Lung Cancer UPDATES
IASLC HIGHLIGTHS
06-09 AGOSTO 2022
Viena, Austria

Iniciativa científica de:
GECP lung cancer research

Immunotherapy in advanced NSCLC

Anna Estival

Servicio Oncología médica
Hospital Universitario Insular de Gran Canaria

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Metastatic NSCLC

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VIENA

Iniciativa científica de:
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1st Line:

• **Avelumab** vs chemotherapy in advanced PDL1+ NSCLC. (JAVELIN Lung 100)

• Asociation between KRAS/STK1/KEAP1 mutations and outcomes in POSEIDON: **Durvalumab** +/- **Tremelimumab** + Chemo in mNSCLC.

2nd Line:

• Hudson: Multidrug **biomarker - directed** study in NSCLC pts progressed on anti-PDL1.

• Outcomes with second – course **pembrolizumab** in NSCLC.

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Avelumab vs chemotherapy for first-line treatment of advanced PD-L1+ NSCLC: primary analysis from JAVELIN Lung 100

Martin Reck,[1] Fabrice Barlesi,[2] James Chih-Hsin Yang,[3] Virginie Westeel,[4] Enriqueta Felip,[5] Mustafa Özgüroğlu,[6] Manuel Cobo Dols,[7] Richard Sullivan,[8] Dariusz Kowalski,[9] Zoran Andric,[10] Dae Ho Lee,[11] Ahmet Sezer,[12] Volodymyr Shamrai,[13] Zsuzsanna Szalai,[14] XiaoZhe Wang,[15] Huiling Xiong,[15*] Natalia Jacob,[16] Keyvan Tadjalli Mehr,[16] Keunchil Park[17]

[1]Airway Research Center North, German Center for Lung Research, LungenClinic, Grosshansdorf, Germany; [2]Aix-Marseille University, Gustave Roussy, Marseille, France; [3]National Taiwan University Hospital, Taipei City, Taiwan, Republic of China; [4]Hôpital Jean Minjoz, Centre Hospitalier Régional Universitaire de Besançon, Besançon, France; [5]Hospital Universitari Vall d'Hebron, Barcelona, Spain; [6]Department of Internal Medicine, Division of Medical Oncology, Cerrahpaşa Medical Faculty, Istanbul University Cerrahpaşa, Istanbul, Turkey; [7]Regional and Virgen de la Victoria University Hospitals, Málaga, Spain; [8]Auckland City Hospital, Auckland, New Zealand; [9]Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; [10]Clinical Center Bezanijska Kosa, Belgrade, Serbia; [11]Asan Medical Center, Seoul, South Korea; [12]Başkent University Adana Application and Research Center, Adana, Turkey; [13]Podilskyi Regional Oncological Center, Vinnytsia, Ukraine; [14]Petz Aladár Megyei Oktató Kórház, Győr, Hungary; [15]EMD Serono Research & Development Institute, Inc., Billerica, MA, USA, an affiliate of Merck KGaA; [16]Merck Healthcare KGaA, Darmstadt, Germany; [17]Division of Hematology-Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

*Affiliation at the time the trial was conducted.

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JAVELIN Lung 100: a multicenter, randomized, phase 3 trial

Before protocol amendment
Randomization 1:1
Stratified by histology

Post protocol amendment
Randomization 1:2:2
Stratified by histology and PD-L1 expression

Key eligibility criteria

- Metastatic or recurrent NSCLC (Stage IV)*
- No *EGFR* mutation or *ALK* rearrangement
- PD-L1 expression in ≥1% of tumor cells
- Measurable disease according to RECIST 1.1
- ECOG PS 0 or 1

Randomized patients: N=1214

Safety run-in: N=10

R1

- **Avelumab Q2W** 10 mg/kg IV **n=205**
- **Platinum-based doublet chemotherapy** Q3W **n=205**

R2

- **Avelumab Q2W** 10 mg/kg IV **n=161**
- **Platinum-based doublet chemotherapy** Q3W **n=321**
- **Avelumab QW** first 12 weeks, then Q2W 10 mg/kg IV **n=322**

Avelumab QW 10 mg/kg IV Safety run-in **N=10**

Primary endpoints

- PFS† and OS‡ in patients with high-expression PD-L1+ tumors§

Key secondary endpoints

- PFS and OS in patients with moderate-to-high-expression PD L1+ tumors¶
- OS in patients with PD L1+ ≥1% tumors
- Best overall response†
- Duration of response†
- Safety

*Patients with pretreated and stable brain metastases were eligible for enrollment. †Per independent review committee. ‡OS was changed to a primary endpoint in the protocol amendment that added the avelumab QW arm. §PD-L1 expression on ≥80% of tumor cells determined by Dako PD-L1 IHC 73-10 pharmDx assay, which is comparable to the TPS ≥50% cutoff for the PD-L1 IHC 22C3 pharmDx (pembrolizumab) assay. ¶PD-L1 expression on ≥50% of tumor cells determined by Dako PD-L1 IHC 73-10 pharmDx assay.

Grote HJ, et al. J Thorac Oncol. 2020;15(8):1306-1316.

ECOG PS, Eastern Cooperative Oncology Group performance status; **IHC**, immunohistochemistry; **IV**, intravenous; **NSCLC**, non-small cell lung cancer; **OS**, overall survival; **PFS**, progression-free survival; **QW**, once weekly; **Q2W**, every 2 weeks; **Q3W**, every 3 weeks; **R1**, randomization before protocol amendment; **R2**, randomization after protocol amendment; **TPS**, tumor proportion score.

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Randomization 1:2:2
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- ECOG PS 0 or 1

Randomized patients: N=1214

Safety run-in: N=10

R1

Avelumab Q2
10 mg/kg IV
n=205

Platinum-bas
doublet chemoth
Q3W
n=205

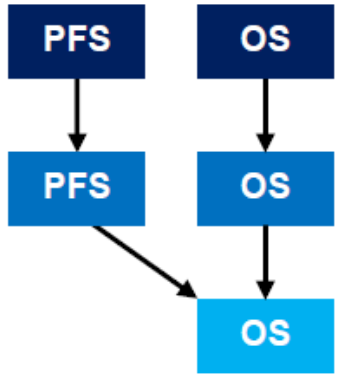
Avelum
10 mg/
Safety
N=

Hierarchical testing procedure
(Avelumab Q2W or QW vs chemotherapy)†

Step 1: High PD-L1+
(≥80% of tumor cells)

Step 2: Moderate and high PD-L1+
(≥50% of tumor cells)

Step 3: Any PD-L1+
(≥1% of tumors cells)



Steps 2 and 3 were tested only if the null hypothesis in step 1 was rejected

Primary endpoints

- PFS† and OS‡ in patients with high-expression PD-L1+ tumors§

Key secondary endpoints

- PFS and OS in patients with moderate-to-high-expression PD L1+ tumors¶
- OS in patients with PD L1+ ≥1% tumors
- Best overall response†
- Duration of response†
- Safety

*Patients with pretreated and stable brain metastases were eligible for enrollment. †Per independent review committee. ‡OS was changed to a primary endpoint in the protocol amendment that added the avelumab QW arm. §PD-L1 expression on ≥80% of tumor cells determined by Dako PD-L1 IHC 73-10 pharmDx assay, which is comparable to the TPS ≥50% cutoff for the PD-L1 IHC 22C3 pharmDx (pembrolizumab) assay. ¶PD-L1 expression on ≥50% of tumor cells determined by Dako PD-L1 IHC 73-10 pharmDx assay.

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Baseline characteristics in the high PD-L1+ populations*

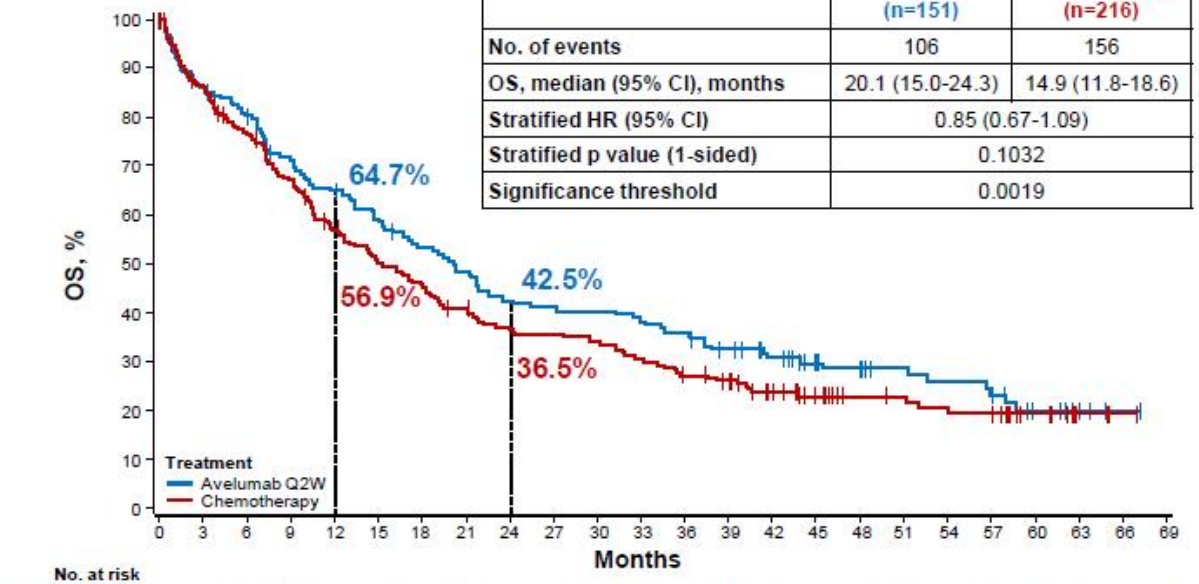
	Avelumab Q2W (n=151)	Chemotherapy (n=216)	Avelumab QW (n=130)	Chemotherapy (n=129)
Male, n (%)	112 (74.2)	158 (73.1)	100 (76.9)	93 (72.1)
Median age, years (range)	64.0 (35-82)	63.0 (29-85)	64.0 (25-80)	64.0 (36-81)
ECOG PS, n (%)†				
0	47 (31.1)	70 (32.4)	44 (33.8)	45 (34.9)
≥1	104 (68.9)	145 (67.1)	86 (66.2)	83 (64.3)
Race, n (%)				
Asian	38 (25.2)	48 (22.2)	28 (21.5)	29 (22.5)
Black or African American	0	1 (0.5)	1 (0.8)	0
White	98 (64.9)	154 (71.3)	96 (73.8)	92 (71.3)
Other	6 (4.0)	6 (2.8)	4 (3.1)	4 (3.1)
Stage at study entry, n (%)‡				
IV	150 (99.3)	215 (99.5)	130 (100.0)	129 (100.0)
History of smoking, n (%)	134 (88.7)	186 (86.1)	112 (86.2)	109 (84.5)
Non-squamous tumor histology, n (%)	104 (68.9)	150 (69.4)	84 (64.6)	86 (66.7)
Metastatic sites, n (%)				
Brain§	10 (6.6)	21 (9.7)	9 (6.9)	12 (9.3)
Visceral	59 (39.1)	70 (32.4)	55 (42.3)	44 (34.1)
Bone	28 (18.5)	49 (22.7)	40 (30.8)	30 (23.3)
Pleural effusion	41 (27.2)	61 (28.2)	34 (26.2)	41 (31.8)

Patients with missing data are not shown.
*High-expression PD-L1+ (≥80% of tumor cells) determined by Dako PD-L1 IHC 73-10 pharmDx assay (avelumab QW vs chemotherapy: in patients randomized post protocol amendment). †Patients had ECOG PS 0 or 1, except for one 1 patient in the avelumab QW arm with ECOG PS 2 (PS of this patient worsened from 1 at screening to 2 at the Week 1 Day 1 visit). ‡One patient in the chemotherapy arm had stage IIIB disease. §Patients with pretreated and stable brain metastases were eligible for enrollment.

Primary endpoint: OS in the high PD-L1+ populations*

Avelumab Q2W vs chemotherapy

	Avelumab Q2W (n=151)	Chemotherapy (n=216)
No. of events	106	156
OS, median (95% CI), months	20.1 (15.0-24.3)	14.9 (11.8-18.6)
Stratified HR (95% CI)	0.85 (0.67-1.09)	
Stratified p value (1-sided)	0.1032	
Significance threshold	0.0019	

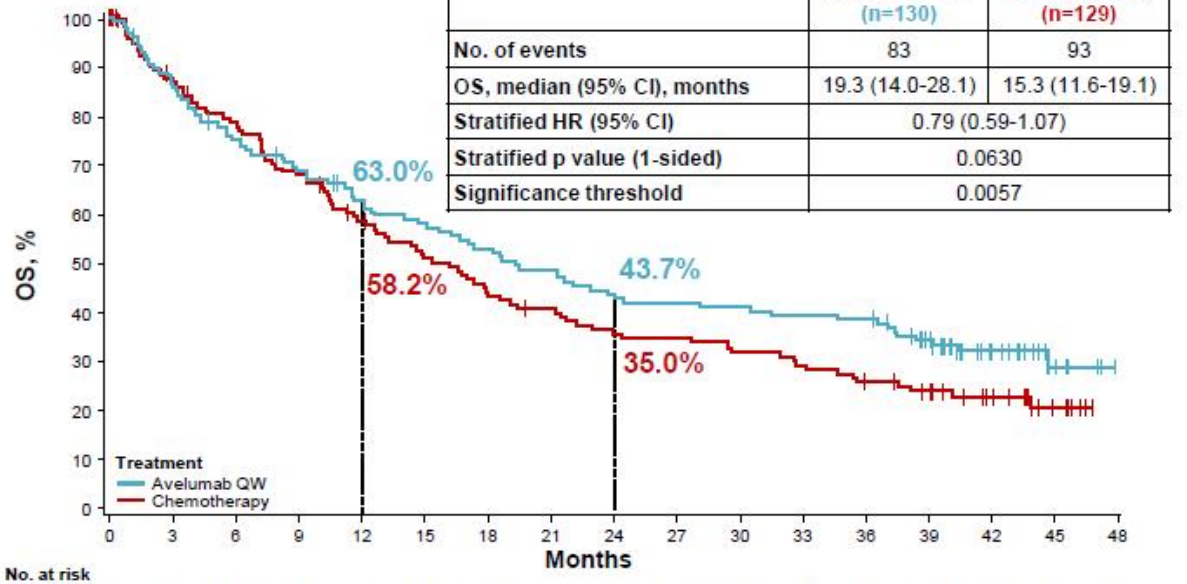


No. at risk

Avelumab Q2W	151	125	116	101	92	83	74	67	59	57	56	53	50	43	37	28	24	21	19	17	10	5	1	0
Chemotherapy	216	178	156	135	113	98	89	79	70	68	65	58	51	47	36	26	20	19	17	16	9	3	1	0

Avelumab QW vs chemotherapy

	Avelumab QW (n=130)	Chemotherapy (n=129)
No. of events	83	93
OS, median (95% CI), months	19.3 (14.0-28.1)	15.3 (11.6-19.1)
Stratified HR (95% CI)	0.79 (0.59-1.07)	
Stratified p value (1-sided)	0.0630	
Significance threshold	0.0057	



No. at risk

Avelumab QW	130	107	93	84	75	69	63	58	52	50	49	47	46	35	20	7	0						
Chemotherapy	129	107	95	82	69	59	51	46	40	39	36	33	28	24	16	6	0						

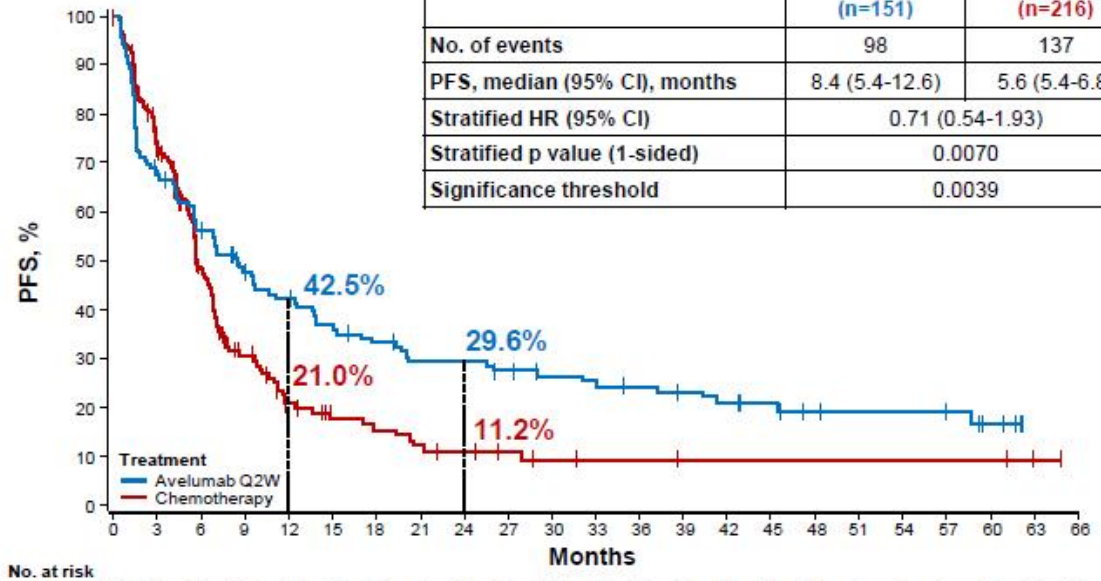
OS analyses favored avelumab vs chemotherapy but differences were not statistically significant

Median follow up in primary analysis populations across all arms was 41.7-48.8 months (data cutoff: October 15, 2021)
*High-expression PD-L1+ (≥80% of tumor cells) determined by Dako PD-L1 IHC 73-10 pharmDx assay (avelumab QW vs chemotherapy: in patients randomized post protocol amendment).

Primary endpoint: PFS by IRC in the high PD-L1+ populations*

Avelumab Q2W vs chemotherapy

	Avelumab Q2W (n=151)	Chemotherapy (n=216)
No. of events	98	137
PFS, median (95% CI), months	8.4 (5.4-12.6)	5.6 (5.4-6.8)
Stratified HR (95% CI)	0.71 (0.54-1.93)	
Stratified p value (1-sided)	0.0070	
Significance threshold	0.0039	

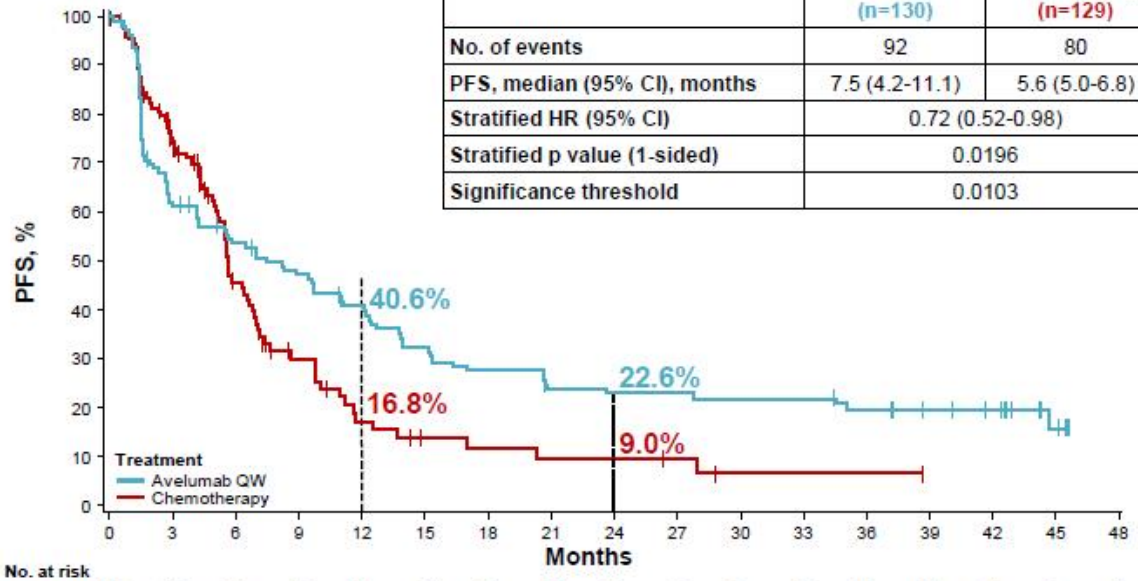


No. at risk

Avelumab Q2W	151	88	69	55	48	41	36	31	31	28	25	23	22	20	18	13	10	9	9	8	4	0	0
Chemotherapy	216	128	69	39	23	16	14	11	9	7	5	4	4	3	3	3	3	3	3	3	1	0	0

Avelumab QW vs chemotherapy

	Avelumab QW (n=130)	Chemotherapy (n=129)
No. of events	92	80
PFS, median (95% CI), months	7.5 (4.2-11.1)	5.6 (5.0-6.8)
Stratified HR (95% CI)	0.72 (0.52-0.98)	
Stratified p value (1-sided)	0.0196	
Significance threshold	0.0103	



No. at risk

Avelumab QW	130	72	60	52	43	34	29	24	23	23	22	22	19	15	12	4	0					
Chemotherapy	129	74	36	19	10	6	5	4	4	3	1	1	1	0	0	0	0					

PFS analyses also favored avelumab vs chemotherapy but differences were not statistically significant

*High-expression PD-L1+ (≥80% of tumor cells) determined by Dako PD-L1 IHC 73-10 pharmDx assay (avelumab QW vs chemotherapy: in patients randomized post protocol amendment).

Tumor responses in the high PD-L1+ populations*

	Avelumab Q2W (n=151)	Chemotherapy (n=216)	Avelumab QW (n=130)	Chemotherapy (n=129)
ORR by IRC (95% CI), %	**37.7 (30.0-46.0)**	**30.1 (24.1-36.7)**	**34.6 (26.5-43.5)**	**30.2 (22.5-38.9)**
Confirmed best overall response, n (%)				
CR	5 (3.3)	1 (0.5)	4 (3.1)	1 (0.8)
PR	52 (34.4)	64 (29.6)	41 (31.5)	38 (29.5)
SD	36 (23.8)	89 (41.2)	30 (23.1)	54 (41.9)
PD	27 (17.9)	19 (8.8)	29 (22.3)	11 (8.5)
NE†	31 (20.5)	43 (19.9)	26 (20.0)	25 (19.4)
Median duration of response (95% CI), months	**35.9 (14.6-NR)**	**8.4 (5.0-15.1)**	**19.4 (10.8-NR)**	**8.4 (4.4-11.1)**

- ORR and median duration of response favored avelumab vs chemotherapy

*High-expression PD-L1+ (≥80% of tumor cells) determined by Dako PD-L1 IHC 73-10 pharmDx assay (avelumab QW vs chemotherapy: in patients randomized post protocol amendment).
†Includes patients with non-CR/non-PD, patients whose tumors were not measurable per IRC and who did not have CR or PD.

Overview of safety in all treated patients*

	Avelumab Q2W (n=361)	Avelumab QW (n=318)	Chemotherapy (n=500)
AE, n (%)			
Any grade	346 (95.8)	308 (96.9)	484 (96.8)
Grade ≥3	217 (60.1)	181 (56.9)	324 (64.8)
Treatment-related AE, n (%)			
Any grade	243 (67.3)	224 (70.4)	430 (86.0)
Grade ≥3	60 (16.6)	44 (13.8)	230 (46.0)
Serious AE, n (%)	181 (50.1)	143 (45.0)	195 (39.0)
Serious treatment-related AE, n (%)	50 (13.9)	31 (9.7)	88 (17.6)
Immune-related AE, n (%)†	70 (19.4)	51 (16.0)	–
Grade ≥3	19 (5.3)	6 (1.9)	–
Infusion-related reaction, n (%)	104 (28.8)	81 (25.5)	6 (1.2)
AE leading to treatment discontinuation, n (%)	100 (27.7)	58 (18.2)	122 (24.4)
Treatment-related AE leading to treatment discontinuation, n (%)	44 (12.2)	27 (8.5)	76 (15.2)
AE leading to death, n (%)	63 (17.5)	51 (16.0)	63 (12.6)
Treatment-related AE leading to death, n (%)‡	3 (0.8)	1 (0.3)	6 (1.2)

*Patients who received ≥1 dose of study treatment. †Immune-related AEs assessed only for the avelumab treatment arms. ‡Avelumab Q2W, cytokine release syndrome, pneumonia, and pneumonitis (all n=1); avelumab QW, dyspnea; chemotherapy, febrile neutropenia (n=2), gastric hemorrhage/ulcer, hepatic cytolysis, pneumonia, and renal failure.

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Association Between *KRAS/STK11/KEAP1* Mutations and Outcomes in POSEIDON: Durvalumab ± Tremelimumab + Chemotherapy in mNSCLC

Solange Peters,[1] Byoung Chul Cho,[2] Alexander Luft,[3] Jorge Alatorre-Alexander,[4] Sarayut Lucien Geater,[5] Sang-We Kim,[6] Grygorii Ursol,[7] Maen Hussein,[8] Farah Louise Lim,[9] Cheng-Ta Yang,[10] Luiz Henrique Araujo,[11] Haruhiro Saito,[12] Niels Reinmuth,[13] Ross Stewart,[14] Zhongwu Lai,[15] Ruth Doake,[14] Lee Krug,[16] Edward B. Garon,[17] Tony Mok,[18] Melissa L. Johnson[19]

[1]Centre Hospitalier Universitaire Vaudois, Lausanne University, Lausanne, Switzerland; [2]Yonsei Cancer Center, Seoul, Korea; [3]Leningrad Regional Clinical Hospital, St Petersburg, Russia; [4]Health Pharma Professional Research, Mexico City, Mexico; [5]Prince of Songkla University, Songkhla, Thailand; [6]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [7]Acinus, Kropyvnytskyi, Ukraine; [8]Florida Cancer Specialists – Sarah Cannon Research Institute, Leesburg, FL, USA; [9]Queen Mary University of London, London, United Kingdom; [10]Chang Gung Memorial Hospital, Taoyuan City, Taiwan; [11]Instituto Nacional de Cancer-INCA, Rio de Janeiro, Brazil; [12]Kanagawa Cancer Center, Yokohama, Japan; [13]Asklepios Lung Clinic, Munich-Gauting, Germany; [14]AstraZeneca, Cambridge, UK; [15]AstraZeneca, Waltham, MA, USA; [16]AstraZeneca, Gaithersburg, MD, USA; [17]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [18]Chinese University of Hong Kong, Hong Kong, China; [19]Sarah Cannon Research Institute, Tennessee Oncology, PLLC, Nashville, TN, USA

POSEIDON Study Design

Phase 3, global, randomised, open-label, multicentre study in 1L mNSCLC

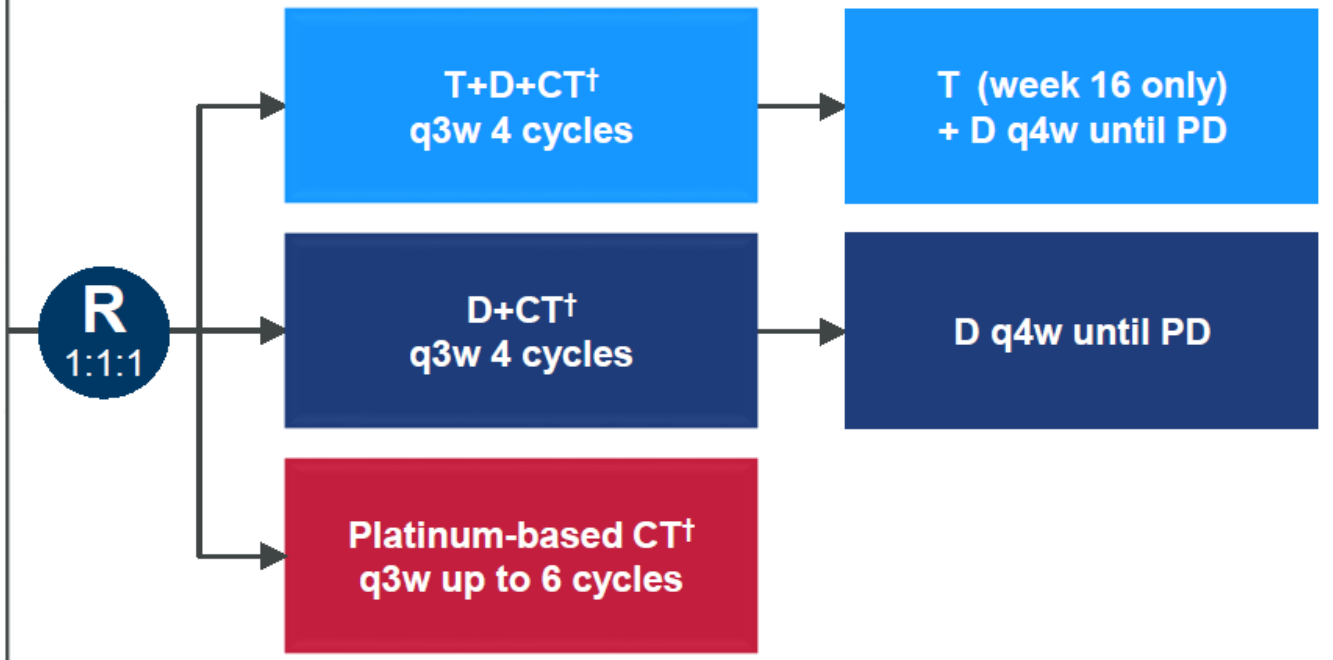
Stage IV NSCLC

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%)
- Histology (NSQ vs SQ)
- Disease stage (IVA vs IVB)



Alpha-controlled endpoints

D+CT vs CT:

- PFS‡
- OS

T+D+CT vs CT:

- PFS‡
- OS

- **Durvalumab** 1500mg **± limited-course tremelimumab** 75mg + **CT** q3w for **4 cycles**
  - One additional dose of tremelimumab post-CT (week 16; 5th dose)
- Followed by **durvalumab q4w maintenance** until PD, and optional pemetrexed q4w§

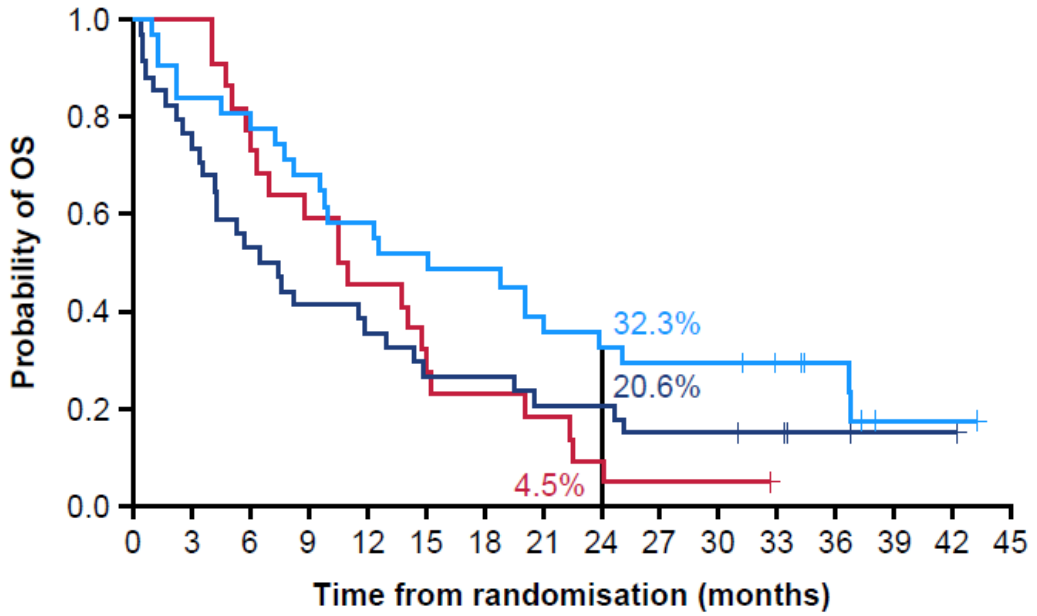
*Newly acquired or archival (<3 months); †CT options: gemcitabine + carboplatin/cisplatin (SQ), pemetrexed + carboplatin/cisplatin (NSQ) or nab-paclitaxel + carboplatin (either histology); ‡By BICR (RECIST v1.1); §Patients with NSQ histology who initially received pemetrexed only (if eligible); pemetrexed q3w also permitted in the CT arm

OS by *STK11* Mutation Status

OS benefit observed for T+D+CT vs CT in STK11m with HR 0.56 and estimated 32.3% alive at 2 yrs vs 4.5%

*STK11*m

	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** (6.0–14.9)
HR* (95% CI)	**0.56** (0.30–1.03)	**1.03** (0.59–1.84)	–

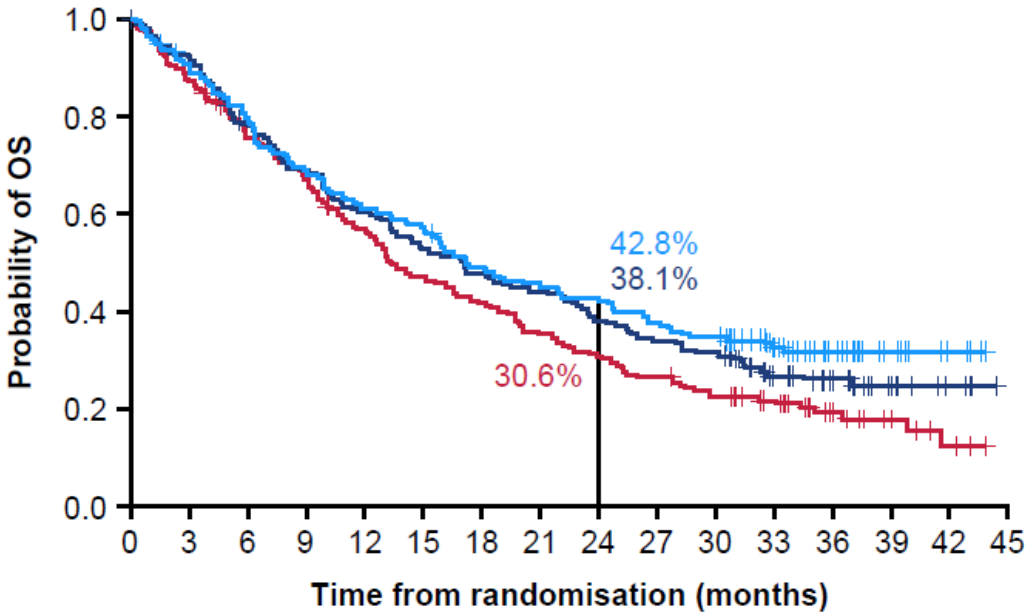


No. at risk

T+D+CT	31	26	24	21	18	15	15	11	10	9	9	7	5	1	1	0
D+CT	34	26	18	14	12	9	9	7	7	5	5	4	2	1	0	0
CT	22	22	16	13	10	6	5	4	1	1	1	0	0	0	0	0

*STK11*wt

	T+D+CT	D+CT	CT
Events, n/N	118/177	123/169	141/179
mOS, mo (95% CI)	**17.2** (14.9–22.1)	**17.1** (13.3–22.3)	**13.4** (11.5–17.5)
HR* (95% CI)	**0.73** (0.57–0.93)	**0.81** (0.64–1.04)	–



No. at risk

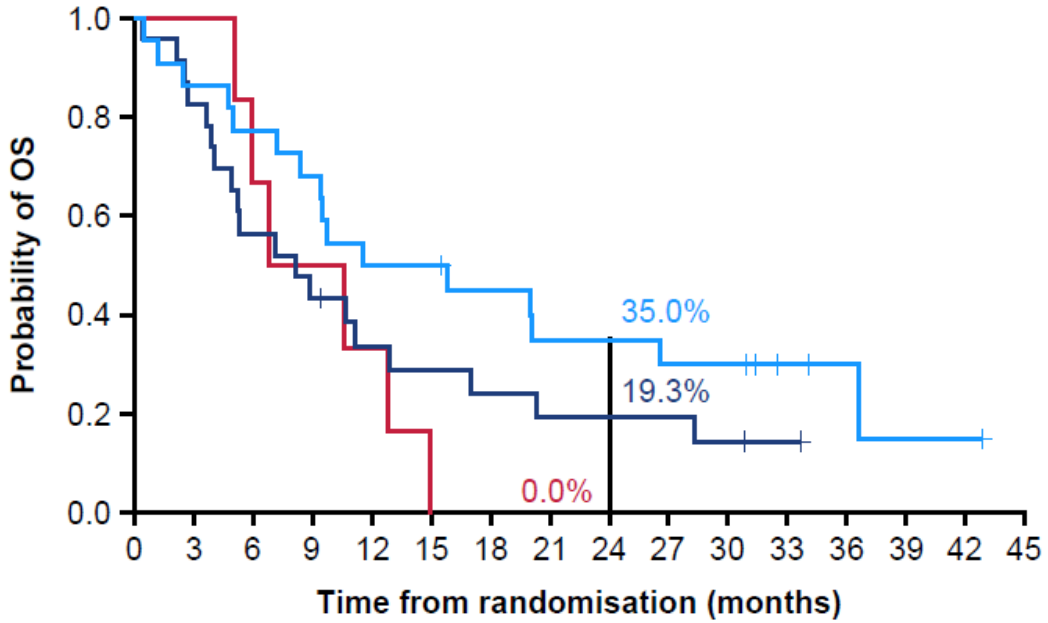
T+D+CT	177	159	140	120	107	100	85	79	74	65	60	40	25	11	5	0
D+CT	169	155	130	114	100	87	79	73	63	56	52	33	23	10	4	0
CT	179	154	131	116	97	80	71	60	52	45	37	29	15	8	4	0

OS by *KEAP1* Mutation Status

OS benefit observed for T+D+CT vs CT in KEAP1m with HR 0.43 (small sample size)

*KEAP1*m

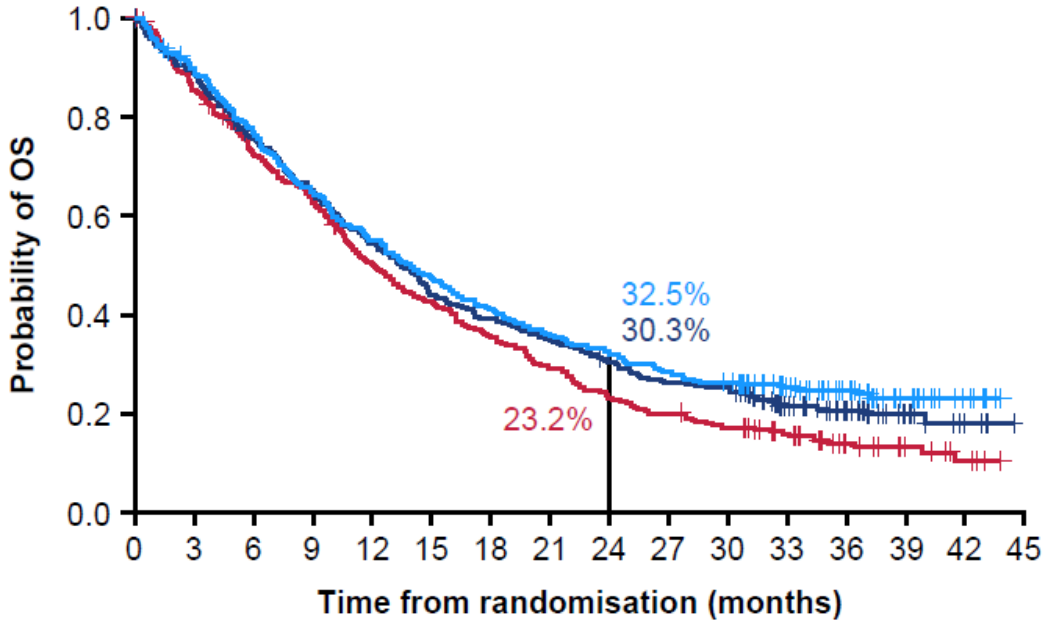
	T+D+CT	D+CT	CT
Events, n/N	16/22	19/23	6/6
mOS, mo (95% CI)	**13.7** (7.2–26.5)	**8.1** (4.0–12.9)	**8.7** (5.1–NE)
HR* (95% CI)	**0.43** (0.16–1.25)	**0.77** (0.31–2.15)	–



No. at risk																
T+D+CT	22	19	17	15	11	11	9	7	7	6	6	3	2	1	1	0
D+CT	23	19	13	10	7	6	5	4	4	4	3	1	0	0	0	0
CT	6	6	4	3	2	0	0	0	0	0	0	0	0	0	0	0

*KEAP1*wt

	T+D+CT	D+CT	CT
Events, n/N	226/303	241/307	262/312
mOS, mo (95% CI)	**14.0** (11.8–16.1)	**13.5** (11.7–14.9)	**12.2** (10.6–13.9)
HR* (95% CI)	**0.79** (0.66–0.94)	**0.85** (0.71–1.01)	–



No. at risk																					
T+D+CT	303	268	230	194	165	142	123	108	97	85	78	57	38	19	8	0
D+CT	307	272	230	198	165	134	119	106	91	79	76	49	33	15	5	0
CT	312	264	221	192	153	129	108	88	70	61	51	38	21	13	6	0

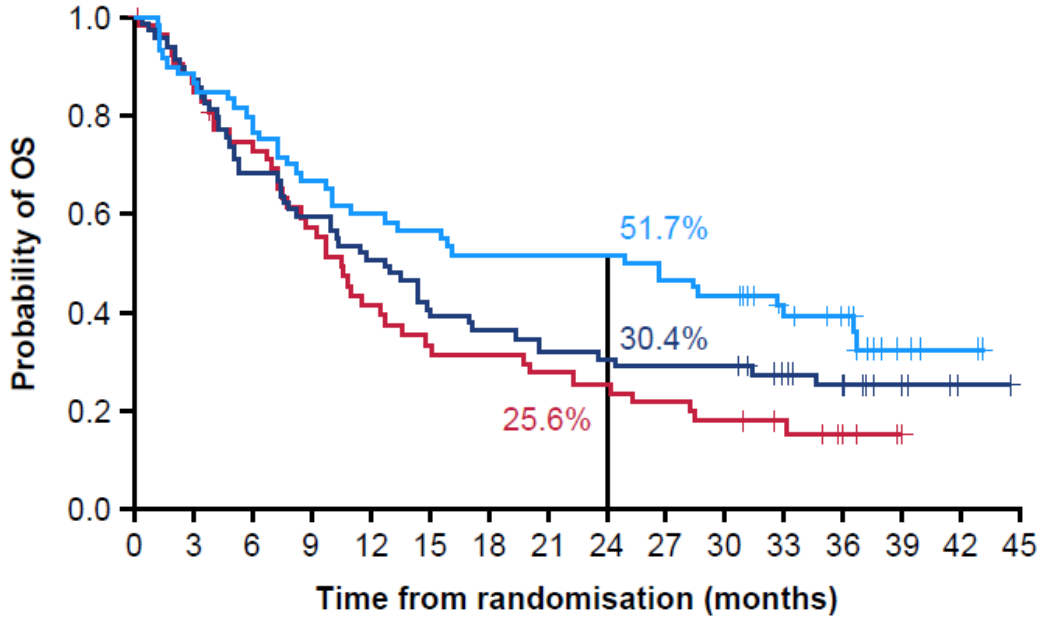
HR (95% CI) vs CT in NSQ *KEAP1*m was 0.33 (0.10–1.15) with T+D+CT and 0.67 (0.23–2.17) with D+CT

OS by *KRAS* Mutation Status

OS benefit observed for T+D+CT vs CT in KRASm with HR 0.56 and estimated 51.7% alive at 2 yrs vs 25.6%

*KRAS*m

	T+D+CT	D+CT	CT
Events, n/N	38/60	51/69	43/53
mOS, mo (95% CI)	**25.7** (9.9–36.5)	**12.6** (7.5–16.9)	**10.4** (7.5–13.6)
HR* (95% CI)	**0.56** (0.36–0.88)	**0.80** (0.53–1.21)	–

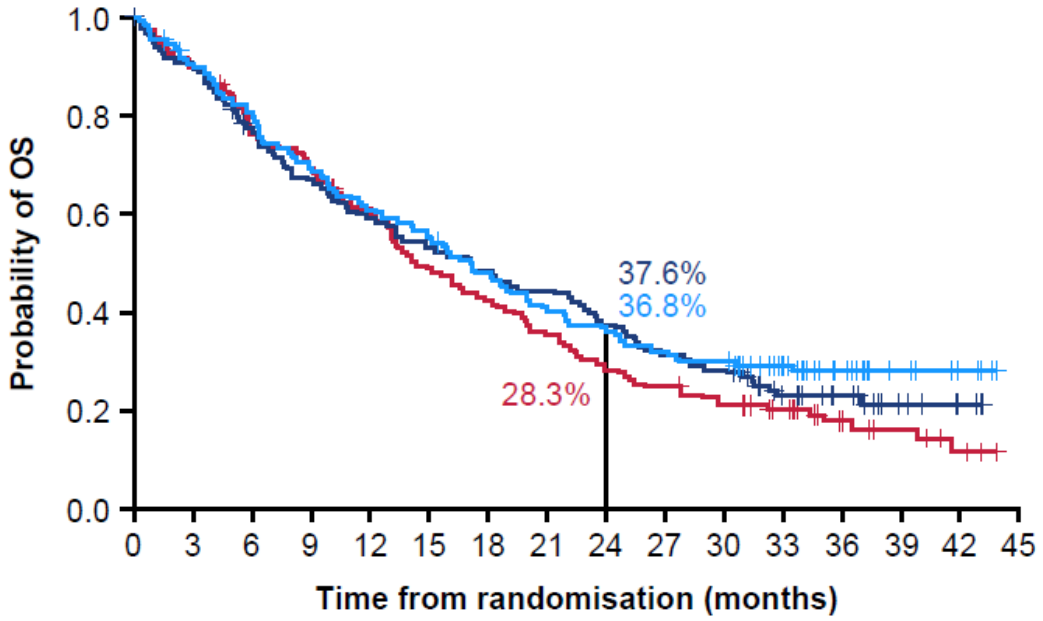


No. at risk

T+D+CT	60	53	46	40	36	34	31	31	31	28	26	17	14	4	2	0
D+CT	69	61	47	41	35	27	25	22	21	20	20	14	9	4	1	0
CT	53	44	37	29	21	17	16	14	13	11	9	7	3	0	0	0

*KRAS*wt

	T+D+CT	D+CT	CT
Events, n/N	104/148	101/134	119/148
mOS, mo (95% CI)	**17.1** (13.4–20.1)	**17.1** (12.3–22.6)	**14.4** (12.6–18.3)
HR* (95% CI)	**0.80** (0.62–1.04)	**0.86** (0.66–1.12)	–



No. at risk

T+D+CT	148	132	118	101	89	81	69	59	53	46	43	30	16	8	4	0
D+CT	134	120	101	87	77	69	63	58	49	41	37	23	16	7	3	0
CT	148	132	110	100	86	69	60	50	40	35	29	22	12	8	4	0

PFS		T + D + CT	D + CT	CT
STK11 mutant	Events, n/N	22/31	27/34	17/22
	mPFS, mo (95%CI)	**6.4** (4.7, 13.8)	2.9 (1.4, 4.7)	4.6 (2.9, 6.4)
	HR (95%CI)	0.47 (0.23, 0.93)	1.02 (0.55, 1.93)	-
KEAP1 mutant	Events, n/N	16/22	17/23	4/6
	mPFS, mo (95%CI)	**5.0** (3.0, 13.7)	2.8 (2.6, 4.9)	5.1 (4.6, NE)
	HR (95%CI)	0.94 (0.33, 3.35)	1.51 (0.55, 5.25)	-
KRAS mutant	Events, n/N	34/60	48/69	34/53
	mPFS, mo (95%CI)	**8.5** (6.0, NE)	6.4 (4.6, 8.6)	4.7 (4.4, 6.5)
	HR (95%CI)	0.57 (0.35, 0.92)	0.82 (0.53, 1.29)	-

The ORR was 45.2%, 45.5% and 55.0% in the *STK11*m, *KEAP1*m and *KRAS*m subgroups, respectively

IASLC 2022 World Conference on Lung Cancer
AUGUST 6-9, 2022 | VIENNA, AUSTRIA

HUDSON: AN OPEN-LABEL, MULTI-DRUG, BIOMARKER-DIRECTED PHASE 2 STUDY IN NSCLC PATIENTS WHO PROGRESSED ON ANTI-PD-(L)1 THERAPY

Benjamin Besse[1], Mark M. Awad[2], Patrick M. Forde[3], Michael Thomas[4], Glenwood Goss[5], Boaz Aronson[6], Rosalind Hobson[7], Emma Dean[7], Jane Peters[7], Sonia Iyer[8], James Conway[6], J. Carl Barrett[8], Jan Cosaert[7], Marlene Dressman[6], Simon T. Barry[7], John V. Heymach[9]

[1]Paris-Saclay University, Institut Gustave Roussy, Villejuif, France; [2]Dana-Farber Cancer Institute, Boston, MA, USA; [3]Johns Hopkins University School of Medicine, Baltimore, MD, USA; [4]Thoraxklinik am Universitätsklinikum Heidelberg, Translational Lung Research Center Heidelberg (TLRC-H), Heidelberg, Germany; [5]The Ottawa Hospital Research Institute, Ottawa, Ontario, Canada; [6]AstraZeneca, Gaithersburg, MD, USA; [7]AstraZeneca, Cambridge, UK; [8]AstraZeneca, Boston, MA, USA; [9]MD Anderson Cancer Center, Houston, TX, USA

IASLC 2022 World Conference on Lung Cancer
AUGUST 6-9, 2022 | VIENNA, AUSTRIA

HUDSON: Phase II multi-arm umbrella study

- Locally advanced or metastatic NSCLC
- Previous platinum-based chemotherapy
- Failure of prior anti-PD-(L)1 immunotherapy
- Suitable for new tumor biopsy / biopsy post-progression on anti-PD-(L)1 therapy
- No targetable alterations in *EGFR*, *ALK*, *ROS1*, *BRAF*, *MET*, or *RET*

Central molecular screen,‡ ***n* = 255** (Jan 26, 2018–Apr 14, 2021)

Primary endpoint: ORR
Secondary endpoints: DCR, PFS, OS, safety and tolerability

Group A: biomarker-matched, *n* = 86

HRRm	Durvalumab + olaparib (PARPi), ***n* = 21**
LKB1	Durvalumab + olaparib (PARPi), ***n* = 21**
ATM	**Durvalumab + ceralasertib (ATRi), *n* = 21***
ATM	Single-agent ceralasertib (ATRi)*
CD73h	Durvalumab + oleclumab (CD73 mAb), ***n* = 23**
HER2e	Durvalumab plus trastuzumab deruxtecan (HER2i)†
HER2m	

Group B: biomarker-non-matched, *n* = 169

Primary resistance (disease progression ≤24 weeks)§	Acquired resistance (disease progression >24 weeks)#
Durvalumab + olaparib (PARPi), ***n* = 22**	Durvalumab + olaparib (PARPi) , ***n* = 23**
Durvalumab + danvatirsen (STAT3i), ***n* = 23**	Durvalumab + danvatirsen (STAT3i), ***n* = 22**
Durvalumab + ceralasertib (ATRi), *n* = 20	**Durvalumab + ceralasertib (ATRi), *n* = 25**
Durvalumab + oleclumab (CD73 mAb), ***n* = 9**	Durvalumab + oleclumab (CD73 mAb), ***n* = 25**
	Durvalumab + cediranib (VEGFi)†

*Ongoing. †Data not mature. ‡Immunohistochemistry was also performed. §/# Progression on prior anti-PD-(L)1 therapy within 24 weeks / after > 24 weeks.

ATM, ataxia telangiectasia mutated; ATRi, ataxia telangiectasia receptor inhibitor; CD73(h), (high expression of) cluster of differentiation 73; DCR, disease control rate; HER2e/i/m, human epidermal growth factor receptor 2 expression/inhibitor/mutated; HRRm, homologous recombination repair mutated; LKB1, LKB1/STK11 aberration; mAb, monoclonal antibody; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PARPi, poly ADP ribose polymerase inhibitor; PD-(L)1, programmed death (ligand)-1; PFS, progression-free survival; STAT3i, signal transducer and activator of transcription 3 inhibitor; VEGFi, vascular endothelial growth factor inhibitor.

Baseline characteristics by regimen (Group A + Group B)

	Durvalumab + ceralasertib n=66	Durvalumab + olaparib n=87	Durvalumab + danvatirsen n=45	Durvalumab + oleclumab n=57
Median age (range), years	64.0 (45–80)	63.0 (35–85)	65.0 (39–80)	64.0 (37–79)
Male, n (%)	43 (65.2)	50 (57.5)	23 (51.1)	30 (52.6)
Histology, n (%)				
Adenocarcinoma	44 (66.7)	62 (71.3)	31 (68.9)	38 (66.7)
Squamous cell carcinoma	17 (25.8)	18 (20.7)	12 (26.7)	13 (22.8)
Other	5 (7.5)	7 (8.0)	2 (4.4)	6 (10.5)
Metastatic sites, n (%)				
0	2 (3.0)	1 (1.1)	2 (4.4)	3 (5.3)
1–2	28 (42.4)	40 (46.0)	37 (82.2)	31 (54.4)
≥3	36 (54.5)	46 (52.9)	6 (13.3)	23 (40.4)
PD-L1 status, n (%)				
Positive (TC ≥1%)	26 (39.4)	22 (25.3)	21 (46.7)	31 (54.4)
Negative	22 (33.3)	27 (31.0)	11 (24.4)	13 (22.8)
Unknown	18 (27.3)	38 (43.7)	13 (28.9)	13 (22.8)
Prior regimens, n (%)				
1–2	33 (50.0)	51 (58.6)	25 (55.6)	32 (56.1)
≥3	33 (50.0)	36 (41.4)	20 (44.4)	25 (43.9)
Current/former smoker, n (%)	58 (87.9)	69 (79.3)	40 (88.9)	52 (91.2)

Treatment efficacy by regimen

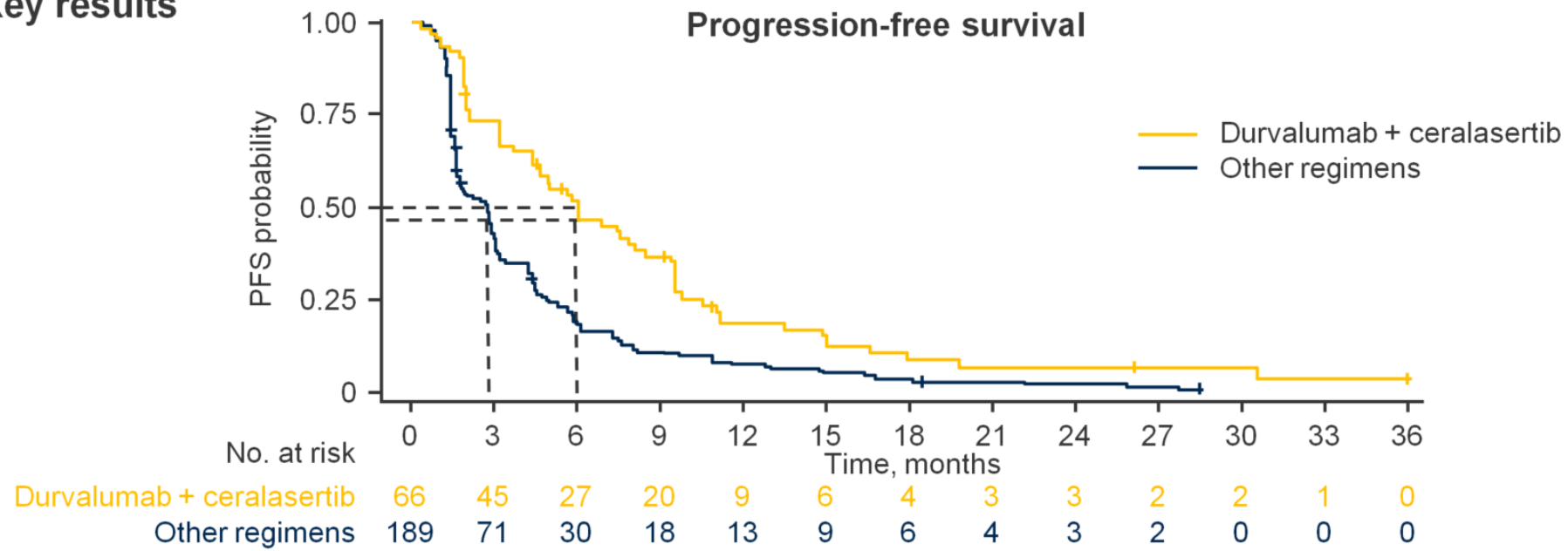
	Durvalumab + ceralasertib n=66	Durvalumab + olaparib n=87	Durvalumab + danvatirsen n=45	Durvalumab + oleclumab n=57
Median treatment duration, months				
Durvalumab*	**7.3**	3.7	2.8	2.9
Other agent†	**6.3**	3.2	2.8	2.9
12-week disease control rate, %	**60.6**	36.8	26.7	29.8
24-week disease control rate, %	**42.4**	17.2	13.3	15.8
ORR, %	**16.7%**	4.6%	0%	1.8%

ORR, objective response rate.
*Treatment duration for durvalumab calculated as (the earliest of (last infusion date + 27, date of death, date of cut-off) – first infusion date + 1) / (365.25/12).
†Treatment duration for:

- Olaparib calculated as (Last dose date – first dose date + 1) / (365.25/12)
- Danvatirsen calculated as (Last infusion date – first infusion date + 1) / (365.25/12), if the last cycle is Cycle 0 and there were less than 3 doses, or (the earliest of (last infusion date + 6, death date, date of cut-off) – first infusion date + 1) / (365.25/12) for all other cases
- Ceralasertib calculated as (Last dose date – first dose date + 1) / (365.25/12)
- Oleclumab calculated as (the earliest of (last infusion date + 13, death date, date of cut-off) – first infusion date + 1) / (365.25/12) if the last cycle is Cycle 1 or 2, or as (the earliest of (last infusion date + 27, death date, date of cut-off) – first infusion date + 1) / (365.25/12), for all other cases.

PFS

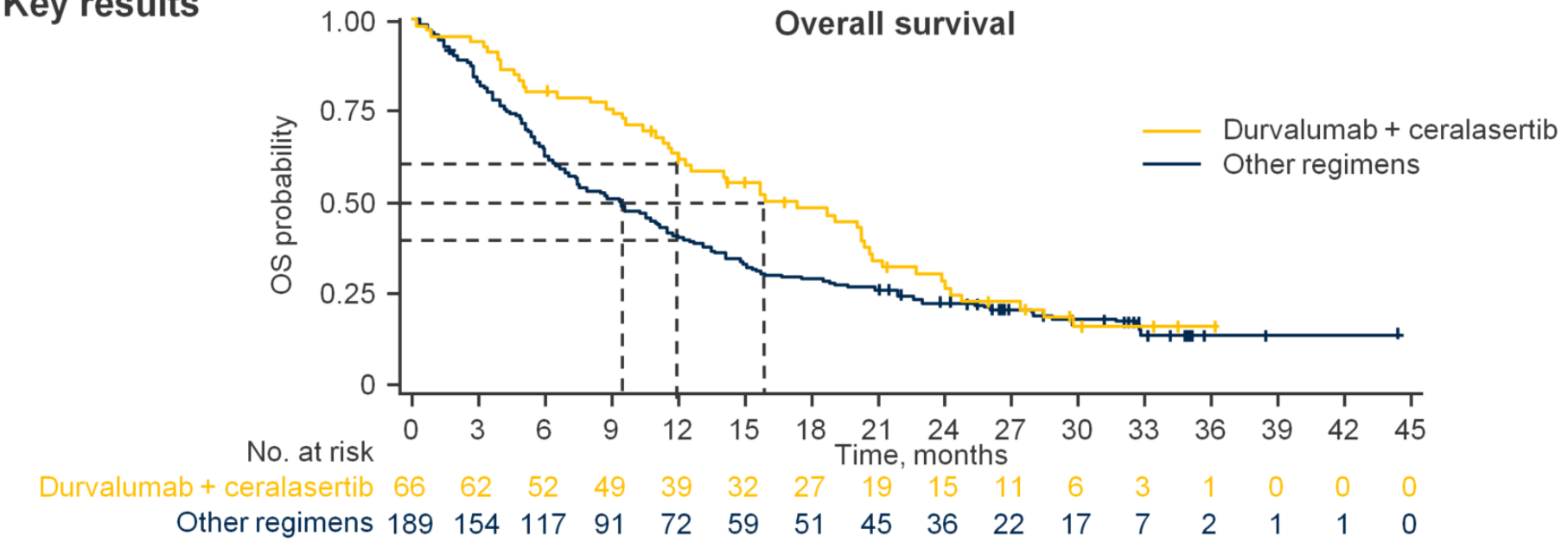
Key results



	Durvalumab + ceralasertib (n=66)	Other regimens (n=189)	Durvalumab + olaparib (n=87)	Durvalumab + danvatirsen (n=45)	Durvalumab + oleclumab (n=57)
mPFS, mo (80%CI)	6.0 (4.6, 7.5)	2.7 (1.8, 2.8)	2.7 (1.6, 3.0)	2.9 (1.7, 3.1)	1.8 (1.6, 2.7)
6-mo PFS, % (80%CI)	46.3 (37.9, 54.2)	18.0 (14.5, 21.9)	18.7 (13.5, 24.5)	18.8 (11.5, 27.6)	16.6 (10.8, 23.6)

OS

Key results



	Durvalumab + ceralasertib (n=66)	Other regimens (n=189)	Durvalumab + olaparib (n=87)	Durvalumab + danvatirsen (n=45)	Durvalumab + oleclumab (n=57)
mOS, mo (80%CI)	15.9 (14.1, 20.3)	9.4 (7.5, 10.6)	9.4 (6.9, 10.8)	7.9 (6.0, 10.6)	11.0 (7.6, 13.5)
6-mo OS, % (80%CI)	61.6 (53.4, 68.8)	39.7 (35.1, 44.3)	40.8 (34.0, 47.5)	28.8 (20.2, 38.0)	46.2 (37.5, 54.5)

Safety by regimen

AE category, n (%)	Durvalumab + ceralasertib n=66	Durvalumab + olaparib n=87	Durvalumab + danvatirsen n=45	Durvalumab + oleclumab n=57
Median treatment duration, months				
Durvalumab	7.3	3.7	2.8	2.9
Other agent	6.3	3.2	2.8	2.9
Any TEAE	**64 (97.0)**	**80 (92.0)**	**43 (95.6)**	**48 (84.2)**
Related to any treatment	52 (78.8)	67 (77.0)	33 (73.3)	34 (59.6)
Any grade ≥3 TEAE	**33 (50.0)**	**47 (54.0)**	**28 (62.2)**	**23 (40.4)**
Related to any treatment	15 (22.7)	30 (34.5)	17 (37.8)	9 (15.8)
Any TEAE with an outcome of death	**2 (3.0)**	**1 (1.1)**	**3 (6.7)**	**1 (1.8)**
Any SAE	**28 (42.4)**	**33 (37.9)**	**20 (44.4)**	**16 (28.1)**
Related to any treatment	8 (12.1)	9 (10.3)	3 (6.7)	4 (7.0)
Any TEAE leading to discontinuation	**8 (12.1)**	**9 (10.3)**	**10 (22.2)**	**7 (12.3)**
Related to any treatment	5 (7.6)	8 (9.2)	7 (15.6)	3 (5.3)
Most common TRAEs (≥15%*)				
Nausea	34 (51.5)	37 (42.5)	1 (2.2)	4 (7.0)
Vomiting	19 (28.8)	18 (20.7)	2 (4.4)	1 (1.8)
Decreased appetite	15 (22.7)	8 (9.2)	2 (4.4)	4 (7.0)
Anemia	14 (21.2)	22 (25.3)	4 (8.9)	2 (3.5)
Fatigue	11 (16.7)	18 (20.7)	6 (13.3)	8 (14.0)
Diarrhea	10 (15.2)	11 (12.6)	5 (11.1)	7 (12.3)

*In the durvalumab + ceralasertib group. AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

Pooled Analysis of Outcomes With Second-Course Pembrolizumab Across Five Phase 3 Studies of Non–Small-Cell Lung Cancer

D. Rodríguez-Abreu[1]; Y.-L. Wu[2]; M. Boyer[3]; M.C. Garassino[4]; T.S.K. Mok[5]; Y. Cheng[6]; R. Hui[7]; D.M. Kowalski[8]; A.G. Robinson[9]; J.R. Brahmer[10]; T.A. Leal[11]; G. Lopes[12]; B.C. Cho[13]; N. Nogami[14]; S. Novello[15]; N. Peled[16]; G. de Castro Jr[17]; M.A. Leiby[18]; D. Chirovsky[18]; J. Lin[18]; M.C. Pietanza[18]; M. Reck[19]

[1]Complejo Hospitalario Universitario Insular Materno-Infantil de Gran Canaria, Universidad de Las Palmas de Gran Canaria, Las Palmas de Gran Canaria, Spain; [2]Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital & Guangdong Academy of Medical Sciences, Guangzhou, China ; [3]Chris O'Brien Lifehouse, Camperdown, NSW, Australia; [4]University of Chicago , Chicago, IL, USA; [5]State Key Laboratory of Translation Oncology, Chinese University of Hong Kong, Hong Kong, China; [6]Jilin Cancer Hospital, Changchun, People's Republic of China ; [7]Westmead Hospital and University of Sydney, Sydney, NSW, Australia; [8]Maria Sklodowska -Curie National Research Institute of Oncology, Warsaw, Poland; [9]Cancer Centre of Southeastern Ontario at Kingston General Hospital, Kingston, ON, Canada; [10]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA; [11]Carbone Cancer Center, University of Wisconsin, Madison, WI, USA; Winship Cancer Institute, Emory University, Atlanta, GA, USA (current affiliation); [12]Sylvester Comprehensive Cancer Center at the University of Miami, Miami, FL, USA; [13]Yonsei Cancer Center, Seoul, South Korea; [14]National Hospital Organization Shikoku Cancer Center, Matsuyama, Japan; [15] AOU San Luigi Orbassano, University of Turin, Orbassano, Italy; [16]Shaare Zedek Medical Center, Jerusalem, Israel; [17]Instituto do Câncer do Estado de São Paulo, São Paulo, Brazil; [18]Merck & Co., Inc., Rahway, NJ, USA; [19]LungenClinic, Airway Research Center North, German Center for Lung Research, Grosshansdorf, Germany

Phase 3 Studies Included in Pooled Analysis

Cohort 1

- **First course:** pembrolizumab monotherapy (200 mg Q3W for up to 35 cycles)
- **Patients:** previously untreated stage IV[a] squamous or nonsquamous NSCLC with no sensitizing *EGFR*/*ALK* alterations
- **Studies included:** KEYNOTE-024,[1] KEYNOTE-042,[2,3] KEYNOTE-598[4b]
- **PD-L1 TPS:** ≥1% (KEYNOTE-042), ≥50% (KEYNOTE-024, KEYNOTE-598)

Cohort 2

- **First course:** pembrolizumab (200 mg Q3W for up to 35 cycles) + chemotherapy[c]
- **Patients:** previously untreated stage IV squamous (KEYNOTE-407) or nonsquamous (KEYNOTE-189) NSCLC with no sensitizing *EGFR*/*ALK* alterations
- **Studies included:** KEYNOTE-189,[5,6] KEYNOTE-407[7,8]
- **PD-L1 TPS:** any

[a]KEYNOTE-042 included patients with locally advanced or metastatic NSCLC.
[b]Only patients from the pembrolizumab plus placebo arm were included in this analysis.
[c]Chemotherapy included cisplatin or carboplatin plus pemetrexed in KEYNOTE-189, and carboplatin plus paclitaxel or nab-paclitaxel in KEYNOTE-407.

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. 3. Wu YL, et al. *Int J Cancer*. 2021;148(9):2313-2320. 4. Boyer M, et al. *J Clin Oncol*. 2021;39(21)2327-2338. 5. Gandhi L, et al. *N Engl J Med*. 2018;378(22):2078-2092. 6. Horinouchi H, et al. *Cancer Sci*. 2021;112(8):3255-3265. 7. Paz-Ares L, et al. *N Engl J Med*. 2018;379(21):2040-2051. 8. Cheng Y, et al. *Ann Oncol*. 2019;30:ix201-ix202.

Second-Course Pembrolizumab

- Dose and schedule
  - Monotherapy with 200 mg Q3W for up to 17 cycles (~1 year)
- Eligibility criteria
  - Completed 35 cycles or ~2 years of first-course pembrolizumab with SD or better

    OR
  - Stopped first-course pembrolizumab following confirmed CR after receiving pembrolizumab for ≥6 months (or ≥8 cycles) and for ≥2 cycles after CR assessment
- Additional eligibility criteria
  - Life expectancy ≥3 months
  - ECOG performance status of 0 or 1
  - Adequate organ function
  - No intervening anticancer treatment since the last dose of pembrolizumab

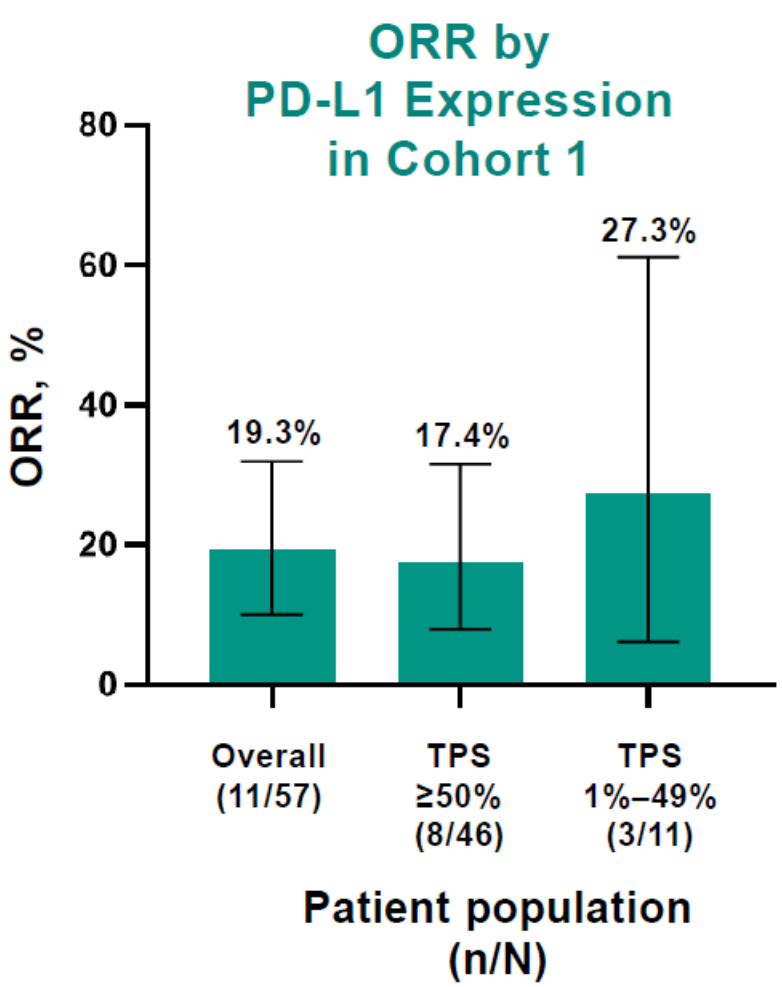
Baseline Characteristics at Time of Initial Study Randomization[a]

Characteristic	Cohort 1 (pembro monotherapy) N = 57	Cohort 2 (pembro + chemo) N = 14
Age, median (range), y	62 (43–82)	62 (49–75)
Men	41 (72)	11 (79)
Enrolled in East Asia	18 (32)	2 (14)
ECOG performance status 1	33 (58)	6 (43)
Current or former smoker	49 (86)	12 (86)
Squamous histology	18 (32)	7 (50)
PD-L1 TPS ≥50%[b]	46 (81)	5 (36)
Liver metastasis at baseline	5 (9)	3 (21)
Brain metastasis at baseline	6 (11)	0

Values are n (%) unless noted otherwise.
[a]Assessment at the start of second course: Median (range) age, 65 y (46–84 y) in cohort 1 and 65 y (51–79 y) in cohort 2; ECOG performance status 1: 33 (58%) in cohort 1 and 6 (43%) in cohort 2.
[b]PD-L1 expression was centrally assessed using PD-L1 IHC 22C3 pharmDx (Agilent Technologies, Carpinteria, CA).
Database cutoff dates: Jun 1, 2020 (KN024); Apr 28, 2021 (KN042); Oct 1, 2021 (KN598); Aug 28, 2020 (KN189); Sep 30, 2020 (KN407).

Tumor Response and Survival During Second-Course Pembrolizumab

	Cohort 1 (pembro monotherapy) N = 57	Cohort 2 (pembro + chemo) N = 14
ORR[a] (95% CI), %	19.3 (10.0–31.9)	0 (0.0–23.2)
DCR[a] (95% CI), %	73.7 (60.3–84.5)	50.0 (23.0–77.0)
Best overall response,[a] n (%)		
CR	0	0
PR	11 (19.3)	0
SD	31 (54.4)	7 (50.0)
PD	8 (14.0)	2 (14.3)
NA[b]	7 (12.3)	5 (35.7)
DOR,[a] median (range), mo	NR (0.0+ to 20.0+)	–
DOR ≥6 mo, %	78.8	–
OS,[c] median (95% CI), mo	27.5 (21.7–NR)	NR (NR–NR)
6-mo rate (95% CI), %	85.1 (72.4–92.3)	85.1 (52.3–96.1)
PFS,[a,c] median (95% CI), mo	10.3 (5.6–14.0)	7.7 (1.8–NR)
6-mo rate (95% CI), %	60.8 (46.0–72.7)	54.5 (22.9–78.0)



"+" indicates no PD at the time of last disease assessment.
[a]Per RECIST v1.1 by investigator review. [b]No postbaseline assessment available for response evaluation. [c]From the start of second course.
Database cutoff dates: Jun 1, 2020 (KN024); Apr 28, 2021 (KN042); Oct 1, 2021 (KN598); Aug 28, 2020 (KN189); Sep 30, 2020 (KN407).

Tumor Response and Survival During Second-Course Pembrolizumab

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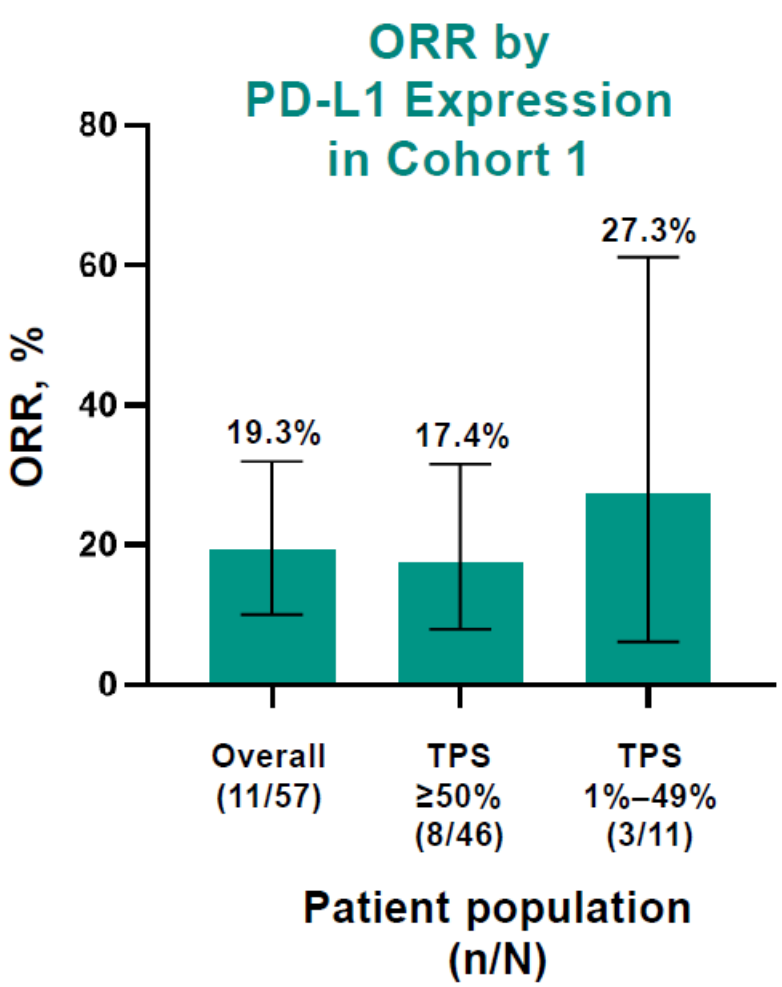
Best overall response,[a] n (%)		
CR	0	0
PR	11 (19.3)	0
SD	31 (54.4)	7 (50.0)
PD	8 (14.0)	2 (14.3)
NA[b]	7 (12.3)	5 (35.7)
DOR,[a] median (range), mo	NR (0.0+ to 20.0+)	–
DOR ≥6 mo, %	78.8	–
OS,[c] median (95% CI), mo	27.5 (21.7–NR)	NR (NR–NR)
6-mo rate (95% CI), %	85.1 (72.4–92.3)	85.1 (52.3–96.1)
PFS,[a,c] median (95% CI), mo	10.3 (5.6–14.0)	7.7 (1.8–NR)
6-mo rate (95% CI), %	60.8 (46.0–72.7)	54.5 (22.9–78.0)



"+" indicates no PD at the time of last disease assessment.
[a]Per RECIST v1.1 by investigator review. [b]No postbaseline assessment available for response evaluation. [c]From the start of second course.
Database cutoff dates: Jun 1, 2020 (KN024); Apr 28, 2021 (KN042); Oct 1, 2021 (KN598); Aug 28, 2020 (KN189); Sep 30, 2020 (KN407).

Tumor Response and Survival During Second-Course Pembrolizumab

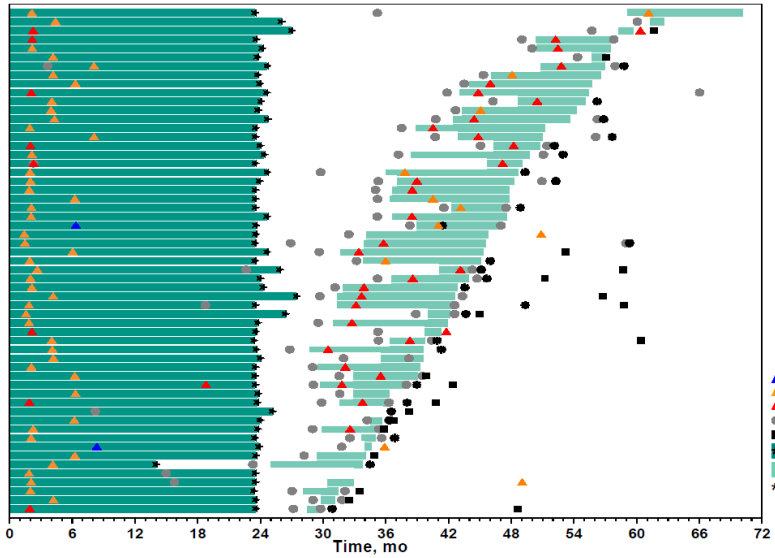
	Cohort 1 (pembro monotherapy) N = 57	Cohort 2 (pembro + chemo) N = 14
ORR[a] (95% CI), %	19.3 (10.0–31.9)	0 (0.0–23.2)
DCR[a] (95% CI), %	73.7 (60.3–84.5)	50.0 (23.0–77.0)
Best overall response,[a] n (%)		
CR	0	0
PR	11 (19.3)	0
SD	31 (54.4)	7 (50.0)
PD	8 (14.0)	2 (14.3)
NA[b]	7 (12.3)	5 (35.7)
DOR,[a] median (range), mo	NR (0.0+ to 20.0+)	–
DOR ≥6 mo, %	78.8	–
OS,[c] median (95% CI), mo	27.5 (21.7–NR)	NR (NR–NR)
6-mo rate (95% CI), %	85.1 (72.4–92.3)	85.1 (52.3–96.1)
PFS,[a,c] median (95% CI), mo	10.3 (5.6–14.0)	7.7 (1.8–NR)
6-mo rate (95% CI), %	60.8 (46.0–72.7)	54.5 (22.9–78.0)

"+" indicates no PD at the time of last disease assessment.

[a]Per RECIST v1.1 by investigator review. [b]No postbaseline assessment available for response evaluation. [c]From the start of second course.

Database cutoff dates: Jun 1, 2020 (KN024); Apr 28, 2021 (KN042); Oct 1, 2021 (KN598); Aug 28, 2020 (KN189); Sep 30, 2020 (KN407).

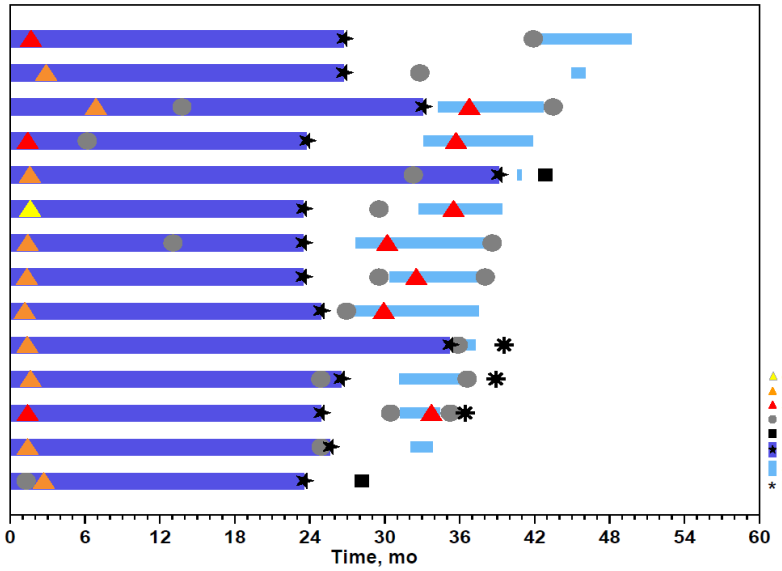
Individual Patient Profiles: Cohort 1



	Median (range), mo
Time from stopping first-course pembro to starting second course	12.0 (3.8–35.6)
Time from start of second course to data cutoff	21.5 (0.6–46.5)

[a]Patient stopped treatment at cycle 21 due to CR assessed per investigator and not BICR (PR). At the time of progression, patient was eligible for second-course pembrolizumab, per protocol.
Database cutoff dates: Jun 1, 2020 (KN024); Apr 28, 2021 (KN042); Oct 1, 2021 (KN598); Aug 28, 2020 (KN189); Sep 30, 2020 (KN407).

Individual Patient Profiles: Cohort 2



	Median (range), mo
Time from stopping first-course pembro to starting second course	5.4 (0.9–18.2)
Time from start of second course to data cutoff	10.3 (1.9–18.0)

Database cutoff dates: Jun 1, 2020 (KN024); Apr 28, 2021 (KN042); Oct 1, 2021 (KN598); Aug 28, 2020 (KN189); Sep 30, 2020 (KN407).

Adverse Events During Second-Course Pembrolizumab

AE, n (%)	Cohort 1 (pembro monotherapy) N = 57		Cohort 2 (pembro + chemo) N = 14	
Treatment-related AEs	14 (25)		4 (29)	
Grade 3/4 AEs	3 (5)		1 (7)	
Led to discontinuation	1 (2)		0	
Led to death	0		0	
	Grade 1/2	**Grade 3[a]**	**Grade 1/2**	**Grade 3[a]**
Immune-mediated AEs[b]	5 (9)	1 (2)	0	0
Hyperthyroidism	1 (2)	0	0	0
Hypothyroidism	3 (5)	0	0	0
Severe skin reactions	1 (2)	1 (2)	0	0
Thyroiditis	1 (2)	0	0	0

[a]There were no grade 4 or 5 immune-mediated AEs.
[b]Events were based on a list of terms specified at the time of analysis and were included regardless of attribution to study treatment or immune relatedness by the investigator. Related terms were included.
Database cutoff dates: Jun 1, 2020 (KN024); Apr 28, 2021 (KN042); Oct 1, 2021 (KN598); Aug 28, 2020 (KN189); Sep 30, 2020 (KN407).

Lung Cancer UPDATES

IASLC HIGHLIGTHS

06-09 AGOSTO 2022

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