ASCO Update Lungenkarzinom

PD Dr. Dr. med. G. Chakupurakal

Praxis für Hämatologie-Onkologie, Koblenz

03.07.2024

Offenlegung und Quellen

- Interessenkonflikte: Keine
- Expertengremien: MSD, Takeda, Roche, BMS, Amgen, Astraseneca
- Drittmittel: Amgen, Biotest, Celgene, CSL Behring, Daiichi Sankyo, Eisai, GSK, Hexal, Lilly, Medac, Mundipharma, Octapharma, Stemline und Takeda

- Quellen: ASCO-Folien, NEJM, Roche, MSD

Was ist neu?

- Neoadjuvante Chemoimmuntherapie in NSCLC
  - Aegean
  - Keynote 671
  - Checkmate 816
- Chemoradiotherapie NSCLC
  - EGFR mutierte
  - ALK mutierte
- Fortgeschrittenes Stadium NSCLC
  - Crown
  - Trop 2
- SCLC
  - Adriatic
- Biomarker
  - Ct DNA

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Early-Stage Lung Cancer Stats with Surgery Alone

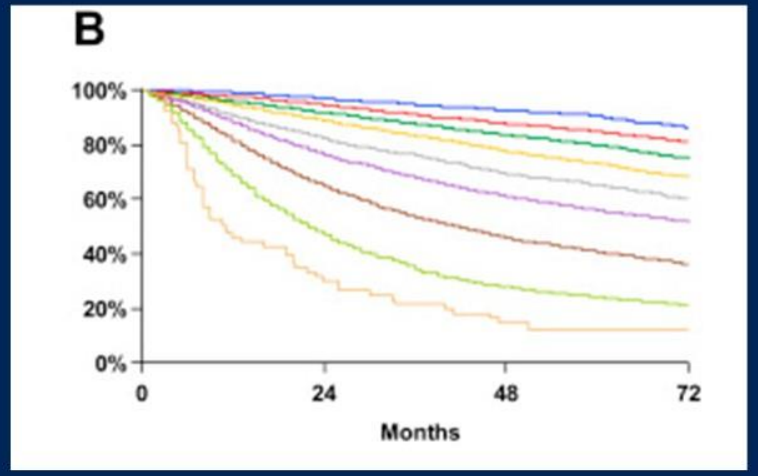
Stage IA1: </= 1cm ~92% 5-yr survival

Stage IA2: >1 - 2 cm ~83-86% 5-yr survival

Stage IA3: >2 – 3 ~76-81% 5-yr survival

Stage IIA: >4 cm 60-65% 5-yr survival

Once LNs are involved the risk of recurrence and death drastically increases



Survival based on pathologic stage

Goldstraw P, et al. Journal of Thoracic Oncology, Volume 11, Issue 1, 2016, 39–51

Keynote 671

RESEARCH SUMMARY

Perioperative Pembrolizumab for Early-Stage Non–Small-Cell Lung Cancer

Wakelee H et al. DOI: 10.1056/NEJMoa2302983

CLINICAL PROBLEM

Adjuvant therapy with the immune checkpoint inhibitor pembrolizumab has been shown to have a disease-free survival benefit in patients with early-stage non–small-cell lung cancer (NSCLC). The effects of neoadjuvant pembrolizumab in these patients are unclear.

CLINICAL TRIAL

Design: A phase 3, double-blind, randomized, placebo-controlled trial assessed whether neoadjuvant pembrolizumab plus chemotherapy followed by surgical resection and adjuvant pembrolizumab would improve outcomes, as compared with neoadjuvant chemotherapy and resection alone, in patients with early-stage NSCLC.

Intervention: 797 adults with previously untreated, resectable stage II, IIIA, or IIIB (N2 node stage) NSCLC were assigned to receive neoadjuvant pembrolizumab (200 mg) or placebo, given intravenously once every 3 weeks for 4 cycles, plus cisplatin-based chemotherapy, followed by surgical resection and then either adjuvant pembrolizumab or placebo for up to 13 cycles. The primary end points were event-free survival and overall survival.

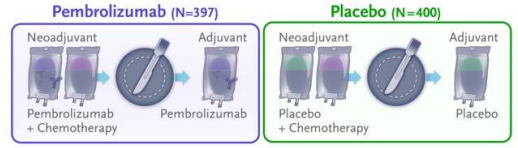
RESULTS

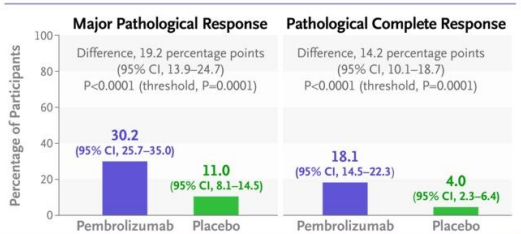
Efficacy: The median follow-up in the prespecified first interim analysis was 25.2 months. Event-free survival was significantly improved in the pembrolizumab group as compared with the placebo group. Overall survival did not differ significantly between the groups at the time of the analysis.

Safety: No new safety signals emerged. Grade ≥3 treatment-related adverse events occurred more often with pembrolizumab than with placebo.

LIMITATIONS AND REMAINING QUESTIONS

- The trial design does not allow for analysis of the relative contributions of neoadjuvant and adjuvant pembrolizumab.
- Follow-up was relatively short, which limits conclusions about long-term outcomes.
- Neoadjuvant chemotherapy included cisplatin-based regimens only.





CONCLUSIONS

Among patients with early-stage NSCLC, neoadjuvant pembrolizumab plus cisplatin-based chemotherapy followed by resection and adjuvant pembrolizumab improved event-free survival, as compared with neoadjuvant chemotherapy and resection alone. Overall survival did not differ significantly between groups in this interim analysis.

Links: Full Article | NEJM Quick Take | Editorial

This Research Summary was updated on August 15, 2023, at NEJM.org.

Aegean

RESEARCH SUMMARY

Perioperative Durvalumab for Resectable Non–Small-Cell Lung Cancer

Heymach JV et al. DOI: 10.1056/NEJMoa2304875

CLINICAL PROBLEM

For patients with resectable, early-stage non–small-cell lung cancer (NSCLC), surgery remains the primary curative-intent treatment; however, many patients have tumor recurrence within 5 years after surgery. Perioperative regimens that combine the benefits of neoadjuvant and adjuvant immunotherapy could improve long-term outcomes.

CLINICAL TRIAL

Design: A phase 3, international, double-blind, randomized, placebo-controlled trial examined the efficacy and safety of neoadjuvant and adjuvant durvalumab (an IgG1 monoclonal antibody specific for programmed death ligand 1 [PD-L1]) plus neoadjuvant chemotherapy, as compared with neoadjuvant chemotherapy alone, in adults with resectable NSCLC.

Intervention: 802 adults with previously untreated, resectable, stage IIA to IIIB (N2 node stage) NSCLC were assigned to receive platinum-based chemotherapy plus either durvalumab or placebo intravenously every 3 weeks for 4 cycles before surgery, followed by adjuvant durvalumab or placebo intravenously every 4 weeks for up to 12 cycles. The primary end points were event-free survival (the time to the occurrence of disease progression, disease recurrence, or death from any cause) and pathological complete response.

RESULTS

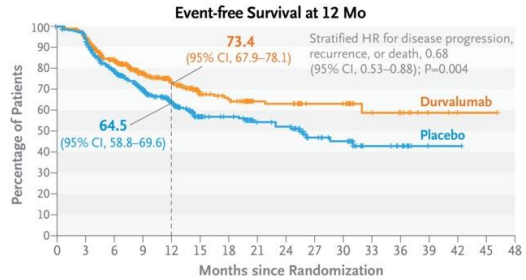
Efficacy: Among evaluable patients at 12 months, event-free survival was significantly longer in the durvalumab group than in the placebo group. The incidence of pathological complete response was also significantly higher in the durvalumab group.

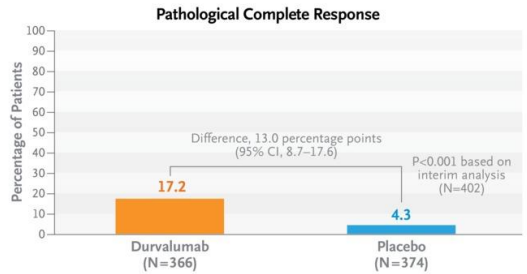
Safety: The percentage of patients with adverse events in whom grade 3 or 4 was the maximum grade was similar in the two groups.

LIMITATIONS AND REMAINING QUESTIONS

- Patients with known *EGFR* or *ALK* alterations were excluded from efficacy analyses.
- Further study is necessary for assessment of longer-term event-free survival, disease-free survival, and overall survival.

Links: Full Article | NEJM Quick Take





CONCLUSIONS

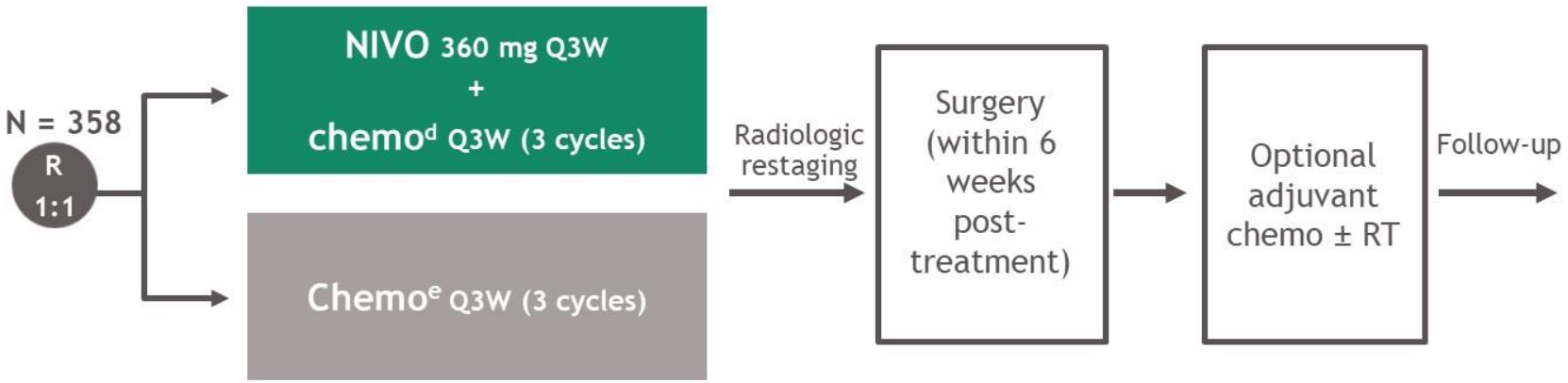
In patients with resectable NSCLC, treatment with perioperative durvalumab plus neoadjuvant chemotherapy resulted in longer event-free survival and a greater incidence of pathological complete response than neoadjuvant chemotherapy alone, with a safety profile that was consistent with the safety profiles of the individual agents.

CheckMate 816 study design[a,1]

Key eligibility criteria

- Newly diagnosed, resectable, stage IB (≥ 4 cm)-IIIA NSCLC (per TNM 7th edition)
- ECOG PS 0-1
- No known sensitizing *EGFR* mutations or *ALK* alterations

Stratified by stage (IB/II vs IIIA), PD-L1[b] (≥ 1% vs < 1%[c]), and sex



Primary endpoints
- pCR by BIPR
- EFS by BICR

Key secondary endpoints
- MPR by BIPR
- OS
- Time to death or distant metastases

Key exploratory endpoints included
- ORR by BICR
- **Feasibility of surgery; peri- and post-operative surgery-related AEs**

Database lock: September 16, 2020; minimum follow-up: 7.6 months for NIVO + chemo and chemo arms.

[a]NCT02998528; this study included an exploratory arm: NIVO 3 mg/kg Q2W (3 cycles) + ipilimumab 1 mg/kg (cycle 1 only). Data from this arm are not included in this presentation; [b]Determined by the PD-L1 IHC 28-8 pharmDx assay (Dako); [c]Included patients with PD-L1 expression status not evaluable and indeterminate; [d]NSQ: pemetrexed + cisplatin or paclitaxel + carboplatin; SQ: gemcitabine + cisplatin or paclitaxel + carboplatin; [e]Vinorelbine + cisplatin, docetaxel + cisplatin, gemcitabine + cisplatin (SQ only), pemetrexed + cisplatin (NSQ only), or paclitaxel + carboplatin.

1. Forde PM, et al. Oral presentation at the AACR Annual Meeting; April 8-10, 2021; virtual. Abstract 5218.

2024 ASCO ANNUAL MEETING

Neoadjuvant nivolumab plus chemotherapy vs chemotherapy in patients with resectable NSCLC: 4-year update from CheckMate 816

Jonathan D. Spicer,[1] Nicolas Girard,[2] Mariano Provencio Pulla,[3] Changli Wang,[4] Tetsuya Mitsudomi,[5] Mark M. Awad,[6] Everett E. Vokes,[7] Janis M. Taube,[8] Lorena Lupinacci,[9] Gene B. Saylors,[10] Fumihiro Tanaka,[11] Moishe Liberman,[12] Sung Yong Lee,[13] Aurelia Alexandru,[14] Manolo D'Arcangelo,[15] Phuong Tran,[16] Javed Mahmood,[16] Vishwanath Gharpure,[16] Apurva Bhingare,[16] Patrick M. Forde[8]

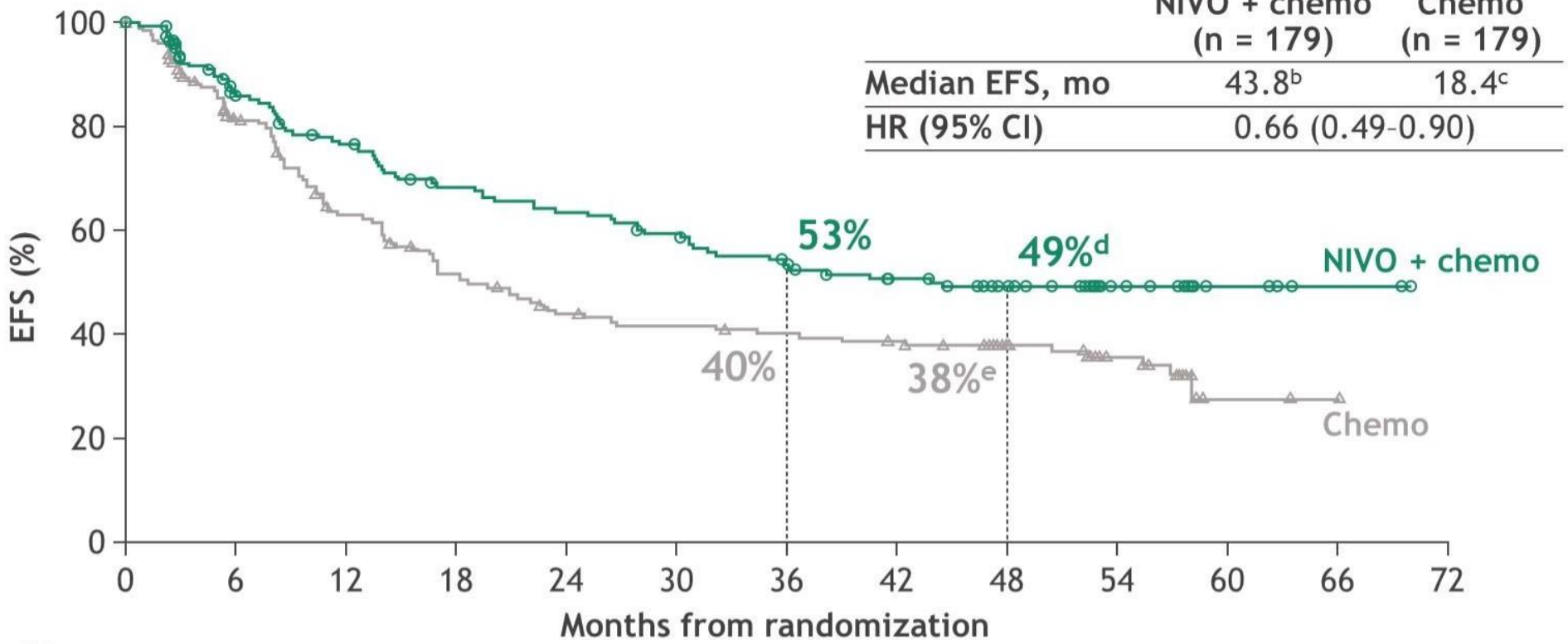
[1]McGill University Health Centre, Montreal, Quebec, Canada; [2]Institut du Thorax Curie-Montsouris, Institut Curie, Paris, France; [3]Hospital Universitario Puerta de Hierro, Madrid, Spain; [4]Tianjin Lung Cancer Center, Tianjin Medical University Cancer Institute & Hospital, Tianjin, China; [5]Kindai University Faculty of Medicine, Ohno-Higashi, Osaka-Sayama, Japan; [6]Dana-Farber Cancer Institute, Boston, MA; [7]University of Chicago Medicine, Chicago, IL; [8]The Bloomberg-Kimmel Institute for Cancer Immunotherapy, Johns Hopkins Medicine, The Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; [9]Hospital Italiano de Buenos Aires, Buenos Aires, Argentina; [10]Charleston Oncology, Charleston, SC; [11]University of Occupational and Environmental Health, Kitakyushu, Japan; [12]Centre Hospitalier de l'Universite de Montreal, Montreal, Quebec, Canada; [13]Korea University Guro Hospital, Korea University College of Medicine, Seoul, Republic of Korea; [14]Institutul Oncologic București Prof. Dr. Alexandru Trestioreanu, Bucharest, Romania; [15]Azienda Unita Sanitaria Locale della Romagna, Ravenna, Italy; [16]Bristol Myers Squibb, Princeton, NJ

Abstract number LBA8010

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

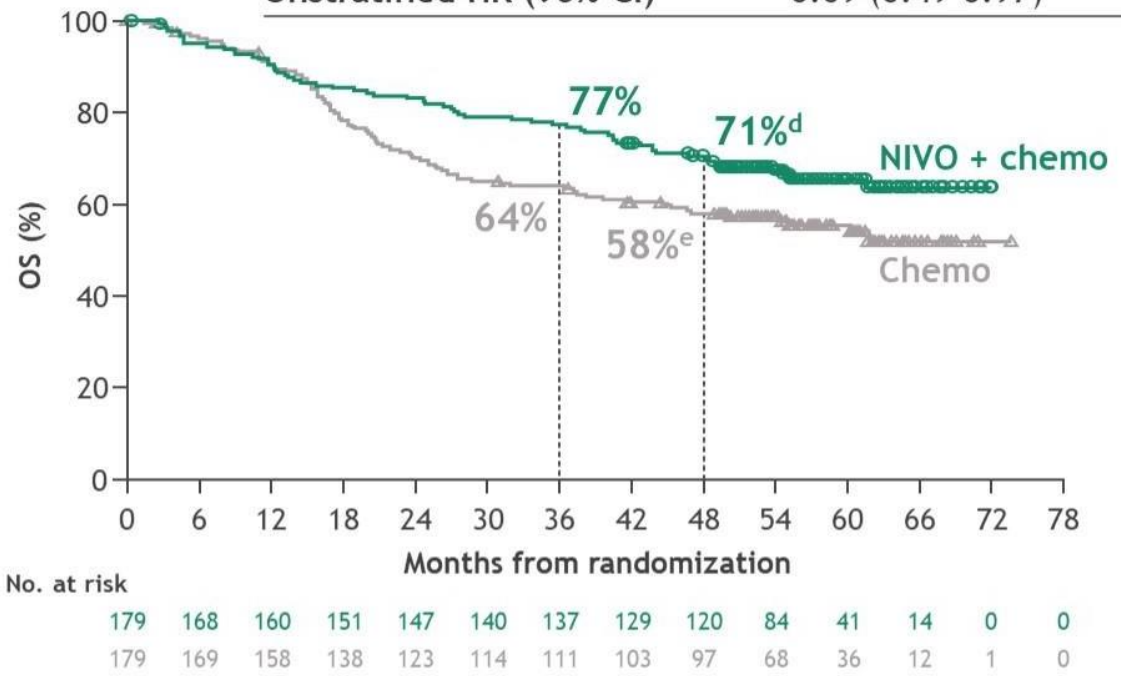
Database lock date, February 23, 2024; minimum/median follow-up, 49.1/57.6 months.

[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.

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)	

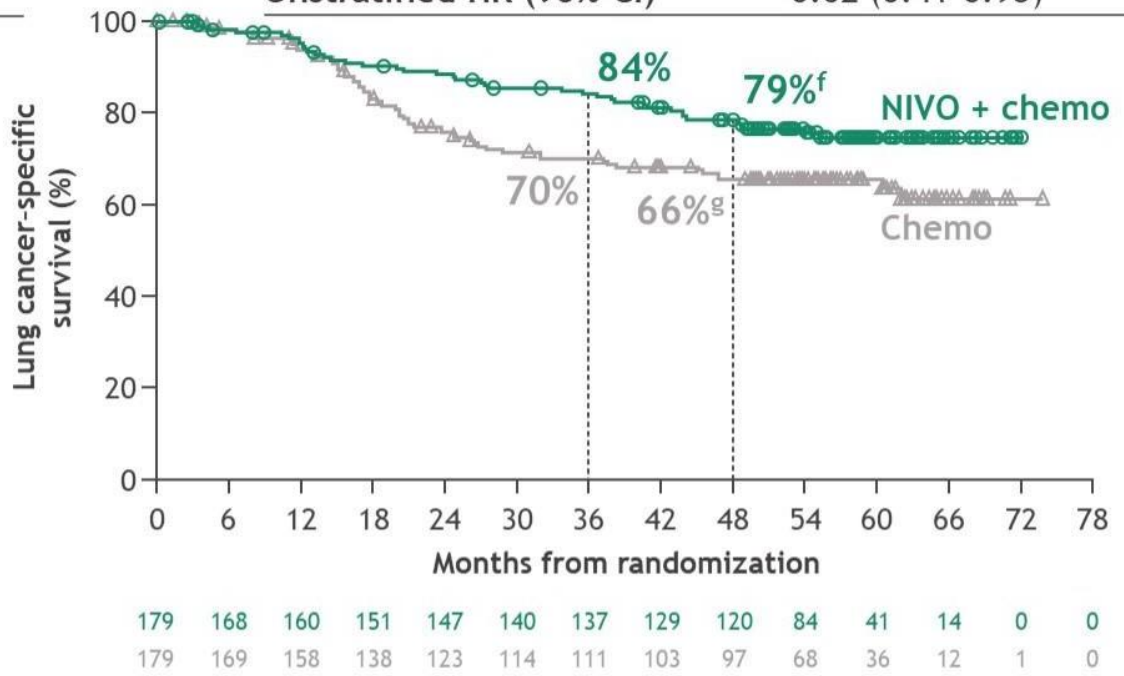


No. at risk

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%**)

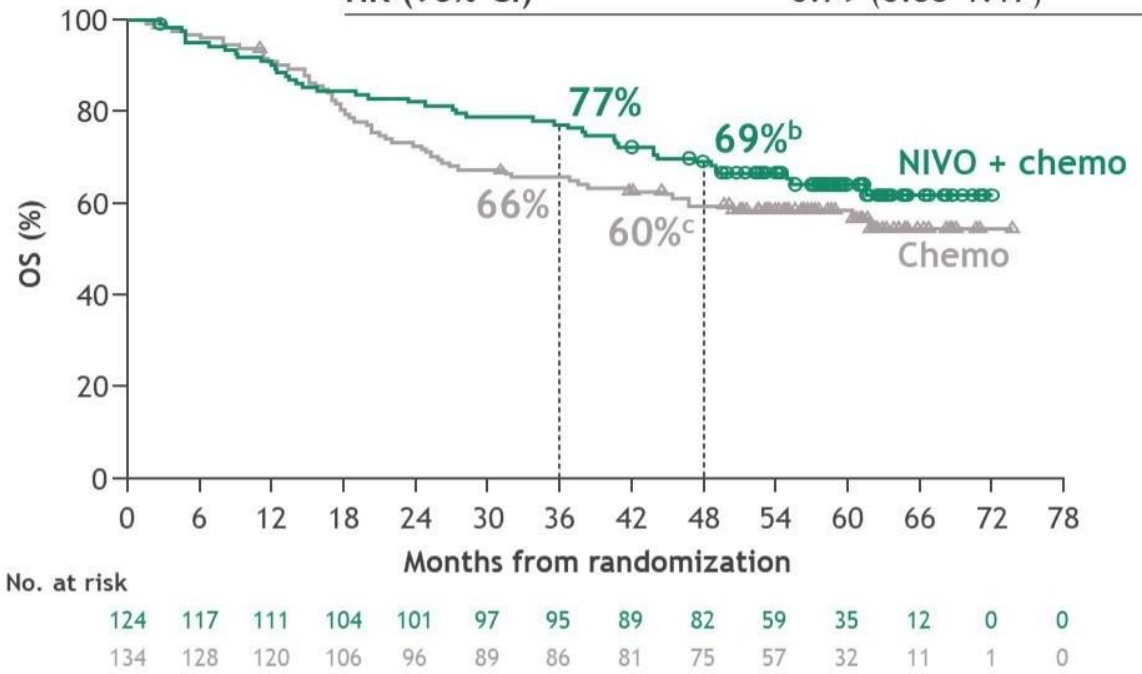
Minimum/median follow-up, 49.1/57.6 months.

[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.

OS by neoadjuvant platinum chemo received

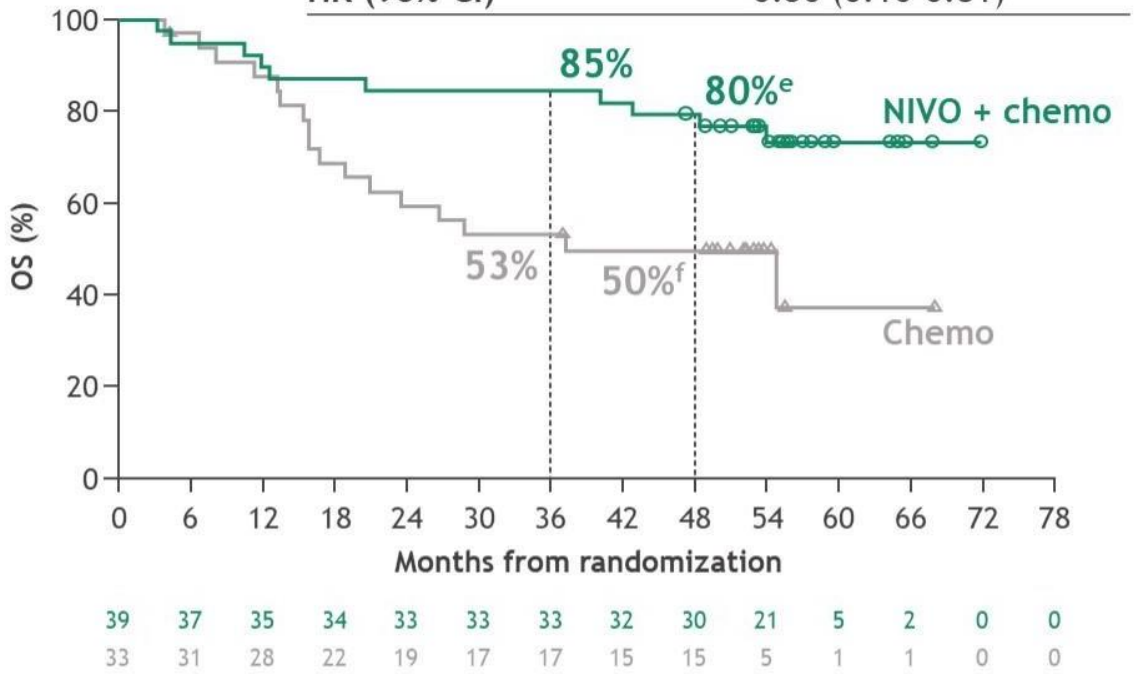
Cisplatin

	NIVO + chemo (n = 124)	Chemo (n = 134)
Median OS, mo	NR	NR[a]
HR (95% CI)	0.79 (0.53-1.17)	



Carboplatin

	NIVO + chemo (n = 39)	Chemo (n = 33)
Median OS, mo	NR	37.2[d]
HR (95% CI)	0.36 (0.16-0.81)	

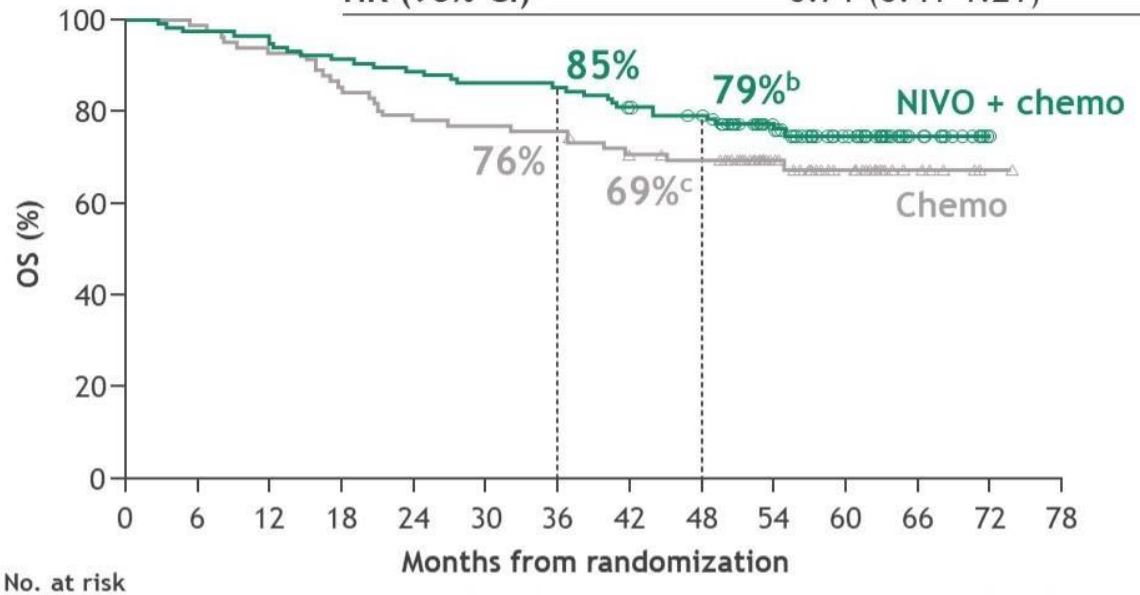


Minimum/median follow-up, 49.1/57.6 months.
[a-f]95% CI: [a]50.4-NR; [b]60-76; [c]51-68; [d]16.8-NR; [e]63-89; [f]32-66.

OS by extent of resection[a]

Lobectomy

	NIVO + chemo (n = 115)	Chemo (n = 82)
Median OS, mo	NR	NR
HR (95% CI)	0.71 (0.41-1.21)	

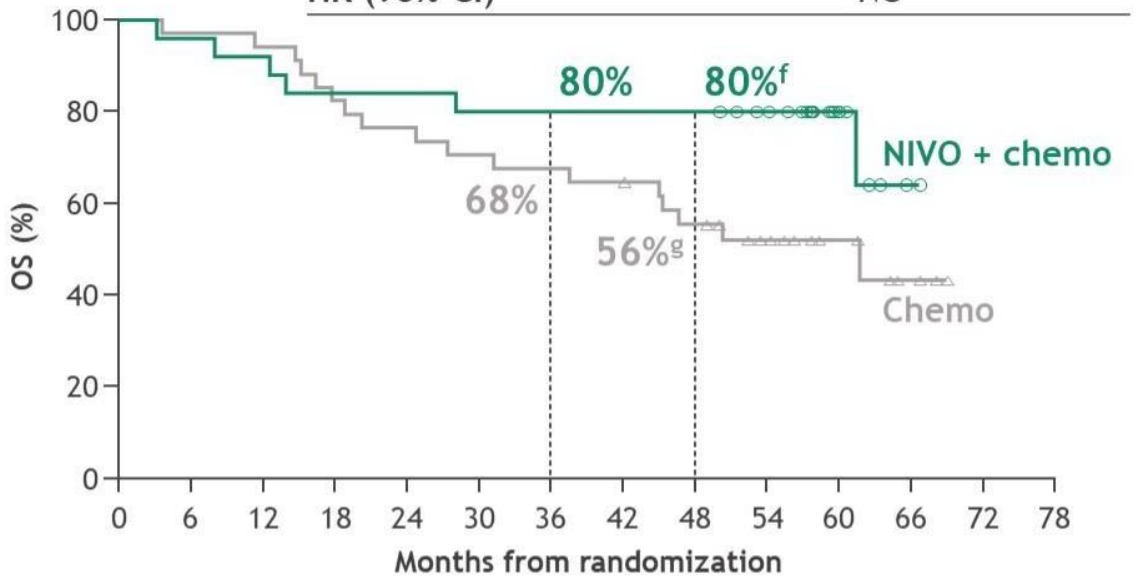


No. at risk

115	112	109	105	102	99	98	92	87	58	33	13	0	0
82	81	76	70	64	63	62	56	54	33	20	6	1	0

Pneumonectomy

	NIVO + chemo (n = 25)	Chemo (n = 34)
Median OS, mo	NR[d]	61.8[e]
HR (95% CI)	NC	



25	24	23	21	21	20	20	20	20	17	7	1	0	0
34	33	32	28	26	24	23	22	18	13	7	3	0	0

- 4-year EFS rates were 56%[h] with NIVO + chemo vs 43%[i] with chemo in patients with lobectomy (HR, 0.59; 95% CI, 0.39-0.90) and 57%[j] vs 40%[k] in patients with pneumonectomy (HR, NC)

Minimum/median follow-up, 49.1/57.6 months.
HRs were NC if there was an insufficient number of events (< 10 per arm). [a]Patients may have had ≥ 1 type of surgery. In the respective NIVO + chemo and chemo arms, surgery types included lobectomy (77% and 61%) and pneumonectomy (17% [11 right; 14 left] and 25% [12 right; 22 left]). [b-k]95% CI: [b]70-86; [c]58-78; [d]61.5-NR; [e]31.2-NR; [f]58-91; [g]37-70; [h]46-65; [i]32-54; [j]33-75; [k]22-56.

2024 ASCO ANNUAL MEETING

Abstract 8011

Outcomes with Perioperative Durvalumab in Patients with Resectable NSCLC and Baseline N2 Lymph Node Involvement (N2 R-NSCLC)

An Exploratory Subgroup Analysis of AEGEAN

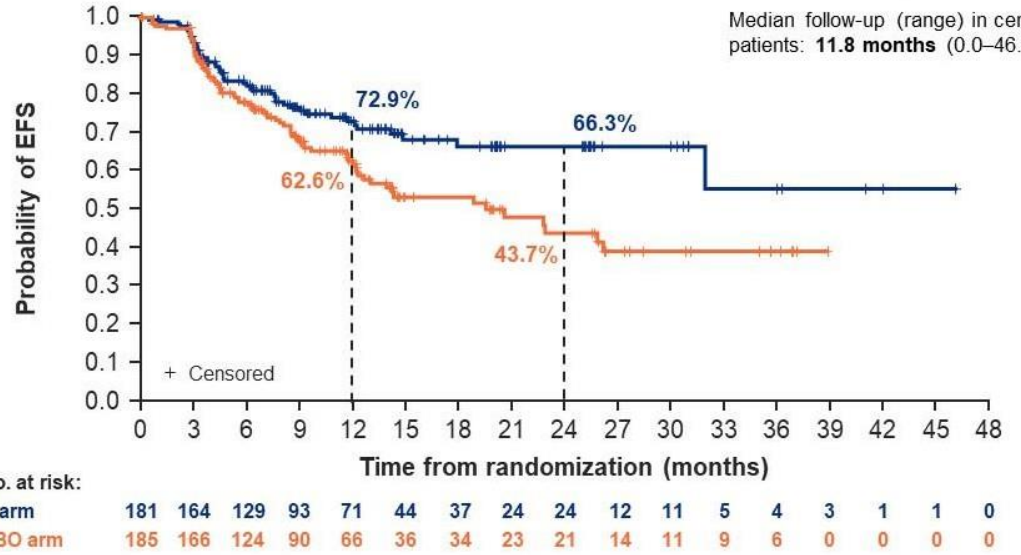
John V. Heymach,[1] Martin Reck,[2] Tetsuya Mitsudomi,[3] Janis M. Taube,[4] Alexander Spira,[5] Jamie Chaft,[6] Gary J. Doherty,[7] Helen Mann,[7] Tamer M. Fouad,[8] David Harpole[9]

[1]Department of Thoracic/Head and Neck Medical Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA; [2]Lung Clinic Grosshansdorf, Airway Research Center North, German Center for Lung Research, Grosshansdorf, Germany; [3]Division of Thoracic Surgery, Department of Surgery, Kindai University Faculty of Medicine, Osaka-Sayama, Japan; [4]Bloomberg–Kimmel Institute for Cancer Immunotherapy, Johns Hopkins Kimmel Cancer Center, Baltimore, MD, USA; [5]Virginia Cancer Specialists Research Institute, Fairfax, VA, & US Oncology Research, The Woodlands, TX, USA; [6]Memorial Sloan-Kettering Cancer Center and Weill Cornell Medical College, New York, NY, USA; [7]AstraZeneca, Cambridge, UK; [8]AstraZeneca, New York, NY, USA; [9]Department of Surgery, Duke University Medical Center, Durham, NC, USA

EFS using RECIST v1.1 (BICR) (baseline N2 subgroup and mITT)*

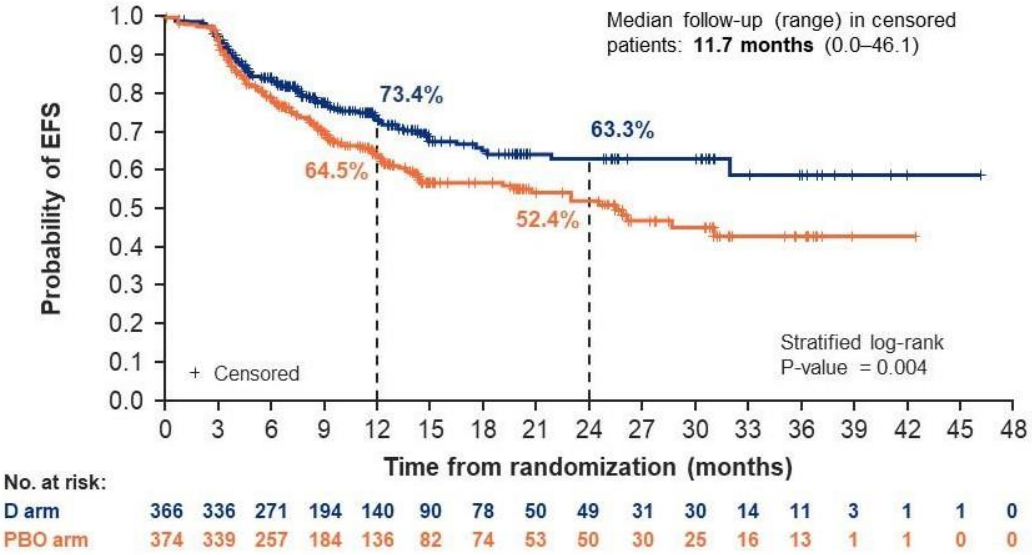
- EFS benefit in this subgroup was consistent with the mITT population and similar among patients with single- and multi-station N2 disease
  - N2 single-station (n=273) HR† (95% CI): 0.61 (0.39–0.94)[1]
  - N2 multi-station (n=74) HR† (95% CI): 0.69 (0.33–1.38)[1]

Baseline N2 subgroup	D arm	PBO arm
No. events / no. patients (%)	48/181 (26.5)	75/185 (40.5)
mEFS, months (95% CI)	NR (31.9, NR)	19.5 (12.6, 26.2)
Unstratified HR† (95% CI)	**0.63 (0.43, 0.90)**	



No. at risk:																	
D arm	181	164	129	93	71	44	37	24	24	12	11	5	4	3	1	1	0
PBO arm	185	166	124	90	66	36	34	23	21	14	11	9	6	0	0	0	0

mITT population[1]	D arm	PBO arm
No. events / no. patients (%)	98/366 (26.8)	138/374 (36.9)
mEFS, months (95% CI)	NR (31.9, NR)	25.9 (18.9, NR)
Stratified HR† (95% CI)	**0.68 (0.53, 0.88)**	



No. at risk:																	
D arm	366	336	271	194	140	90	78	50	49	31	30	14	11	3	1	1	0
PBO arm	374	339	257	184	136	82	74	53	50	30	25	16	13	1	1	0	0

DCO = Nov 10, 2022. *EFS is defined as time from randomization to the earliest of: (A) progressive disease (PD) that precludes surgery; (B) PD discovered and reported by the investigator upon attempting surgery that prevents completion of surgery; (C) local/distant recurrence using BICR per RECIST v1.1; or (D) death from any cause. HR <1 favours the D arm versus the PBO arm. Median and landmark EFS estimates calculated using the Kaplan–Meier method. †HR for the baseline N2 subgroup calculated from an unstratified Cox proportional hazards model; HR for the mITT population calculated using a stratified Cox proportional hazards model. CI, confidence interval; D, durvalumab; HR, hazard ratio; mEFS, median EFS; NR, not reached; PBO, placebo.

PRESENTED BY: John V. Heymach, MD, PhD; Professor and Chair

[1]From Perioperative Durvalumab for Resectable Non–Small-Cell Lung Cancer, Heymach JV, et al, N Engl J Med 2023;389:1672–84, Copyright © (2023) Massachusetts Medical Society. Reproduced with permission.

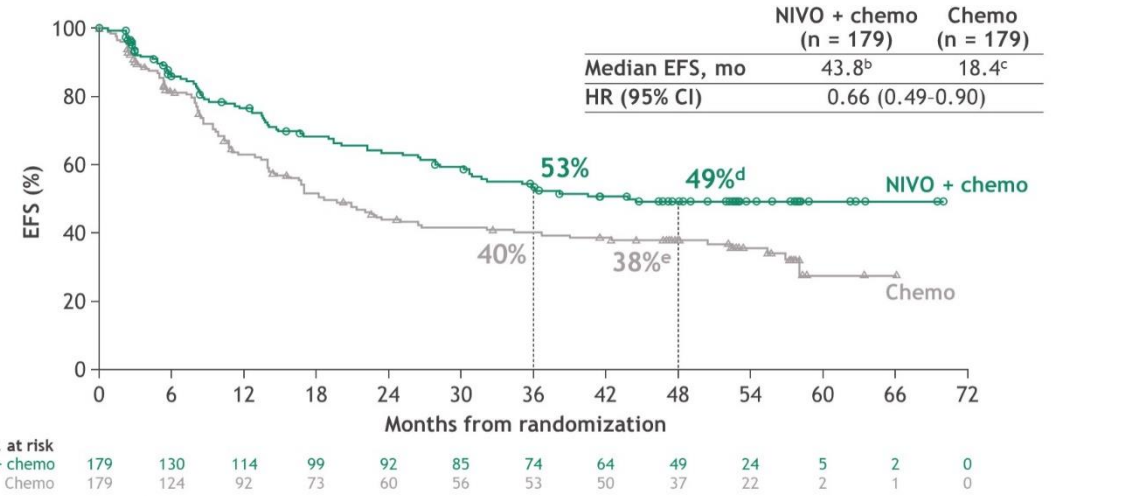
EFS und OS

	EFS 1 Jahr	EFS 2 Jahre	EFS 4 Jahre	OS 1 Jahr	OS 2 Jahre
Keynote 671		62.4		90	80.9
Aegean	73.4	63.3			
Checkmate 816	76.1	63.8	49	90.3	82.7

CheckMate 816: 4-y survival update

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]



Database lock date, February 23, 2024; minimum/median follow-up, 49.1/57.6 months.
[a]Exploratory analysis. [b,c]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.

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Stage IIA: >4 cm 60-65% 5-yr survival

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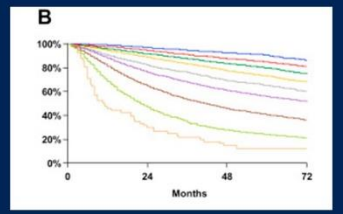
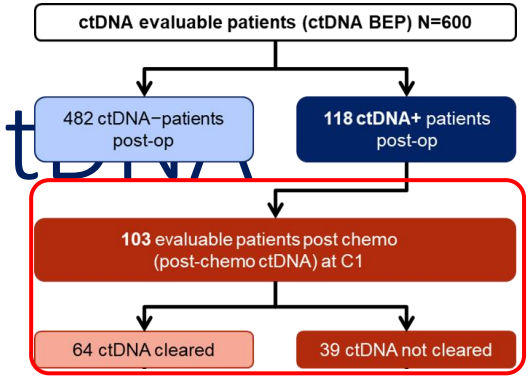
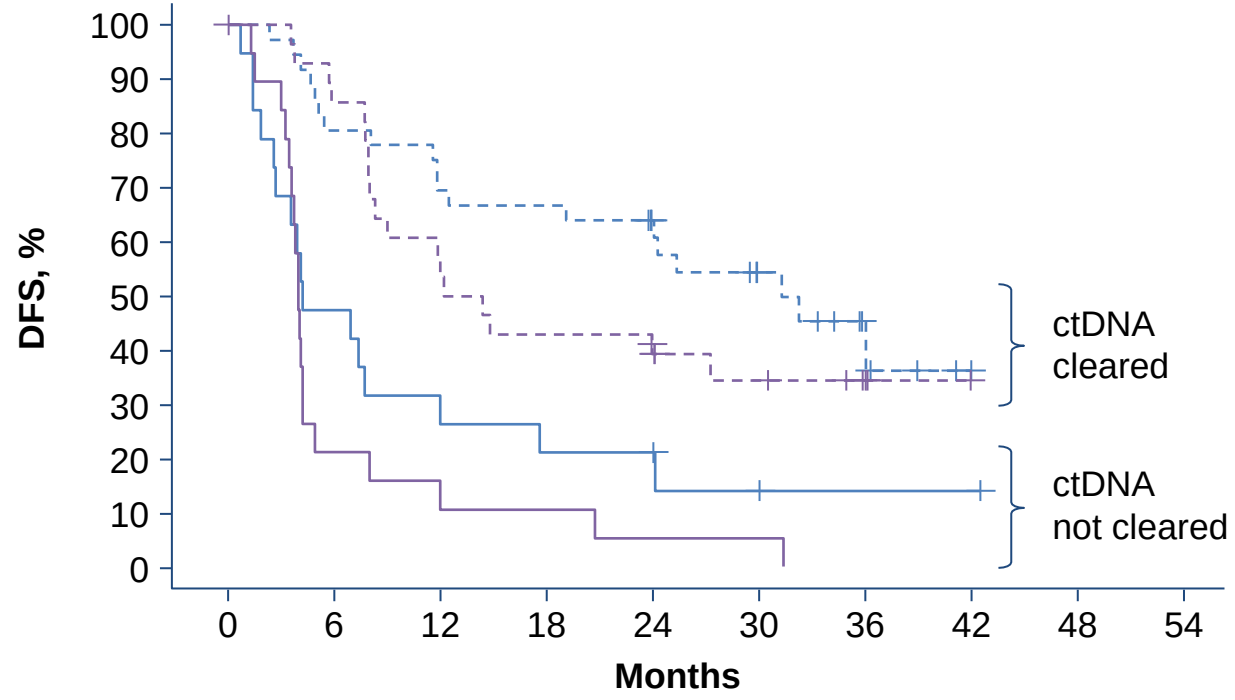


Survival based on pathologic stage

Goldstraw P, et al. Journal of Thoracic Oncology, Volume 11, Issue 1, 2016, 39–51

DFS by treatment arm and post-chemo ctDNA clearance status





Atezo, ctDNA cleared	36	35	29	28	25	24	24	23	21	17	12	10	5	2	1	0	0	0	0
Atezo, ctDNA not cleared	19	13	9	6	5	5	4	4	4	2	2	1	1	1	1	0	0	0	0
BSC, ctDNA cleared	28	28	24	18	15	12	12	12	12	8	7	6	4	1	1	0	0	0	0
BSC, ctDNA not cleared	20	16	4	3	2	2	2	1	1	1	1	0	0	0	0	0	0	0	0

ctDNA cleared	Atezo (n=36)	BSC (n=28)
mDFS, mo	31.3	13.3
HR (95% CI)	**0.7** (0.37, 1.34)	

ctDNA not cleared	Atezo (n=19)	BSC (n=20)
mDFS, mo	4.2	3.9
HR (95% CI)	**0.67** (0.34, 1.32)	

Impower 010

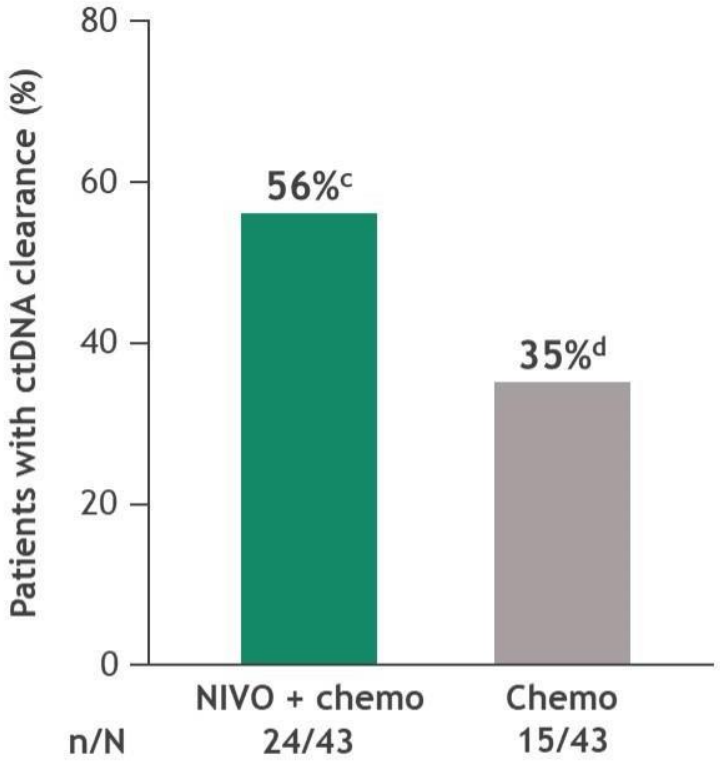
Clinical cutoff: 21 January 2021.
Data are hypothesis generating and should be interpreted with caution due to the exploratory nature of the analysis and small sample size.

Mod. Felip E et al; IMpower010: ctDNA status in patients with resected NSCLC who received adjuvant chemotherapy followed by Atezolizumab or Best Supportive Care; ESMO IO Congress 2022; Abstract 10

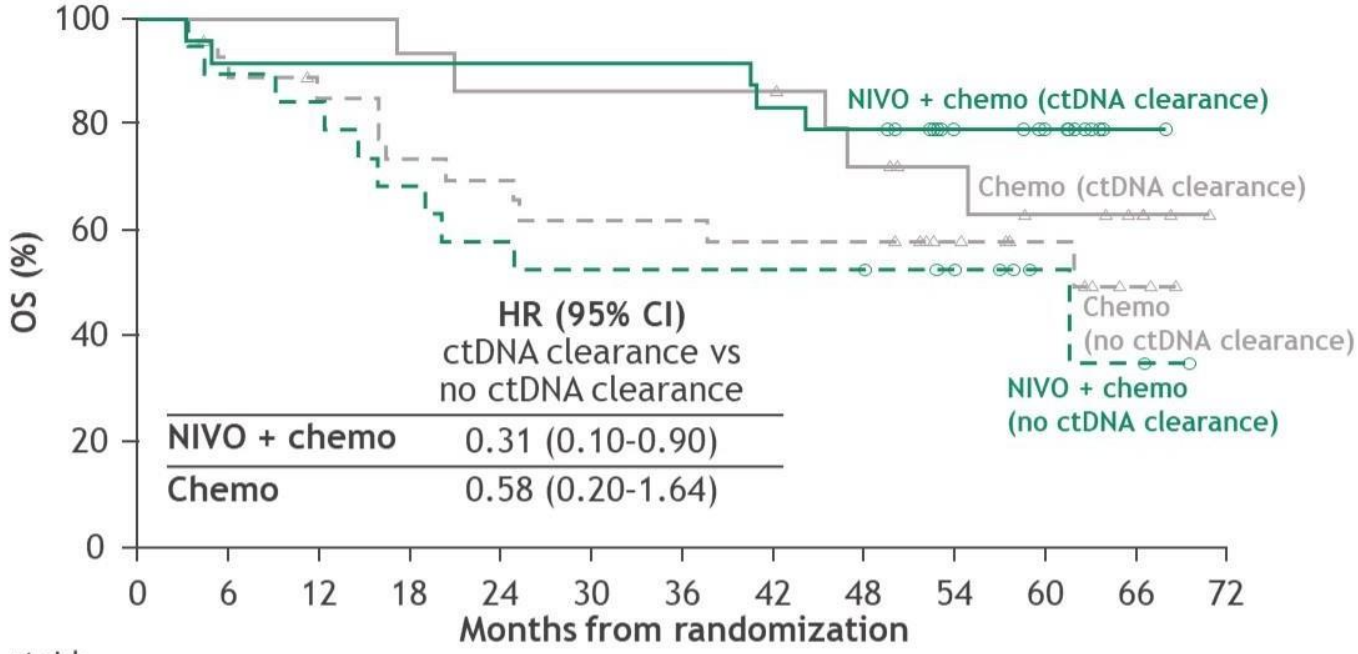
ctDNA clearance rate and OS by ctDNA clearance

- Among concurrently randomized patients, 89 (25%) had evaluable ctDNA levels, and 86 (24%) had detectable ctDNA levels at baseline[1,a]

ctDNA clearance rate[1,b]



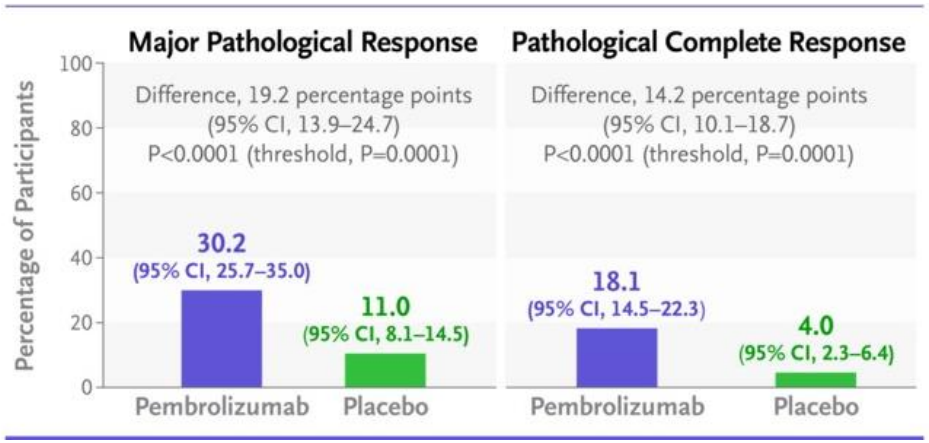
OS



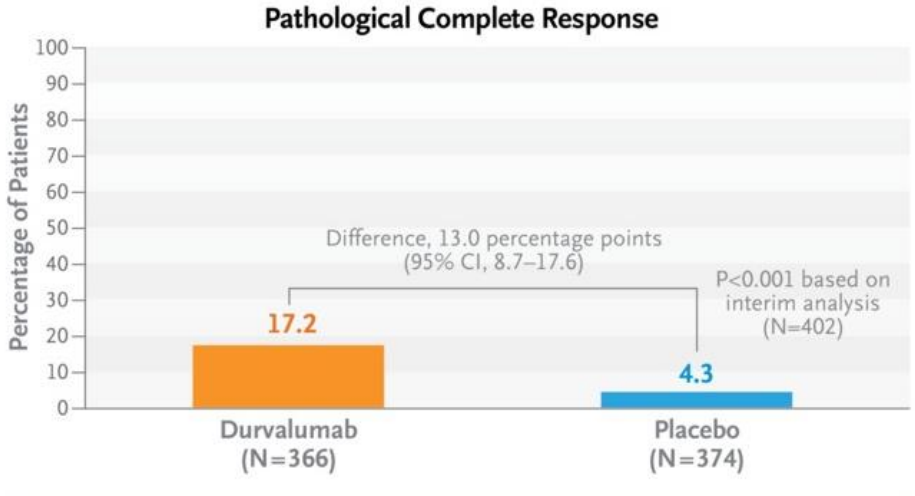
No. at risk													
ctDNA clearance	24	22	22	22	22	22	22	20	19	12	9	2	0
ctDNA clearance	15	15	15	14	13	13	13	13	10	8	6	4	0
No ctDNA clearance	19	17	16	13	11	10	10	10	9	7	3	2	0
No ctDNA clearance	28	24	22	19	18	16	16	15	15	11	7	2	0

Minimum/median follow-up, 49.1/57.6 months.

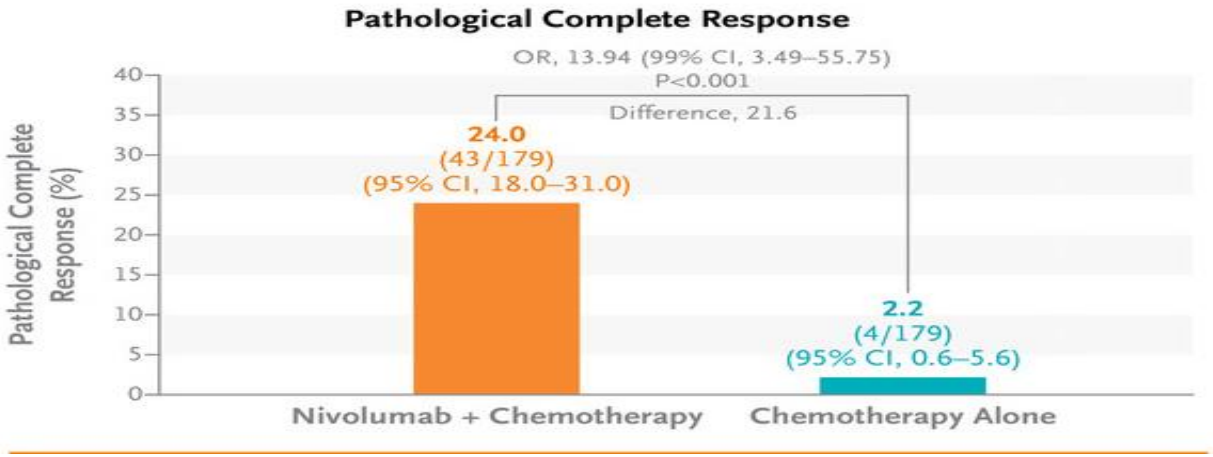
[a]The main reasons for sample attrition were lack of tissue for WES and lack of quality control pass for tissue and plasma. [b]ctDNA clearance was defined as pre-surgical change from detectable ctDNA levels before cycle 1 to undetectable ctDNA levels before cycle 3. Analysis was performed using a WES tumor-guided personalized ctDNA panel (ArcherDX Personalized Cancer Monitoring). [c,d]95% CI: [c]40-71; [d]21-51. 1. Forde PM, et al. *N Engl J Med* 2022;386:1973-1985.



Keynote 671



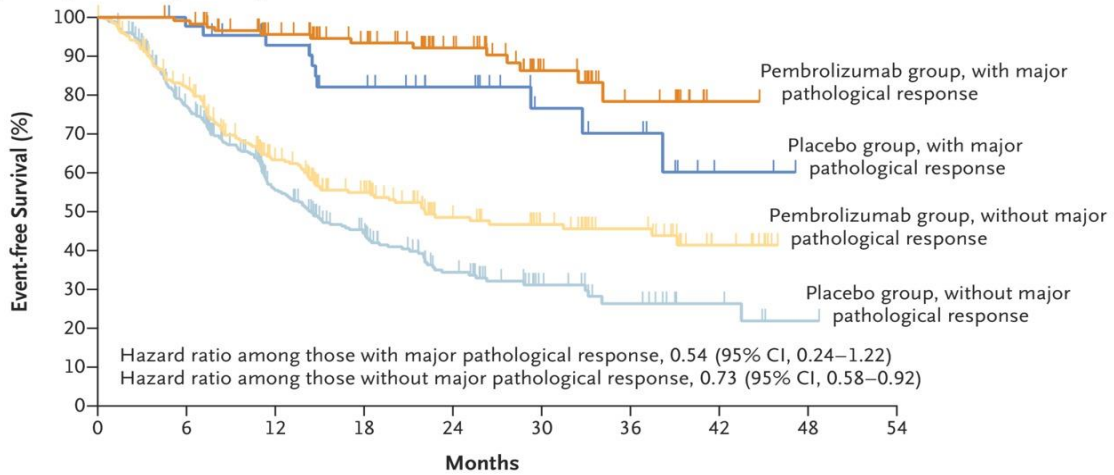
Aegean



Checkmate 816

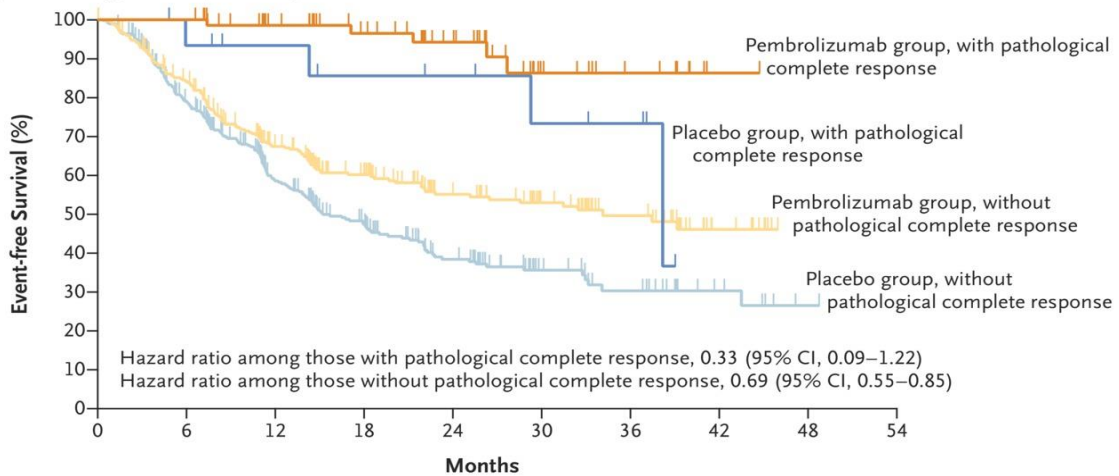
? Zeitvorteil

A Event-free Survival According to Major Pathological Response



No. at Risk										
With major pathological response										
Pembrolizumab group	120	117	99	79	60	30	15	1	0	0
Placebo group	44	42	36	28	22	12	10	2	0	0
Without major pathological response										
Pembrolizumab group	277	213	137	93	57	42	27	10	0	0
Placebo group	356	252	147	96	52	26	14	7	1	0

B Event-free Survival According to Pathological Complete Response



No. at Risk										
With pathological complete response										
Pembrolizumab group	72	72	59	46	33	15	8	1	0	0
Placebo group	16	14	12	10	9	5	4	0	0	0
Without pathological complete response										
Pembrolizumab group	325	258	177	126	84	57	34	10	0	0
Placebo group	384	280	171	114	65	33	20	9	1	0

Exploratory Analysis of Event-Free Survival According to Major Pathological Response and Pathological Complete Response (Intention-to-Treat Population).

The NEW ENGLAND JOURNAL of MEDICINE

FAZIT

- Neoadjuvante Chemoimmuntherapie ist der neue Standard
- Nach Operation ist eine Adjuvante Immuntherapie mittels Pembrolizumab zugelassen (9 Monate)
- Es könnte sein, dass wir hier eine Gruppe von Patienten übertherapieren
- Tumorbiomarker z. B. Ct-DNA und Pathologische CR-Informationen könnten hier hilfreich sein

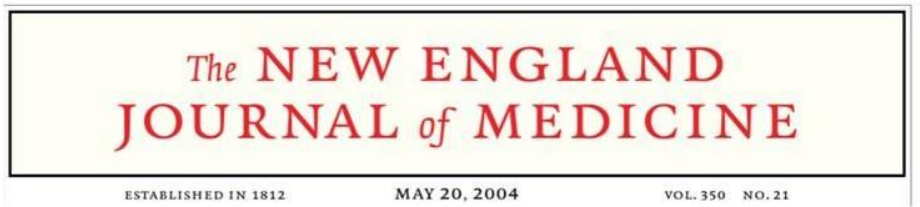
Was ist neu?

- Neoadjuvante Chemoimmuntherapie in NSCLC
  - Aegean
  - Keynote 671
  - Checkmate 816
- **Chemoradiotherapie NSCLC**
  - EGFR mutierte
  - ALKmutierte
- Fortgeschrittenes Stadium NSCLC
  - Crown
  - Trop 2
- SCLC
  - Adriatic
- Biomarker
  - Ct DNA

Celebrating 20 Years Since EGFR Mutation Discovery!

Thank you for your guidance on my presentation: Zosia Piotrowska, Charu Aggarwal, Jessica Lin, Justin Gainor, Becca Heist, Jennifer Temel, Ibiayi Dagogo-Jack, Nate Pennell, Nasser Hanna, Catherine Meador, Allison Chang, Jaime Schneider, Chris Nabel, Mary Boulanger

Global community of EGFR Researchers: Tom Lynch, Daniel Haber, Pasi Jänne, Bruce Johnson, Matthew Meyerson, William Pao, Jeff Engelman, Roy Herbst, Paul Bunn, Tetsuya Mitsudomi, Ming Tsao, John Iafrate, Tony Mok, Makoto Maemondo, Mark Kris, Rafael Rosell, Caicun Zhou, James Yang, Katie Politi, Zosia Piotrowska, Christine Lovly, Helena Yu, Suresh Ramalingam, Fred Hirsch, Frances Shepard, Rafal Dziadziuszko, David Carbone, John Heymach, Joel Neal, Heather Wakelee, Nate Pennell, Aaron Hata, Sarah Goldberg, Jean-Charles Soria, Takashi Seto, David Gandara, Vince Miller, Karen Kelly, Nobuyuki Yamamoto, Enriqueta Felip, Masahiro Fukuoka, Marina Garassino, Ross Camidge, Terufumi Kato, Shirish Gadgeel, Jonathan Goldman, Karen Reckamp, Greg Riely, Geoff Oxnard, Natasha Leighl, Ignatious Ou, Max Diehn, Yi-Long Wu, Fiona Blackhall, Kwok Wong, Daniel Tan, Sumitra Thongprasert, Luis Paz-Ares, Keunchil Park, Jürgen Wolf, Ken O'Byrne, Michael Boyer, Myung-Ju Ahn, Benjamin Besse, Masahiro Tsuboi, Shun Lu, Ben Solomon, Ed Kim, Tom John, David Spigel, John Iafrate, Trevor Bivona, Ed Garon, Charlie Rudin, Lynette Sholl, Xiuning Le, Elaine Shum, Martin Reck, Scott Gettinger, David Gerber, Mark Socinski, Julie Brahmer, Josh Sabari, Balazs Halmos, Renato Martins, Matt Guebens, Vamsi Velcheti, Alex Spira, Mari Mino-Kenudson, Estela Rodriguez, Jair Bar, Alfredo Addeo, David Planchard, Luda Bazhenova, Tom Stinchcombe, Daniel Costa, Ryan Gentzler, Egbert Smit, Dara Aisner, Jack West, Jyoti Patel, Martin Schuler, Nir Peled, Vanita Noronha, Akira Inoue, Annemarie Dingemans, Solange Peters, Henning Willers, Mark Awad, Charlie Swanton, Collin Blakely, Julia Rotow, Leora Horn, Josh Bauml, Aaron Lisberg, Byong Chul Cho, Marc Ladanyi, Dong Wan Kim, Ignacio Wistuba, Eric Haura, Jhanelle Gray, Stephen Liu, Jonathan Riess, Christian Rolfo, Barbara Gitlitz, Jerry Azzoli, Jamie Chaft, Ross Soo, Dave Jackman, Jacqueline Aredo, Kristin Marrone, Tim Burns, Sanjay Popat, Glen Goss, Rogerio Lilenbaum, Taofeek Owonikoko, Hoss Borghaei, Corey Langer, Misako Nagasaka, and many others…



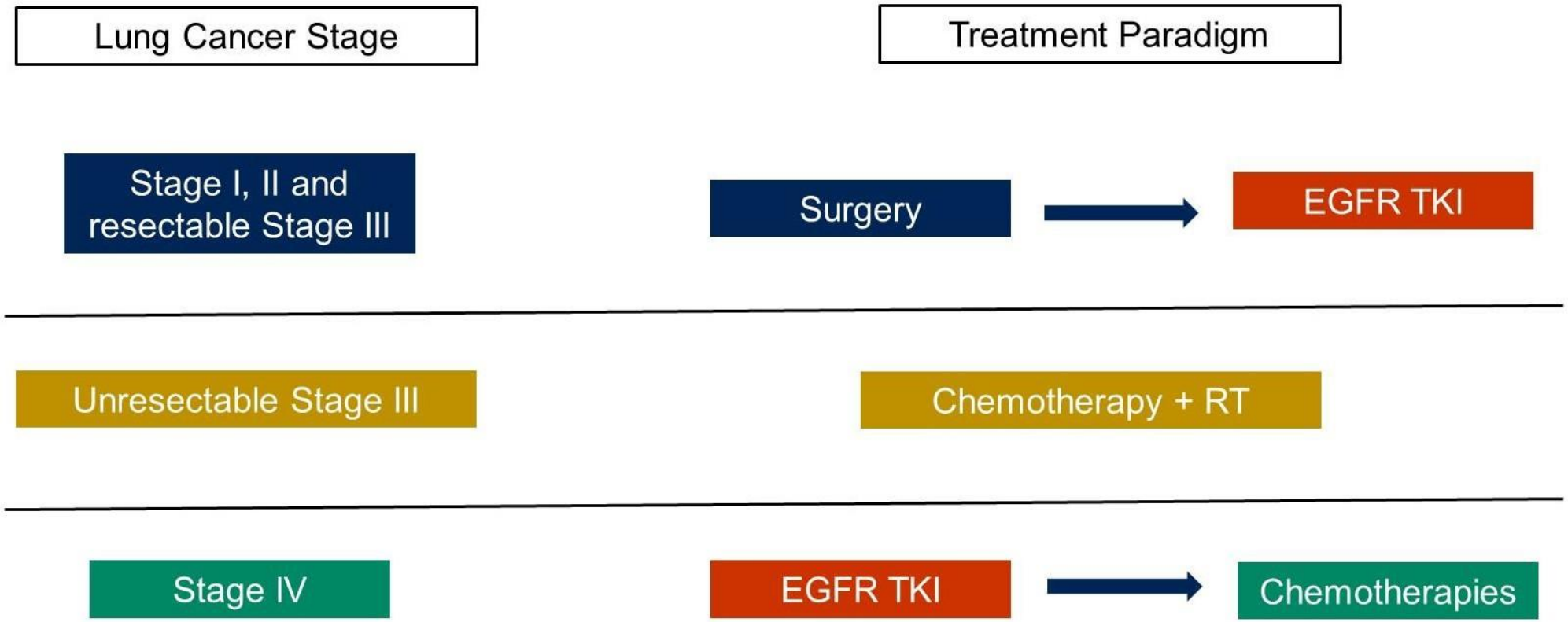
Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non–Small-Cell Lung Cancer to Gefitinib

Thomas J. Lynch, M.D., Daphne W. Bell, Ph.D., Raffaella Sordella, Ph.D., Sarada Gurubhagavatula, M.D., Ross A. Okimoto, B.S., Brian W. Brannigan, B.A., Patricia L. Harris, M.S., Sara M. Haserlat, B.A., Jeffrey G. Supko, Ph.D., Frank G. Haluska, M.D., Ph.D., David N. Louis, M.D., David C. Christiani, M.D., Jeff Settleman, Ph.D., and Daniel A. Haber, M.D., Ph.D.

Gratitude to those who participate in clinical trials

PRESENTED BY: Lecia V. Sequist, MD, MPH

Current Landscape of Therapy for EGFR + NSCLC



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

LAURA Phase 3 double-blind study design

Patients with locally advanced, unresectable stage III* EGFRm NSCLC with no progression during / following definitive CRT† treatment

Key inclusion criteria:
- ≥18 years (Japan: ≥20)
- WHO PS 0 / 1
- Confirmed locally advanced, unresectable stage III* NSCLC
- Ex19del / L858R‡
- Maximum interval between last dose of CRT and randomization: 6 weeks

Osimertinib 80 mg, once daily

Randomization 2:1 (N=216)

Stratification by:
Concurrent vs sequential CRT
Stage IIIA vs stage IIIB/IIIC
China vs non-China

Placebo, once daily

Treatment duration until BICR-assessed progression (per RECIST v1.1), toxicity, or other discontinuation criteria

Open-label osimertinib after BICR-confirmed progression offered to both treatment arms§

Tumor assessments:
- Chest CT / MRI and brain MRI
- At baseline, every 8 weeks to Week 48, then every 12 weeks until BICR-assessed progression

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

Baseline characteristics

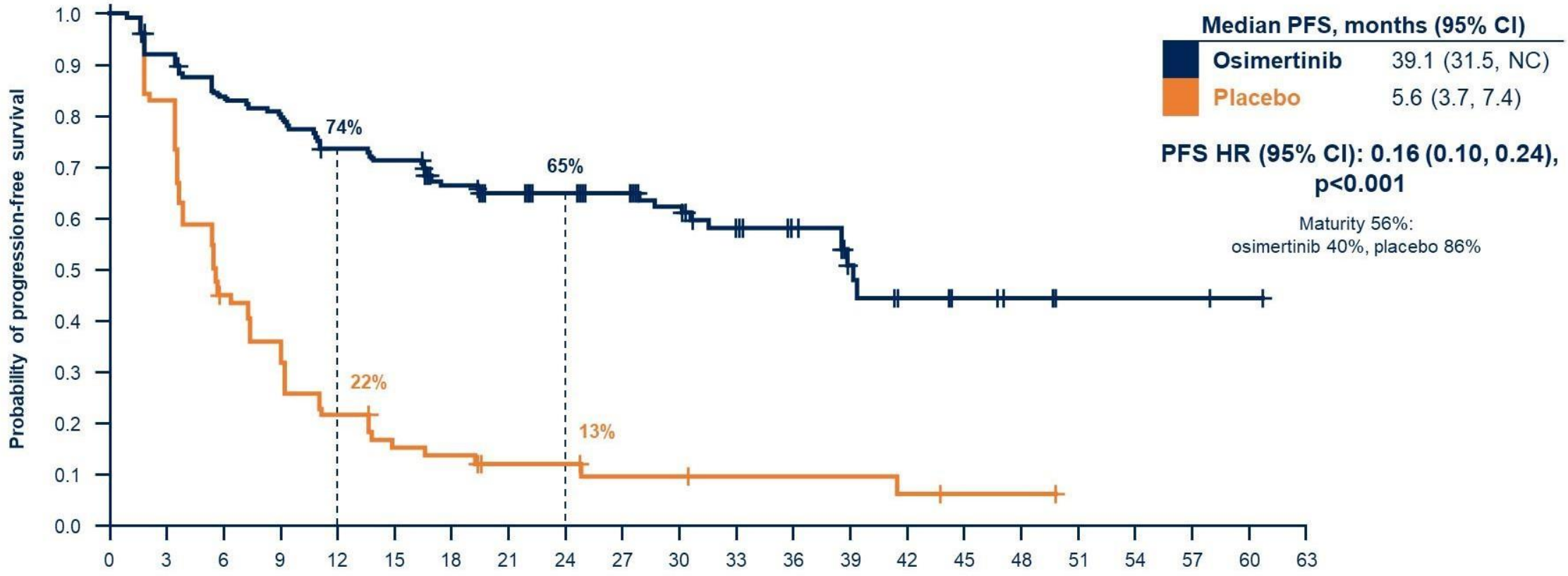
Characteristics, %	Osimertinib (n=143)	Placebo (n=73)
Sex: male / female	37 / 63	42 / 58
Age: median (range), years	62 (36–84)	64 (37–83)
Smoking history: formerly / currently / never	26 / 3 / 71	32 / 1 / 67
Race: Asian / non-Asian	81 / 19	85 / 15
WHO PS: 0 / 1	56 / 44	42 / 58
AJCC / UICC staging (8th edition) at diagnosis: IIIA / IIIB / IIIC	36 / 47 / 17	33 / 52 / 15
Histology: adenocarcinoma / other	97 / 3	95 / 5
EGFR mutation at randomization:* Ex19del / L858R	52 / 48†	59 / 41
Type of CRT: concurrent CRT / sequential CRT	92 / 8	85 / 15
Response to prior CRT: CR / PR / SD / PD / NE	3 / 47 / 43 / 0 / 8	4 / 37 / 51 / 0 / 8
Target lesion size by BICR:‡ mean (SD), mm	33 (18)	36 (17)

Data cut-off: January 5, 2024.
*Tissue tested by central or FDA-approved local test from a CLIA-approved laboratory, or accredited local laboratory for sites outside the USA;
†One patient in the osimertinib arm had missing EGFR mutation;
‡Post-CRT.

PRESENTED BY: Dr Suresh S. Ramalingam

AJCC, American Joint Committee on Cancer; BICR, blinded independent central review; CLIA, Clinical Laboratory Improvement Amendments; CR, complete response; CRT, chemoradiotherapy; EGFR, epidermal growth factor receptor; Ex19del, exon 19 deletion; FDA, Food and Drug Administration; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease; UICC, Union for International Cancer Control; WHO PS, World Health Organization performance status

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

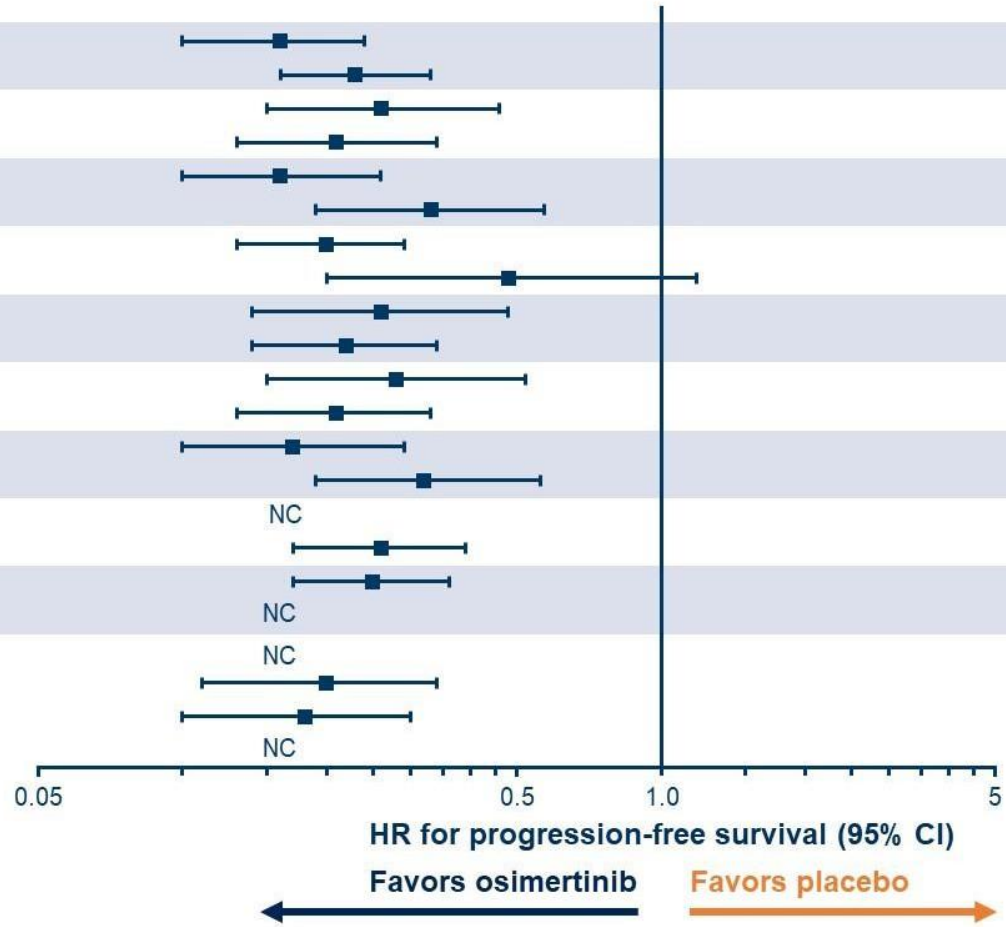
Tick marks indicate censored data. Median follow-up for PFS (all patients): osimertinib 22.0 months, placebo 5.6 months. Median follow-up for PFS (censored patients): osimertinib 27.7 months, placebo 19.5 months.

Data cut-off: January 5, 2024.

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

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);

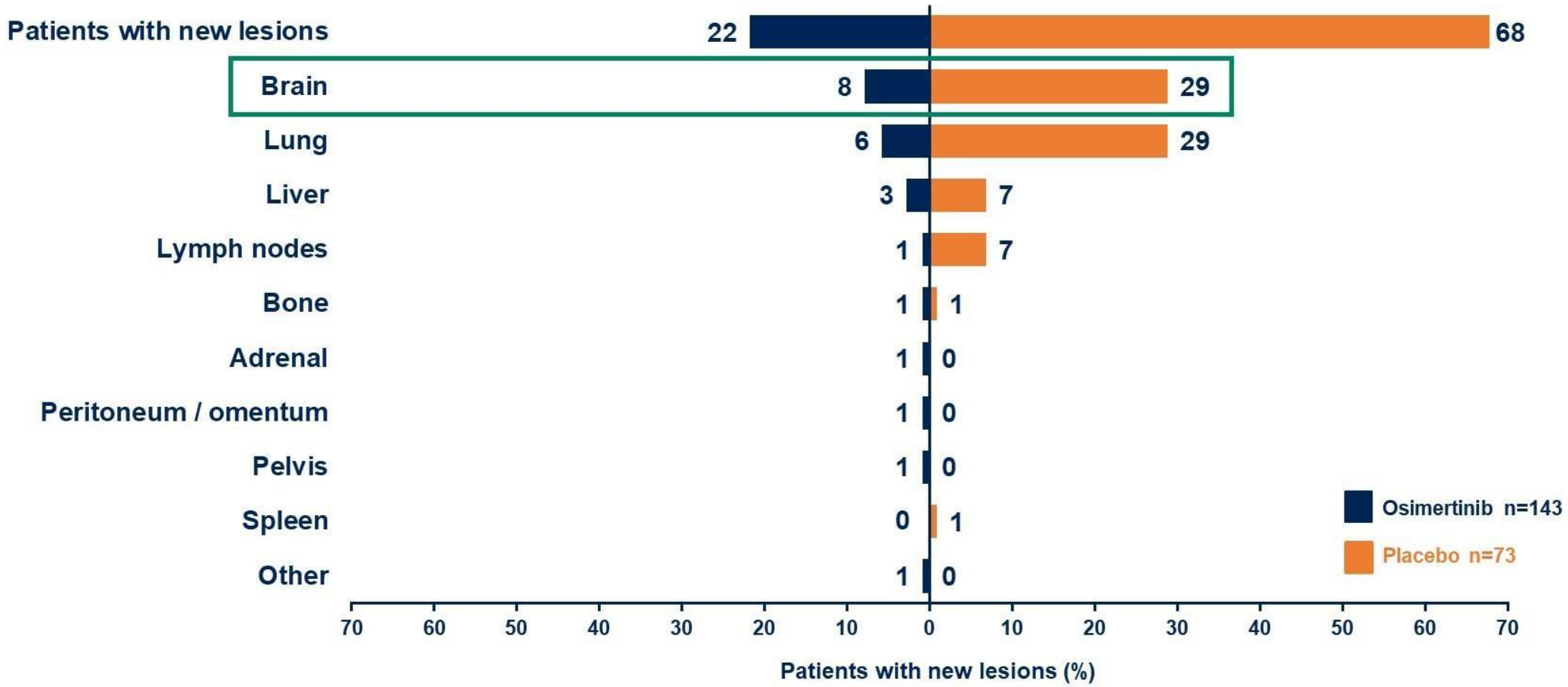
*Stage prior to CRT by AJCC / UICC staging (8th edition);

†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

Sites of new lesions by BICR



Percentages based on number of patients in each treatment arm. Patients can have more than one new lesion site. Based on BICR assessments according to RECIST v1.1 and includes all new lesions at any time (including those whose RECIST progression event had been censored).

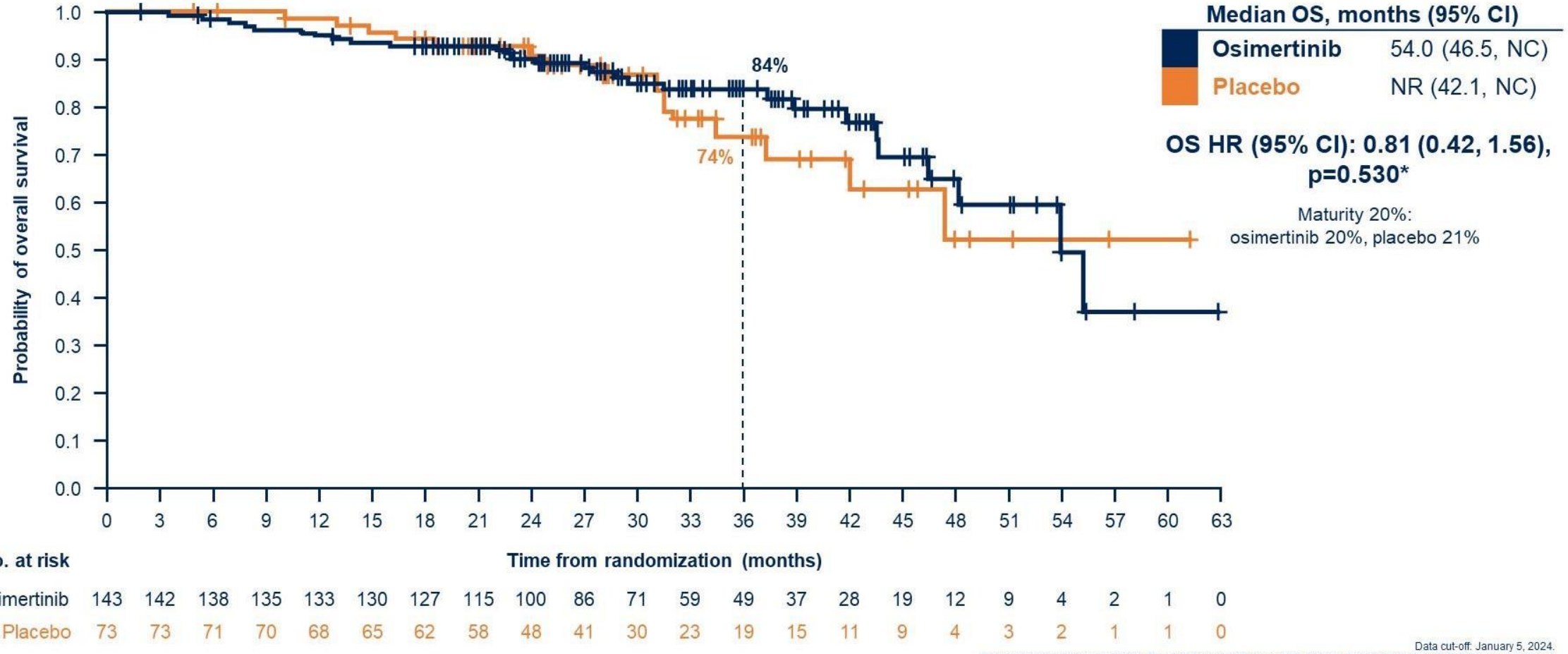
Data cut-off: January 5, 2024.

BICR, blinded independent central review

PRESENTED BY: Dr Suresh S. Ramalingam

Interim analysis of overall survival

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



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.

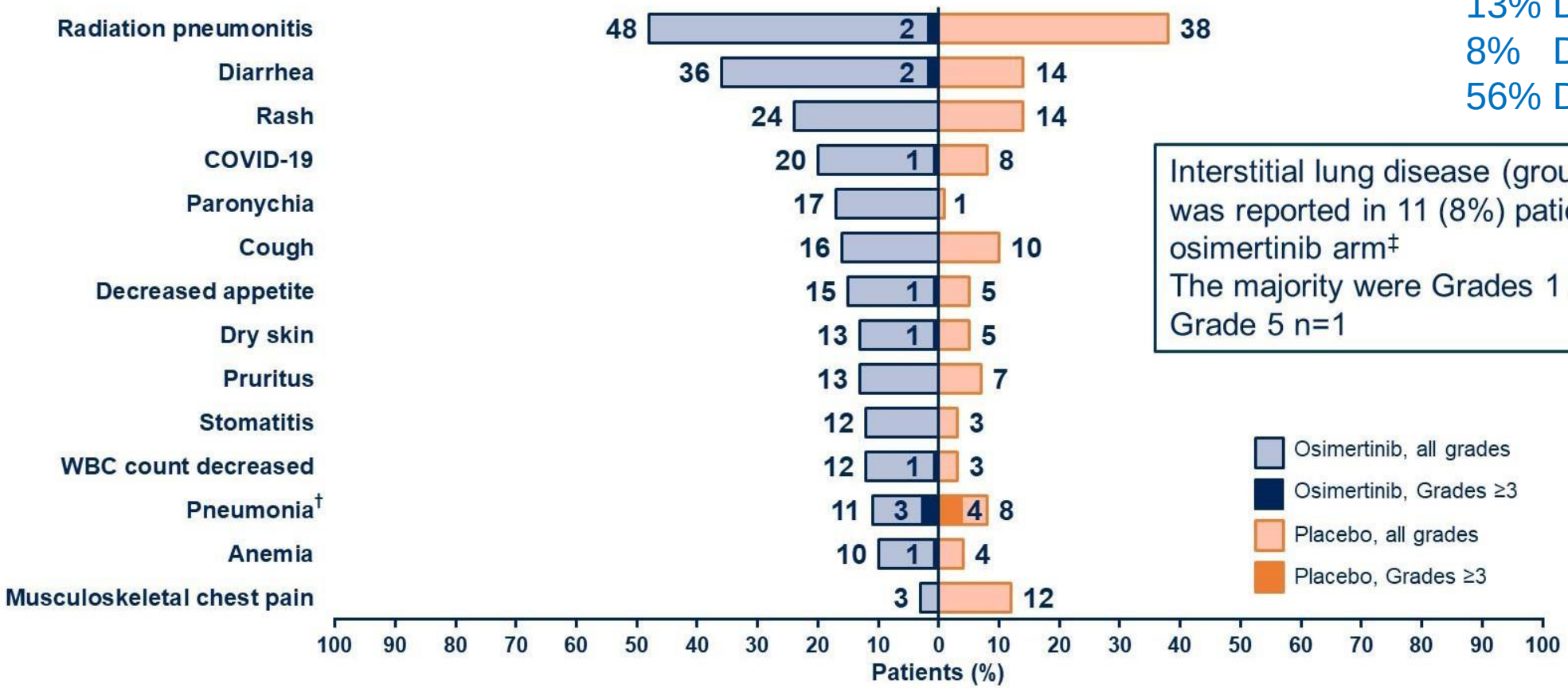
BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; NC, not calculable; NR, not reached; OS, overall survival

PRESENTED BY: Dr Suresh S. Ramalingam

All-causality adverse events (≥10%)*

- The most common AE in both arms was radiation pneumonitis; the majority were low grade (no Grade 4 / 5), non-serious and manageable

≥10% Adverse events
13% Discontinuation
8% Dose reduction
56% Dose interruption



Interstitial lung disease (grouped term) was reported in 11 (8%) patients in the osimertinib arm‡
The majority were Grades 1 / 2; Grade 5 n=1

Data cut-off: January 5, 2024.

*AEs with incidence of 10% or more in either treatment arm are shown. Patients with multiple events in the same category counted only once in that category. Patients with events in more than one category are counted once in each of those categories. Includes AEs with an onset date on or after the date of first dose and up to and including 28 days following the discontinuation of study treatment and before starting subsequent cancer therapy; †One grade 5 AE of pneumonia was reported in the osimertinib arm; ‡Interstitial lung disease (grouped term) was reported in 1 patient (1%) in placebo arm; AE was pneumonitis, Grade 1.

AE, adverse event; WBC, white blood cells

Conclusions

- In LAURA, osimertinib demonstrated a statistically significant and clinically meaningful improvement in PFS vs placebo by BICR in unresectable stage III EGFRm NSCLC following definitive chemoradiotherapy
  - **Median PFS** was **39.1 months** (95% CI 31.5, NC) with osimertinib, **5.6 months** (95% CI 3.7, 7.4) with placebo; **HR 0.16** (95% CI 0.10, 0.24), p<0.001
  - PFS benefit was consistent across subgroups
- Interim OS data showed a positive trend in favor of osimertinib, despite a high proportion of patients crossing over to osimertinib in the placebo arm (81%)
- Safety profile of osimertinib post-chemoradiotherapy was as expected and manageable
- EGFR mutation testing is critical in stage III disease to ensure optimal outcomes for patients with EGFRm NSCLC

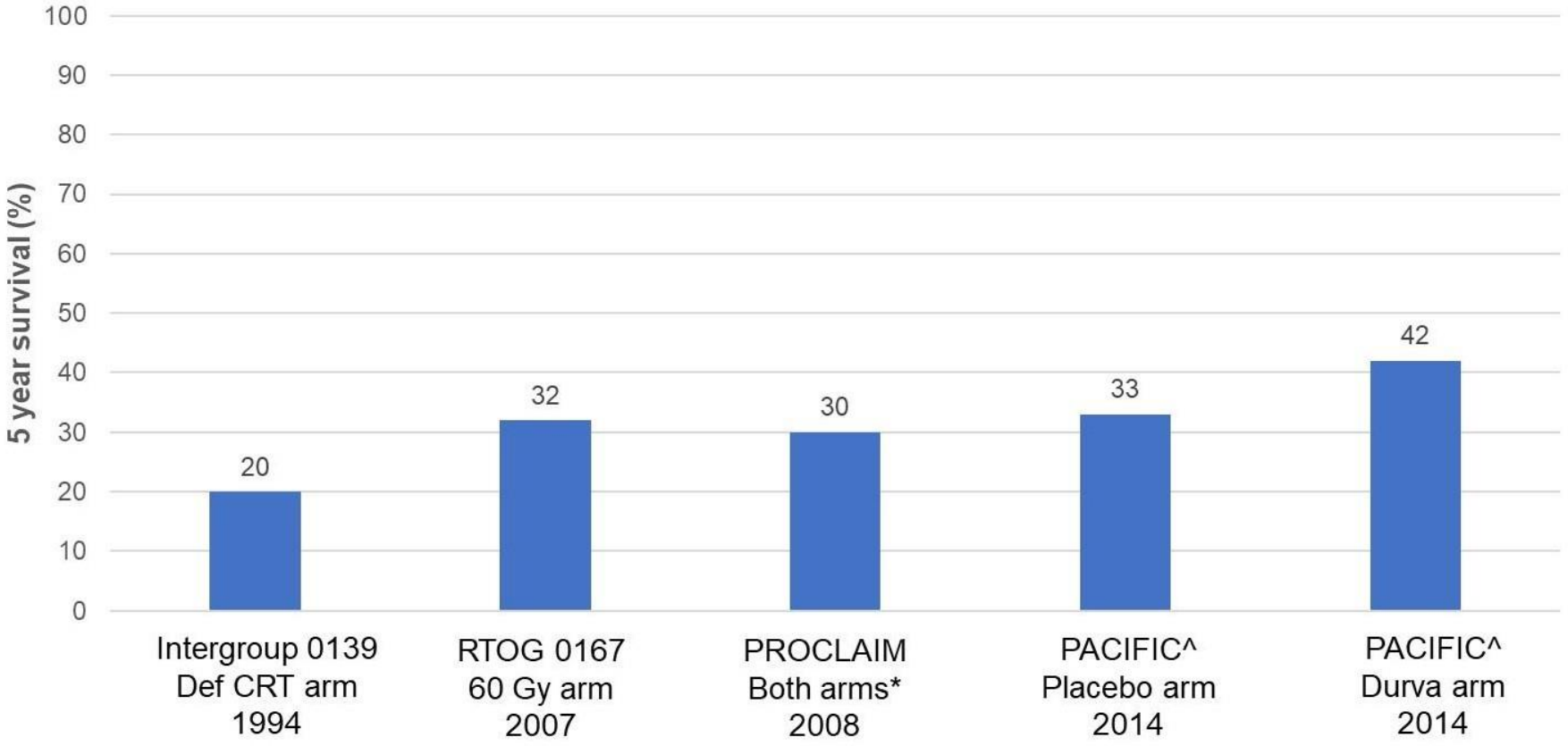
Osimertinib will become the new standard of care for patients with unresectable stage III EGFRm NSCLC who have not progressed after definitive chemoradiotherapy

PRESENTED BY: Dr Suresh S. Ramalingam

BICR, blinded independent central review; CI, confidence interval; EGFR, epidermal growth factor receptor; EGFRm, EGFR-mutated; HR, hazard ratio; NC, not calculable; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival

Data cut-off: January 5, 2024.

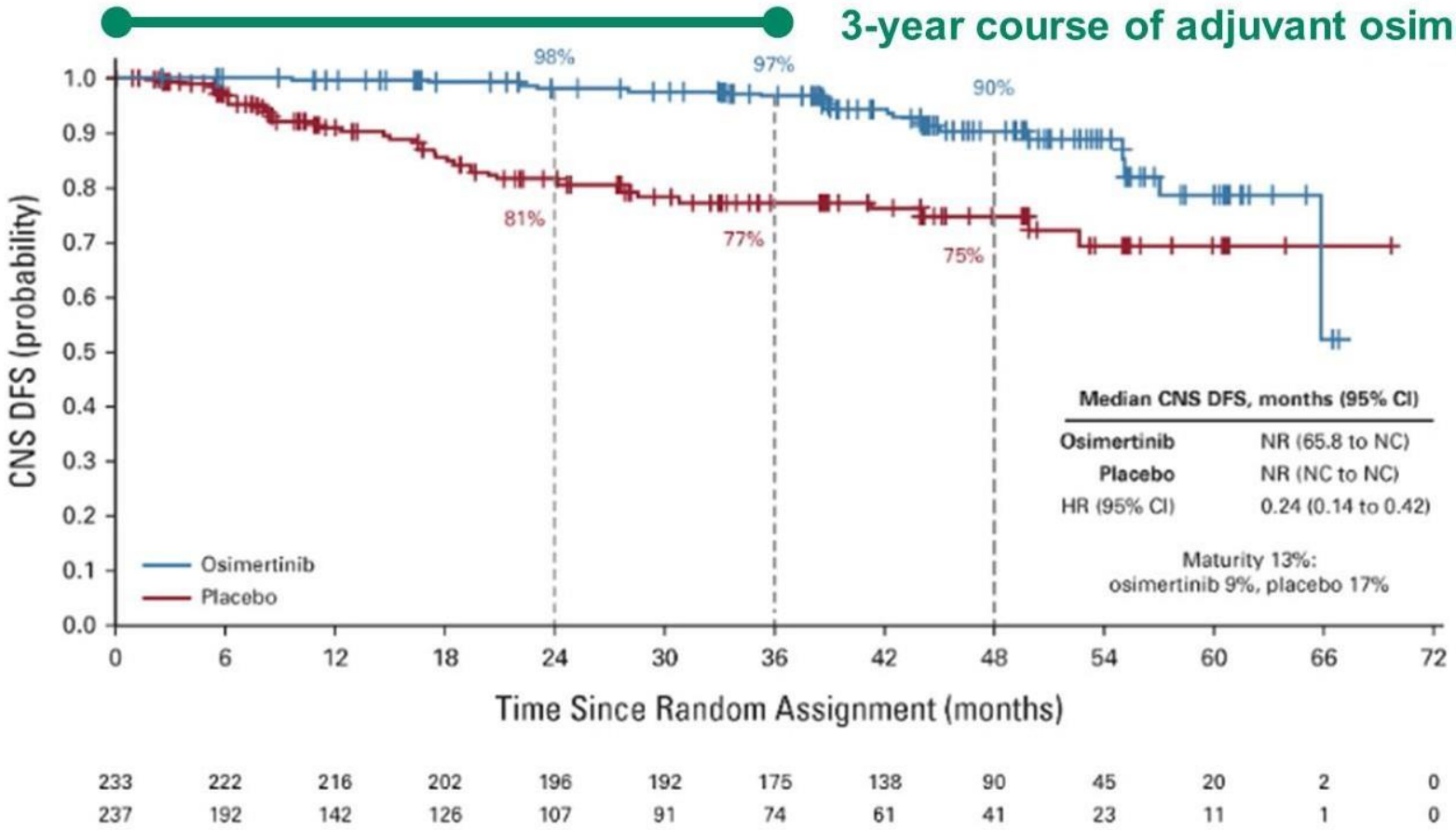
Is Stage III NSCLC Curable with ChemoRT?



Albain Lancet 2015, Bradley JCO 2020, Senan JCO 2016, Spigel JCO 2022
*PROCLAIM data estimated from published KM curves, ^PACIFIC study measured events from post-chemoRT timeframe

Long Term CNS Protection with Osimertinib

ADAURA study: adjuvant osimertinib or placebo after surgery ± chemo; stages IB, II, and IIIA



CNS DFS = time from start of protocol therapy until CNS recurrence or death

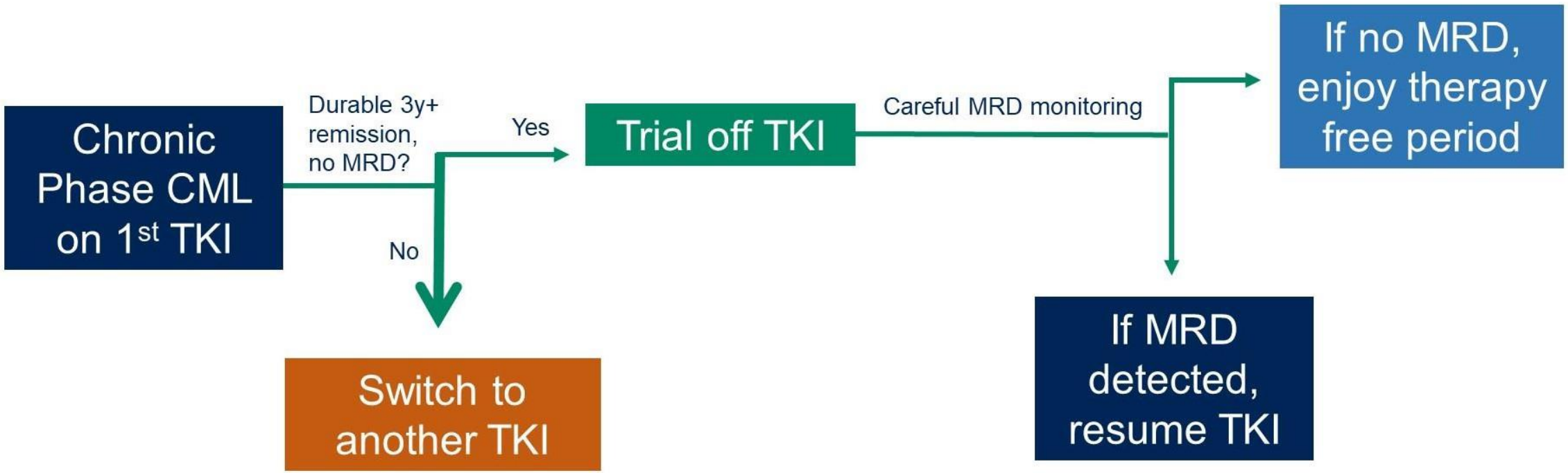
Herbst, JCO 2023

Factors to Consider with Indefinite Osimertinib

- CNS protection

- Cost
- Side effects/QoL
- Not all patients need

Treatment De-Escalation: Borrowing from CML



Schiffer and Atallah, Up To Date

Was ist neu?

- Neoadjuvante Chemoimmuntherapie in NSCLC
  - Aegean
  - Keynote 671
  - Checkmate 816
- Chemoradiotherapie NSCLC
  - EGFR mutierte
  - **ALKmutierte**
- Fortgeschrittenes Stadium NSCLC
  - Crown
  - Trop 2
- SCLC
  - Adriatic
- Biomarker
  - Ct DNA

2024 ASCO® ANNUAL MEETING

Global Retrospective Study Comparing Consolidation *ALK* TKI to Durvalumab or Observation after Chemoradiation in Unresectable Locally Advanced *ALK*+ NSCLC

Ritujith Jayakrishnan, Amin H. Nassar, Jamie Feng, Frances Shepherd, Elio Adib, Justin M. Cheung, Jessica J. Lin, Yufei Liu, Steven H. Lin, Kaushal Parikh, Arthi Sridhar, Purnima Shakya, Thomas J. Dilling, David Kaldas, Jhanelle E. Gray, Anastasiya Lobachov, Jair Bar, Heike Luders, Christian Grohe, Shruti Gupta, Ticiana Leal, Bailey Fitzgerald, Fionnuala Crowley, Yu Fujiwara, Thomas U. Marron, Molly Wilgucki, Joshua Reuss, Luxi Chen, Kamya Sankar, Jacqueline V. Aredo, Joel W. Neal, Heather A. Wakelee, Rohit Thummalapalli, Helena Yu, Ryan Whitaker, Ana Velazquez, Meera Ragavan, Alessio Cortellini, David J. Kwiatkowski, Abdul Rafeh Naqash, Sarah B. Goldberg, So Yeon Kim

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Internal Medicine, PGY3
Yale School of Medicine

CONQUER CANCER® THE ASCO FOUNDATION MERIT AWARD

Diane L. Keith Merit Award in Lung Cancer
*Supported by **Family of Diane L. Keith***

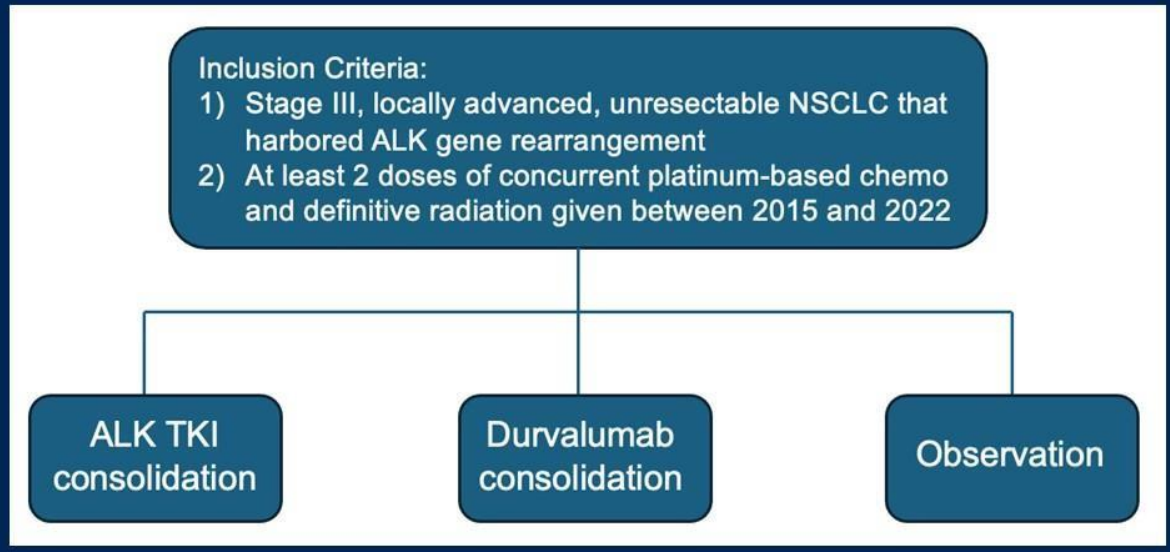
Background

- In unresectable stage III NSCLC, consolidation durvalumab is associated with improved survival after concurrent chemoradiation[1]
- In patients with *ALK*-positive NSCLC, benefit of durvalumab is not established[2]
- Adjuvant *ALK*-directed therapy after resection of early-stage *ALK*+ NSCLC shows an improvement in disease-free survival[3]
- The benefit of *ALK*-directed therapy in patients with locally-advanced *ALK*+ NSCLC after chemoradiation has not been established

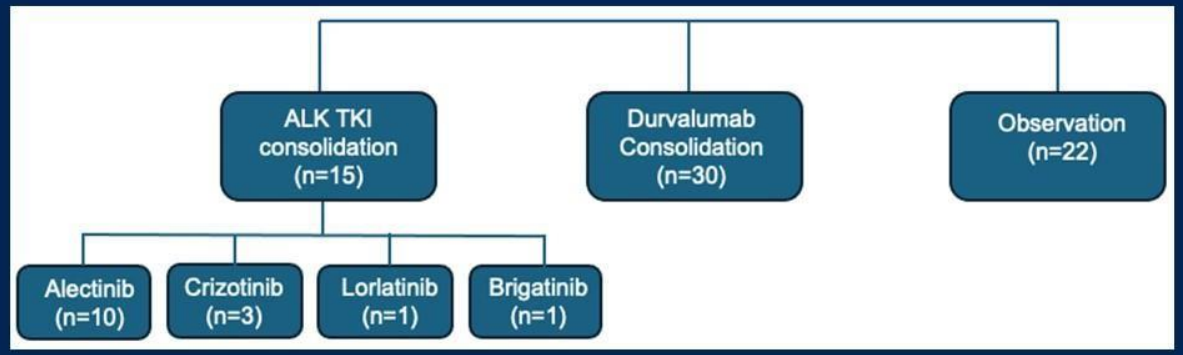
[1]Spigel et al., JCO, 2022, [2]Girard et al., JTO, 2023 and Mazieres et al., Annals of Oncology, 2019, [3]Wu, NEJM, 2024

Methods

- Global retrospective study (17 institutions)
- Primary endpoints:
  - Real-world progression free survival
  - Overall survival
- Secondary endpoints:
  - Treatment related adverse events
  - Intracranial real-world progression free survival
  - Time to first subsequent therapy

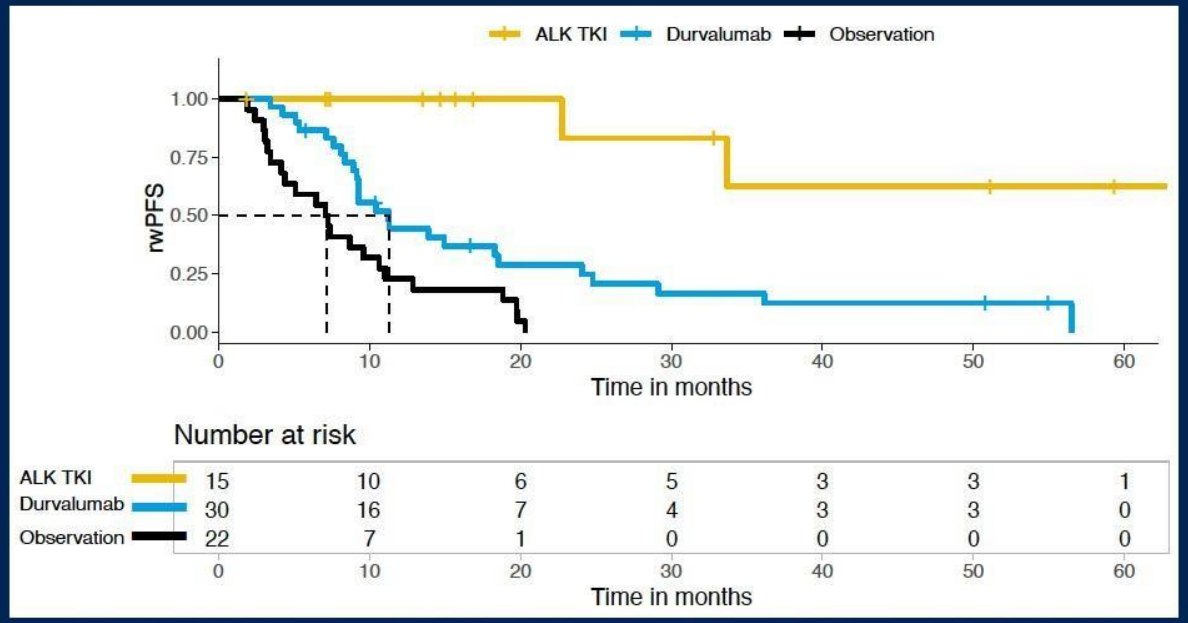


Baseline Characteristics



	Total (N=67)	ALK TKI (n=15)	Durvalumab (n=30)	Observation (n=22)	P-value
Age – Median (IQR)		50 [49-83]	57 [50-65]	60 [49-67]	0.9
Sex					0.4
Female	39 (58%)	11 (73%)	17 (57%)	11 (50%)	
Male	28 (42%)	4 (27%)	13 (43%)	11 (50%)	
Race					0.03
White	39 (63%)	6 (40%)	20 (71%)	13 (69%)	
Asian	19 (30%)	6 (40%)	8 (29%)	5 (26%)	
Black	1 (2%)	0 (0%)	0 (0%)	1 (5%)	
Other	3 (5%)	3 (20%)	0 (0%)	0 (0%)	
Not Reported	5	0	2	3	
PD-L1 TPS					0.6
<1%	13 (27%)	4 (31%)	5 (21%)	4 (36%)	
≥1%	35 (73%)	9 (69%)	19 (79%)	7 (64%)	
Not Reported	19	2	6	11	
Stage					0.3
IIIA	18 (27%)	2 (13%)	7 (23%)	9 (41%)	
IIIB	39 (58%)	11 (73%)	17 (57%)	11 (50%)	
IIIC	10 (15%)	2 (13%)	6 (20%)	2 (9%)	
ECOG PS Status					0.6
0	24 (39%)	6 (40%)	13 (46%)	5 (26%)	
1	36 (58%)	9 (60%)	14 (50%)	13 (69%)	
2	2 (3%)	0 (0%)	1 (4%)	1 (5%)	
Not Reported	5	0	2	3	

Progression-Free Survival



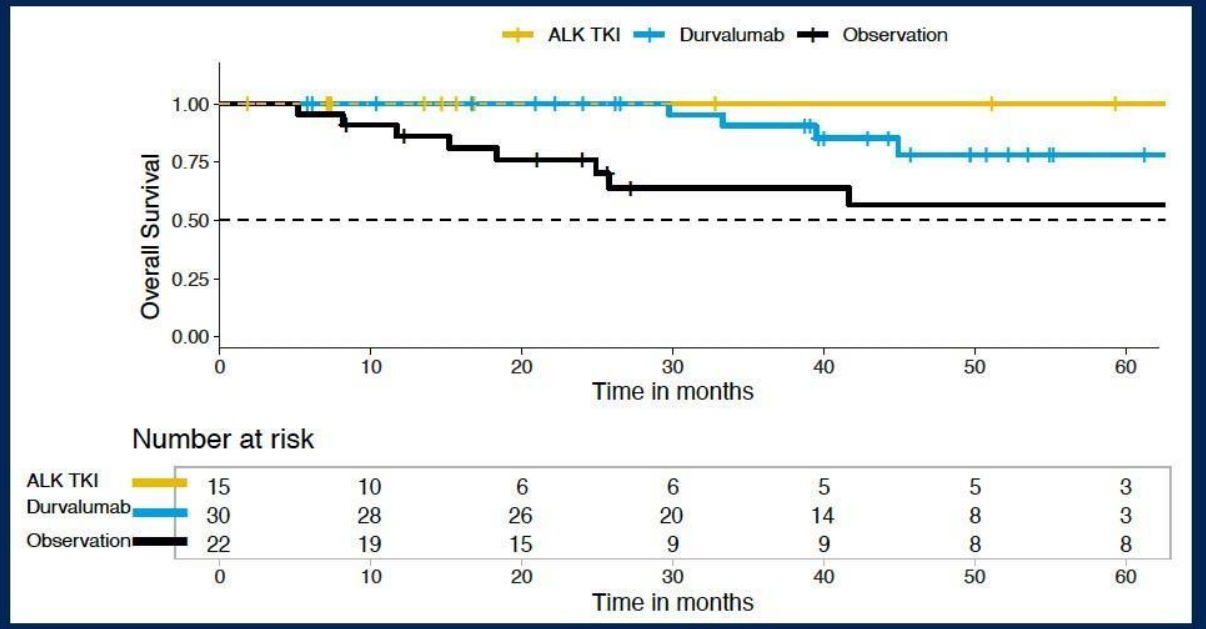
Median Follow Up (95% CI): ALK TKI: 15.7 months (7.1-51.1 months), Durvalumab 44.2 months (38.7-50.7 months), Observation 64.8 months (25.6-95.3 months)

	ALK TKI	Durvalumab	Observation
Median rwPFS (95% CI)	Not reached (22.7 months-NR)	11.3 months (9.2-18.5 months)	7.2 months (3.4-10.6 months)

- *ALK* TKI vs durvalumab HR_{adj}=0.12*, p=0.006
- *ALK* TKI vs observation HR_{adj}=0.04*, p=0.002

*adjusted for nodal status, stage, and age

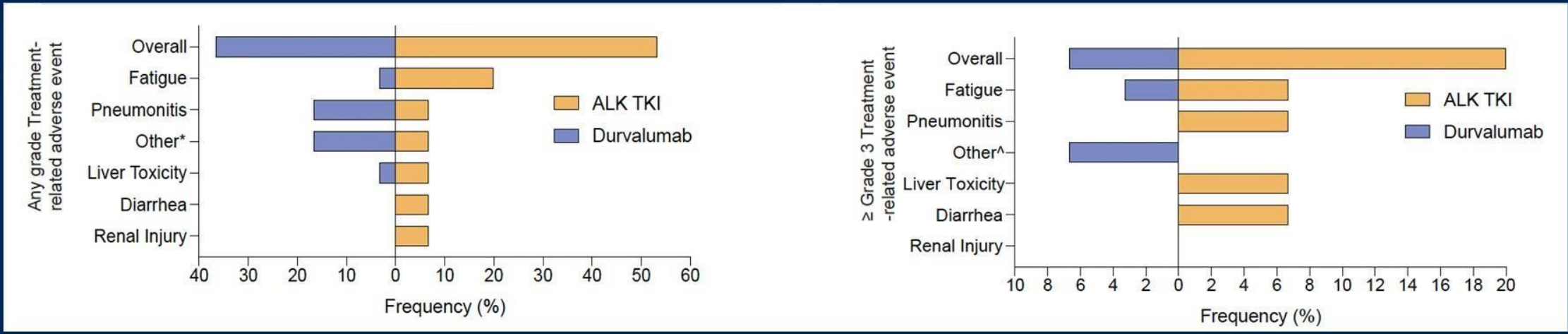
Overall Survival



	ALK TKI	Durvalumab	Observation
Median OS (95% CI)	Not reached (NR-NR)	Not reached (NR-NR)	70.6 months (24.9 months-NR)

- *ALK* TKI vs observation p = 0.04
- Durvalumab vs observation p=0.04

Toxicity with Consolidation Therapy



- TrAE occurred in 8 (53%) treated with *ALK* TKI and 11 (37%) with durvalumab
- Grade ≥ 3 trAE occurred in 4 (27%) with *ALK* TKI and 2 (7%) with durvalumab
  - *ALK* TKI (n=1 patient for each): fatigue, pneumonitis, liver toxicity, diarrhea
  - Durvalumab: fatigue and cognitive disturbance (n=1 patient), neutropenia (n=1 patient)

Conclusion

In this retrospective, multicenter study of consolidation strategies in locally advanced *ALK*+ NSCLC after concurrent chemoradiation, we found:

- Improved rwPFS with consolidation *ALK* TKI compared to durvalumab or observation
- Improved OS with consolidation *ALK* TKI compared to observation alone
- No unanticipated toxicity signal with consolidation *ALK* TKI

Consolidation *ALK* TKI after chemoradiation in unresectable stage III *ALK*+ NSCLC is a potential treatment option.

FAZIT

- Frühe Next-Generation Sequencing um EGFR und ALK Mutationen zu bestimmen ist wichtig
- Osimertinib nach Chemoradiotherapie ist der neue Standard für Patienten mit inoperabelem Stadium III EGFR-mutiertem NSCLC
- ALK-TKIs könnten auch ein Vorteil für Patientin nach einer Chemoradiotherapie für inoperable Stadium III ALKmutierte NSCLC erreichen

Was ist neu?

- Neoadjuvante Chemoimmuntherapie in NSCLC
  - Aegean
  - Keynote 671
  - Checkmate 816
- Chemoradiotherapie NSCLC
  - EGFR mutierte
  - ALK mutierte
- **Fortgeschrittenes Stadium NSCLC**
  - **Crown**
  - Trop 2
- SCLC
  - Adriatic
- Biomarker
  - Ct DNA

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]

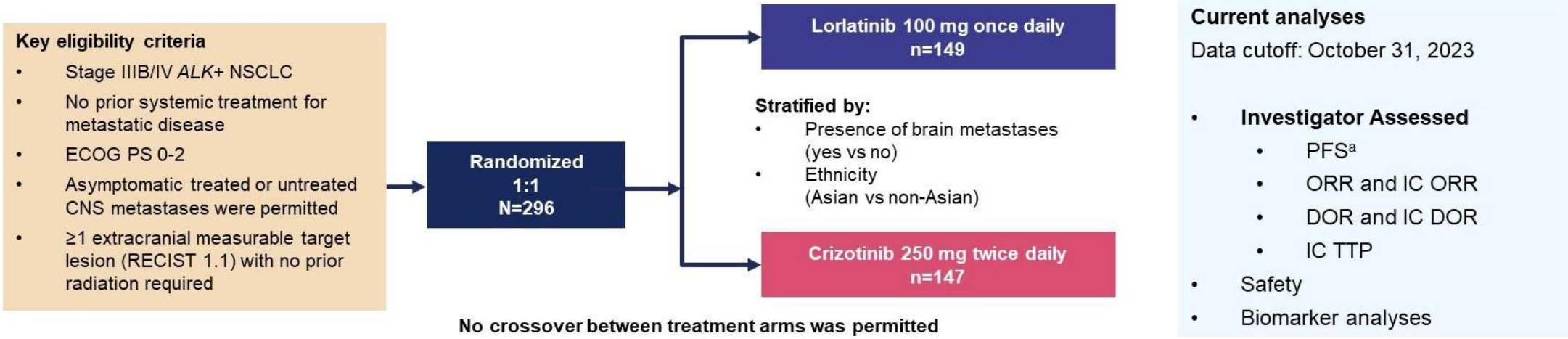
[1]Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; [2]Princess Margaret Cancer Centre, Toronto, ON, Canada; [3]Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, Barcelona, Spain; [4]State Key Laboratory of Translational Oncology, Chinese University of Hong Kong, Hong 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)

Current Post Hoc Analyses at 5 Years

Endpoint evaluation by BICR stopped after the 3-year analysis



- 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.

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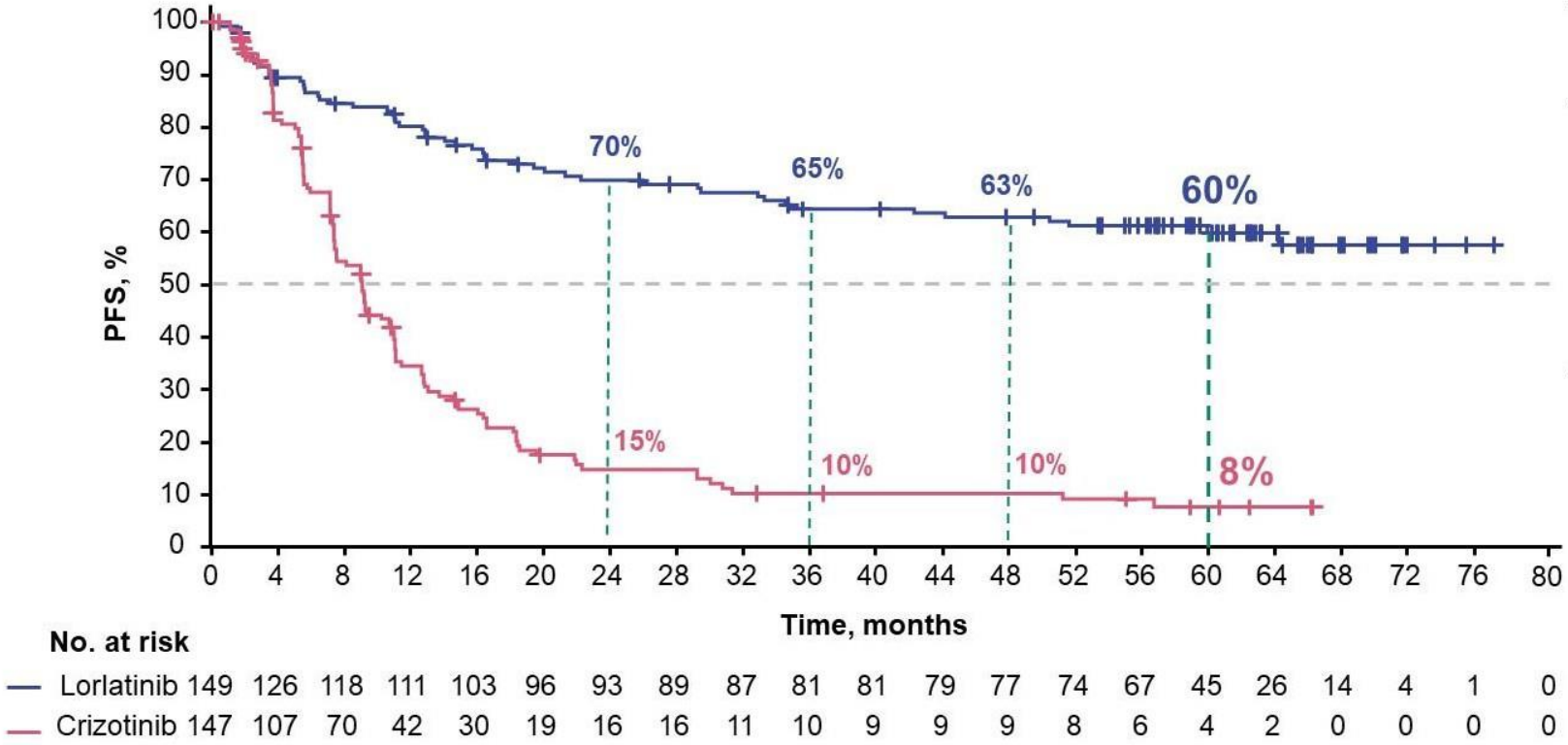
At 60.2 Months of Median Follow-Up, Median PFS by Investigator Was Still Not Reached With Lorlatinib



	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.

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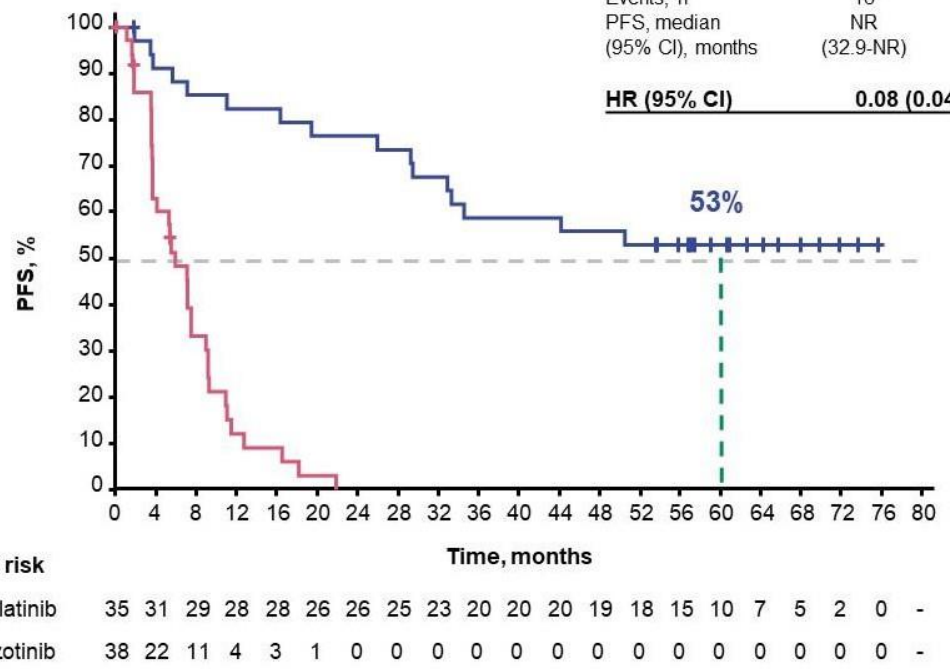
Lorlatinib Showed Superior PFS Benefit Irrespective of Presence or Absence of Baseline Brain Metastases

With Baseline Brain Metastases

	Lorlatinib (n=35)	Crizotinib (n=38)
Events, n	16	34
PFS, median (95% CI), months	NR (32.9-NR)	6.0 (3.7-7.6)
HR (95% CI)	**0.08 (0.04-0.19)**	

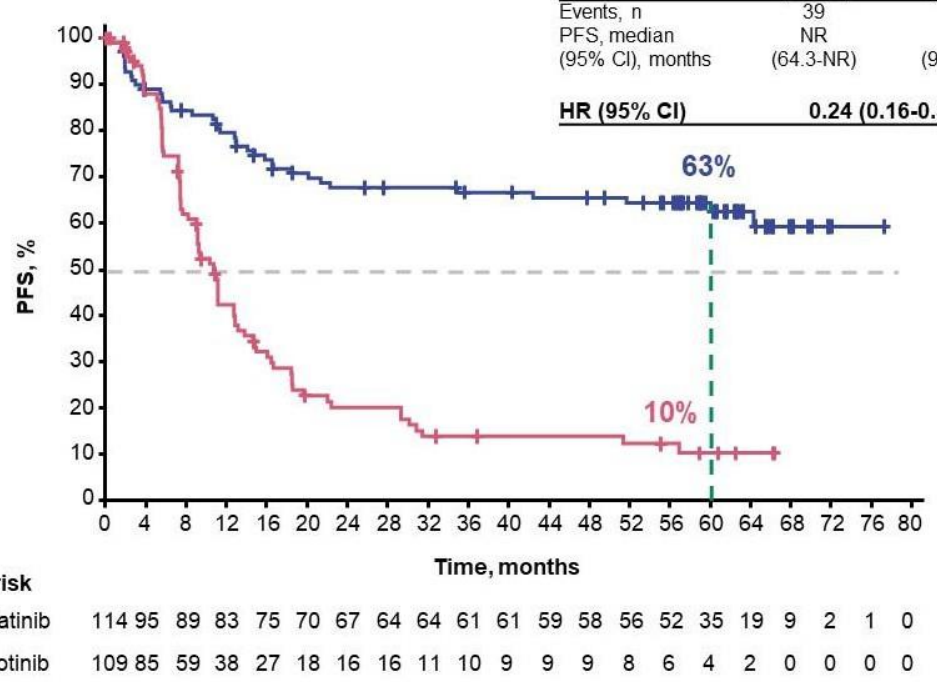


No. at risk

Lorlatinib	35	31	29	28	28	26	26	25	23	20	20	20	19	18	15	10	7	5	2	0	-
Crizotinib	38	22	11	4	3	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-

Without Baseline Brain Metastases

	Lorlatinib (n=114)	Crizotinib (n=109)
Events, n	39	81
PFS, median (95% CI), months	NR (64.3-NR)	10.8 (9.0-12.8)
HR (95% CI)	**0.24 (0.16-0.36)**	



No. at risk

Lorlatinib	114	95	89	83	75	70	67	64	64	61	61	59	58	56	52	35	19	9	2	1	0
Crizotinib	109	85	59	38	27	18	16	16	11	10	9	9	9	8	6	4	2	0	0	0	0

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

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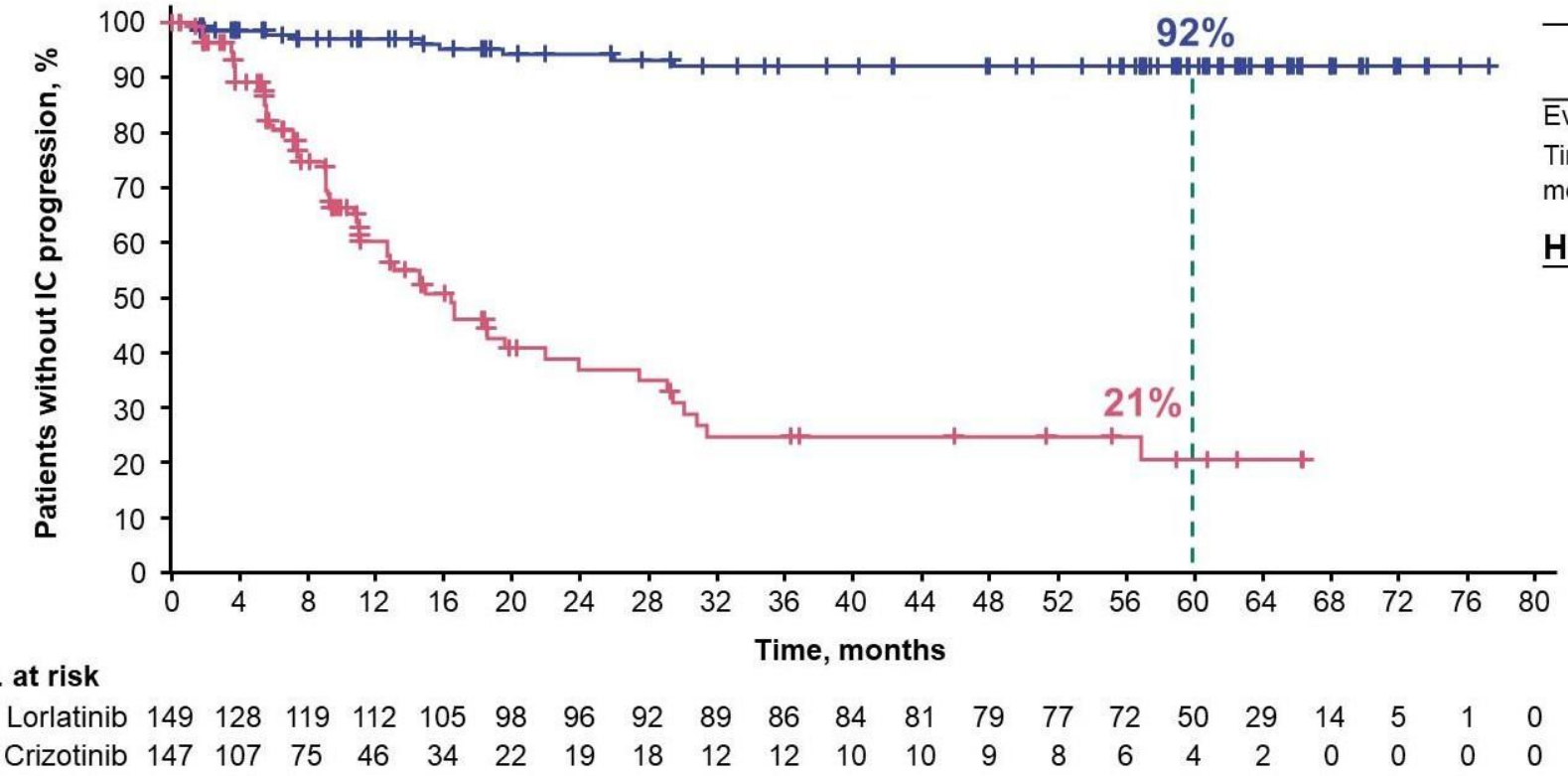
Time to IC Progression by Investigator Assessment Was Longer With Lorlatinib (ITT Population)



	Lorlatinib (n=149)	Crizotinib (n=147)
Events, n	9	65
Time to IC progression, median (95% CI), months	NR (NR-NR)	16.4 (12.7-21.9)
HR (95% CI)	**0.06 (0.03-0.12)**	

Tumor assessments, including brain MRI, have been performed every 8 weeks in all patients throughout the study

HR, hazard ratio; IC, intracranial; ITT, intention to treat; NR, not reached. MRI, magnetic resonance imaging

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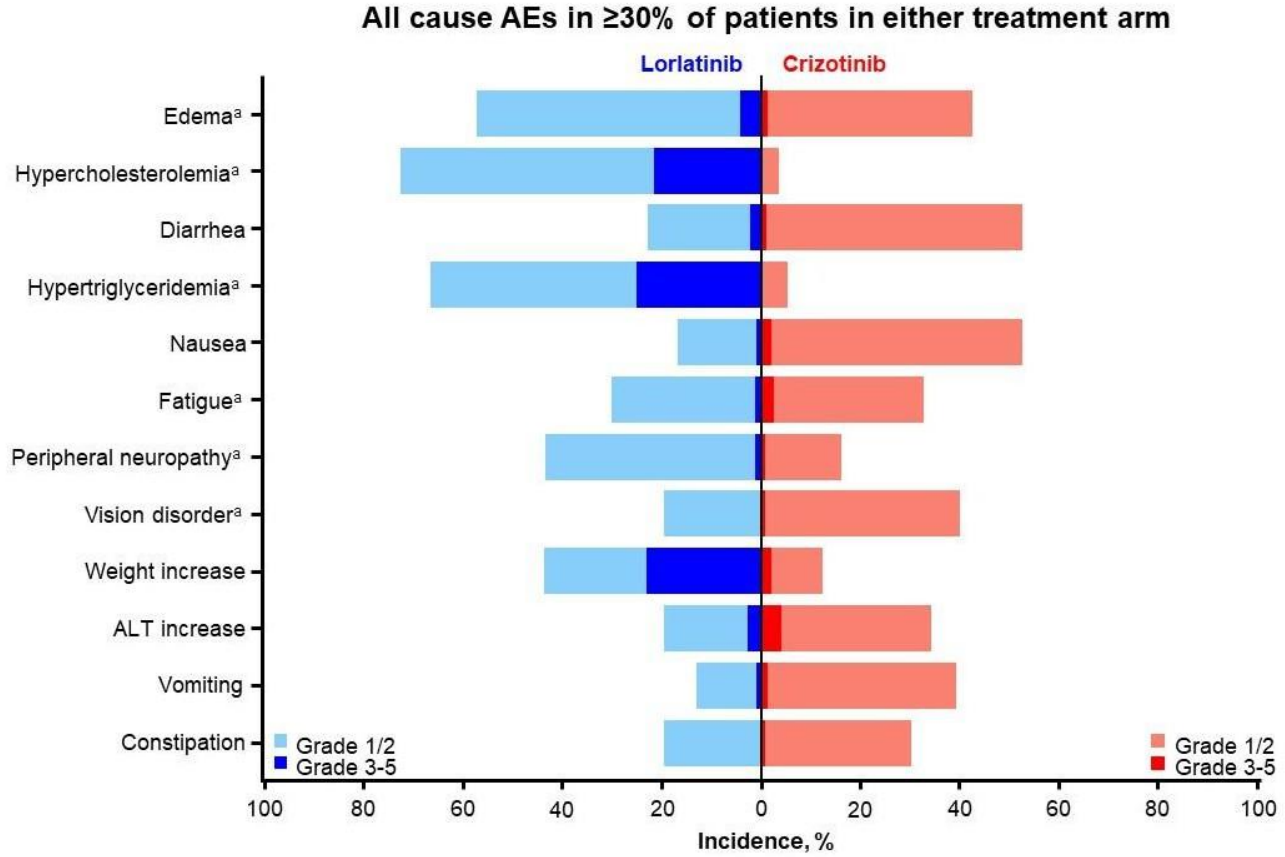
Safety Profile of Lorlatinib Was Consistent With That Observed in Prior Analyses

All-causality AEs observed in the lorlatinib arm:

- AEs of any-grade, grade 3/4, and serious occurred in 100%, 77%, and 44% of patients
- The higher incidence of grade 3/4 AEs was largely due to hypertriglyceridemia (25%), weight increase (23%), hypercholesterolemia (21%), and hypertension (12%)
- CNS AEs[b] occurred in 42% of patients in the lorlatinib arm, 86% of which were grade 1/2
- AEs led to dose reduction in 23% of patients, temporary treatment discontinuation in 62%, and permanent discontinuation in 11%; of which 5% were due to treatment-related AEs, all reported during the first 26 months



AE, adverse event; CNS, central nervous system.
[a]This category comprised a cluster of AEs that may represent similar clinical symptoms or syndromes. [b]Includes cognitive effects (28%), mood effects (21%), speech effects (6%), and psychotic effects (5%),

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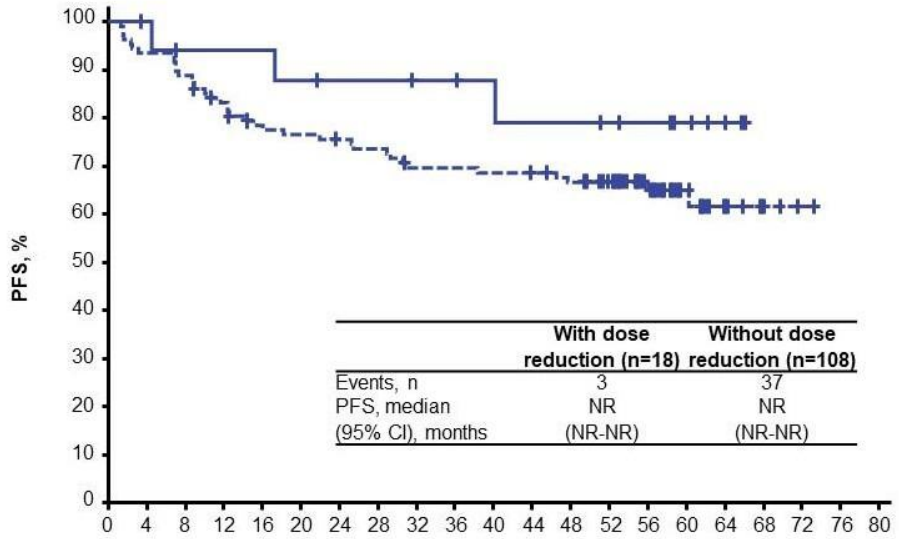
Dose Reduction Did Not Impact Efficacy of Lorlatinib in Patients Who Had Dose Reduction in the First 16 Weeks

PFS

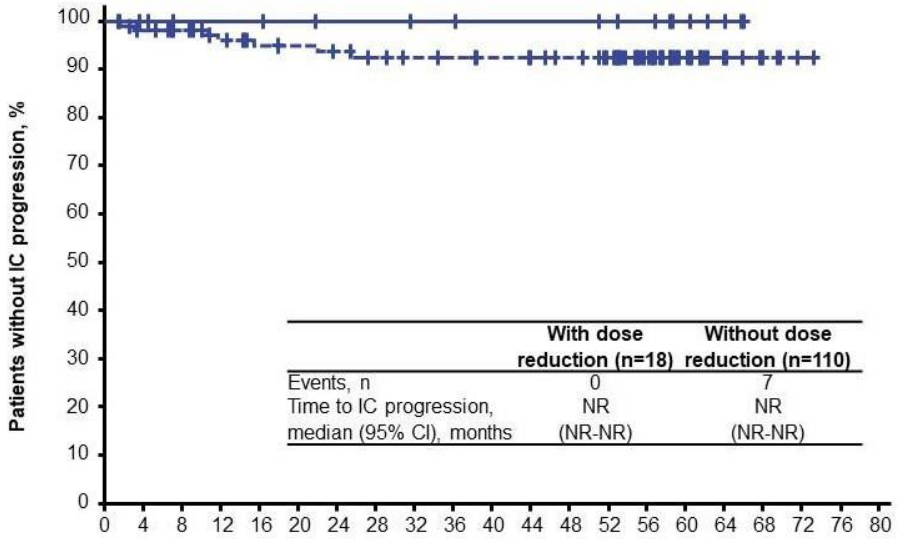


	With dose reduction (n=18)	Without dose reduction (n=108)
Events, n	3	37
PFS, median (95% CI), months	NR (NR-NR)	NR (NR-NR)

No. at risk

With dose reduction	18	17	15	15	15	14	12	12	11	11	10	9	9	8	7	5	3	0	0	0	-
Without dose reduction	108	101	96	88	81	79	77	75	70	70	69	68	65	59	38	21	11	4	1	0	-

Time to IC Progression



	With dose reduction (n=18)	Without dose reduction (n=110)
Events, n	0	7
Time to IC progression, median (95% CI), months	NR (NR-NR)	NR (NR-NR)

No. at risk

With dose reduction	18	17	15	15	15	14	12	12	11	11	10	10	10	9	8	5	3	0	0	0	-
Without dose reduction	110	102	97	90	83	82	80	77	75	73	71	69	67	63	42	24	11	5	1	0	-

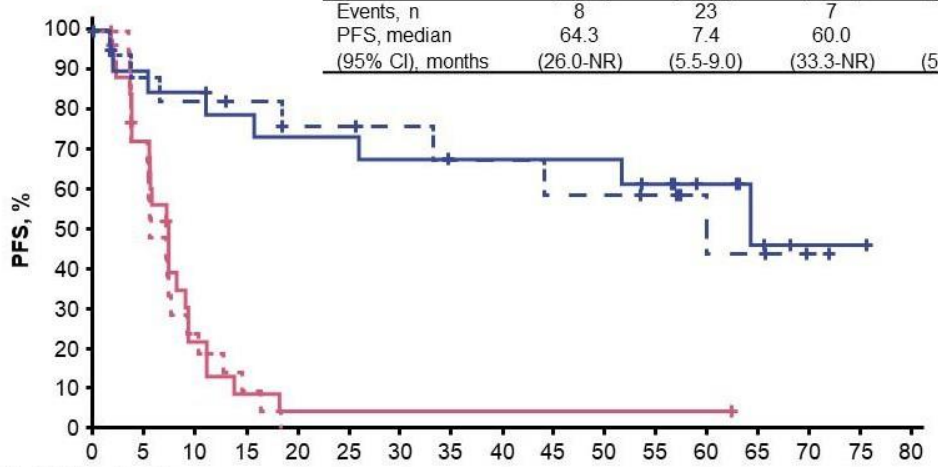
IC, intracranial; NR, not reached; PFS, progression-free survival.

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

Lorlatinib Treatment Benefited Patients With Poor Prognostic Biomarkers

PFS by *EML4::ALK* Fusion Variant

	Variant 1		Variant 3a/b	
	Lorlatinib (n=20)	Crizotinib (n=26)	Lorlatinib (n=18)	Crizotinib (n=23)
Events, n	8	23	7	21
PFS, median (95% CI), months	64.3 (26.0-NR)	7.4 (5.5-9.0)	60.0 (33.3-NR)	5.6 (5.3-7.6)



***EML4::ALK* variant 1**
No. at risk

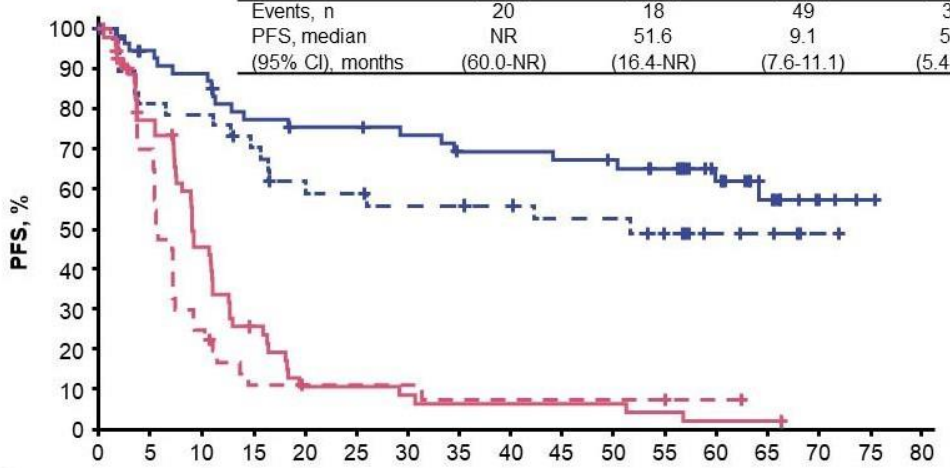
Lorlatinib	20	17	16	14	13	13	12	11	11	11	11	9	6	3	1	1	0
Crizotinib	26	18	5	2	1	1	1	1	1	1	1	1	1	0	0	0	0

***EML4::ALK* variant 3**
No. at risk

Lorlatinib	18	15	14	13	11	11	9	8	8	7	7	6	3	3	1	0	-
Crizotinib	23	15	5	2	0	0	0	0	0	0	0	0	0	0	0	0	-

PFS by *TP53* Status

	Lorlatinib		Crizotinib	
	TP53 mut (-) (n=56)	*TP53* mut (+) (n=41)	*TP53* mut (-) (n=58)	*TP53* mut (+) (n=42)
Events, n	20	18	49	36
PFS, median (95% CI), months	NR (60.0-NR)	51.6 (16.4-NR)	9.1 (7.6-11.1)	5.7 (5.4-7.2)



Lorlatinib
No. at risk

TP53 mut (-)	56	50	47	40	38	38	36	33	33	32	31	28	20	12	4	1	0
TP53 mut (+)	41	30	29	25	21	20	18	18	17	15	15	12	6	4	1	0	0

Crizotinib
No. at risk

TP53 mut (-)	58	40	23	12	5	5	4	3	3	3	3	2	1	1	0	-	-
TP53 mut (+)	42	28	10	4	3	3	3	2	2	2	2	2	1	0	0	-	-

ctDNA, circulating tumor DNA; mut, mutation; NR, not reached; PFS, progression-free survival. Based on ctDNA from plasma collected at screening.

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

Emerging New *ALK* Mutations Were Not Detected in ctDNA Collected at the End of Lorlatinib Treatment

	Lorlatinib (n=31) n (%)	Crizotinib (n=89) n (%)
Resistance mechanisms		
New single ALK mutation	0	8 (9)
ALK compound mutation	0	2 (2)
Bypass mechanism	9 (29)	10 (11)
MAPK pathway aberration	3 (10)	1 (1)
PI3K/MTOR/PTEN pathway aberration	2 (6)	0
RTK pathway aberration	4 (13)	5 (6)
Cell cycle pathway aberration	2 (6)	5 (6)
Other gene aberration	11 (35)	19 (21)
Unknown	13 (42)	56 (63)

ctDNA from plasma collected at screening was analyzed with a validated, commercially available, 74-gene ctDNA next-generation sequencing assay (Guardant360 panel version 2.11; bioinformatics pipeline version 3.5.3; Guardant Health, Inc., Redwood City, CA).
ctDNA, circulating tumor DNA.

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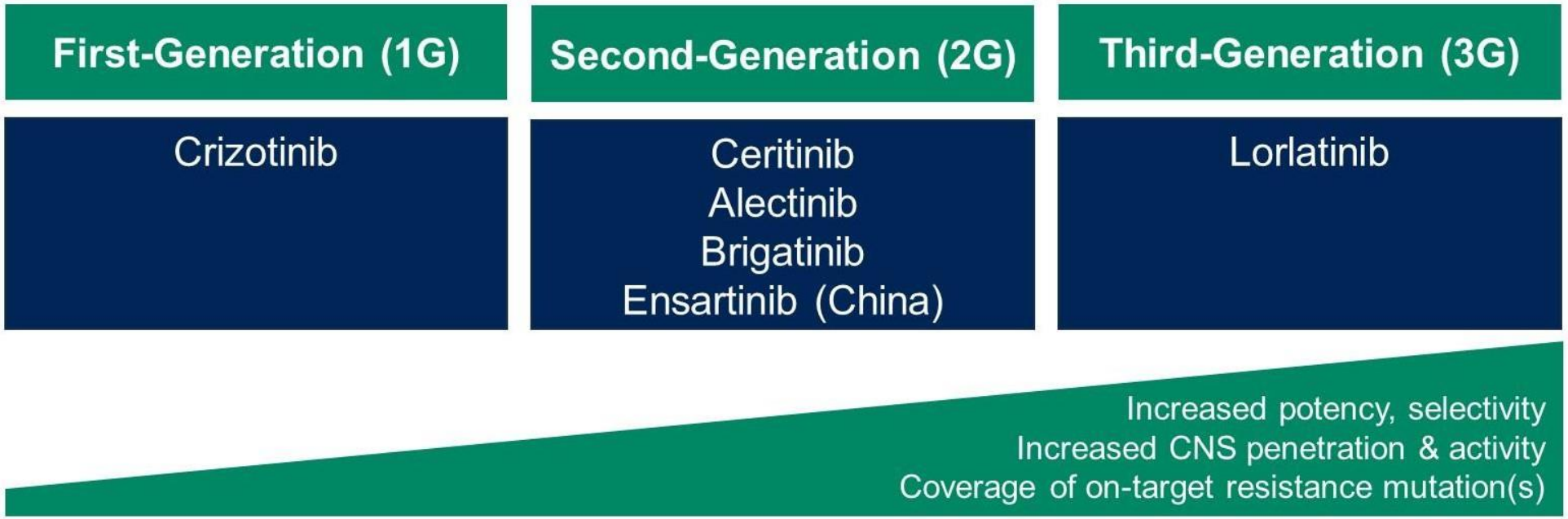
Evolution of First- and Next-Generation ALK Inhibitors for ALK+ NSCLC

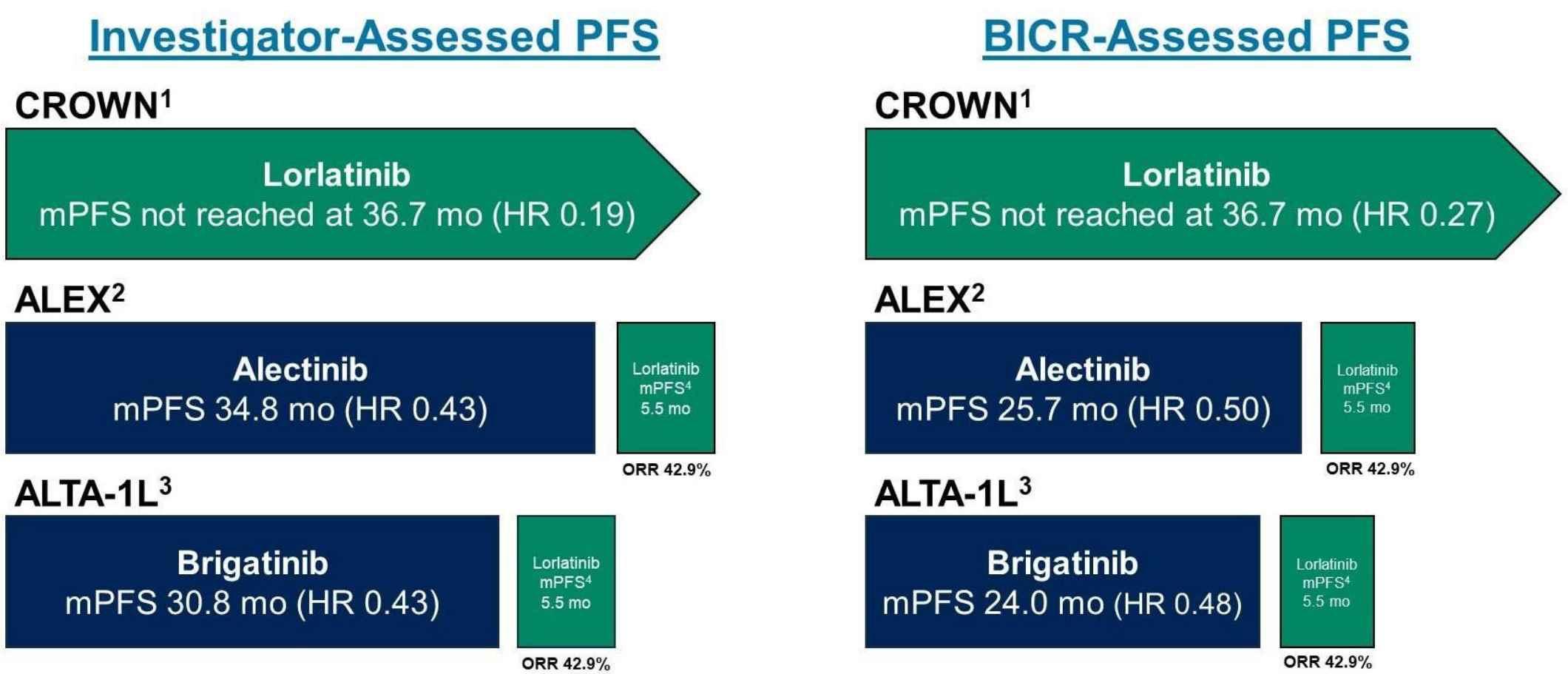


Note: ALK inhibitors approved around the world are shown, with others in development

PRESENTED BY: Jessica J. Lin (jjlin1@mgb.org)

First-Line Treatment Options for ALK+ NSCLC

Until 5/30/24

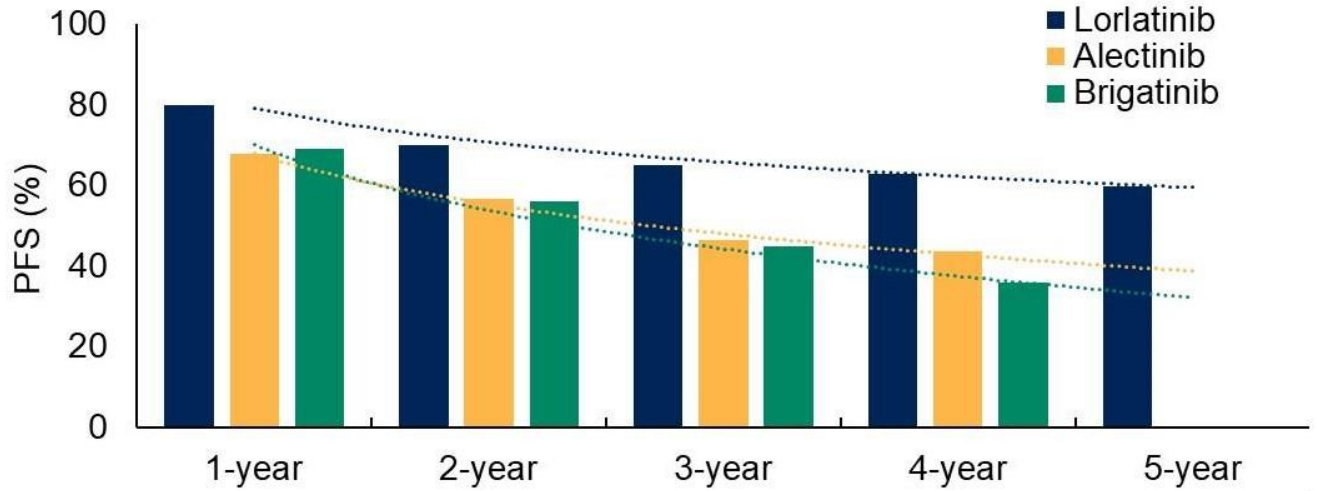


Please note that this figure is not meant for cross-trial comparisons; all 1L trials shown here were comparing against crizotinib

1. Solomon BJ et al., Lancet Respir Med 2023;11(4):354-66; 2. Mok T et al., Ann Oncol 2020;31(8):1056-64; 3. Camidge DR et al., J Thorac Oncol 2021;16(12):2091-108; 4. Felip E et al., Ann Oncol 2021;32(5):620-30

PRESENTED BY: Jessica J. Lin (jjlin1@mgb.org)

Evaluating CROWN in the Context of ALK Treatment Landscape: Systemic Efficacy



	Median PFS	1-year PFS (%)	2-year PFS (%)	3-year PFS (%)	4-year PFS (%)	5-year PFS (%)
Lorlatinib[1-3]	**Not reached at 60.2 mos**	80	70	63	63	60
Alectinib[4]	**34.8 mos**	67.8	56.6	46.4	43.7	N/A
Brigatinib[5-7]	**30.8 mos**	69	56	45	36	N/A

**PFS results per investigator assessment in CROWN, global ALEX (alectinib), and ALTA-1L (brigatinib) trials. N/A, not available; mos, months*

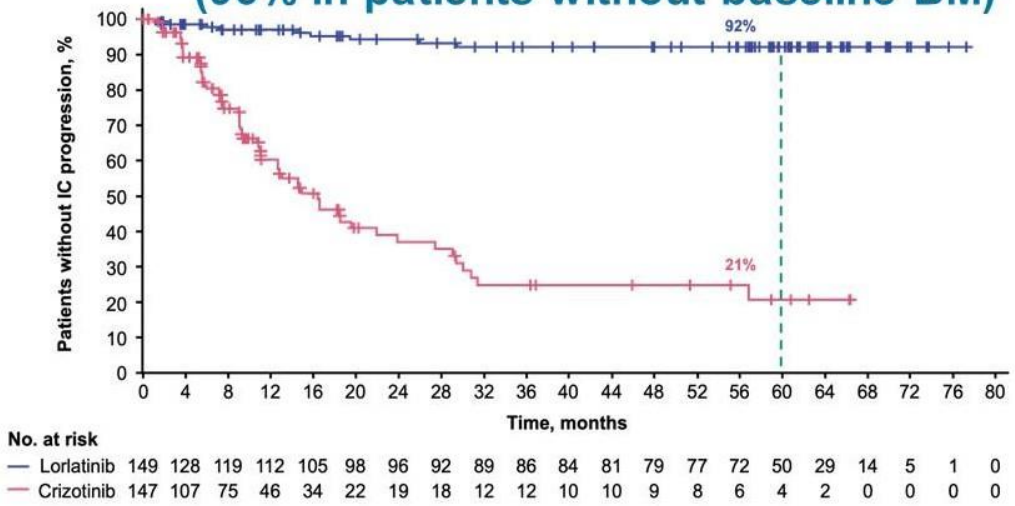
1. Shaw AT et al., N Engl J Med 2020;383:2018-29
2. Solomon BJ et al., Lancet Respir Med 2023;11(4):354-66
3. Solomon BJ et al., ASCO 2024
4. Mok T et al., Ann Oncol 2020;31(8):1056-64
5. Camidge DR et al., N Engl J Med 2018; 379:2027-39
6. Camidge DR et al., J Clin Oncol 2020;38(31):3592-603
7. Camidge DR et al., J Thorac Oncol 2021;16(12):2091-108

PRESENTED BY: Jessica J. Lin (jjlin1@mgb.org)

Evaluating CROWN in the Context of ALK Treatment Landscape: CNS Efficacy

- **Brain metastases are common** at initial diagnosis (25-40%) and cumulatively (>70% at 5 years)[1-2]
- Despite CNS activity of 2G ALK TKIs, **CNS relapses** occur
  - **1L Alectinib**: 12-month cumulative incidence rate for CNS progression 9.4%[3]
  - **1L Brigatinib**: 3-year intracranial PFS rate 57%[4]

5-year IC PFS of 92% in ITT (96% in patients without baseline BM)



	Lorlatinib (n=149)	Crizotinib (n=147)
Events, n	9	65
Time to IC progression, median (95% CI), months	NR (NR-NR)	16.4 (12.7-21.9)
HR (95% CI)	**0.06 (0.03-0.12)**	

1. Gainor JF et al., JCO Precis Oncol 2017:PO.17.00063; 2. Pacheco JM et al., J Thorac Oncol 2019;14(4):691-700
3. Peters S et al., N Engl J Med 2017;377(9):829-38; 4. Camidge DR et al., J Thorac Oncol 2021;16(12):2091-108

PRESENTED BY: Jessica J. Lin (jjlin1@mgb.org)

92% keine CNS Progression @5 Jahre
Zwischen 3 und 5 Jahre keine ZNS Ereignisse

Conclusions

- After 5 years of follow-up in the CROWN study, with lorlatinib treatment:
  - Median PFS has still not been reached and PFS was 60%
  - The probability of being free of intracranial progression was 92%
  - No new safety signals emerged
  - Efficacy benefit was seen across all subgroups, including patients with poor prognostic biomarkers
- The PFS observed with lorlatinib corresponds to the longest PFS reported in advanced NSCLC
- These systemic efficacy results coupled with protection from intracranial progression and absence of new safety signals, indicates that first-line lorlatinib provides an unprecedented improvement in outcomes for patients with advanced *ALK*+ NSCLC

NSCLC, non-small cell lung cancer; PFS, progression-free survival.

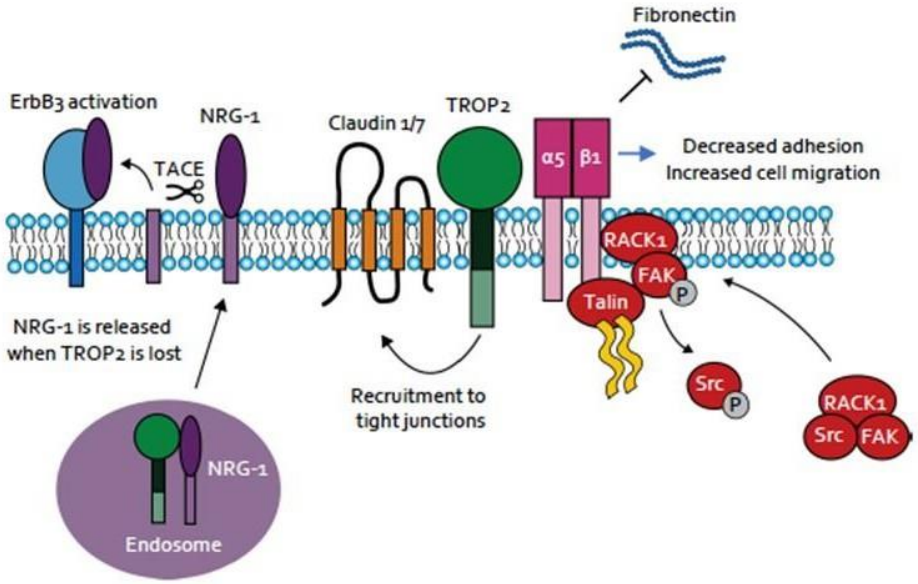
PRESENTED BY: Benjamin J. Solomon (Ben.Solomon@petermac.org)

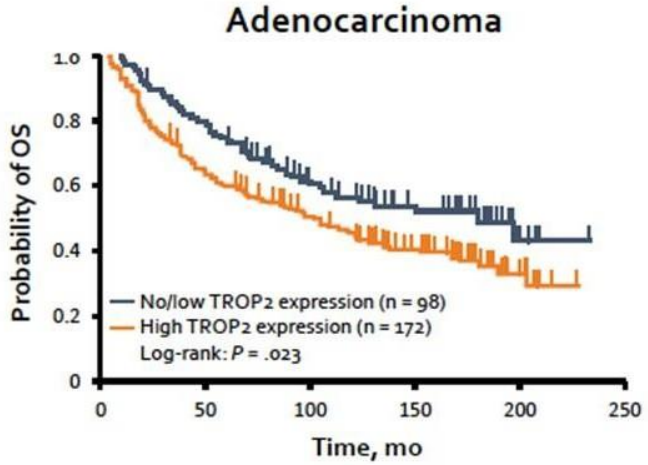
Was ist neu?

- Neoadjuvante Chemoimmuntherapie in NSCLC
  - Aegean
  - Keynote 671
  - Checkmate 816
- Chemoradiotherapie NSCLC
  - EGFR mutierte
  - ALK mutierte
- **Fortgeschrittenes Stadium NSCLC**
  - Crown
  - **Trop 2**
- SCLC
  - Adriatic
- Biomarker
  - Ct DNA

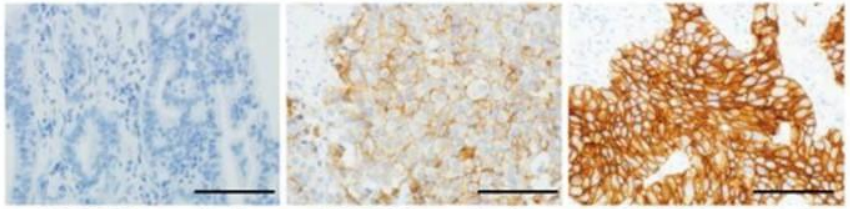
Why Target TROP2?

- TROP2, a transmembrane glycoprotein, is highly expressed in NSCLC (65% adeno, 75% SCC) and other solid tumors
  - High TROP2 expression is associated with poor prognosis, making it a promising therapeutic target



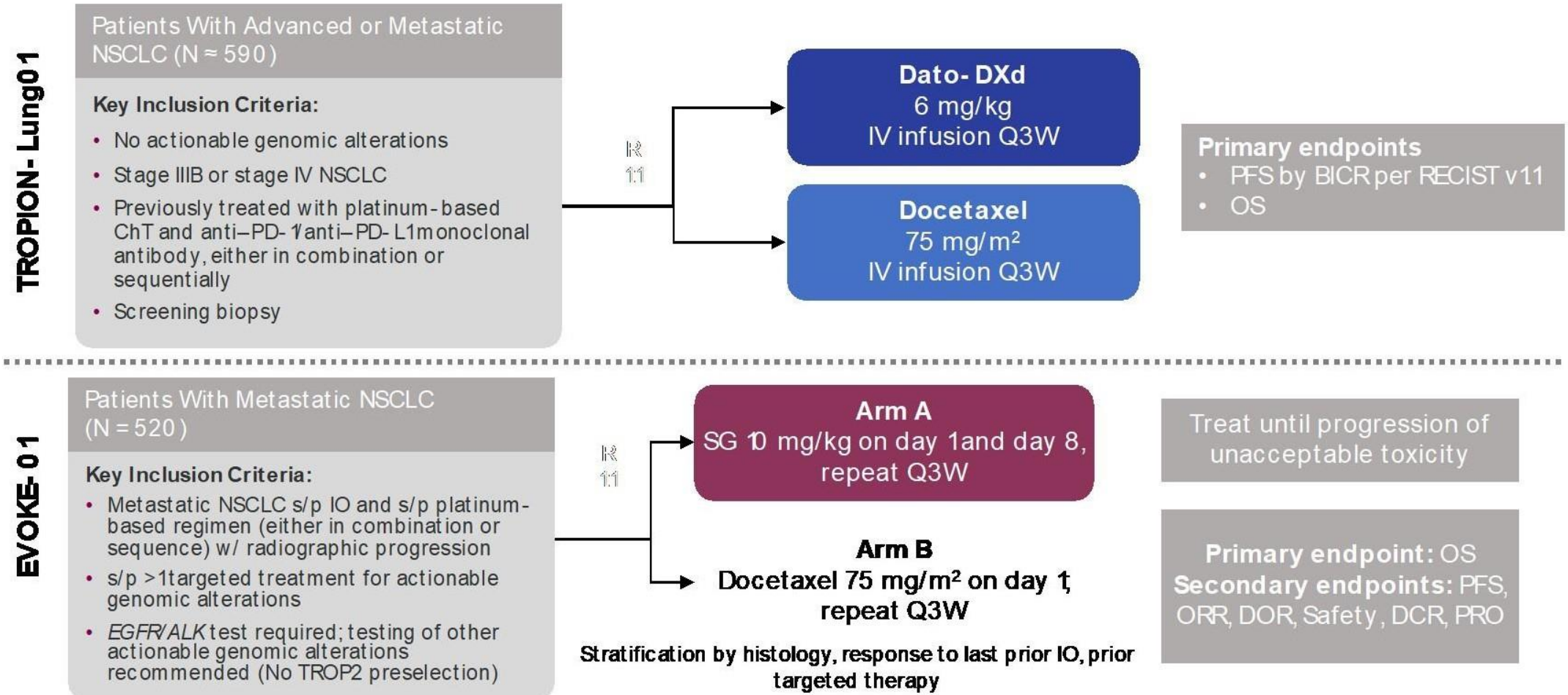


- There is no current testing recommendation for TROP2
- Identified by IHC



1. Lenart S et al. *Cancers (Basel)*. 2020;12:3328.

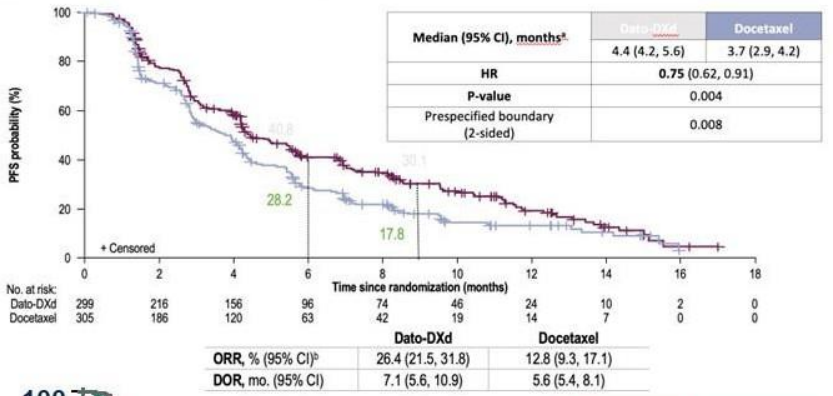
Phase 3 Trials of Anti-TROP2 ADCs in Pretreated Patients



DCR: disease control rate; IO: immunotherapy; PRO: patient-reported outcomes; s/p: status post.
Ahn et al. ESMO 2023. Paz Ares et al ASCO 2024.

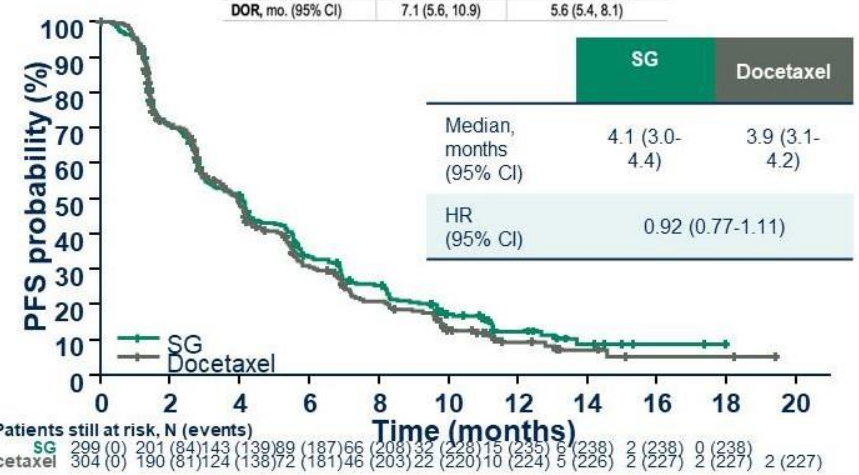
Similar Outcomes

Progression-Free Survival - ITT



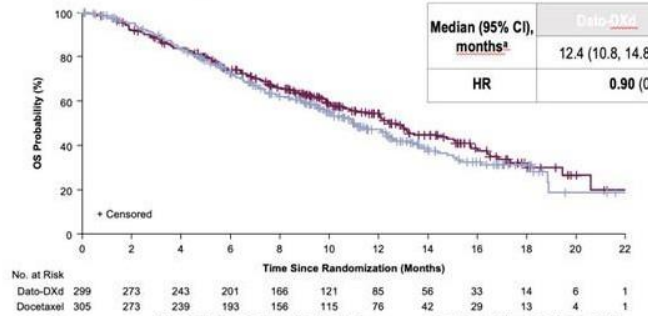
Median (95% CI), months[a]	Dato-DXd	Docetaxel
	4.4 (4.2, 5.6)	3.7 (2.9, 4.2)
HR	0.75 (0.62, 0.91)	
P-value	0.004	
Prespecified boundary (2-sided)	0.008	

	Dato-DXd	Docetaxel
ORR, % (95% CI)[b]	26.4 (21.5, 31.8)	12.8 (9.3, 17.1)
DOR, mo. (95% CI)	7.1 (5.6, 10.9)	5.6 (5.4, 8.1)



	SG	Docetaxel
Median, months (95% CI)	4.1 (3.0-4.4)	3.9 (3.1-4.2)
HR (95% CI)	0.92 (0.77-1.11)	

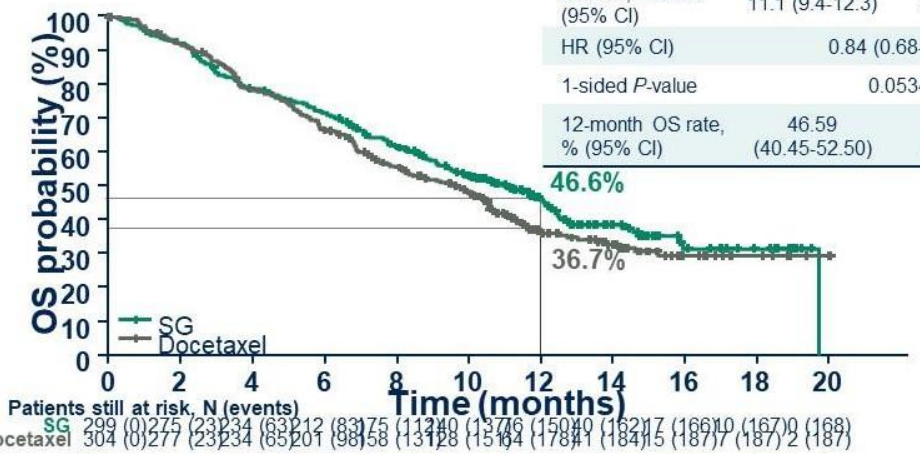
Interim Overall Survival - ITT



Median (95% CI), months[a]	Dato-DXd	Docetaxel
	12.4 (10.8, 14.8)	11.0 (9.8, 12.5)
HR	0.90 (0.72, 1.13)	

Non-squamous HR (95% CI): **0.77** (0.59, 1.01); **Squamous HR** (95% CI): **1.32** (0.87, 2.00)

Trial is continuing until final OS analysis



	SG	Docetaxel
Median, months (95% CI)	11.1 (9.4-12.3)	9.8 (8.1-10.6)
HR (95% CI)	0.84 (0.68-1.04)	
1-sided *P*-value	0.0534	
12-month OS rate, % (95% CI)	46.59 (40.45-52.50)	36.72 (30.88-42.57)

Allow ADC's for the administration of cytoxics @ the expense of less toxicity with similar outcomes?

- More ≥ grade 3 toxicities with docetaxel, mainly neutropenia/leukopenia
- More GI toxicity with SG
- Discontinuation rate with SG lower

FAZIT

- Lorlatinib ist der neue Standard für Alk-mutierte NSCLC im fortgeschrittenem Stadium
- Trop 2 Antibody Drug Konjugate sind nicht dem Docetaxel überlegen

Was ist neu?

- Neoadjuvante Chemoimmuntherapie in NSCLC
  - Aegean
  - Keynote 671
  - Checkmate 816
- Chemoradiotherapie NSCLC
  - EGFR mutierte
  - ALK mutierte
- Fortgeschrittenes Stadium NSCLC
  - Crown
  - Trop 2
- **SCLC**
  - Adriatic
- Biomarker
  - Ct DNA

Current standard of care for Limited Stage SCLC

Concurrent ChemoRadioTherapy (cCRT)

Concurrent once-daily versus twice-daily chemoradiotherapy in patients with limited-stage small-cell lung cancer (CONVERT): an open-label, phase 3, randomised, superiority trial

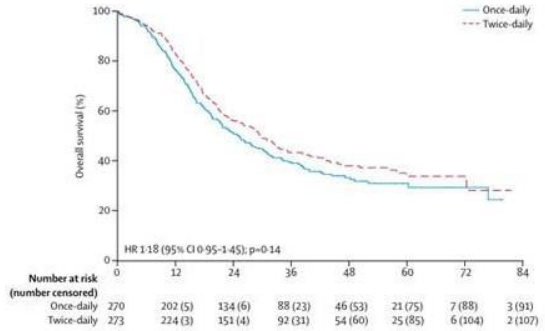
Corinne Faivre-Finn, Michael Snee, Linda Ashcroft, Wiebke Appel, Fabrice Barlesi, Adityanarayan Bhatnagar, Andrea Bezjak, Felipe Cardenal, Pierre Fournel, Susan Harden, Cecile Le Pechoux, Rhona McMenemin, Nazia Mohammed, Mary O'Brien, Jason Pantarotto, Veerle Surmont, Jan P Van Meerbeeck, Penella J Woll, Paul Lorigan, Fiona Blackhall, for the CONVERT Study Team

FREQUENCY OF THORACIC RADIOTHERAPY WITH CHEMOTHERAPY IN LIMITED SMALL-CELL LUNG CANCER

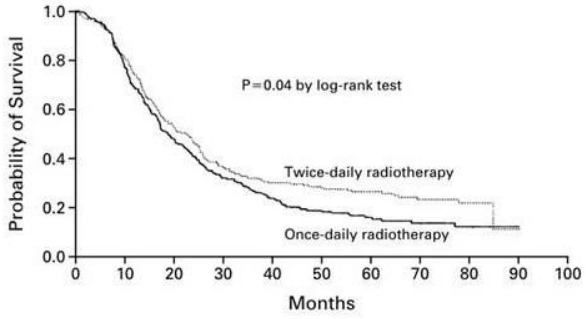
TWICE-DAILY COMPARED WITH ONCE-DAILY THORACIC RADIOTHERAPY IN LIMITED SMALL-CELL LUNG CANCER TREATED CONCURRENTLY WITH CISPLATIN AND ETOPOSIDE

ANDREW T. TURRISI, III, M.D., KYUNGMANN KIM, PH.D., RONALD BLUM, M.D., WILLIAM T. SAUSE, M.D., ROBERT B. LIVINGSTON, M.D., RITSUKO KOMAKI, M.D., HENRY WAGNER, M.D., SEENA AISNER, M.D., AND DAVID H. JOHNSON, M.D.

Median Overall Survival 25-30 months



5-year Survival 16%-26%



The majority of patients with LS-SCLC are not cured by current "curative intent" treatment

Faivre-Finn et al, Lancet 2017; Turrisi et al, NEJM 1999; NCCN Guidelines; mOS = median overall survival

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

Background

- No major advances in systemic treatment for LS-SCLC for several decades
  - Current standard of care concurrent chemoradiotherapy (cCRT): median OS 25–30 months; 5-year survival rate 29–34%[1,2]
- ADRIATIC was designed to evaluate durvalumab (anti-PD-L1), ± tremelimumab (anti-CTLA-4), as consolidation treatment in patients with LS-SCLC who had not progressed following cCRT
  - PACIFIC provided evidence for consolidation durvalumab post-cCRT with PFS and OS benefit in unresectable, stage III NSCLC[3,4]
- CASPIAN further supported the use of durvalumab in SCLC
  - Durvalumab plus platinum-etoposide significantly improved OS vs platinum-etoposide alone in first-line ES-SCLC (HR 0.73 [95% CI 0.59–0.91])[5]
- Here we present results for durvalumab vs placebo from the first planned interim analysis

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

cCRT, concurrent chemoradiotherapy; CTLA-4, cytotoxic T lymphocyte antigen-4; ES, extensive-stage; HR, hazard ratio; LS, limited-stage; NSCLC, non-small-cell lung cancer; OS, overall survival; PD-L1, programmed cell death ligand-1; PFS, progression-free survival; SCLC, small-cell lung cancer.

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.

PRESENTED BY: Dr David R. Spigel

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.

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

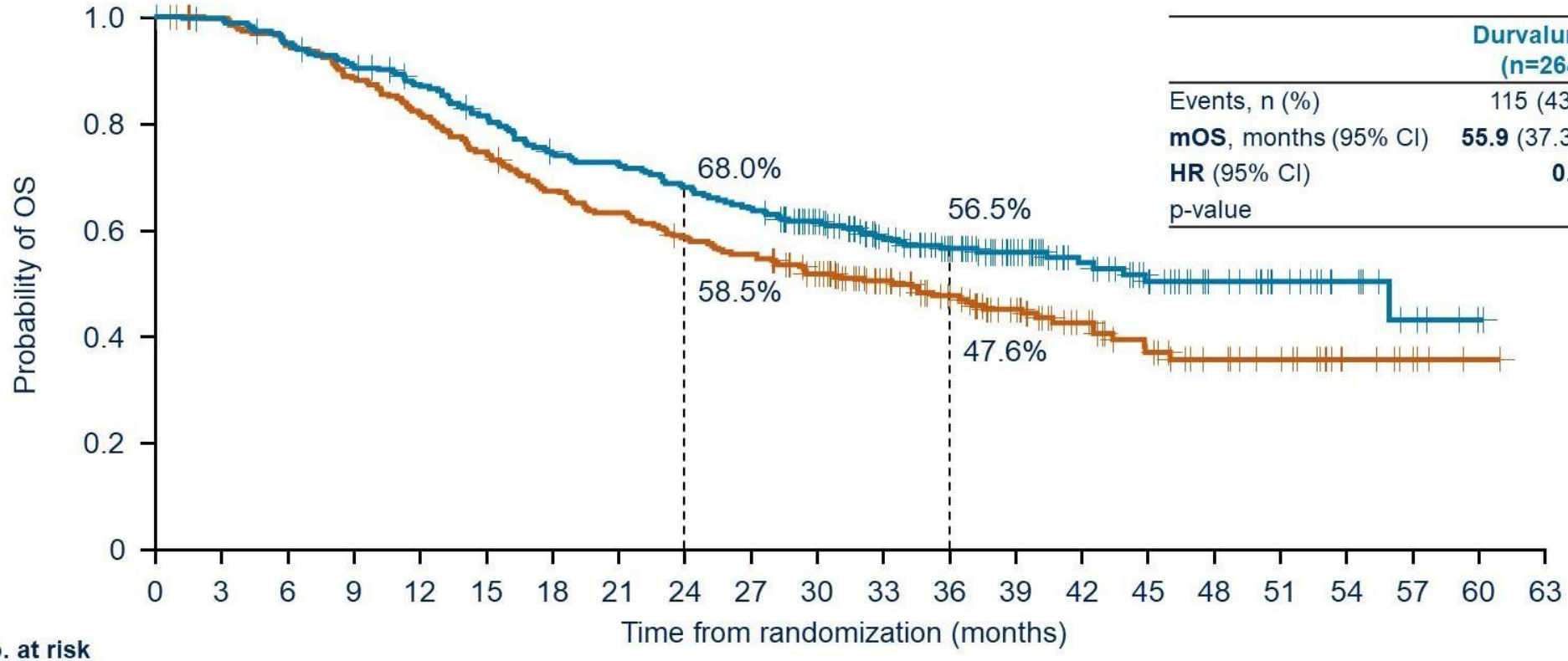
*Based on the first cycle of chemotherapy.

PRESENTED BY: Dr David R. Spigel

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

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

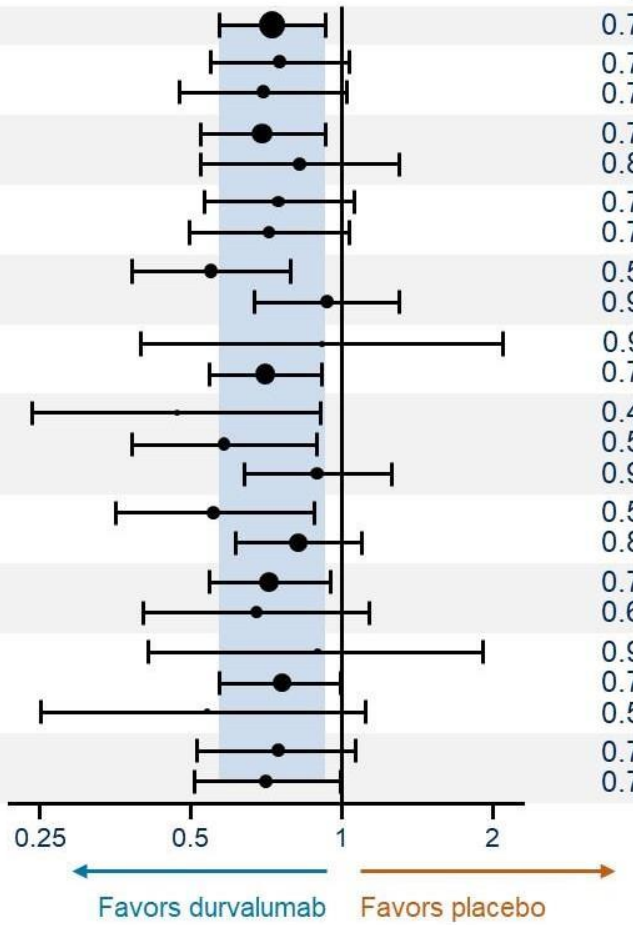
OS was analyzed using a stratified log-rank test adjusted for receipt of PCI (yes vs no). The significance level for testing OS at this interim analysis was 0.01679 (2-sided) at the overall 4.5% level, allowing for strong alpha control across interim and final analysis timepoints.

PRESENTED BY: Dr David R. Spigel

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

OS subgroup analysis

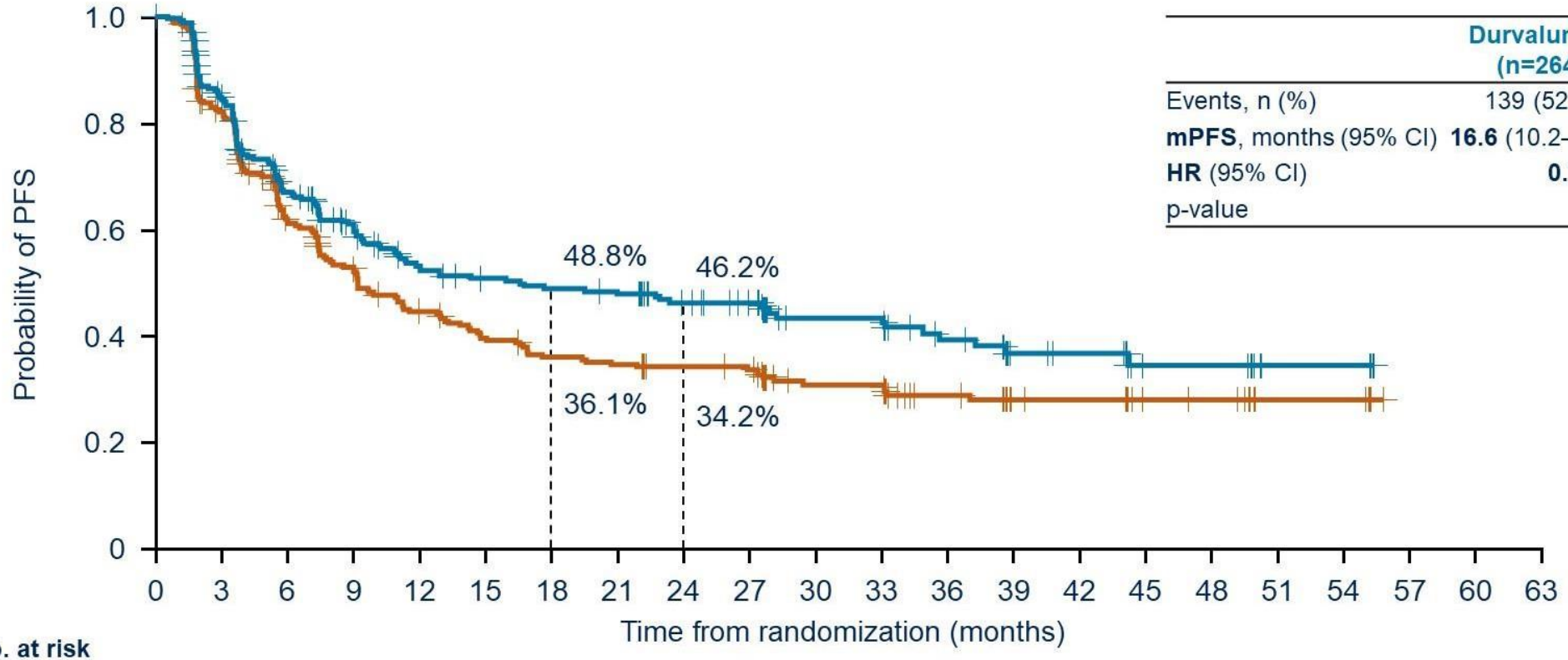
		Events/Patients n/N		HR (95% CI)
		Durvalumab	Placebo	
All patients		115/264	146/266	0.73 (0.57–0.93)
Age	<65 years	69/160	83/162	0.76 (0.55–1.04)
	≥65 years	46/104	63/104	0.70 (0.48–1.02)
Sex	Male	79/178	108/188	0.70 (0.52–0.93)
	Female	36/86	38/78	0.83 (0.52–1.31)
Race	White	60/130	77/137	0.75 (0.53–1.05)
	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.

Progression-free survival* (dual primary endpoint)

- 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.

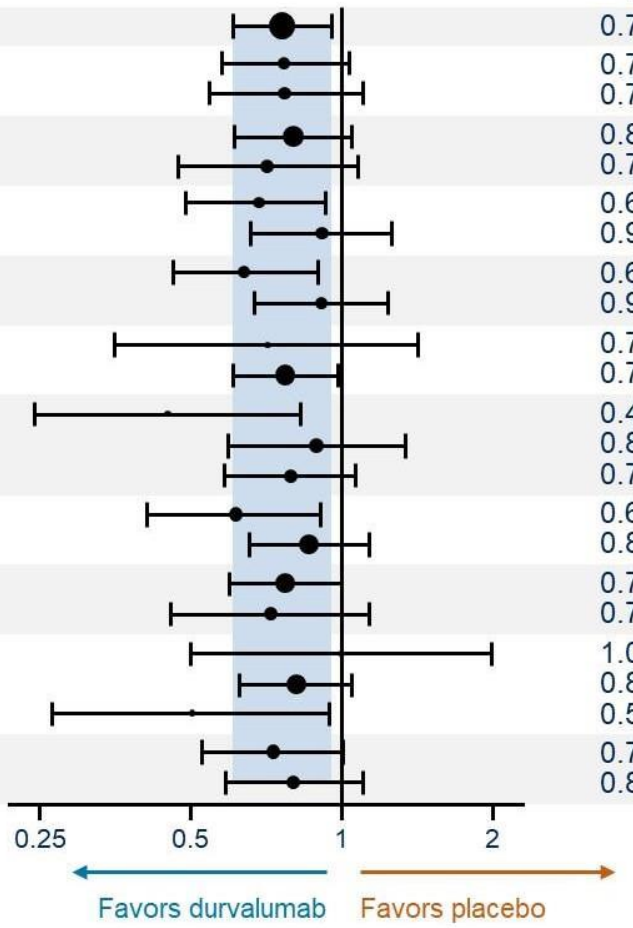
PFS was analyzed using a stratified log-rank test adjusted for disease stage (I/II vs III) and receipt of PCI (yes vs no). The significance level for testing PFS at this interim analysis was 0.00184 (2-sided) at the 0.5% level, and 0.02805 (2-sided) at the overall 5% level. Statistical significance for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

PRESENTED BY: Dr David R. Spigel

mPFS, median PFS.

PFS subgroup analysis

		Events/Patients n/N		HR (95% CI)
		Durvalumab	Placebo	
All patients		139/264	169/266	0.76 (0.61–0.95)
Age	<65 years	83/160	98/162	0.77 (0.58–1.03)
	≥65 years	56/104	71/104	0.77 (0.54–1.10)
Sex	Male	96/178	120/188	0.80 (0.61–1.04)
	Female	43/86	49/78	0.71 (0.47–1.08)
Race	White	65/130	90/137	0.68 (0.49–0.93)
	Asian	72/131	75/121	0.91 (0.66–1.26)
WHO performance status	0	60/133	82/131	0.64 (0.46–0.90)
	1	79/131	87/135	0.91 (0.67–1.24)
AJCC disease stage at diagnosis	I/II	14/33	19/34	0.71 (0.35–1.42)
	III	125/231	150/232	0.77 (0.61–0.98)
Time from end of cCRT* to randomization	<14 days	18/32	27/32	0.45 (0.24–0.83)
	≥14 days to <28 days	43/79	50/80	0.89 (0.59–1.34)
	≥28 days	78/153	92/154	0.79 (0.58–1.07)
Prior chemotherapy regimen	Carboplatin-etoposide	44/91	57/88	0.61 (0.41–0.90)
	Cisplatin-etoposide	95/173	112/178	0.86 (0.65–1.13)
Prior radiation schedule	Once daily	108/195	122/187	0.77 (0.60–1.00)
	Twice daily	31/69	47/79	0.72 (0.45–1.13)
Best response to prior cCRT	Complete response	15/31	18/34	1.00 (0.50–1.99)
	Partial response	106/191	130/200	0.81 (0.62–1.04)
	Stable disease	18/42	21/32	0.50 (0.26–0.94)
Prior PCI	Yes	65/142	84/143	0.73 (0.53–1.01)
	No	74/122	85/123	0.80 (0.59–1.09)



*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.

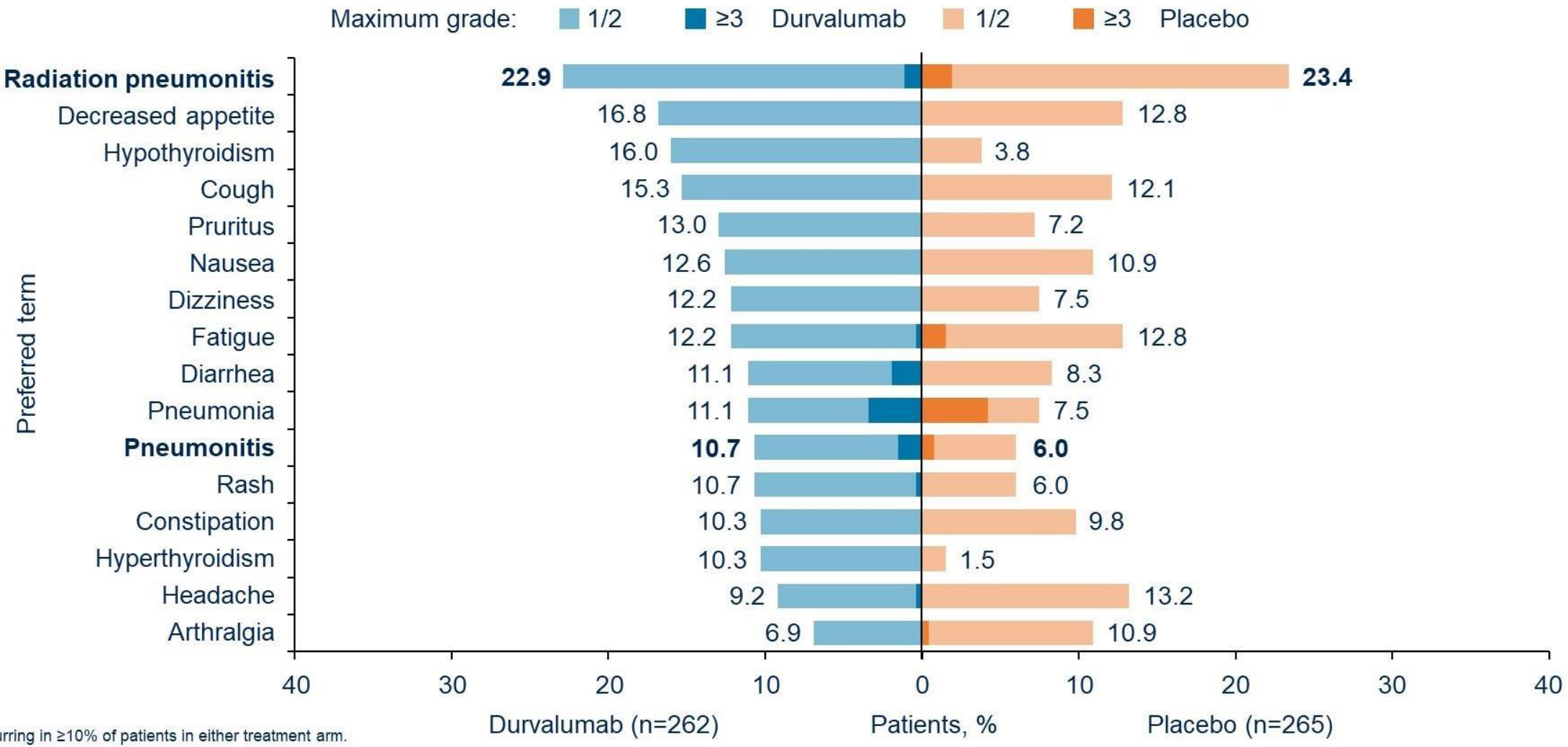
PRESENTED BY: Dr David R. Spigel

Exposure and safety summary

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

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

Most frequent AEs*



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

PRESENTED BY: Dr David R. Spigel

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)

*Includes the preferred terms of immune-mediated lung disease, interstitial lung disease, pneumonitis, radiation fibrosis – lung, and radiation pneumonitis. Events are included irrespective of etiology and AE management.

Conclusions

- **Durvalumab as consolidation treatment after cCRT demonstrated statistically significant and clinically meaningful improvement in OS and PFS compared with placebo in patients with LS-SCLC**
  - **OS HR 0.73** (95% CI 0.57–0.93), p=0.0104; mOS 55.9 (95% CI 37.3–NE) vs 33.4 (95% CI 25.5–39.9) months
  - **PFS HR 0.76** (95% CI 0.61–0.95), p=0.0161; mPFS 16.6 (95% CI 10.2–28.2) vs 9.2 (95% CI 7.4–12.9) months
  - Treatment benefit was generally consistent across predefined patient subgroups for both OS and PFS
- **Durvalumab consolidation treatment for up to 2 years was well tolerated, and safety findings were consistent with the known safety profile of durvalumab monotherapy in the post-cCRT setting**

Consolidation durvalumab will become the new standard of care for patients with LS-SCLC who have not progressed after cCRT

ADRIATIC: First Interim Analysis

Phase 3, randomized, double-blind, placebo-controlled global study for Limited Stage SCLC

Overall survival (dual primary endpoint)

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

Patient population:

- Stage I-III LS-SCLC (stage I/II inoperable)
- No progression after cCRT
- Randomized 1:1 (Durvalumab vs. Placebo - *up to 24 months*)

Dual primary endpoints

- **Overall Survival (OS)**
- **Progression Free Survival (PFS)**
- *Durva/Treme arm remains blinded*

ADRIATIC – First Interim Analysis

	Durvalumab	Placebo	Hazard Ratio (HR)	P-value
mOS	**55.9 mo**	**33.4 mo**	HR=0.73	p=0.010
mPFS	**16.6 mo**	**9.2 mo**	HR=0.76	p=0.016

With a median of 3 years of follow up, patients who received durvalumab consolidation were 25% less likely to experience cancer progression or death

Median duration of follow up in censored patients: Overall survival (OS) – 37.2mo, Progression Free Survival (PFS) –27.6, durva (durvalumab – anti-PDL1), treme (tremelimumab - anti-CTLA4)

PRESENTED BY: Lauren Averett Byers, MD, MSc @LaurenByersMD

Anti-PDL1 in Locally Advanced Lung Cancer (vs. ES-SCLC)

Global approvals of Durvalumab

PACIFIC – 71 independent regions
CASPIAN – 69 independent regions*

Limited Stage-SCLC	PACIFIC (NSCLC)	Extensive Stage-SCLC	
~23 mo improvement in Overall Survival	~18 mo improvement in Overall Survival	~2 mo improvement in Overall Survival	
ADRIATIC (Interim) (cCRT → durvalumab vs Placebo) mOS -- 55.9 vs. 33.4 (HR 0.73)	**PACIFIC (5-year followup)** (cCRT → durvalumab vs Placebo) mOS -- 47.5 vs. 29.1 (HR 0.72)	**CASPIAN** (EP +/- Durva) mOS – 13.0mo vs. 10.3mo (HR 0.73)	**IMpower133** (EP-Atezo vs. EP-Placebo) mOS – 12.3mo vs 10.3mo (HR 0.77)
	Spigel et al, JCO 2022	Paz-Ares et al, Lancet 2019	Horn et al, NEJM 2018

Global map - Rachel Davidowitz, Ph.D., MD. Anderson Cancer Center
**CASPIAN approved in all 71 regions except Costa Rica and Cuba, EP (etoposide-platinum)*

FAZIT

- Durvalumumab Erhaltung ist der neue Standard für inoperable SCLC nach Chemoradiotherapie
- Nach 3 Jahre Beobachtung, 25%ige Reduktion der tumorspezifischen Progression

Was ist neu?

- Neoadjuvante Chemoimmuntherapie in NSCLC
  - Aegean
  - Keynote 671
  - Checkmate 816
- Chemoradiotherapie NSCLC
  - EGFR mutierte
  - ALK mutierte
- Fortgeschrittenes Stadium NSCLC
  - Crown
  - Trop 2
- SCLC
  - Adriatic
- **Biomarker**
  - Ct DNA

2024 ASCO ANNUAL MEETING

CONQUER CANCER® THE ASCO FOUNDATION MERIT AWARD

ctDNA-Lung-DETECT: rate of ctDNA detection and outcomes for clinical stage I NSCLC

Sam Khan[1], Jamie Feng[1], Tom Waddell[2], Kazuhiro Yasufuku[2], Andrew Pierre[2], Shaf Keshavjee[2], Jonathan Yeung[2], Marcelo Cypel[2], Laura Donahoe[2], Elliot Wakeam[2], Marc de Perrot[2], Najib Safieddine[3], Michael Ko[4], David Parente[4], Mary Rabey[1], Michael Cabanero[4], Lisa Le[5], Christodoulos Pipinikas[6], Amber Chevalier[6], Natasha B. Leighl[1]

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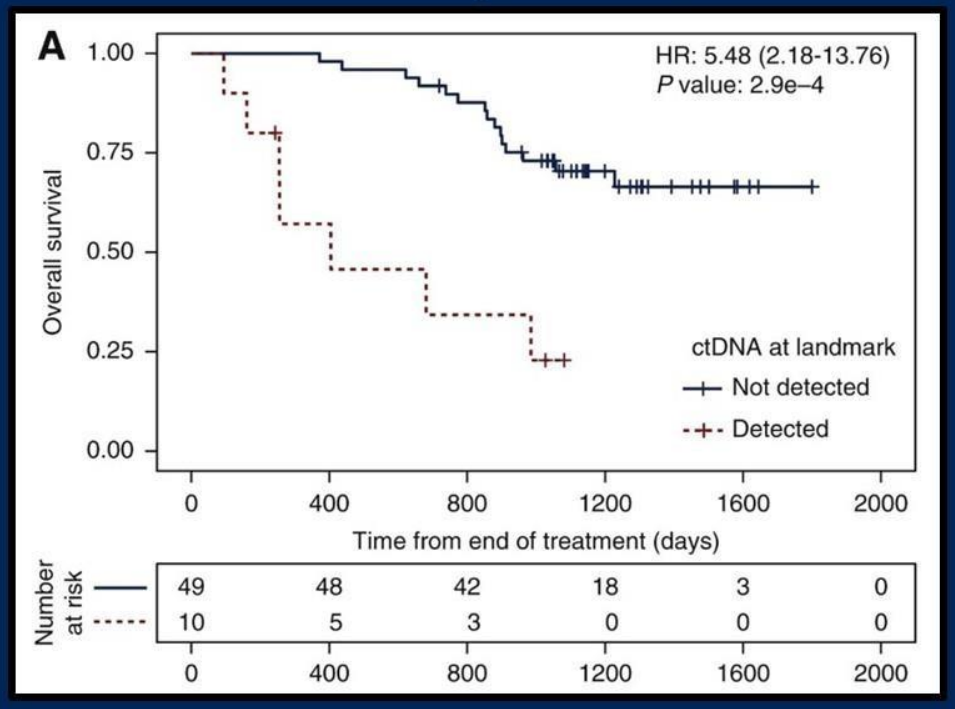
[2] **Division of Thoracic Surgery, UHN, Toronto ON, Canada**
[3] **Division of Thoracic Surgery, Michael Garron Hospital, Toronto ON, Canada**
[4] **Division of Thoracic Surgery, St Joseph's Health Centre, Toronto ON, Canada**
[5] Department of Biostatistics, UHN, Toronto ON, Canada
[6] NeoGenomics, Babraham Research Campus, Cambridge, UK and Research Triangle Park, NC, USA

The challenge of stage I non-small cell lung cancer (NSCLC)

- ~20% of lung cancer patients in Canada are diagnosed with stage I NSCLC [1]
- Despite curative intent treatment, 19-38% of patients with stage I NSCLC develop recurrence and die within 5 years [1-2]
- Post-operative detection of plasma ctDNA is a strong prognostic biomarker in patients with stage I-III NSCLC [3-7] using both tumor informed and uninformed panels

Survival outcomes by ctDNA detection post treatment for stage I-III NSCLC [5]



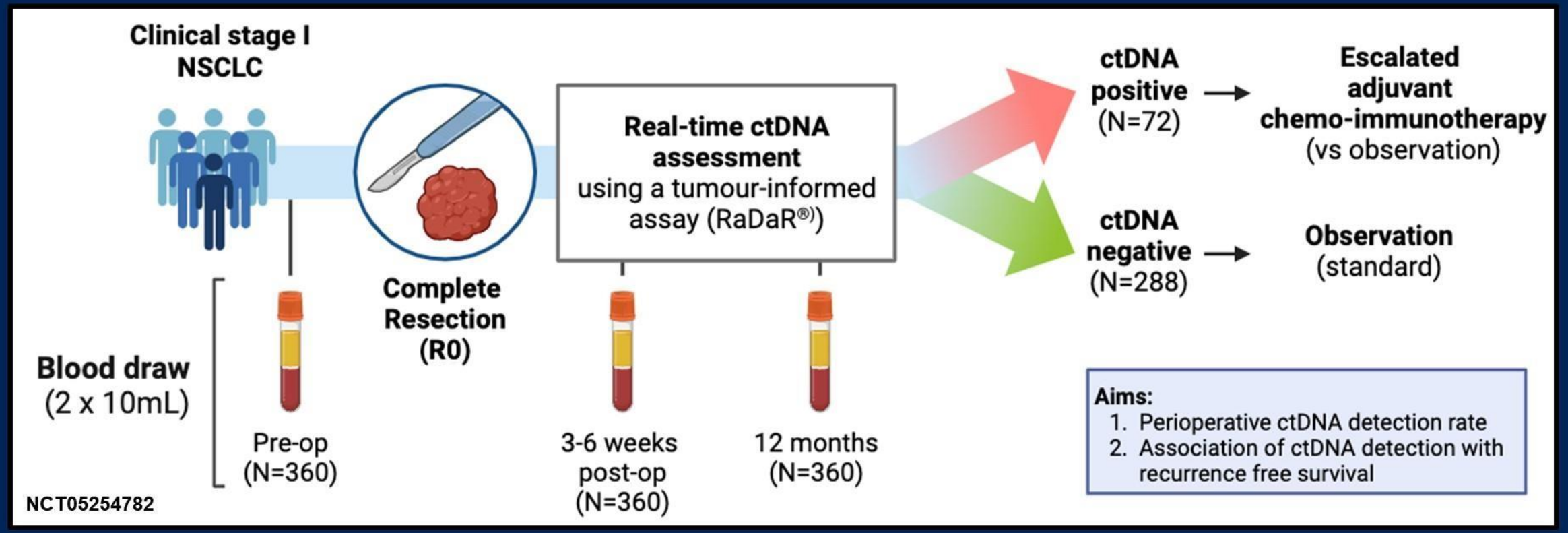
ctDNA: circulating tumour DNA

[1]Ellison & Saint-Jacques, *Health Rep* 2023; [2]Rami-Porta et al., *J Thorac Oncol* 2015; [3]Abbosh et al., *Nature* 2023; [4]Chaudhuri et al., *Cancer Discov* 2017; [5]Gale et al., *Ann Oncol* 2022; [6]Martin et al., *JTCVS* 2024; [7]Heider et al., *Cancer Res* 2020.

PRESENTED BY: Sam Khan MRCP(UK) PhD, Princess Margaret Cancer Centre, Toronto

ctDNA-Lung-DETECT

Multicentre investigator-initiated prospective study in Toronto, Canada



RaDaR® assay: up to 43 tumour specific variants were identified by whole exome sequencing with subsequent generation of an amplicon-based personalized ctDNA panel for each patient

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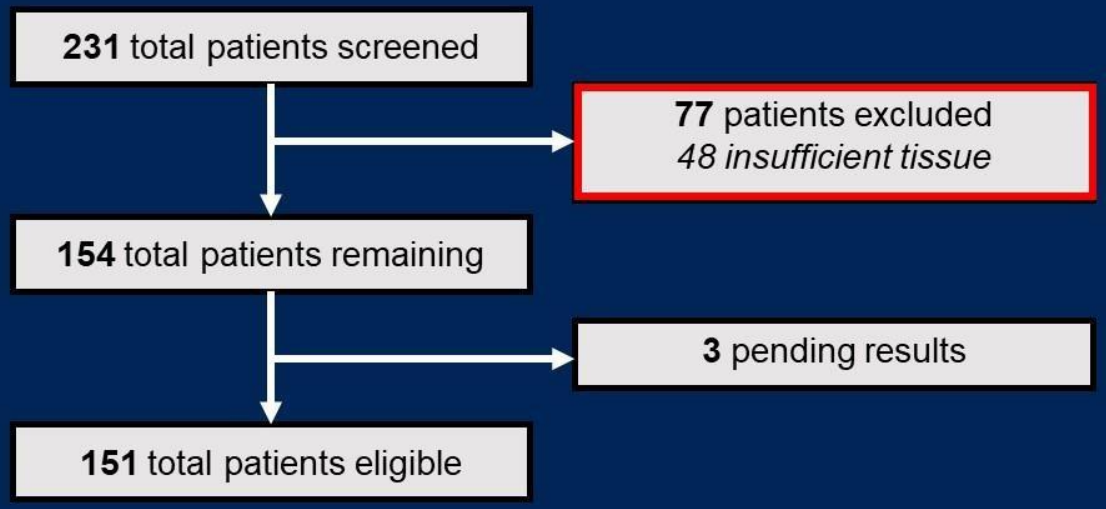
Patient demographics



20.7% had insufficient tissue for tumour informed panel

Characteristic		Total population (n=151)
Female n (%)		91 (60.3%)
Age median (range years)		71.0 (32.0 – 87.0)
Smoking status n (%)	Never	53 (35.8%)
	Smoker	95 (64.2%)
Pathology – adenocarcinoma n (%)		127 (84.1%)
PD-L1<1% n (%)		70 (50.0%)
AJCC 8th edition stage n (%)*	I	114 (75.5%)
	II	24 (15.9%)
	III/IV	12 (7.9%)

*1 patient had stage 0 (adenocarcinoma in situ)

24% of eligible patients upstaged at resection

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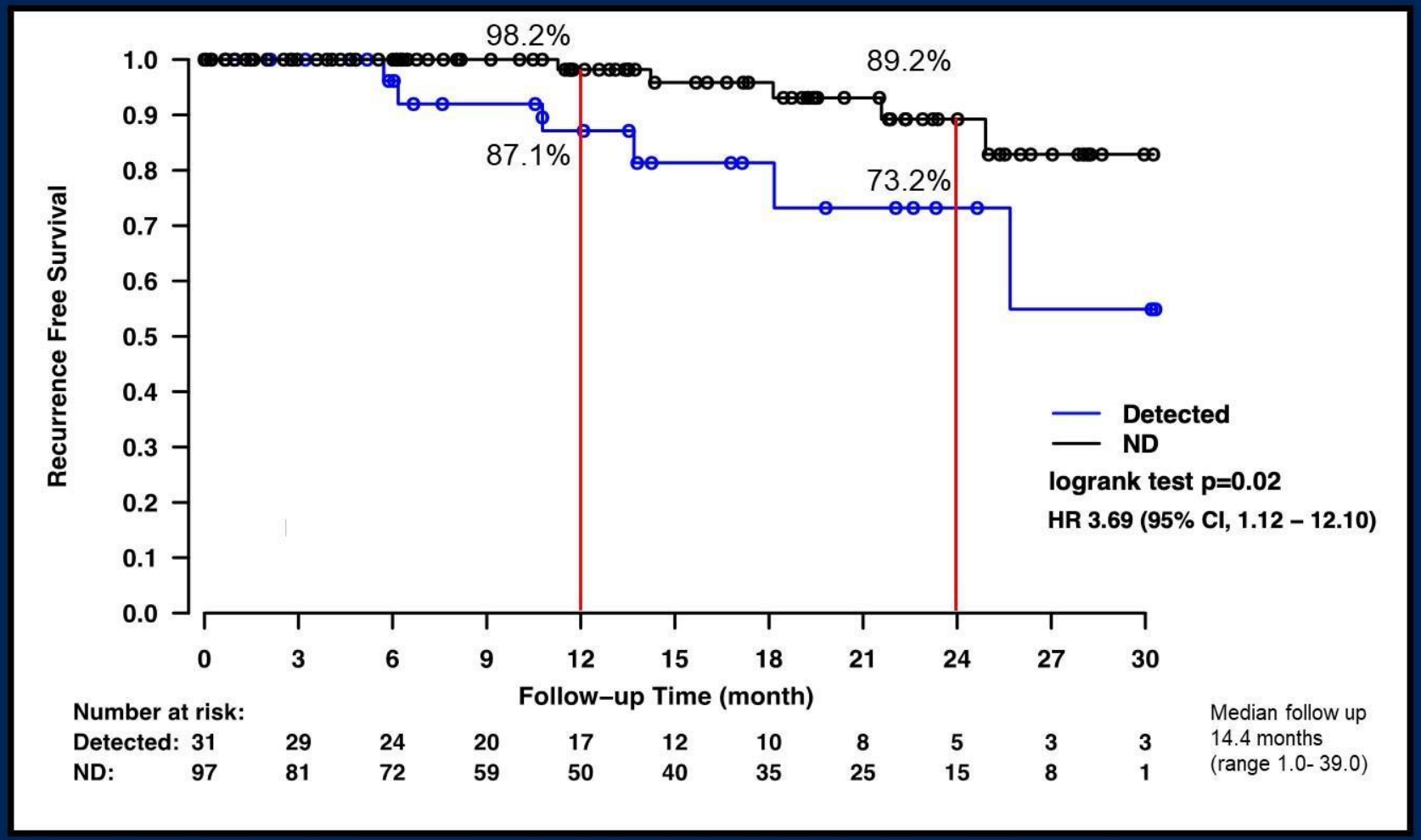
Pre-operative ctDNA detection and recurrence free survival (n= 129)



All eligible patients with at least 3 months of follow-up by 1 April 2024 were included in the recurrence free survival analysis

PRESENTED BY: Sam Khan MRCP(UK) PhD, Princess Margaret Cancer Centre, Toronto

Conclusion

In this study of patients with **clinical stage I** NSCLC:

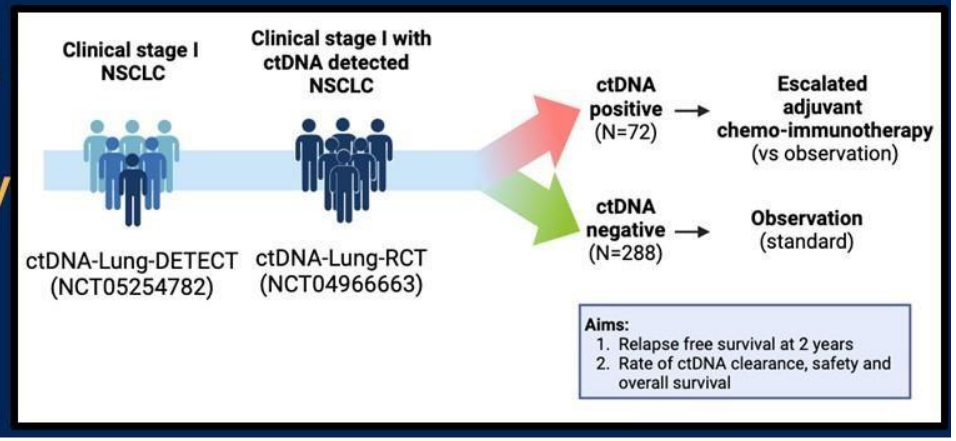
- Pre-operative ctDNA was detected in 22.7% using a tumour-informed assay
- Post-operative ctDNA was only detected in the setting of pathologic upstaging (occult N2 disease)
- In patients with pathologic stage I NSCLC, pre-operative ctDNA was detected in 14.0%

- Recurrence-free survival was significantly associated with detection of pre-operative ctDNA [HR 3.69, 95% CI: 1.12-12.1]
- Pathologic invasive tumour size but not radiographic size associated with pre-operative ctDNA detection
- ctDNA detection was more frequent in patients with high risk pathologic features and tumour suppressor alterations

Pre-operative ctDNA identifies stage I NSCLC patients at higher risk of relapse that may benefit from intensified curative therapy

Demonstration of the clinical utility of this approach is underway

More sensitive assays are needed to increase the value of this promising technology in clinical practice



PRESENTED BY: Sam Khan MRCP(UK) PhD, Princess Margaret Cancer Centre, Toronto

Zusammenfassung

- Neoadjuvante Therapie in NSCLC
- Chemoradiotherapie in NSCLC
  - EGFR mutierte
  - Alk mutiert
- Fortgeschrittenes Stadium NSCLC
  - Crown
  - Trop 2
- SCLC
  - Adriatic
- CtDNA

- Perioperative Chemoimmuntherapie und Adjuvante Immuntherapie ist der neue Standard. Ob Adjuvante Immuntherapie bei allem Patienten notwendig ist, steht noch aus.
- Osimertinib ist der neue Standard nach Chemoradiotherapie für inoperable Stadium III EGFRm NSCLC
- Lorlatinib ist der neue Standard für fortgeschrittene Stadium Alkm NSCLC
- Trop2 Antibody Drug Konjugate sind nicht überlegen zu Docetaxel
- 2 Jahre Durvalumumab ist der neue Standard nach Chemoradiotherapie in SCLC
- Könnte als relevanter Biomarker sich etablieren

Herzlichen DANK