Advancements in Systemic Therapy for Patients with Lung Cancer

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Disclosures

- I have no financial disclosures.

NSCLC

Predictive biomarkers	Estimated frequency in NSCLC adenocarcinoma[a]	NCCN-recommended testing technologies	NCCN-recommended targeted therapy
EGFR mutations[b]	Common *EGFR* mutations, 10.0% Less common *EGFR* mutations, ≤ 10%	Real-time PCR, Sanger sequencing (ideally paired with tumor enrichment), and NGS	**First-line therapy:** afatinib, dacomitinib, erlotinib, gefitinib, osimertinib, erlotinib/ramucirumab, erlotinib/bevacizumab **Subsequent therapy:** amivantamab-vmjw, osimertinib
KRAS G12C mutations	25.0%	Real-time PCR, Sanger sequencing (ideally paired with tumor enrichment), and NGS	**Subsequent therapy:** adagrasib, sotorasib
ALK rearrangements[b]	5.0%	FISH, IHC, NGS, and real-time PCR	**First-line therapy:** alectinib, brigatinib, ceritinib, crizotinib, lorlatinib **Subsequent therapy:** alectinib, brigatinib, ceritinib, lorlatinib
ROS1 rearrangements[b]	1.0%-2.0%	FISH, IHC, NGS, and real-time PCR	**First-line therapy:** ceritinib, crizotinib, entrectinib **Subsequent therapy:** entrectinib, lorlatinib
BRAF V600E mutations[c]	1.0%-2.0%	Real-time PCR, Sanger sequencing (ideally paired with tumor enrichment), and NGS	**First-line therapy:** dabrafenib/trametinib, encorafenib/binimetinib, dabrafenib, vemurafenib **Subsequent therapy:** dabrafenib/trametinib, encorafenib/binimetinib
NTRK1/2/3 gene fusions[b]	> 1.0%-3.0%	FISH, IHC, PCR, and NGS	**First-line/subsequent therapy:** larotrectinib, entrectinib
MET exon 14 skipping mutation	3.0%-4.0%	NGS	**First-line/subsequent therapy:** capmatinib, crizotinib, tepotinib
RET rearrangements	1.0%-2.0%	FISH, real-time reverse-transcriptase PCR, and NGS	**First-line/subsequent therapy:** selpercatinib, pralsetinib, cabozantinib
ERBB2 (*HER2*) mutations	3%	NGS, Sanger sequencing, and PCR	**Subsequent therapy:** fam-trastuzumab deruxtecan-nxki, ado-trastuzumab emtansine
PD-L1 expression levels[d]	TPS ≥ 50.0%, 33%; TPS = 1.0%-49.0%, 30.0%; TPS < 1.0%, 37.0%	IHC	Immune checkpoint inhibitors (pembrolizumab, nivolumab, atezolizumab, cemiplimab-rwlc, ipilimumab, tremelimumab-actl, durvalumab) alone or in combination with each other and/or with chemotherapy

+ HER2 IHC 3+ (T-Dxd)

Emerging biomarkers[e]	Estimated frequency in NSCLC adenocarcinoma	Potential testing technology	Targeted therapies under investigation
NRG1 rearrangement	< 1.0%	NGS	Afatinib, GSK2849330, AMG 888, seribantumab, zenocutuzumab
FGFR1 amplifications	Data not available	NGS	Infigratinib, rogaratinib

https://www.onclive.com/ipubs/biomarker-consortium/nsclc/01_OSL1789_NSCLC_BiomarkerConsortium_WEB.pdf

CROWN: Lorlatinib Versus Crizotinib in Patients With Advanced ALK-Positive Non-Small Cell Lung Cancer

Endpoint evaluation by BICR stopped after the 3-year analysis

Key eligibility criteria

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

Randomized 1:1 N=296

Lorlatinib 100 mg once daily n=149

Stratified by:

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

Crizotinib 250 mg twice daily n=147

No crossover between treatment arms was permitted

Current analyses

Data cutoff: October 31, 2023

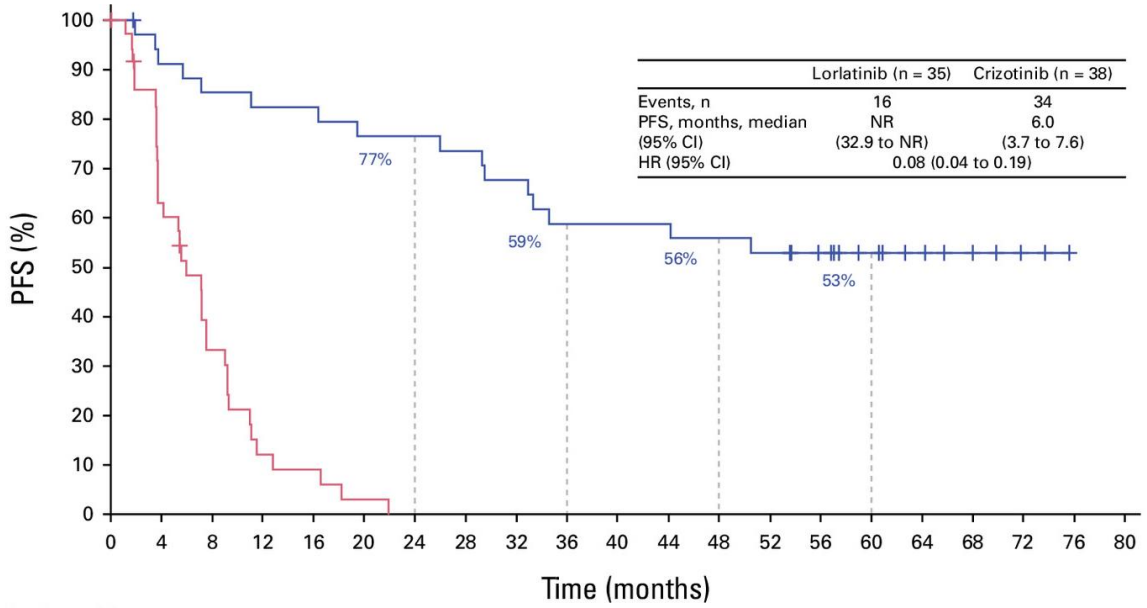
- **Investigator Assessed**
  - PFS[a]
  - ORR and IC ORR
  - DOR and IC DOR
  - IC TTP
- Safety
- Biomarker analyses

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

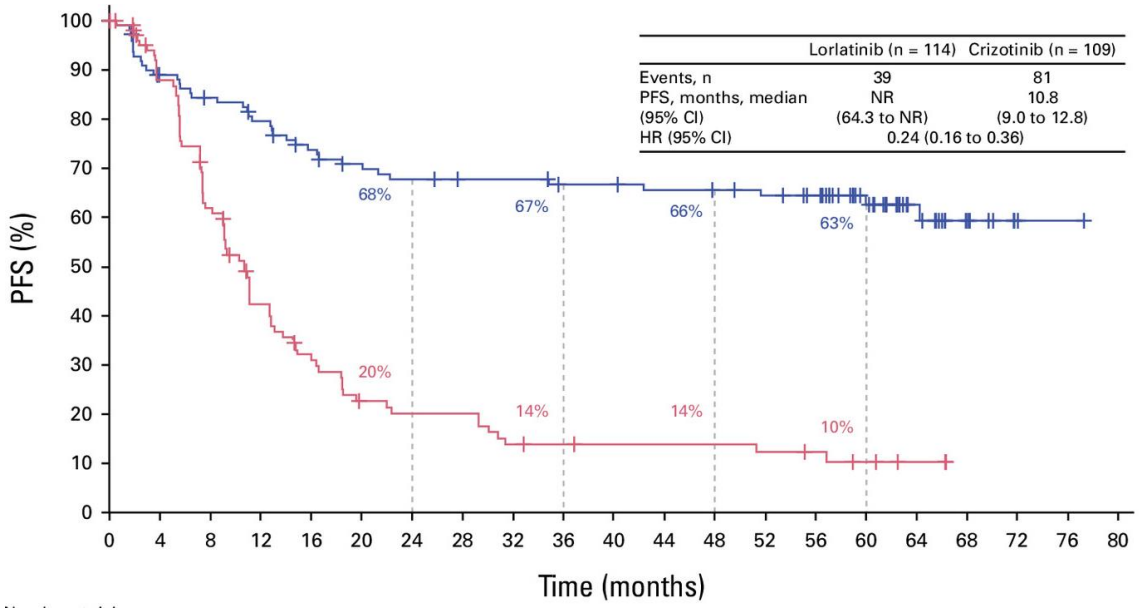
Solomon et al. ASCO 2024

CROWN: 5-Year Outcomes

PFS in patients with baseline CNS metastasis
mPFS was **NR** for lorlatinib



PFS in patients without baseline CNS metastasis
mPFS was **NR** for lorlatinib



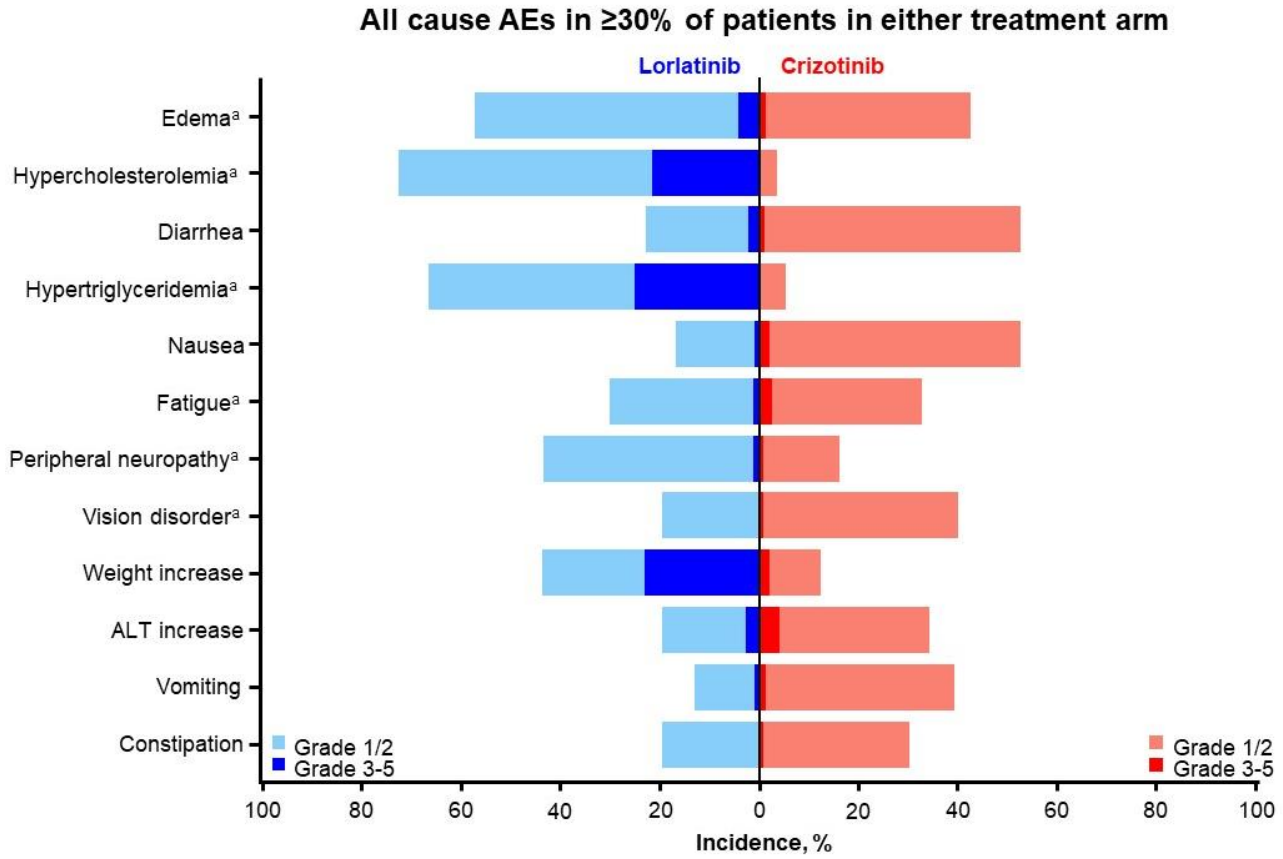
Median follow-up of 60.2 months

Solomon et al. JCO 2024

CROWN: Safety of Lorlatinib

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

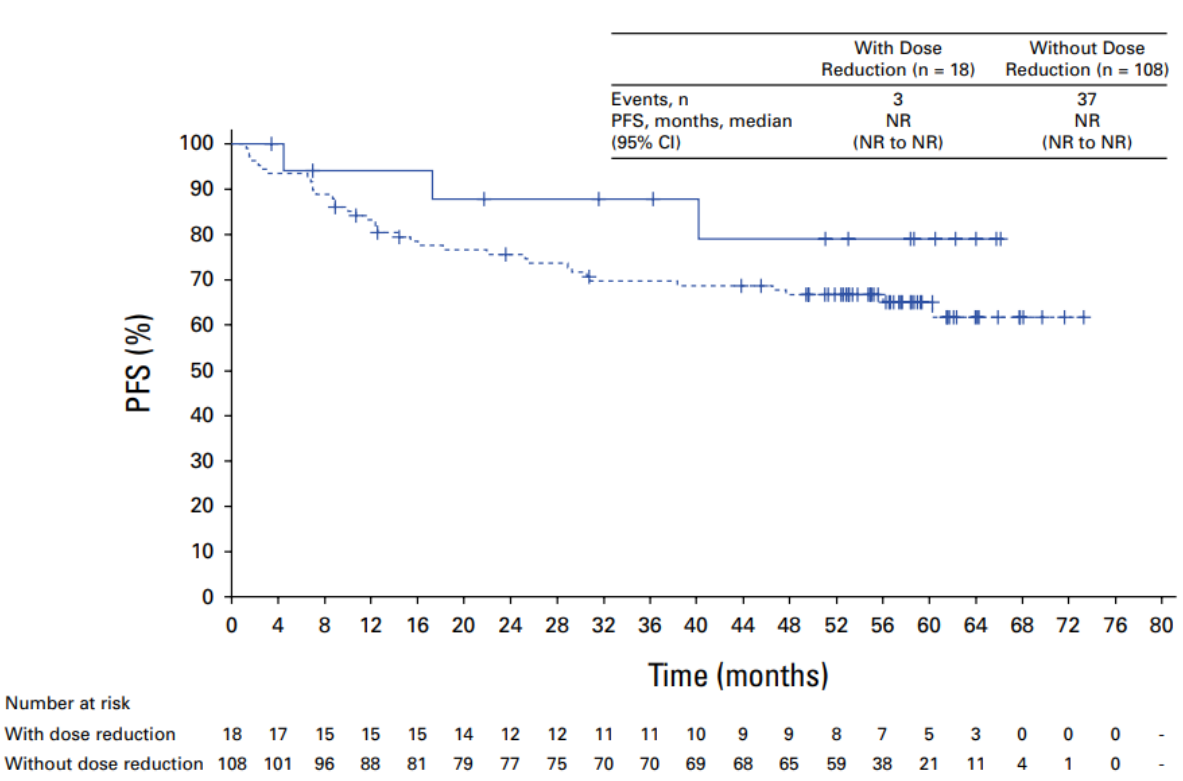


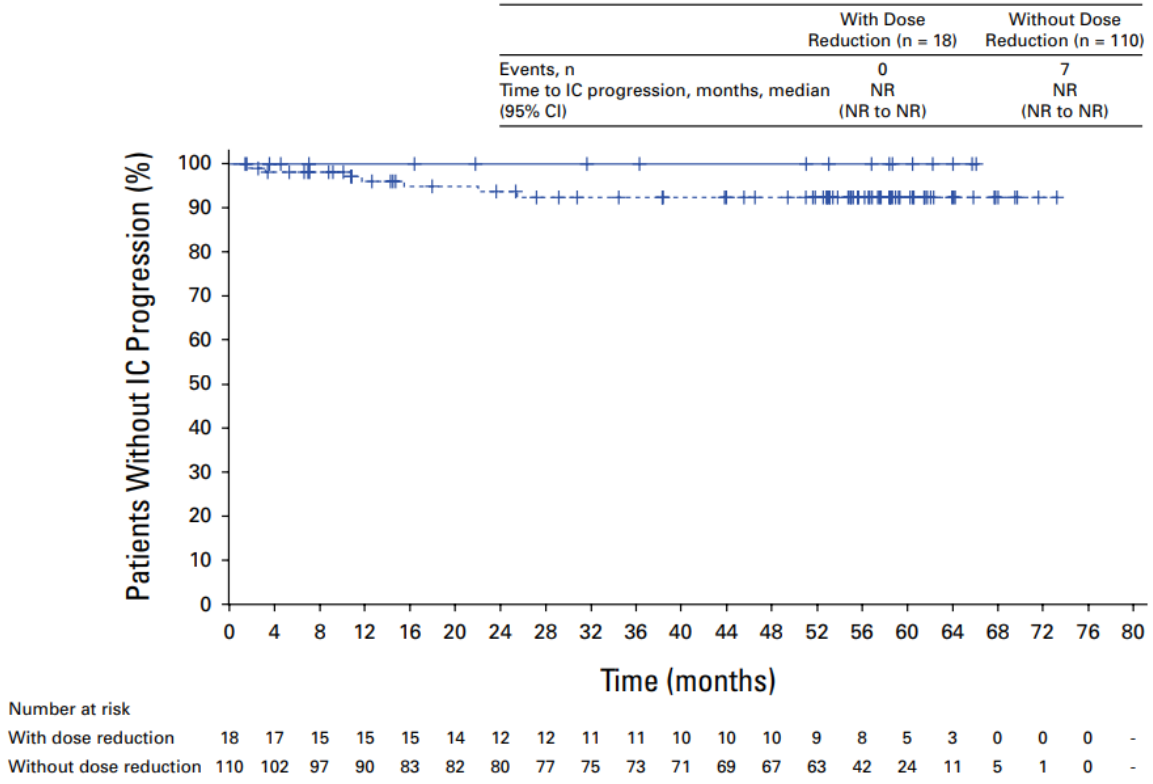
AE, adverse event; CNS, central nervous system.
[a]This category comprised a cluster of AEs that may represent similar clinical symptoms or syndromes. [b]Includes cognitive effects (28%), mood effects (21%), speech effects (6%), and psychotic effects (5%),

Solomon et al. ASCO 2024

CROWN: Efficacy in Patients with Dose Reduction

PFS and time to intracranial progression were **NR** in patients who had dose reductions in lorlatinib.





Solomon et al. JCO 2024

No Emergence of New ALK Mutations Detected with Lorlatinib

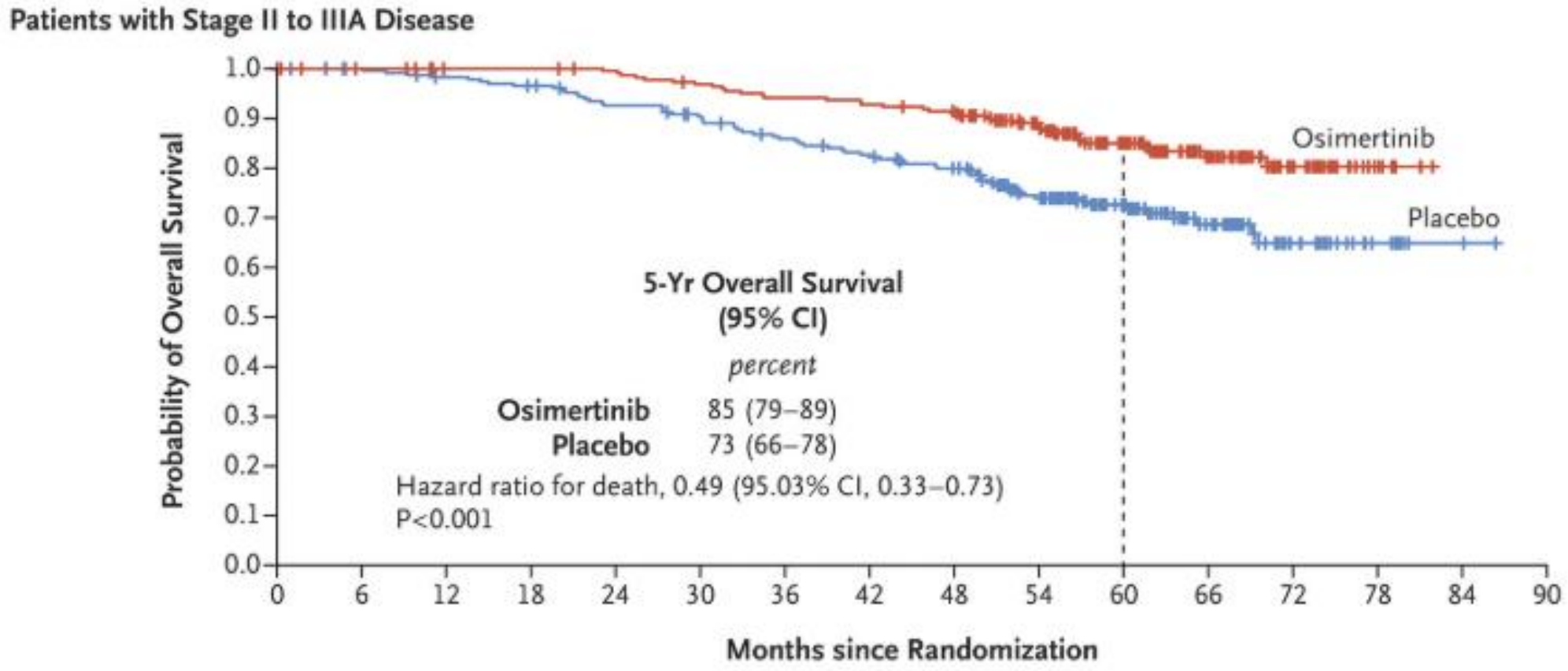
	Lorlatinib (n=31) n (%)	**Crizotinib (n=89)** n (%)
Resistance mechanisms		
New single ALK mutation	0	8 (9)
ALK compound mutation	0	2 (2)
Bypass mechanism	9 (29)	10 (11)
MAPK pathway aberration	3 (10)	1 (1)
PI3K/MTOR/PTEN pathway aberration	2 (6)	0
RTK pathway aberration	4 (13)	5 (6)
Cell cycle pathway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

Solomon et al. JCO 2024

Unresectable NSCLC

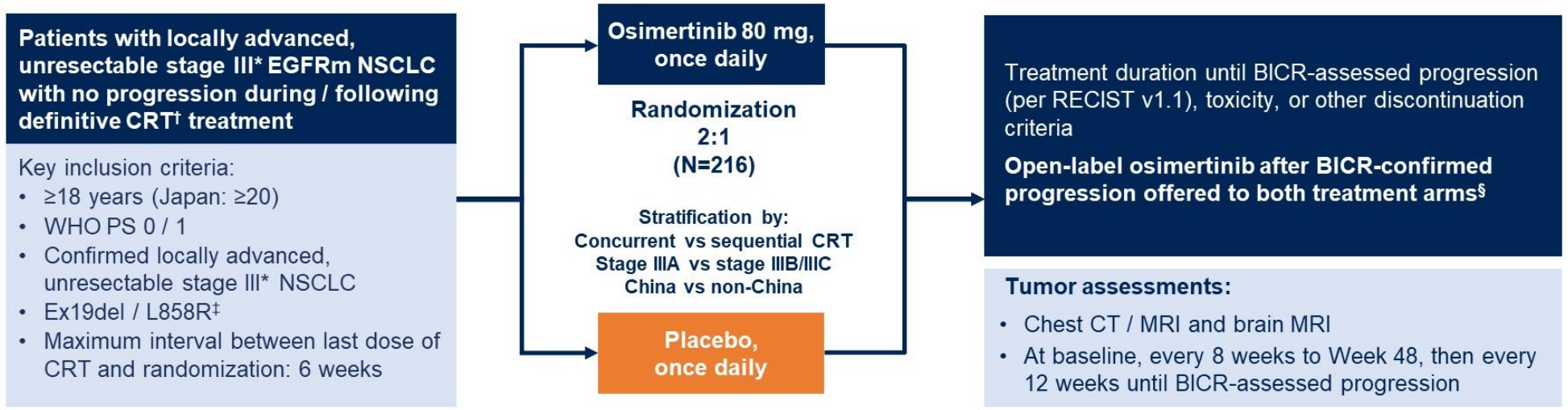
- Approximately 30% of patients diagnosed with NSCLC have locally advanced disease and 60-90% of those patients have unresectable disease.
- Standard of care treatment for unresectable stage III NCSLC has been concurrent chemoradiation followed by 1 year of consolidative durvalumab.
- However, there was no survival benefit with immunotherapy in patients with EGFR/ALK alterations in the subgroup analysis of the PACIFIC trial.

ADAURA: Osimertinib Showed OS Benefit in Patients with Resected EGFR-Mutated NSCLC



Tsuboi et al. NEJM 2023

LAURA: Osimertinib after Chemoradiotherapy in Patients with Stage III EGFR-Mutated NSCLC

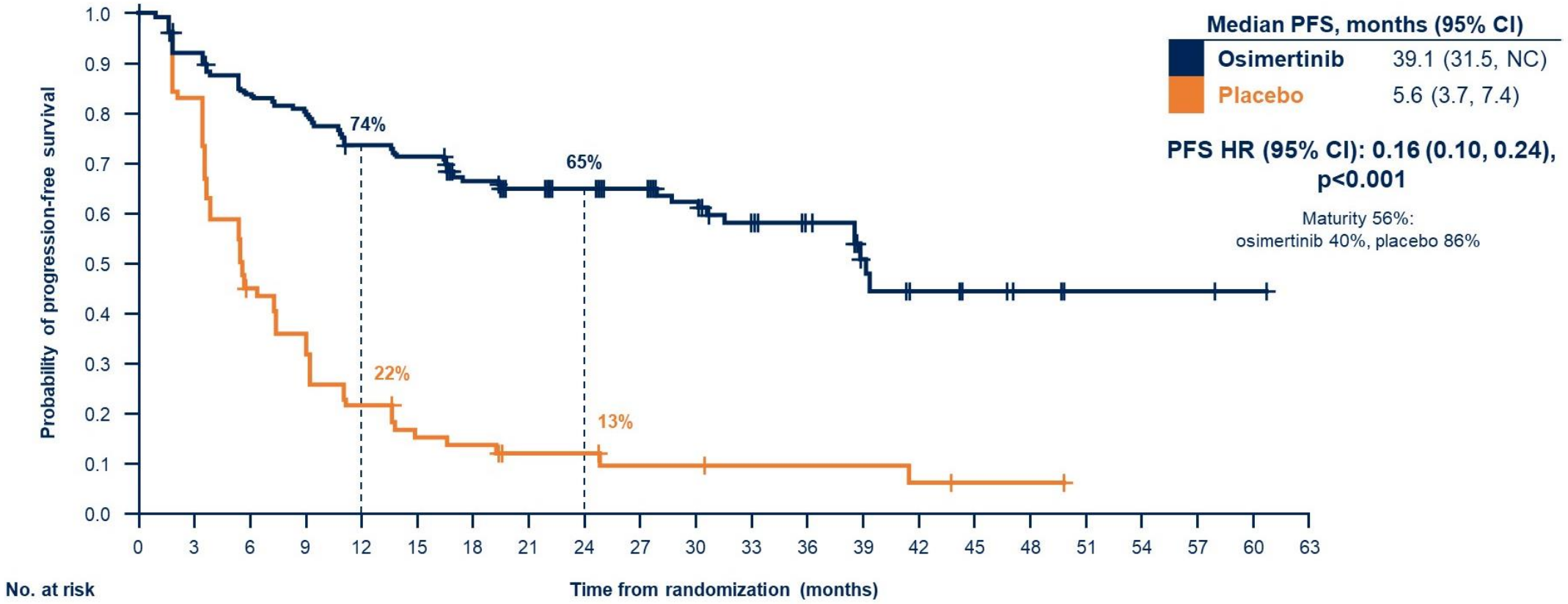


Endpoints

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

Ramalingam et al. ASCO 2024

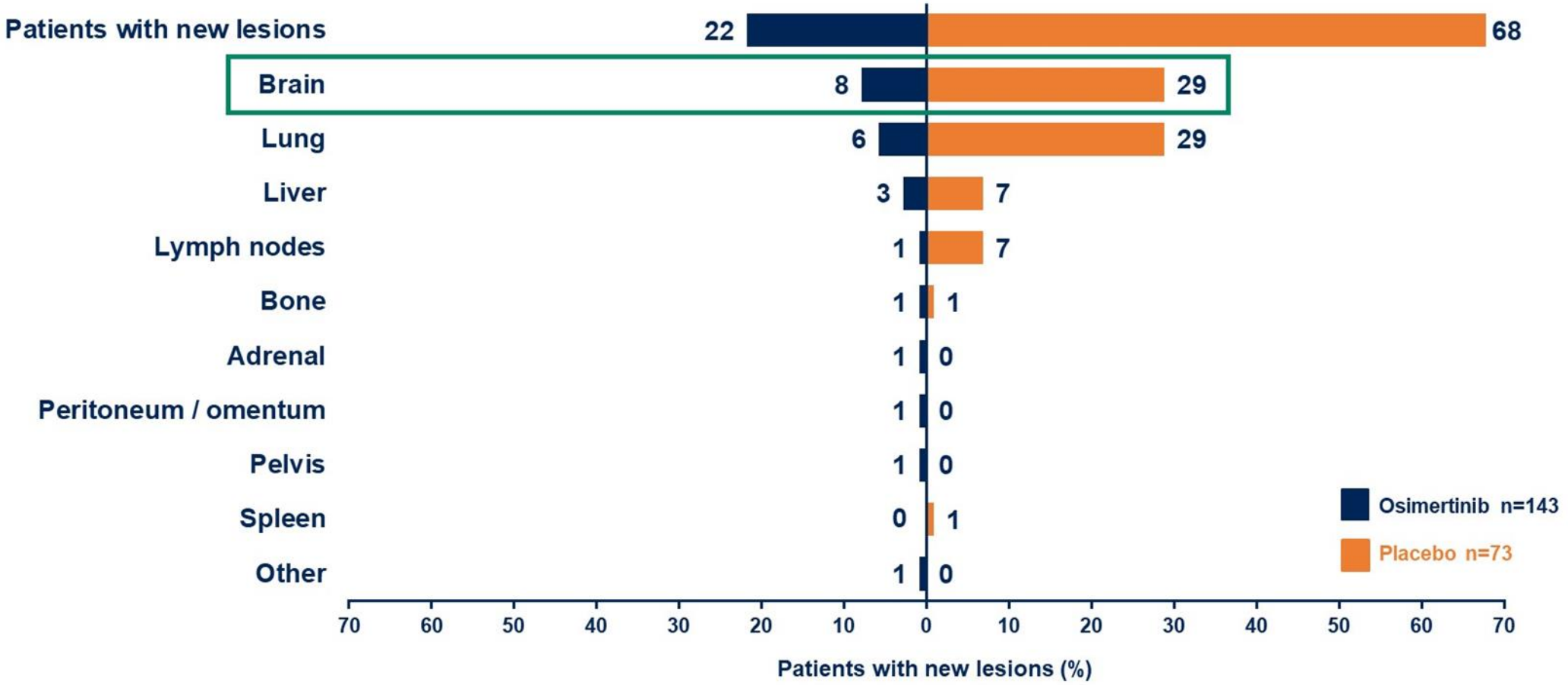
LAURA: PFS by BICR



OS data is immature but 36-month OS was 84% with osimertinib and 74% with placebo.

Ramalingam et al. ASCO 2024

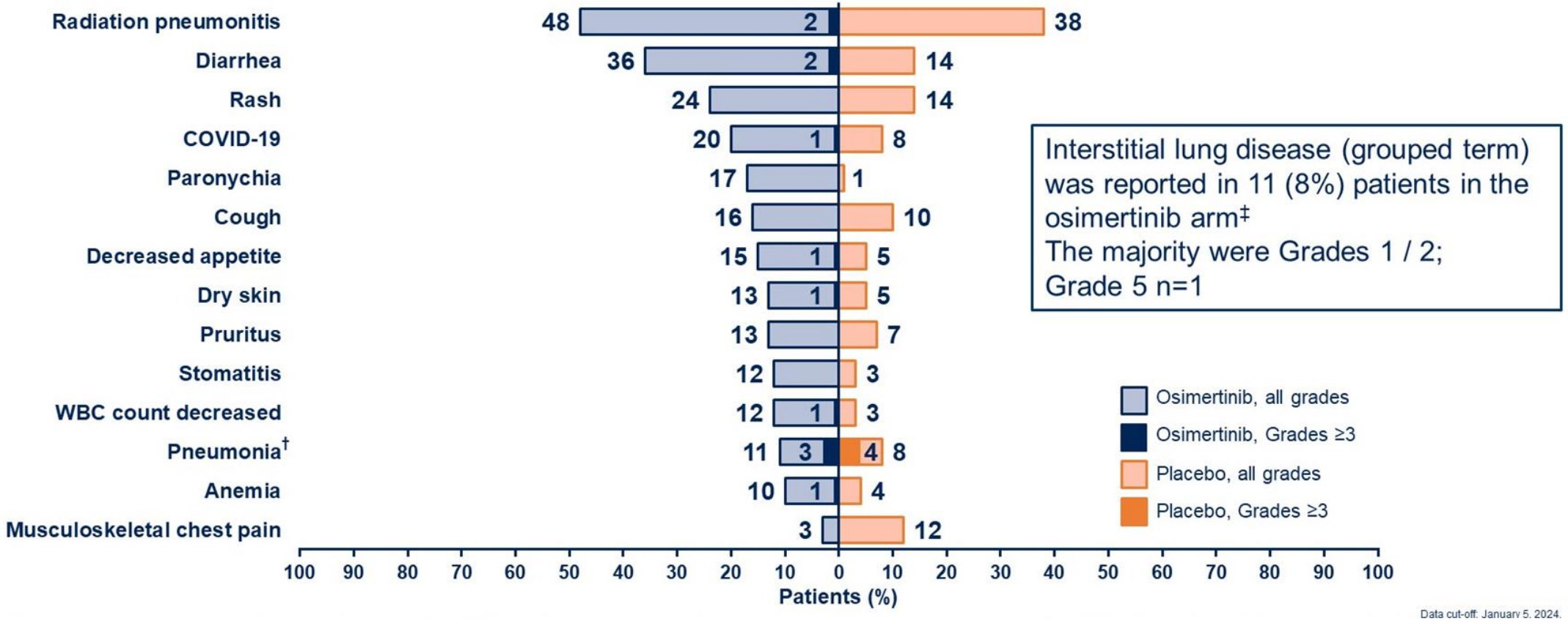
LAURA: Sites of New Lesions



Ramalingam et al. ASCO 2024

LAURA: Sites of New Lesions

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



Ramalingam et al. ASCO 2024

Unresectable NSCLC

- Several small phase 2 studies have shown efficacy with induction EGFR-TKI in stage III EGFR-mutated NSCLC.
  - Induction osimertinib followed by RT with or without surgery showed an ORR of 95.2%
  - Induction gefitinib followed by CRT showed a 2-year OS of 90%
- NEOLA is a phase II, open-label, single-arm study of osimertinib as induction therapy prior to CRT and maintenance osimertinib in patients with unresectable stage III EGFR-mutated NSCLC.
  - Osimertinib 80 mg QD as induction treatment for 8 weeks followed by platinum-based CRT
  - Within 6 weeks post-CRT, patients without progressive disease will receive osimertinib 80 mg QD until PD or toxicities
  - Primary endpoint is 12-month PFS rate
  - Open at UCSD

Peled et al. Int J Radiat Oncol Biol Phys 2023, Hotta et al. ESMO 2021

NSCLC Summary

- Biomarker testing is important not only for metastatic NSCLC but also in early-stage NSCLC.
- Studies are underway to understand the role of induction targeted therapy in the treatment of early-stage NSCLC.

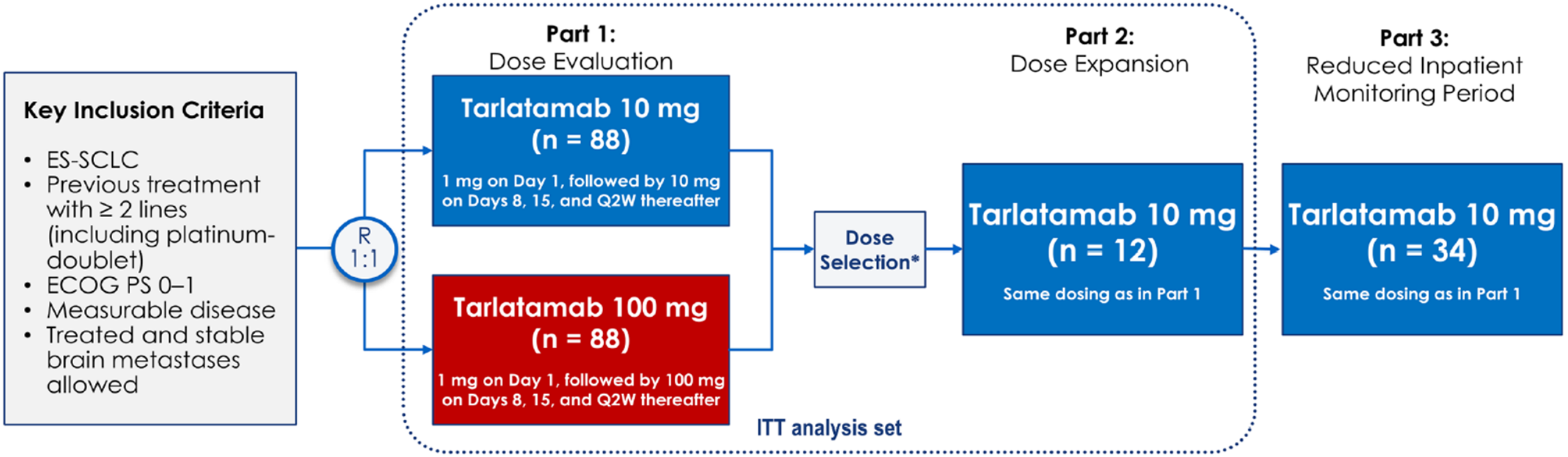
SCLC

ES-SCLC

- Immunotherapy plus platinum-etoposide chemotherapy is the standard of care first-line treatment in extensive-stage SCLC.
  - Median OS of 13 months
- Prognosis in the relapsed or refractory setting is poor. Single agent chemotherapy is the standard of care in the second line setting.
  - Lurbinectedin has an ORR of 35%, median PFS of 3.5 months and median OS of 9 months
  - Rechallenge with platinum doublet for those with relapse >6 months
  - Clinical trials

Horn et al. NEJM 2018, Paz Ares et al. Lancet 2019, Trigo et al. 2020 Lancet Oncology

DeLLphi-301: Tarlatamab for Patients with Previously Treated ES- SCLC



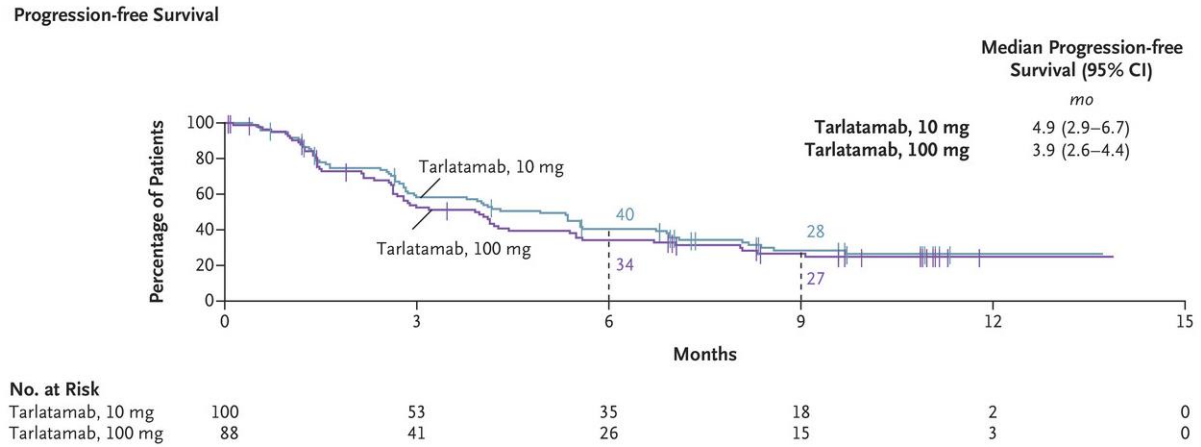
Primary Endpoint: ORR per RECIST v1.1 by BICR, TEAEs, tarlatamab serum concentrations
Secondary Endpoints Included: DOR, DCR, PFS per RECIST v1.1 by BICR, OS

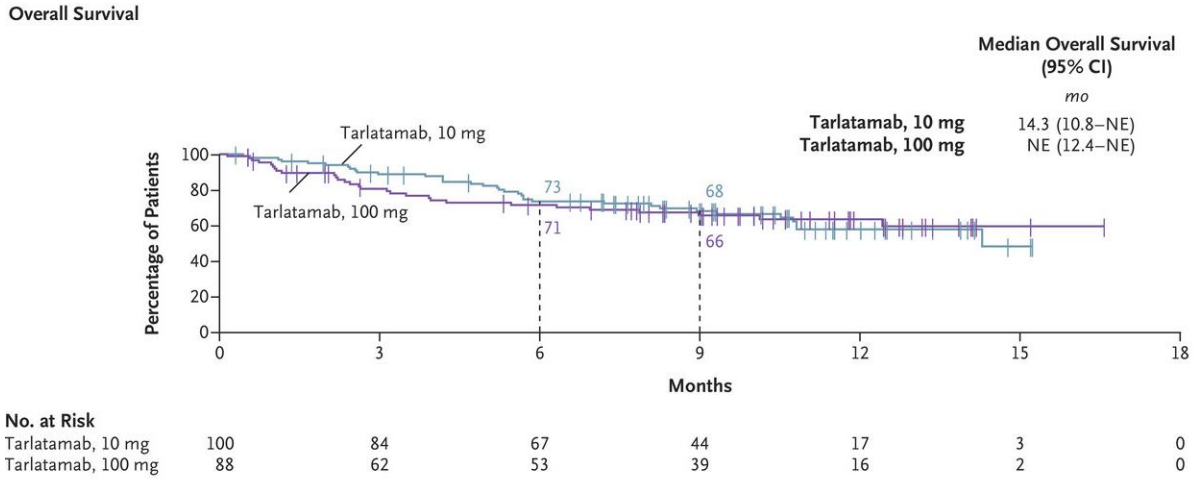
Paz-Ares et al. ESMO 2023

DeLLphi-301: Results

- ORR 40% with tarlatamab 10 mg
  - Objective responses at the time of data cutoff were ongoing in 55% of patients
- ORR 32% with tarlatamab 100 mg

- Median PFS 4.9 months (10 mg)
- Median OS 14.3 months (10 mg)

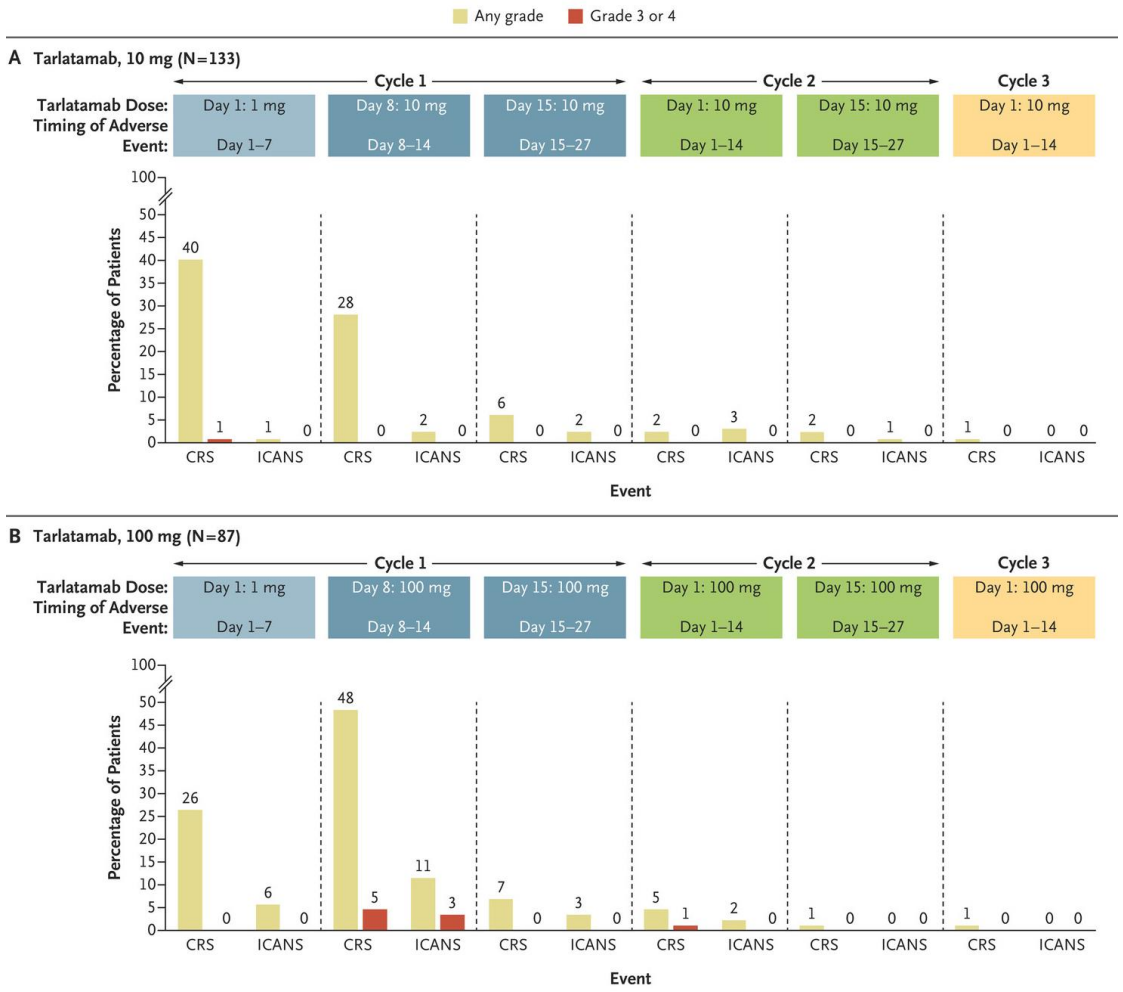




Ahn et al. NEJM 2023

DeLLphi-301: Safety Profile of Tarlamatab

- The most common adverse events were cytokine-release syndrome (CRS) (**51%** in the 10-mg group and 61% in the 100-mg group), decreased appetite (**29%** and 44%), and pyrexia (**35%** and 33%).
- CRS occurred primarily during cycle 1 and generally grade 1 or 2 in severity.
- Median time for onset of CRS is 13.1 hours from the last dose of tarlatamab.
- Grade 3 CRS occurred less frequently in the 10-mg group (1%) than in the 100-mg group (6%).
- ICANS occurred in 9% of patients.



Ahn et al. NEJM 2023

Tarlatamab-dlle Workflow at UCSD

- Step-up dosing Cycle 1 Day 1 and 8 - observation admission (22-24 hours)
- Step-up dosing Cycle 1 Day 15 and subsequent infusions – outpatient as long as CRS and ICANS < Grade 2
- Cell and Regenerative Medicine (CRM) team will manage C1D1 and C1D8
- Safety calls, C1D17 and C1D22 follow-up at the discretion of provider
- Outpatient authorization must be secured before inpatient admission
- Outpatient observation admission if stay < 2 midnights utilizing 340B pricing
- Negative COVID test required prior to admission Cycle Day 1 and 8

- *Ensure patients have a caregiver and will remain within 1-hour distance from UCSD for 24-48 hours observation after C1D1 and C1D8*

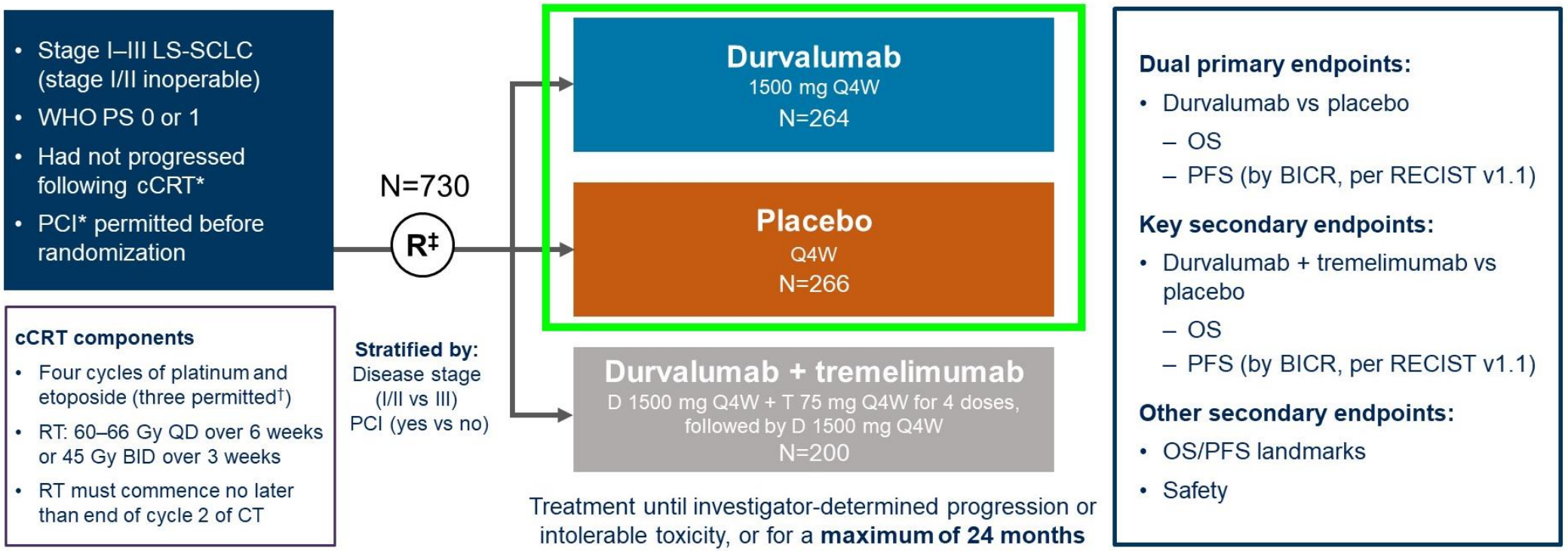
LS-SCLC

- Patients with unresectable LS-SCLC are treated with concurrent chemoradiation.
  - Median survival is approximately 17 months
  - 5-year survival rate is approximately 20%

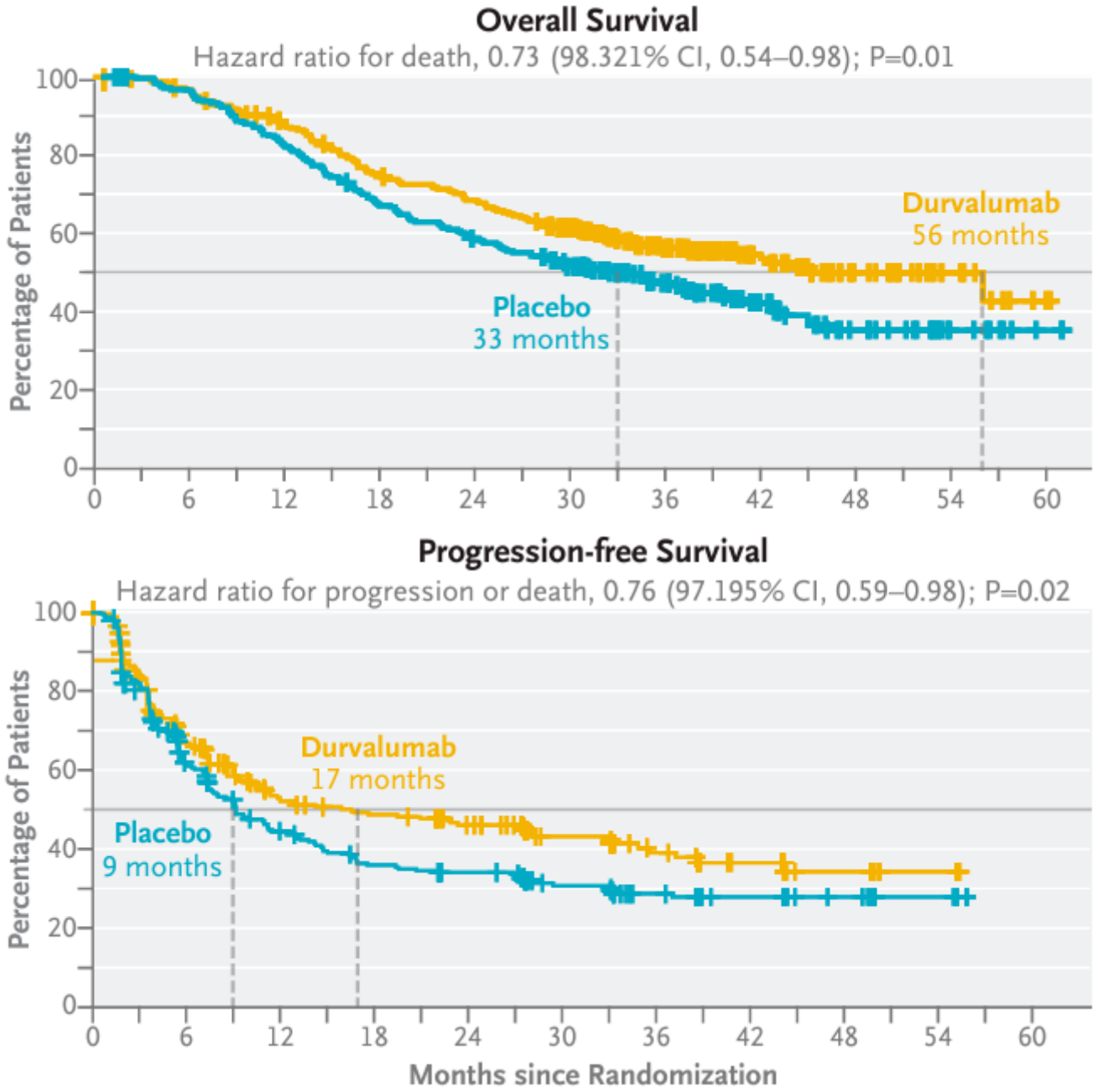
Gaspar et al. Clin Lung Cancer 2005, Janne et al. Cancer 2002

ADRIATIC: Durvalumab after Chemoradiotherapy in LS-SCLC

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



Spigel et al. ASCO 2024



Cheng et al. NEJM 2024

SCLC Summary

- Tarlatamab received accelerated approval in May 2024 for treatment of ES-SCLC with disease progression on or after platinum-based chemotherapy.
  - CRS and ICAHNs risk so inpatient observation for 24 hours after C1D1 and C1D8 is necessary

- Durvalumab was awarded breakthrough therapy designation in August 2024 as consolidative therapy after chemoradiation in LS-SCLC
  - Subgroup analysis showed larger benefit in patients with stage III disease and those who received carboplatin
  - 2 years of IO

Thank You!

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