Immunotherapy in Lung Cancer

2024 ASCO and ESMO update

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UCI Health

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Overview

SCLC

ADRIATIC (Durvalumab) – Changed practice

NSCLC

Early Stage: CheckMate 77T (Nivolumab) and others – Changing practice

Advanced: HARMONi-A and HARMONi-2 (Ivonescimab) – Will change practice

Overview

SCLC

ADRIATIC (Durvalumab)

NSCLC

Early Stage: CheckMate 77T (Nivolumab)

Advanced: HARMONi-A and HARMONi-2 (Ivonescimab)

2024 ASCO® ANNUAL MEETING

ADRIATIC: durvalumab as consolidation treatment for patients with limited-stage small-cell lung cancer (LS-SCLC)

David R. Spigel, Ying Cheng, Byoung Chul Cho, Konstantin Laktionov, Jian Fang, Yuanbin Chen, Yoshitaka Zenke, Ki Hyeong Lee, Qiming Wang, Alejandro Navarro, Reyes Bernabe, Eva Buchmeier, John Wen-Cheng Chang, Isamu Okamoto, Sema Sezgin Goksu, Andrzej Badzio, Bethany Gill, Hema Gowda, Haiyi Jiang, Suresh Senan

Slide credit: Spigel, D (ASCO 2024)

Background

No major advances in systemic treatment for LS-SCLC for several decades

- Current standard of care was concurrent chemoradiotherapy (cCRT): median OS 25–30 months; 5-year survival rate 29–34%[1,2]
- PACIFIC provided evidence for consolidation durvalumab post-cCRT with PFS and OS benefit in unresectable, stage III NSCLC[3,4]
- CASPIAN provided evidence for durvalumab plus platinum-etoposide significantly improved OS vs platinum-etoposide alone in first-line ES-SCLC[5]

1. Faivre-Finn C, et al. Lancet Oncol 2017;18:1116–25; 2. Bogart J, et al. J Clin Oncol 2023;41:2394–402;
3. Antonia SJ, et al. N Engl J Med 2017;377:1919–29; 4. Antonia SJ, et al. N Engl J Med 2018;379:2342–50;
5. Paz-Ares L, et al. Lancet 2019;394:1929–39.

Slide credit: Spigel, D (ASCO 2024)

ADRIATIC study design

Phase 3, randomized, double-blind, placebo-controlled, multicenter, international study (NCT03703297)

- Stage I–III LS-SCLC (stage I/II inoperable)
- WHO PS 0 or 1
- Had not progressed following cCRT*
- PCI* permitted before randomization

N=730

R‡

Durvalumab
1500 mg Q4W
N=264

Placebo
Q4W
N=266

Durvalumab + tremelimumab
D 1500 mg Q4W + T 75 mg Q4W for 4 doses, followed by D 1500 mg Q4W
N=200

Stratified by:
Disease stage (I/II vs III)
PCI (yes vs no)

cCRT components

- Four cycles of platinum and etoposide (three permitted†)
- RT: 60–66 Gy QD over 6 weeks or 45 Gy BID over 3 weeks
- RT must commence no later than end of cycle 2 of CT

Treatment until investigator-determined progression or intolerable toxicity, or for a **maximum of 24 months**

Dual primary endpoints:

- Durvalumab vs placebo
  - OS
  - PFS (by BICR, per RECIST v1.1)

Key secondary endpoints:

- Durvalumab + tremelimumab vs placebo
  - OS
  - PFS (by BICR, per RECIST v1.1)

Other secondary endpoints:

- OS/PFS landmarks
- Safety

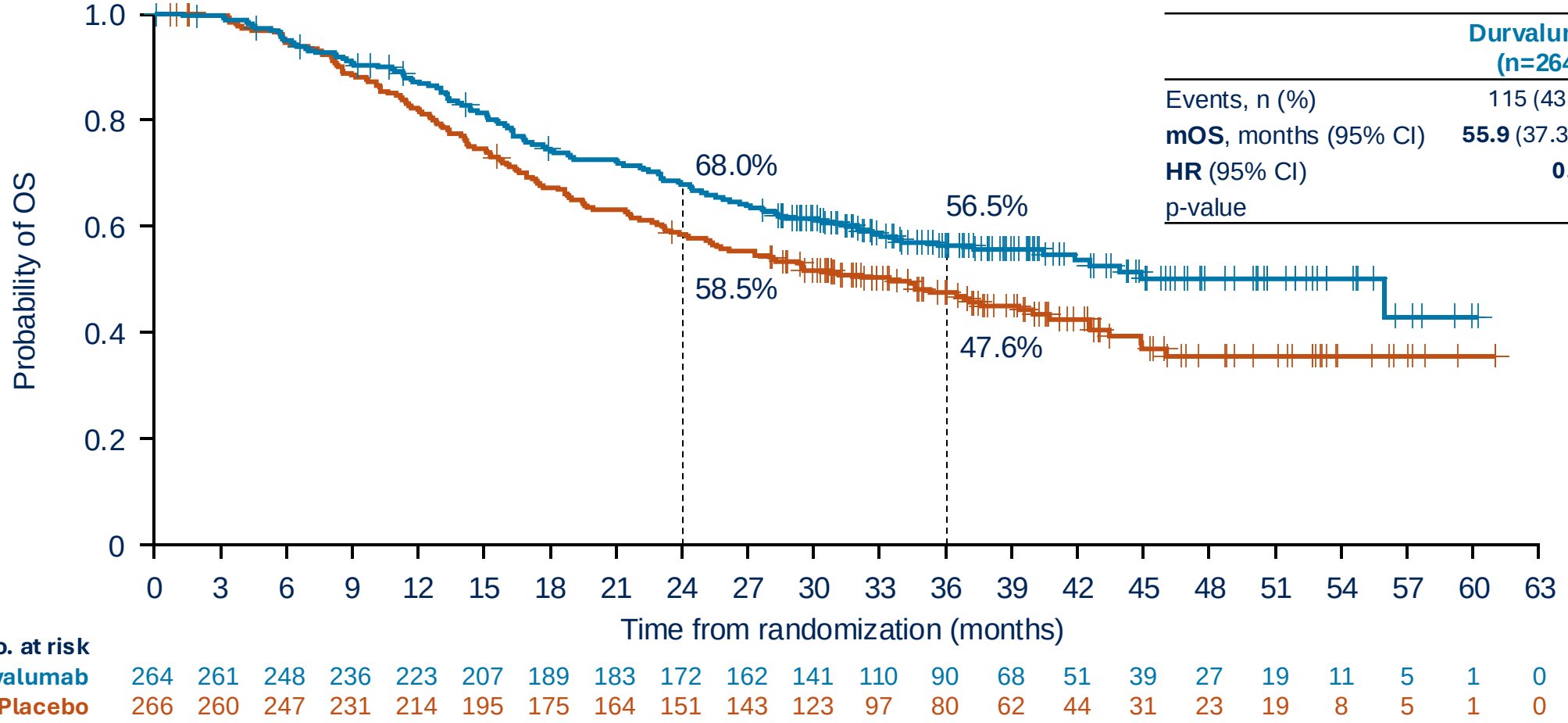
BICR, blinded independent central review; BID, twice daily; CT, chemotherapy; D, durvalumab; PCI, prophylactic cranial irradiation; PS, performance status; Q4W, every 4 weeks; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; RT, radiotherapy; T, tremelimumab; WHO, World Health Organization.

‡The first 600 patients were randomized in a 1:1:1 ratio to the 3 treatment arms; subsequent patients were randomized 1:1 to either durvalumab or placebo.

Slide credit: Spigel, D (ASCO 2024)

Overall survival

- Median duration of follow up in censored patients: 37.2 months (range 0.1–60.9)



	Durvalumab (n=264)	Placebo (n=266)
Events, n (%)	115 (43.6)	146 (54.9)
mOS, months (95% CI)	**55.9** (37.3–NE)	**33.4** (25.5–39.9)
HR (95% CI)	**0.73** (0.57–0.93)	
p-value	0.0104	

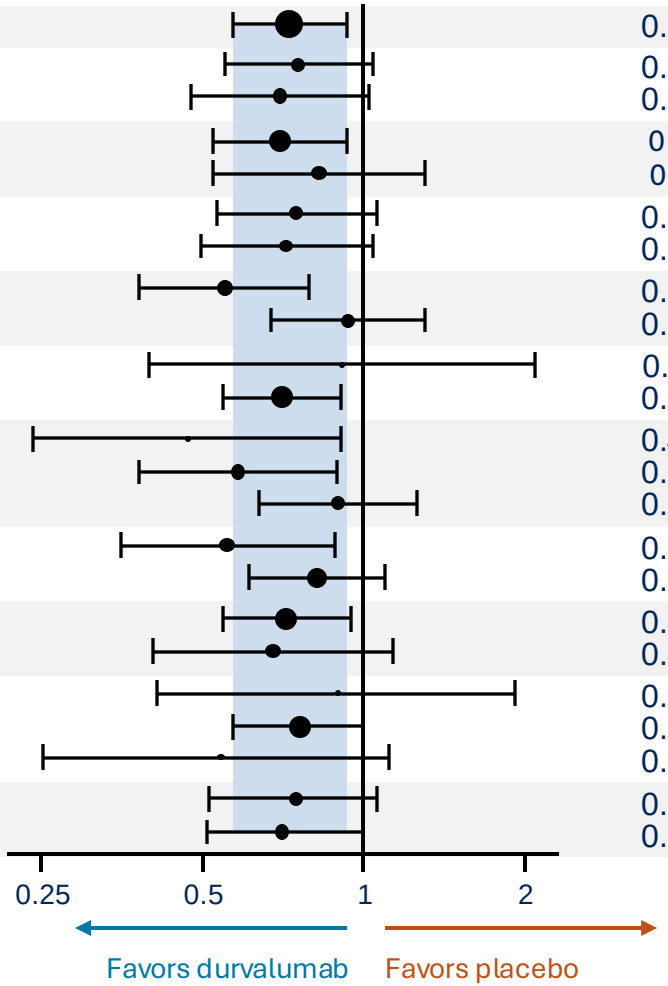
No. at risk																					
Durvalumab	264	261	248	236	223	207	189	183	172	162	141	110	90	68	51	39	27	19	11	5	1	0
Placebo	266	260	247	231	214	195	175	164	151	143	123	97	80	62	44	31	23	19	8	5	1	0

OS was analyzed using a stratified log-rank test adjusted for receipt of PCI (yes vs no). The significance level for testing OS at this interim analysis was 0.01679 (2-sided) at the overall 4.5% level, allowing for strong alpha control across interim and final analysis timepoints.

Slide credit: Spigel, D (ASCO 2024)

OS subgroup analysis

		Events/Patients n/N Durvalumab	Placebo	HR (95% CI)
All patients		115/264	146/266	0.73 (0.57–0.93)
Age	<65 years	69/160	83/162	0.76 (0.55–1.04)
	≥65 years	46/104	63/104	0.70 (0.48–1.02)
Sex	Male	79/178	108/188	0.70 (0.52–0.93)
	Female	36/86	38/78	0.83 (0.52–1.31)
Race	White	60/130	77/137	0.75 (0.53–1.05)
	Asian	53/131	64/121	0.72 (0.50–1.04)
WHO performance status	0	48/133	74/131	0.55 (0.38–0.79)
	1	67/131	72/135	0.94 (0.67–1.31)
AJCC disease stage at diagnosis	I/II	11/33	12/34	0.92 (0.40–2.11)
	III	104/231	134/232	0.71 (0.55–0.91)
Time from end of cCRT* to randomization	<14 days	14/32	24/32	0.47 (0.24–0.91)
	≥14 days to <28 days	37/79	51/80	0.59 (0.38–0.90)
	≥28 days	64/153	71/154	0.90 (0.64–1.27)
Prior chemotherapy regimen	Carboplatin-etoposide	31/ 91	46/88	0.56 (0.35–0.89)
	Cisplatin-etoposide	84/173	100/178	0.82 (0.61–1.10)
Prior radiation schedule	Once daily	92/195	107/187	0.72 (0.55–0.95)
	Twice daily	23/69	39/79	0.68 (0.40–1.14)
Best response to prior cCRT	Complete response	12/31	15/34	0.90 (0.41–1.92)
	Partial response	88/191	116/200	0.76 (0.57–1.00)
	Stable disease	15/42	15/32	0.54 (0.25–1.13)
Prior PCI	Yes	53/142	67/143	0.75 (0.52–1.07)
	No	62/122	79/123	0.71 (0.51–0.99)

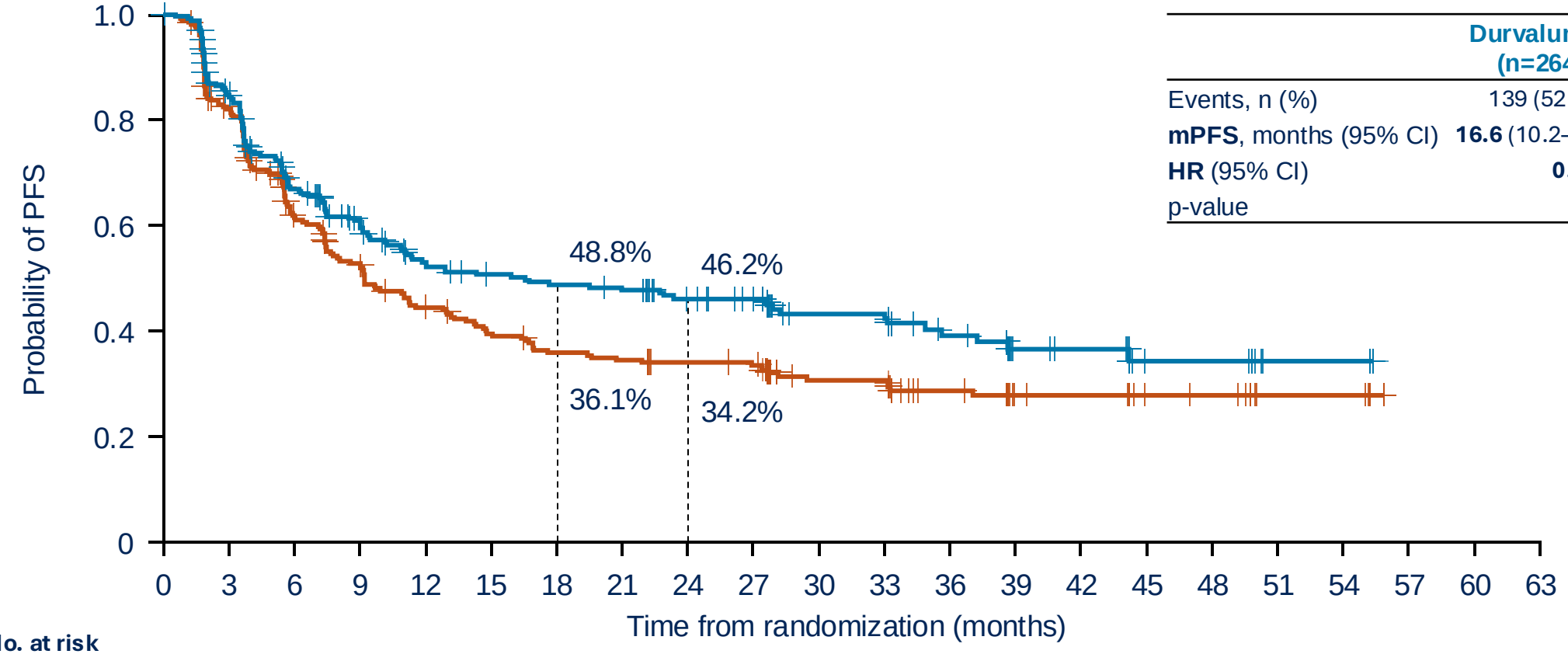


*End of chemotherapy or radiotherapy, whichever was latest.
Intention-to-treat analysis stratified, subgroup analyses unstratified. Not all prespecified subgroups are included in the plot.
Size of circle is proportional to number of events across both arms.

Slide credit: Spigel, D (ASCO 2024)

Progression-free survival

- Median duration of follow up in censored patients: 27.6 months (range 0.0–55.8)



	Durvalumab (n=264)	Placebo (n=266)
Events, n (%)	139 (52.7)	169 (63.5)
mPFS, months (95% CI)	**16.6** (10.2–28.2)	**9.2** (7.4–12.9)
HR (95% CI)	**0.76** (0.61–0.95)	
p-value	0.0161	

No. at risk																						
Durvalumab	264	212	161	135	113	105	101	98	84	78	51	51	33	21	19	10	10	4	4	0	0	0
Placebo	266	208	146	122	100	88	79	76	71	69	47	47	34	23	22	15	14	5	5	0	0	0

*By BICR per RECIST v1.1.

PFS was analyzed using a stratified log-rank test adjusted for disease stage (I/II vs III) and receipt of PCI (yes vs no). The significance level for testing PFS at this interim analysis was 0.00184 (2-sided) at the 0.5% level, and 0.02805 (2-sided) at the overall 5% level. Statistical significance for PFS was achieved through the recycling multiple testing procedure framework and testing at the 5% (2-sided) alpha level (adjusted for an interim and final analysis).

Slide credit: Spigel, D (ASCO 2024)

Safety summary

		Durvalumab (n=262)	Placebo (n=265)
Number of durvalumab or placebo doses	Median (range)	9.0 (1–26)	9.0 (1–26)
	Mean (standard deviation)	12.9 (9.6)	11.8 (9.2)
Any-grade all-cause AEs, n (%)		247 (94.3)	234 (88.3)
Maximum grade 3/4 AEs		64 (24.4)	64 (24.2)
Serious AEs		78 (29.8)	64 (24.2)
AEs leading to treatment discontinuation		43 (16.4)	28 (10.6)
AEs leading to death		7 (2.7)	5 (1.9)
Treatment-related* AEs leading to death		2 (0.8)‡	0
Any-grade immune-mediated AEs†		84 (32.1)	27 (10.2)
Maximum grade 3/4 immune-mediated AEs		14 (5.3)	4 (1.5)

Includes AEs with an onset date following first dose of study treatment, or pre-treatment AEs that increased in severity following first dose of study treatment, through to 90 days after last dose or until start of the first subsequent systemic anticancer therapy (whichever occurred first).
*Assessed by investigator. †Defined as an AE of special interest (excluding infusion related/hypersensitivity/anaphylactic reaction) that is consistent with an immune-mediated mechanism that required treatment with systemic corticosteroids, other immunosuppressants, or endocrine therapy. ‡Causes of death were encephalopathy and pneumonitis.

Slide credit: Spigel, D (ASCO 2024)

Conclusions

- Durvalumab as consolidation treatment after cCRT demonstrated statistically significant and clinically meaningful improvement in OS and PFS compared with placebo in patients with LS-SCLC

- Durvalumab consolidation treatment for up to 2 years was well tolerated, and safety findings were consistent with the known safety profile of durvalumab monotherapy in the post-cCRT setting

ADRIATIC supported consolidation durvalumab as a new standard of care for patients with LS-SCLC who have not progressed after cCRT

Slide credit: Spigel, D (ASCO 2024)

Updated NCCN Guidelines

PRIMARY OR ADJUVANT THERAPY FOR LIMITED STAGE SCLC:

Four cycles of cytotoxic chemotherapy are recommended.
Planned cycle length should be every 21–28 days during concurrent RT.
During cytotoxic chemotherapy + RT, cisplatin/etoposide is recommended (category 1).
The use of myeloid growth factors is not recommended during concurrent cytotoxic chemotherapy therapy plus RT (category 1 for not using GM-CSF).[1]

Preferred Regimens

- **Cisplatin 75 mg/m^2 day 1 and etoposide 100 mg/m^2 days 1, 2, 3[2]**
- **Cisplatin 60 mg/m^2 day 1 and etoposide 120 mg/m^2 days 1, 2, 3[3]**
- **Consolidation Therapy**
  - **Durvalumab 1500 mg day 1 every 28 days[a,4]**

Ongoing LS-SCLC phase 3 trials

DelLphi-306 (NCT06117774) : chemoRT-> Tarlatamab

NGR-LU005 (NCT03811002): chemoRT +/- Atezolizumab

HLX10-020-SCLC302 (NCT05353257): chemoRT +/- Serplulimab

Keylynk-013 (NCT04624204): (chemoRT+pembro-> pembro+/- Olaparib vs. chemoRT)

Overview

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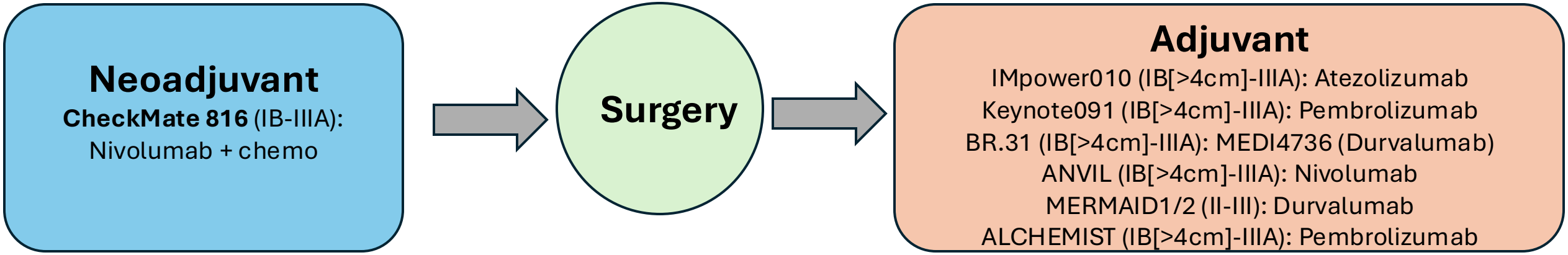
ADRIATIC (Durvalumab)

NSCLC

Early Stage: CheckMate 77T and CheckMate 816 (Nivolumab)

Advanced: HARMONi-A and HARMONi-2 (Ivonescimab)

Ongoing phase III clinical trials of perioperative immunotherapy in operable NSCLC



Perioperative

Keynote 671 (II-IIIB): Neoadjuvant Pembrolizumab + chemo; Adjuvant Pembrolizumab
CheckMate 77T (II-IIIB): Neoadjuvant Nivolumab + chemo; Adjuvant Nivolumab
IMpower 030 (II-IIIB): Neoadjuvant Atezolizumab + chemo; Adjuvant Atezolizumab
AEGEAN (IIA-IIIB): Neoadjuvant Durvalumab+chemo; Adjuvant Durvalumab
RATIONALE 315 (II-IIIA): Neoadjuvant Tislelizumab + chemo; Adjuvant Tislelizumab
JS001-029 (IIIA): Neoadjuvant Toripalimab + chemo; Adjuvant Toripalimab
NCT05157776 (IIIA): Neoadjuvant Sintilimab + chemo; Adjuvant Sintilimab

2024 World Conference on Lung Cancer
SEPTEMBER 7-10, 2024 | SAN DIEGO, CA USA

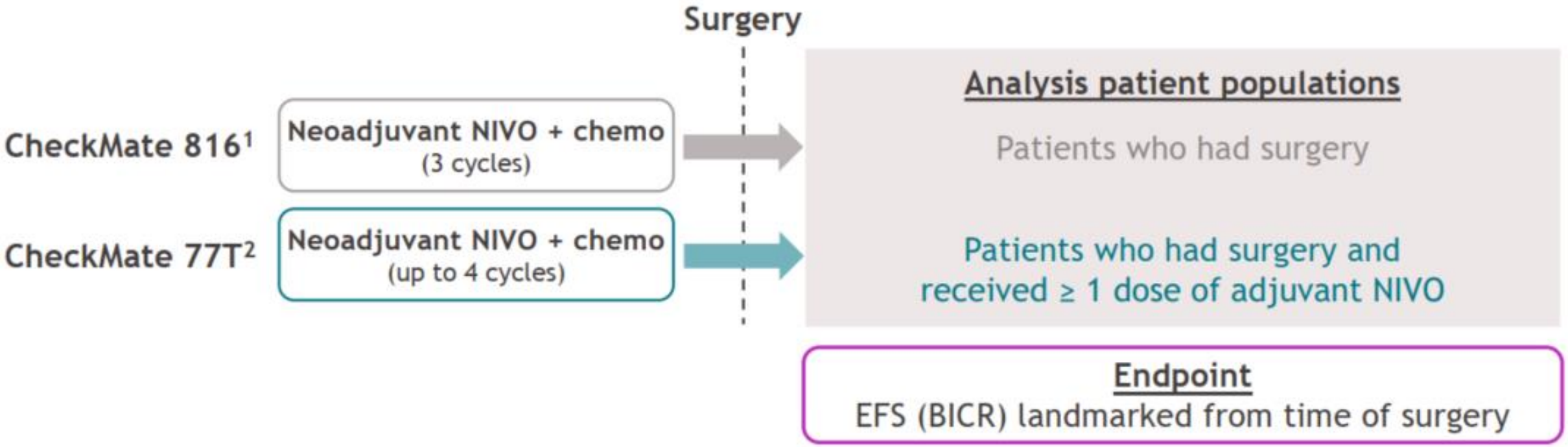
Perioperative vs neoadjuvant nivolumab for resectable NSCLC: patient-level data analysis of CheckMate 77T vs CheckMate 816

Patrick M. Forde,[1] Solange Peters,[2] Jessica Donington,[3] Stephanie Meadows-Shropshire,[4] Phuong Tran,[4] Stefano Lucherini,[5] Cinthya Coronado Erdmann,[6] Hong Sun,[6] Tina Cascone[7]

[1]The Bloomberg-Kimmel Institute for Cancer Immunotherapy, The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins Medicine, Baltimore, MD, USA; [2]Lausanne University Hospital, Lausanne, Switzerland; [3]The University of Chicago, Chicago, IL, USA; [4]Bristol Myers Squibb, Princeton, NJ, USA; [5]Bristol Myers Squibb, Uxbridge, UK; [6]Bristol Myers Squibb, Boudry, Switzerland; [7]The University of Texas MD Anderson Cancer Center, Houston, TX, USA

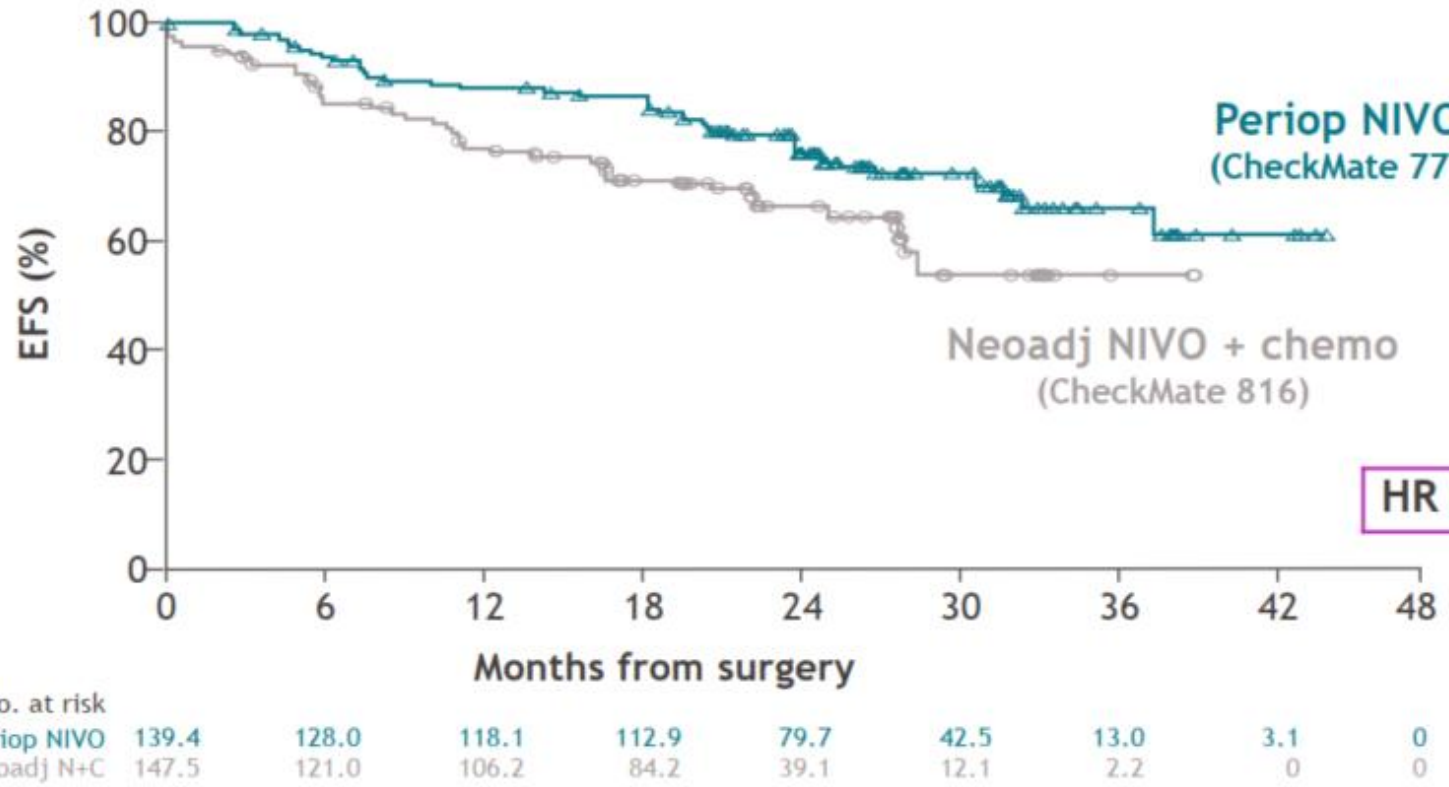
Slide credit: Forde P (WCLC 2024)

Perioperative NIVO vs neoadjuvant NIVO +chemo



Slide credit: Forde P (WCLC 2024)

EFS

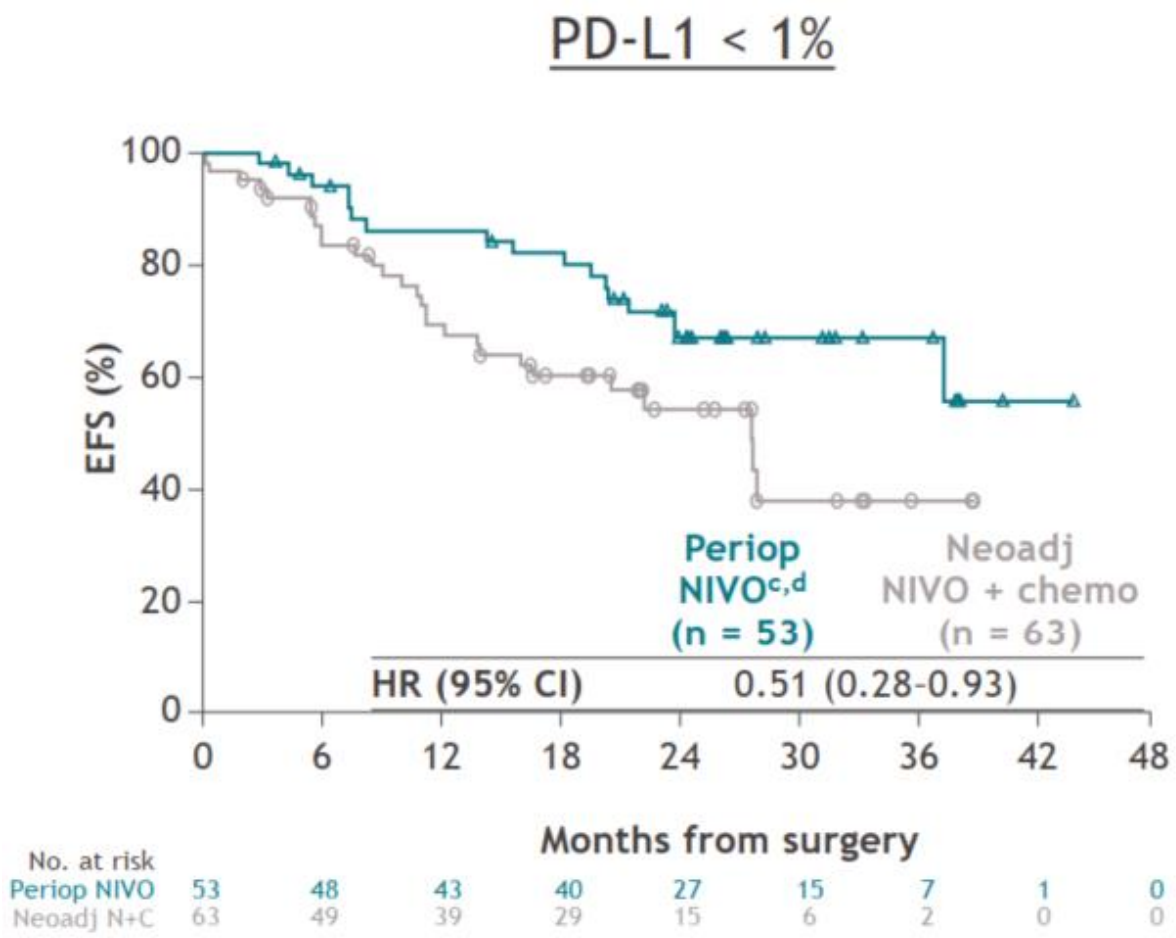


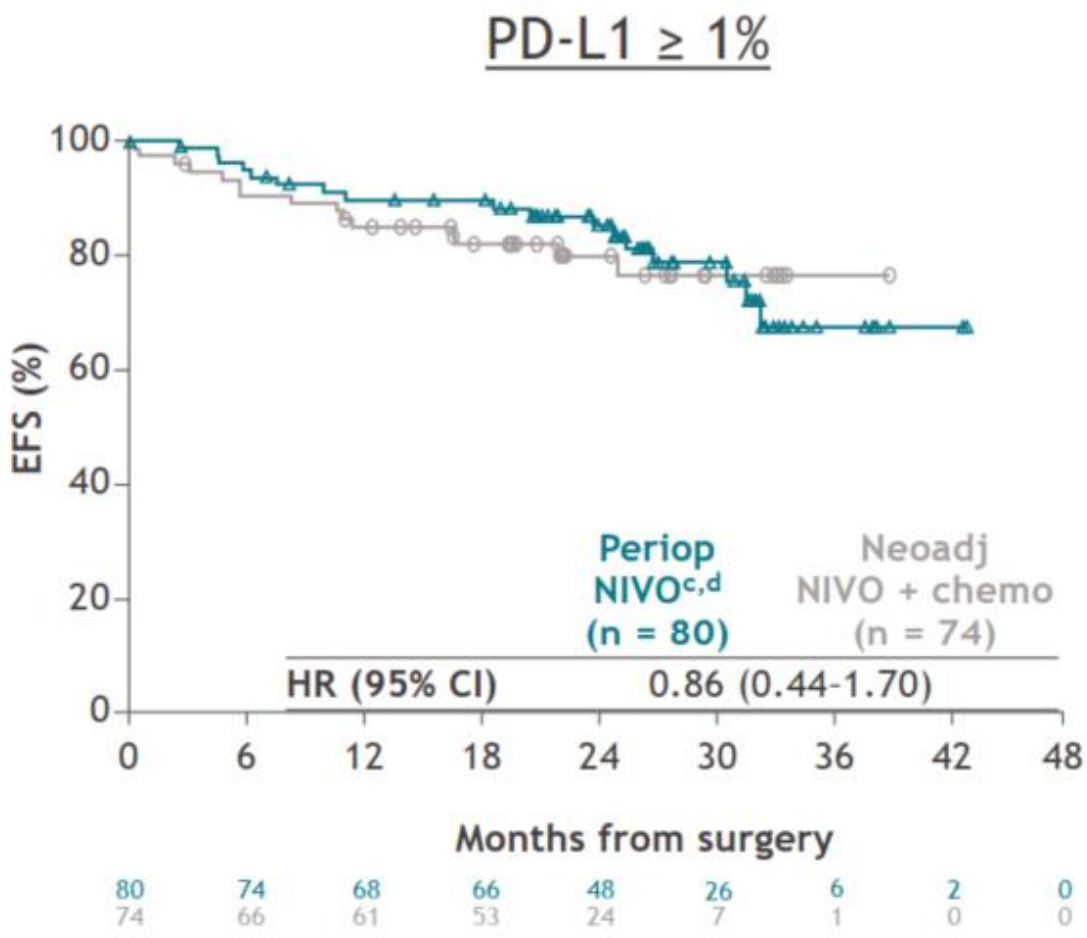
	Weighted (ATE)[b]	
	Periop NIVO[a] (n = 139.4[c])	Neoadj NIVO + chemo (n = 147.5[c])
HR (95% CI)	0.61 (0.39-0.97)	

- HR (95% CI): ATT[d] weighted analysis, 0.56 (0.35-0.90); unweighted analysis, 0.59 (0.38-0.92)

Slide credit: Forde P (WCLC 2024)

EFS by PD-L1 expression





Slide credit: Forde P (WCLC 2024)

Safety

Patients, n (%)	Perioperative NIVO (n = 139)		Neoadjuvant NIVO + chemo (n = 147)	
	Any grade[b]	Grade 3-4[b]	Any grade[c]	Grade 3-4[c]
All AEs	137 (99)	64 (46)	138 (94)	63 (43)
TRAEs	130 (94)	38 (27)	125 (85)	52 (35)
All AEs leading to discontinuation	29 (21)	10 (7)	16 (11)	8 (5)
TRAEs leading to discontinuation	22 (16)	9 (6)	16 (11)	8 (5)
All SAEs	57 (41)	37 (27)	23 (16)	16 (11)
Treatment-related SAEs	23 (16)	14 (10)	17 (12)	13 (9)
Surgery-related AEs[d]	53 (38)	15 (11)	61 (42)	17 (12)
Treatment-related deaths[e]	0		0	

Slide credit: Forde P (WCLC 2024)

Summary

- In the absence of a randomized-controlled trial, this analysis represents the only comparison of perioperative vs neoadjuvant-only immunotherapy treatments for patients with resectable NSCLC, using individual patient-level data from 2 randomized phase 3 trials
- Approximately 40% reduction in risk of disease recurrence or death after surgery was observed in patients who received ≥ 1 dose of adjuvant NIVO following neoadjuvant NIVO + chemo
- These results further support perioperative NIVO as a treatment option for eligible patients with resectable NSCLC

Slide credit: Forde P (WCLC 2024)

NCCN guideline update

Neoadjuvant

-**Nivolumab** 360 mg and platinum-based doublet chemotherapy every 3 weeks for 3 cycles

Perioperative

-**Pembrolizumab** 200 mg and cisplatin-based doublet chemotherapy every 3 weeks for 4 cycles and then continued as single-agent pembrolizumab as adjuvant treatment after surgery (category 1)

-**Durvalumab** 1500 mg and platinum-based doublet chemotherapy every 3 weeks for 4 cycles and then continued as single-agent durvalumab as adjuvant treatment after surgery (category 1)

Trial	Stage	Treatment	Control	Primary Endpoint	Primary Outcome
Neoadjuvant CheckMate 816	IB-IIIA	Nivolumab + chemotherapy x 3 cycles	Chemotherapy	EFS	EFS: 31.6 vs. 20.8months
Adjuvant IMpower010	IB[>4cm]-IIIA	Chemotherapy -> Atezolizumab 16 cycles	Chemotherapy ->Observation	DFS	DFS: HR=0·81 (0·67–0·99)
Keynote091	IB[>4cm]-IIIA	Chemotherapy (optional)-> Pembrolizumab 18 cycles	Chemotherapy (optional)-> ->Placebo	DFS	mDFS: 53.6 vs. 42 months (HR =0·76 [95% CI 0·63–0·91]
BR.31	IB[>4cm]-IIIA	Chemotherapy(optional)-> Durvalumab 12 months	Chemotherapy (optional) ->Placebo	DFS	N/A
ANVIL	IB[>4cm]-IIIA	Chemotherapy(optional)-> Nivolumab 16 cycles	Chemotherapy (optional)-> ->Observation	DFS, OS	N/A
MERMAID 1	II-III	Durvalumab + SoC chemotherapy	Placebo + SoC chemotherapy	DFS	N/A
MERMAID 2	II-III	Durvalumab 1 year	Placebo	DFS	N/A
ALCHEMIST	IB[>4cm]-IIIA	Chemotherapy-> Pembrolizumab 16 cycles; Or chemotherapy+ pembrolizumab 4 cycles-> pembrolizumab 12 cycles	Chemotherapy ->Observation	DFS, OS	N/A
Perioperative Keynote 671	II-IIIB	Neoadjuvant Pembrolizumab + chemotherapy 4 cycles; Adjuvant Pembrolizumab	Neoadjuvant chemotherapy; Adjuvant Placebo	EFS, OS	EFS at 24 months: 62.4% vs. 40.6% (HR=0.58, [95% CI 0.46-0.72] OS at 24 months: 80.9% vs. 77.6% (P=0.02)
CheckMate 77T	II-IIIB	Neoadjuvant Nivolumab + chemotherapy 4 cycles; Adjuvant Nivolumab	Neoadjuvant chemotherapy; Adjuvant Placebo	EFS	EFS at 18 months: 70.2% vs. 50.0% (HR=0.58, [97.36% CI 0.42-0.91]
IMpower 030	II-IIIB	Neoadjuvant Atezolizumab + chemotherapy 4 cycles; Adjuvant Atezolizumab 16 cycles	Neoadjuvant chemotherapy; Adjuvant monitoring	EFS	N/A
AEGEAN	IIA-IIIB	Neoadjuvant Durvalumab+ chemotherapy 4 cycles; Adjuvant Durvalumab 12 cycles	Neoadjuvant chemotherapy; Adjuvant Placebo	EFS, PCR	EFS at 12 months: 73.4% vs. 64.5% (HR=0.68, [95% CI 0.53-0.88] PCR: 17.2% vs. 4.3% [95% CI, 8.7 to 17.6]
RATIONALE 315	II-IIIA	Neoadjuvant Tislelizumab + chemotherapy 3-4 cycles; Adjuvant Tislelizumab up to 8 cycles	Neoadjuvant chemotherapy; Adjuvant Placebo	EFS	Median EFS was not reached at 22 months for either arm; however, a statistically significant difference in EFS (HR [95% CI], 0.56 [0.40–0.79];
JS001-029	IIIA	Neoadjuvant Toripalimab + chemotherapy 4 cycles; Adjuvant Toripalimab 13 cycles	Neoadjuvant chemotherapy; Adjuvant Placebo	MPR, EFS	N/A
NCT05157776	IIIA	Neoadjuvant Sintilimab + chemo 4 cycles;	Neoadjuvant Sintilimab + chemotherapy 2 cycles; Adjuvant: optional Sintilimab +chemotherapy 2 cycles	PCR	N/A

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SCLC

ADRIATIC (Durvalumab)

NSCLC

Early Stage: CheckMate 77T (Nivolumab)

Advanced: HARMONi-A and HARMONi-2 (Ivonescimab)

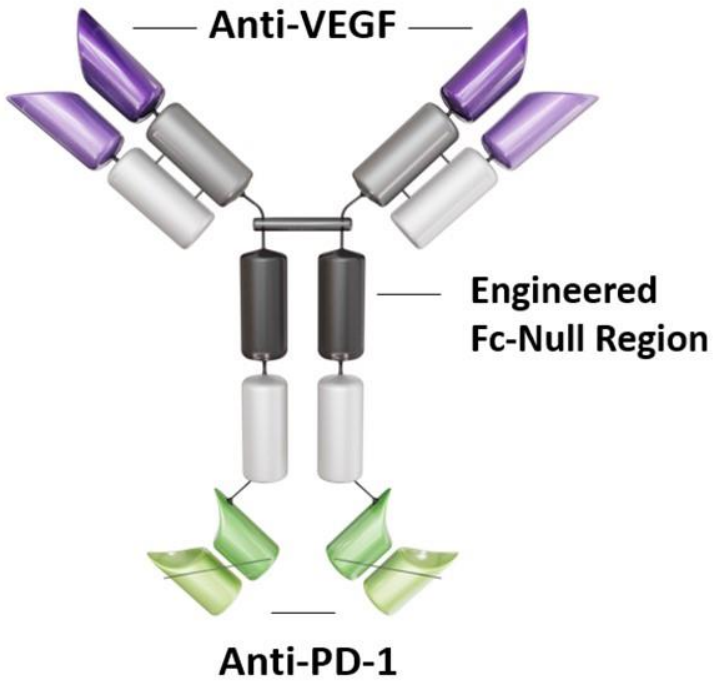
2024 ASCO ANNUAL MEETING

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)

Li Zhang[1], Wenfeng Fang[1], Yuanyuan Zhao[1], Yongzhong Luo[2], Runxiang Yang[3], Yan Huang[1], Zhiyong He[4], Hui Zhao[5], Mingjun Li[6], Kai Li[7], Qibing Song[8], Xiaobo Du[9], Yulan Sun[10], Wei Li[11], Fei Xu[12], Zhiyu Wang[13], Kunning Yang[14], Yun Fan[15], Wenting Li[16], Michelle Xia[16]

Slide credit: Zhang L (ASCO 2024)

Background

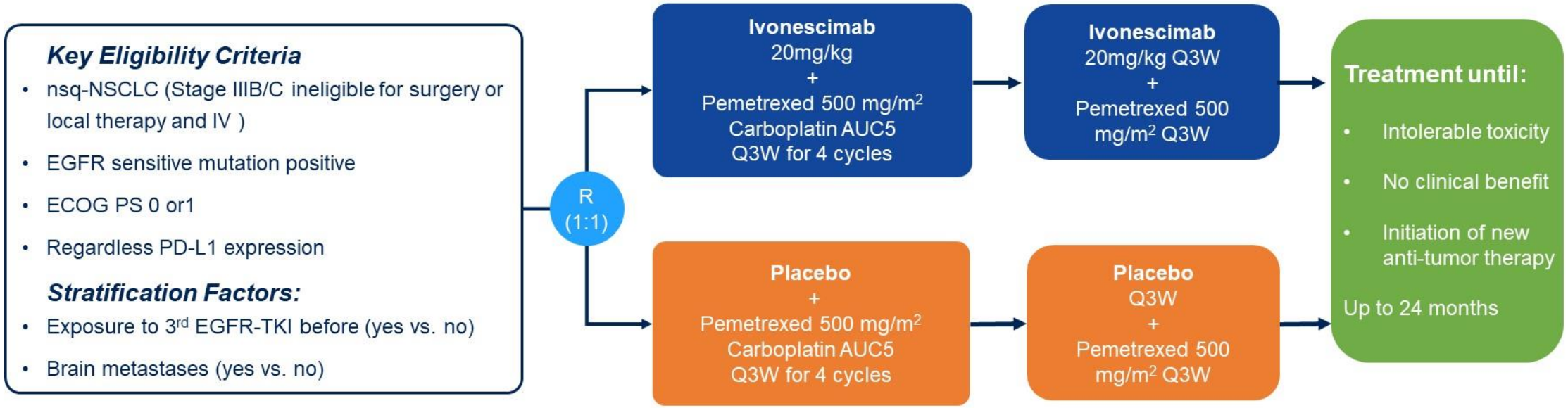


- For patients with EGFR-mutant NSCLC, upfront treatment with tyrosine kinase inhibitors is standard. However, drug resistance remains a challenge, and an effective therapy after progression is needed.
- Ivonescimab (AK112/SMT112) is an anti-PD-1/VEGF bispecific antibody displaying cooperative binding characteristics.
- Phase II clinical studies have shown potential efficacy of Ivonescimab plus chemotherapy in NSCLC patients with EGFR mutations who progressed on prior EGFR-TKIs therapies[1-2].
- This phase 3 study aimed to evaluate and confirm the efficacy and safety of ivonescimab combined with chemotherapy compared to chemotherapy alone in this population (NCT05184712).

1. L Zhang et al: ASCO 2023; 2. YY Zhao et al: eClinicalMedicine 2023;62: 102106.

Slide credit: Zhang L (ASCO 2024)

HARMONi-A Study Design

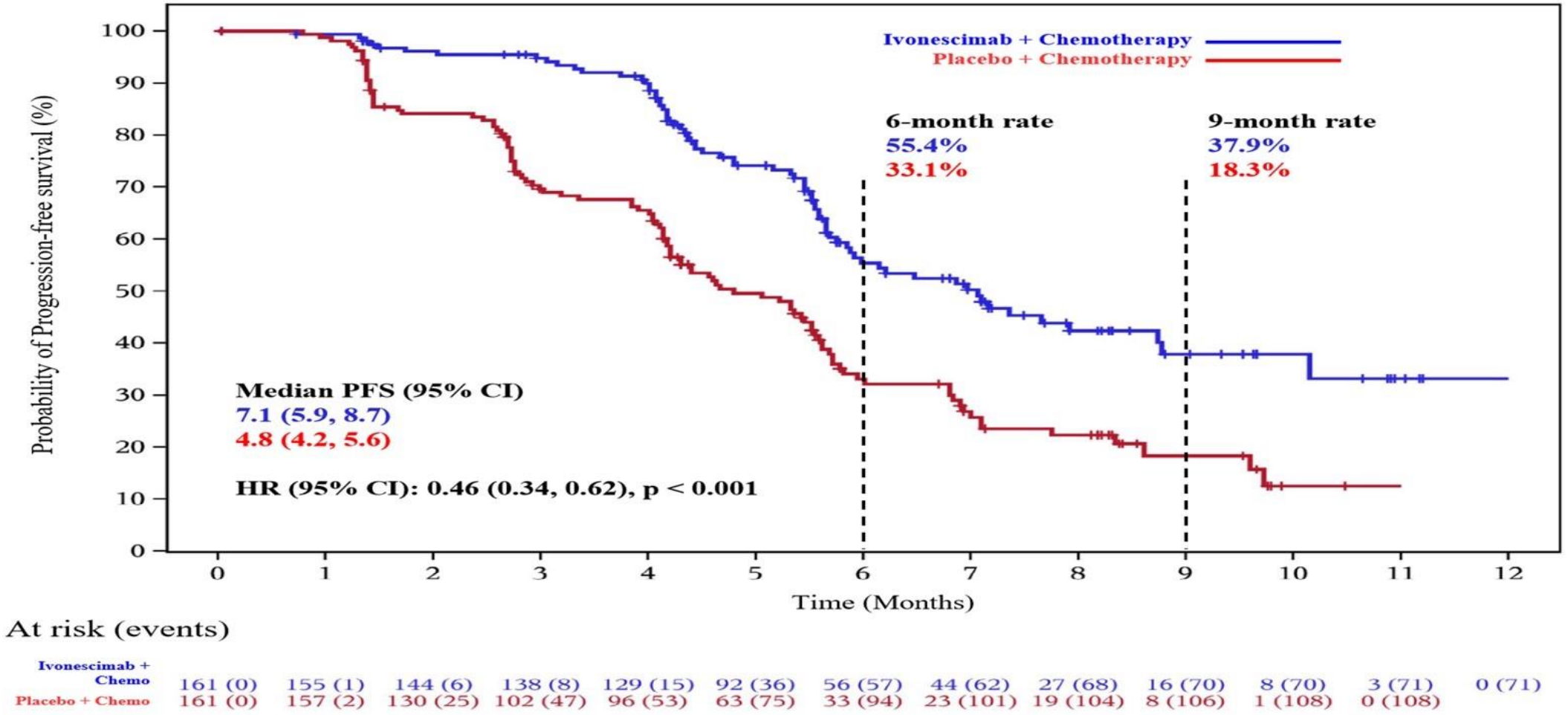


Endpoints

- Primary: Progression-free survival by independent radiologic review committee (IRRC)
- Secondary: Overall survival, Response rate, Duration of response, Time to response and Safety

Slide credit: Zhang L (ASCO 2024)

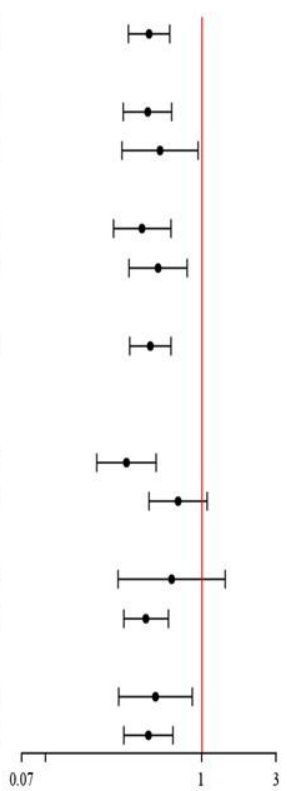
Study Met Primary Endpoint of PFS per IRRC



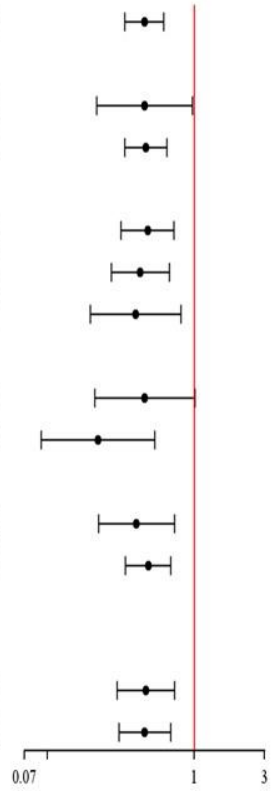
Slide credit: Zhang L (ASCO 2024)

Subgroup Analysis of PFS per IRRC

	No. of events/No. of patients		HR (95% CI)
	Ivonescimab + Chemo	Placebo + Chemo	
All Subjects	71/161	108/161	0.46 (0.34, 0.62)
Age			
<65 years	51/111	75/110	0.45 (0.31, 0.64)
>=65 years	20/50	33/51	0.54 (0.31, 0.95)
Sex			
Male	34/77	57/79	0.41 (0.27, 0.64)
Female	37/84	51/82	0.52 (0.34, 0.80)
Clinical Stage at Study Entry			
IV	69/158	105/156	0.47 (0.34, 0.63)
Number of Distant Metastasis Sites at Baseline			
<3	30/87	64/93	0.33 (0.21, 0.51)
>=3	41/74	44/68	0.70 (0.46, 1.08)
Liver Metastasis			
Presence	13/21	12/17	0.64 (0.29, 1.41)
Absence	58/140	96/144	0.44 (0.32, 0.61)
Smoking History			
Yes	23/49	31/46	0.50 (0.29, 0.87)
No	48/112	77/115	0.45 (0.32, 0.65)

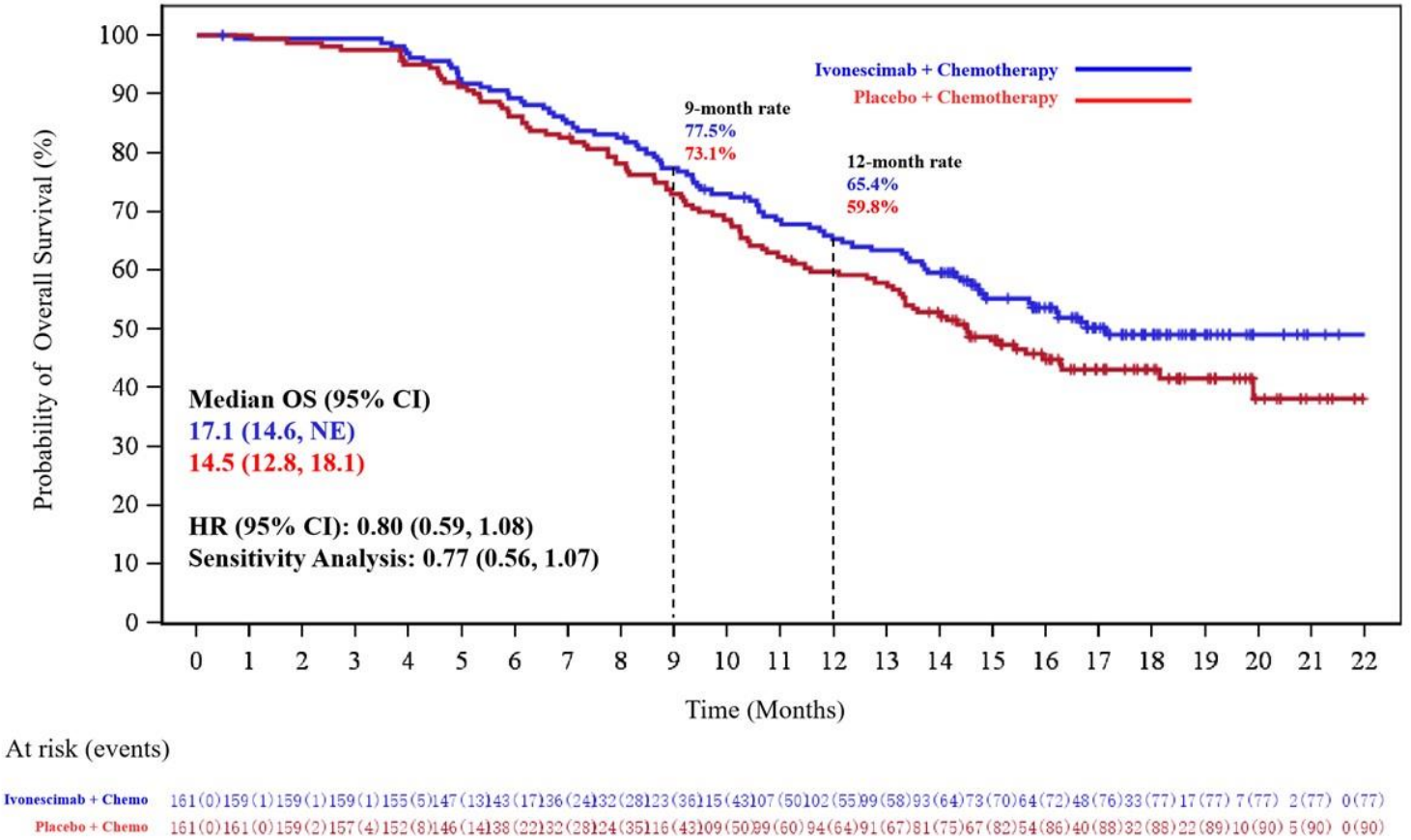


	No. of events/No. of patients		HR (95% CI)
	Ivonescimab + Chemo	Placebo + Chemo	
All Subjects	71/161	108/161	0.46 (0.34, 0.62)
Baseline ECOG Score			
0	10/24	22/34	0.46 (0.22, 0.97)
1	61/137	86/127	0.47 (0.33, 0.65)
Baseline EGFR Mutation			
19Del	39/92	53/78	0.48 (0.32, 0.73)
L858R	29/60	54/78	0.43 (0.27, 0.67)
Other	15/35	17/25	0.40 (0.20, 0.81)
T790M Mutation Status			
Negative	10/26	17/27	0.46 (0.21, 1.01)
Positive	12/26	13/18	0.22 (0.09, 0.54)
Baseline Brain Metastasis			
Presence	19/35	28/37	0.40 (0.22, 0.73)
Absence	52/126	80/124	0.48 (0.34, 0.69)
Previously Received EGFR-TKI Treatment			
One Line	30/71	52/82	0.47 (0.30, 0.73)
Two or More Lines	41/90	56/79	0.46 (0.31, 0.69)



Slide credit: Zhang L (ASCO 2024)

Overall Survival (at 52% of Data Maturity)



HR: 0.80 (0.59, 1.08) after 52% of data maturity

OS is consistent for both analysis

Data cutoff date: December 2023 (median follow-up of 17.6 months)

HR, hazard ratio; CI, confidence interval.

Slide credit: Zhang L (ASCO 2024)

Safety Summary

TRAE, n(%)	Ivonescimab + Chemotherapy (N=161)	Placebo + Chemotherapy (N=161)
Any grade	158 (98.1)	153 (95.0)
Grade≥3	87 (54.0)	69 (42.9)
Serious*	46 (28.6)	26 (16.1)
Led to discontinuation of ivonescimab/placebo	9 (5.6)	4 (2.5)
Led to death	0 (0.0)	0 (0.0)
Grade≥3 immune-related	10 (6.2)	4 (2.5)
Grade≥3 VEGF-related	5 (3.1)	4 (2.5)

* For any PT (excluding PD) in SAE, the PT with more than 2 cases in the experimental group compared to the control group were platelet count decreased (7.5% vs. 4.3%) and hepatic function abnormal (2.5% vs. 0%).
TRAE, treatment-related adverse event (related to any drug); PT, preferred term; PD, disease progression; SAE, serious adverse event.

Slide credit: Zhang L (ASCO 2024)

Conclusions

- Ivonescimab plus chemotherapy significantly improved PFS in patients who progressed on prior EGFR-TKIs treatments: **PFS HR 0.46 (95% CI: 0.34, 0.62), P<0.001**
- The prespecified subgroup analysis showed PFS benefit favoring patients receiving ivonescimab over those receiving the placebo across all subgroups.
- OS analyses show a favorable trend for prolonged OS for ivonescimab-chemotherapy
- The safety profile was generally manageable, without any unexpected adverse events and a low rate of treatment discontinuation.
- This study is being expanded globally, HARMONi (NCT06396065), to include patients from North America and Europe.

With the recent approval in China, ivonescimab plus chemotherapy is a new standard treatment option for NSCLC patients who progress after EGFR-TKI treatment

Slide credit: Zhang L (ASCO 2024)

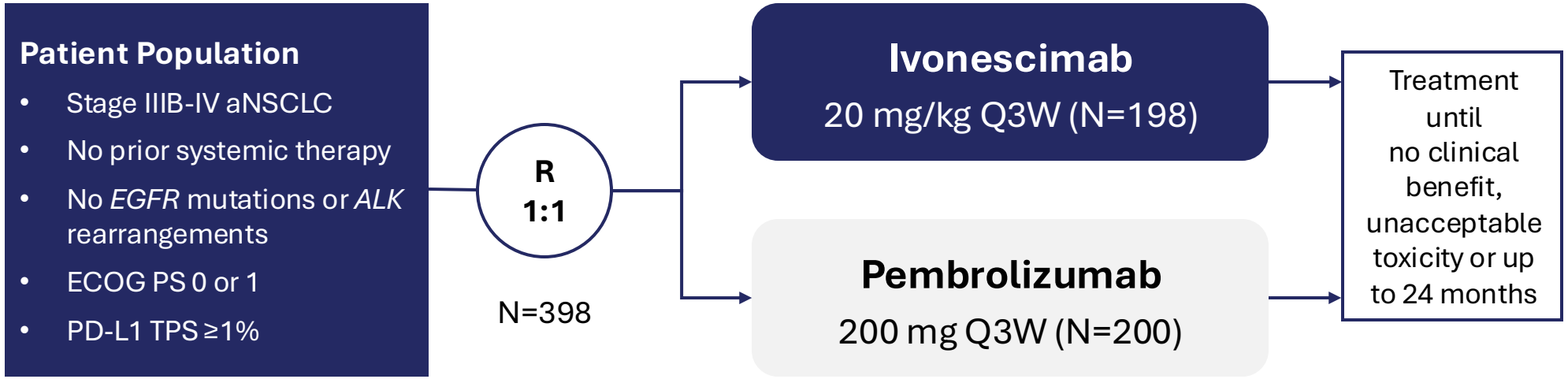
Phase 3 Study of Ivonescimab (AK112) vs. Pembrolizumab as First-line Treatment for PD-L1-positive Advanced NSCLC: Analysis of HARMONi-2

C. Zhou[1,2], J. Chen[3], L. Wu[3], L. Wang[1], A. Xiong[1], B. Liu[4], J. Yao[5], H. Zhong[6], J. Li[7], Y. Cheng[8], Y. Sun[9], H. Ge[10], Q. Shi[11], M. Zhou[12], Z. Han[13], J. Wang[14], Q. Bu[15], Y. Zhao[16], J. Chen[17], J. Yang[18], M. Xia[18]

Slide credit: Zhou C (WCLC 2024)

HARMONi-2 Study Design

A randomized, double-blind, phase 3 study



Stratification

- Clinical stage (IIIB/C vs. IV)
- Histology (SQ vs. non-SQ)
- PD-L1 TPS (≥50% vs. 1-49%)

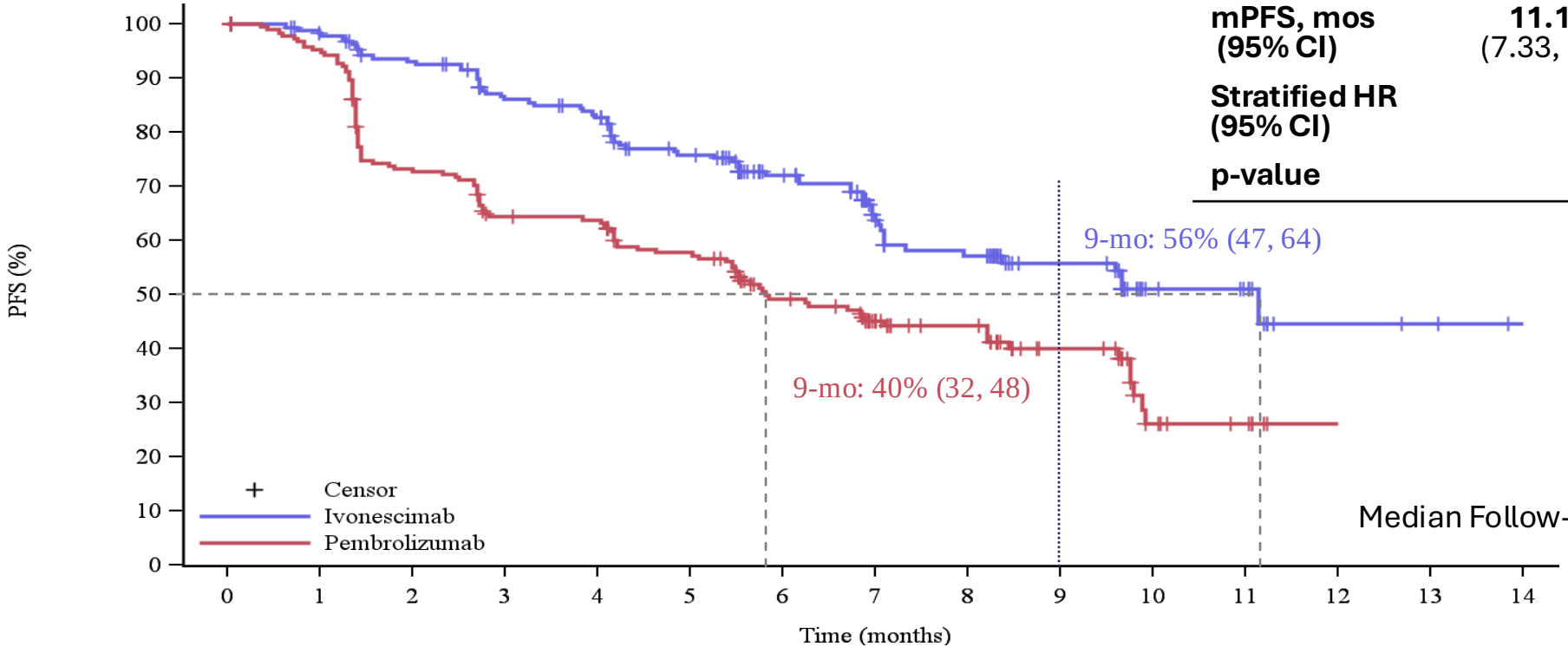
Endpoints

Primary: PFS by blind IRRC per RECIST v1.1
Secondary: OS, PFS assessed by INVs, ORR, DoR, TTR and safety
Exploratory: QoL

Slide credit: Zhou C (WCLC 2024)

PFS

	Ivonescimab (n = 198)	Pembrolizumab (n = 200)
mPFS, mos (95% CI)	**11.14** (7.33, NE)	5.82 (5.03, 8.21)
Stratified HR (95% CI)	**0.51** (0.38, 0.69)	
p-value	**<0.0001**	



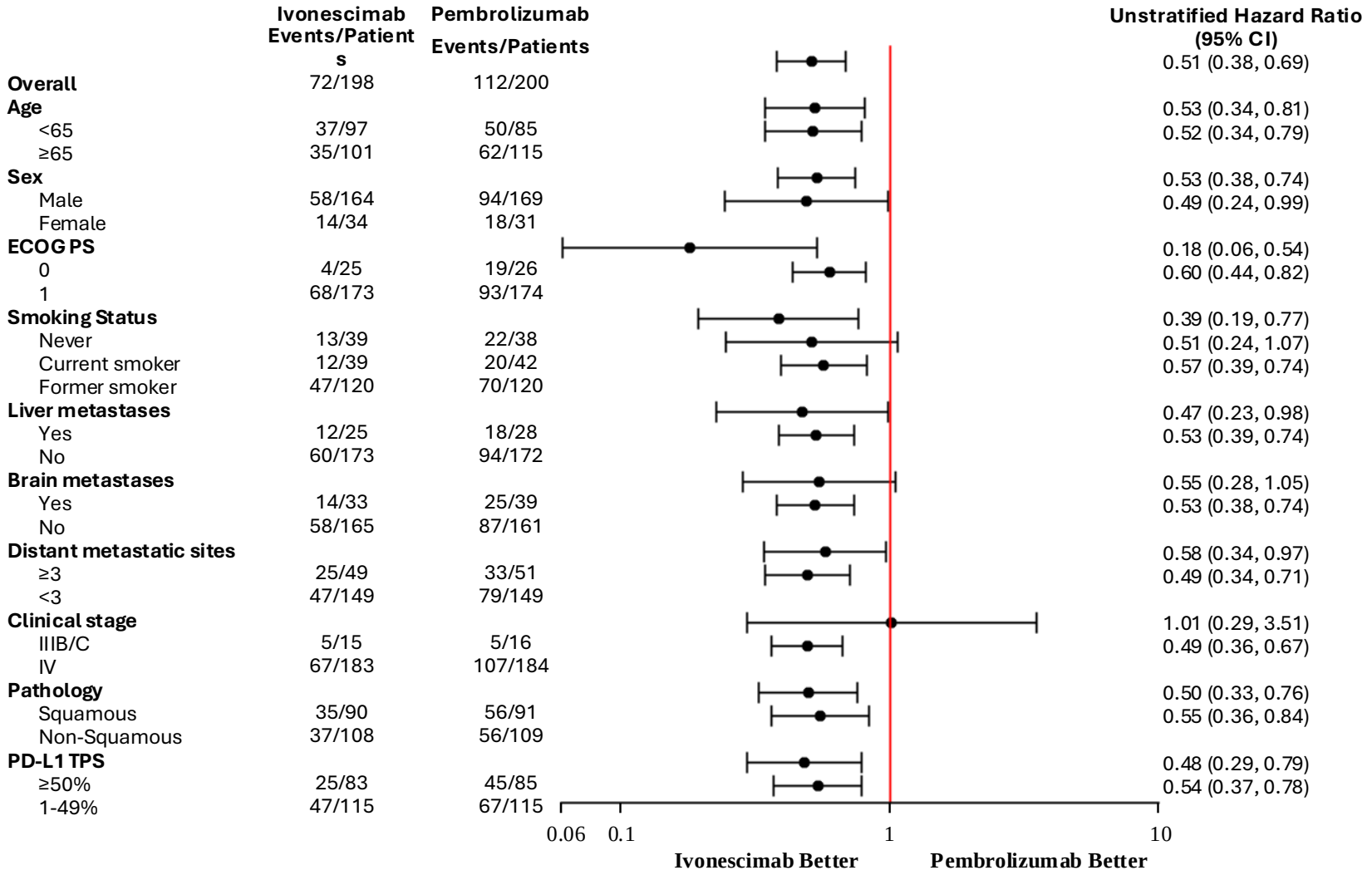
Median Follow-up: 8.67 months

Number at risk (Events)

Ivonescimab	198(0)	189(3)	175(13)	156(26)	148(32)	128(44)	99(50)	68(60)	59(67)	38(68)	14(71)	11(71)	3(72)	2(72)	0(72)
Pembrolizumab	200(0)	187(9)	141(52)	121(69)	119(70)	103(81)	74(95)	53(101)	45(102)	25(106)	9(112)	5(112)	0(112)		

Slide credit: Zhou C (WCLC 2024)

PFS Subgroup

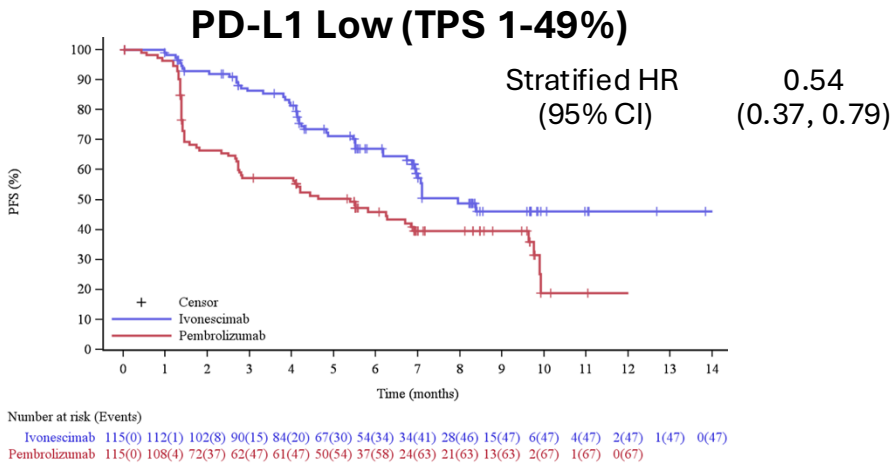


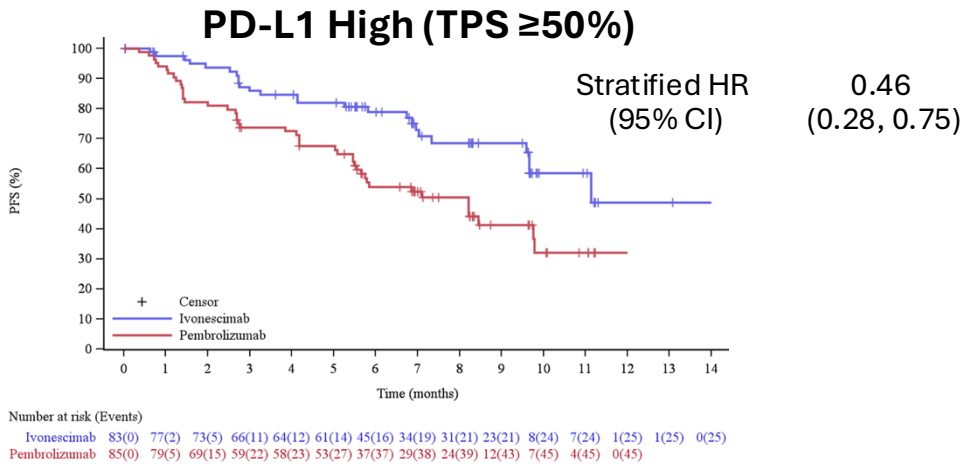
SQ, squamous cell carcinoma;

Slide credit: Zhou C (WCLC 2024)

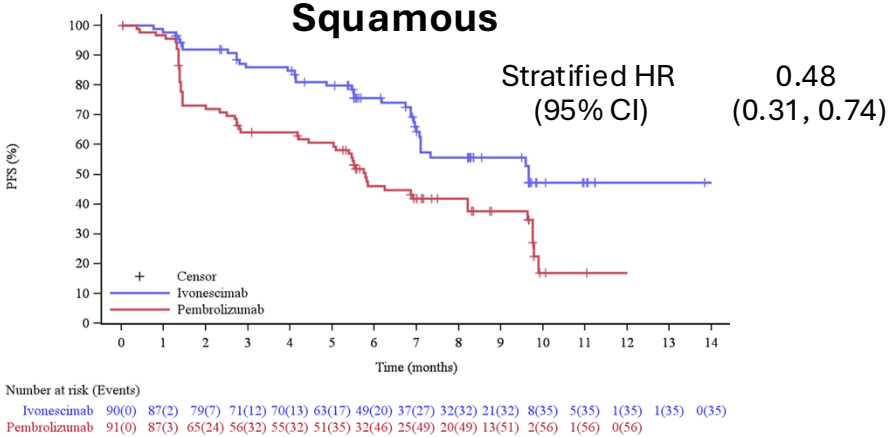
Key PFS Subgroup

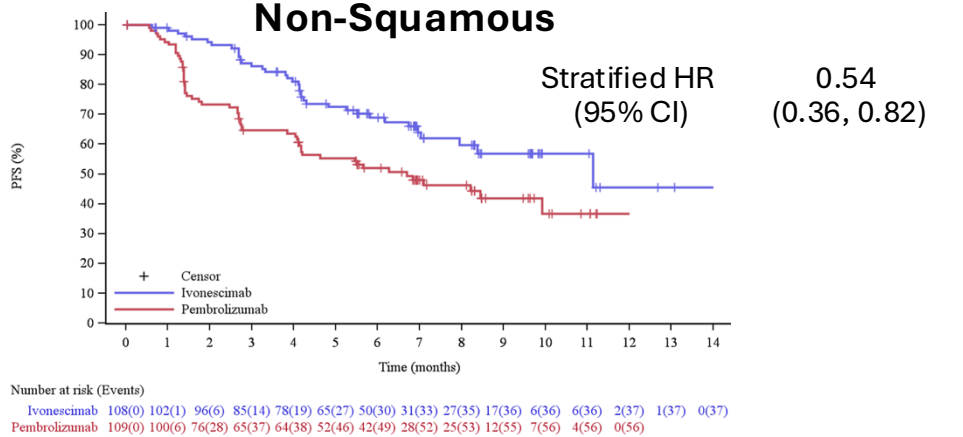
PD-L1 expression





NSCLC Histology





Slide credit: Zhou C (WCLC 2024)

Safety Summary

Safety Summary, n (%)	Ivonescimab (n = 197[a])	Pembrolizumab (n = 199[a])
TRAEs (all grades)	177 (89.8)	163 (81.9)
Grade≥3	58 (29.4)	31 (15.6)
Serious TRAEs	41 (20.8)	32 (16.1)
Leading to discontinuation	3 (1.5)	6 (3.0)
Leading to death	1 (0.5)	2 (1.0)

Ivonescimab showed manageable safety profile, which was consistent with previous studies.

[a] Patients who received ≥1 dose of study treatment.

Slide credit: Zhou C (WCLC 2024)

Conclusions

- First-line ivonescimab significantly improve IRRC-assessed PFS in aNSCLC patients with PD-L1 TPS ≥1%, compared with pembrolizumab
- PFS benefit with ivonescimab were consistent across major clinical subgroups:
- OS was not matured at this time; the OS analysis is event-driven and will be reported in the future.
- The safety profile of ivonescimab was consistent with prior studies and well tolerated in patients with squamous cell carcinoma.

This was the first randomized phase 3 study to demonstrate a clinically significant improvement in efficacy with a novel drug compared to pembrolizumab in aNSCLC.

Ivonescimab is a novel 1st line treatment for aNSCLC patients with positive PD-L1(TPS ≥1%).

Slide credit: Zhou C (WCLC 2024)

Take home points

SCLC

-Durvalumab has emerged as the new standard consolidation therapy following cCRT in patients with LS-SCLC base on ADRIATIC.

NSCLC

Early Stage:

-Perioperative IO (nivo) demonstrates superior outcomes compared to neoadjuvant nivo alone.

-Current perioperative therapeutic options include nivo, pembro, and durva, with additional data anticipated.

Advanced:

-Awaiting additional U.S. data, but ivonescimab is anticipated to potentially replace traditional IO and become the new standard of care for first-line advanced NSCLC treatment in patients with positive PD-L1 (TPS ≥1%).

Acknowledgments

- Special thanks to Drs. Sai-Hong Ignatius Ou, Misako Nagasaka and Lei Deng for their valuable discussions and for providing some of the slides used in this presentation.