Updates in Lung Cancer Treatment

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Disclosures

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- Research Funding: Bristol Myers Squib Foundation
- Advisory Board: Genentech

Outline

Introduction

Updates in Small Cell Lung Cancer (SCLC)

- Early Stage - ADRIATIC
- Metastatic - DeLLphi-301

Updates in Non-Small Cell Lung Cancer (NSCLC)

- Early stage
  - ALK + : ALINA
  - EGFR+: LAURA TRIAL
- Metastatic
  - ALK +: CROWN
  - KRAS+: KRYSTAL 12, SUNRAY -01
  - HER2+: Zongertinib
  - EGFR – IV vs SC Amivantamab

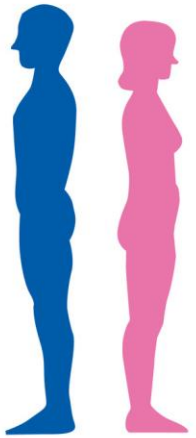
Summary

Introduction

Lung cancer remains the leading cause of cancer mortality

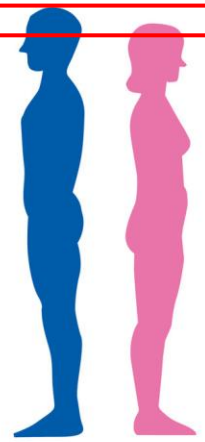
Estimated New Cases

Males			Females		
Prostate	268,490	27%	Breast	287,850	31%
Lung & bronchus	117,910	12%	Lung & bronchus	118,830	13%
Colon & rectum	80,690	8%	Colon & rectum	70,340	8%
Urinary bladder	61,700	6%	Uterine corpus	65,950	7%
Melanoma of the skin	57,180	6%	Melanoma of the skin	42,600	5%
Kidney & renal pelvis	50,290	5%	Non-Hodgkin lymphoma	36,350	4%
Non-Hodgkin lymphoma	44,120	4%	Thyroid	31,940	3%
Oral cavity & pharynx	38,700	4%	Pancreas	29,240	3%
Leukemia	35,810	4%	Kidney & renal pelvis	28,710	3%
Pancreas	32,970	3%	Leukemia	24,840	3%
All Sites	**983,160**	**100%**	**All Sites**	**934,870**	**100%**



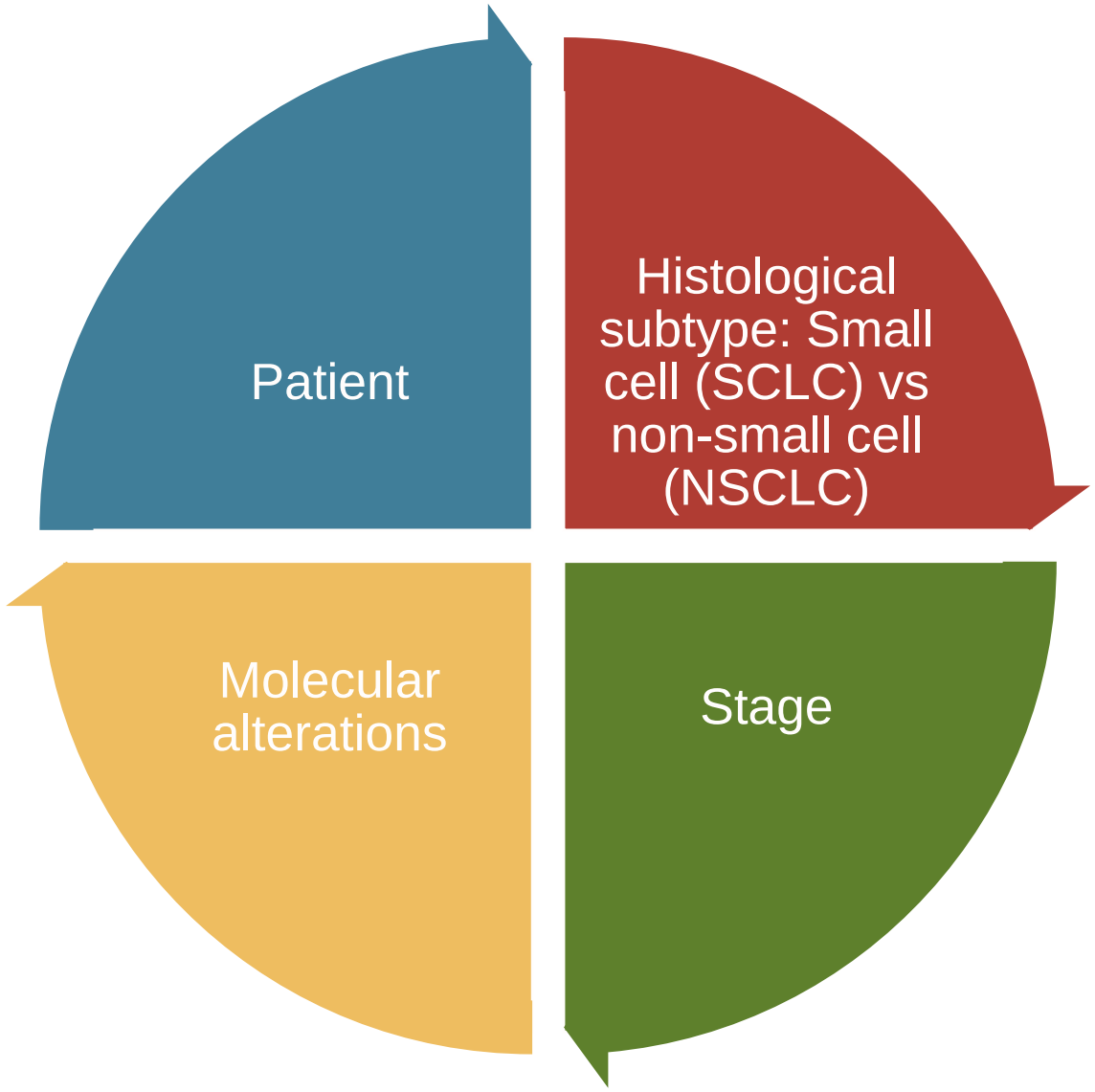
Estimated Deaths

Males			Females		
Lung & bronchus	68,820	21%	Lung & bronchus	61,360	21%
Prostate	34,500	11%	Breast	43,250	15%
Colon & rectum	28,400	9%	Colon & rectum	24,180	8%
Pancreas	25,970	8%	Pancreas	23,860	8%
Liver & intrahepatic bile duct	20,420	6%	Ovary	12,810	4%
Leukemia	14,020	4%	Uterine corpus	12,550	4%
Esophagus	13,250	4%	Liver & intrahepatic bile duct	10,100	4%
Urinary bladder	12,120	4%	Leukemia	9,980	3%
Non-Hodgkin lymphoma	11,700	4%	Non-Hodgkin lymphoma	8,550	3%
Brain & other nervous system	10,710	3%	Brain & other nervous system	7,570	3%
All Sites	**322,090**	**100%**	**All Sites**	**287,270**	**100%**



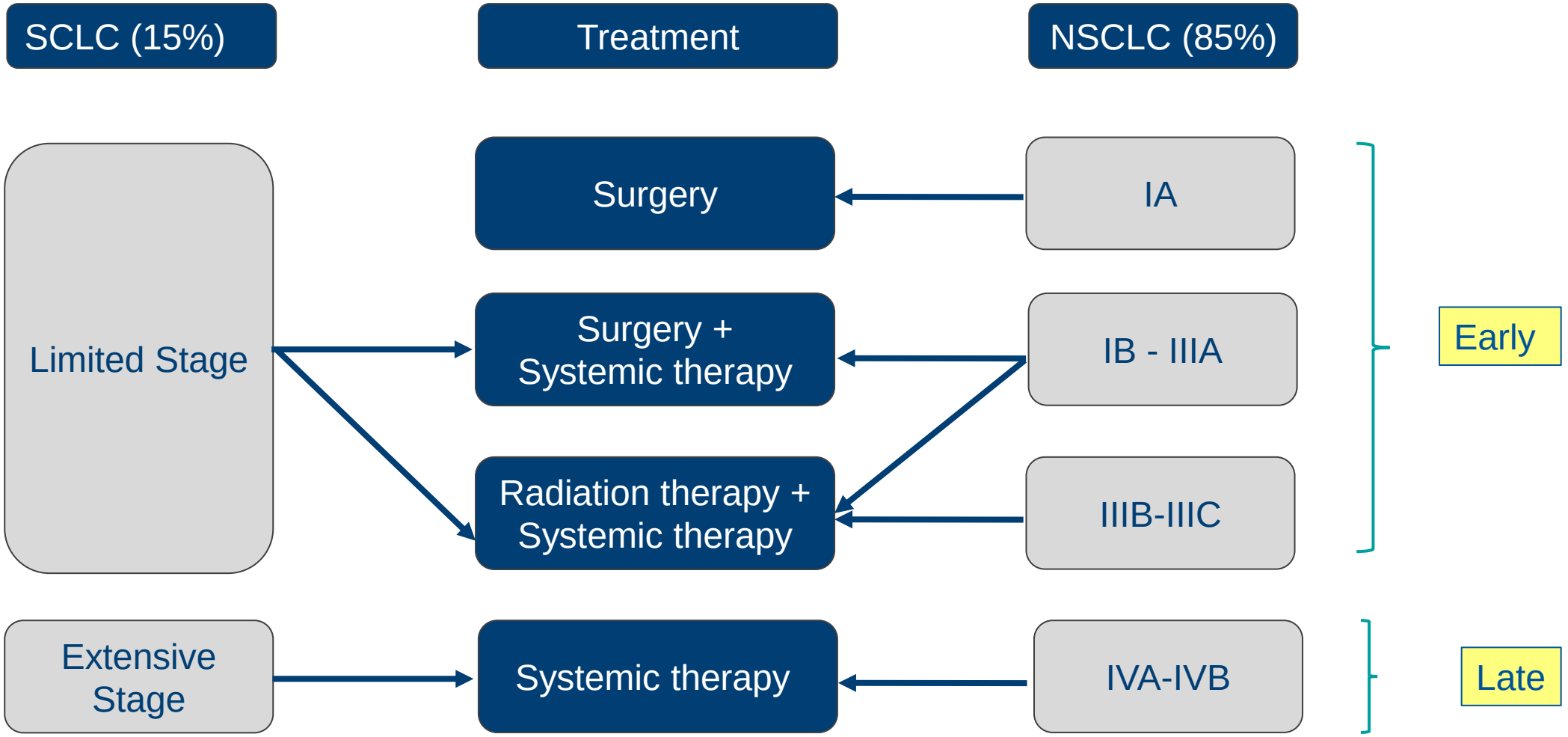
Seigel et al, Cancer statistics 2022

Considerations for the treatment of lung cancer

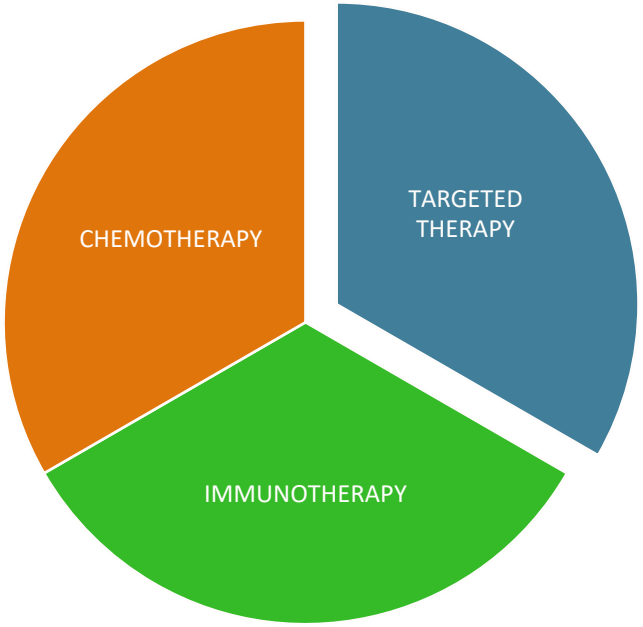


Seigel et al, Cancer statistics 2022

Therapeutic landscape of lung cancer



Landscape of systemic therapies for lung lancer



Molecular Targets in NSCLC

- EGFR
- ALK
- RET
- ROS
- MEK
- KRAS
- BRAF
- HER2

Updates in SCLC

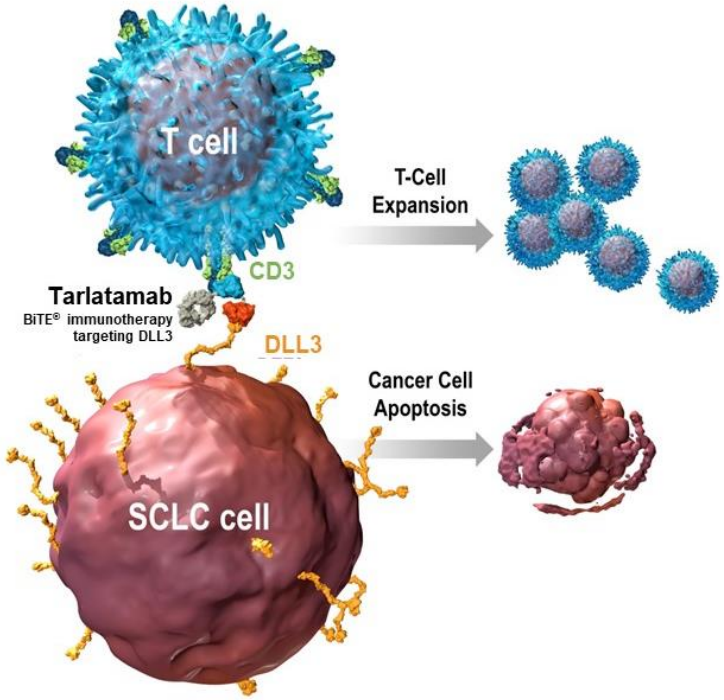
2024 ASCO ANNUAL MEETING

DeLLphi 301

DeLLphi-301: Tarlatamab phase 2 trial in small cell lung cancer (SCLC)—Efficacy and safety analyzed by presence of brain metastases

Anne-Marie C. Dingemans,[1] Myung-Ju Ahn,[2] Fiona Blackhall,[3] Martin Reck,[4] Horst-Dieter Hummel,[5] Suresh S. Ramalingam,[6] Melissa L. Johnson,[7] Hiroaki Akamatsu,[8] Jürgen Wolf,[9] Jacob Sands,[10] Taofeek K.Owonikoko,[11] Hossein Borghaei,[12] Sujoy Mukherjee,[13] Shuang Huang,[13] Pablo Martinez,[13] Luis Paz-Ares[14]

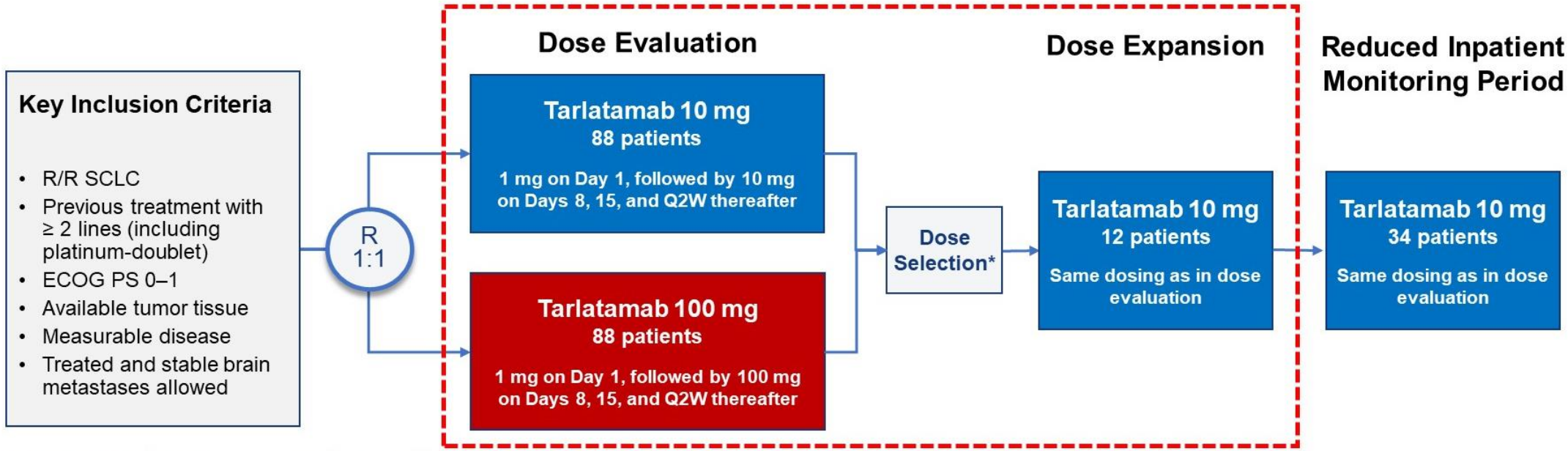
[1]Department of Pulmonary Medicine, Erasmus MC Cancer Institute, Rotterdam, Netherlands; [2]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [3]The Christie NHS Foundation Trust, Manchester, UK; [4]Interdisciplinary Study Center, Translational Oncology/Early Clinical Trial Unit (ECTU), Comprehensive Cancer Center Mainfranken, Würzburg, Germany; [5]Translational Oncology/Early Clinical Trial Unit, Universitätsklinikum Würzburg, Comprehensive Cancer Center Mainfranken, Würzburg, Germany; [6]Winship Cancer Institute of Emory University, Atlanta, GA, USA; [7]Sarah Cannon Research Institute at Tennessee Oncology, Nashville, TN, USA; [8]Wakayama Medical University Hospital, Wakayama, Japan; [9]Department I Internal Medicine - Center for Integrated Oncology, Universitätsklinikum Köln (AöR), Cologne, Germany; [10]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; [11]Division of Hematology-Oncology, University of Maryland, Marlene and Stewart Greenebaum Comprehensive Cancer Center, Baltimore, MD, USA; [12]Fox Chase Cancer Center, Philadelphia, PA, USA; [13]Amgen Inc., Thousand Oaks, CA, USA; [14]Hospital Universitario 12 de Octubre, CNIO-H12o Lung Cancer Unit, Complutense University and Ciberonc, Madrid, Spain.



PRESENTED BY: Anne-Marie C. Dingemans, MD, PhD

Updates in SCLC

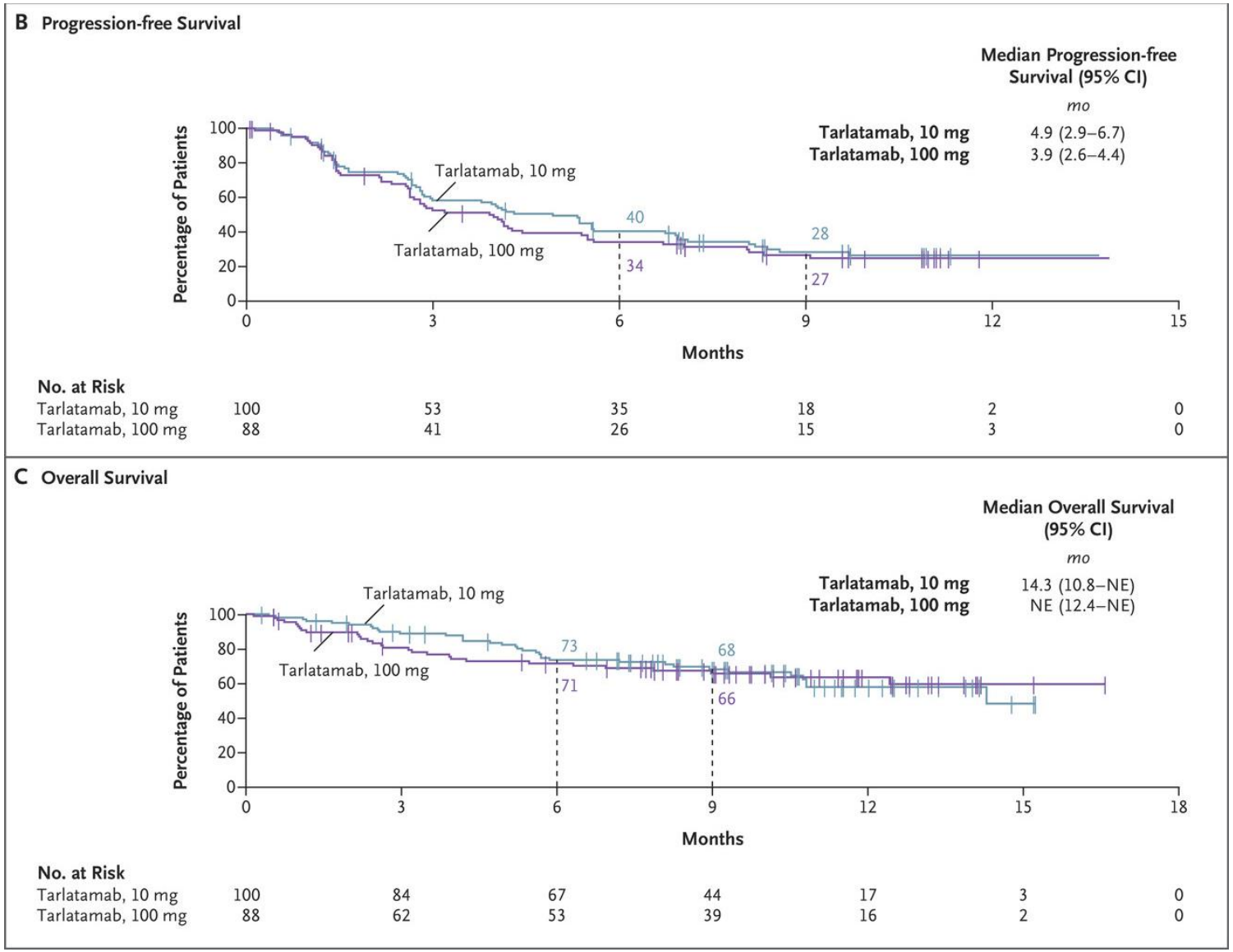
Phase 2 DeLLphi-301 Study Design



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

Updates in SCLC



Ahn et al, N Engl J Med 2023;389:2063-2075

Updates in SCLC

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 analysis 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.

PRESENTED BY: Anne-Marie C. Dingemans, MD, PhD

Updates in SCLC

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2024
Small Cell Lung Cancer

SCLC SUBSEQUENT SYSTEMIC THERAPY (PS 0–2)[f,] Consider dose reduction or growth factor support for patients with PS 2.
CHEMOTHERAPY-FREE INTERVAL (CTFI) >6 MONTHS
Preferred Regimens • Clinical trial enrollment • Re-treatment with platinum-based doublet[g,34,35,37-39] **Other Recommended Regimens** • Lurbinectedin[17,36] • Topotecan oral (PO) or intravenous (IV)[14-16,28] • Irinotecan[h,21,28] • Tarlatamab-dlle[i,47]
CTFI ≤6 MONTHS
Preferred Regimens • Clinical trial enrollment • Lurbinectedin[17,36] • Topotecan oral (PO) or intravenous (IV)[14-16,28,37] • Irinotecan[h,21,28] • Tarlatamab-dlle[i,47] • Re-treatment with platinum-based doublet may be considered for CTFI 3–6 months[g,37,38,39] **Other Recommended Regimens** • Nivolumab or pembrolizumab (if not previously treated with an ICI)[b, 29,30,31,32,33] • Paclitaxel[18,19] • Temozolomide[22,23] • Cyclophosphamide/doxorubicin/vincristine (CAV)[14] • Docetaxel[20] • Gemcitabine[26,27,40] • Oral etoposide[24,25]

Updates in SCLC

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

PRESENTED BY: Dr David R. Spigel, Sarah Cannon Research Institute, Nashville, TN, USA

Updates in SCLC

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

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

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

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

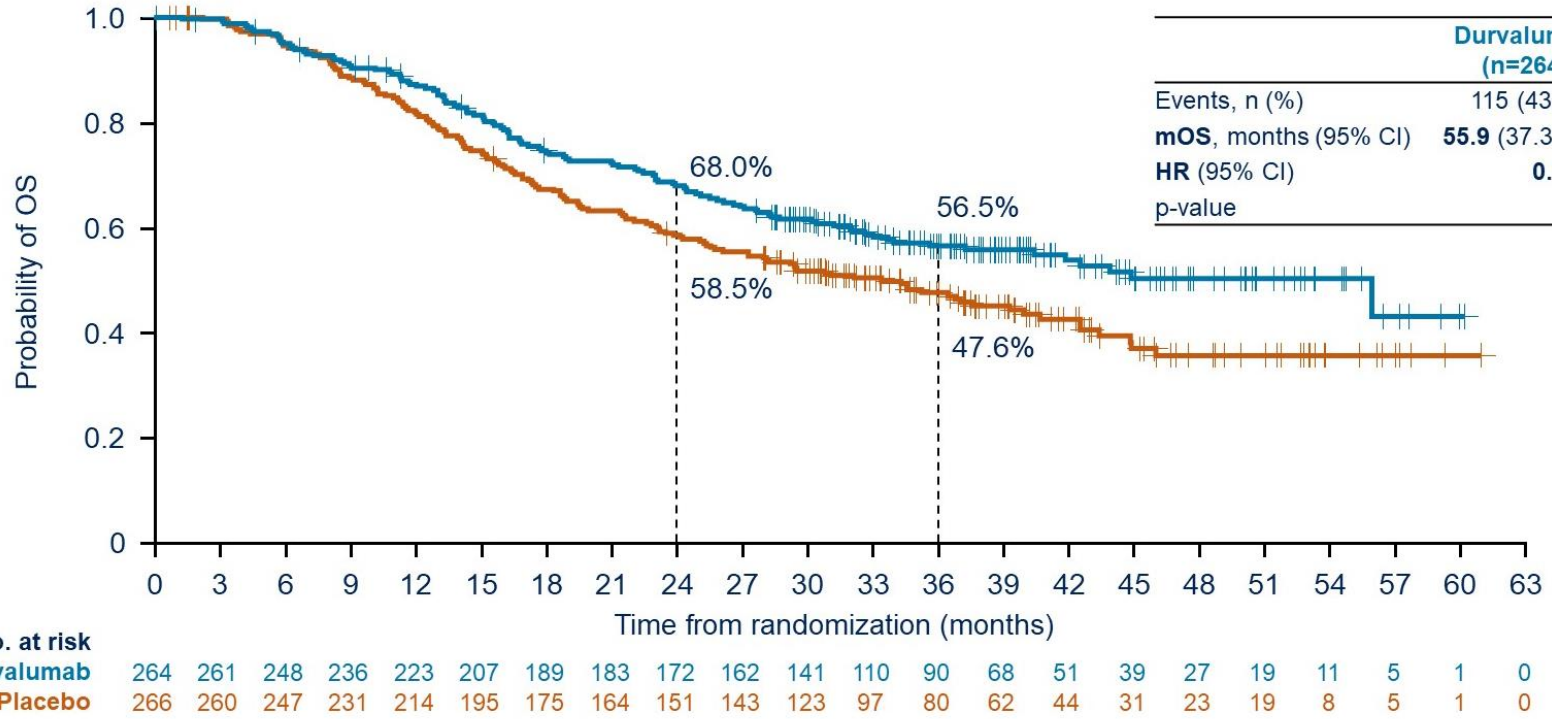
*cCRT and PCI treatment, if received per local standard of care, must have been completed within 1–42 days prior to randomization.
†If disease control was achieved and no additional benefit was expected with an additional cycle of chemotherapy, in the opinion of the investigator.
‡The first 600 patients were randomized in a 1:1:1 ratio to the 3 treatment arms; subsequent patients were randomized 1:1 to either durvalumab or placebo.

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.

Updates in SCLC

Overall survival (dual primary endpoint)

- 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.

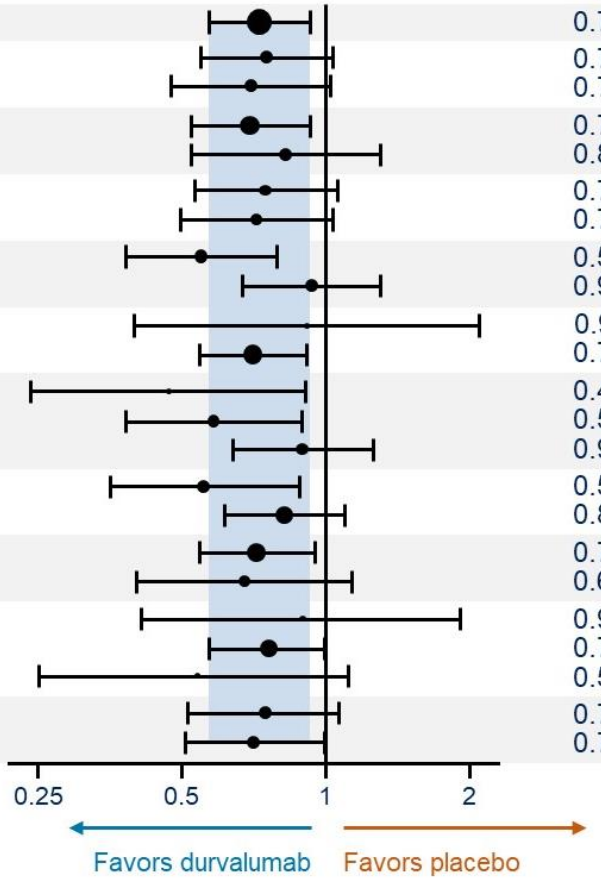
PRESENTED BY: Dr David R. Spigel

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

Updates in SCLC

OS subgroup analysis

		Events/Patients n/N		HR (95% CI)
		Durvalumab	Placebo	
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.

Summary: Updates in SCLC

- ✓Tarlatamab is FDA approved and in NCCN guidelines for extensive stage SCLC in the 2L.
- ✓Consolidation Durvalumab should be the new SOC for limited stage SCLC patients after concurrent chemoRT.
- ✓Molecular profiling and stratification of SCLC is promising.

Updates in Early Stage NSCLC: ALK +

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Alectinib in Resected *ALK*-Positive Non–Small-Cell Lung Cancer

Authors: Yi-Long Wu, M.D., Rafal Dziadziuszko, M.D., Ph.D., Jin Seok Ahn, M.D., Ph.D., Fabrice Barlesi, M.D., Ph.D., Makoto Nishio, M.D., Ph.D., Dae Ho Lee, M.D., Ph.D., Jong-Seok Lee, M.D., Ph.D., +15, for the ALINA Investigators* Author Info & Affiliations

Published April 10, 2024 | N Engl J Med 2024;390:1265-1276 | DOI: 10.1056/NEJMoa2310532 | VOL. 390 NO. 14

Updates in Early Stage NSCLC: ALK +

ALINA study design*

Resected Stage IB (≥4cm)–IIIA *ALK*+ NSCLC
per UICC/AJCC 7th edition

Other key eligibility criteria:
- ECOG PS 0–1
- Eligible to receive platinum-based chemotherapy
- Adequate end-organ function
- No prior systemic cancer therapy

Stratification factors:
- Stage: IB (≥ 4cm) vs II vs IIIA
- Race: Asian vs non-Asian

R 1:1

N=257

Alectinib 600 mg BID 2 years → **Recurrence**

Platinum-based chemotherapy† Q3W; 4 cycles → **Recurrence**

Further treatments at investigator's choice and survival follow-up

Primary endpoint
- DFS per investigator,‡ tested hierarchically:
  - Stage II–IIIA → ITT (Stage IB–IIIA)

Other endpoints
- CNS disease-free survival
- OS
- Safety

Disease assessments (including brain MRI)§ were conducted: at baseline, every 12 weeks for year 1–2, every 24 weeks for year 3–5, then annually

MADRID 2023 ESMO congress

Data cut-off: 26 June 2023; CNS, central nervous system; DFS, disease-free survival; ITT, intention to treat
*Superiority trial; †Cisplatin + pemetrexed, cisplatin + vinorelbine or cisplatin + gemcitabine; cisplatin could be switched to carboplatin in case of intolerability; ‡DFS defined as the time from randomisation to the first documented recurrence of disease or new primary NSCLC as determined by the investigator, or death from any cause, whichever occurs first; §Assessment by CT scan where MRI not available; NCT03456076

Updates in Early Stage NSCLC: ALK +

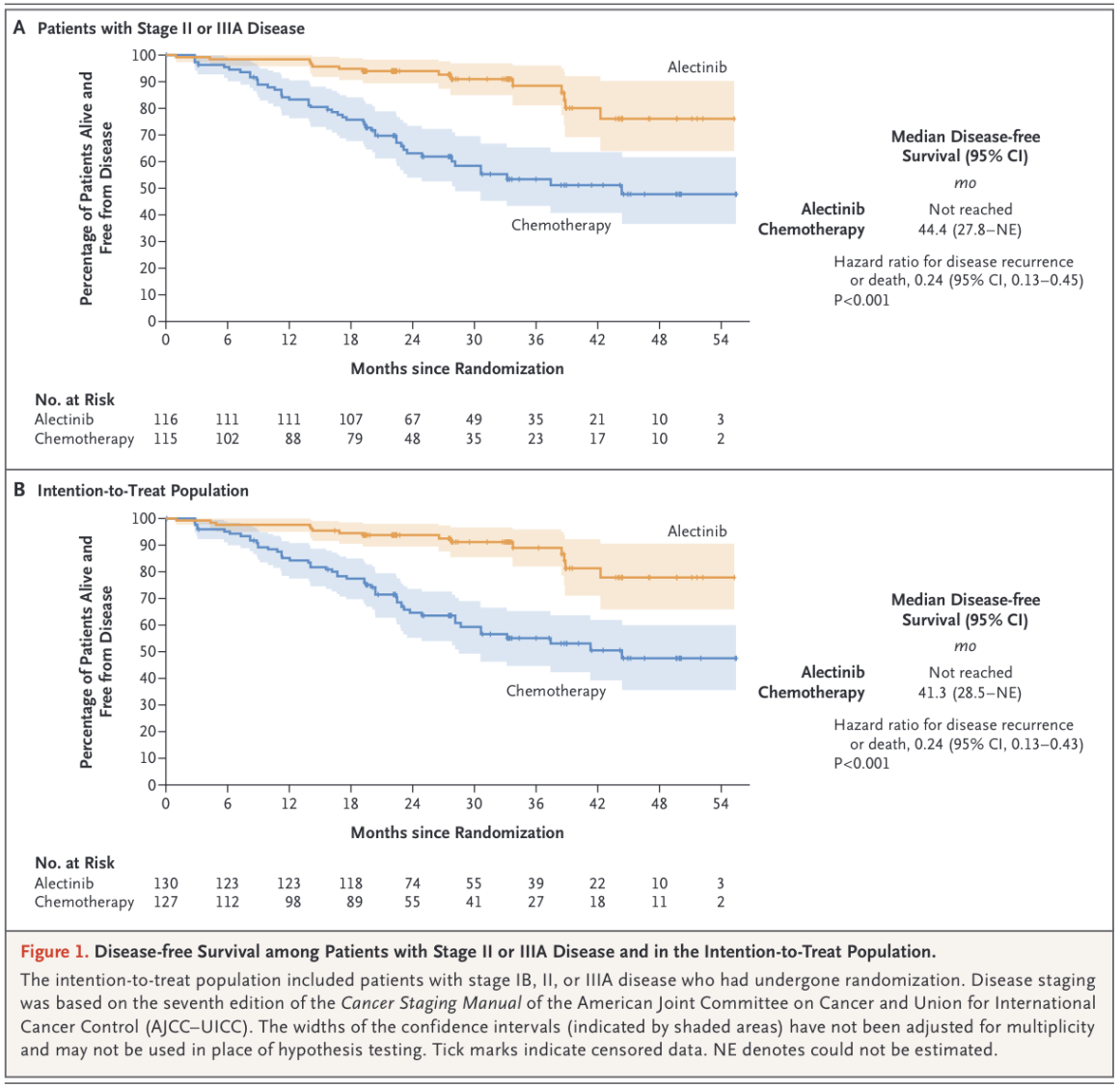
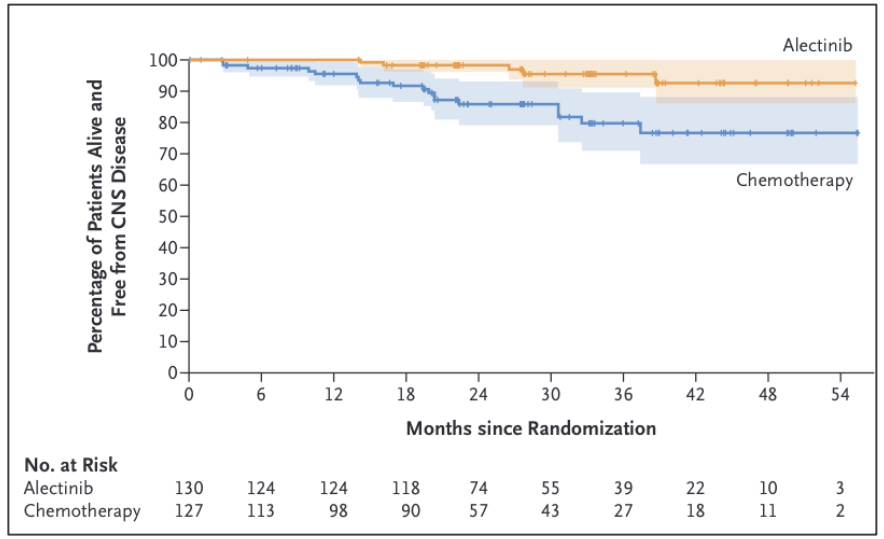


Figure 1. Disease-free Survival among Patients with Stage II or IIIA Disease and in the Intention-to-Treat Population.

The intention-to-treat population included patients with stage IB, II, or IIIA disease who had undergone randomization. Disease staging was based on the seventh edition of the *Cancer Staging Manual* of the American Joint Committee on Cancer and Union for International Cancer Control (AJCC–UICC). The widths of the confidence intervals (indicated by shaded areas) have not been adjusted for multiplicity and may not be used in place of hypothesis testing. Tick marks indicate censored data. NE denotes could not be estimated.



CNS Disease–free Survival (95% CI) at 24 Months

percent

Alectinib	98.4 (96.1–100)
Chemotherapy	85.8 (78.8–92.8)

Hazard ratio for CNS disease recurrence or death, 0.22 (95% CI, 0.08–0.58)

Wu et al, N Engl J Med 2024;390:1265-1276

Updates in Early Stage NSCLC: ALK +

National Comprehensive Cancer Network®

NCCN Guidelines Version 7.2024
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PERIOPERATIVE SYSTEMIC THERAPY

Systemic Therapy Following Surgical Resection[c]

- Test for PD-L1 status, *EGFR* mutations, and *ALK* rearrangements (stages IB–IIIA, IIIB [T3,N2]). Principles of Molecular and Biomarker Analysis (NSCL-H).

- Alectinib 600 mg twice daily for 24 months[12]
  - For patients with completely resected stage II–IIIA or stage IIIB (T3, N2) NSCLC and positive for *ALK* rearrangements (category 1).
- Osimertinib 80 mg daily for 3 years[13]
  - For patients with completely resected stage IB–IIIA or stage IIIB (T3, N2) NSCLC and positive for *EGFR* (exon 19 deletion, exon 21 L858R) mutations who received previous adjuvant chemotherapy or are ineligible to receive platinum-based chemotherapy.
- Atezolizumab 840 mg every 2 weeks, 1200 mg every 3 weeks, or 1680 mg every 4 weeks for up to 1 year[14]
  - For patients with completely resected stage IIB–IIIA, stage IIIB (T3, N2), or high-risk stage IIA NSCLC with PD-L1 ≥1% and negative for *EGFR* exon 19 deletion or exon 21 L858R mutations or *ALK* rearrangements who received previous adjuvant chemotherapy and with no contraindications to immune checkpoint inhibitors.[a]
- Pembrolizumab 200 mg every 3 weeks or 400 mg every 6 weeks for up to 1 year
  - For patients with completely resected stage IIB–IIIA, stage IIIB (T3, N2), or high-risk stage IIA NSCLC and negative for *EGFR* exon 19 deletion or exon 21 L858R mutations or *ALK* rearrangements who received previous adjuvant chemotherapy and with no contraindications to immune checkpoint inhibitors.[a,15] The benefit for patients with PD-L1 <1% is unclear.
  - For patients with completely resected stage II–IIIA or stage IIIB (T3, N2) NSCLC who received previous neoadjuvant pembrolizumab + chemotherapy (category 1).[2]

Updates in Early Stage NSCLC: EGFR exon19/L858R

2024 ASCO ANNUAL MEETING

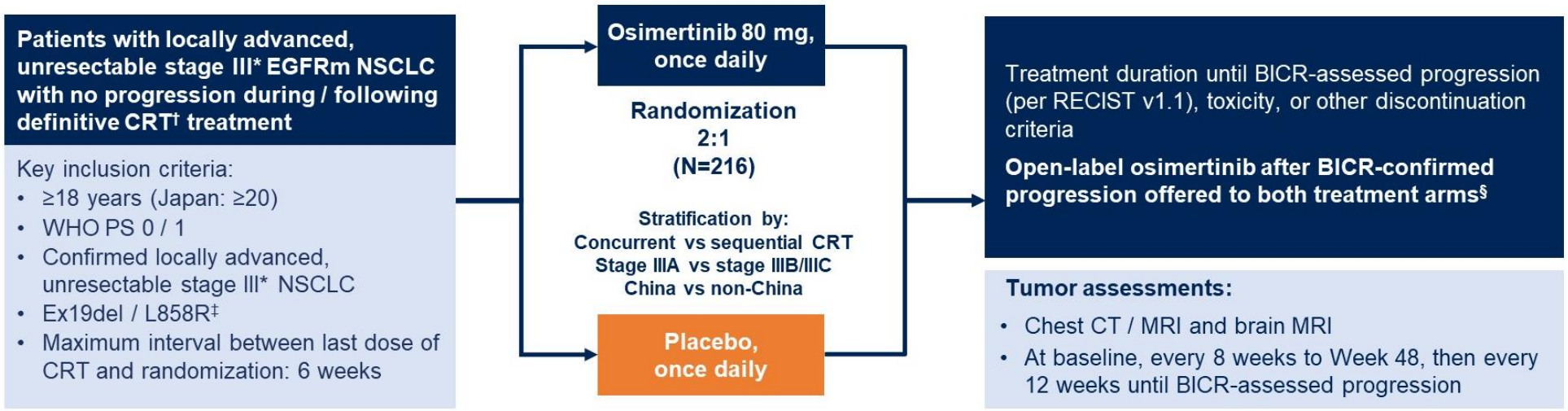
Osimertinib after definitive chemoradiotherapy in patients with unresectable stage III epidermal growth factor receptor-mutated (EGFRm) NSCLC: primary results of the Phase 3 LAURA study

Suresh S. Ramalingam,[1] Terufumi Kato, Xiaorong Dong, Myung-Ju Ahn, Le-Van Quang, Nopadol Soparattanapaisarn, Takako Inoue, Chih-Liang Wang, Meijuan Huang, James Chih-Hsin Yang, Manuel Cobo, Mustafa Özgüroğlu, Ignacio Casarini, Dang-Van Khiem, Virote Sriuranpong, Eduardo Cronemberger, Xiangning Huang, Toon van der Gronde, Dana Ghiorghiu, Shun Lu

[1]Emory University School of Medicine, Winship Cancer Institute, Atlanta, GA, USA

Updates in Early Stage NSCLC: EGFR exon19/L858R

LAURA Phase 3 double-blind study design



Endpoints

- **Primary endpoint:** PFS assessed by BICR per RECIST v1.1 (sensitivity analysis: PFS by investigator assessment)
- **Secondary endpoints included:** OS, CNS PFS, safety

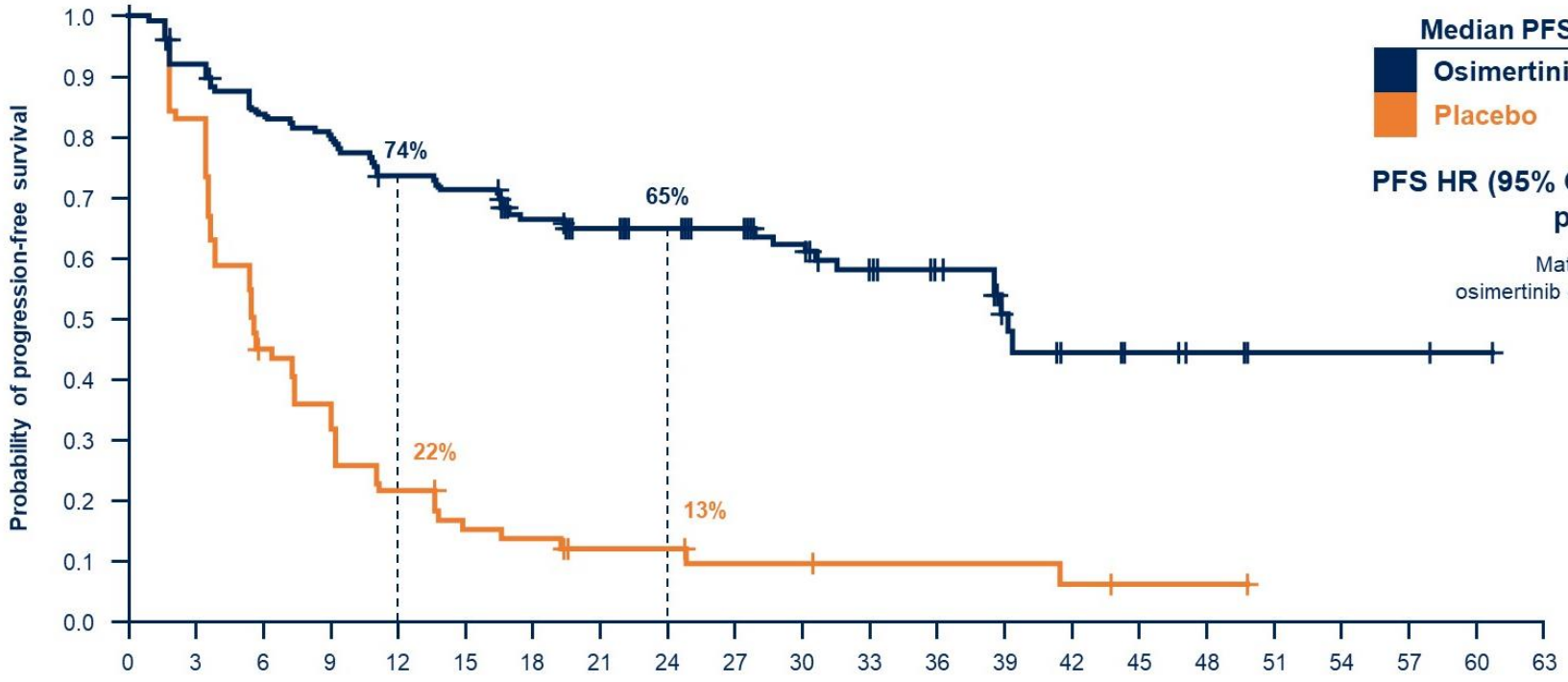
*According to AJCC / UICC staging (8th edition);
†Concurrent or sequential CRT comprising ≥2 cycles of platinum-based chemotherapy (or 5 doses of weekly platinum-based chemotherapy) and a total dose of radiation of 60 Gy ±10%;
‡Central or FDA-approved local testing (from a CLIA-approved laboratory, or accredited local laboratory for sites outside of USA) based on tissue;
§If deriving clinical benefit (osimertinib arm); by the judgement of treating physician (placebo arm).

AJCC, American Joint Committee on Cancer; BICR, blinded independent central review; CLIA, Clinical Laboratory Improvement Amendments; CNS; central nervous system; CRT, chemoradiotherapy; CT, computed tomography; EGFRm, epidermal growth factor receptor-mutated; Ex19del, exon 19 deletion; FDA, Food and Drug Administration; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; UICC, Union for International Cancer Control; WHO PS, World Health Organization performance status

PRESENTED BY: Dr Suresh S. Ramalingam

Updates in Early Stage NSCLC: EGFR exon19/L858R

Progression-free survival by BICR



No. at risk																						
Osimertinib	143	127	114	109	99	96	83	76	69	61	49	37	28	16	9	6	4	2	2	2	1	0
Placebo	73	59	31	25	15	10	9	6	6	4	4	3	3	3	2	1	1	0	0	0	0	0

Data cut-off: January 5, 2024.

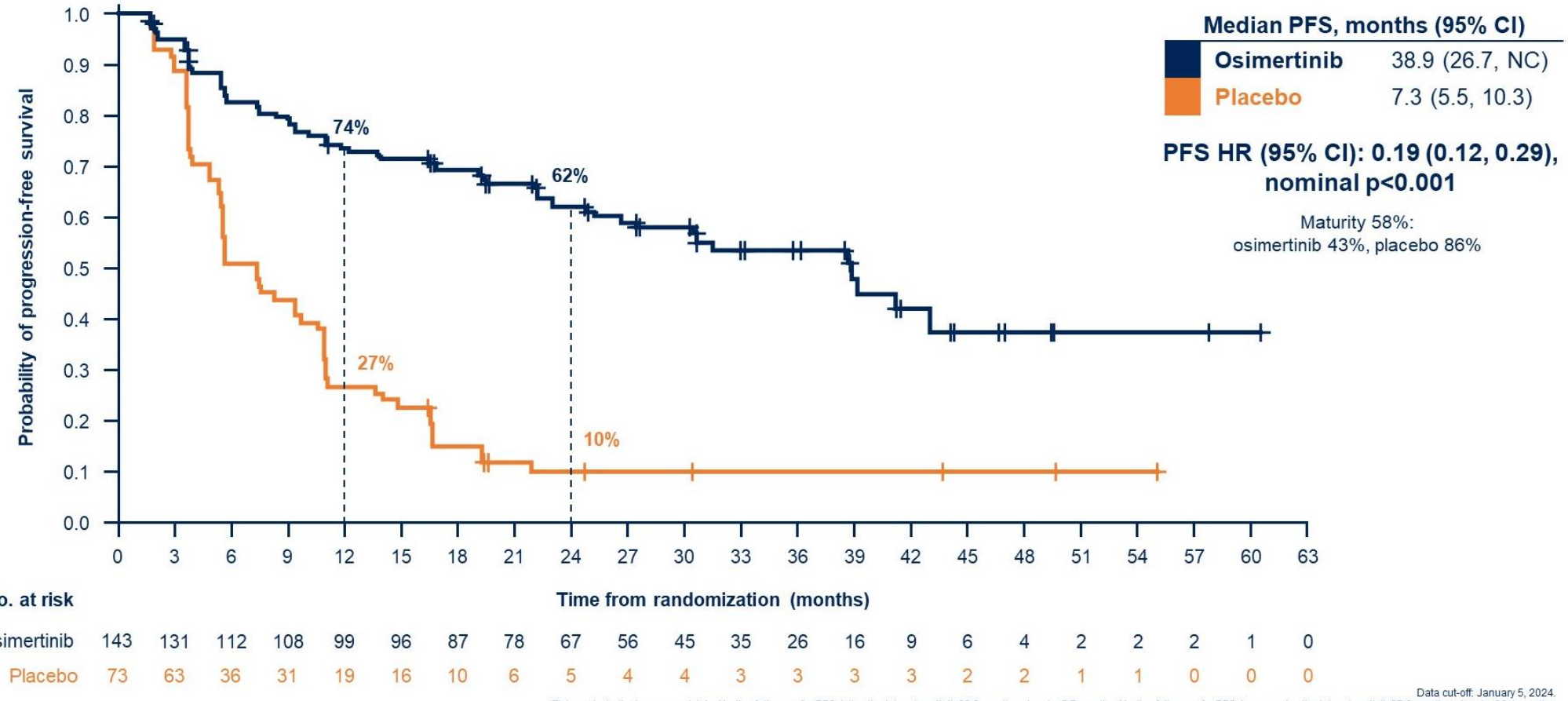
Tick marks indicate censored data. Median follow-up for PFS (all patients): osimertinib 22.0 months, placebo 5.6 months. Median follow-up for PFS (censored patients): osimertinib 27.7 months, placebo 19.5 months.

BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; NC, not calculable; PFS, progression-free survival

PRESENTED BY: Dr Suresh S. Ramalingam

Updates in Early Stage NSCLC: EGFR exon19/L858R

Progression-free survival by investigator assessment



No. at risk																						
Osimertinib	143	131	112	108	99	96	87	78	67	56	45	35	26	16	9	6	4	2	2	2	1	0
Placebo	73	63	36	31	19	16	10	6	5	4	4	3	3	3	3	2	2	1	1	0	0	0

Tick marks indicate censored data. Median follow-up for PFS (all patients): osimertinib 22.2 months, placebo 5.7 months. Median follow-up for PFS (censored patients): osimertinib 27.6 months, placebo 22.1 months.

Data cut-off: January 5, 2024.

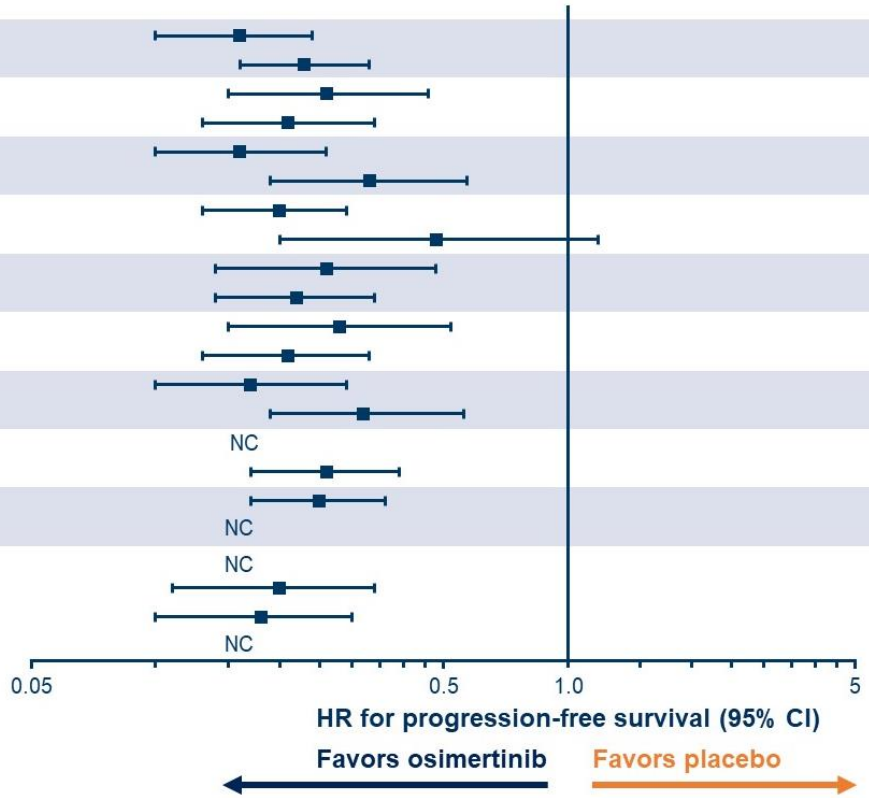
CI, confidence interval; HR, hazard ratio; NC, not calculable; PFS, progression-free survival

PRESENTED BY: Dr Suresh S. Ramalingam

Updates in Early Stage NSCLC: EGFR exon19/L858R

Progression-free survival by BICR across subgroups

Subgroup		No. of events / patients	HR	95% CI
Overall (N=216)	Stratified log-rank	120 / 216	0.16	0.10, 0.24
	Unadjusted Cox PH	120 / 216	0.23	0.16, 0.33
Sex	Male	50 / 84	0.26	0.15, 0.46
	Female	70 / 132	0.21	0.13, 0.34
Age	<65 years	67 / 120	0.16	0.10, 0.26
	≥65 years	53 / 96	0.33	0.19, 0.57
Race	Asian	98 / 178	0.20	0.13, 0.29
	Non-Asian	22 / 38	0.48	0.20, 1.19
Smoking history	Current / former (yes)	42 / 65	0.26	0.14, 0.48
	Never (no)	78 / 151	0.22	0.14, 0.34
Stage*	IIIA	42 / 76	0.28	0.15, 0.52
	IIIB / IIIC	78 / 140	0.21	0.13, 0.33
EGFR mutation†	Ex19del	65 / 117	0.17	0.10, 0.29
	L858R	55 / 98	0.32	0.19, 0.56
China cohort	Chinese	18 / 40	NC	NC, NC
	Non-Chinese	102 / 176	0.26	0.17, 0.39
Chemoradiotherapy	Concurrent	107 / 193	0.25	0.17, 0.36
	Sequential	13 / 23	NC	NC, NC
Response to prior CRT	Complete response	3 / 7	NC	NC, NC
	Partial response	53 / 94	0.20	0.11, 0.34
	Stable disease	58 / 98	0.18	0.10, 0.30
	Non-evaluable	6 / 17	NC	NC, NC



Data cut-off: January 5, 2024.

Note: HRs were calculated only for subgroups with >20 events across both arms to allow for meaningful analysis. Subgroup (not prespecified) of WHO PS: PS=0 HR 0.17 (95% CI 0.10, 0.28); PS=1 HR 0.34 (95% CI 0.20, 0.56);
*Stage prior to CRT by AJCC / UICC staging (8th edition);
†Central test of tumor tissue at screening, or local pre-existing test result; one patient in the osimertinib arm had missing EGFR mutation information.

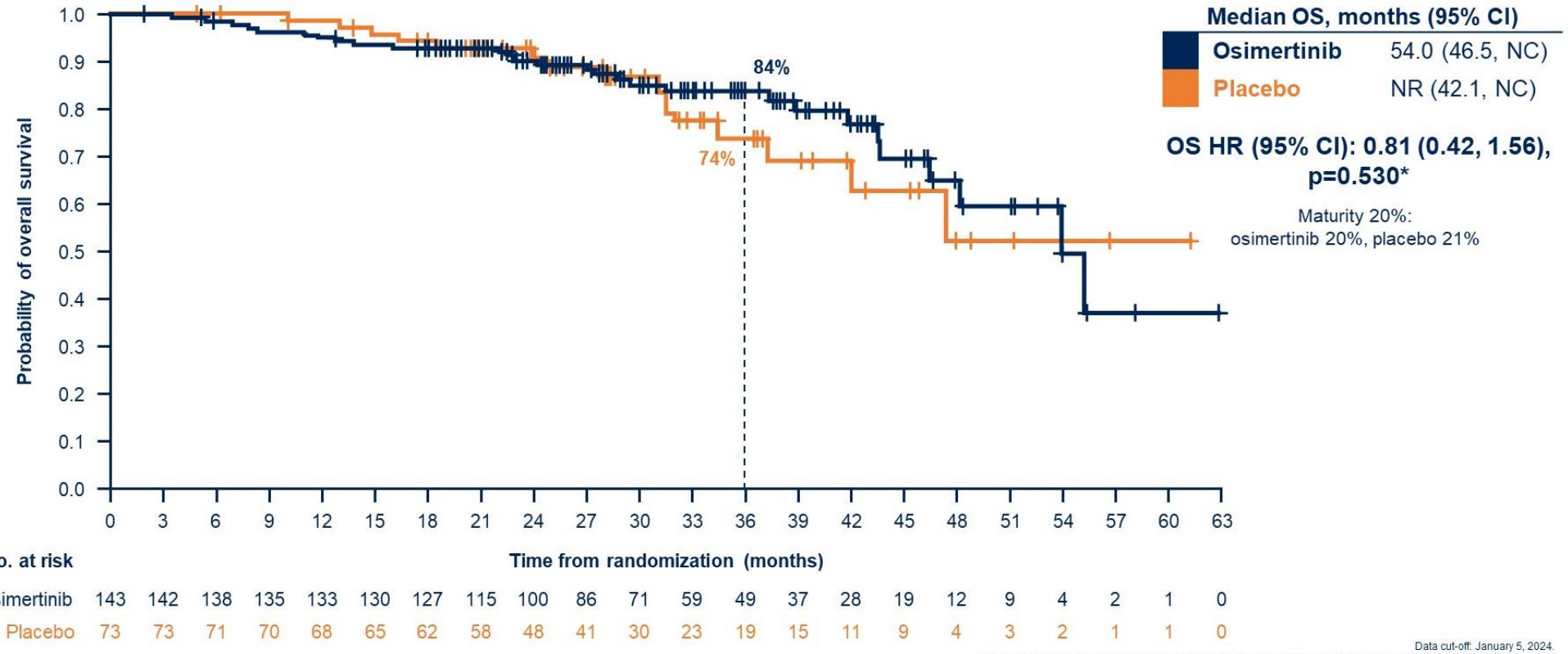
AJCC, American Joint Committee on Cancer; BICR, blinded independent central review; CI, confidence interval; CRT, chemoradiotherapy; EGFR, epidermal growth factor receptor; Ex19del, exon 19 deletion; HR, hazard ratio; NC, not calculable; PFS, progression-free survival; PH, proportional-hazards model; UICC, Union for International Cancer Control; WHO PS, World Health Organization performance status

PRESENTED BY: Dr Suresh S. Ramalingam

Updates in Early Stage NSCLC: EGFR exon19/L858R

Interim analysis of overall survival

- In the placebo arm, 81% of patients with BICR-confirmed progression crossed over to osimertinib



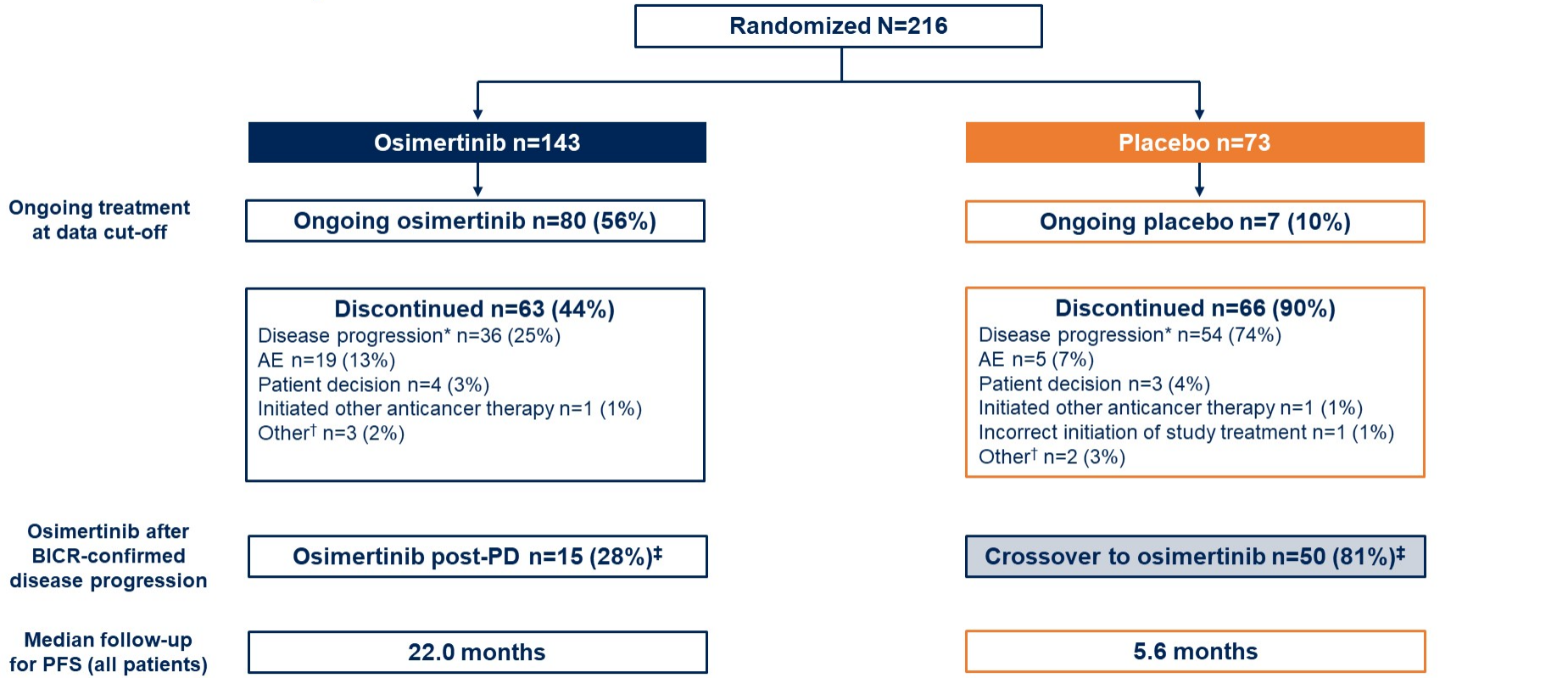
No. at risk																					
Osimertinib	143	142	138	135	133	130	127	115	100	86	71	59	49	37	28	19	12	9	4	2	1	0
Placebo	73	73	71	70	68	65	62	58	48	41	30	23	19	15	11	9	4	3	2	1	1	0

Data cut-off: January 5, 2024.
Tick marks indicate censored data. *For statistical significance at this interim analysis, a p-value of <0.00036 was required;
Median follow-up for OS (all patients): osimertinib 29.5 months, placebo 28.1 months. Median follow-up for OS (censored patients): osimertinib 30.9 months, placebo 28.1 months.
BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; NC, not calculable; NR, not reached; OS, overall survival

PRESENTED BY: Dr Suresh S. Ramalingam

Updates in Early Stage NSCLC: EGFR exon19/L858R

Patient disposition

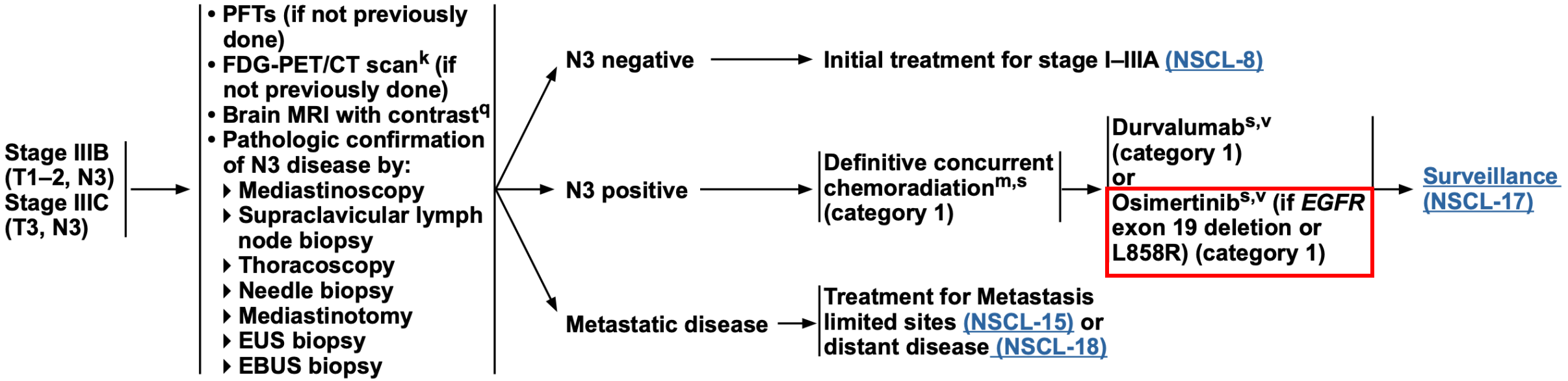


Data cut-off: January 5, 2024.
*Assessed by BICR per RECIST v1.1 prior to primary PFS analysis;
†Any other reason not specifically captured in earlier categories. Osimertinib arm: death (n=2), disease progression by investigator (n=1); placebo arm: death (n=1), disease progression by investigator (n=1);
‡Percentages calculated using patients with BICR-confirmed disease progression in each treatment arm as denominator: osimertinib, n=53; placebo, n=62.

AE, adverse event; BICR, blinded independent central review; PD, progressive disease; PFS, progression-free survival

PRESENTED BY: Dr Suresh S. Ramalingam

Updates in Early Stage NSCLC: EGFR exon19/L858R



Summary: Updates in Early Stage SCLC

- ✓ Adjuvant Alectinib after surgery is a standard of care for Stage II-IIIB NSCLC after surgical resection.
- ✓Consolidation Osimertinib is the new standard of care of for EGFR Exon 19/L858R after chemoradiation therapy.
- ✓Neoadjuvant/perioperative immunotherapy remains the standard of care for ALK/EGFR non-mutated NSCLC. Clinical trials to improve pathological complete responses in this stage.

Updates in Late Stage NSCLC: ALK+

2024 ASCO ANNUAL MEETING

Lorlatinib vs Crizotinib in Treatment-Naive Patients With Advanced *ALK*+ Non-Small Cell Lung Cancer: 5-Year Progression-Free Survival and Safety From the CROWN Study

Benjamin J. Solomon,[1] Geoffrey Liu,[2] Enriqueta Felip,[3] Tony S. K. Mok,[4] Ross A. Soo,[5] Julien Mazieres,[6] Alice T. Shaw,[7] Filippo de Marinis,[8] Yasushi Goto,[9] Yi-Long Wu,[10] Dong-Wan Kim,[11] Jean-François Martini,[12] Rossella Messina,[13] Jolanda Paolini,[13] Anna Polli,[13] Despina Thomaidou,[14] Francesca Toffalorio,[13] Todd M. Bauer[15]

[1]Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; [2]Princess Margaret Cancer Centre, Toronto, ON, Canada; [3]Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, Barcelona, Spain; [4]State Key Laboratory of Translational Oncology, Chinese University of Hong Kong, Hong Kong; [5]National University Cancer Institute, Singapore; [6]Toulouse University Hospital and Centre de Recherche Cancérologie Toulouse CRCT, INSERM, France; [7]Massachusetts General Hospital Cancer Center, Boston, MA, USA; [8]European Institute of Oncology, IRCCS, Milan, Italy; [9]National Cancer Center Hospital, Tokyo, Japan; [10]Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital and Guangdong Academy of Medical Sciences, Guangdong, China; [11]Seoul National University College of Medicine and Seoul National University Hospital, Seoul, South Korea; [12]Pfizer, La Jolla, CA, USA; [13]Pfizer, Milan, Italy; [14]Pfizer, Athens, Greece; [15]Greco-Hainsworth Centers for Research/Tennessee Oncology, Nashville, TN, USA

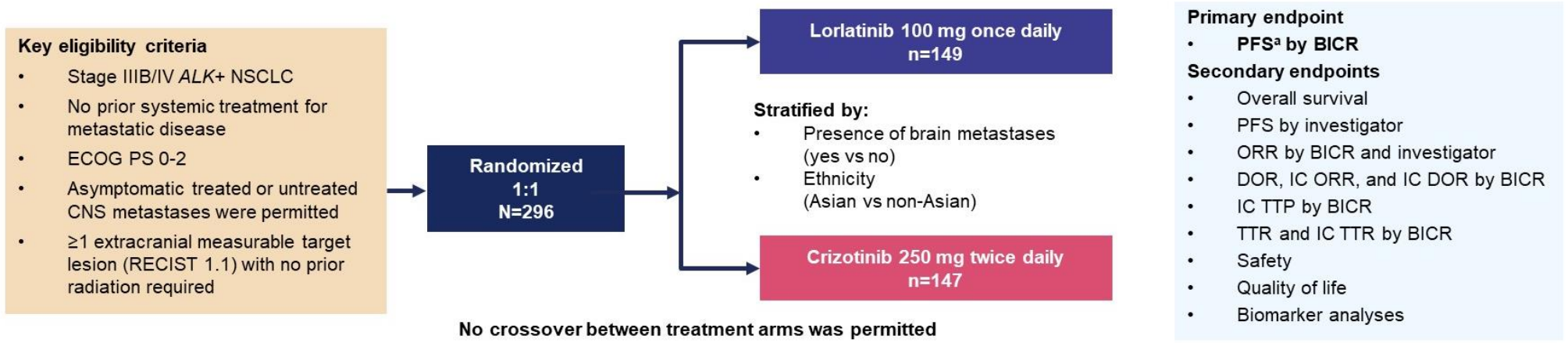
Benjamin J. Solomon, MBBS, PhD
Peter MacCallum Cancer Centre, Melbourne, VIC, Australia

PRESENTED BY: Benjamin J. Solomon (Ben.Solomon@petermac.org)

Updates in Late Stage NSCLC: ALK+

CROWN: A Randomized Global Phase 3 Study

- Lorlatinib is a brain-penetrant, third-generation ALK TKI that has broader coverage of *ALK* resistance mutations than second-generation ALK TKIs[1,2]



- At the planned interim analysis, at 18.3 months of median follow-up in the lorlatinib arm, median PFS by BICR was not reached (95% CI, NR-NR) with lorlatinib and 9.3 months (95% CI, 7.6-11.1 months) with crizotinib, with an HR of 0.28 (95% CI, 0.19-0.41) and P<0.001[3]
- In a subsequent post hoc analysis, at 3 years of follow-up, median PFS by BICR was still not reached (95% CI, NR-NR) with lorlatinib and 9.3 months (95% CI, 7.6-11.1 months) with crizotinib (HR, 0.27; 95% CI, 0.18-0.39)[4]

ALK, anaplastic lymphoma kinase; BICR, blinded independent central review; CNS, central nervous system; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; IC, intracranial; NR, not reached; NSCLC, non-small cell lung cancer; ORR, objective response rate; PFS, progression-free survival; PS, performance status; RECIST, Response Evaluation Criteria in Solid Tumors; TKI, tyrosine kinase inhibitor; TTP, time to tumor progression; TTR, time to tumor response.
[a]Defined as the time from randomization to RECIST-defined progression or death due to any cause.
1. Johnson TW, et al. *J Med Chem*. 2014;57:4720-4744. 2. Shaw AT, et al. *Lancet Oncol*. 2017;18:1590-1599. 3. Shaw AT, et al. *N Engl J Med*. 2020;383:2018-2029. 4. Solomon BJ, et al. *Lancet Respir Med*. 2023;11:354-366.

PRESENTED BY: Benjamin J. Solomon (Ben.Solomon@petermac.org)

Updates in Late Stage NSCLC: ALK+

Current Post Hoc Analyses at 5 Years

Endpoint evaluation by BICR stopped after the 3-year analysis

Key eligibility criteria

- Stage IIIB/IV *ALK*+ NSCLC
- No prior systemic treatment for metastatic disease
- ECOG PS 0-2
- Asymptomatic treated or untreated CNS metastases were permitted
- ≥1 extracranial measurable target lesion (RECIST 1.1) with no prior radiation required

Randomized 1:1 N=296

Lorlatinib 100 mg once daily n=149

Crizotinib 250 mg twice daily n=147

Stratified by:

- Presence of brain metastases (yes vs no)
- Ethnicity (Asian vs non-Asian)

No crossover between treatment arms was permitted

Current analyses

Data cutoff: October 31, 2023

- **Investigator Assessed**
  - PFS[a]
  - ORR and IC ORR
  - DOR and IC DOR
  - IC TTP
- Safety
- Biomarker analyses

- The median duration of follow-up for PFS was 60.2 months (95% CI, 57.4-61.6) in the lorlatinib arm and 55.1 months (95% CI, 36.8-62.5) in the crizotinib arm

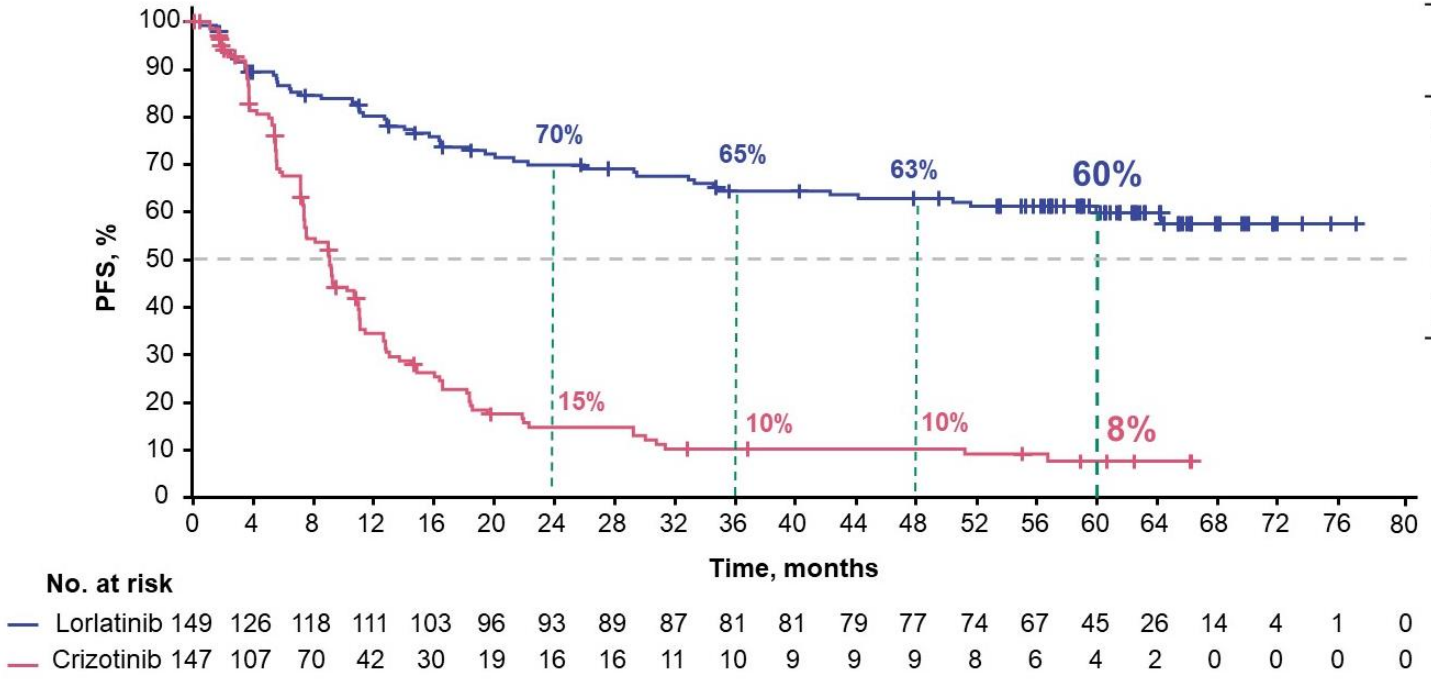
CNS, central nervous system; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; IC, intracranial; ORR, objective response rate; NSCLC, non-small cell lung cancer; PFS, progression-free survival; PS, performance status; RECIST, Response Evaluation Criteria in Solid Tumors; TTP, time to tumor progression.

[a] Defined as the time from randomization to RECIST-defined progression or death due to any cause.

PRESENTED BY: Benjamin J. Solomon (Ben.Solomon@petermac.org)

Updates in Late Stage NSCLC

At 60.2 Months of Median Follow-Up, Median PFS by Investigator Was Still Not Reached With Lorlatinib



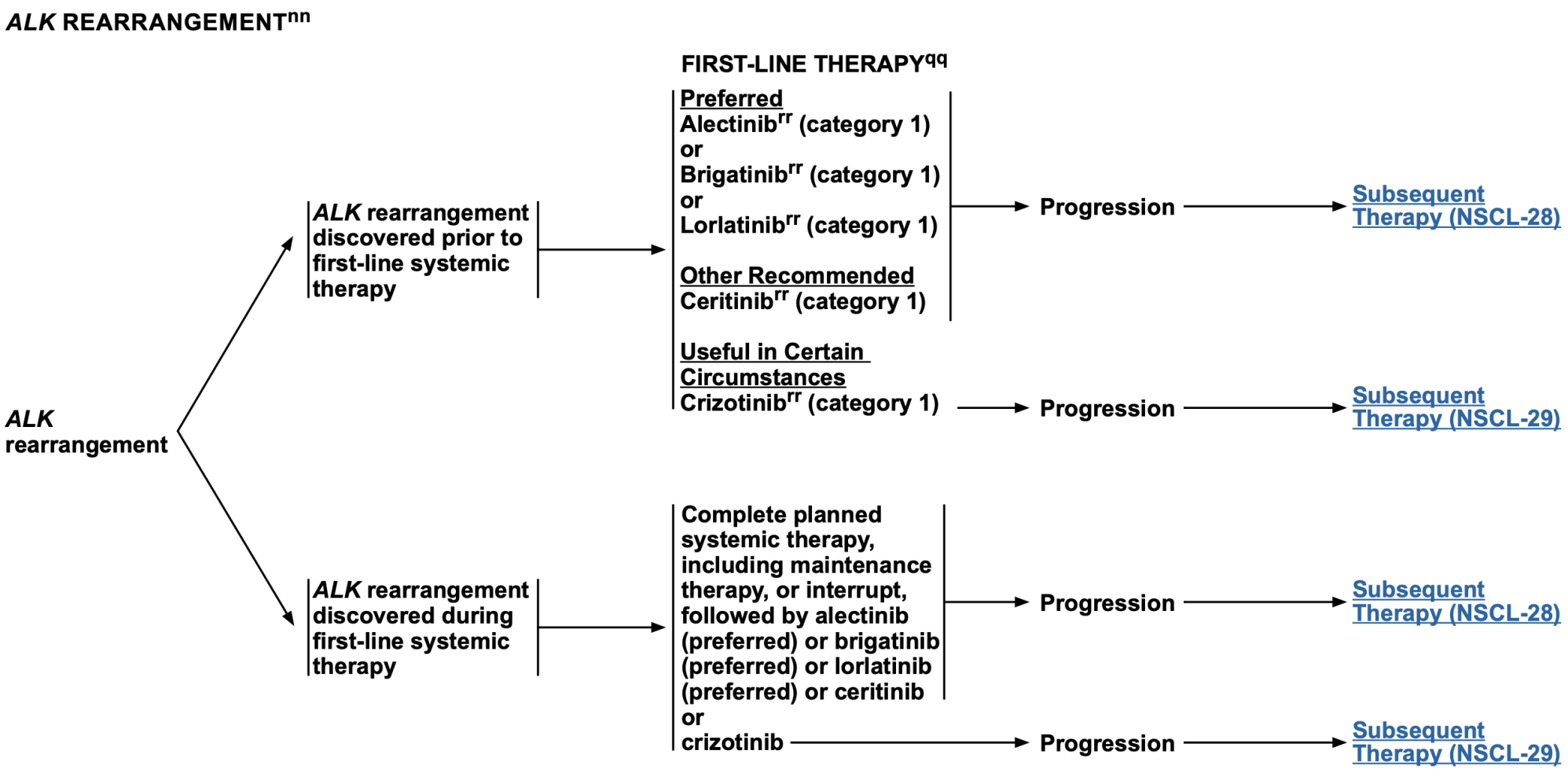
	Lorlatinib (n=149)	Crizotinib (n=147)
Events, n	55	115
PFS, median (95% CI), months	NR (64.3-NR)	9.1 (7.4-10.9)
HR (95% CI)	**0.19 (0.13-0.27)**	

At the time of this analysis, the required number of OS events for a protocol-specified second interim analysis **has not been reached**. OS follow up is ongoing

HR, hazard ratio; NR, not reached; OS, overall survival; PFS, progression-free survival.

PRESENTED BY: Benjamin J. Solomon (Ben.Solomon@petermac.org)

Updates in Late Stage NSCLC: ALK+



Updates in Late Stage NSCLC: KRAS G12C

KRYSTAL-12[a] study design

Key eligibility criteria
- Locally advanced or metastatic NSCLC with *KRAS*^{G12C} mutation[b]
- Prior treatment with platinum-based chemotherapy and anti-PD-(L)1 therapy[c]
- ECOG PS 0-1
- Stable brain metastases allowed

N = 453
R
2:1

- ADA 600 mg BID PO[d]
- DOCE 75 mg/m^2 Q3W IV

Crossover from DOCE to ADA was allowed in cases where disease progression per RECIST v1.1 was confirmed by real-time BICR[e]

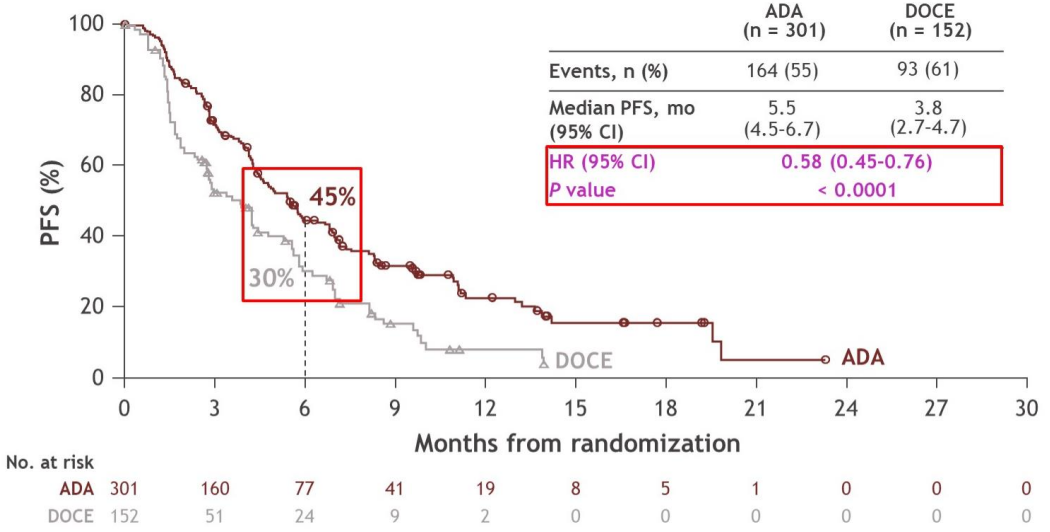
Stratified by:
- Region (non-Asia-Pacific vs Asia-Pacific)
- Prior treatment (sequential vs concurrent chemotherapy and immunotherapy)

Primary endpoint
- PFS by BICR (RECIST v1.1)

Secondary endpoints
- ORR by BICR (RECIST v1.1)
- DOR
- OS
- Safety
- Patient-reported outcomes

Database lock: March 19, 2024. Data cut-off: December 31, 2023.
[a]NCT04685135. [b]Detected in tumor tissue using sponsor-approved local or central testing. [c]No washout period was required between prior therapy and study treatment. [d]Tablet formulation, except for four patients who initially received the capsule formulation. [e]Other crossover criteria: ECOG PS 0-2, recovery from DOCE-related AEs to grade 1 or baseline (except peripheral neuropathy and alopecia for which grade 2 is acceptable).

Primary endpoint: PFS[a] per BICR



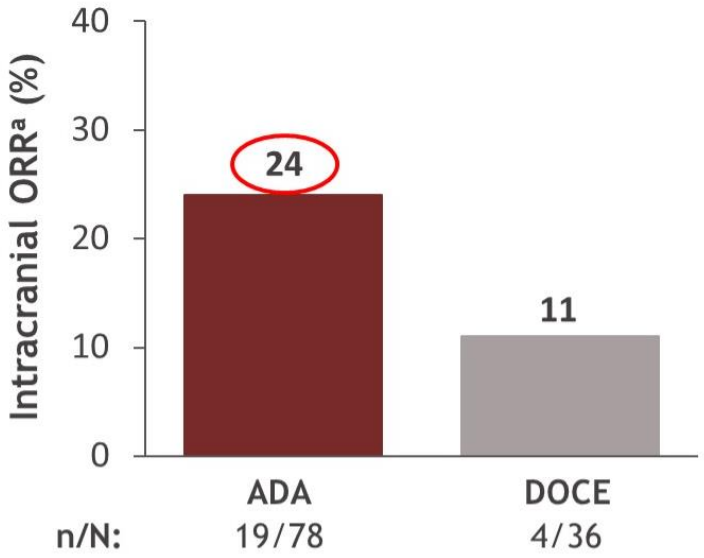
	ADA (n = 301)	DOCE (n = 152)
Events, n (%)	164 (55)	93 (61)
Median PFS, mo (95% CI)	5.5 (4.5-6.7)	3.8 (2.7-4.7)
HR (95% CI)	0.58 (0.45-0.76)	
P value	< 0.0001	

Median follow-up: 7.2 months.
[a]Time from randomization to the date of disease progression per BICR or death due to any cause, whichever occurs first. For patients who started a subsequent anticancer therapy prior to disease progression or death, PFS was censored at the date of the last tumor assessment prior to the start of the new therapy.

Updates in Late Stage NSCLC: KRAS G12C

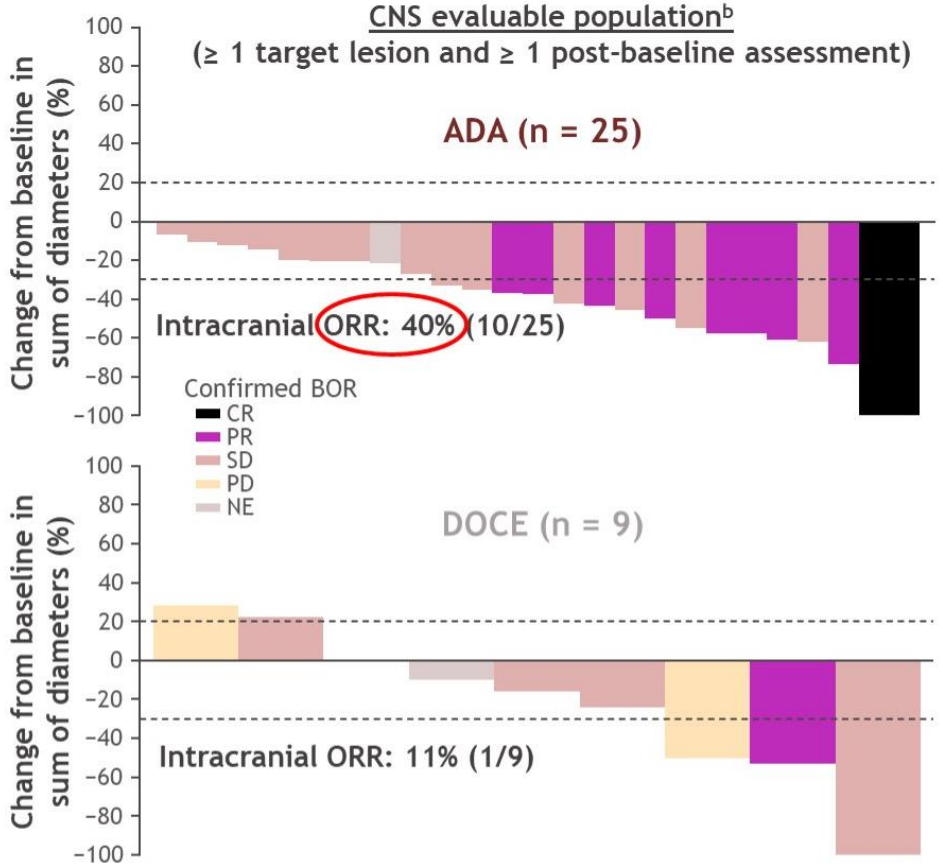
Intracranial response per BICR[a]

All patients with baseline CNS metastases[a]



Intracranial response[a]	ADA (n = 78)	DOCE (n = 36)
Intracranial DCR, n (%)	64 (82)	20 (56)

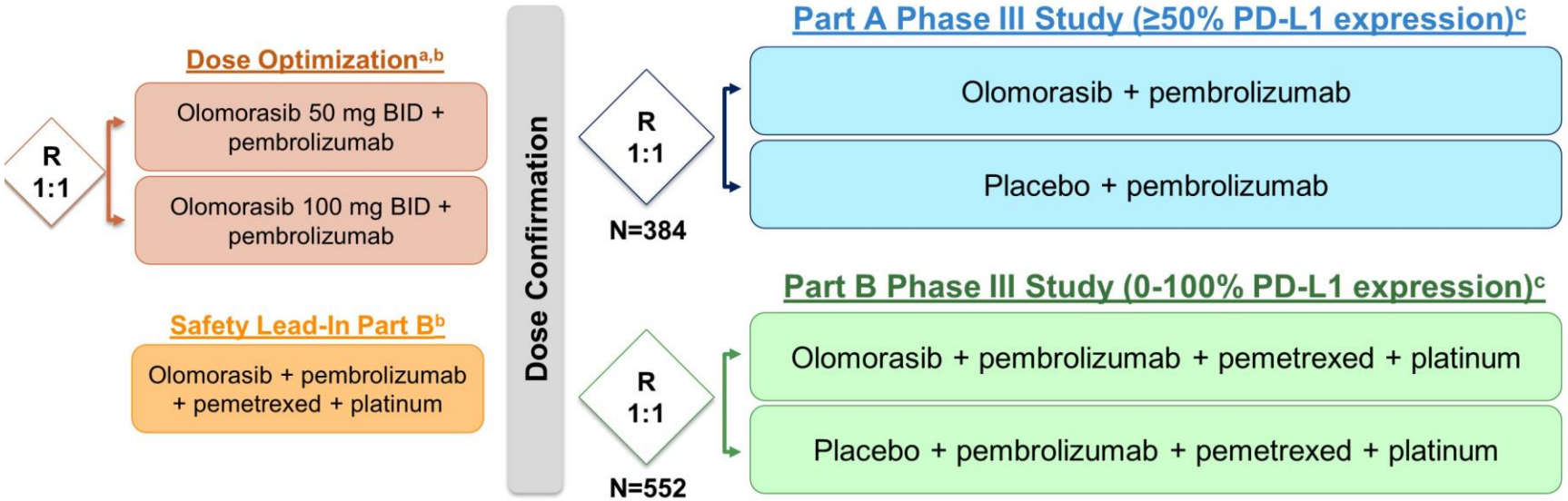
CNS evaluable population[b]
(≥ 1 target lesion and ≥ 1 post-baseline assessment)



[a]In accordance with CNS-adapted RECIST v1.1. CNS RECIST data (including identification of patients with baseline CNS metastases) were based on a separate CNS imaging charter and neuroradiologist review. [b]Waterfall plots show CNS evaluable population including patients with at least one CNS target lesion at baseline and at least one post-baseline CNS tumor assessment. For lesions to be considered target lesions, they must have been measurable and either not previously treated with CNS-directed therapy or must have progressed after prior CNS-directed therapy.

Updates in Late Stage NSCLC: KRAS G12C

SUNRAY-01 is a pivotal, global, phase 3 study in 1L advanced KRAS G12C-mutated NSCLC (NCT06119581)



- Olomorasib/placebo are administered orally, twice daily
- Pembrolizumab, pemetrexed, and platinum (cisplatin or carboplatin) are each administered intravenously per label. After completing 4 cycles of chemotherapy without disease progression, patients will receive maintenance therapy with olomorasib/placebo, pembrolizumab and pemetrexed

[a]Participants should be suitable for pembrolizumab monotherapy
[b]PD-L1 expression 0-100%, N~40 for each study part (randomized Dose Optimization and Safety Lead-In Part B)
[c]Participants with PD-L1 ≥50% are eligible to be enrolled to Part A or Part B at the discretion of the investigator

Negrao at al, Asco 2024

Updates in Late Stage NSCLC: HER2

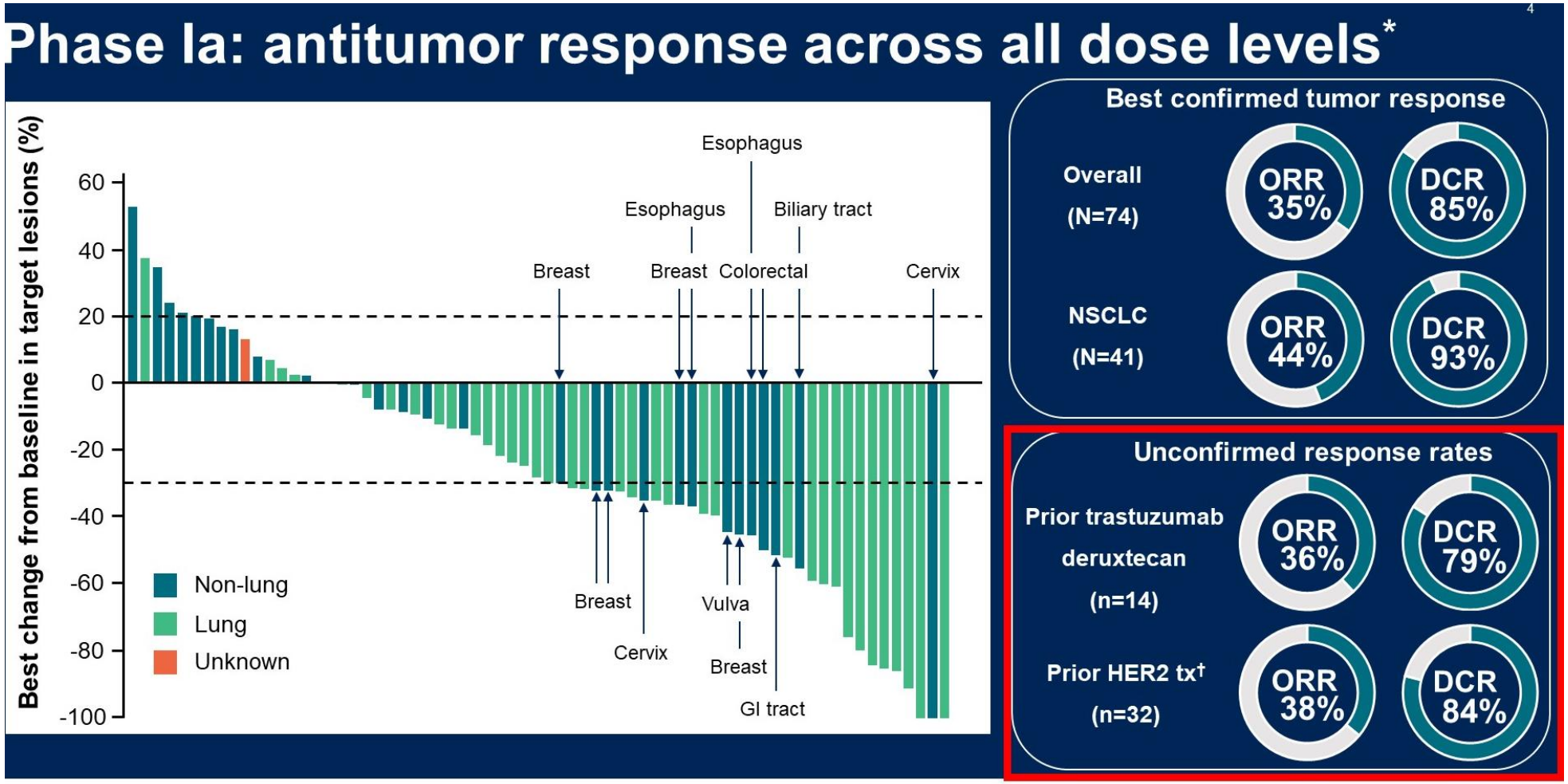
2024 ASCO ANNUAL MEETING

Phase Ia/Ib trial of zongertinib (BI 1810631), a HER2-specific tyrosine kinase inhibitor in patients with HER2 aberration-positive solid tumors: updated Phase Ia data from Beamion LUNG-1, including progression-free survival data

John Heymach,[1] Frans Opdam,[2] Minal Barve,[3] Hai-Yan Tu,[4] Yi-Long Wu,[4] David Berz,[5] Maren Rohrbacher,[6] Behbood Sadrolhefazi,[7] Josep Serra,[8] Kiyotaka Yoh,[9] Noboru Yamamoto[10]

1. Department of Thoracic-Head and Neck Medical Oncology, University of Texas MD Anderson Cancer Center, Houston, TX, USA; 2. Department of Clinical Pharmacology, The Netherlands Cancer Institute, Amsterdam, The Netherlands; 3. Mary Crowley Cancer Research, Dallas, TX, USA; 4. Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, China; 5. Valkyrie Clinical Trials, Inc., Los Angeles, CA, USA; 6. Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach an der Riss, Germany; 7. Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, USA; 8. Boehringer Ingelheim España S.A., Barcelona, Spain; [9]Department of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa, Japan; [10]Department of Experimental Therapeutics, National Cancer Center Hospital, Tokyo, Japan

Updates in Late Stage NSCLC: HER2



2024 ASCO ANNUAL MEETING #ASCO24

PRESENTED BY: Dr John Heymach

Data cut-off: January 29, 2024.*Responses are restricted to non-CNS lesions by RECIST 1.1.†Prior treatment with other HER2 therapies was permitted
CNS, central nervous system; DCR, disease control rate; GI, gastrointestinal; HER2, human epidermal growth factor receptor 2; NSCLC, non-small cell lung cancer; ORR, objective response rate; tx, treatment

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

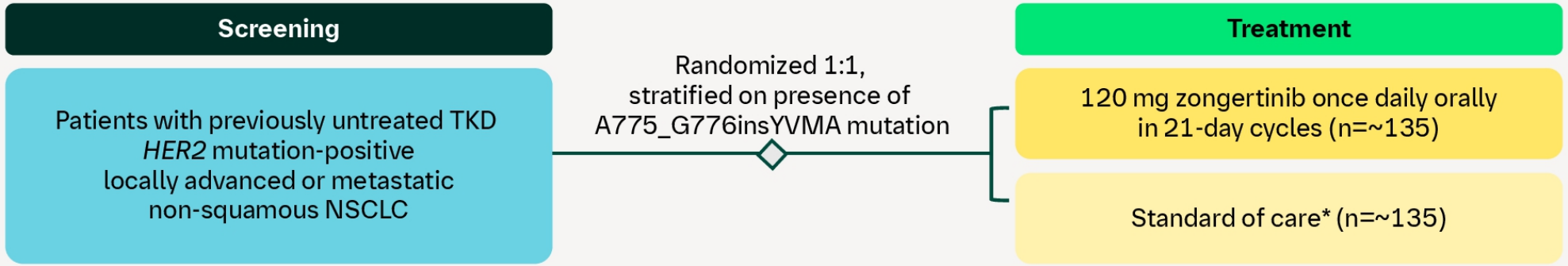
Updates in Late Stage NSCLC: HER2

#TPS8654

Beamion LUNG-2: a Phase III randomized controlled trial of zongertinib (BI 1810631) versus standard of care in patients with locally advanced/metastatic non-squamous non-small cell lung cancer (NSCLC) harboring *HER2* tyrosine kinase domain (TKD) mutations

Trial design

- Beamion LUNG-2 is a Phase III, open-label, randomized, active-controlled, multi-center trial of zongertinib compared with standard of care*
- The trial will recruit ~270 patients from ~160 sites across 30 countries



- Treatment across both arms will continue until documented progressive disease (RECIST v1.1, according to independent central review), undue toxicity, withdrawal of consent or other defined criteria are met

*Intravenous 500 mg/m^2 pemetrexed chemotherapy plus 200 mg intravenous pembrolizumab followed by either 75 mg/m^2 cisplatin or carboplatin Area Under the Curve 5 on Day 1 (determined by investigator prior to randomization), every three weeks, for four 21-day treatment cycles, followed by maintenance therapy with 200 mg pembrolizumab plus pemetrexed 500 mg/m^2 every three weeks for up to 35 cycles

Melissa Johnson,

Presented at the American Society of Clinical Oncology (ASCO), Chicago, IL, USA, May 31–June 4, 2024

*Corresponding author email address: melissa.johnson@scri.com

Summary: Updates in Late Stage NSCLC

- ✓ Lorlatinib remains one standard of care option for Stage IV ALK+ NSCLC.
- ✓Adagrasib remains one standard of care for Stage IV KRAS G12C NSCLC.
- ✓New KRAS targeted molecules in clinical development, being tested alone and in combination with immunotherapy and chemotherapy.
- ✓Zongertinib is a promising HER2 targeted therapy.

Acknowledgements

- Lung Cancer Initiative
- Summit Organizers
- Patients and their families
- Duke thoracic oncology program