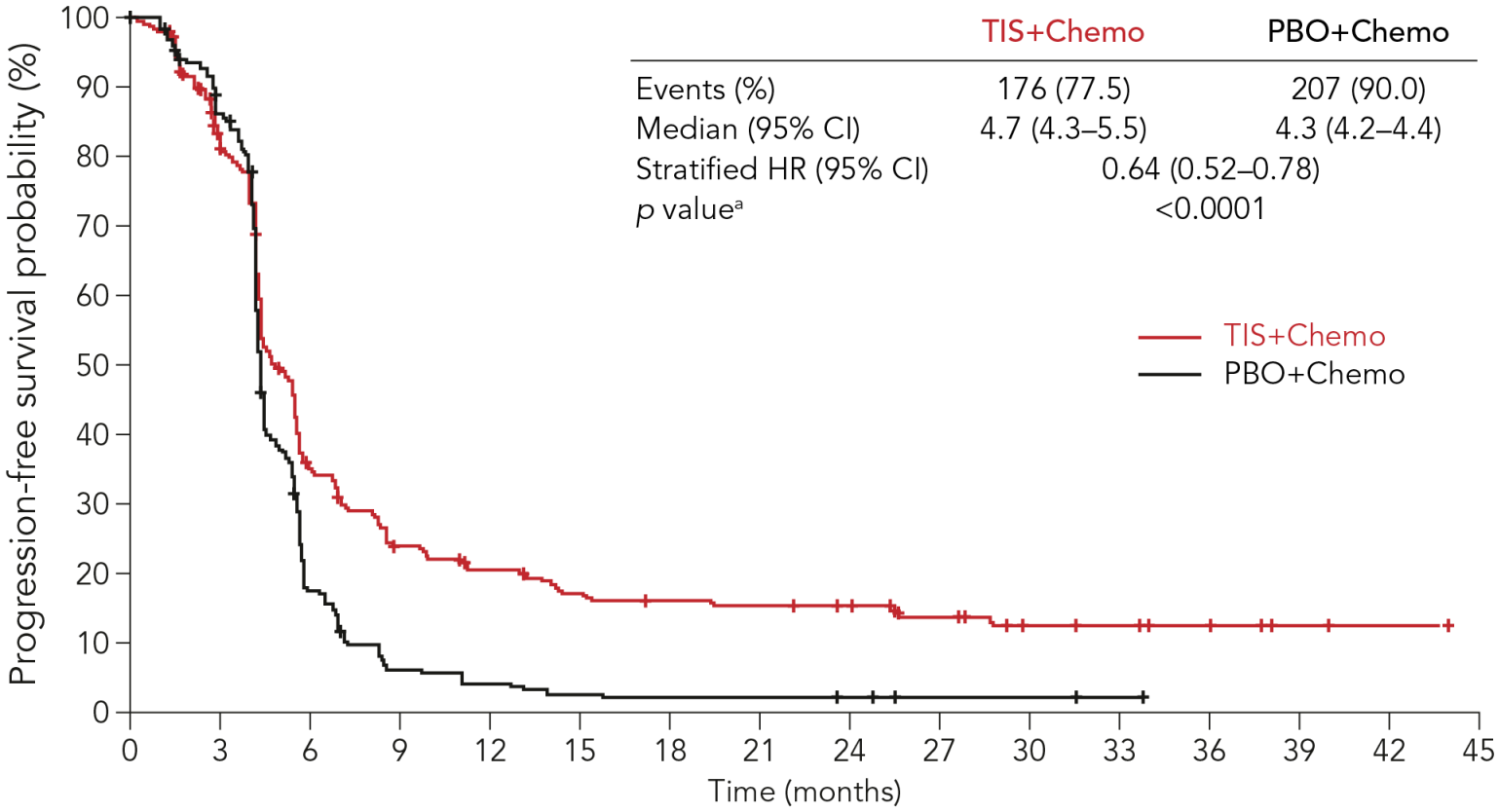
[a] HR and 95% CIs for the subgroup analysis of OS were estimated using an unstratified Cox regression model.

AJCC, American Joint Committee on Cancer; chemo, chemotherapy; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; OS, overall survival; ULN, upper limit of normal.

Extracted from Cheng Y et al. J Thorac Oncol. 2024;19(7):1073-1085.

Tislelizumab and ES-SCLC: Progression-Free Survival

RATIONALE-312



	TIS+Chemo	PBO+Chemo
Events (%)	176 (77.5)	207 (90.0)
Median (95% CI)	4.7 (4.3–5.5)	4.3 (4.2–4.4)
Stratified HR (95% CI)	0.64 (0.52–0.78)	
p value[a]	<0.0001	

No at Risk																
TIS+Chemo	227	211	198	166	141	119	96	83	74	50	33	17	13	10	1	0
PBO+Chemo	230	221	197	165	132	98	78	62	48	34	17	9	3	2	0	0

Data cut-off: April 19, 2023

[a] One-sided p-value from stratified log-rank test.

HRs and 95% CIs for the primary analysis of OS and the analysis of PFS were estimated using a stratified Cox regression model with the treatment arm as a factor and stratified by the actual value of the stratification factors.

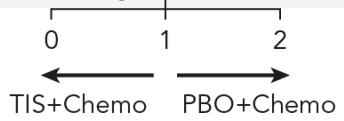
Chemo, chemotherapy; CI, confidence interval; mo, months; PFS, progression-free survival.

Extracted from Cheng Y et al. J Thorac Oncol. 2024;19(7):1073-1085.

Tislelizumab and ES-SCLC: Progression-Free Survival Subgroup Analyses

RATIONALE-312

Subgroup	Event/total TIS+Chemo	Event/total PBO+Chemo	HR for PD (95% CI)	HR (95% CI)[a]
Overall	176/227	207/230		0.63 (0.52–0.78)
Age				
< 65 years	106/138	138/149		0.59 (0.45–0.77)
≥ 65 years	70/89	69/81		0.74 (0.53–1.05)
Sex				
Male	144/186	165/186		0.70 (0.56–0.88)
Female	32/41	42/44		0.38 (0.23–0.63)
ECOG performance status				
0	28/35	29/34		0.65 (0.39–1.10)
1	148/192	178/196		0.63 (0.50–0.79)
Smoking status				
Never	41/53	55/59		0.50 (0.32–0.77)
Smoker	135/174	152/171		0.68 (0.53–0.86)
AJCC staging at study entry				
III	14/20	25/29		0.50 (0.25–1.00)
IV	162/207	182/201		0.63 (0.50–0.78)
Liver metastasis				
Yes	52/64	56/59		0.71 (0.48–1.05)
No	124/163	151/171		0.60 (0.47–0.77)
Brain metastasis				
No	175/226	204/226		0.63 (0.51–0.78)
Baseline LDH				
≤ULN	91/114	97/109		0.63 (0.47–0.84)
>ULN	85/113	110/121		0.65 (0.48–0.87)
Choice of platinum				
Cisplatin	38/47	43/49		0.75 (0.48–1.18)
Carboplatin	138/180	164/181		0.61 (0.48–0.77)



Data cut-off: April 19, 2023

[a] HR and 95% CIs were estimated using an unstratified Cox regression model.

AJCC, American Joint Committee on Cancer; chemo, chemotherapy; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; ULN, upper limit of normal.

Extracted from Cheng Y et al. J Thorac Oncol. 2024;19(7):1073-1085 (suppl. data).

Tislelizumab and ES-SCLC: Tumor Response Outcomes

RATIONALE-312

	Tislelizumab + chemo (n=227)	Placebo + chemo (n =230)
ORR [95% CI]	155 (68%) [62–74]	142 (62%) [55–68]
Best overall response, n (%)		
CR	1 (<1)	0 (0)
PR	154 (68)	142 (62)
Stable disease	46 (20)	60 (26)
Non-CR/Non-PD	0 (0)	1 (<1)
PD	11 (5)	15 (7)
NE[a]/NA[b]	15 (7)	12 (5)
DCR, n (%) [95% CI]	201 (89) [84–92]	203 (88) [83–92]
Median DoR, months [95% CI]	4.3 [4.1–5.6]	3.7 [3.0–4.1]

Data cut-off: April 19, 2023

[a] Patients who had at least 1 postbaseline tumor assessment, none of which were evaluable for response determination (e.g., not all target lesions captured) on the basis of RECIST v1.1.

[b] Patients with no postbaseline tumor assessment by the data cutoff, including those who discontinued the study (any reason) or died without having any post-baseline tumor assessment.

Chemo, chemotherapy; CI, confidence interval; CR, complete response; DCR, disease control rate; DoR, duration of response; mo, months; NA, not available; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.

Extracted from Cheng Y et al. J Thorac Oncol. 2024;19(7):1073-1085.

Tislelizumab and ES-SCLC: Safety Summary (Safety Analysis Set)[1,2]

RATIONALE-312

The most common immune-mediated AEs in the tislelizumab plus chemo arm were hypothyroidism (14%), rash (13%), and hyperthyroidism (6%)

	Tislelizumab + chemo (n=227)	Placebo + chemo (n=229)
Duration of exposure, weeks		
Mean (SD)	39.0 (43.2)	23.6 (19.0)
Median (IQR)	19.4 (15.4–41.1)	19.1 (17.3–25.7)
Tislelizumab/placebo cycles		
Mean (SD)	11.8 (13.0)	7.3 (5.7)
Median (IQR)	6.0 (5–13)	6.0 (5–8)
>16 cycles, n (%)	44 (19)	10 (4)
Chemotherapy cycles, median, n (IQR)	4.0 (4–4)	4.0 (4–4)
Any TEAE, n (%)	226 (>99%)	228 (>99%)
Treatment-related	226 (>99%)	228 (>99%)
Grade ≥3	201 (89%)	206 (90%)
Serious	94 (41%)	69 (30%)
Leading to discontinuation	30 (13%)	7 (3%)
Leading to death	14 (6%)	4 (2%)
Immune-mediated AEs, n (%)	87 (38%)	41 (18%)
Leading to death	1 (0.4)	0 (0.0)

Data cut-off: April 19, 2023

Duration of exposure was calculated as last dose date - first dose date + 1 day. For patients with treatment ongoing, last dose date = cutoff date; for patients who discontinued tislelizumab/placebo, last dose date = min (cutoff date, death date, last dose date + 20); for patients who discontinued treatment with cisplatin or carboplatin, last dose date = min (cutoff date, death date, last dose date + 20 days); for patients who discontinued the treatment of etoposide, last dose date = min (cutoff date, death date, last cycle first dose date + 20 days).

AE, adverse event; Chemo, chemotherapy; TEAE, treatment emergent adverse event.

Extracted from 1) Cheng Y et al. J Thorac Oncol. 2024;19(7):1073-1085; 2) Cheng Y et al. J Thorac Oncol. 2024;19(7):1073-1085 (suppl. data).

Author Conclusions

RATIONALE-312

- RATIONALE-312 met its primary endpoint, demonstrating a statistically significant and clinically meaningful improvement in OS with tislelizumab plus chemotherapy compared with placebo plus chemotherapy in 1L ES-SCLC
  - Median OS 15.5 vs 13.5 months (HR 0.75 [95% CI: 0.61, 0.93]; P=0.0040)
  - Survival benefit was consistently observed across all the pre-defined subgroups, accompanied by significant improvement in PFS, increase in ORR, and more durable responses compared with placebo plus chemotherapy
- Tislelizumab plus chemotherapy showed a manageable safety profile

The results from this study confirm that the PD-1 inhibitor tislelizumab, in combination with chemotherapy, can improve OS in ES-SCLC, adding supporting evidence for the use of PD-1 inhibitors in 1L treatment of ES-SCLC

Data cut-off: April 19, 2023
CI, confidence interval; ES-SCLC, extensive-stage small cell lung cancer; HR, hazard ratio; L, line of therapy; ORR, overall response rate; OS, overall survival; PD-1, programmed cell death protein 1; PFS, progression-free survival.
Extracted from Cheng Y et al. J Thorac Oncol. 2024;19(7):1073-1085.

Randomized studies of PE ± immune-checkpoints inhibitors (ICPIs) in first-line treatment of ED-SCLC: **RATIONALE-312 in context**

	IMPOWER-133[1]	CASPIAN[2]	KEYNOTE-604[3]	EA 5161[4]	ASTRUM[5]	CAPSTONE[6]	RATIONALE[7]
No. of pts	403 (2 arms)	805 (3 arms)	453 (2 arms)	160 (2 arms)	585 (2 arms)	462 (2 arms)	456 (2 arms)
ICPI	Atezolizumab (anti-PDL1)	Durvalumab (anti-PDL1)	Pembrolizumab (anti-PD1)	Nivolumab (anti-PD1)	Serplulimab (anti-PD1)	Adebrelimab (anti-PDL1)	Tislelizumab (anti-PD1)
Platinum*	Carboplatin	Carboplatin or Cisplatin	Carboplatin or Cisplatin	Carboplatin or Cisplatin	Carboplatin	Carboplatin	Carboplatin or Cisplatin
No. tx cycles	4 vs 4	4-6 (ctr) vs 4	4 vs 4	4 vs 4	4 vs 4	4-6 vs 4-6	4 vs 4
PCI/TRT	Yes/No	Yes (ctr arm)/No	Yes/No	Yes/No	No/No	Yes/No	-
Asian%	16	15	19	nr	68	100	100
RR%	64.4 vs 60.2	58 vs 68§	61.8 vs 70.6	47.51 vs 52.29	70.4 vs 80.2	65.0 vs 70.4	62 vs 68
mPFS(months)	4.3 vs 5.2 (P=0.02)	5.4 vs 5.1§ (P not tested)	4.3 vs 4.5 (P=0.002)	4.7 vs 5.5 (P=0.047)	4.3 vs 5.7 (P not tested)	5.6 vs 5.8 (P=0.0001)	4.3 vs 4.7 (P<0.0001)
mOS(months)	10.3 vs 12.3 (P=0.007)#	10.3 vs 13 (P=0.004)#	9.7 vs 10.8 (P=0.016)	9.3 vs 11.3 (P=0.14)	10.9 vs 15.4 (P=0.001)#	12.8 vs 15.3 (P=0.0017)#	13.5 vs 15.5 (P=0.0040)#

*second Chemotherapy drug in each trial: etoposide; § : PE vs PE+Durva; #: stat. significant

ED-SCLC, extensive disease small cell lung cancer; ICPI, immune checkpoint inhibitor; mPFS, median progression-free survival; mOS, median overall survival; nr, not recorded; Pbo, placebo; PCI, prophylactic cranial irradiation; PD1, programmed death cell protein 1; PE, platinum and etoposide; RR, response rate; TRT, thoracic radiation therapy; tx, treatment.

Extracted from 1) Horn L et al. N Engl J Med. 2018;379(23):2220-2229; 2) Paz Ares L et al. Lancet. 2019;394(10212):1929-1939; 3) Rudin CM et al. J Clin Oncol. 2020;38(21):2369-2379; 4) Leal TA et al. J Clin Oncol. 2020;38(15 suppl):9000; 5) Cheng Y et al. JAMA. 2022;328(12):1223–1232; 6) Wang J et al. Lancet Oncol. 2022 Jun;23(6):739-747; 7) Cheng Y et al. J Thorac Oncol. 2024;19(7):1073-1085.

Randomized studies of PE + ICPIs in first-line treatment of ED-SCLC: Safety

Study	Safety conclusion
IMPOWER-133[1]	The safety profile of atezolizumab plus carboplatin and etoposide was consistent with the previously reported safety profile of the individual agents, with no new findings observed
CASPIAN[2]	Safety findings were consistent with the known safety profiles of all drugs received
KEYNOTE-604[3]	No unexpected toxicities were seen with pembrolizumab plus PE
EA 5161[4]	No new safety signals were observed
ASTRUM[5]	The incidence and severity of treatment-emergent adverse events were similar between the 2 groups. Adverse events attributed to serplulimab reflect the toxic effects frequently observed with immunotherapy in patients with SCLC
CAPSTONE[6]	Adding adebrelimab to chemotherapy showed an acceptable safety profile in patients with ES-SCLC
RATIONALE-312[7]	Tislelizumab plus chemotherapy showed a manageable safety profile

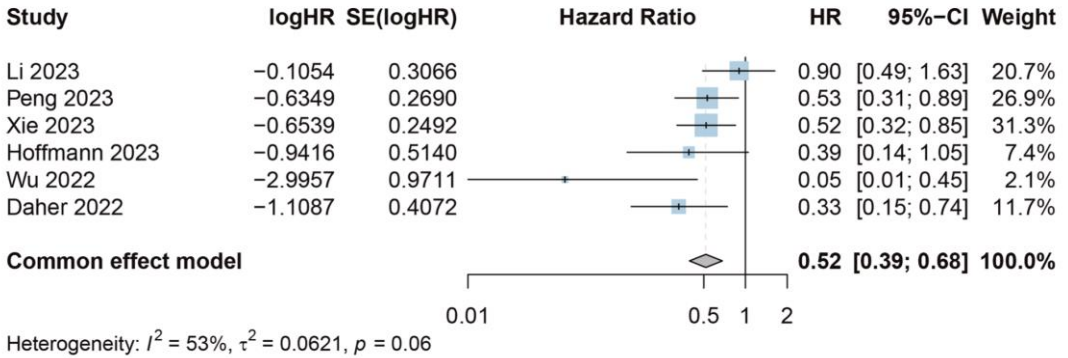
ES-SCLC, extensive stage-small cell lung cancer; ICPI, immune checkpoint inhibitor; PE, platinum and etoposide.

Extracted from 1) Horn L et al. N Engl J Med. 2018;379(23):2220-2229; 2) Paz Ares L et al. Lancet. 2019;394(10212):1929-1939; 3) Rudin CM et al. J Clin Oncol. 2020;38(21):2369-2379; 4) Leal TA et al. J Clin Oncol. 2020;38(15 suppl):9000; 5) Cheng Y et al. JAMA. 2022;328(12):1223–1232; 6) Wang J et al. Lancet Oncol. 2022 Jun;23(6):739-747; 7) Cheng Y et al. J Thorac Oncol. 2024;19(7):1073-1085.

Is there room for consolidative thoracic radiotherapy for ES-SCLC in the era of immunotherapy?

Table 1
Main characteristics of studies included in the *meta*-analysis.

Author (Year)	Study type	Systemic therapy	Control	Dose of cTRT	Sample size (systemic therapy / control)	Median age (Years)	Gender (Male %)	Smoking history (%)
Xie (2023) [20]	Retrospective	chemo + ICI + cTRT	chemo + ICI	30–60 Gy	118 (45/73)	62	83.1	83
Peng (2023) [14]	Retrospective	chemo + atezolizumab or durvalumab + cTRT	chemo + atezolizumab or durvalumab	30–60 Gy	114 (57/57)	–	81	66.7
Yuying Li (2023) [21]	Retrospective	chemo + atezolizumab or durvalumab + cTRT	chemo + atezolizumab or durvalumab	45–54 Gy	100 (47/53)	60	84	63
Lijuan Li (2023) [7]	Retrospective	chemo + atezolizumab or durvalumab + cTRT	–	52–113 Gy	36	63	86.1	72
Kim (2023) [22]	Retrospective	chemo + atezolizumab + cTRT	chemo + atezolizumab	52–66 Gy (5 pts), 24 Gy (1pt)	41 (6/35)	66	90	95
Hoffmann (2023) [23]	Retrospective	chemo + atezolizumab or durvalumab + cTRT	chemo + atezolizumab or durvalumab	3 Gy*10f	41 (23/18)	62.43	53.7	–
Wu (2022) [24]	Retrospective	chemo + atezolizumab or durvalumab + cTRT	chemo + atezolizumab or durvalumab	28–64 Gy	22 (11/11)	64	86.4	90.9
Turner (2022) [25]	Retrospective	chemo + ICI + cTRT	chemo + ICI	30–50 Gy	50 (7/43)	–	54	–
Shi (2022) [26]	Retrospective	chemo + atezolizumab or durvalumab + cTRT	–	52–113 Gy	36	–	–	–
Diamond (2022) [27]	Retrospective	chemo + atezolizumab + cTRT	–	30–60 Gy	20	66	35	–
Daher (2022) [28]	Retrospective	chemo + atezolizumab or durvalumab + cTRT	chemo + atezolizumab or durvalumab	24–60 Gy	126 (25/101)	Systemic therapy: 63Control: 66	Systemic therapy: 68Control: 71	–
Chen (2022) [29]	Prospective	chemo + SHR-1316 (PD-L1 antibody) + cTRT	–	≥3Gy * 10f or ≥ 2 Gy * 25f	31	64	80.6	71
Perez (2021) [16]	Prospective	chemo + ipilimumab + nivolumab + cTRT	–	3 Gy*10f	21	66	61.9	–
Gross (2021) [6]	Retrospective	chemo + ICI + cTRT	chemo + ICI	–	244 (63/181)	65	–	–
Welsh (2020) [17]	Prospective	chemo + pembrolizumab + cTRT	–	45 Gy	33	62	60.6	–



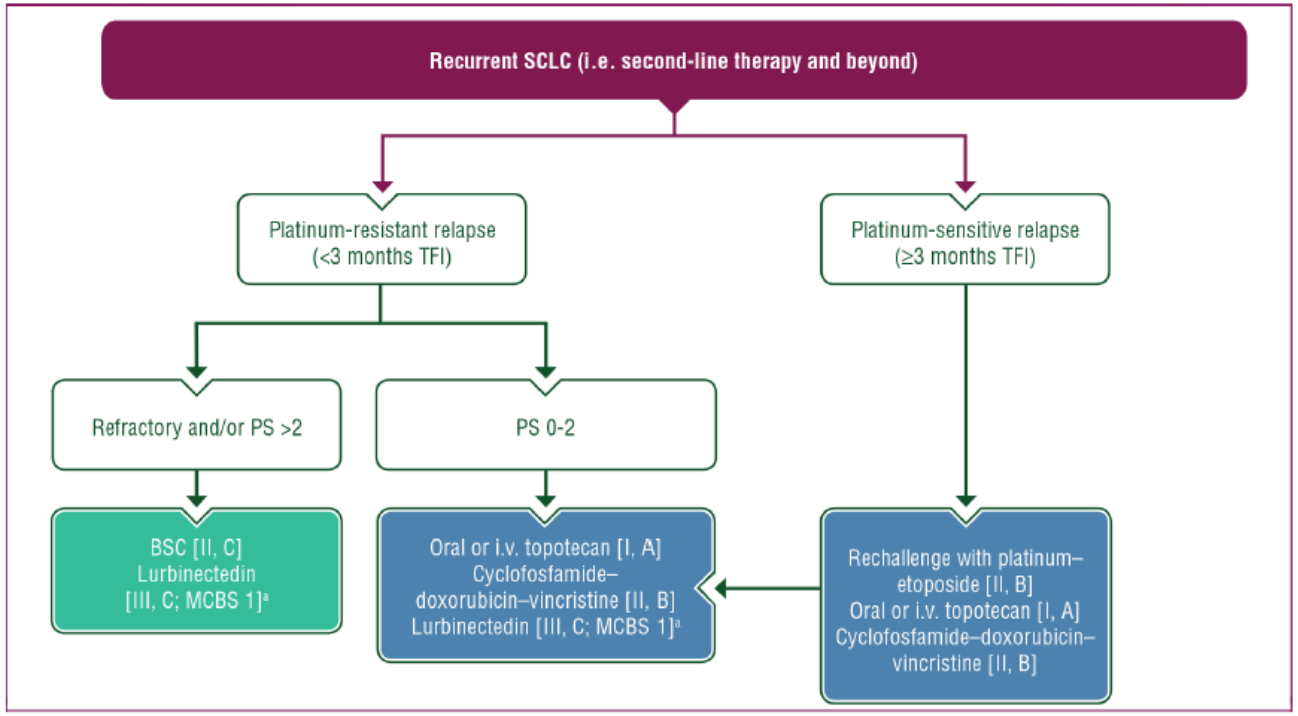
Chemo, chemotherapy; ICI, immune checkpoint inhibitor; cTRT, consolidative thoracic radiation therapy; ES-SCLC, extensive stage-small cell lung cancer; PD-L1, programmed cell death ligand 1.
Extracted from Feng B et al. Radiother Oncol. 2024:190:110014.

ES-SCLC: second-line options

ASCO Educational Book (2024)[1]

«The philosophy that suits me is Stoicism - my cancer will come back or it won't come back and, other than my healthy lifestyle, there is not a whole lot I can do about that. Other people are scared about scans - for me, before the scan, I imagine what it would be like if it showed progression , and what I would do. ***I have to have that Plan B****. But this way, I'm still able to live my life and be at peace with it....»*

ESMO Guidelines[2]

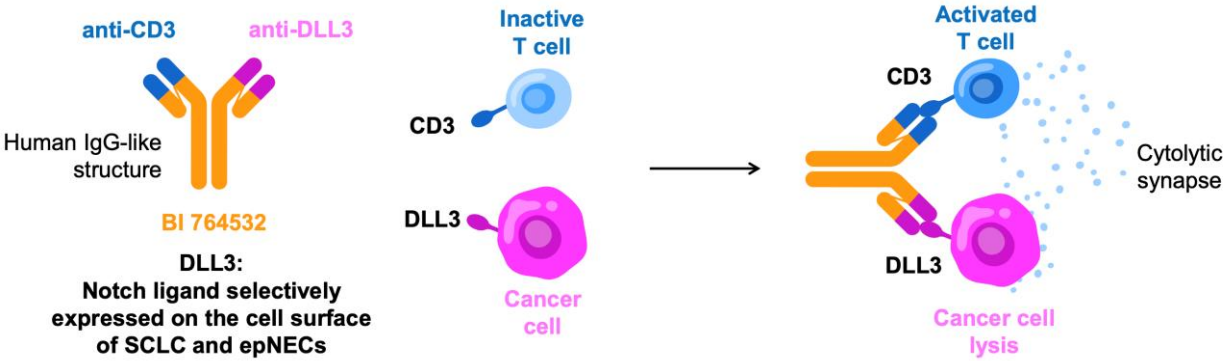


ES-SCLC, extensive stage-small cell lung cancer.
Extracted from 1) Wang X and Chiang AC. Am Soc Clin Oncol Educ Book. 2024 ;44(3):e432520; 2) Dingemans A et al. Ann Oncol. 2021;32:839–853.

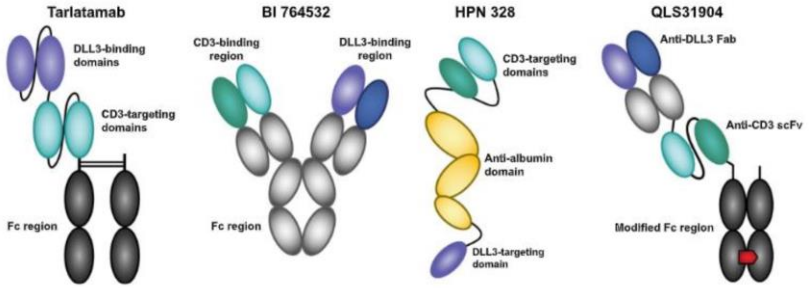
ES-SCLC: second line options

«that plan B» some examples

BI 764532: a novel DLL3-targeting T cell engager [1]

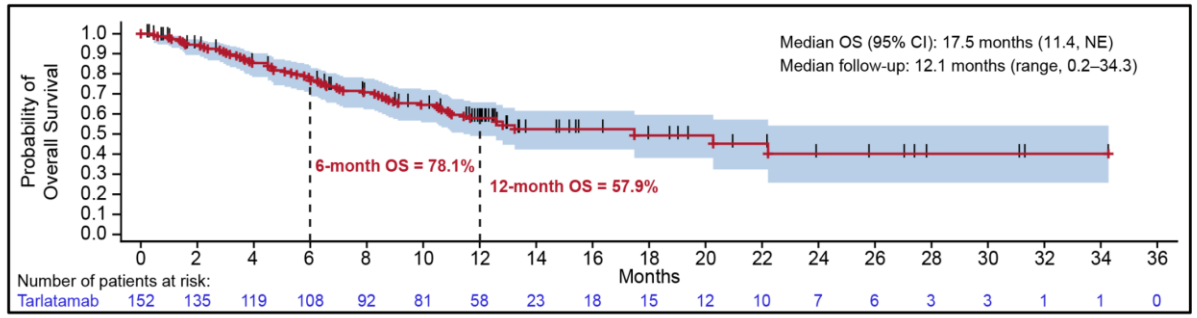


HPN328	Trispecific (DLL3/CD3/Albumin)	p1/2
QLS31904	Bispecific (DLL3/CD3)	p1



Tarlatamab: DeLLphi-301 phase II trial[2]

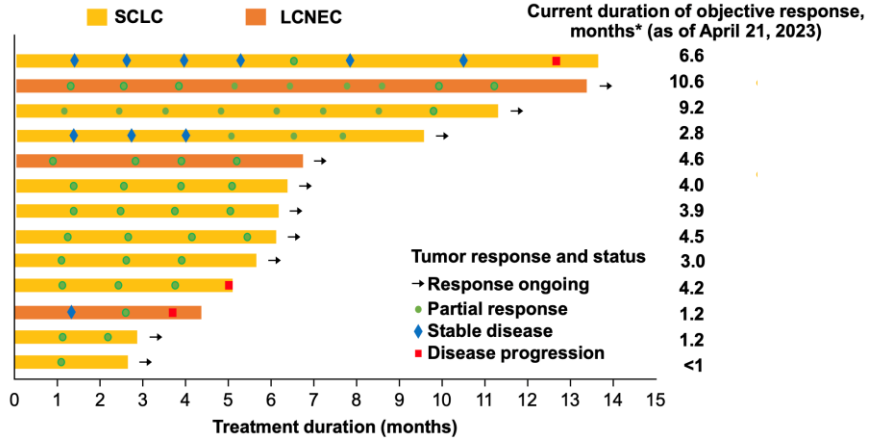
Kaplan-Meier estimate of OS across clinically relevant (≥ 10 mg) dose levels‡



Median follow-up: 12.1 months (range, 0.2–34.3)

- **Among 17 patients receiving the tarlatamab 10 mg dose, median OS was 20.3 months (95% CI: 5.1 to NE)**

BI 764532 a DLL3-targeting T cell engager[3]



CI, confidence interval; DLL3, delta-like ligand 3; ES-SCLC, extensive stage-small cell lung cancer; LCNEC, large cell neuroendocrine lung carcinoma; NE, not estimable; OS, overall survival.
Extracted from 1) Tanizaki J et al. Presented at ELCC 2024; March 20-23 March 2024; Prague, Czech Republic; 2) Paz-Ares L at al. Presented at ESMO 2023; October 20-24 October 2023; Madrid, Spain; 3) Wermke M et al. Presented at the WCLC 2023; September 9-12, 2023; Singapore.

Conclusions (Speaker's own)

- Chemo-immunotherapy is SOC for 1st line treatment of ED-SCLC
- Second-line treatments are still a huge unmet need: nothing really tailored, but (more or less) novel agents are being tested!
- Not managing SCLC as a unique entity may lead to better results in the next future BUT we still need reliable and reproducible ways to define them
- Behind the disease there are patients and caregivers demanding and aware of an unfavorable situation

Panel discussion and Audience Q&A

Prof. Silvia Novello (Co-chair)
San Luigi Hospital (part of University of Turin),
Orbassano, Italy

Prof. Tony Mok (Co-chair)
Li Shu Fan Medical Foundation
Professor of Clinical Oncology
The Chinese University of Hong Kong

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Autonomous University Madrid, Spain

Dr. Luis Paz-Ares
Hospital Universitario “12 de Octubre”
Universidad Complutense de Madrid
Lung Cancer Unit at National Oncology
Research Center

Prof. Martin Reck
Lung Clinic Grosshansdorf,
Grosshansdorf, Germany

Take-home messages

Professor Tony Mok

Li Shu Fan Medical Foundation
Professor of Clinical Oncology

The Chinese University of Hong Kong

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