Immunotherapy Updates in Lung Cancer from ASCO 2024

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ASCO 2024 = ASCO LUNG!

Advances in:

- Early Stage NSCLC
- Locally advanced NSCLC
- Metastatic NSCLC
- Small Cell Lung Cancer (SCLC)
- Mesothelioma
- Palliative care

Your Lung Cancer “Dream Team” for today

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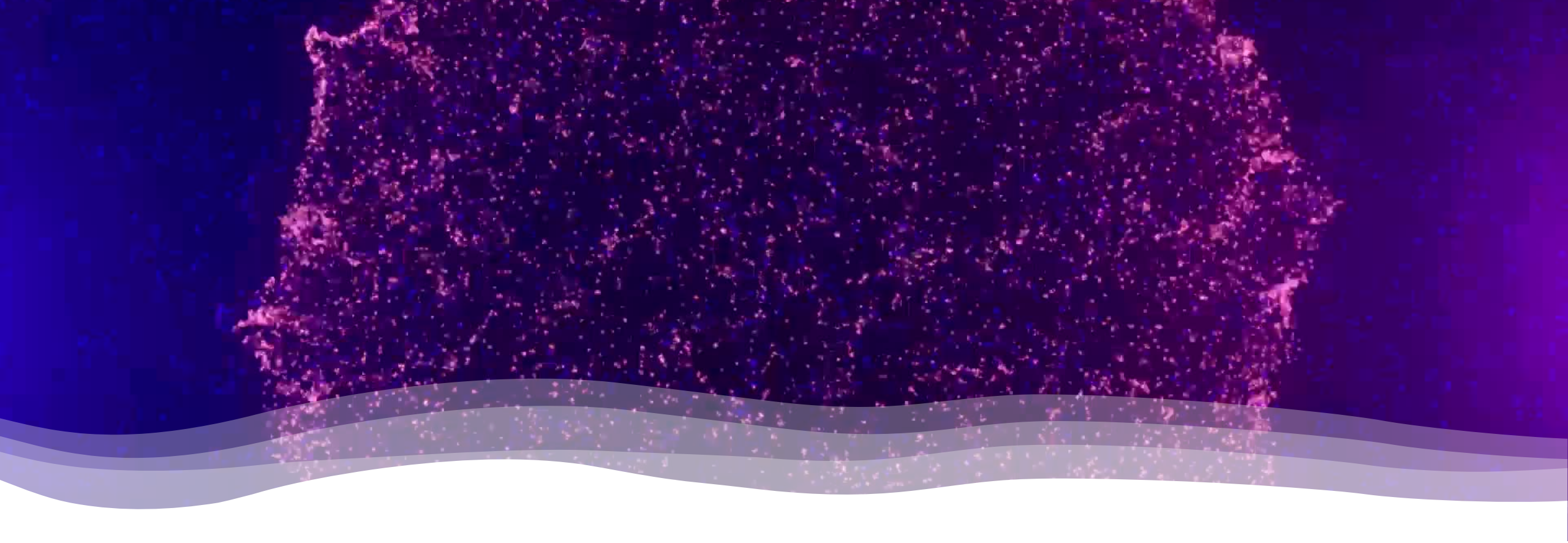
Discussion Agenda

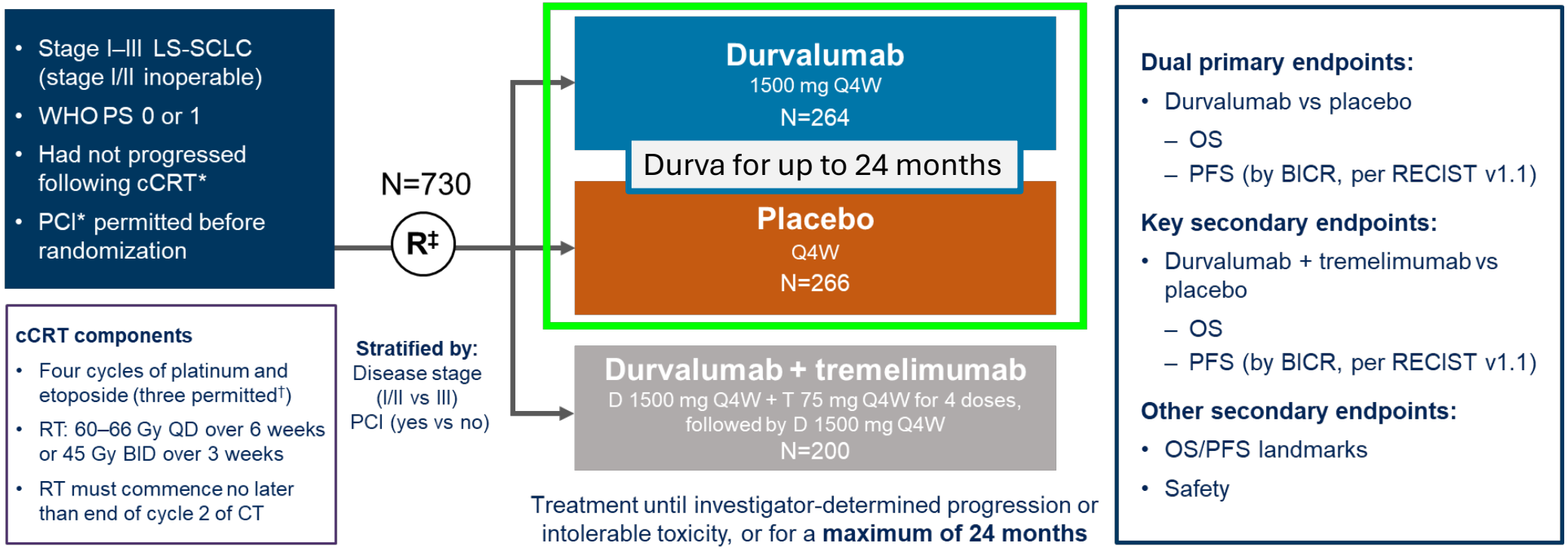
1. Small Cell Lung Cancer
    1. LS-SCLC
    2. ES-SCLC

2. Non-Small Cell Lung Cancer
    1. Early Stage NSCLC
    2. Advanced/metastatic NSCLC



Small Cell Lung Cancer

ADRIATIC trial: durvalumab as consolidation treatment for patients with limited-stage SCLC



Key Advance:

- **consolidation durvalumab increased both PFS (9.2 → 16.6 months) and OS (33.4 → 55.9 months) for patients with LS-SCLC.**
- **practice changing!**

ADRIATIC trial - Baseline characteristics

		Durvalumab (n=264)	Placebo (n=266)
Age, years	Median (range)	62.0 (28–84)	62.0 (28–79)
Sex, %	Male / Female	67.4 / 32.6	70.7 / 29.3
Race, %	White / Asian / Other	49.2 / 49.6 / 1.1	51.5 / 45.5 / 3.0
WHO performance status, %	0 / 1	50.0 / 50.0	47.4 / 52.6
Smoking status, %	Current / Former / Never	23.9 / 67.4 / 8.7	20.7 / 69.5 / 9.8
AJCC disease stage at diagnosis, %	I / II / III	3.0 / 9.5 / 87.5	4.1 / 8.6 / 87.2
Prior chemotherapy regimen, %*	Cisplatin-etoposide / Carboplatin-etoposide	65.5 / 34.5	66.9 / 33.1
Prior radiation schedule, %	Once daily / Twice daily	73.9 / 26.1	70.3 / 29.7
Best response to prior cCRT, %	CR / PR / SD	11.7 / 72.3 / 15.9	12.8 / 75.2 / 12.0
Prior PCI, %	Yes / No	53.8 / 46.2	53.8 / 46.2

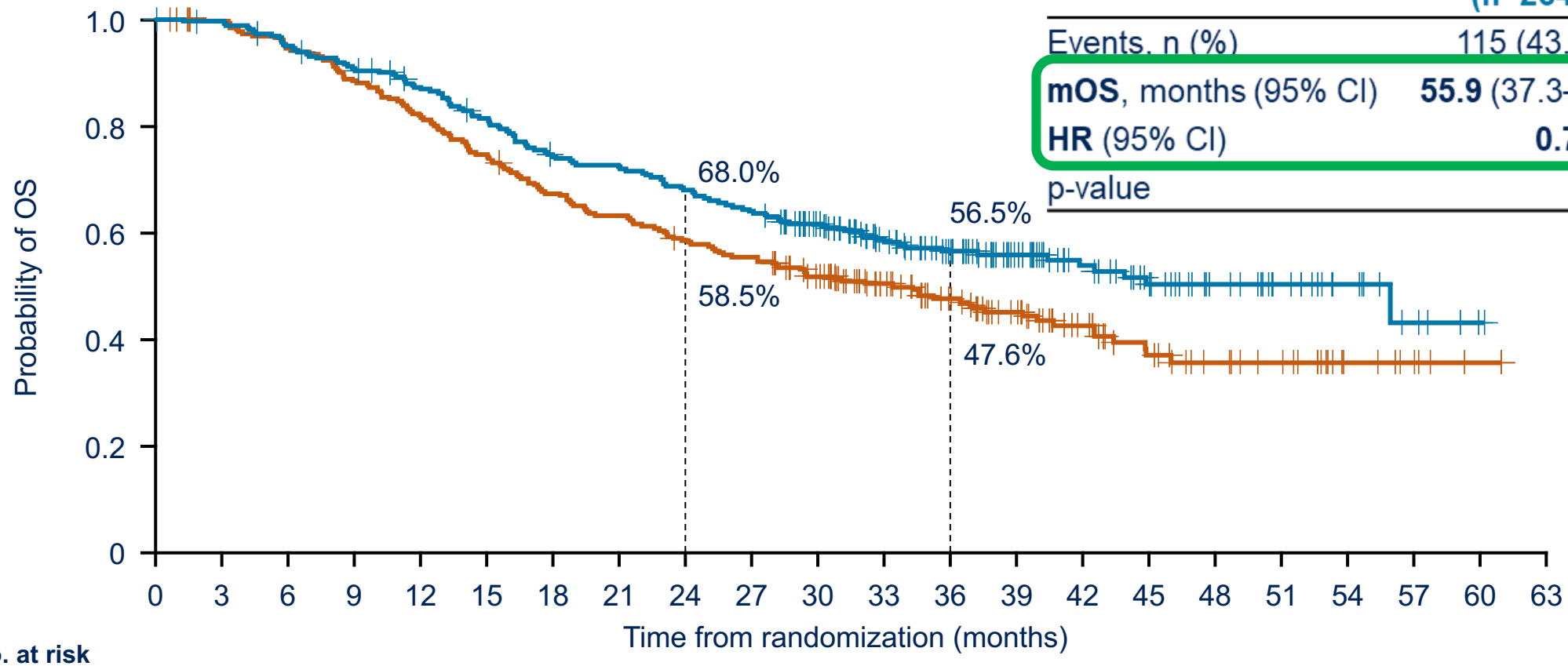
*Based on the first cycle of chemotherapy.

AJCC, American Joint Committee on Cancer; CR, complete response; PR, partial response; SD, stable disease.

ADRIATIC trial - 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.

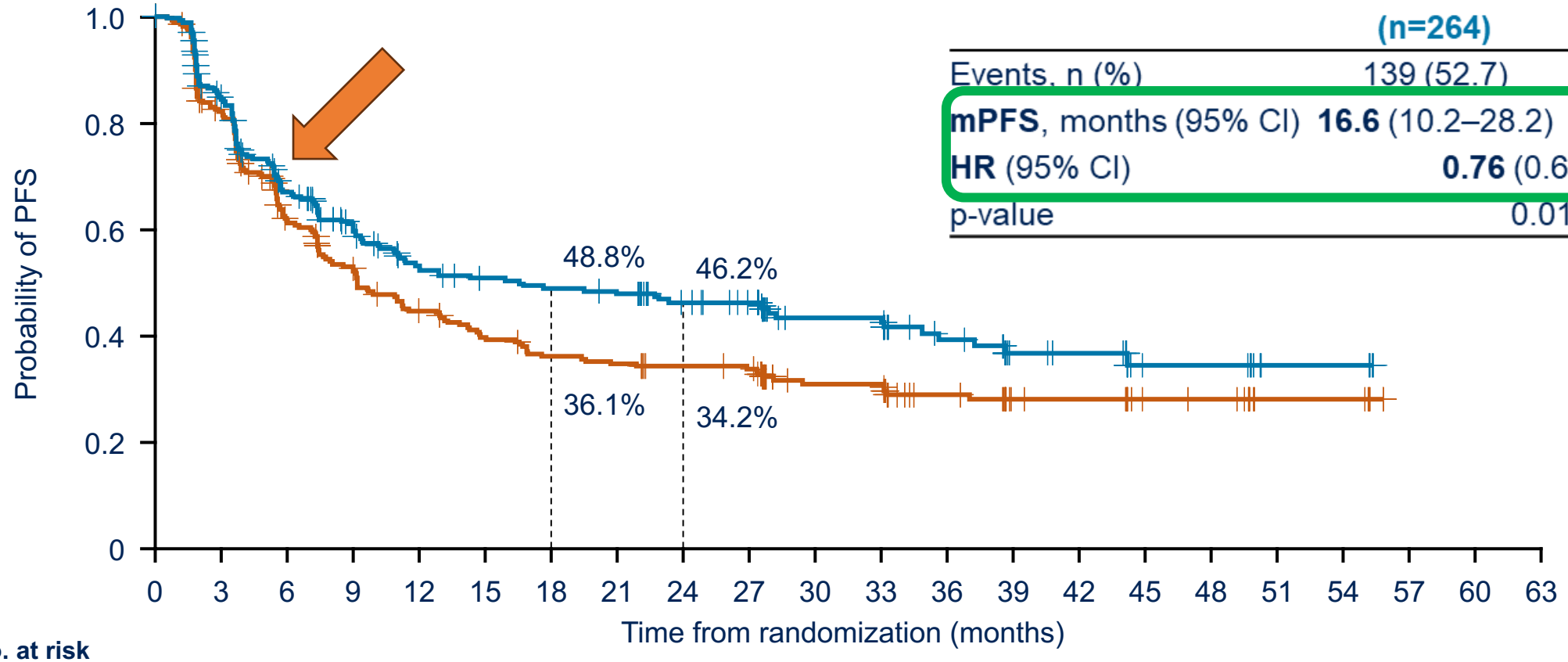
PRESENTED BY: Dr David R. Spigel

CI, confidence interval; mOS, median OS; NE, not estimable.

ADRIATIC trial - 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	



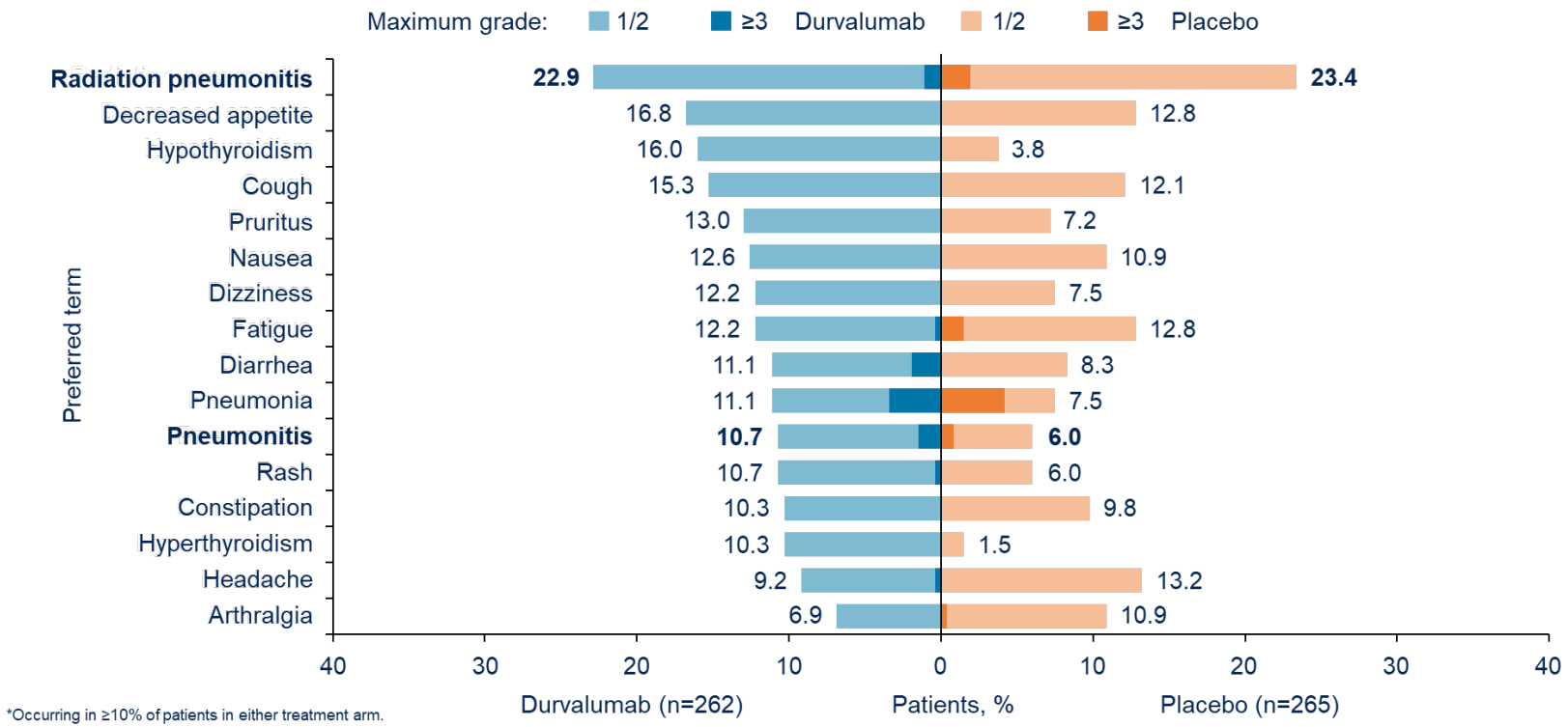
No. at risk																					
Durvalumab	264	212	161	135	113	105	101	98	84	78	51	51	33	21	19	10	10	4	4	0	0	0
Placebo	266	208	146	122	100	88	79	76	71	69	47	47	34	23	22	15	14	5	5	0	0	0

*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).

mPFS, median PFS.

ADRIATIC trial - Most frequent AEs*



*Occurring in ≥10% of patients in either treatment arm.

Pneumonitis/radiation pneumonitis

Pneumonitis or radiation pneumonitis (grouped terms*), n (%)	Durvalumab (n=262)	Placebo (n=265)
Any grade	100 (38.2)	80 (30.2)
Maximum grade 3/4	8 (3.1)	7 (2.6)
Leading to death	1 (0.4)	0
Leading to treatment discontinuation	23 (8.8)	8 (3.0)

SYNOPSIS and PERSPECTIVE: ADRIATIC Trial in LS-SCLC

Where we were

- No major advances in systemic treatment for LS-SCLC for several decades.
- Standard of care remained concurrent chemotherapy-radiation (cCRT).
- Median OS 25–30 months; 5-year survival rate 29–34%.
- Reference: Faivre-Finn C Lancet Oncol 2017; Bogart J, et al. J Clin Oncol 2023.

Where we are now

- ADRIATIC is the first phase 3 trial to show benefit of immune checkpoint blockade (in this case, Durvalumab anti PDL1) in patients with LS-SCLC)
- Almost 2 year survival benefit! (With median f/u of 37.2 months) → 55.9 months versus 33.4 months.

Where we need to go

- Predictive biomarkers of response to checkpoint blockade in SCLC
- Personalization of care for patients with SCLC.
- Better methods for screening and early detection for patients with SCLC.

ORIGINAL ARTICLE

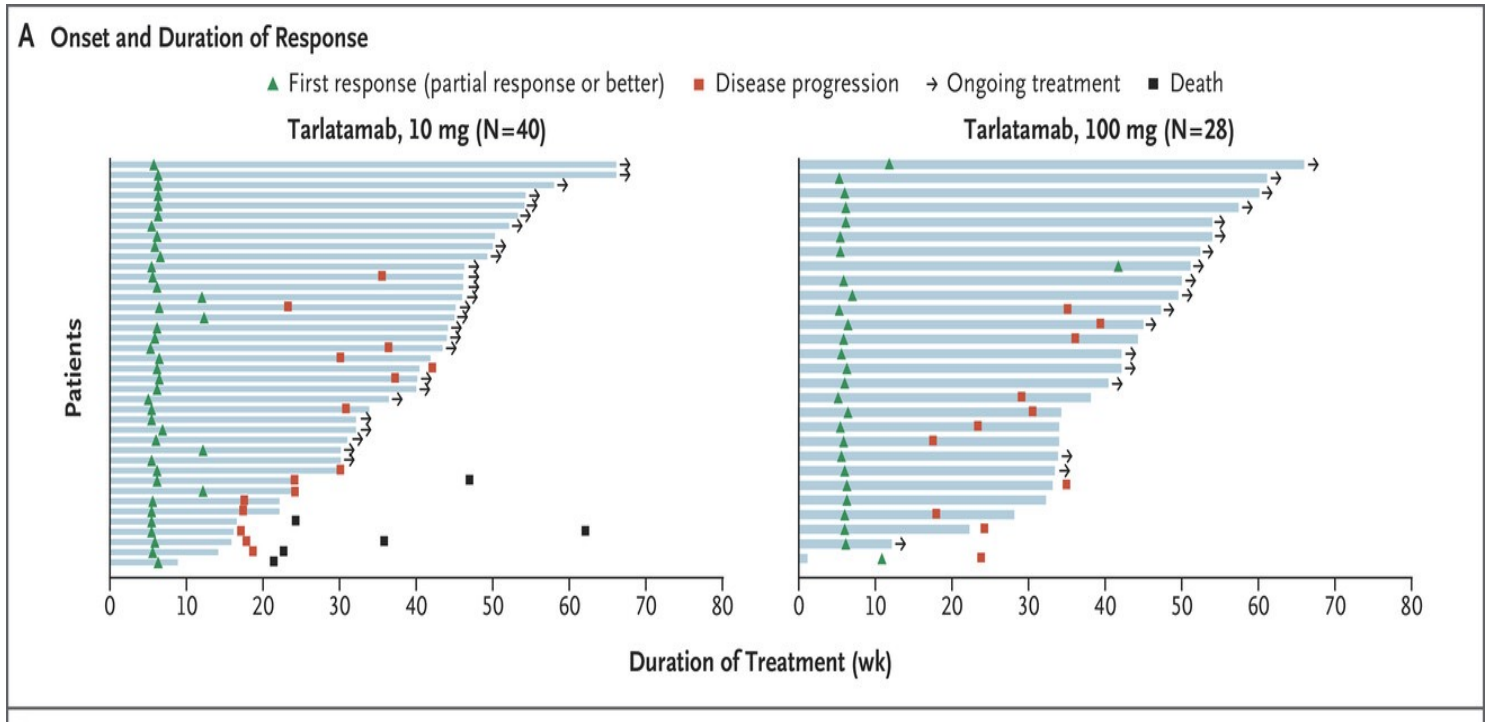
Tarlatamab for Patients with Previously Treated Small-Cell Lung Cancer

Authors: Myung-Ju Ahn, M.D., Ph.D., Byoung Chul Cho, M.D., Ph.D., Enriqueta Felip, M.D., Ph.D., Ippokratis Korantzis, M.D., Kadoaki Ohashi, M.D., Ph.D., Margarita Majem, M.D., Ph.D., Oscar Juan-Vidal, M.D., Ph.D. , +23 , for the DeLLphi-301 Investigators* Author Info & Affiliations

Published October 20, 2023 | N Engl J Med 2023;389:2063-2075
DOI: 10.1056/NEJMoa2307980 | VOL. 389 NO. 22

The NEW ENGLAND JOURNAL of MEDICINE

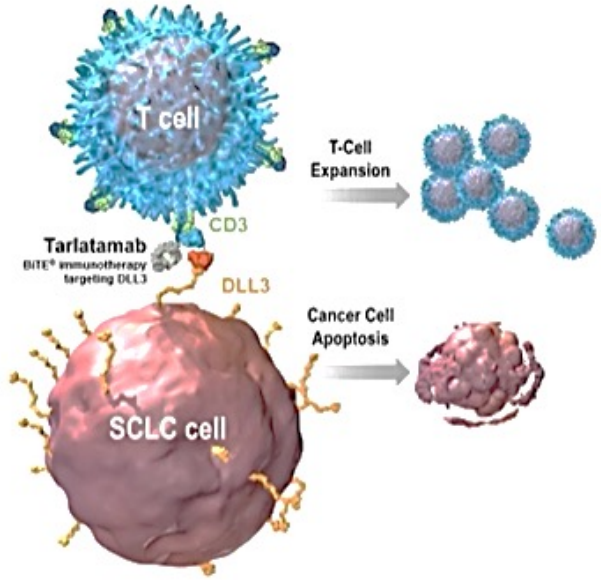
DeLLphi-301 trial, NCT05060016.



- Tarlatamab is a bispecific T-cell engager targeting DLL3 (on the tumor) and CD3 (on immune cells).
- Patients with treatment refractory ES-SCLC.
- ≥98% of patients in the study had ≥ 2 lines of prior therapy for ES-SCLC.
- 23% of patients had brain metastases.
- Objective response occurred in 40% (97.5% CI, 29 to 52) of patients in the 10-mg group and in 32% (97.5% CI, 21 to 44) of patients in the 100-mg group.
- At median follow-up time 10.6 months / 10.3 months, objective response still ongoing in 55% and 57% of patients in the 10-mg group versus the 100-mg group.
- AEs: CRS (51% vs. 61%), decreased appetite (29% vs. 44%), and pyrexia (35% vs. 33%).
- Tarlatamab FDA approved 05/16/2024.

DeLLphi-301 trial: Tarlatamab phase 2 in ES-SCLC – Efficacy and safety analyzed by presence of brain metastases

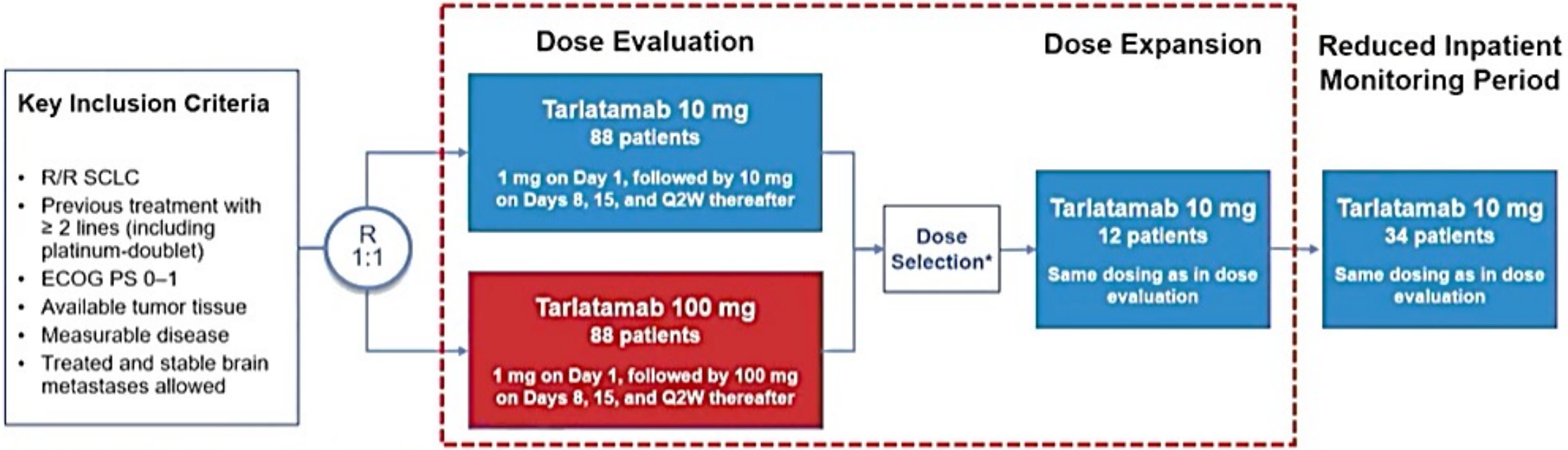
- Subgroup analysis of the phase 2 DeLLphi-301 study by the presence or absence of stable brain metastases at baseline.
- Exploration of CNS tumor shrinkage in patients with CNS lesions >= 10mm.



<u>Key Advance</u>:

- **The DLL2 BiTE, Tarlatamab, demonstrated durable anti-cancer activity regardless of the presence of stable brain metastases at baseline.**
- **CNS tumor shrinkage was observed after radiotherapy in some patients treated with tarlatamb.**

Phase 2 DeLLphi-301 Study Design



Primary Endpoint: ORR per RECIST v1.1 by BICR, TEAEs, tarlatamab serum concentrations
Secondary Endpoints: DOR, DCR, PFS per RECIST v1.1 by BICR, OS

Subgroup Analysis: Efficacy by BICR and safety, by presence or absence of baseline brain metastases
Post-hoc Analysis: Intracranial activity

NCT06060016 Post-enrollment, brain imaging was performed if clinically indicated. *Once 30 patients per dose level had the opportunity to confirm an objective response after the first post-treatment scan or up to 13 weeks of follow-up, whichever occurred first. **BICR**, blinded independent central review; **DCR**, disease control rate; **DOR**, duration of response; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **ORR**, objective response rate; **OS**, overall survival; **PFS**, progression-free survival; **Q2W**, every 2 weeks; **R**, randomization; **RECIST**, Response Evaluation Criteria in Solid Tumors; **R/R SCLC**, relapsed/refractory small cell lung cancer; **TEAE**, treatment-emergent adverse event.
Ahn MJ, et al. *N Engl J Med*. 2023;389:2063-2075.

Patient Baseline Clinical Characteristics

Baseline brain metastases:	Tarlatamab 10 mg Q2W* (n = 100)†	
	Yes (n = 23)	No (n = 77)
ECOG PS 0 / 1, n (%)	4 (17) / 19 (83)	22 (29) / 55 (71)
Median prior lines of therapy, n (range)	2 (2–5)	2 (1–6)
Prior anti-PD-(L)1 treatment, n (%)	19 (83)	55 (71)
DLL3 expression (> 0% of tumor cells), x/X (%)	21/22 (95)	59/61 (97)

Median follow-up period: 10.6 months‡

*Given as 1 mg on Day 1, followed by 10 mg on Days 8, 15, and Q2W thereafter. For 100 mg data, scan QR code or see https://meetings.asco.org/abstracts-presentations/232383. †The intention-to-treat analysis set consists of all patients who were randomized and enrolled according to assigned treatment dose level
‡OS data yet to mature. **DLL3**, delta-like ligand 3; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **PD-(L)1**, programmed cell death 1 protein/programmed cell death ligand-1 protein; **Q2W**, every 2 weeks.

Efficacy Summary

Baseline brain metastases:	Tarlatamab 10 mg Q2W* (n = 100)†	
	Yes (n = 23)	No (n = 77)
ORR, % (95% CI)	52 (31–73)	38 (27–49)
Median DOR, months (range)	NE (3–12+)	NE (2–12+)
DOR probability at 12 months, KM estimate, % (95% CI)	55 (22–78)	50 (29–68)
Median PFS, months (95% CI)	6.7 (3–NE)	4.0 (3–6)
Median OS‡, months (95% CI)	14.3 (14–NE)	NE (9–NE)

Tarlatamab demonstrated durable response with promising survival regardless of the presence of treated, stable brain metastases at baseline

Data cutoff, June 27, 2023. Median follow-up 10.6 months. *Given as 1 mg on Day 1, followed by 10 mg on Days 8, 15, and Q2W thereafter. For 100 mg data, scan QR code or see https://meetings.asco.org/abstracts-presentations/232383. †The intention-to-treat analyses set consists of all patients who were randomized and enrolled according to assigned treatment dose levels. ‡OS data yet to mature. **CI**, confidence interval; **DOR**, duration of response; **KM**, Kaplan-Meier; **NE**, not estimable; **ORR**, objective response rate; **OS**, overall survival; **PFS**, progression-free survival; **Q2W**, every 2 weeks.

Treatment-Related Adverse Events (TRAEs)

Baseline brain metastases:	Tarlatamab 10 mg Q2W* (n = 99)†	
	Yes (n = 22)	No (n = 77)
TRAEs, n (%)	21 (95)	71 (92)
Grade ≥3	8 (36)	25 (32)
Fatal (grade 5)§	0	0
Leading to dose interruption and / or reduction of tarlatamab	3 (14)	11 (14)
Leading to discontinuation of tarlatamab	1 (5)	3 (4)
TRAEs of interest		
CRS‡	12 (55)	39 (51)
Grade ≥3	0	0
Leading to discontinuation of tarlatamab	0	0
ICANS and associated neurological events§	3 (14)	5 (6)
Grade ≥3	0	0
Leading to discontinuation of tarlatamab	0	1 (1)

*Given as 1 mg on Day 1, followed by 10 mg on Days 8, 15, and Q2W thereafter. For 100 mg data, scan QR code or see https://meetings.asco.org/abstracts-presentations/232383. †The safety analysis includes all patients who received ≥ 1 dose of tarlatamab. One patient in the tarlatamab 10 mg group did not receive tarlatamab. Coded using MedDRA version 26.1. CRS and ICANS events were graded using American Society for Transplantation and Cellular Therapy 2019 Consensus Grading. ‡CRS based on AMQ narrow search. §ICANS and associated neurological events based on 61 selected preferred terms with AMQ broad search. ¶One patient (1%) in the tarlatamab 10 mg group died during part 3 from respiratory failure assessed by the investigator to be related to the trial treatment; contributing factors include baseline chronic obstructive pulmonary disease requiring supplemental oxygen, baseline compromised functional reserve, concurrent Grade 3 CRS and pneumonitis after cycle 1 day 1 treatment, and a decision against escalation to ICU-level care. This patient did not have brain metastases at baseline screening. **AMQ**, Amgen MedDRA query; **CRS**, cytokine release syndrome; **ICANS**, immune effector cell-associated neurotoxicity syndrome; **MedDRA**, Medical Dictionary for Regulatory Activities; **Q2W**, every 2 weeks; **TRAE**, treatment-related adverse event.

SYNOPSIS and PERSPECTIVE: DeLLphi-301 trial in ES-SCLC – Brain Metastases data

Where we were

- Limited treatment options for patients with ES-SCLC, available options had low response rates.
- CNS metastases was a major cause of morbidity and mortality for patients with SCLC.

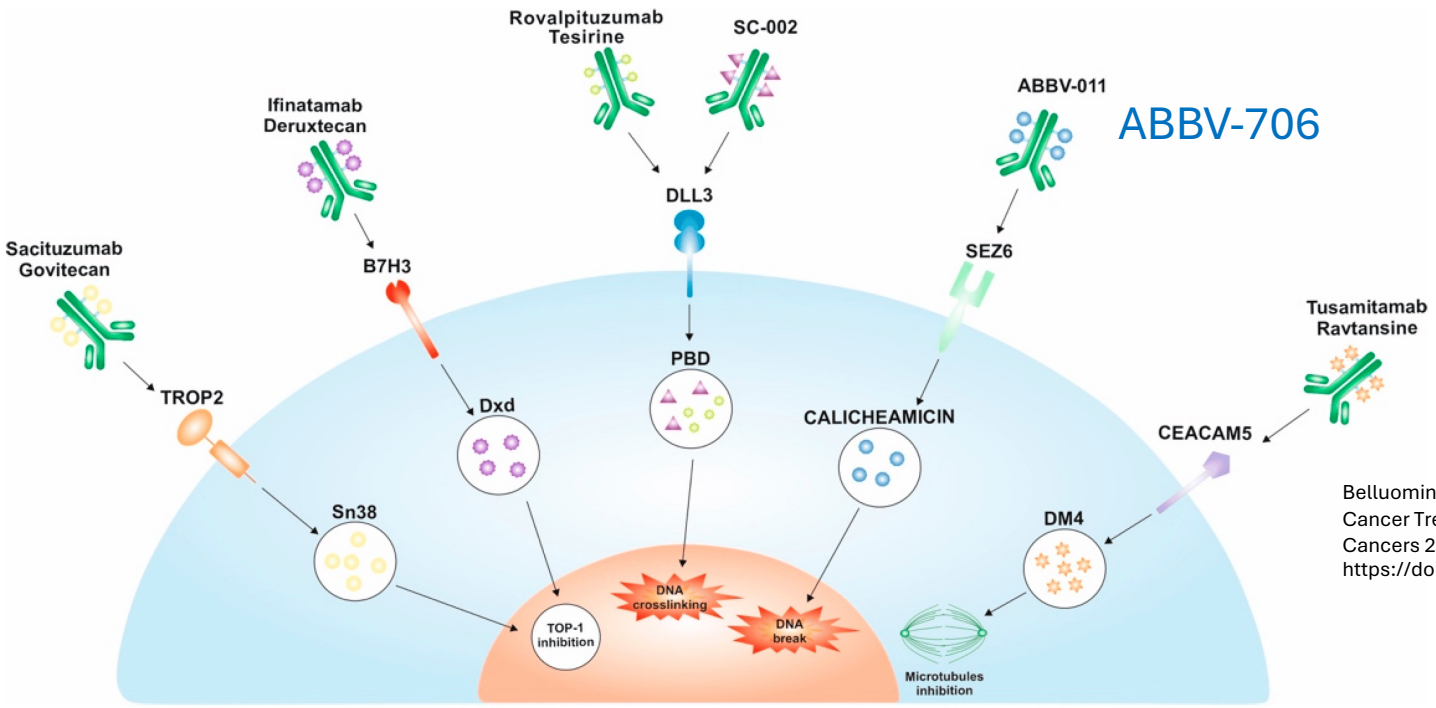
Where we are now

- Very promising new agents that is FDA approved, showing promising systemic activity in patients with heavily pre-treated ES-SCLC, including patients with baseline brain metastases.
- Some challenges in operationalizing deployment of tarlatamab.

Where we need to go

- Consideration of tarlatamab in earlier lines of therapy → first line study in combination with platinum/etoposide/atezo NCT05361395.
- Better biomarkers of response (since most tumors express DLL3, but not all patients respond).

Another New Target in SCLC – SEZ6



Belluomini, L. et al. Unlocking New Horizons in Small-Cell Lung Cancer Treatment: The Onset of Antibody–Drug Conjugates. Cancers 2023, 15, 5368. https://doi.org/10.3390/cancers15225368

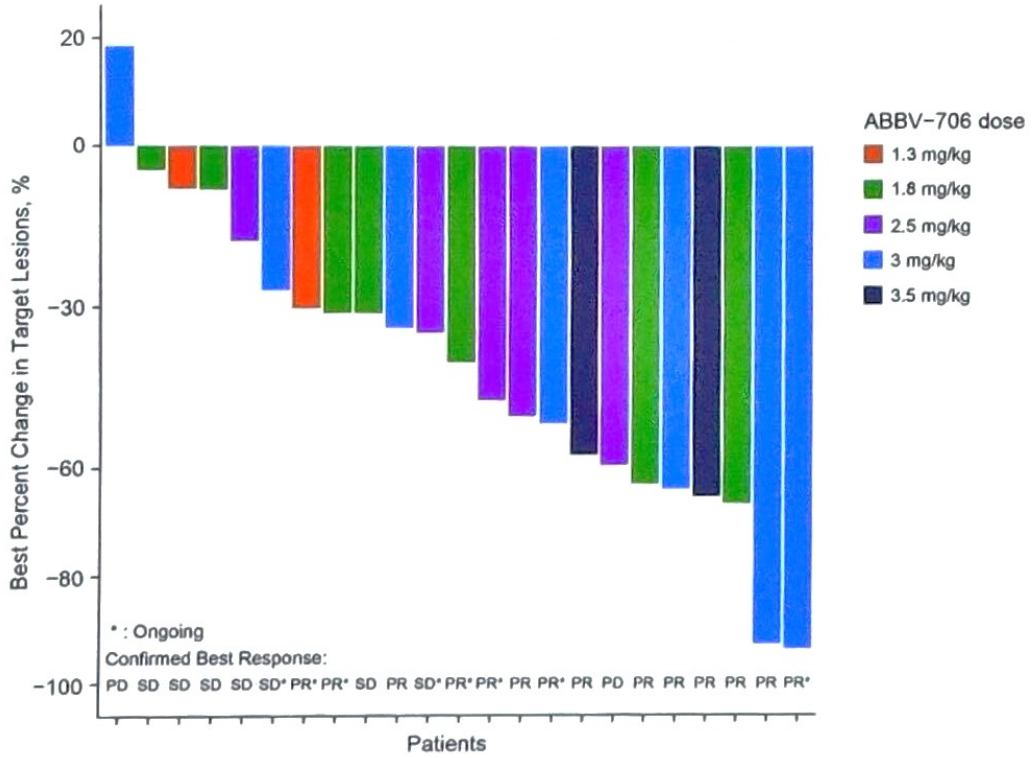
- SEZ6 is a transmembrane protein expressed SCLC, other neuroendocrine, and some CNS tumors.
- ABBV-706 is an ADC targeting SEZ6 conjugated to a topoisomerase 1 inhibitor payload at a drug-to-antibody ratio of 6.
- Phase I trial update presented at ASCO 2024: https://doi.org/10.1200/JCO.2024.42.16_suppl.300

Key Advance:

- **New targets on the horizon for SCLC – finally!**

ABBV-706 is highly efficacious across doses in R/R SCLC (N=23)

Change in Target Lesion Size by Dose



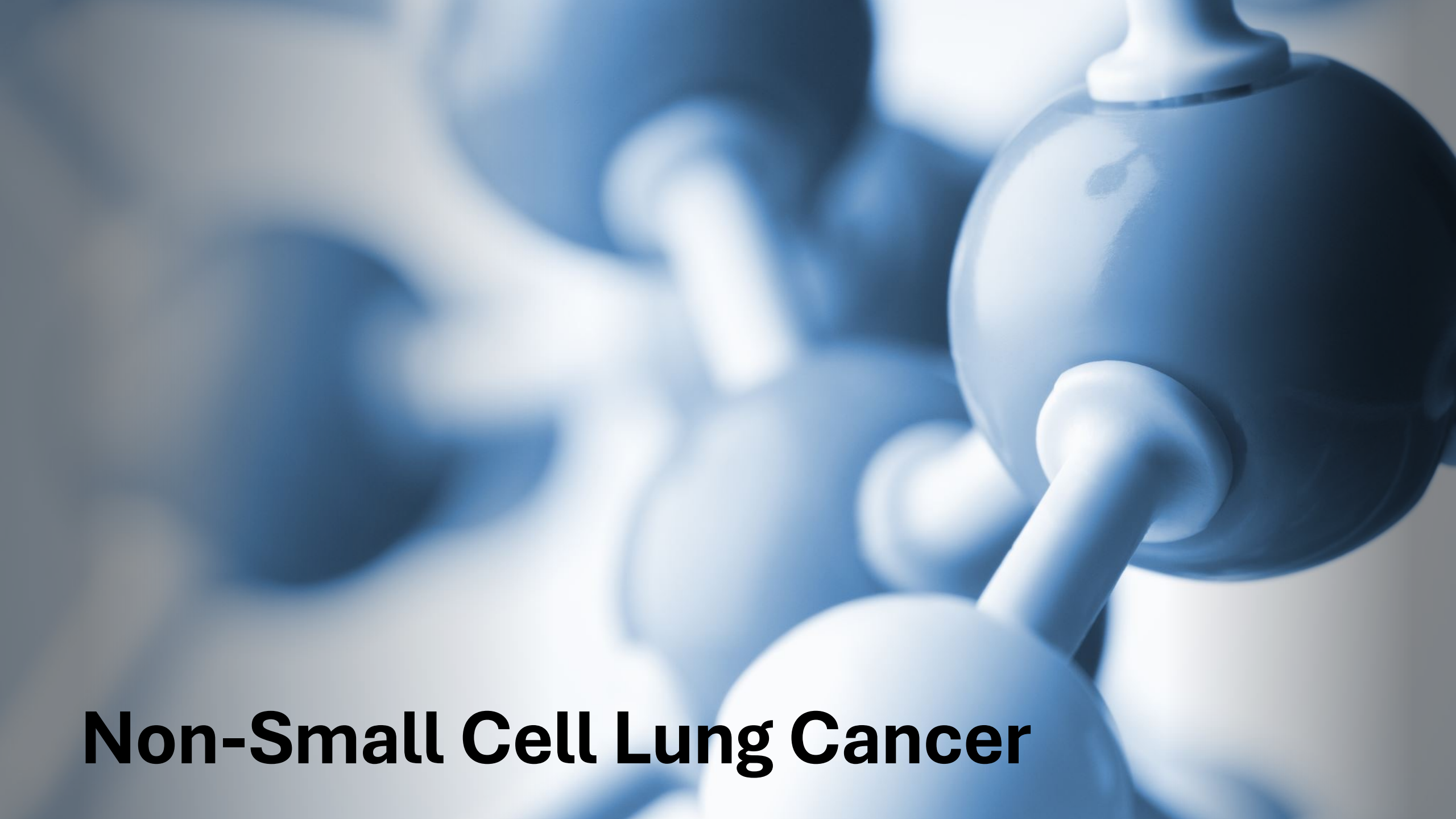
Ongoing	3.0 mg/kg	2.5 mg/kg	1.8 mg/kg	1.3 mg/kg
n=8	3	2	2	1

Outcome	SCLC (N=23)
ORR,[a] n (%) [90% exact CI]	**14 (60.9)** [41.7, 77.8]
Best response,[b] n (%)	
CR	0
PR	14 (60.9)
SD	7 (30.4)
PD	2 (8.7)
CBR,[c] n (%) [90% exact CI]	21 (91.3) [75.1, 98.4]

- 21/23 patients with SCLC were 3L+ at study enrollment
- 11/18 patients with available 1L CTFI data were platinum resistant

AEs: anemia and neutropenia were most common, with grade 3 or higher events seen in 42% of patients.

[a]Requires a CR or PR confirmed in an assessment ≥4 weeks later; [b]Response according to RECIST v1.1; [c]Requires CR or PR confirmed in an assessment ≥4 weeks later or SD lasting ≥5 weeks



Non-Small Cell Lung Cancer

UPDATES FROM NEOADJUVANT TRIALS IN NSCLC

Checkmate 816

- Neoadjuvant Nivolumab in Resectable Lung Cancer
- Spicer JD et al ASCO 2024, #LBA8010
- Update: 4 year update, neoadjuvant nivolumab plus chemo led to durable EFS and trend in OS improvement.
- Most mature data yet for neoadjuvant chemo-IO in lung cancer.

AEGEAN

- Perioperative Durvalumab in Resectable Lung Cancer
- Heymach JV et al ASCO 2024, Volume 42, Number 16_suppl
- Update: Among patients with baseline N2 nodal status, perioperative durvalumab plus neoadjuvant chemotherapy prolonged EFS and increased pCR rate(by 11.7%) versus neoadjuvant chemotherapy alone, similar to that observed in the ITT group.
- EFS HR = 0.63 (95% CI, 0.43-0.90), with benefit in both single and multi-statin disease (HR = 0.61 and 0.69, respectively).

Checkmate 77T

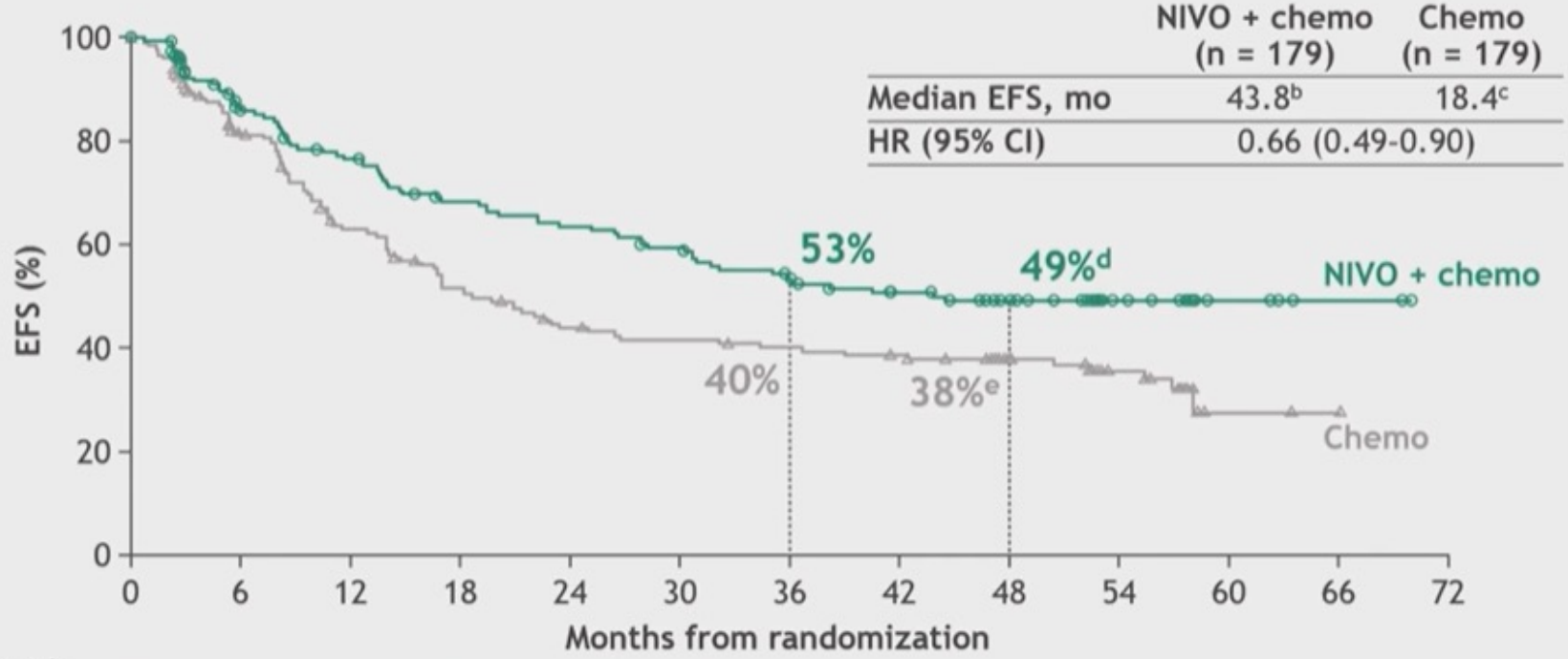
- Perioperative Nivolumab in Resectable Lung Cancer
- Cascone T et al ASCO 2024, LBA8007
- Update: Over half of pts with stg III disease had nodal downstaging with nivolumab (including N2 disease); majority downstaged to ypN0

Checkmate 816 - Neoadjuvant nivolumab plus platinum chemo in resectable lung cancer

EFS: 4-year update[a]

- In CheckMate 816, neoadjuvant NIVO + chemo significantly improved the primary endpoints of EFS and pCR vs chemo and demonstrated a favorable OS trend in patients with resectable NSCLC[1,2]

	NIVO + chemo (n = 179)	Chemo (n = 179)
Median EFS, mo	43.8[b]	18.4[c]
HR (95% CI)	0.66 (0.49-0.90)	



No. at risk												
NIVO + chemo	179	130	114	99	92	85	74	64	49	24	5	2	0
Chemo	179	124	92	73	60	56	53	50	37	22	2	1	0

Database lock date, February 23, 2024; minimum/median follow-up, 49.1/57.6 months.

[a]Exploratory analysis. [b-e]95% CI: [b]30.6-NR; [c]14.0-26.7; [d]41-57; [e]30-46. 1. Forde PM, et al. *N Engl J Med* 2022;386:1973-1985. 2. Forde PM, et al. Oral presentation at European Lung Cancer Congress (ELCC); March 29-April 1, 2023; Copenhagen, Denmark. Presentation 840.

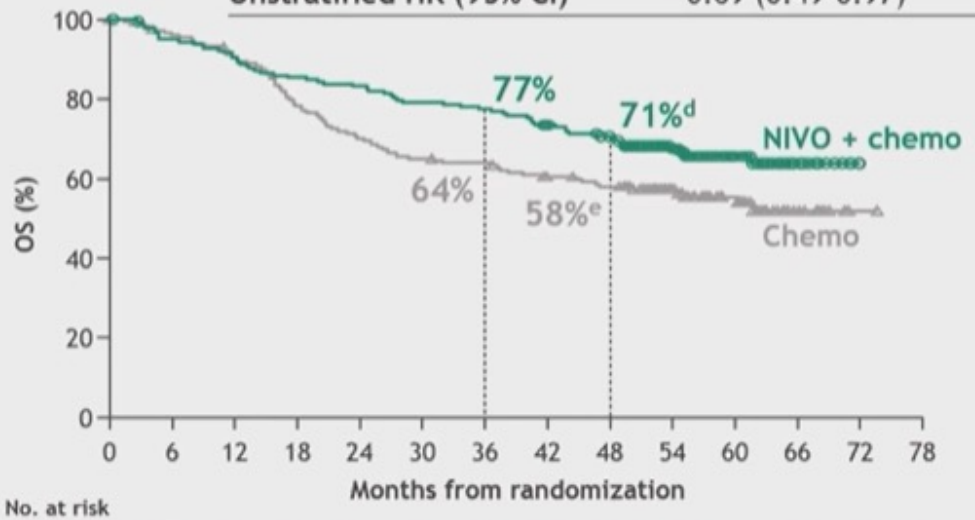
Nivolumab plus chemotherapy improved lung cancer specific survival vs. chemo

CheckMate 816: 4-y survival update

OS and lung cancer-specific survival: 4-year update

OS

	NIVO + chemo (n = 179)	Chemo (n = 179)
Median OS,[a] mo	NR	NR[c]
HR (98.36% CI); *P* value	0.71 (0.47-1.07); 0.0451[b]	
Unstratified HR (95% CI)	0.69 (0.49-0.97)	

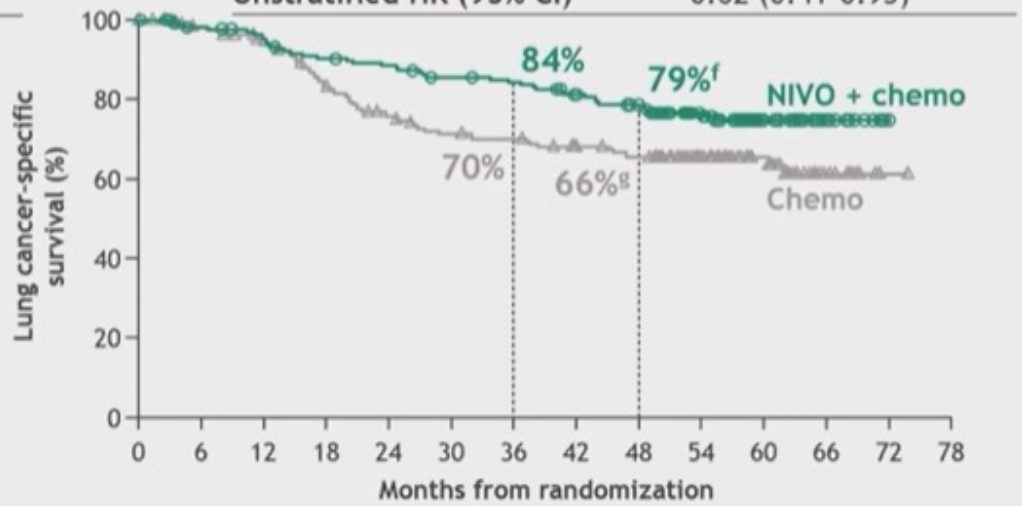


No. at risk

179	168	160	151	147	140	137	129	120	84	41	14	0	0
179	169	158	138	123	114	111	103	97	68	36	12	1	0

Lung cancer-specific survival[h]

	NIVO + chemo (n = 179)	Chemo (n = 179)
Median lung cancer-specific survival, mo	NR	NR
Unstratified HR (95% CI)	0.62 (0.41-0.93)	



179	168	160	151	147	140	137	129	120	84	41	14	0	0
179	169	158	138	123	114	111	103	97	68	36	12	1	0

- Patients in the NIVO + chemo arm who had pCR continued to have improved OS vs those who did not (HR [95% CI], 0.08 [0.02-0.34]; **4-year OS rates, 95% vs 63%**)

Minimum/median follow-up, 49.1/57.6 months.
[a]Reasons for OS events (deaths) in all treated patients in the NIVO + chemo vs chemo arms (N = 176 in each arm) were disease (23% vs 33%), study drug toxicity (0% vs 2%), unknown (3% vs 3%), and other (7% vs 5%).
[b]Significance boundary for OS (0.0164) was not met at this interim analysis. [c-g]95% CI: [c]50.4-NR; [d]63-77; [e]50-65; [f]72-84; [g]58-72. [h]Exploratory analysis; events were deaths with noted reason of "disease" per investigator assessment.

NEOADJUVANT TRIALS IN NSCLC – MANY QUESTIONS

- How do you manage multi nodal N2 station?
- How do you determine resectable versus non-resectable?
- Who needs neoadjuvant chemo/io?
- Who needs adjuvant IO?
- How we INTENSIFY the non path-CR group?

Efficacy and Safety of Olomorasib plus Pembrolizumab in Patients with KRAS G12C-mutated advanced NSCLC (NCT04956640)

- Olomorasib is a “next generation” KRAS G12C inhibitor.
- Initial clinical data from olomorasib: mostly grade 1/2 TEAEs with signs of efficacy, including CNS efficacy (also shown at ASCO 2024 by Dr. R. Heist).
- Results from Phase 1/2 study of olomorasib plus pembrolizumab in patients with KRAS G12C mutant solid tumors, including NSCLC. (LOXO-RAS-20001 study)
- Two doses of olomorasib (50mg, 100mg)

Key Advance:

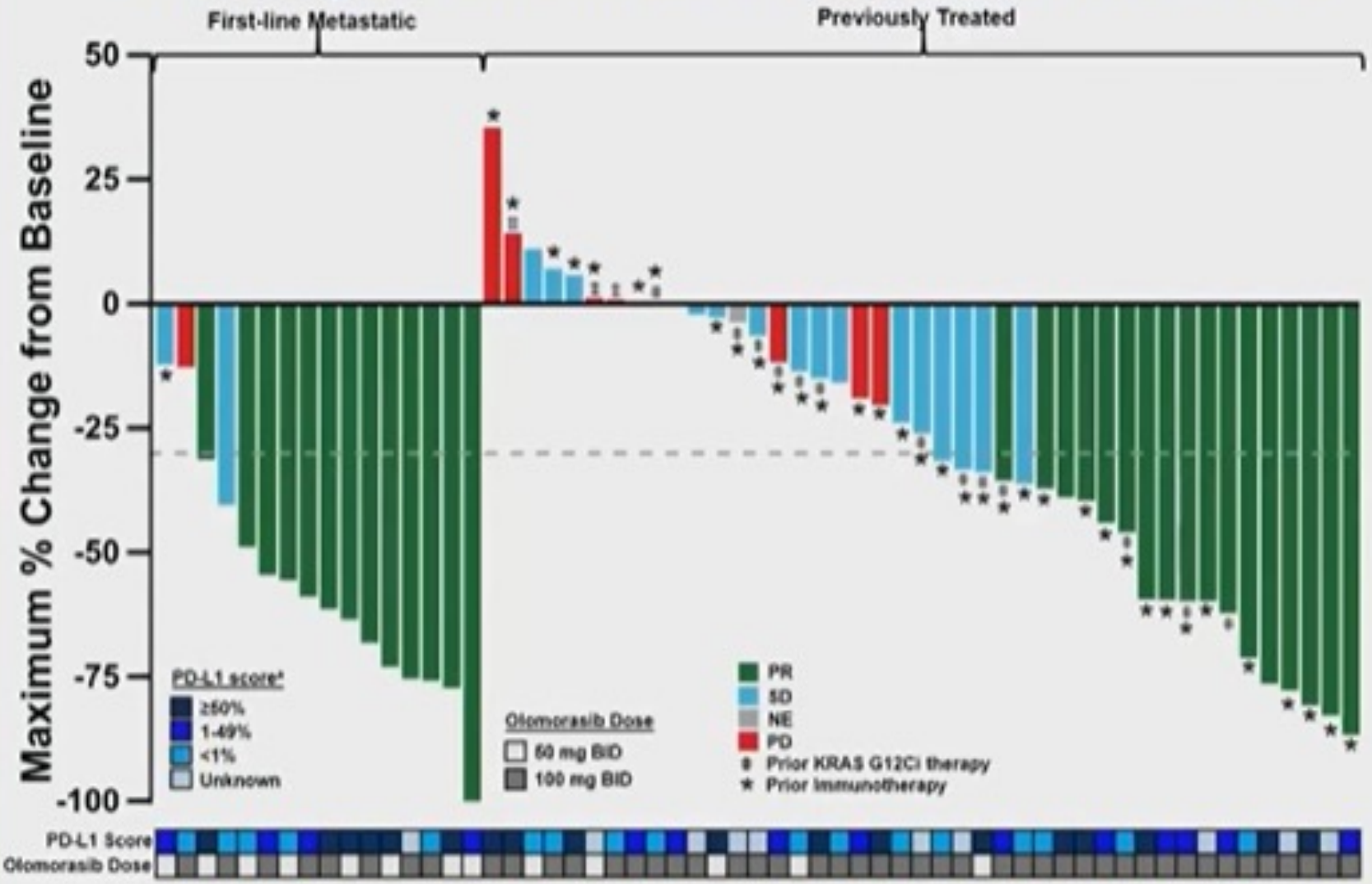
- **Addition of a KRAS G12C inhibitor to pembrolizumab appeared both safe and efficacious.**
- **Promising anti-tumor activity in first line metastatic NSCLC with 77% ORR across PD-L1 expression levels.**

Patient and Disease Characteristics

Characteristics	Olomorasib 50 mg BID (n=15) and 100 mg BID (n=49) + Pembrolizumab N=64
Median age, years (range)	67 (42-83)
Sex, n (%)	
Male / Female	34 (53) / 30 (47)
Race, n (%)	
White / Asian / Black or African American / Not reported	30 (47) / 17 (27) / 3 (5) / 14 (22)
ECOG PS, n (%)	
0 / 1	16 (25) / 48 (75)
PD-L1 score[a], n (%)	
<1%	17 (27)
1-49%	17 (27)
≥50%	18 (28)
Unknown[b]	12 (19)
Brain metastases, n (%)	24 (38)
Median number of prior systemic therapies (range)	2 (0-8)
First-line metastatic, n (%)	20 (31)
Previously treated, n (%)[c]	44 (69)
Platinum-based chemotherapy/anti-PD-(L)1 therapy	36 (82)
Platinum-based chemotherapy alone	8 (18)
KRAS G12C inhibitor	17 (39)
Reason discontinued most recent KRAS G12C inhibitor, n (%)[d]	
Progressive disease / Toxicity / Other	13 (76) / 3 (18) / 1 (6)

Data cutoff date of 18 Mar 2024. [a]Local testing allowed for PD-L1 score. [b]Includes not reported and missing data. Known PD-L1 score not required for cohort B4. [c]Calculated as percentage of patients who had prior treatment in the metastatic setting, n=44. [d]Calculated as percentage of patients who received most recent KRAS G12C inhibitor, n=17. Total % may be different from the individual components due to rounding.

Efficacy of Olomorasib + Pembrolizumab



Efficacy Evaluable Patients[b]	First-line Metastatic (N=17)	Previously Treated (N=43)
Objective Response Rate[c], % (n/N)	77% (13/17)	40% (17/43)
Best overall response		
CR, n (%)	-	-
PR, n (%)	13 (77)	17 (40)
SD, n (%)	2 (12)	18 (42)
PD, n (%)	1 (6)	7 (16)
NE, n (%)	1 (6)	1 (2)
DCR, % (n/N)	88% (15/17)	81% (35/43)

- 81% (35/43) of previously treated patients had received prior immunotherapy
- Median time to response was 1.4 months; median duration of response was NE

- ✓ Responses across all PDL1 levels
- ✓ Responses regardless of PDL1
- ✓ Responses regardless of prior KRAS G12C

Data cutoff date of 18 Mar 2024. *PD-L1 frequency - 30% with ≥50%, 25% with 1-49%, 28% with <1%, and 17% unknown. [b]Efficacy evaluable patients are those treated at 50 and 100 mg olomorasib doses who had at least one post-baseline response assessment or had discontinued treatment before the first post-baseline response assessment. Data for 5 patients are not shown in the waterfall plot; 1 discontinued prior to first post-baseline response assessment, and 4 did not have a first post-baseline response assessment and are ongoing. [c]ORR includes patients with a best response of PR (confirmed, and pending confirmation and ongoing); 2 patients in first-line metastatic and 1 patient in previously treated have unconfirmed PRs pending confirmation and ongoing. Investigator assessed response per RECIST v1.1.

Safety Profile: Olomorasib + Pembrolizumab

All Doses and Patients (50 mg BID and 100 mg BID, N=64)							
	Treatment-Emergent AEs (>10%), %		Treatment-Related AEs[a], %				
Adverse Event	Any grade	Grade ≥3	Any grade	Grade 1	Grade 2	Grade 3	Grade 4[b]
Any AE	86%	47%	70%	20%	23%	25%	2%
Diarrhea	28%	13%	23%	8%	3%	13%	-
Fatigue	27%	-	16%	8%	8%	-	-
ALT increased	25%	8%	20%	11%	3%	6%	-
Pruritus	25%	3%	19%	11%	5%	3%	-
Nausea	23%	-	14%	6%	8%	-	-
Arthralgia	19%	-	8%	8%	-	-	-
AST increased	17%	8%	16%	6%	2%	8%	-
Vomiting	17%	-	8%	5%	3%	-	-
Anemia	16%	2%	3%	3%	-	-	-
Decreased appetite	14%	2%	9%	8%	-	2%	-
Cough	13%	-	-	-	-	-	-
Dyspnea	11%	5%	-	-	-	-	-
Headache	11%	-	2%	2%	-	-	-
Hypokalemia	11%	3%	-	-	-	-	-

- TRAEs led to olomorasib dose holds in 25% of patients (16/64) and olomorasib dose reductions in 17% of patients (11/64)
- TRAEs led to permanent discontinuation of olomorasib only in 3% of patients (2/64) and pembrolizumab only in 11% of patients (7/64); 5% of patients (3/64) discontinued both drugs due to TRAEs
- Grade ≥2 diarrhea was usually brief (median 9 days), and 92% resolved to grade 1/baseline with dose modification and antidiarrheals

Data cutoff date of 18 Mar 2024. [a]TRAEs are olomorasib and/or pembrolizumab related. [b]1 patient had a grade 4 TRAE (pneumonitis). Total % may be different from the individual components due to rounding. AE, adverse event; ALT alanine aminotransferase; AST, aspartate aminotransferase.

SYNOPSIS and PERSPECTIVE: LOXO-RAS-20001 study - Olomorasib plus Pembrolizumab in Patients with KRAS G12C-mutated advanced NSCLC

Where we were

- Concomitant administration of FDA-approved KRAS G12C inhibitors plus immunotherapy has been challenged by toxicity.

Where we are now

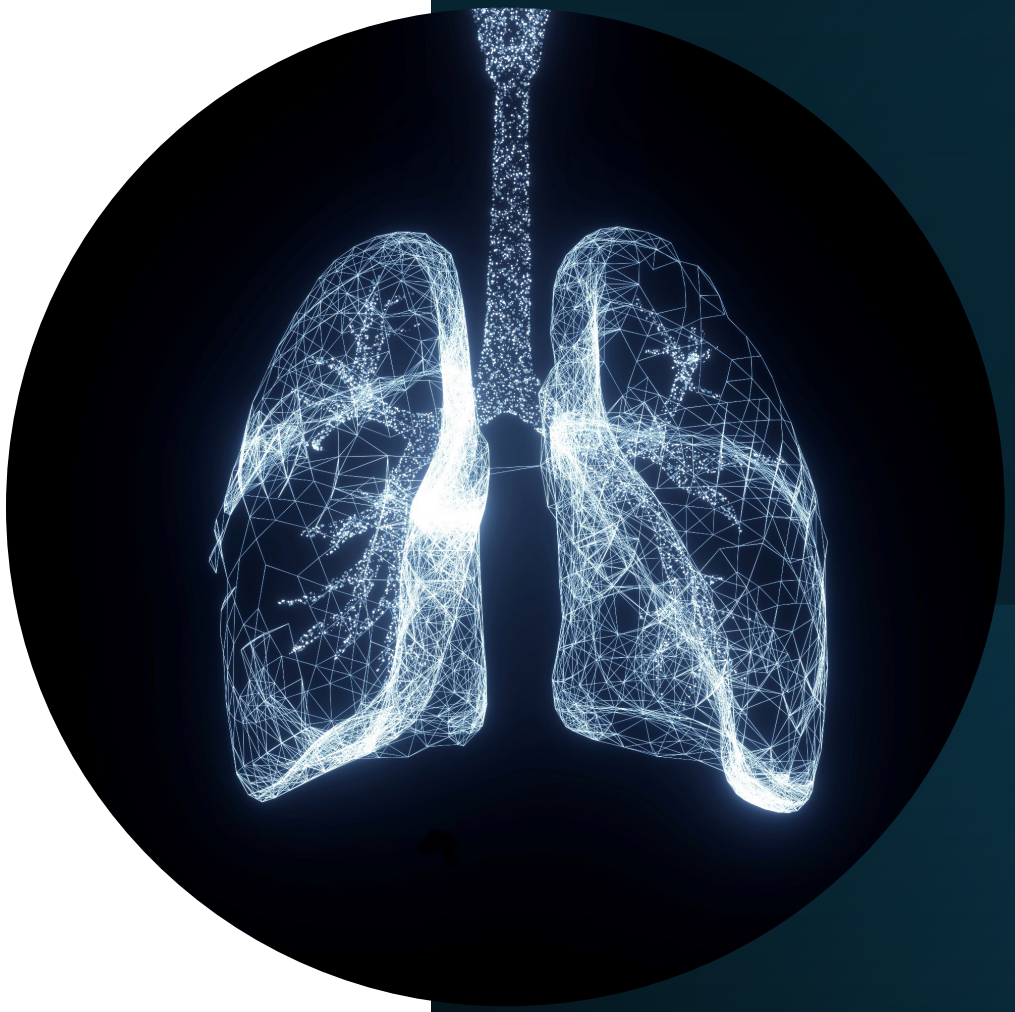
- Very promising activity and safety profile of “next generation” KRAS G12C inhibitor, Olomorasib, plus Pembrolizumab in first line metastatic and refractory settings.

Where we need to go

- First line combination trial has started enrollment: SUNRAY-01, NCT06119581
- What are the mechanisms of acquired resistance to KRAS G12C targeted therapies?
- What about KRAS G12C subtypes/co-mutations (STK11, KEAP1, etc.)

Summary ASCO Lung IO 2024

- Practice changing data in LS-SCLC
- New targets in ES-SCLC
  - DLL3, SEZ6, B7-H3
- Updates and confirmation of neoadjuvant strategies in early stage NSCLC
- Novel IO-targeted therapy combinations in advanced KRAS G12C mutated NSCLC
- MANY targeted therapy advances (Dr. Porter to cover)
- Much more we could not cover today



Please feel free to reach out any time to discuss / connect!

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