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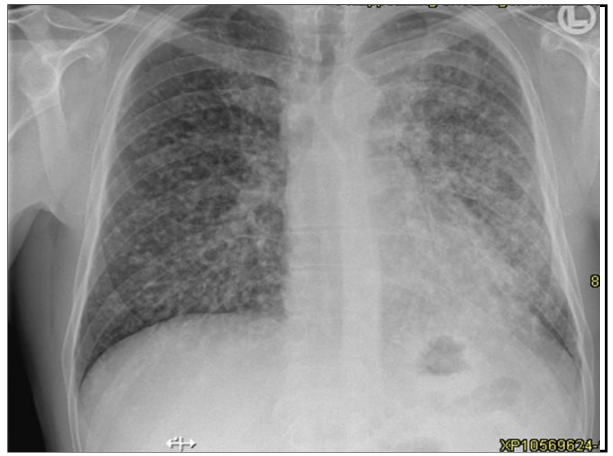
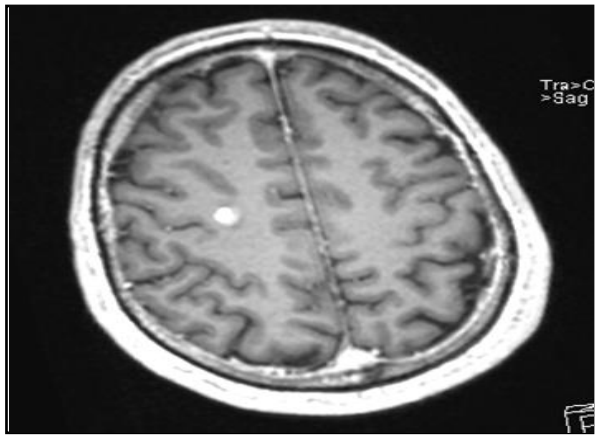
Leitlinie

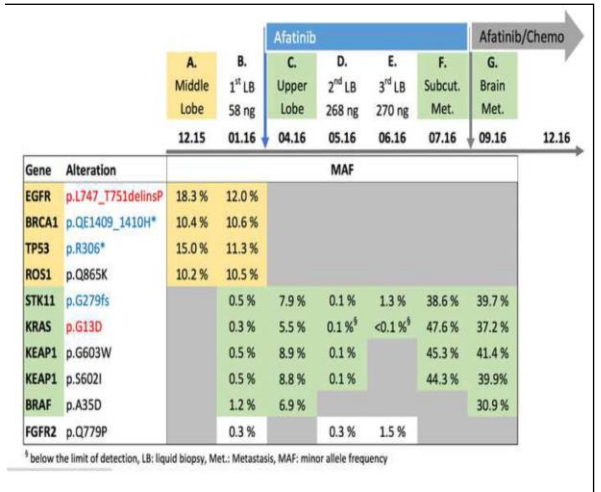
Frank Griesinger

ONKOPEDIA – Online-Seminar

05.07.2024







Offenlegung Interessenskonflikte

1. Anstellungsverhältnis oder Führungsposition: Pius-Hospital, Universitätsmedizin Oldenburg

2. Beratungs- bzw. Gutachtertätigkeit: ASTRA, Boehringer, BMS, Celgene, Lilly, MSD, Novartis, Pfizer, Roche, Takeda, Ariad, Abbvie, Tesaro/GSK, Siemens, Tesaro, Amgen, Eisai, Beigene, Janssen, Pierre Fabre

3. Besitz von Geschäftsanteilen, Aktien oder Fonds: keine

4. Patent, Urheberrecht, Verkaufslizenz: keine

5. Honorare: ASTRA, Boehringer, BMS, Celgene, Lilly, MSD, Novartis, Pfizer, Roche, Takeda, Ariad, Abbvie, Tesaro/GSK, Siemens, Tesaro, Amgen, Sanofi, GSK, Janssen, Beigene, Pierre Fabre

6. Finanzierung wissenschaftlicher Untersuchungen; ASTRA, Boehringer, BMS, Celgene, Lilly, MSD, Novartis, Pfizer, Roche, Takeda, Ariad, Abbvie, Tesaro/GSK, Siemens, Amgen, Janssen

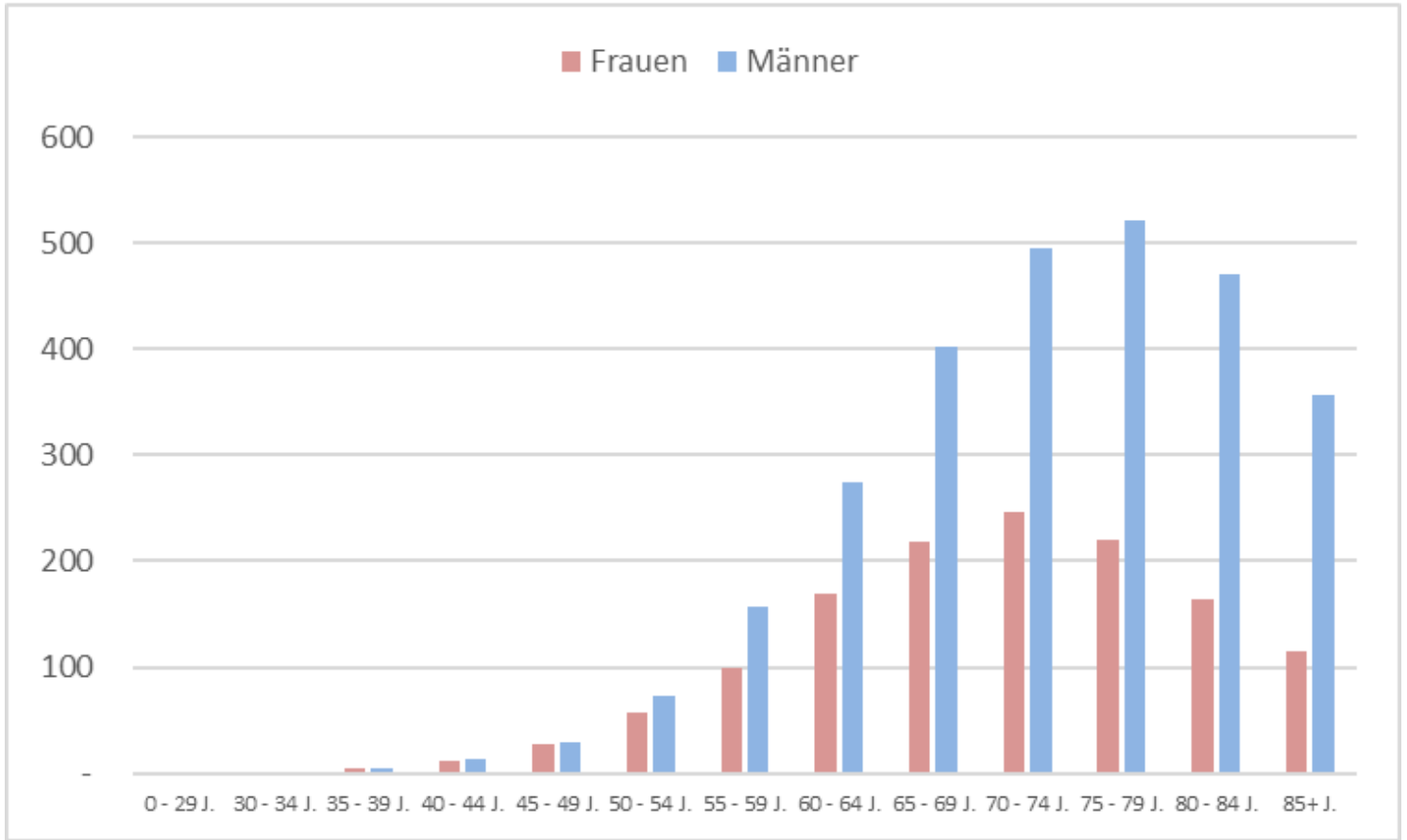
7. Andere finanzielle Beziehungen: keine

8. Immaterielle Interessenkonflikte: keine

Agenda

Aufbau

- Epidemiologie
- Biologie
- Früherkennung / Prophylaxe
- Klinisches Bild
- Diagnostik
- Therapie
  - Struktur (Algorithmus)
  - Stadien
  - Arzneimittel
- Nachsorge und Rehabilitation
- Fallbeispiel


Frauen
Männer
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500
400
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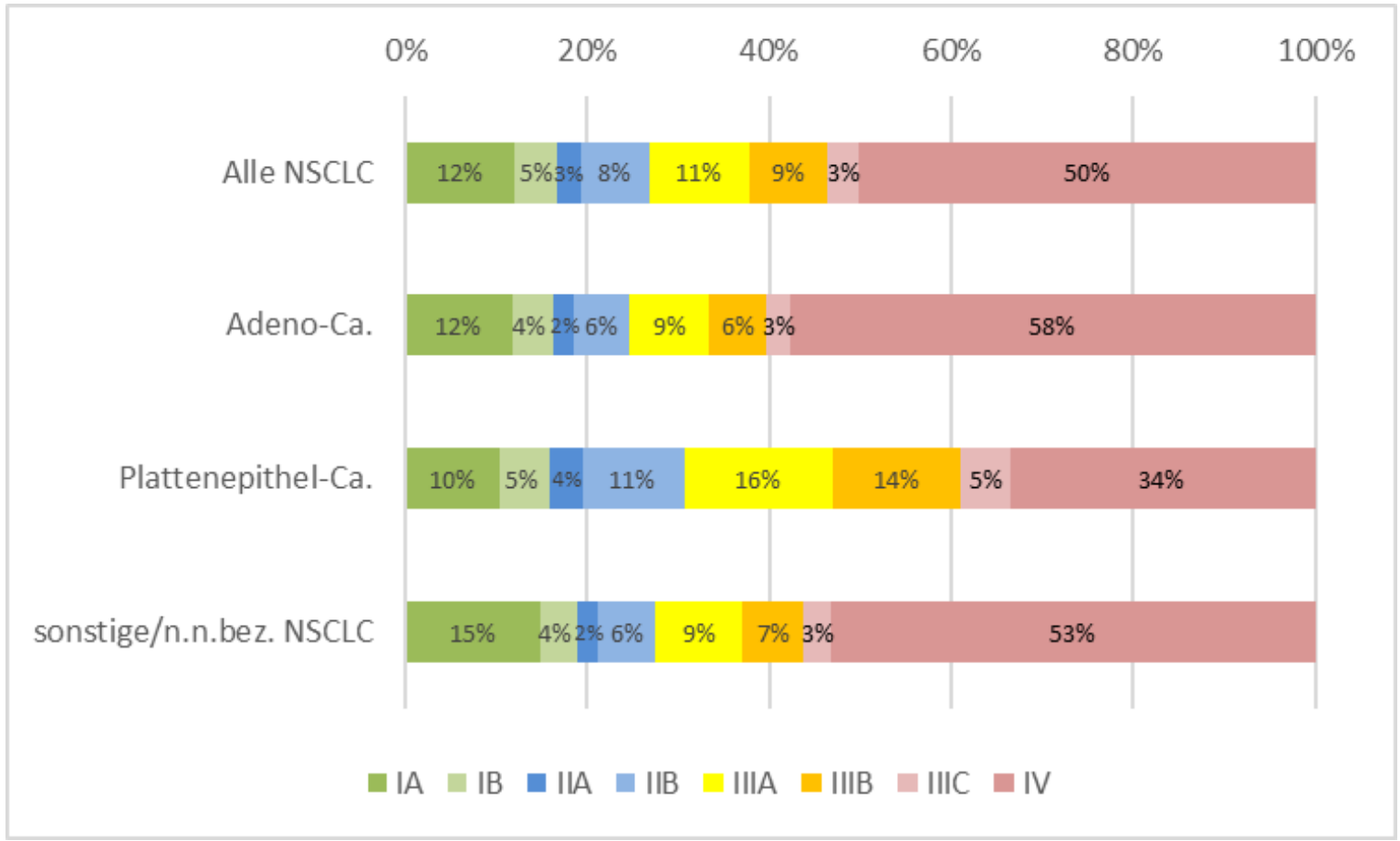
85+ J.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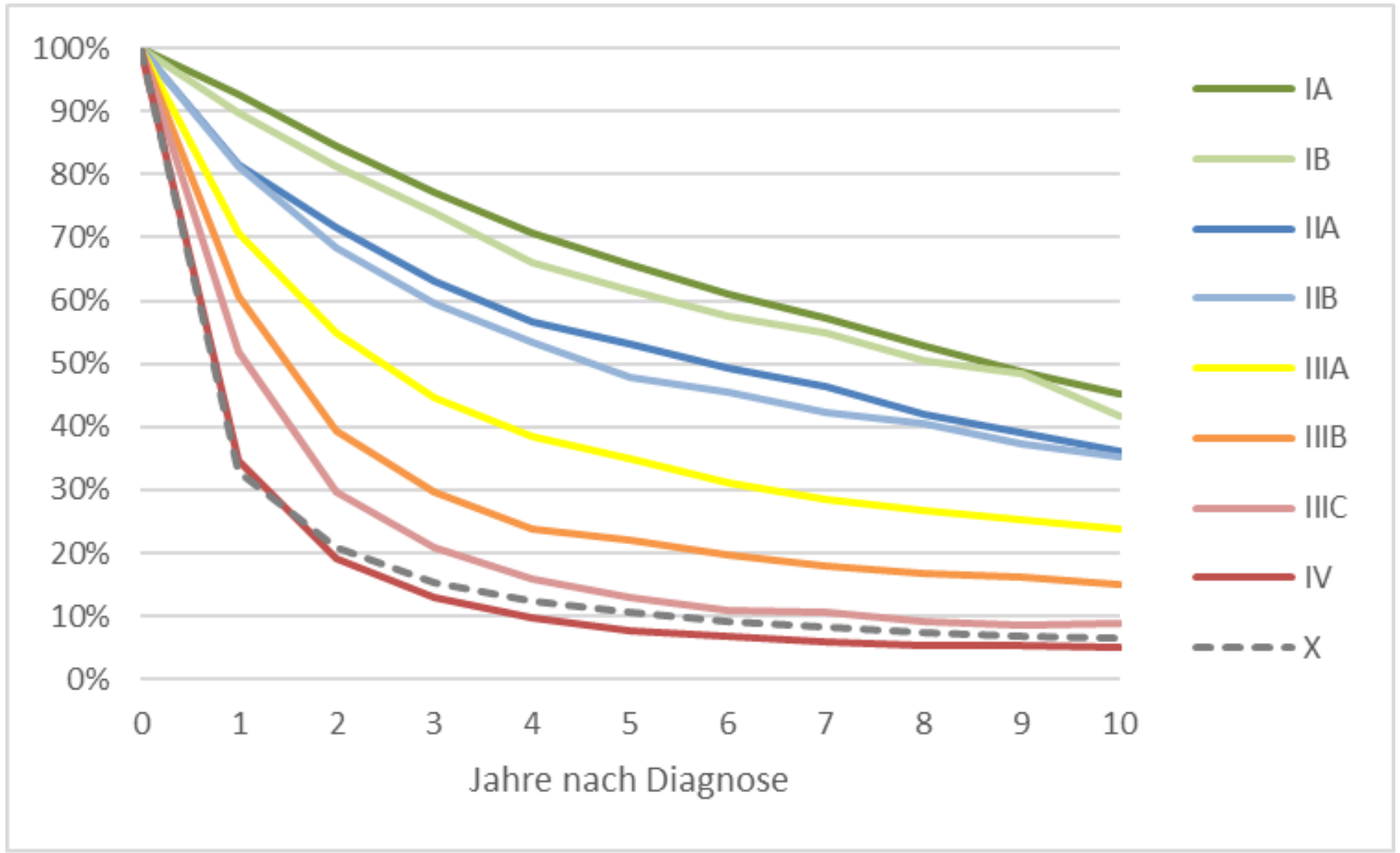
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Jahre nach Diagnose
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IIIB
IIIC
IV
X

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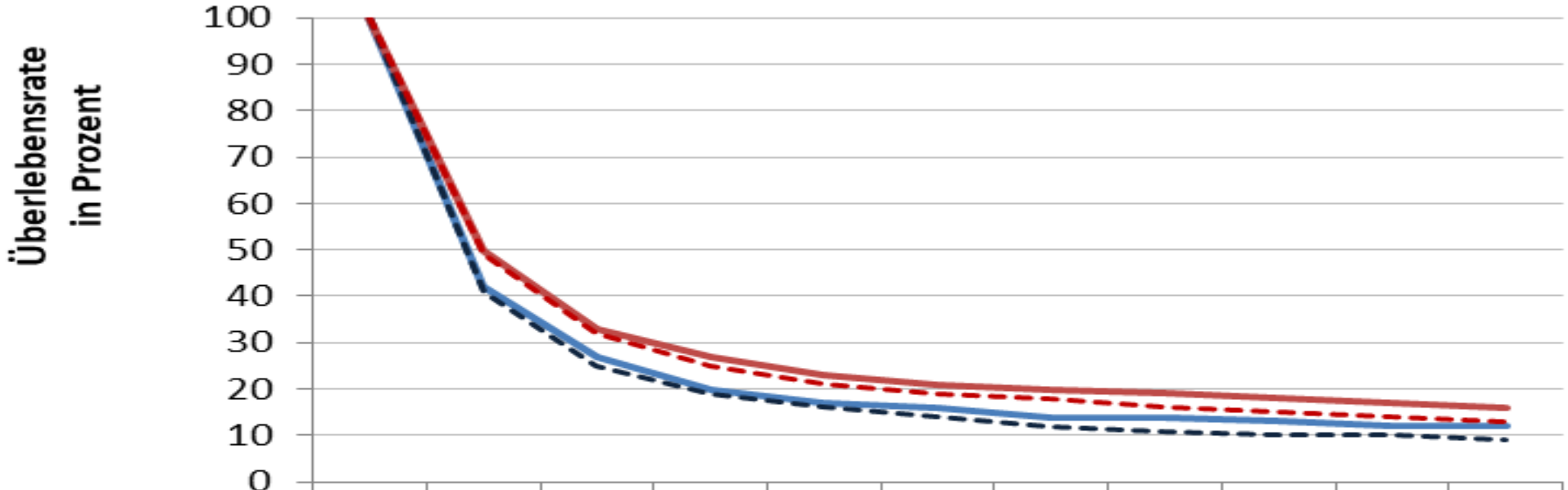
Absolute und relative Überlebensraten 2015/2016

Lungenkrebs (ICD10: C33-C34) in Deutschland

GEKID



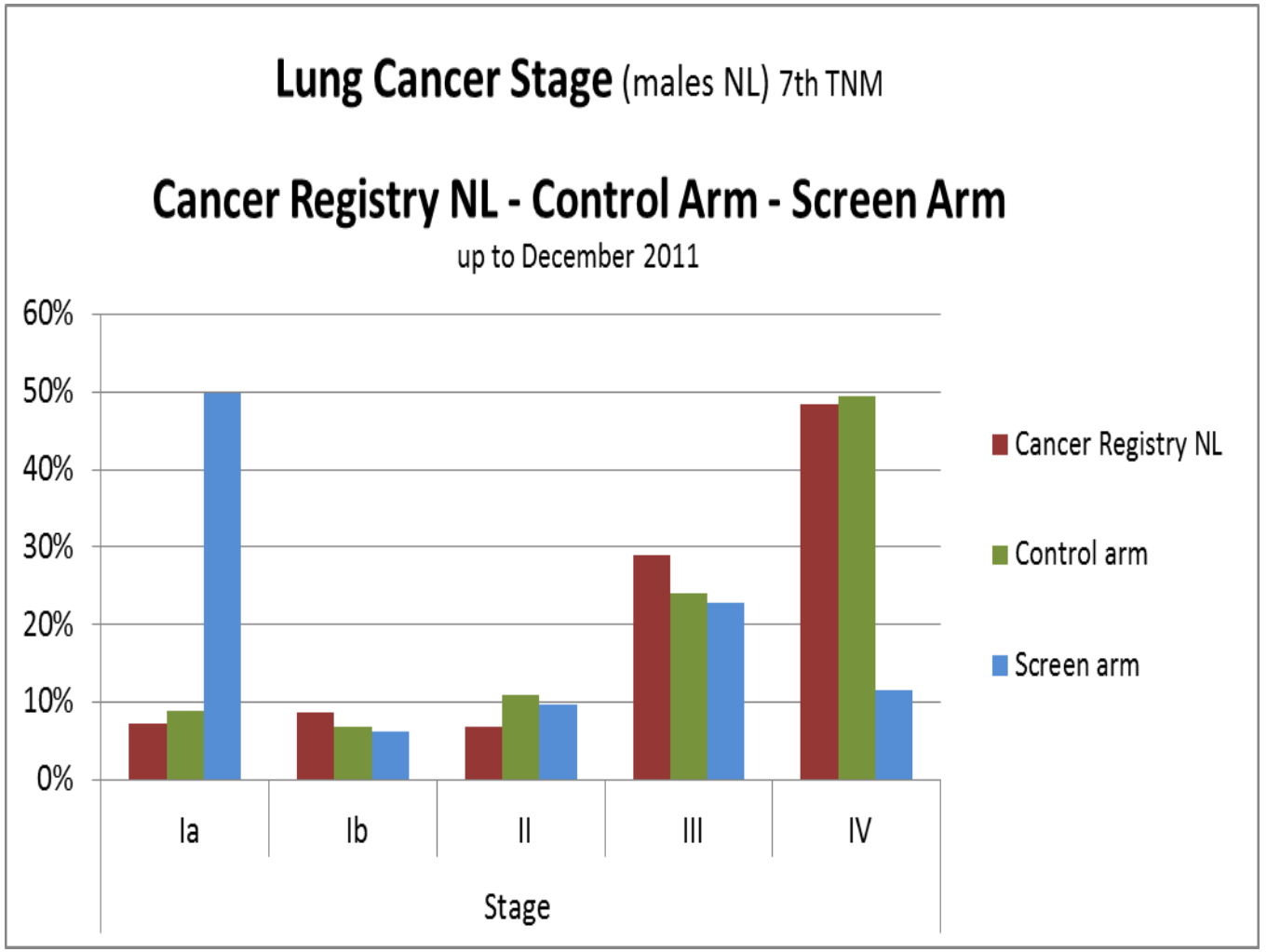
	0	1	2	3	4	5	6	7	8	9	10
Relative Überlebensrate Männer	100	42	27	20	17	16	14	14	13	12	12
Relative Überlebensrate Frauen	100	50	33	27	23	21	20	19	18	17	16
Absolute Überlebensrate Männer	100	41	25	19	16	14	12	11	10	10	9
Absolute Überlebensrate Frauen	100	49	32	25	21	19	18	16	15	14	13

Jahre

Histologische Einteilung

Plattenepithelkarzinom	verhornend	
	nicht verhornend (p40+, TTF1-)	(p40+, TTF1-)
	basaloid	p40+/TTF1-
Adenokarzinom	präinvasiv	<3cm mit <5mm Invasion
	minimal invasiv	
	invasiv G1 lepidisch G2 azinär, papillär G3 mikropapillär, solide	
	Varianten	
Großzelliges Karzinom		
Neuroendokrine Tumore	Karzinoid typisches Karzinoid atypisches Karzinoid	siehe auch Onkopedia neuroendokrine Neoplasien
	kleinzelliges Karzinoid (SCLC9)	
	großzelliges neuroendokrines Karzinom (LCNEC)	

NELSON Screening Studie bei Hoch-Risiko-Personen



Screening wird derzeit betreffs der Ausführungsbestimmungen bearbeitet, Beginn wohl 2022 oder 2023

Lungenkarzinom-Mortalitäts-rate (95% CI)	Jahr 8	Jahr 9	Jahr 10
Männer	**0.75** P=0.015 (0.59-0.95)	**0.76** P=0.012 (0.60-0.95)	**0.74** P=0.003 (0.60-0.91)
Frauen	**0.39** P=0.0037 (0.18-0.78)	**0.47** P=0.0069 (0.25-0.84)	**0.61** P=0.0543 (0.35-1.04)

Rand: 23-12-2003 – 06-07-2006

FU: 23-12-2003 – 31-12-2015

FU 94% complete year 10

Screening: timelines in 2022

Oktober 2020: Positive Nutzen-Risiko Bewertung des Niedrigdosis-CT-Screenings durch das IQWIG

Dezember 2021: BfS: positive Einschätzung des Nutzen-Risiko-Verhältnisses, unter strengen Bedingungen.

Seit Dezember 2021: politische Diskussionen zwischen G-BA und BfS

Ende 2022: erforderliche Genehmigung durch Bundesministerium für Umweltschutz, Naturschutz, nukleare Sicherheit und Verbraucherschutz (BMUV) wird erwartet.

Ende 2022 + 18 Monate: G-BA: genaue Ausführungsbestimmungen für die Lungenkrebsfrüherkennungsmaßnahme mittels LDCT.

2024: frühester Beginn eines nationalen Früherkennungsprogramms für Lungenkarzinom: derzeit als IGEL Leistung für Selbstzahler möglich

2025 / 2026: Beginn des bundesweiten Screenings??

Diagnostik

Notwendige Staging-Untersuchungen bei NSCLC

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Untersuchung	Primär-tumor	Mediastinale LK	Fern-Metastasen Gehirn	Knochen	Abdomen
Röntgen Thorax	X			X	
Sonographie					X
CT Thorax/Abdomen	X	X			X
MRT (CT)			X		
Skelettszintigraphie				X	
Bronchoskopie	X				
EBUS/EUS		X			
Mediastinoskopie		X			
18FDG-PET (s. Abb.)	X	X		X	X

Therapie

Neu: 2022

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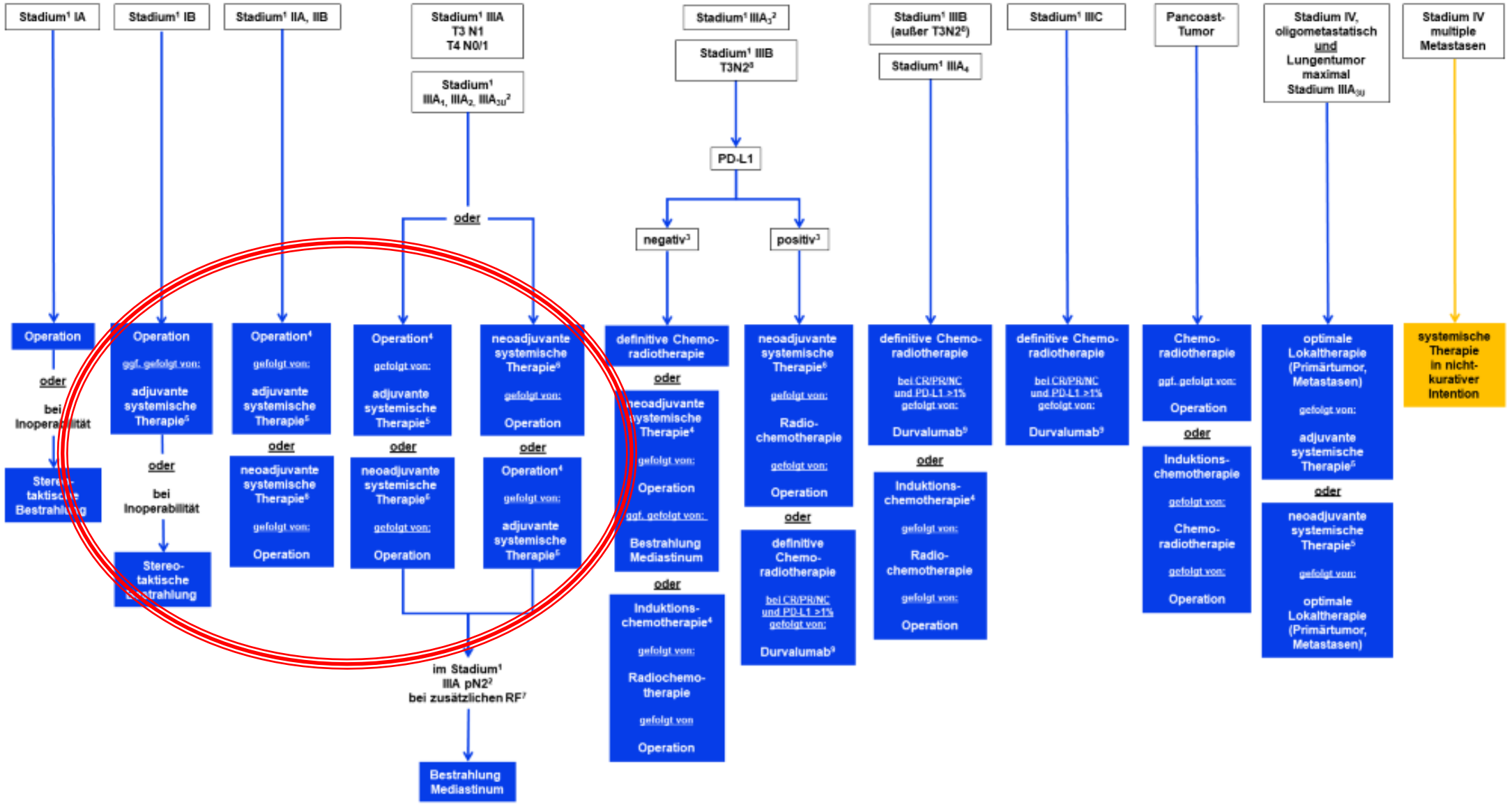
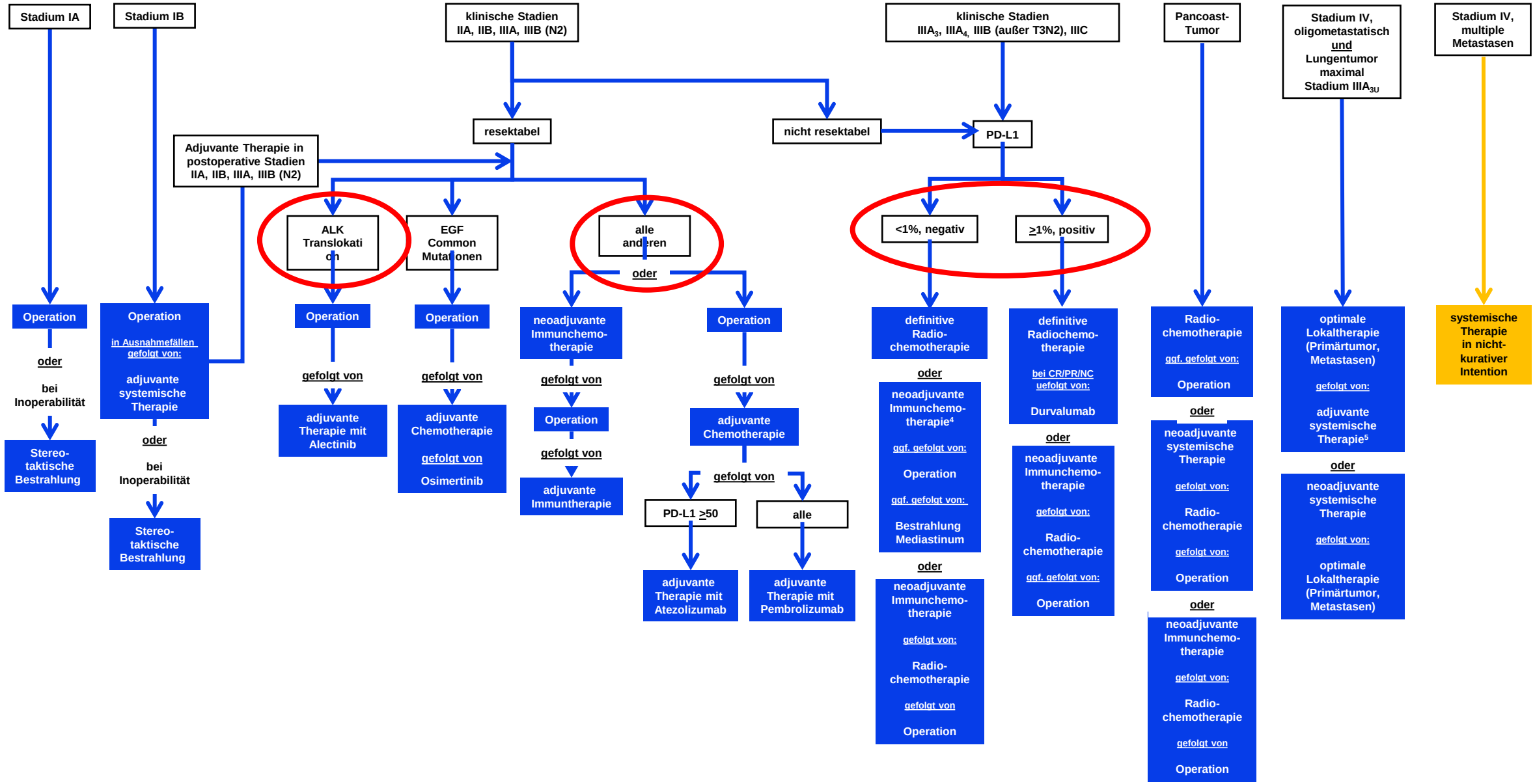


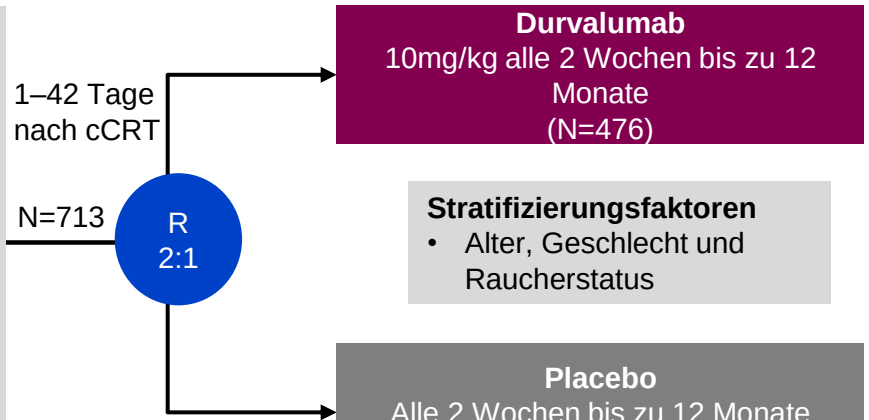
Therapie


Stadium IA
Stadium IB
klinische Stadien IIA, IIB, IIIA, IIIB (N2)
klinische Stadien IIIA3, IIIA4, IIIB (außer T3N2), IIIC
Pancoast-Tumor
Stadium IV, oligometastatisch und Lungentumor maximal Stadium IIIA3U
Stadium IV, multiple Metastasen
Operation
oder
bei Inoperabilität
Stereo-taktische Bestrahlung
Operation
in Ausnahmefällen gefolgt von:
adjuvante systemische Therapie
oder
bei Inoperabilität
Stereo-taktische Bestrahlung
Adjuvante Therapie in postoperative Stadien IIA, IIB, IIIA, IIIB (N2)
resektabel
nicht resektabel
PD-L1
ALK Translokation
EGF Common Mutationen
alle anderen
oder
Operation
gefolgt von
adjuvante Therapie mit Alectinib
Operation
gefolgt von
adjuvante Chemotherapie
gefolgt von
Osimertinib
neoadjuvante Immunchemo-therapie
gefolgt von
Operation
gefolgt von
adjuvante Immuntherapie
Operation
gefolgt von
adjuvante Chemotherapie
gefolgt von
PD-L1 ≥50
alle
adjuvante Therapie mit Atezolizumab
adjuvante Therapie mit Pembrolizumab
<1%, negativ
≥1%, positiv
definitive Radio-chemotherapie
oder
neoadjuvante Immunchemo-therapie4
ggf. gefolgt von:
Operation
ggf. gefolgt von:
Bestrahlung Mediastinum
oder
neoadjuvante Immunchemo-therapie
gefolgt von:
Radio-chemotherapie
gefolgt von
Operation
definitive Radiochemo-therapie
bei CR/PR/NC uefolgt von:
Durvalumab
oder
neoadjuvante Immunchemo-therapie
gefolgt von:
Radio-chemotherapie
ggf. gefolgt von:
Operation
Radio-chemotherapie
ggf. gefolgt von:
Operation
oder
neoadjuvante systemische Therapie
gefolgt von:
Radio-chemotherapie
gefolgt von:
Operation
oder
neoadjuvante Immunchemo-therapie
gefolgt von:
Radio-chemotherapie
gefolgt von
Operation
optimale Lokaltherapie (Primärtumor, Metastasen)
gefolgt von:
adjuvante systemische Therapie5
oder
neoadjuvante systemische Therapie
gefolgt von:
optimale Lokaltherapie (Primärtumor, Metastasen)
systemische Therapie in nicht-kurativer Intention

Randomisierte, doppelblinde, Placebo-kontrollierte, multizentrische, internationale Phase-III-Studie

Haupteinschlusskriterien
- Nicht-resezierbares, lokal fortgeschrittenes NSCLC Stadium III ohne Progression nach definitiver platinbasierter cCRT* (≥2 Zyklen)
- ≥18 Jahre
- WHO PS Score 0 oder 1
- Falls verfügbar, archiviertes Tumorgewebe vor cCRT für PD-L1-Testung**

All-comers Population
(d.h. unabhängig vom PD-L1-Status)



Stratifizierungsfaktoren
- Alter, Geschlecht und Raucherstatus

Ko-primäre Endpunkte
- PFS (per BICR) mittels RECIST v1.1***
- OS

Wichtigste sekundäre Endpunkte
- ORR, DoR und TTDM durch BICR mittels RECIST v1.1
- Sicherheit
- PROs

Aktualisierte Analysen von OS und PFS (~4 Jahre nach Randomisierung des letzten Patienten; geplantes exploratives Update)

- Die Behandlungseffekte für die ITT-Population wurden mittels stratifiziertem Log-Rank-Ansatz (mit Studien-Stratifizierungsfaktoren) geschätzt.
- Die Behandlungseffekte für Patienten-Subgruppen wurden anhand von nicht stratifizierten Cox-Proportional-Hazard-Modellen (mit der Behandlung als einziger Kovariate) geschätzt.

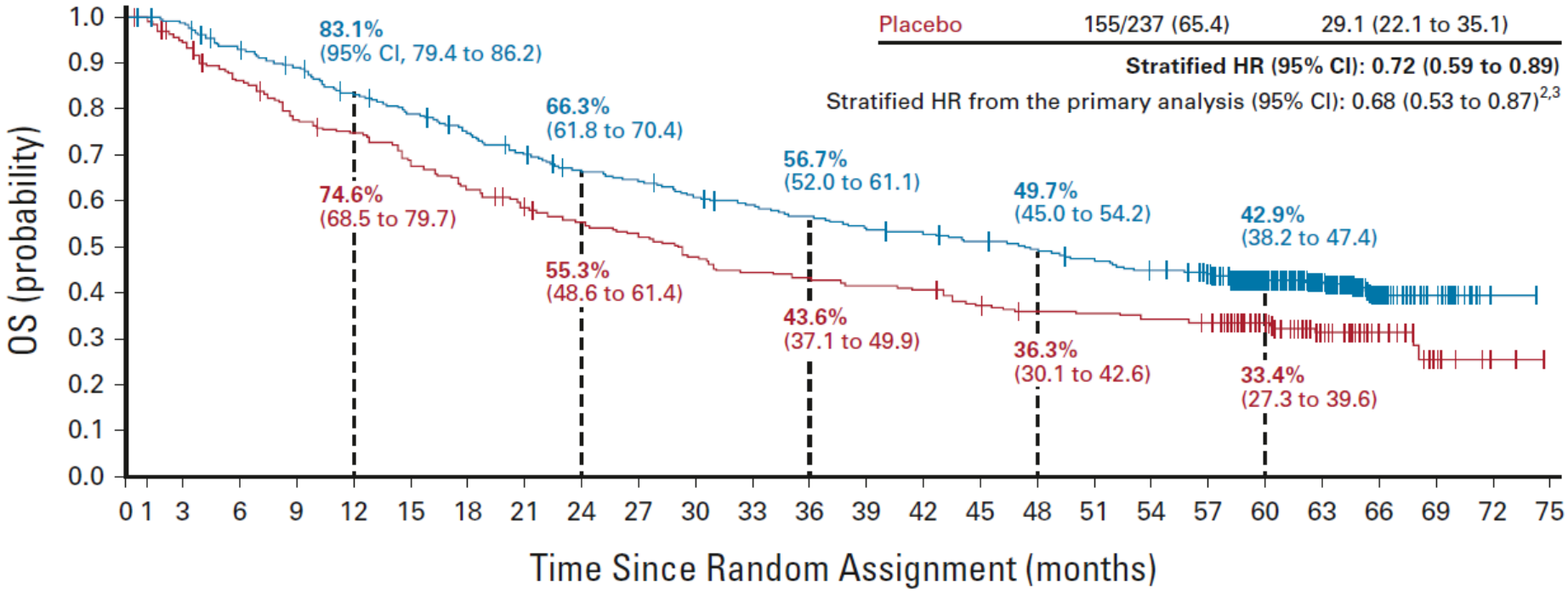
Pacific Update: Durvalumab Erhaltung Stadium III nach RTx-CT: alle Patienten

A

Arm	No. of Events/ Total No. of Patients (%)	Median OS (95% CI), Months
Durvalumab	264/476 (55.5)	47.5 (38.1 to 52.9)
Placebo	155/237 (65.4)	29.1 (22.1 to 35.1)

Stratified HR (95% CI): 0.72 (0.59 to 0.89)

Stratified HR from the primary analysis (95% CI): 0.68 (0.53 to 0.87)[2,3]

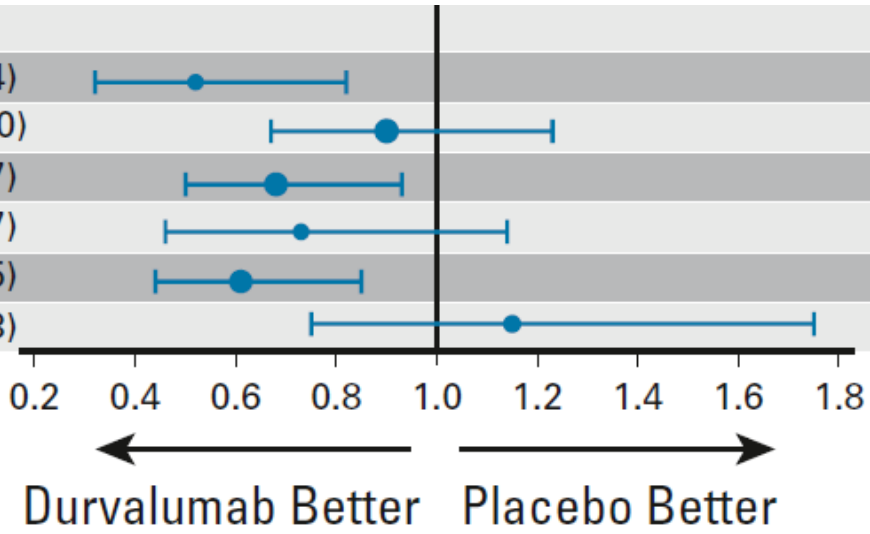


No. at risk:

Durvalumab	476	464	431	414	385	364	343	319	298	289	273	264	252	241	236	227	218	207	196	183	134	91	40	18	2	0
Placebo	237	220	199	179	171	156	143	133	123	116	107	99	97	93	91	83	78	77	74	72	56	33	16	7	2	0

OS 5 Jahre Durvalumab bei PD-L1 ≥1%: Zulassungsrelevant EMA

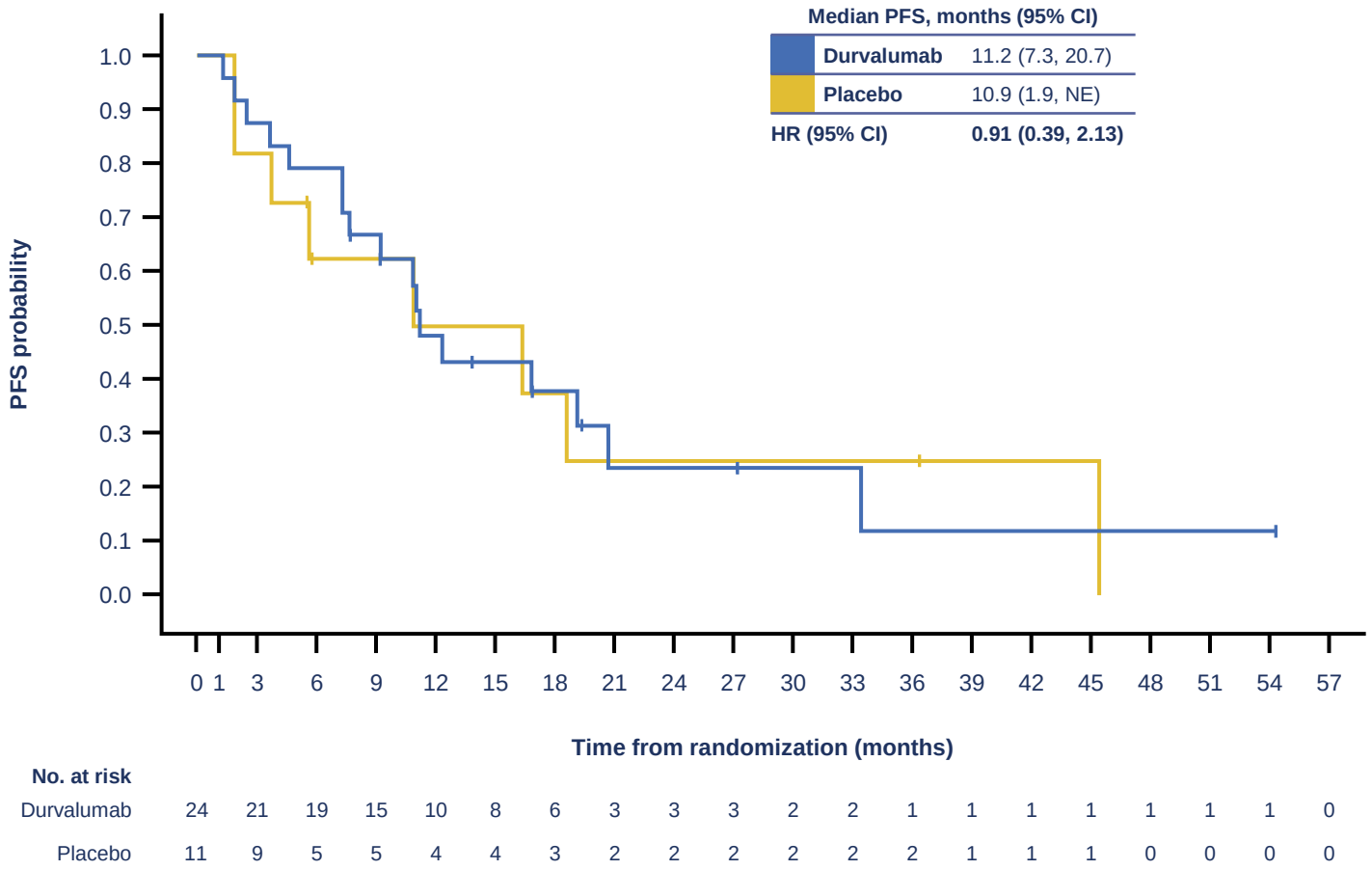
Group	No. of Events / No. of Patients (%) Durvalumab	Placebo	Unstratified HR (95% CI)
PD-L1 expression level			
≥ 25%	51/115 (44.3)	27/44 (61.4)	0.52 (0.32 to 0.82)
< 25%	111/187 (59.4)	64/105 (61.0)	0.90 (0.67 to 1.23)
Unknown	102/174 (58.6)	64/88 (72.7)	0.68 (0.50 to 0.93)
1%-24% (post hoc analysis)	52/97 (53.6)	29/47 (61.7)	0.73 (0.46 to 1.14)
≥ 1% (post hoc analysis)	103/212 (48.6)	56/91 (61.5)	0.61 (0.44 to 0.85)
< 1% (post hoc analysis)	59/90 (65.6)	35/58 (60.3)	1.15 (0.75 to 1.75)



Unmet need in unresectable stage III EGFRm NSCLC

- In unresectable stage III NSCLC following CRT without progression, standard of care is consolidation durvalumab
- Benefit of consolidation durvalumab in EGFRm NSCLC is uncertain based on PACIFIC *post-hoc* subgroup analysis
- Efficacy of EGFR-TKIs is supported by the Phase 2 RECEL study and real-world data but prospective Phase 3 data are needed
- No approved targeted therapies for unresectable stage III EGFRm NSCLC

PACIFIC EGFRm *post-hoc* subgroup analysis



Daly et al. J Clin Oncol 2022;40:1356–1384; Remon et al. Ann Oncol 2021;32:1637–1642; Naidoo et al. J Thorac Oncol 2023;18:657–663; Xing et al. Int J Rad Oncol Biol Phys 2021;109:1349–1358; Sun et al. BMC Cancer 2020;20:646; Aredo et al. J Thorac Oncol 2021;16:1994–1998; Nassar et al. J Thorac Oncol 2024; S1556-0864(24)00032-7.

CI, confidence interval; CRT, chemoradiotherapy; EGFR, epidermal growth factor receptor; EGFRm, EGFR-mutated; HR, hazard ratio; NSCLC, non-small cell lung cancer; NE, not evaluable; PFS progression-free survival; TKI, tyrosine kinase inhibitor

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§

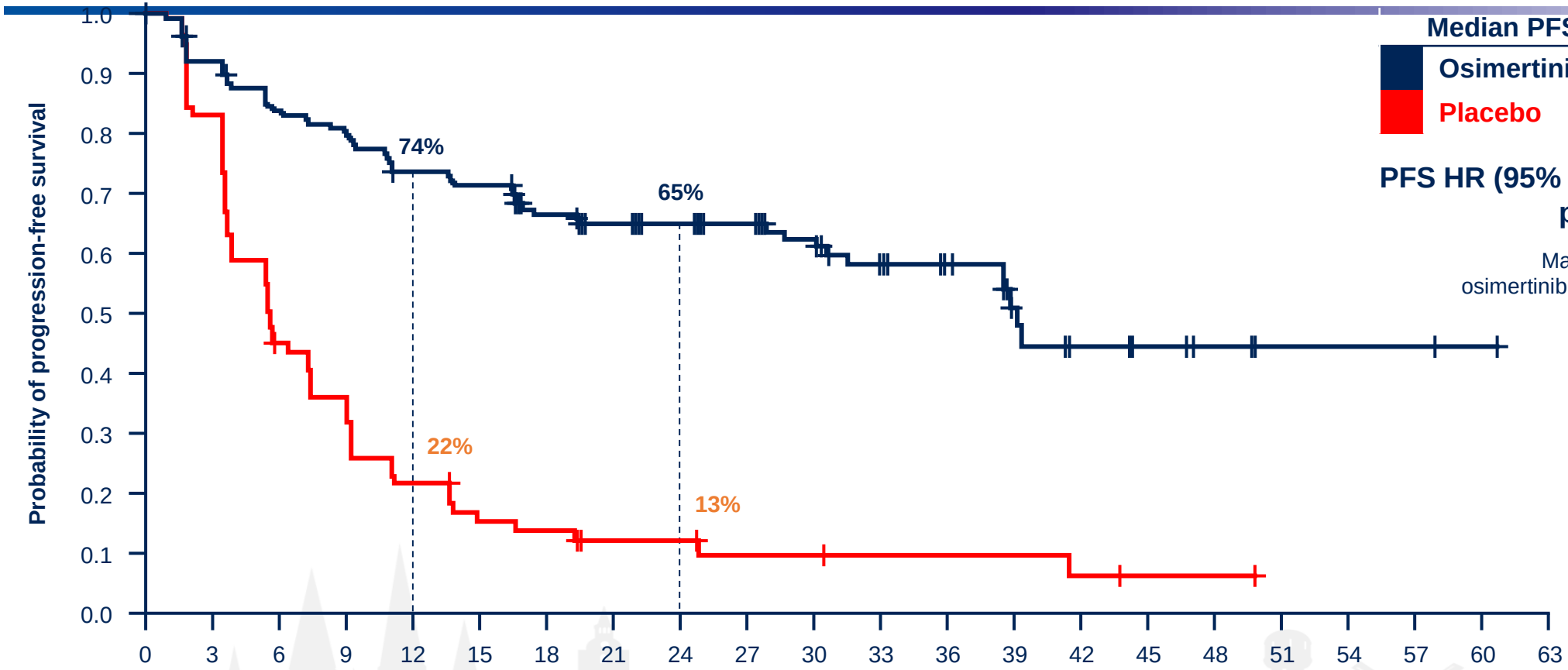
Tumor assessments:
- Chest CT / MRI and brain MRI
- At baseline, every 8 weeks to Week 48, then every 12 weeks until BICR-assessed progression

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;

Progression-free survival by BICR



Median PFS, months (95% CI)

Osimertinib	39.1 (31.5, NC)
Placebo	5.6 (3.7, 7.4)

PFS HR (95% CI): 0.16 (0.10, 0.24), p<0.001

Maturity 56%:
osimertinib 40%, placebo 86%

No. at risk

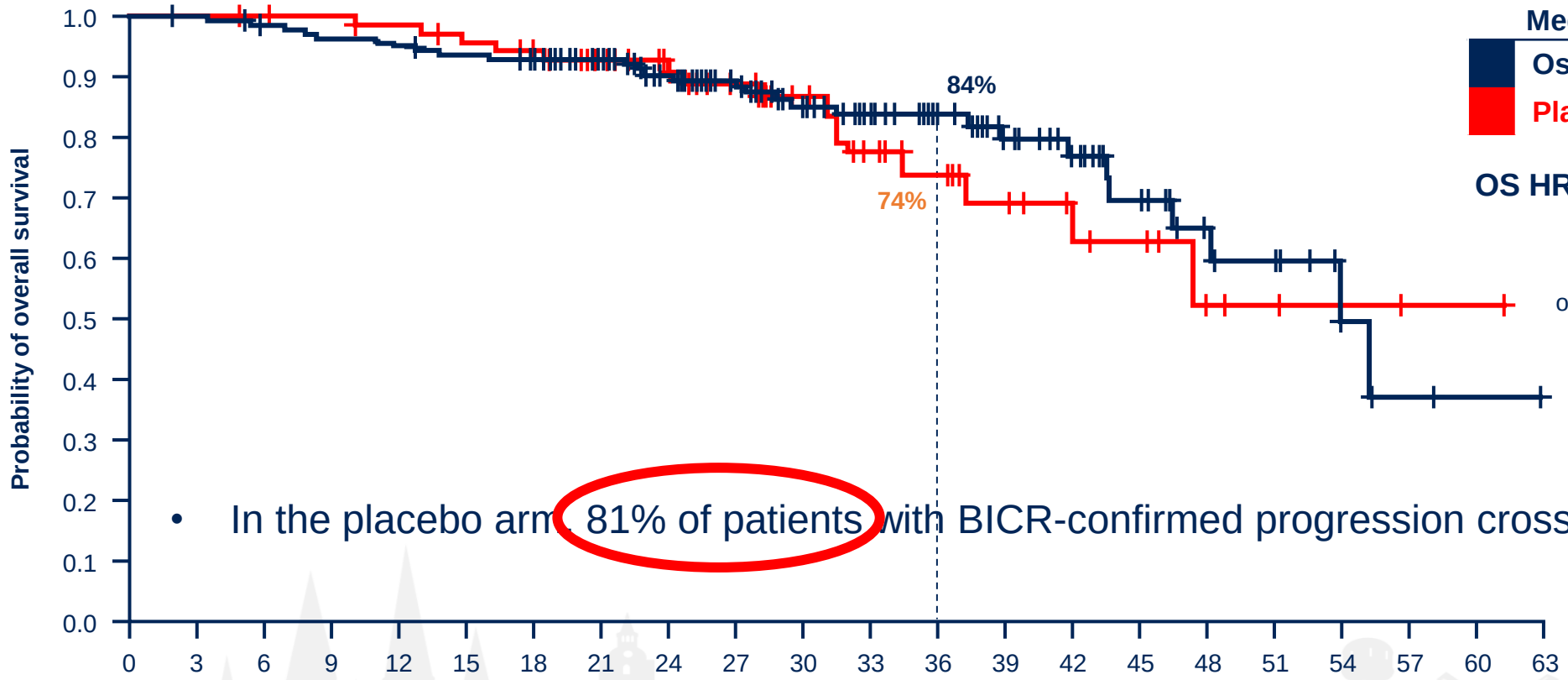
Osimertinib	143	127	114	109	99	96	83	76	69	61	49	37	28	16	9	6	4	2	2	2	1	0
Placebo	73	59	31	25	15	10	9	6	6	4	4	3	3	3	2	1	1	0	0	0	0	0

Data cut-off: January 5, 2024.

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

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

Interim analysis of overall survival



Median OS, months (95% CI)

Osimertinib	54.0 (46.5, NC)
Placebo	NR (42.1, NC)

OS HR (95% CI): 0.81 (0.42, 1.56), p=0.530*

Maturity 20%:
osimertinib 20%, placebo 21%

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

No. at risk

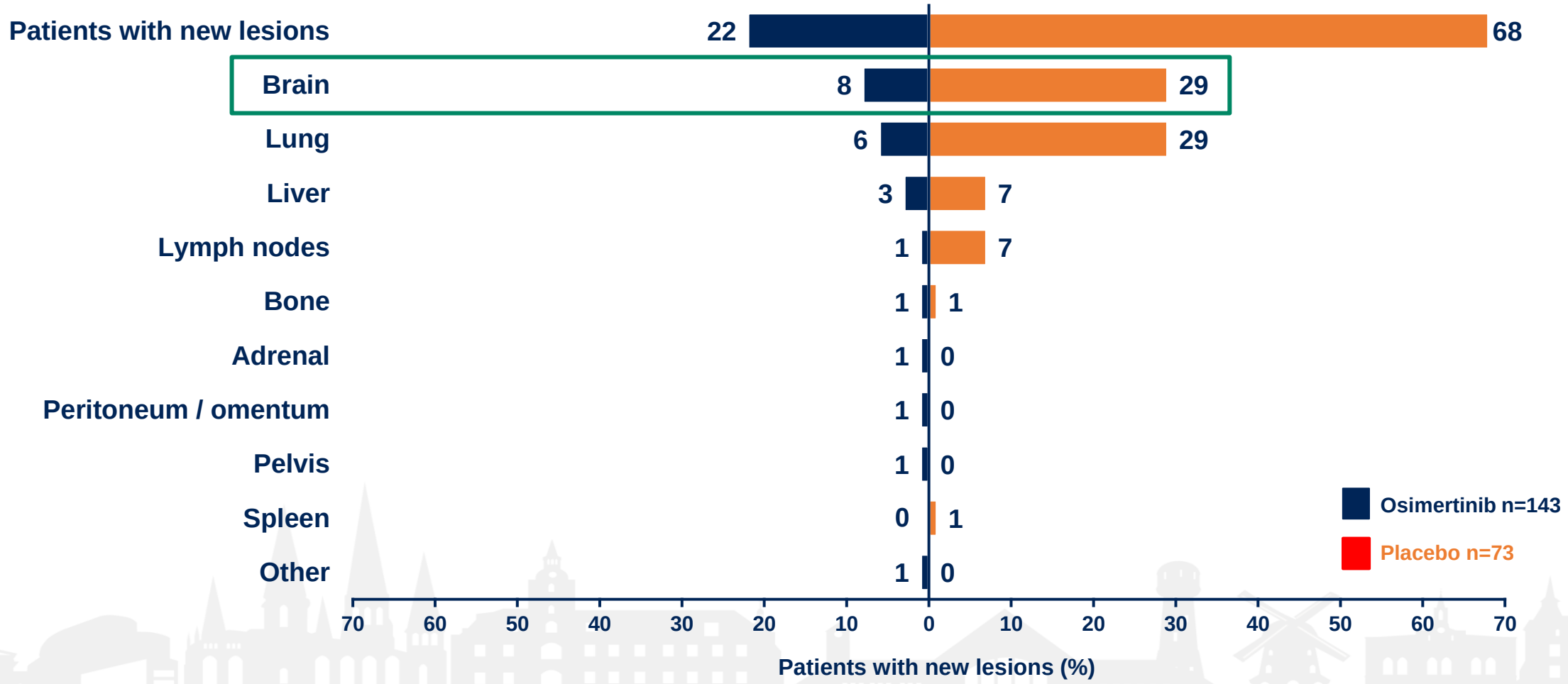
Osimertinib	143	142	138	135	133	130	127	115	100	86	71	59	49	37	28	19	12	9	4	2	1	0
Placebo	73	73	71	70	68	65	62	58	48	41	30	23	19	15	11	9	4	3	2	1	1	0

Data cut-off: January 5, 2024.

Tick marks indicate censored data. *For statistical significance at this interim analysis, a p-value of <0.00036 was required.
Median follow-up for OS (all patients): osimertinib 29.5 months, placebo 28.1 months. Median follow-up for OS (censored patients): osimertinib 30.9 months, placebo 28.1 months.

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

Sites of new lesions by BICR



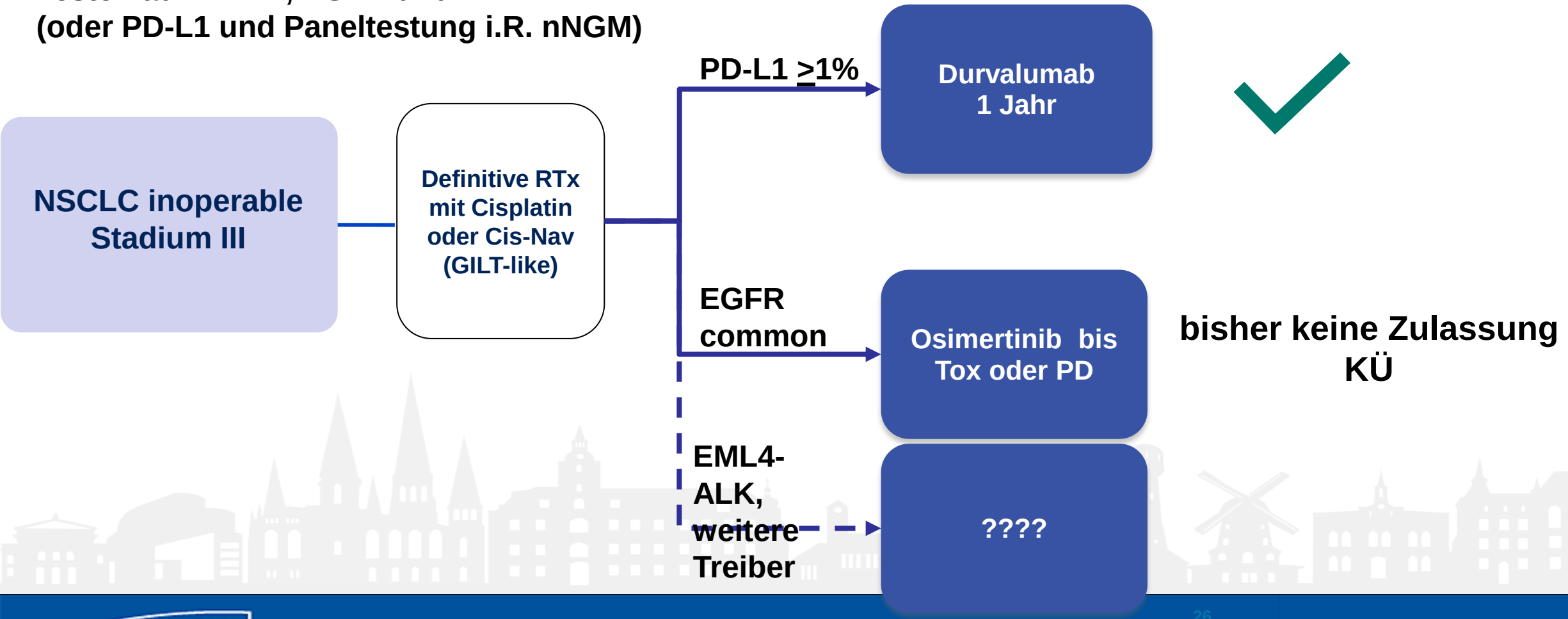
Percentages based on number of patients in each treatment arm. Patients can have more than one new lesion site. Based on BICR assessments according to RECIST v1.1 and includes all new lesions at any time (including those whose RECIST progression event had been censored).

Data cut-off: January 5, 2024.

BICR, blinded independent central review

Konsolidierung nach RTx-CTx bei inoperablen Patienten

Testen auf PD-L1, EGFR und ALK
(oder PD-L1 und Paneltestung i.R. nNGM)



bisher keine Zulassung KÜ

ADAURA Phase III double-blind study design

Patients with completely resected stage* IB, II, IIIA NSCLC, with or without adjuvant chemotherapy†

Key inclusion criteria:
≥18 years (Japan / Taiwan: ≥20)
WHO performance status 0 / 1
Confirmed primary non-squamous NSCLC Ex19del / L858R‡
Brain imaging, if not completed pre-operatively
Complete resection with negative margins§
Max. interval between surgery and randomization:
- 10 weeks without adjuvant chemotherapy
- 26 weeks with adjuvant chemotherapy

Stratification by:
stage (IB vs II vs IIIA)
EGFRm (Ex19del vs L858R)
race (Asian vs non-Asian)

Osimertinib 80 mg, once daily

Randomization 1:1 (N=682)

Placebo, once daily

Planned treatment duration: 3 years

Treatment continues until:
- Disease recurrence
- Treatment completed
- Discontinuation criterion met

Follow up:
- Until recurrence: Week 12 and 24, then every 24 weeks to 5 years, then yearly
- After recurrence: every 24 weeks for 5 years, then yearly

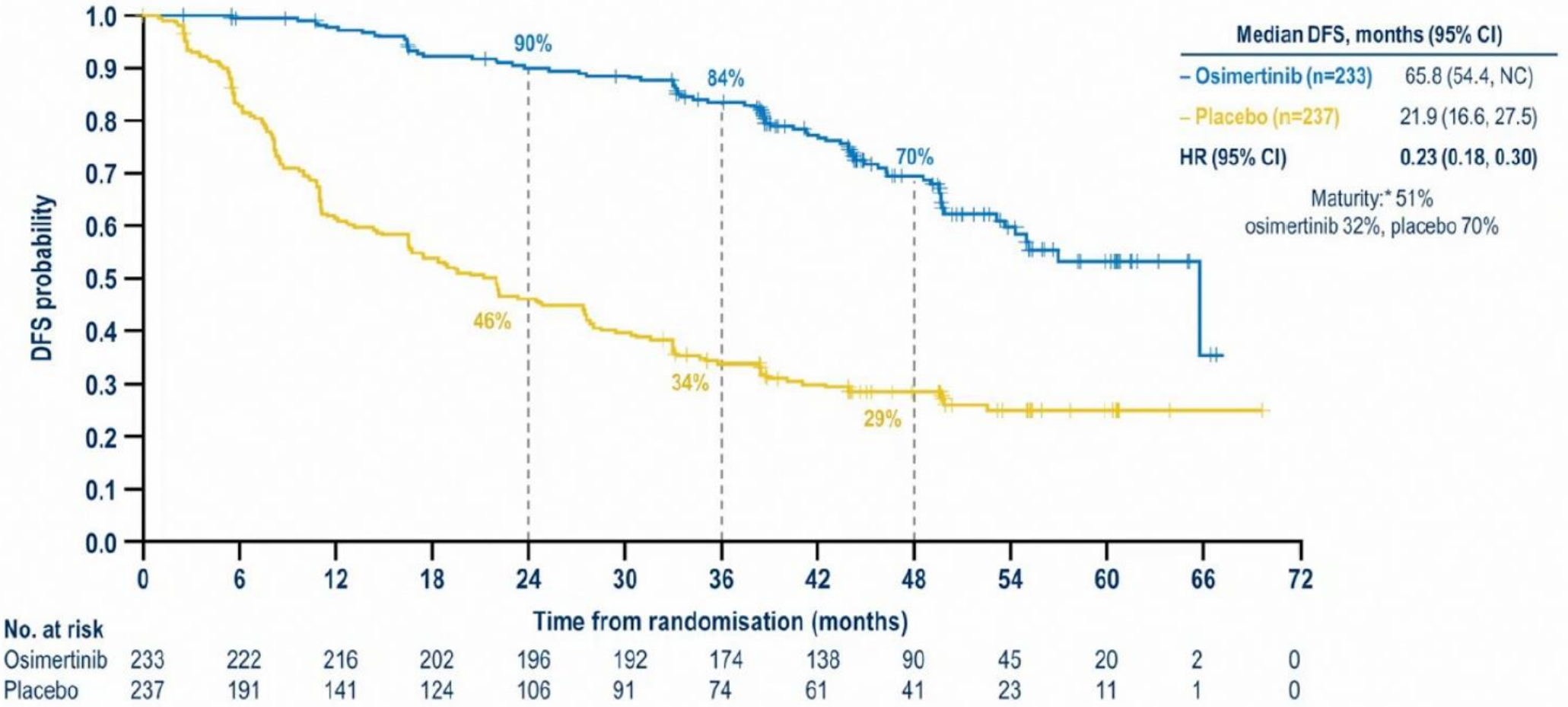
Endpoints

- **Primary**: DFS, by investigator assessment, in stage II/IIIA patients; designed for superiority under the assumed DFS HR of 0.70
- **Secondary**: DFS in the overall population¶, DFS at 2, 3, 4, and 5 years, OS, safety, health-related quality of life

- **Following IDMC recommendation, the study was unblinded early due to efficacy; here we report an unplanned interim analysis**
- **At the time of unblinding the study had completed enrollment and all patients were followed up for at least 1 year**

NCT02511106; ADAURA data cut-off: January 17, 2020. *AJCC 7th edition; †Prior, post, or planned radiotherapy was not allowed; ‡Centrally confirmed in tissue; §Patients received a CT scan after resection and within 28 days prior to treatment; ¶Stage IB / II / IIIA.
CT, computed tomography; Ex19del, exon 19 deletion; IDMC, Independent Data Monitoring Committee; WHO, World Health Organization.

PRIMARY ENDPOINT: UPDATED DFS IN STAGE II / IIIA DISEASE



No. at risk													
Osimertinib	233	222	216	202	196	192	174	138	90	45	20	2	0
Placebo	237	191	141	124	106	91	74	61	41	23	11	1	0

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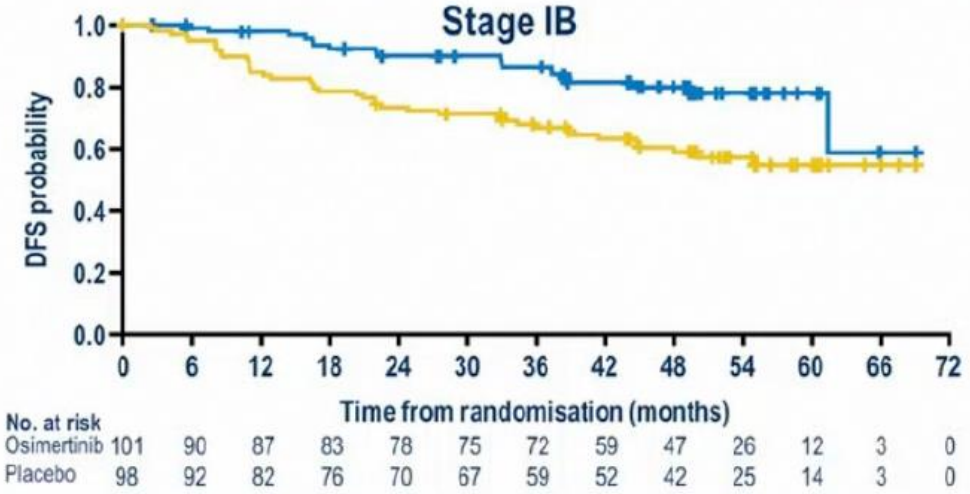
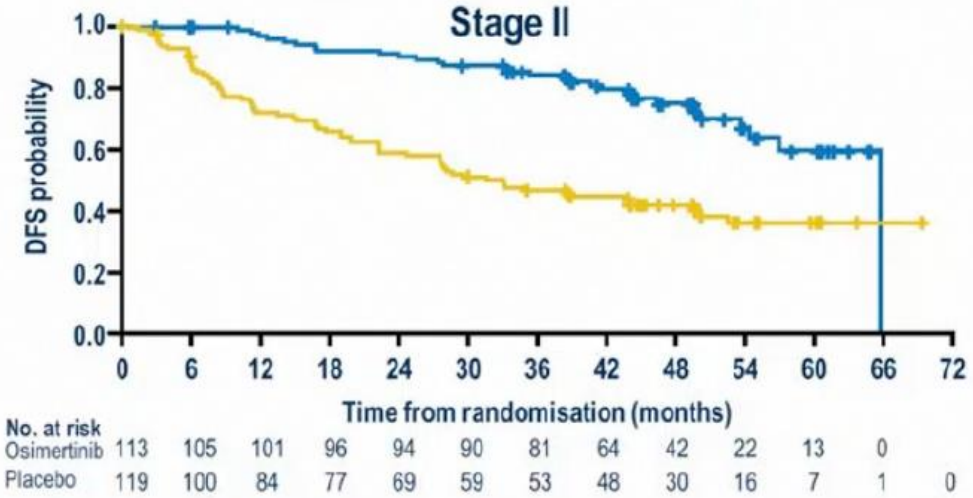
Median follow-up: osimertinib 44.2 months (range 0 to 67), placebo 19.6 months (range 0 to 70); DFS by investigator assessment; Tick marks indicate censored data. *Planned maturity for DFS analysis: 50%.

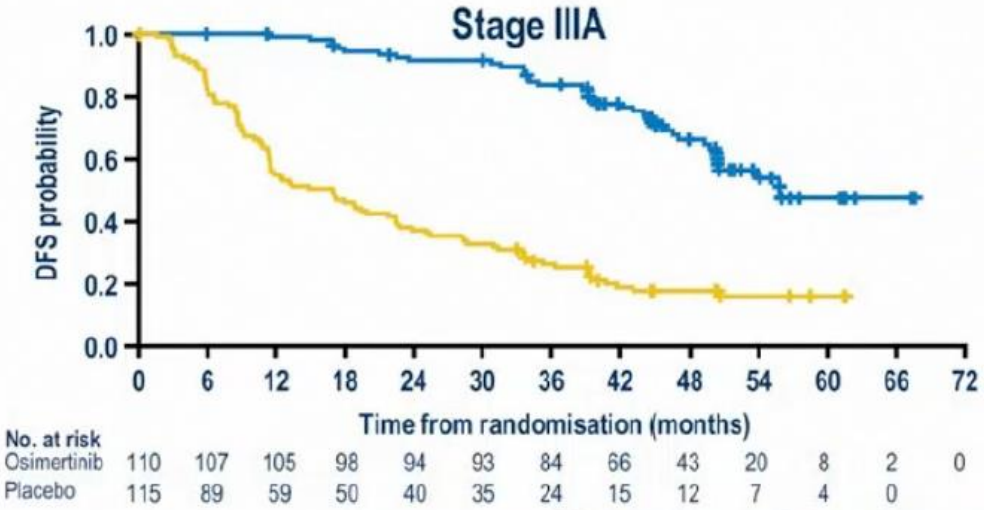
CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; NC, not calculable
Data cut-off: April 11, 2022.

UPDATED DFS BY STAGE (AJCC / UICC 8TH EDITION*)





	Stage IB	Stage II	Stage IIIA
4 year DFS rate, % (95% CI)			
– Osimertinib	80 (69, 87)	75 (65, 83)	66 (55, 75)
– Placebo	60 (49, 69)	43 (34, 52)	16 (10, 24)
Overall HR (95% CI)	0.44 (0.25, 0.76)	0.33 (0.21, 0.50)	0.22 (0.15, 0.31)



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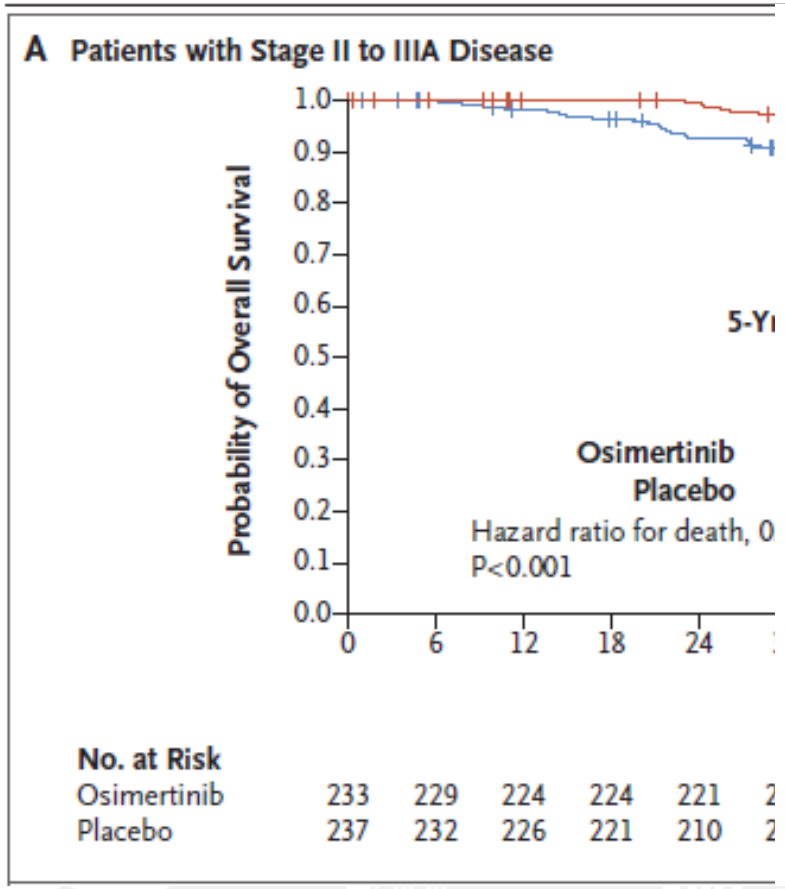
DFS by investigator assessment; Tick marks indicate censored data.

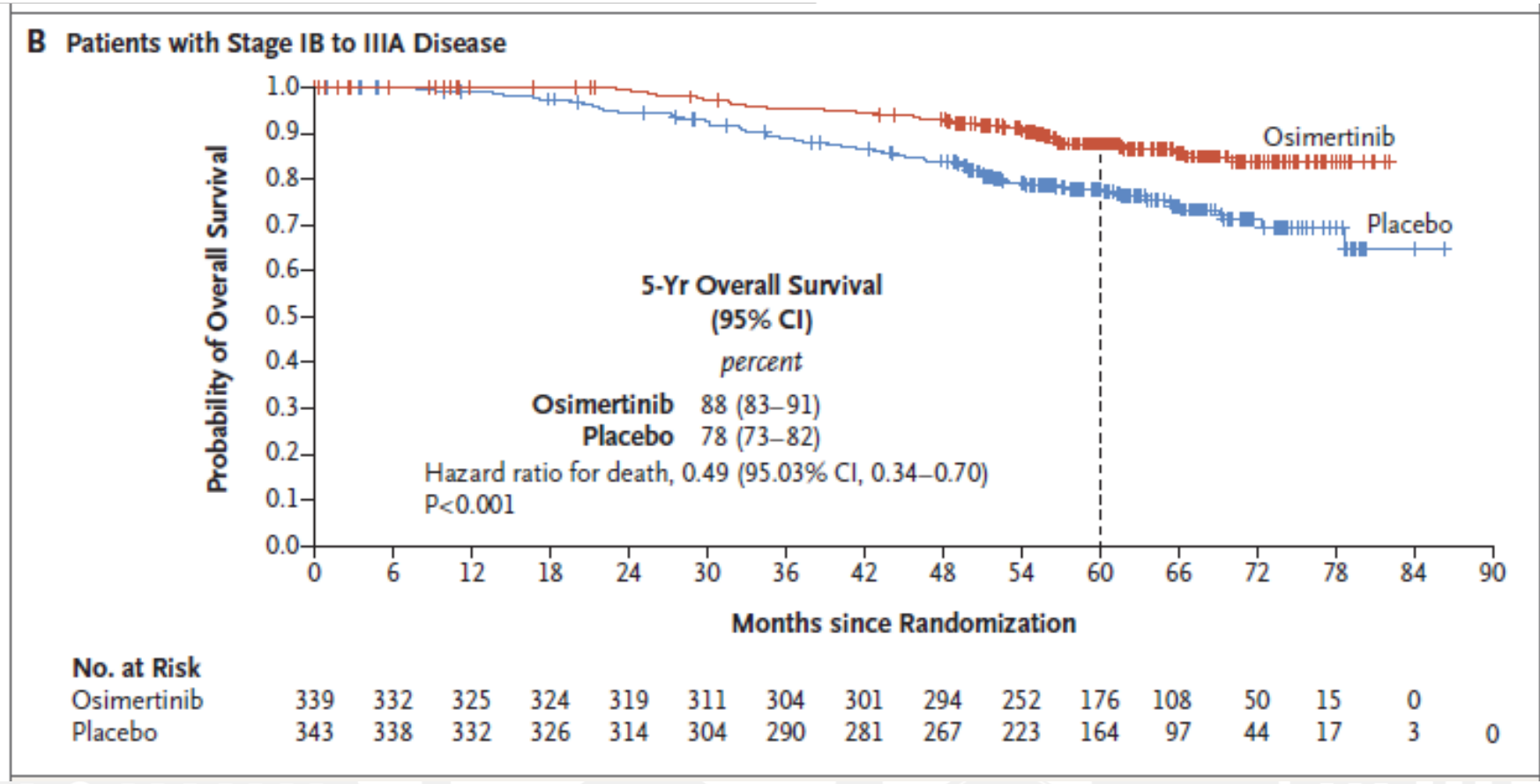
*Re-staging based on data captured in the Pathology at Diagnosis AJCC / UICC 8th edition manual, per investigator assessment requested before the primary analysis.

AJCC / UICC, American Joint Committee on Cancer / Union for International Cancer Control; CI, confidence interval; DFS, disease-free survival; HR, hazard ratio

Data cut-off: April 11, 2022.

Adaura: OS: 3 Jahre Osimertinib





Tsuboi et al., NEJM 2023

Subsequent treatments

- At data cut-off for this final OS analysis, 76 patients (22%) in the osimertinib arm and 184 patients (54%) in the placebo arm had received any subsequent anti-cancer treatment.
- 64/93 (78%) in the Osi arm and 174/205 (84%) in the placebo arm relapsed and got subsequent anti cancer treatment (at final DFS analysis)
- EGFR-TKIs were the most common subsequent anti-cancer treatment received across both arms; most frequently osimertinib

Subsequent treatments, n (%)	Osimertinib (n=339)	Placebo (n=343)
Patients who received subsequent anti-cancer treatment*	76 (22)	184 (54)
EGFR-TKIs	58 (76)	162 (88)
Osimertinib	31 (41)	79 (43)
Other EGFR-TKIs	28 (37)	114 (62)
Chemotherapy	20 (26)	46 (25)
Radiotherapy	30 (39)	53 (29)
Other anti-cancer treatments	12 (16)	29 (16)

Data cut-off: January 27, 2023.

Percentages of patients by treatment type are calculated from the number of patients who received a subsequent anti-cancer treatment. *Subsequent anti-cancer treatments were identified by medical review and included anti-cancer treatments with a start date on or after the date of discontinuation of study treatment, and before withdrawal from the study. Surgeries and procedures were not included. Patients could have received more than one subsequent anti-cancer treatment.

PRESENTED BY: Roy S. Herbst

EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; OS, overall survival

ALINA study design*

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

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

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

R 1:1

N=257

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

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

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

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

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

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

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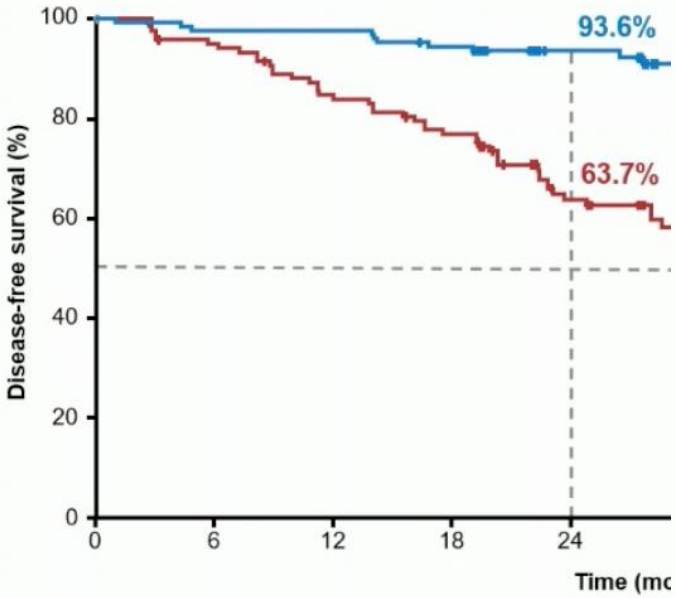
Data cut-off: 26 June 2023; CNS, central nervous system; DFS, disease-free survival; ITT, intention to treat
*Superiority trial; †Cisplatin + pemetrexed, cisplatin + vinorelbine or cisplatin + gemcitabine; cisplatin could be switched to carboplatin in case of intolerability; ‡DFS defined as the time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

ALINA: primärer Endpunkt

Disease-free survival: ITT (stage IB–IIIA)*



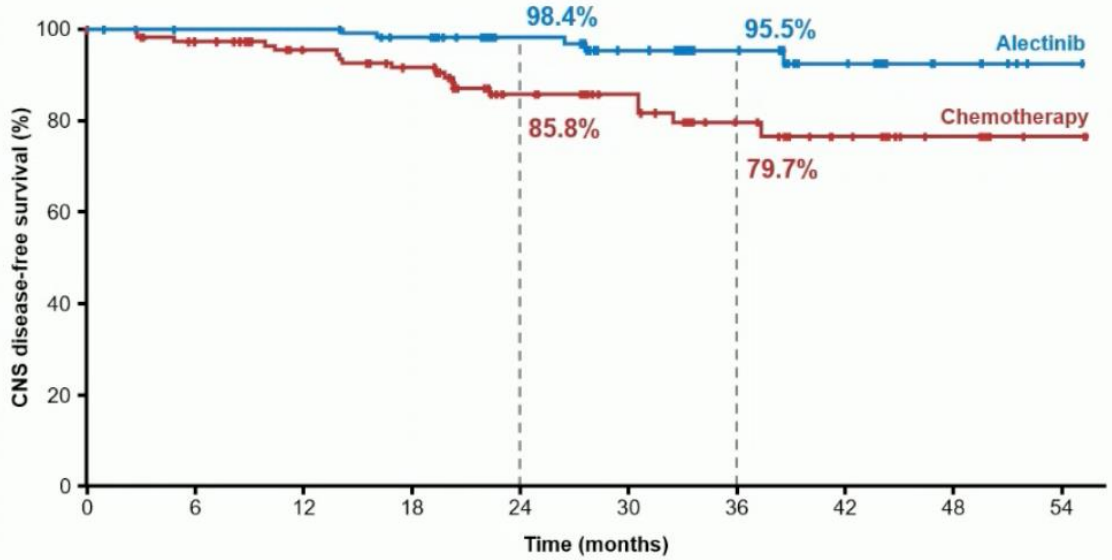
No. at risk

Alectinib	130	123	123	118	74
Chemo	127	112	98	89	55

Median survival follow

*Per a

CNS disease-free survival in the ITT population



No. at risk

Alectinib	130	124	124	118	74	55	39	22	10	3
Chemo	127	113	98	90	57	43	27	18	11	2

	Alectinib (N=130)	Chemotherapy (N=127)
Patients with event	5	18
Death	1	4
Brain recurrence	4	14
CNS-DFS HR* (95% CI)	**0.22** (0.08, 0.58)	

Median survival follow up: alectinib, 27.8 months; chemotherapy, 28.4 months

Data cut-off: 26 June 2023

*Stratified analysis with race and stage as stratification factors

CNS-DFS defined as time from randomisation to the first documented recurrence of disease in the CNS or death from any cause

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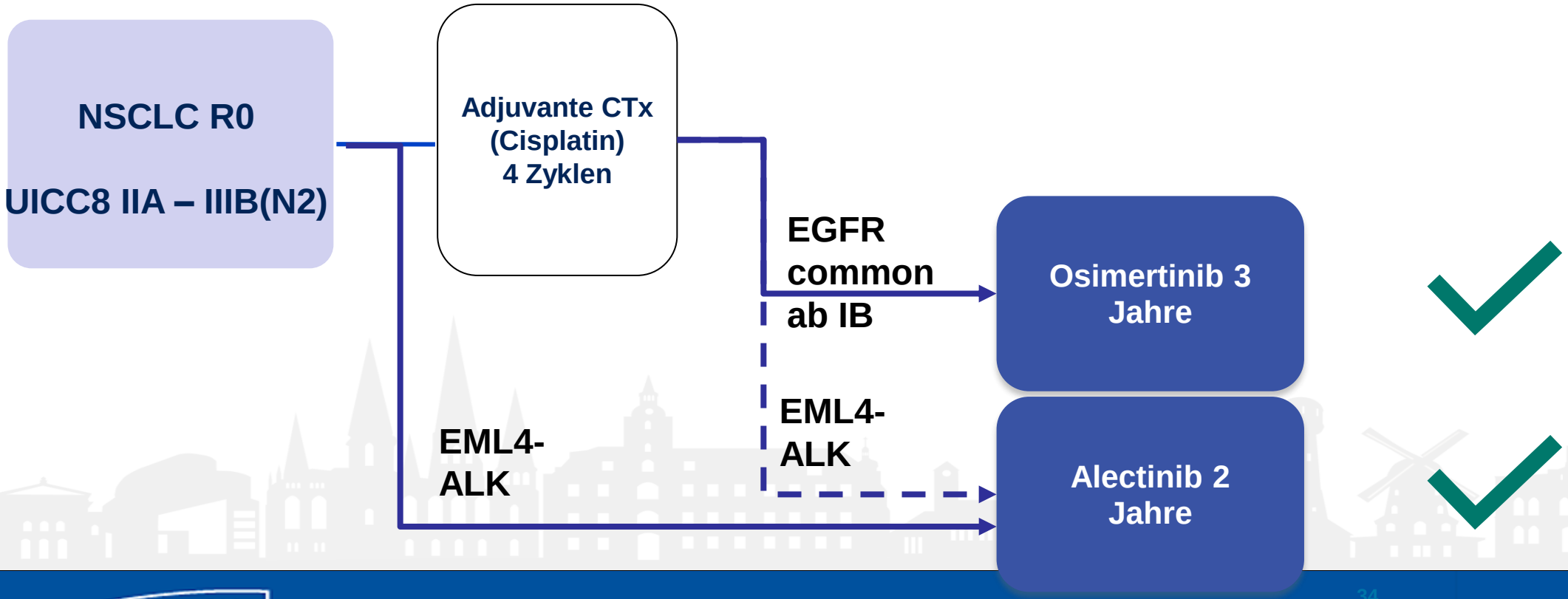
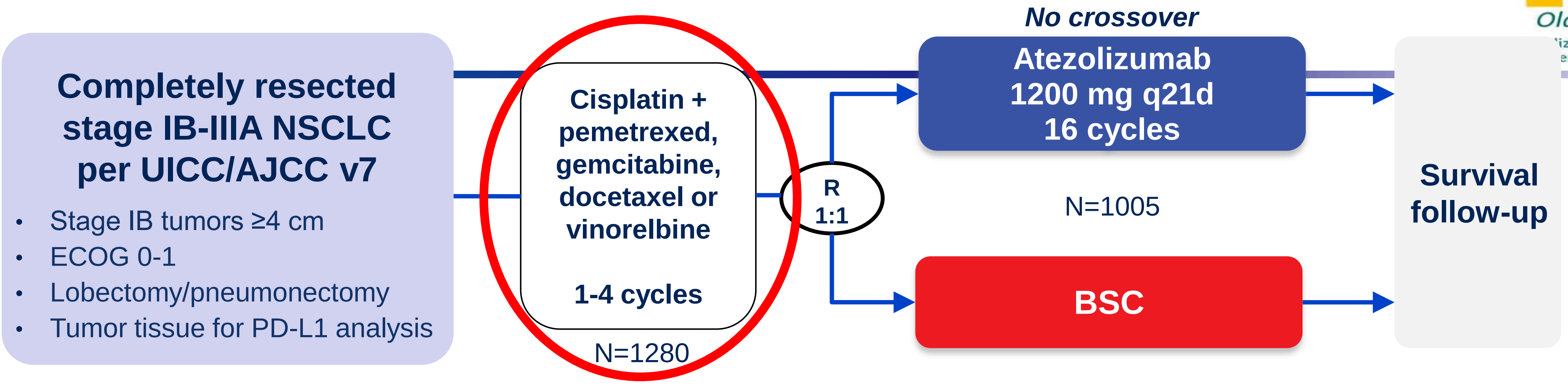
Solomn B et al, ESMO 2023

Adjuvanz

Testen auf PD-L1, EGFR und ALK
(oder PD-L1 und Paneltestung i.R. nNGM)



IMpower010: study design



Stratification factors
- Male/female
- Stage (IB vs II vs IIIA)
- Histology
- **PD-L1 tumor expression status[a]: TC2/3 and any IC vs TC0/1 and IC2/3 vs TC0/1 and IC0/1**

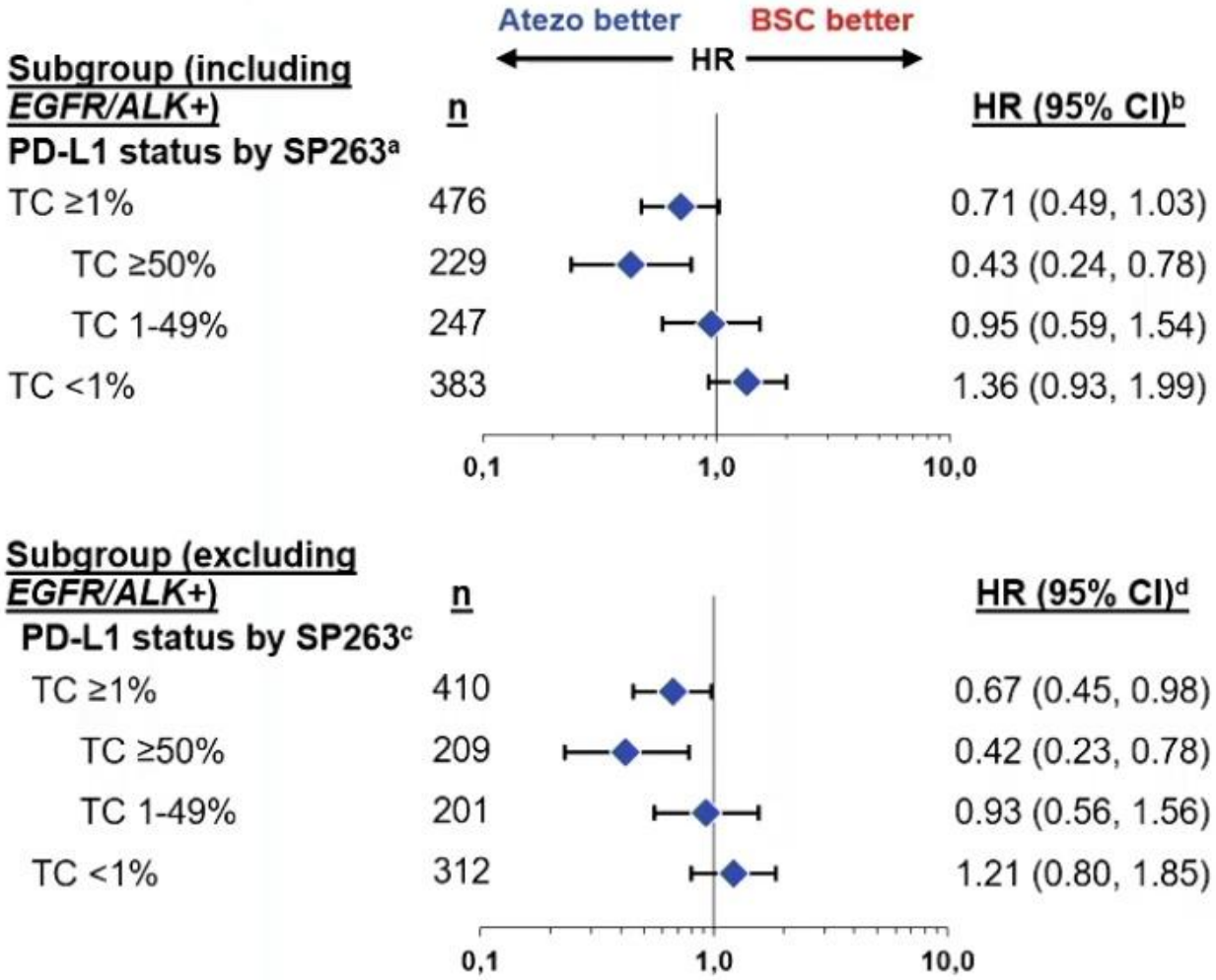
Primary endpoints
- Investigator-assessed DFS tested hierarchically:
  - **PD-L1 TC ≥1% (per SP263) stage II-IIIA population: post hoc**
  - **97% aller Patienten getestet**
  - All-randomized stage II-IIIA population
  - ITT population (stage IB-IIIA)

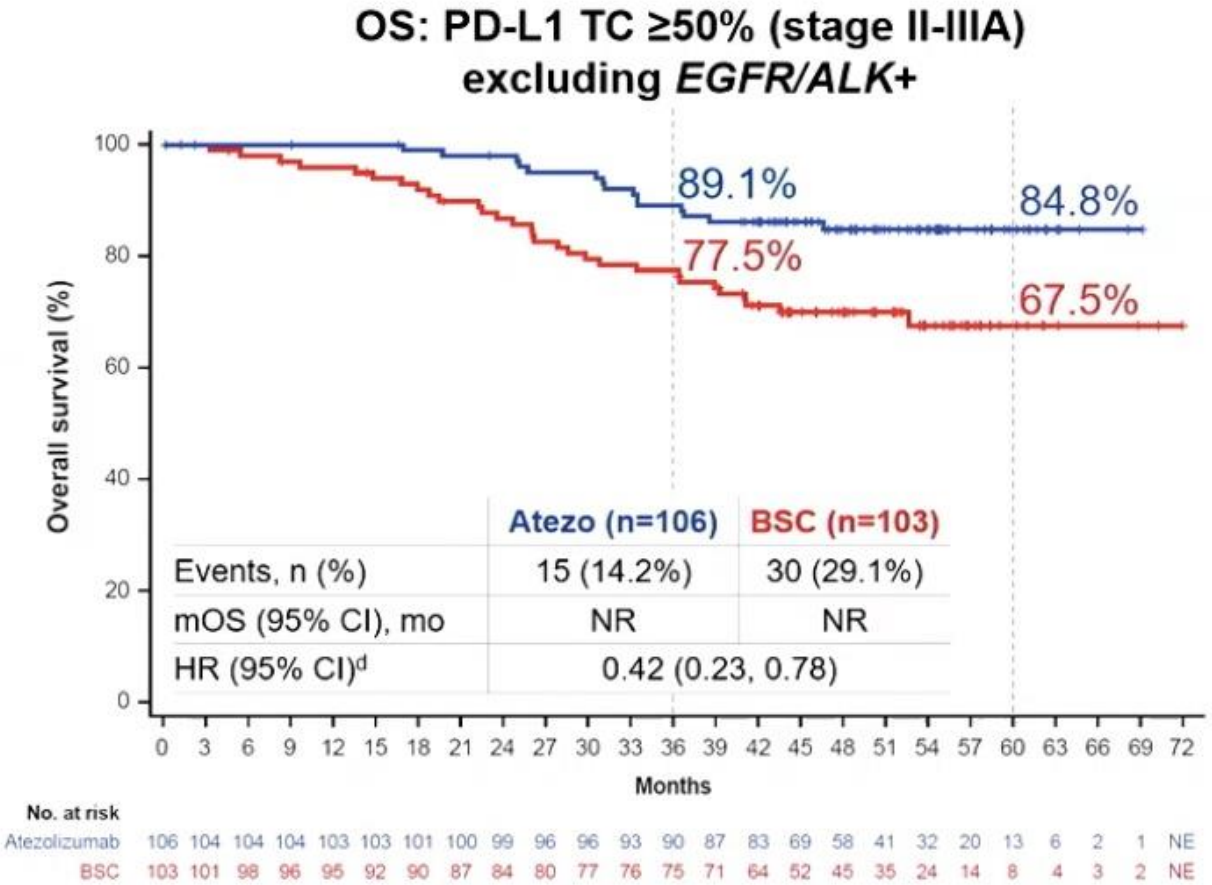
Key secondary endpoints
- OS in ITT population
- DFS in PD-L1 TC ≥50% (per SP263) stage II-IIIA population
- 3-y and 5-y DFS in all 3 populations

Both arms included observation and regular scans for disease recurrence on the same schedule.
ECOG, Eastern Cooperative Oncology Group; IC, tumor-infiltrating immune cells; ITT, intent to treat; TC, tumor cells. [a] Per SP142 assay.

OS by biomarker status (stage II-IIIA)
(data cutoff: 18 Apr '22)

UICC7 II = UICC8 IIB





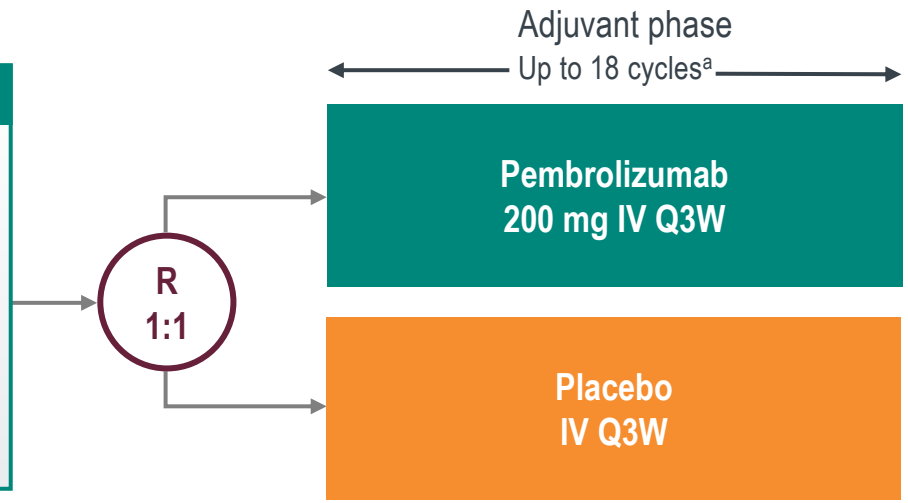
[a] 23 patients had unknown PD-L1 status. [b] Stratified for PD-L1 TC ≥1%; unstratified for all other subgroups. [c] 21 patients had unknown PD-L1 status. [d] Unstratified.

KEYNOTE-091: Phase 3 Study of Pembrolizumab vs Placebo for Patients with Stage IB-IIIA NSCLC After Resection With or Without Adjuvant Chemotherapy

Cooperative Group Study

Patients (N=1,177)

- Confirmed diagnosis of NSCLC stage IB (T ≥4 cm), II–IIIA per UICC v7, any histology
- No residual disease (R0) after surgical resection, documented on the pathology report
- Complete Surgical Resection by IASLC criteria
- ECOG PS 0–1
- Availability of tumor sample for PD-L1 expression
- No ILD or pneumonitis requiring steroids



Stratification Factors

- Stage (IB vs II vs IIIA)
- Adjuvant chemotherapy (No vs Yes)
- PD-L1 status: TPS = <1% vs
  TPS = 1%–49% vs
  TPS ≥50%
- Regions (Western vs Eastern Europe vs Asia vs RoW)

Dual Primary End Points

- DFS (all patients)
- DFS (PD-L1 TPS ≥50%)

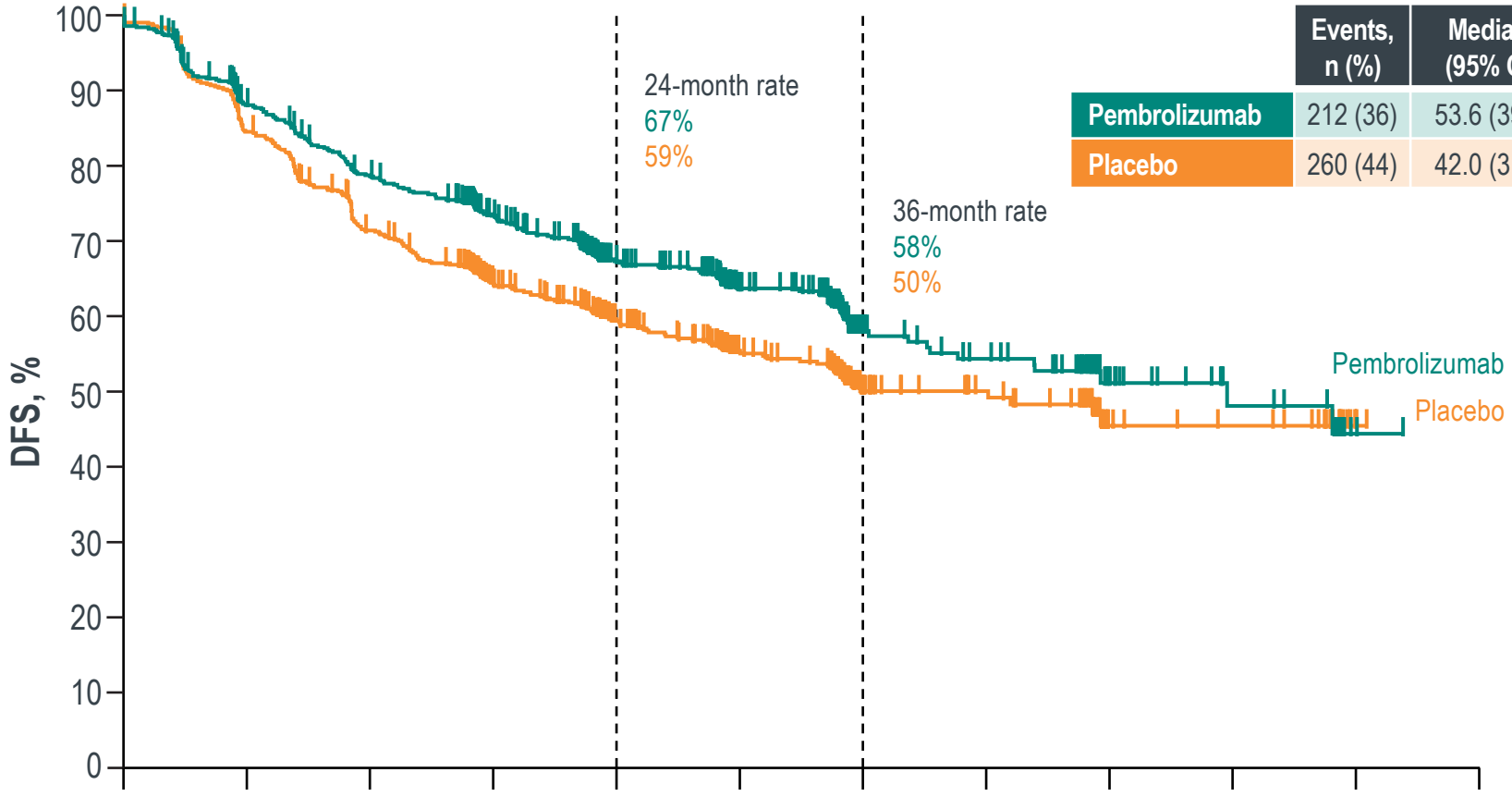
Secondary End Points

- DFS (PD-L1 TPS ≥1%)
- OS (all patients, PD-L1 TPS ≥50%, PD-L1 TPS ≥1%)
- Lung cancer-specific survival (LCSS; all patients)
- Safety

[a]Adjuvant chemotherapy was considered for stage IB (T ≥4 cm) disease and strongly recommended for stage II and IIIA disease; limited to ≤4 cycles

O'Brien et al. *Lancet Oncol*. 2022;23(10):1274-1286. Paz-Ares L, et al. ESMO Virtual Plenary. March 17, 2022. O'Brien et al. Presented at ASCO 2022. Abstract 8512. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02504372. Accessed April 14, 2022.

KEYNOTE-091: DFS (Overall Population)



	Events, n (%)	Median DFS (95% CI), mo	HR (95% CI)	P-value
Pembrolizumab	212 (36)	53.6 (39.2-NR)	0.76 (0.63–0.91)	0.0014
Placebo	260 (44)	42.0 (31.3-NR)		

No. at risk (no. censored)												
Pembrolizumab	590 (0)	493 (30)	434 (36)	358 (84)	264 (150)	185 (216)	82 (306)	70 (313)	28 (352)	16 (363)	1 (377)	0 (378)
Placebo	587 (0)	493 (5)	409 (13)	326 (56)	241 (118)	160 (183)	72 (259)	57 (273)	22 (305)	18 (309)	1 (326)	0 (327)

Median follow-up = 35.6 months (range: 16.5–68.0 months). Data cutoff date: September 20, 2021.
Response assessed per RECIST v1.1 by investigator review.

O'Brien et al. *Lancet Oncol*. 2022;23(10):1274-1286. Paz-Ares L, et al. ESMO Virtual Plenary. March 17, 2022.

Figure adapted with permission from Elsevier:
O'Brien et al. Lancet Oncol. 2022;23(10):1274-1286

KEYNOTE-091: DFS in Key Subgroups (Overall Population) (2 of 2)

Subgroup	Events/participants		DFS HR (95% CI)
	Pembrolizumab	Placebo	
Disease stage			
IB	21/84	25/85	0.76 (0.43 to 1.37)
II	102/329	144/338	0.70 (0.55 to 0.91)
IIIA	89/177	89/162	0.92 (0.69 to 1.24)
Received adjuvant chemotherapy			
No	35/84	29/83	1.25 (0.76 to 2.05)
Yes	177/506	231/504	0.73 (0.60 to 0.89)
Histology			
Non-squamous	146/398	184/363	0.67 (0.54 to 0.83)
Squamous	66/192	76/224	1.04 (0.75 to 1.45)
PD-L1 TPS			
<1%	89/233	106/232	0.78 (0.58 to 1.03)*
1–49%	69/189	91/190	0.67 (0.48 to 0.92)*
≥50%	54/168	63/165	0.82 (0.57 to 1.18)*
***EGFR* mutation**			
No	84/218	102/216	0.78 (0.59 to 1.05)
Yes	18/39	22/34	0.44 (0.23 to 0.84)
Unknown	110/333	136/337	0.82 (0.63 to 1.05)
Overall population	**212/590**	**260/587**	**0.76 (0.63 to 0.91)[a]**

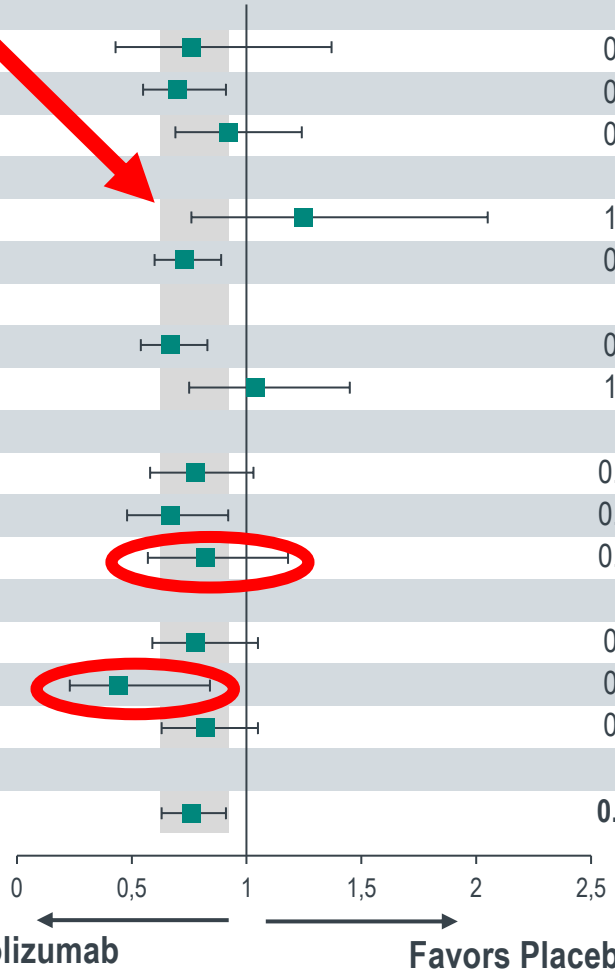


Figure adapted with permission from Elsevier: O'Brien et al. Lancet Oncol. 2022;23(10):1274-1286

Median follow-up = 35.6 months (range: 16.5–68.0 months). Data cutoff date: September 20, 2021.

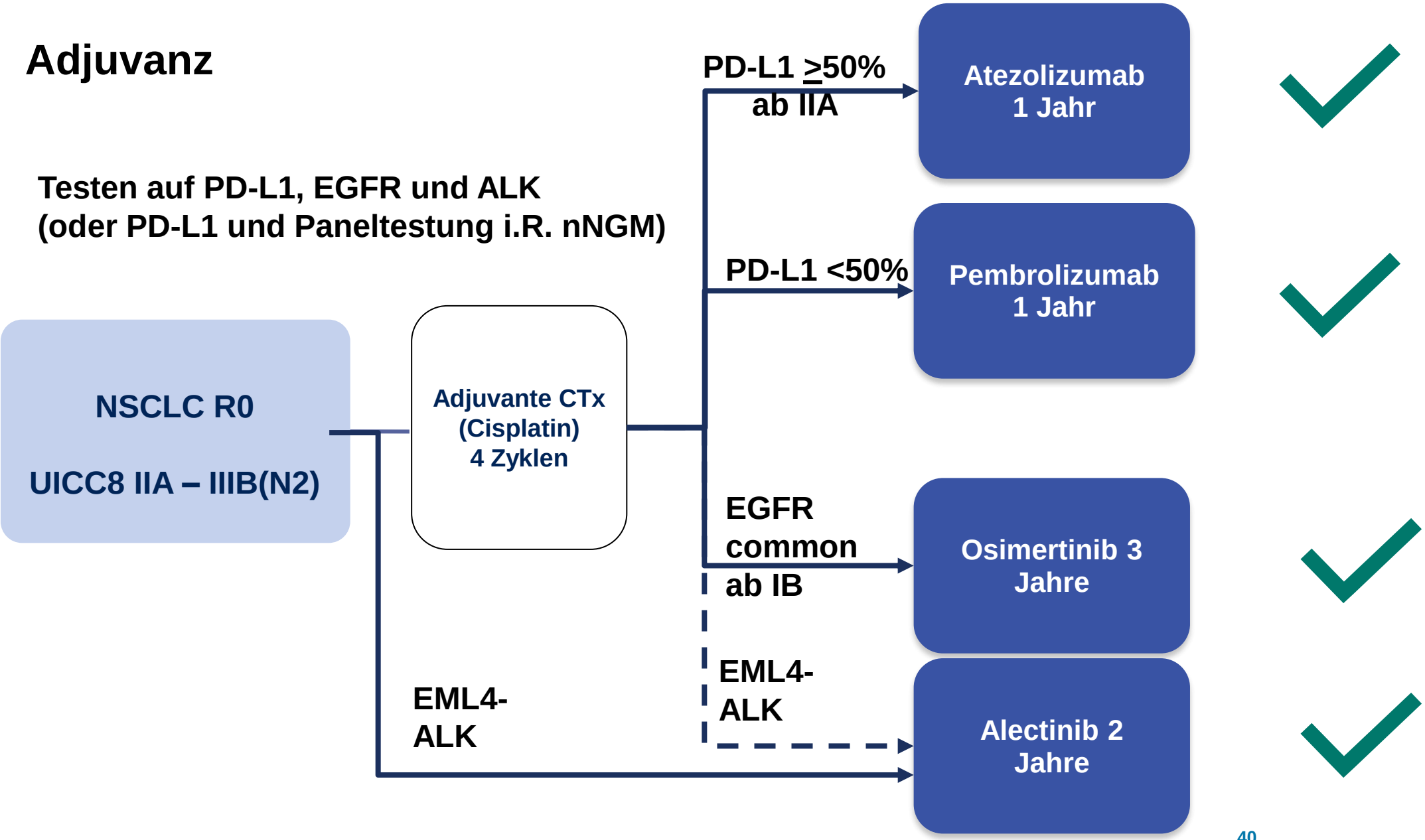
The vertical grey shaded band indicating the 95% CI for the overall population.

[a]Hazard ratios are adjusted for the stratification factors at randomization and the additional factors of histology (squamous vs non-squamous) and smoking status (never vs former or current); all other hazard ratios and associated 95% CIs were derived from a univariate Cox model with treatment as a single covariate.

O'Brien et al. *Lancet Oncol.* 2022;23(10):1274-1286. Paz-Ares L, et al. ESMO Virtual Plenary. March 17, 2022.

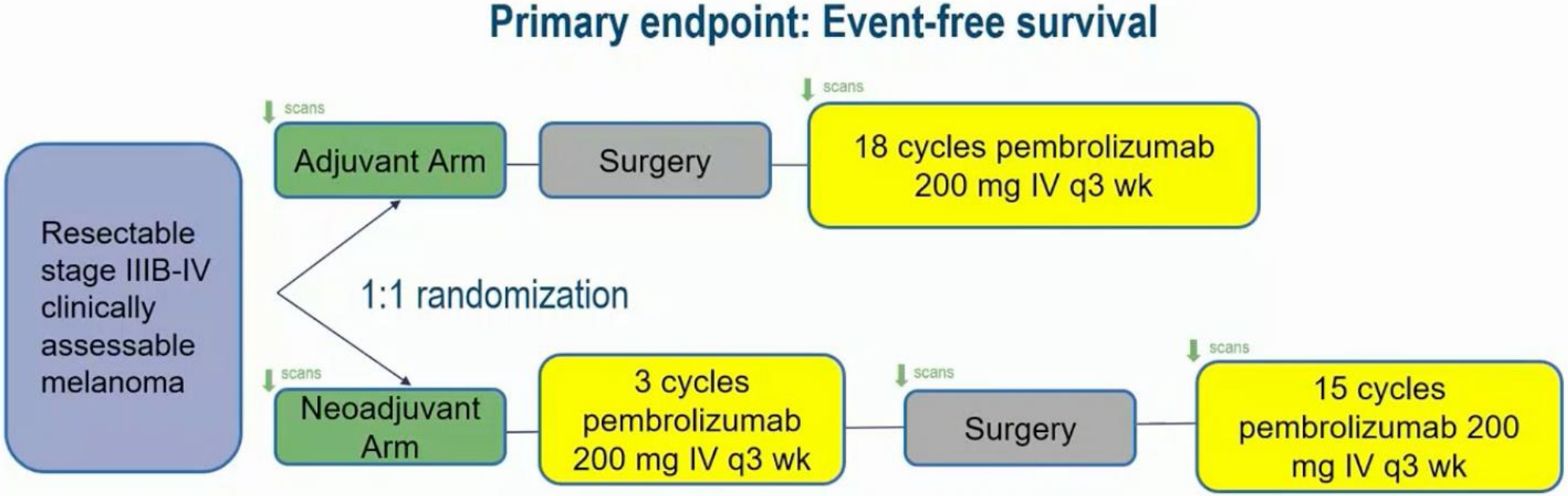
Adjuvanz

Testen auf PD-L1, EGFR und ALK
(oder PD-L1 und Paneltestung i.R. nNGM)



Felip et al. IMpower010 Relapse Patterns.
https://bit.ly/3mNMSAi

S1801 Study Schema



Additional criteria: strata included AJCC 8th ed. stage and LDH, adjuvant radiation allowed, concomitant radiation & pembrolizumab was not allowed, brain metastasis excluded, uveal melanoma excluded

Surgery type and extent was required to be pre-specified and carried out regardless of radiologic response to therapy

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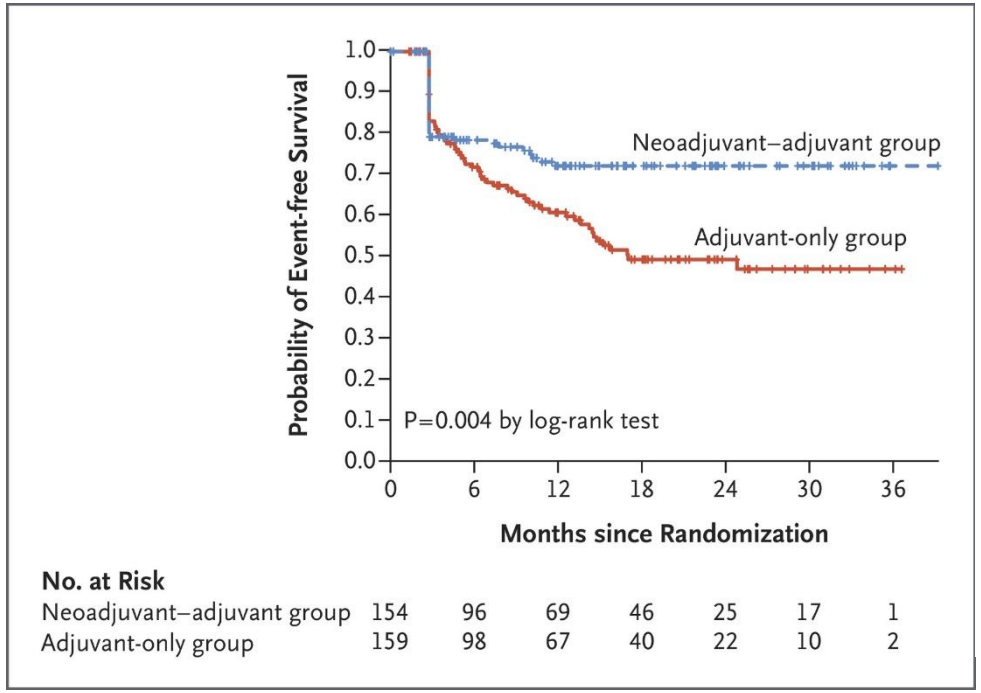
Sapna P. Patel, MD

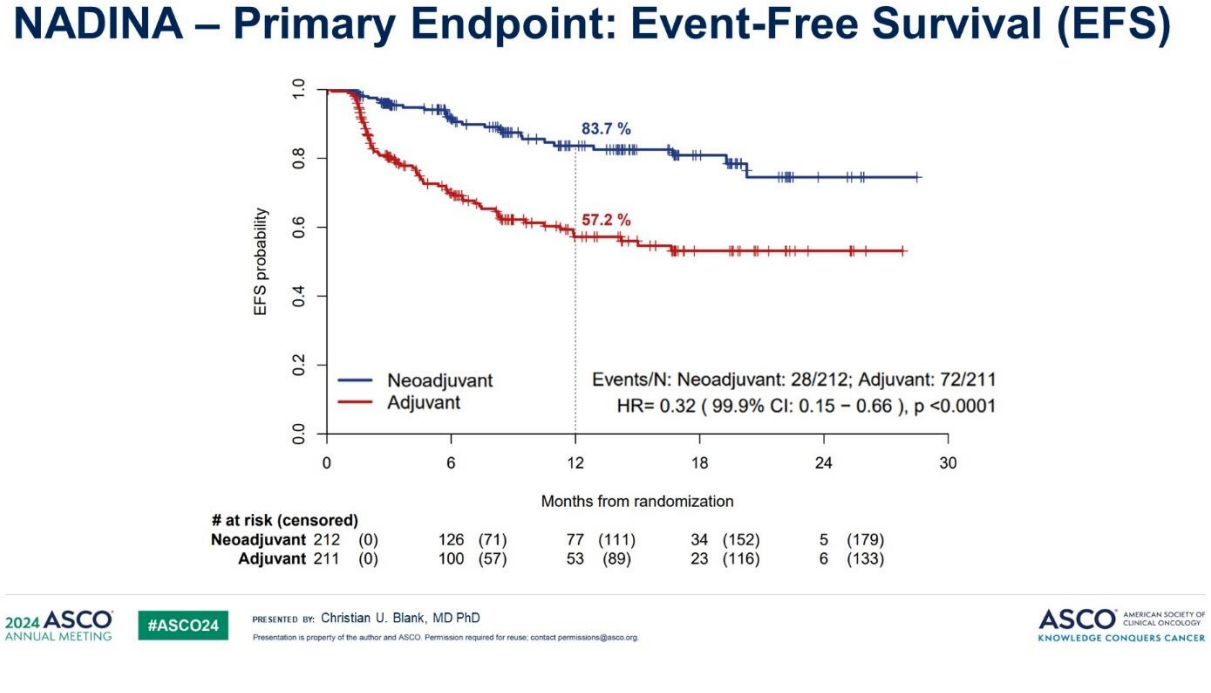
SWOG

Patel SP et al., N Engl J Med 2023; 388:813-823 DOI: 10.1056/NEJMoa2211437

Patel: Neoadjuvant vs. adjuvant Pembro

Blank: Neoadjuvant Ipi Nivo + Adj (non responders) vs. adjuvant Nivo





Patel SP et al., N Engl J Med 2023; 388:813-823 DOI: 10.1056/NEJMoa2211437, Bank et al., NEJM Jun 2024

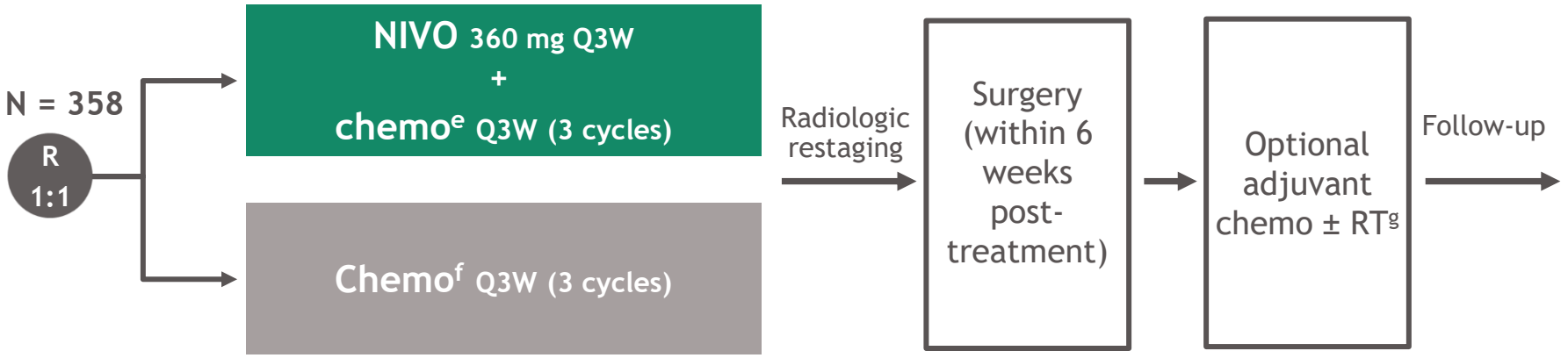
CheckMate 816 study design[a]

Key eligibility criteria

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

Stratified by

Stage (IB-II vs IIIA), PD-L1[c] (≥ 1% vs < 1%[d]), and sex



Primary endpoints

- **pCR by BIPR**
- **EFS[h] by BICR**

Secondary endpoints

- MPR by BIPR
- **OS**
- Time to death or distant metastases

Key exploratory analysis

- **EFS by pCR status**

Database lock: October 20, 2021; minimum follow-up: 21 months for NIVO + chemo and chemo arms; median follow-up, 29.5 months.

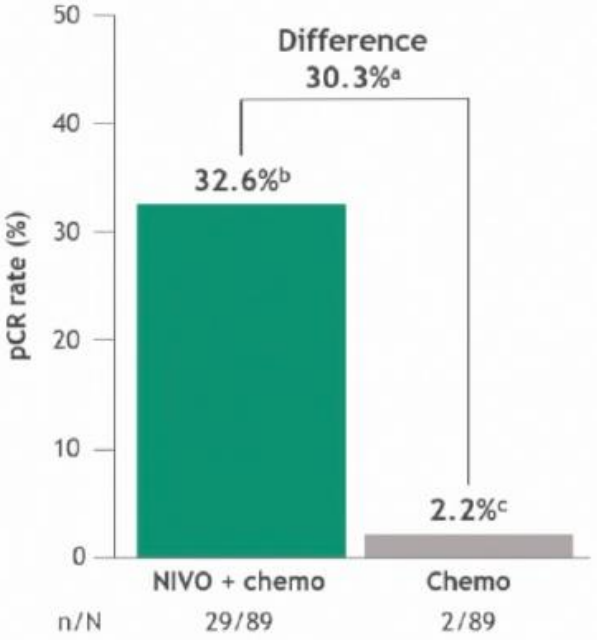
[a]NCT02998528; [b]TNM Classification of Malignant Tumors 7th edition; [c]Determined by the PD-L1 IHC 28-8 pharmDx assay (Dako); [d]Included patients with PD-L1 expression status not evaluable and indeterminate; [e]NSQ: pemetrexed + cisplatin or paclitaxel + carboplatin; SQ: gemcitabine + cisplatin or paclitaxel + carboplatin; [f]Vinorelbine + cisplatin, docetaxel + cisplatin, gemcitabine + cisplatin (SQ only), pemetrexed + cisplatin (NSQ only), or paclitaxel + carboplatin; [g]Per healthcare professional choice; [h]EFS defined as the time from randomization to any progression of disease precluding surgery, progression or recurrence of disease after surgery, progression for patients without surgery, or death due to any cause; patients with subsequent therapy were censored at the last evaluable tumor assessment on or prior to the date of subsequent therapy.

CM 816: zulassungsrelevante Population PD_L1≥1%

CheckMate 816 (NIVO + chemo vs chemo): 3-y results by tumor PD-L1 expression

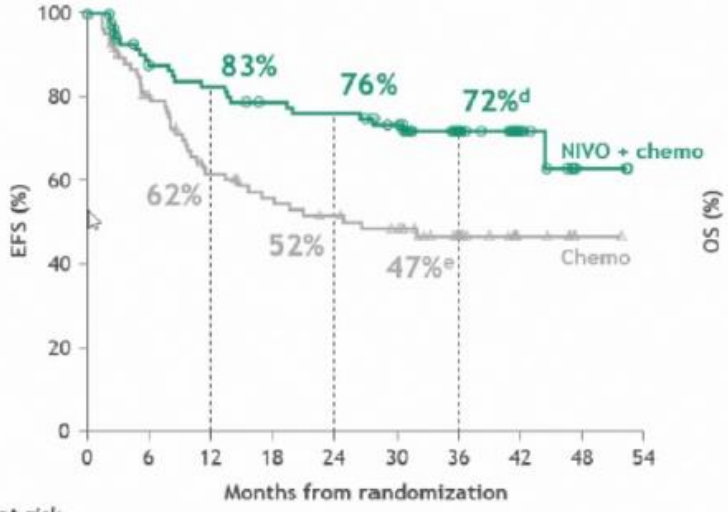
Efficacy outcomes in patients with tumor PD-L1 ≥ 1%

pCR



EFS

	NIVO + chemo (n = 89)	Chemo (n = 89)
Median EFS, mo (95% CI)	NR (44.4-NR)	26.7 (13.4-NR)
HR (95% CI)	0.46 (0.28-0.77)	

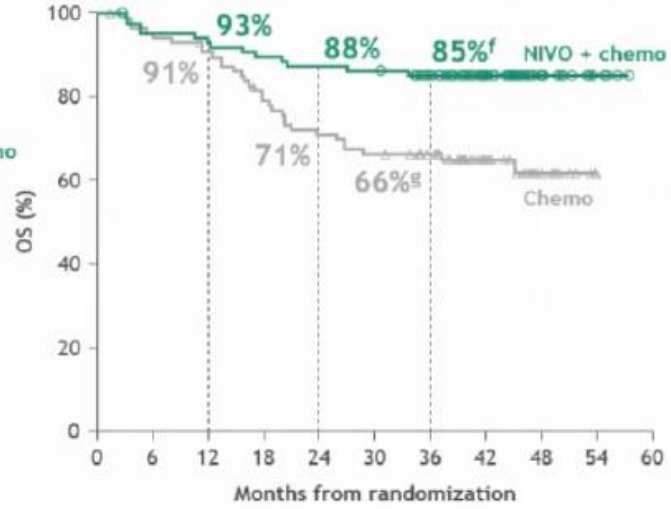


No. at risk

NIVO + chemo	89	69	65	60	58	53	37	11	2	0
Chemo	89	61	45	39	35	31	19	7	1	0

OS

	NIVO + chemo (n = 89)	Chemo (n = 89)
Median OS, mo (95% CI)	NR (NR-NR)	NR (45.1-NR)
HR (95% CI)	0.37 (0.20-0.71)	

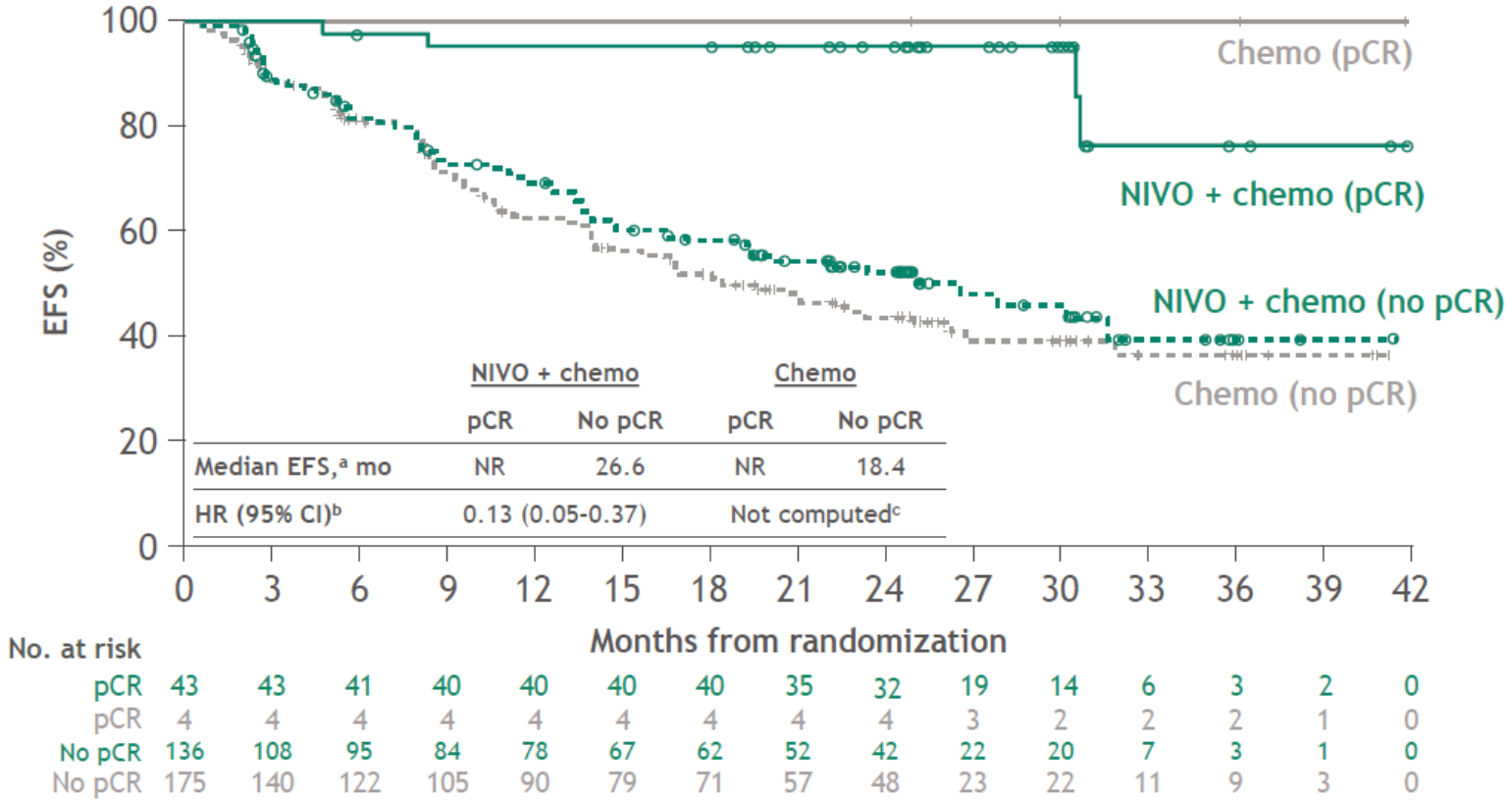


NIVO + chemo	89	84	82	79	77	76	66	37	13	4	0
Chemo	89	83	79	68	61	57	51	27	10	0	0

- Median TTDM (95% CI) in months was NR vs NR (18.8-NR) for NIVO + chemo vs chemo (HR, 0.35; 95% CI, 0.19-0.62); 3-year TTDM rates were 82%h vs 53%i

Minimum/median follow-up: 32.9/41.4 months.
MPR rates were 44.9% (95% CI, 34.4-55.9) with NIVO + chemo and 5.6% (95% CI, 1.8-12.6) with chemo (difference, 39.3%; 95% CI, 27.3-50.1). Unweighted differences in pCR and MPR rates between treatment arms were calculated using the Newcombe method. a-e95% CI: a19.9-40.7; b23.0-43.3; c0.3-7.9; d61-81; e35-58; f76-91; g56-75; h71-88; i41-63.

Exploratory analysis: EFS by pCR status



	NIVO + chemo		Chemo	
	pCR	No pCR	pCR	No pCR
Median EFS,[a] mo	NR	26.6	NR	18.4
HR (95% CI)[b]	0.13 (0.05-0.37)		Not computed[c]	

No. at risk															
pCR	43	43	41	40	40	40	40	35	32	19	14	6	3	2	0
pCR	4	4	4	4	4	4	4	4	4	3	2	2	2	1	0
No pCR	136	108	95	84	78	67	62	52	42	22	20	7	3	1	0
No pCR	175	140	122	105	90	79	71	57	48	23	22	11	9	3	0

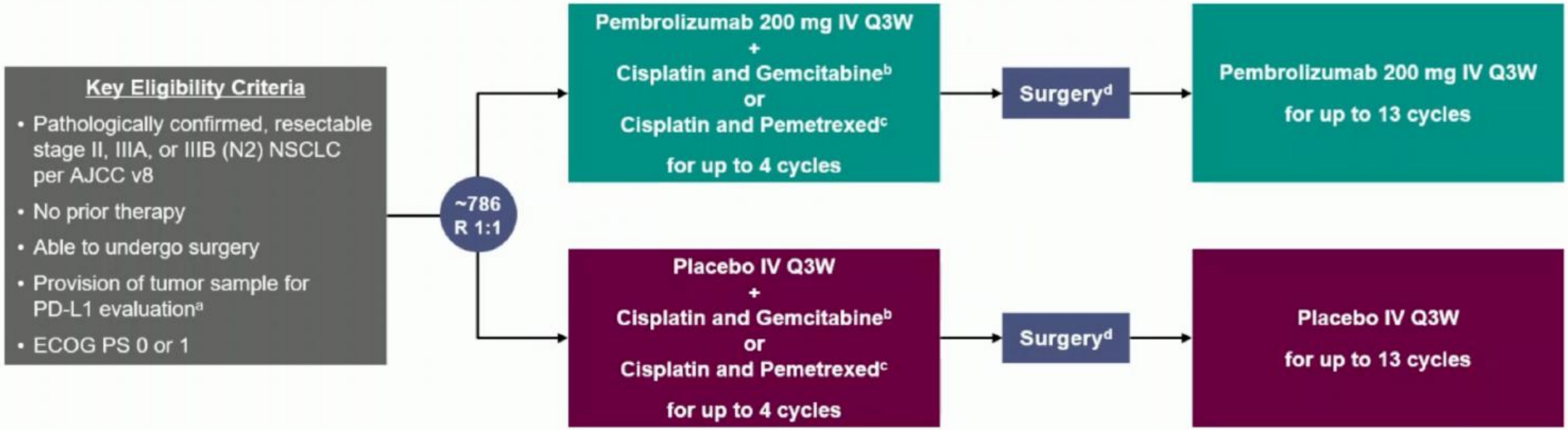
- pCR rates were significantly improved with NIVO + chemo vs chemo (24.0% vs 2.2%)
- In patients without pCR, HR (95% CI) for NIVO + chemo vs chemo was 0.84 (0.61-1.17)

Minimum follow-up: 21 months; median follow-up, 29.5 months.

[a]95% CI = 30.6-NR (NIVO + chemo, pCR), 16.6-NR (NIVO + chemo, no pCR) and NR-NR (chemo, pCR), 13.9-26.2 (chemo, no pCR); [b]In the pooled patient population (NIVO + chemo and chemo arms combined), EFS HR (95% CI) was 0.11 (0.04-0.29) for patients with pCR vs those without pCR; [c]HR was not computed for the chemo arm due to only 4 patients having a pCR.

KEYNOTE-671 Study Design

Randomized, Double-Blind, Phase 3 Trial



Stratification Factors

- Disease stage (II vs III)
- PD-L1 TPS[a] (<50% vs ≥50%)
- Histology (squamous vs nonsquamous)
- Geographic region (east Asia vs not east Asia)

Dual primary end points: EFS per investigator review and OS

Key secondary end points: mPR and pCR per blinded, independent pathology review and safety

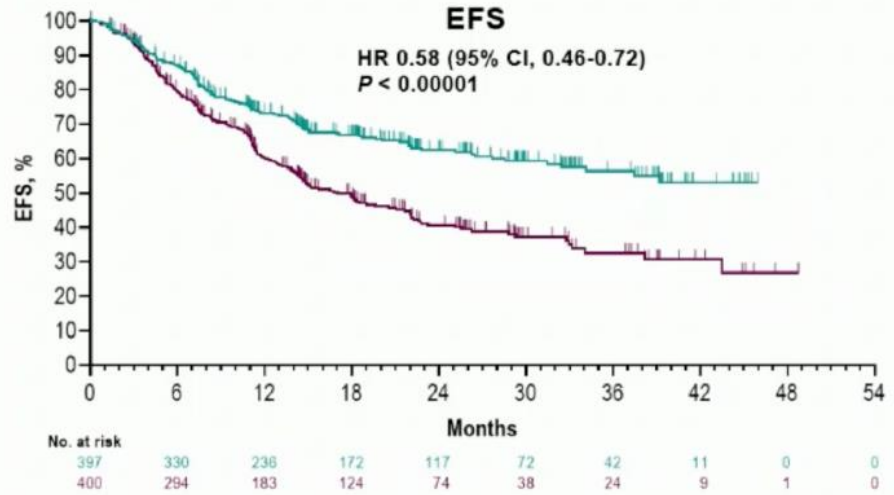
[a] Assessed at a central laboratory using PD-L1 IHC 22C3 pharmDx. [b] Cisplatin 75 mg/m^2 IV Q3W + gemcitabine 1000 mg/m^2 IV on days 1 and 8 Q3W was permitted for squamous histology only. [c] Cisplatin 75 mg/m^2 IV Q3W + pemetrexed 500 mg/m^2 IV Q3W was permitted for nonsquamous histology only. [d] Radiotherapy was to be administered to participants with microscopic positive margins, gross residual disease, or extracapsular nodal extension following surgery and to participants who did not undergo planned surgery for any reason other than local progression or metastatic disease.
ClinicalTrials.gov identifier: NCT03425643.

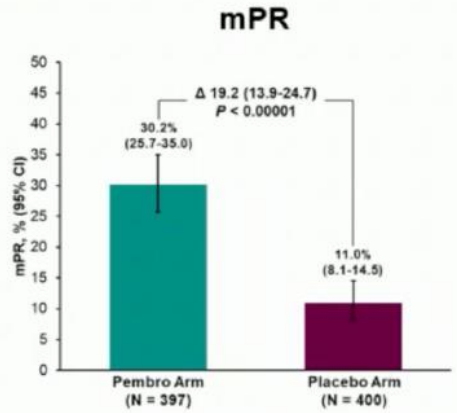
Spicer et al., ESMO 2023

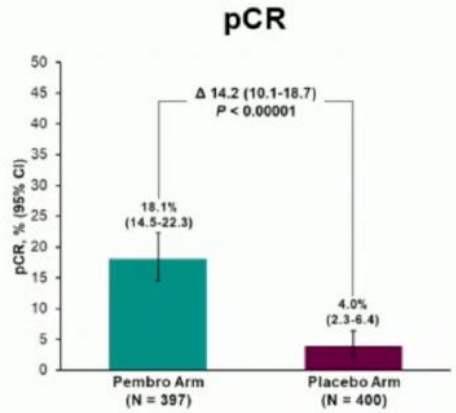
KN 671: PFS und pCR

KEYNOTE-671 Results: Interim Analysis 1
Median Follow-Up[a]: 25.2 months (range, 7.5-50.6)

- Neoadjuvant pembrolizumab + chemotherapy followed by surgery and adjuvant pembrolizumab significantly improved EFS, mPR, and pCR compared with neoadjuvant chemotherapy and surgery alone
- AE profile was as expected based on the known profiles of the individual treatment components





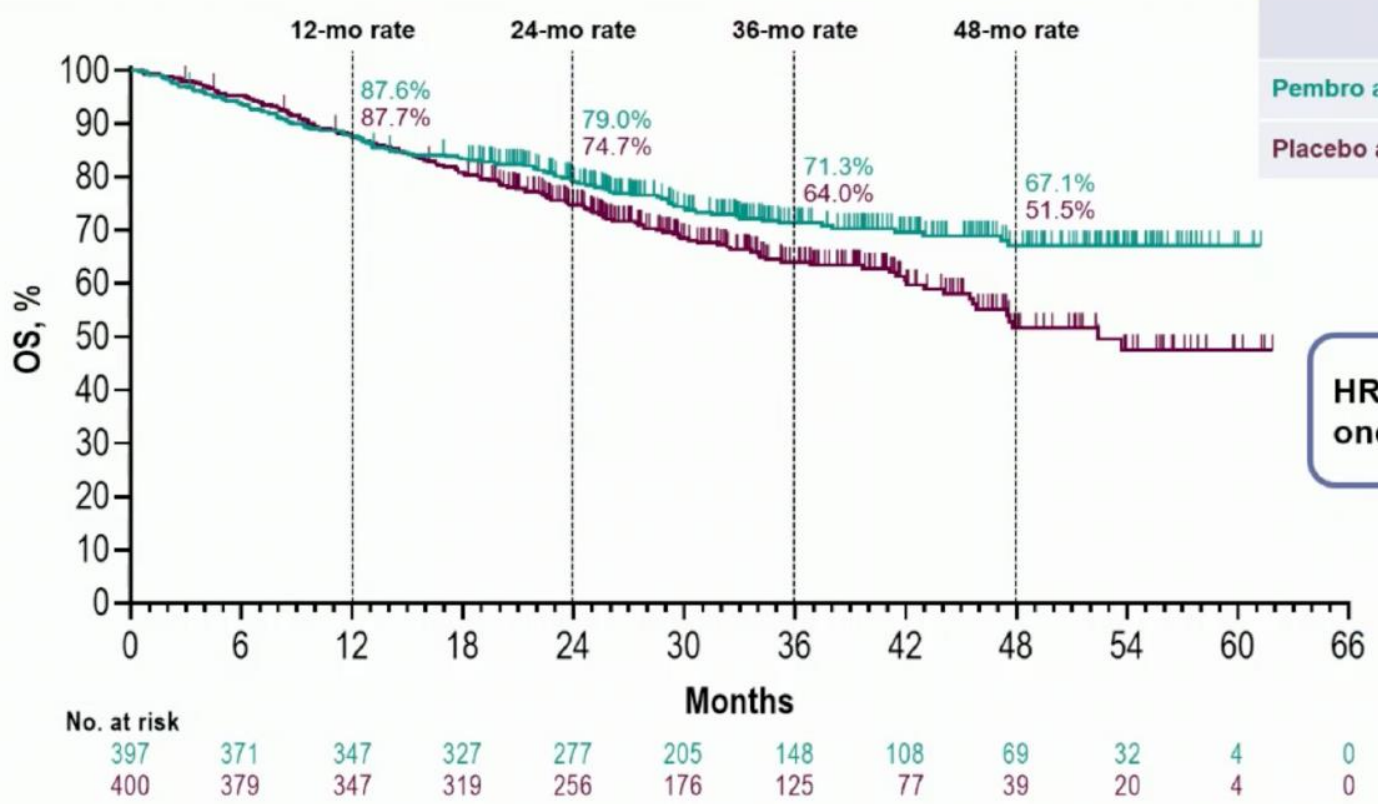


[a] Defined as time from randomization to data cutoff date of July 29, 2022.
Wakelee H et al. *N Engl J Med* 2023;389:491-503.

Spicer et al., ESMO 2023

Overall Survival, IA2

Median Follow-Up: 36.6 months (range, 18.8-62.0)



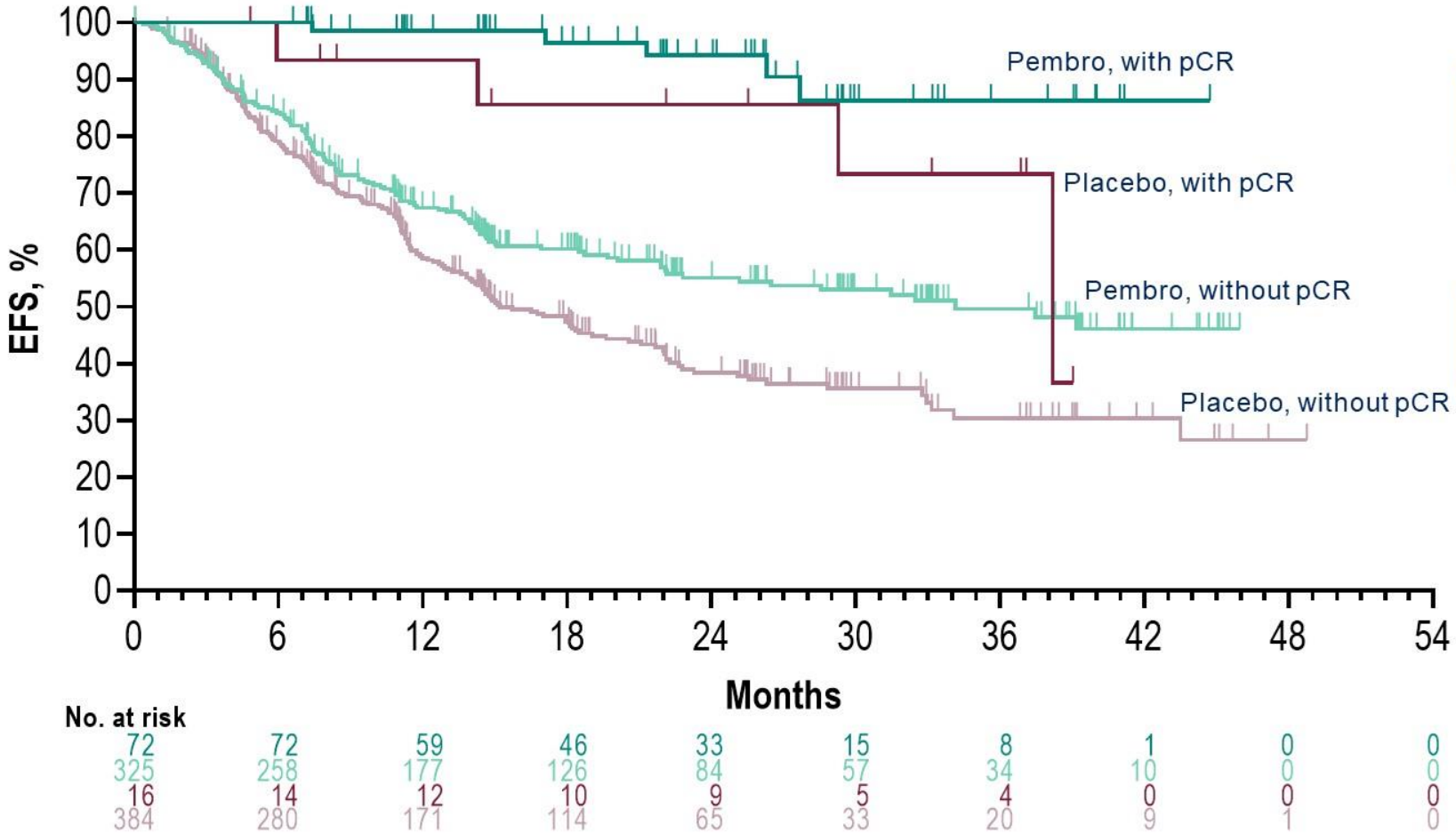
	Pts w/ Event	Median (95% CI), mo
Pembro arm	27.7%	NR (NR-NR)
Placebo arm	36.0%	52.4 (45.7-NR)

HR 0.72 (95% CI, 0.56-0.93)
one-sided *P* = 0.00517[a]

S defined as time from randomization to death from any cause. [a] Significance boundary at IA2, one-sided *P* = 0.00543.
ata cutoff date for IA2: July 10, 2023.

Spicer et al., ESMO 2023

Exploratory Analysis of EFS by pCR Status



With pCR
HR 0.33 (95% CI, 0.09-1.22)

Without pCR
HR 0.69 (95% CI, 0.55-0.85)

pCR defined as absence of residual invasive cancer in resected primary tumor and lymph nodes (ypT0/Tis ypN0). EFS defined as time from randomization to first occurrence of local progression precluding planned surgery, unresectable tumor, progression or recurrence per RECIST v1.1 by investigator assessment, or death from any cause. Data cutoff date for IA1: July 29, 2022 (median follow-up, 25.2 mo [range, 7.5-50.6]).

Neoadjuvantes Therapie: CM 816

Zulassung 06/24

Prä-interventionelles Tumorboard: Kategorisierung: primär, poteintell operabel

II- IIIB (N2) resectable UICC/AJCC 8 PD-L1 ≥1% (EGFR ALK WT)

Induktions-CTx + Nivo 3 Zyklen 94% completion

Nachbeobachtung

Perioperatives Konzept: KN 671

II- IIIB (N2) resectable UICC/AJCC 8 (PD-L1 alle)

Induktions-CTx + Pembro 4 Zyklen 87% completion

insbesondere bei non-pCR

Pembrolizumab 1 Jahr adjuvante Therapie

Zusammenfassung

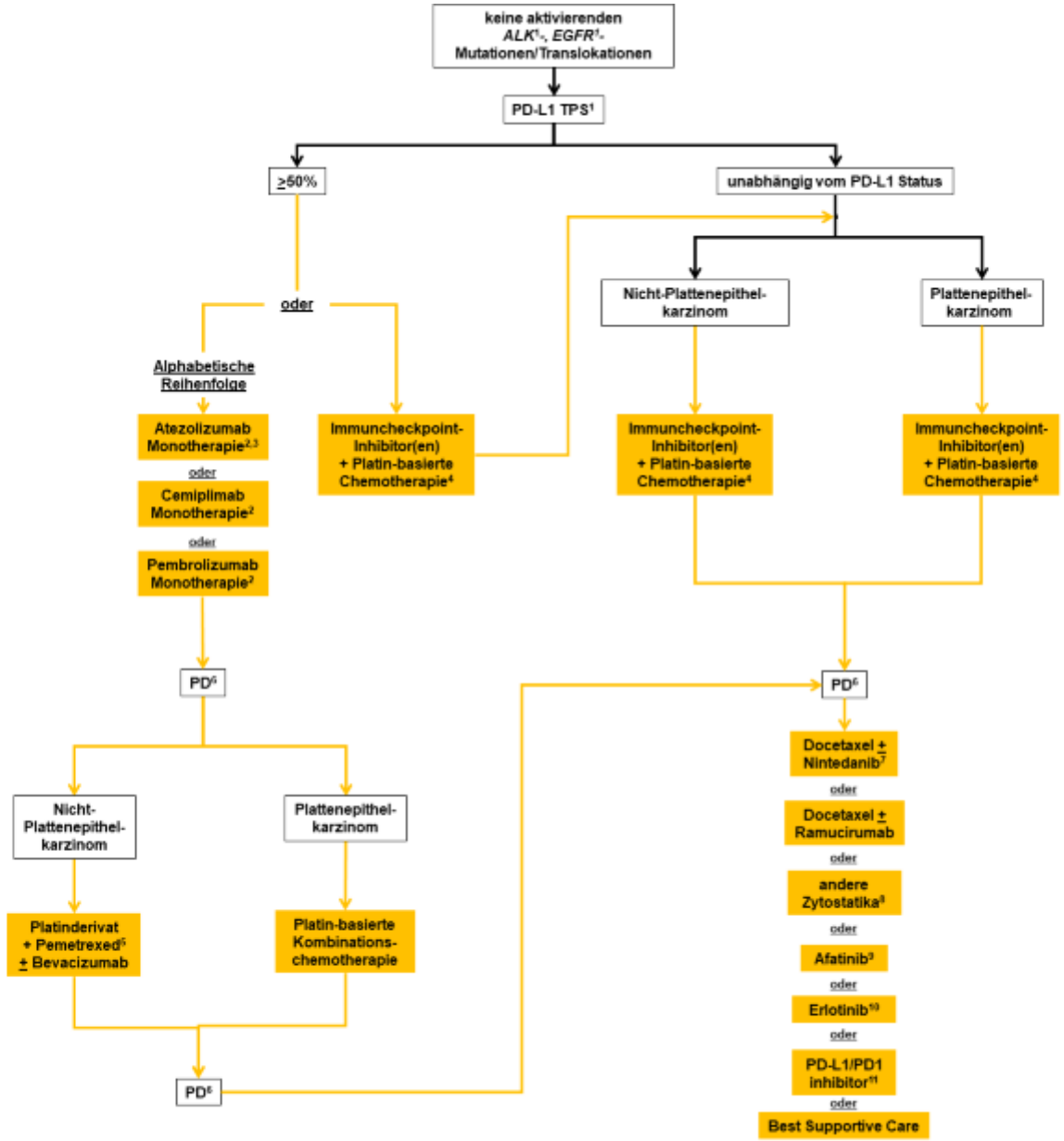
Neoadjuvante / Induktionstherapie: bevorzugt bei N+ (IIB-IIIB(N2), unklar bei Stadium IIA N0?)

Adjuvante Therapie: insbesondere bei N0 und N1 oder N2 (intraoperativ)

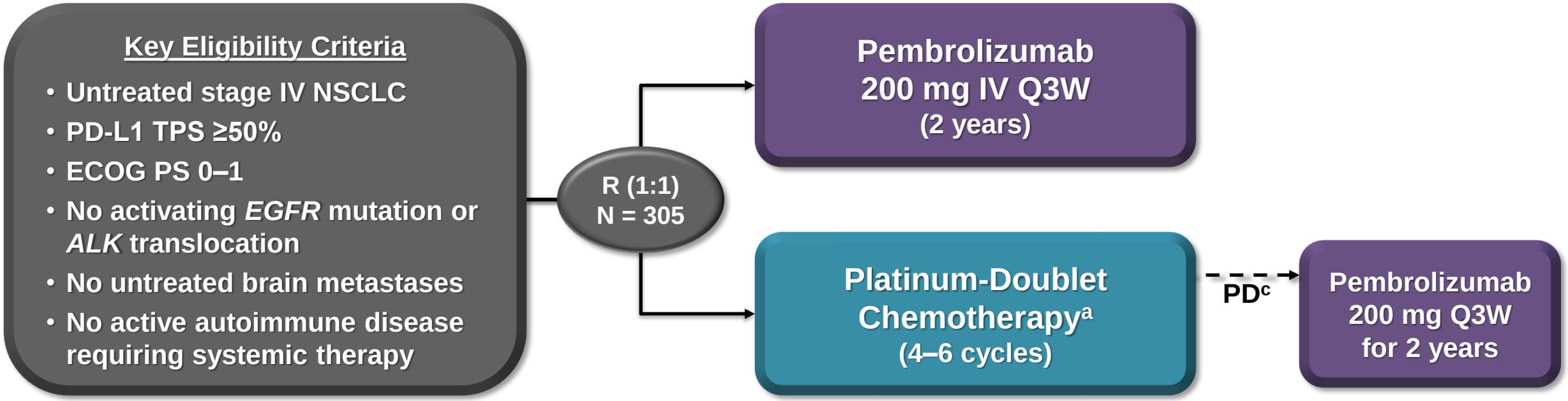
Prä-interventionelle Diskussion im Tumorboard bei jedem Patienten essentiell

Festlegung auf primär operabel, potentiell operabel, definitiv inoperabel

Testung auf PD-L1, EGFR und ALK in den frühen und lokal fortgeschrittenen Stadien


keine aktivierenden ALK[1]-, EGFR[1]-Mutationen/Translokationen
PD-L1 TPS[1]
≥50%
unabhängig vom PD-L1 Status
oder
Alphabetische Reihenfolge
Atezolizumab Monotherapie[2,3]
oder
Cemiplimab Monotherapie[2]
oder
Pembrolizumab Monotherapie[2]
Immuncheckpoint-Inhibitor(en) + Platin-basierte Chemotherapie[4]
Nicht-Plattenepithel-karzinom
Plattenepithel-karzinom
Immuncheckpoint-Inhibitor(en) + Platin-basierte Chemotherapie[4]
Immuncheckpoint-Inhibitor(en) + Platin-basierte Chemotherapie[4]
PD[5]
PD[5]
Nicht-Plattenepithel-karzinom
Plattenepithel-karzinom
Platinderivat + Pemetrexed[5] ± Bevacizumab
Platin-basierte Kombinations-chemotherapie
PD[5]
Docetaxel ± Nintedanib[7]
oder
Docetaxel ± Ramucirumab
oder
andere Zytostatika[8]
oder
Afatinib[9]
oder
Erlotinib[10]
oder
PD-L1/PD1 inhibitor[11]
oder
Best Supportive Care

Updated Analysis of KEYNOTE-024: Pembrolizumab Versus Platinum-based Chemotherapy for Advanced NSCLC With PD-L1 TPS ≥50%: Study Design



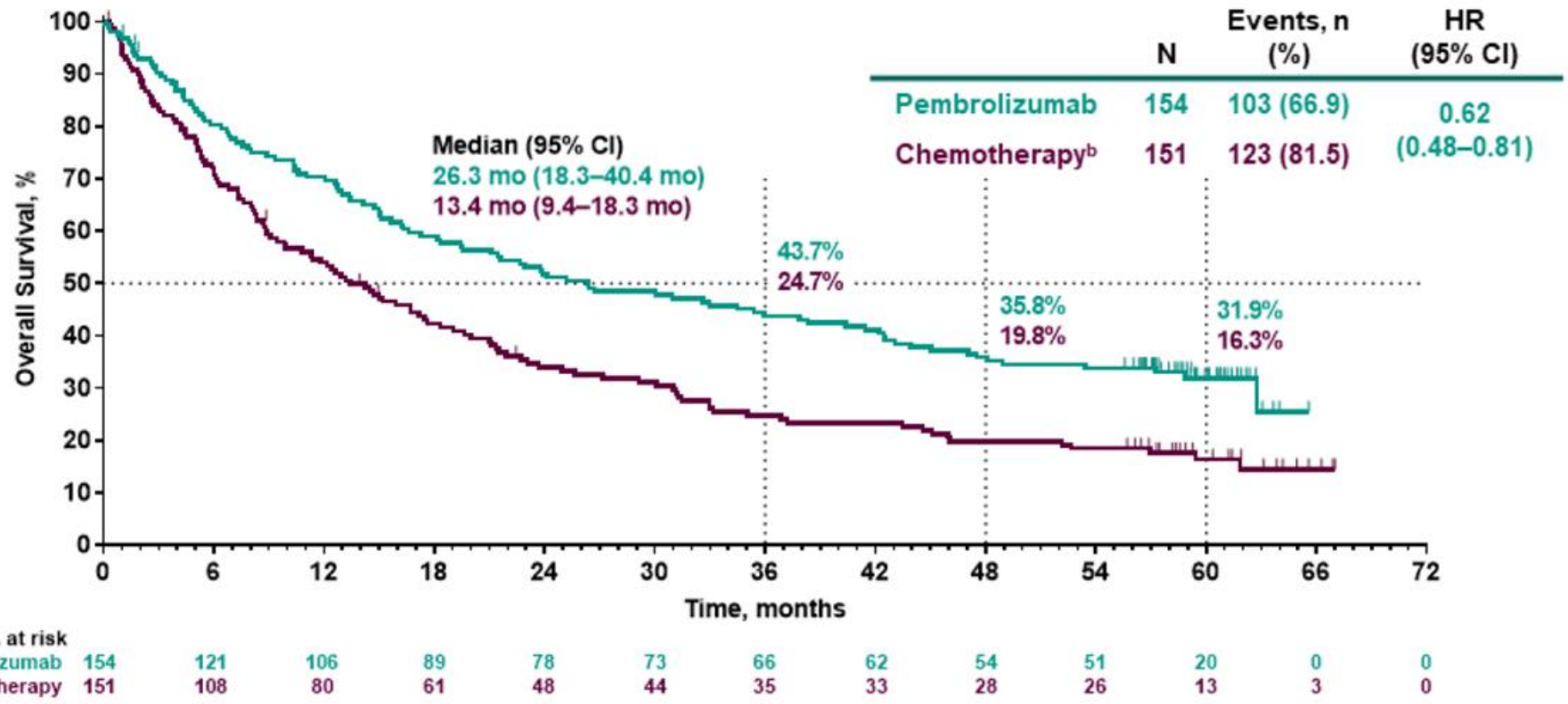
End Points

Primary:	PFS (RECIST v1.1, blinded independent central review)
Key secondary:	OS
Secondary:	ORR, safety
Exploratory:	DOR

Brahmer et al. J Thoracic Oncology Abstract 17.06 – WCLC 2017

5 Jahres Überleben Keynote 24

Overall Survival[a]



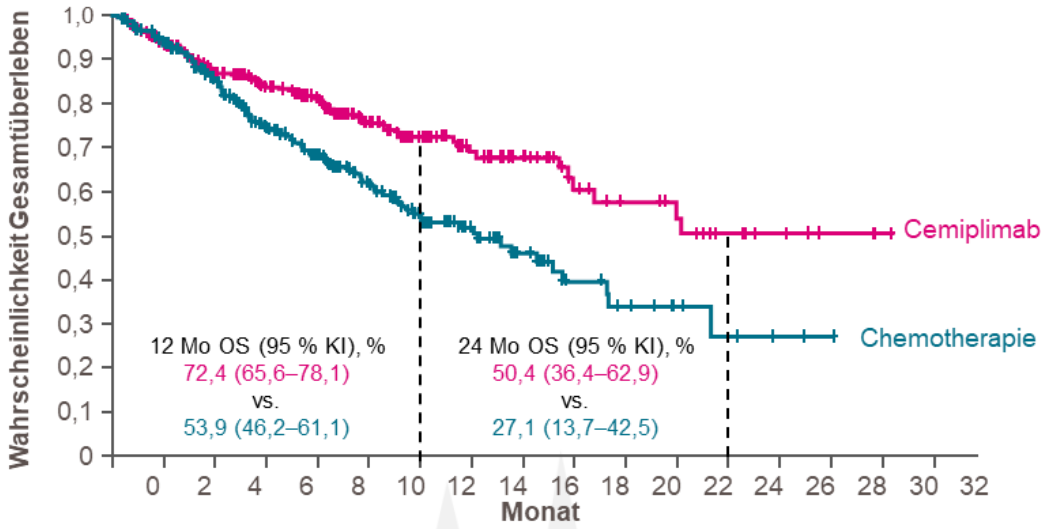
Brahmer J. et al., ESMO 2020

EMPOWER 1L: Gesamtüberleben, und Überleben nach PD-L1 Expression: Zulassung in 2021 erwartet

PD-L1 ≥ 50 %

	Anzahl Patienten	Medianes OS (95% KI) *Monate*
Cemiplimab	283	nicht erreicht (95 % KI: 17,9–NE)
Chemotherapie	280	14,2 (95 % KI: 11,2–17,5)

HR 0,57 (95 % KI: 0,42–0,77), p = 0,0002

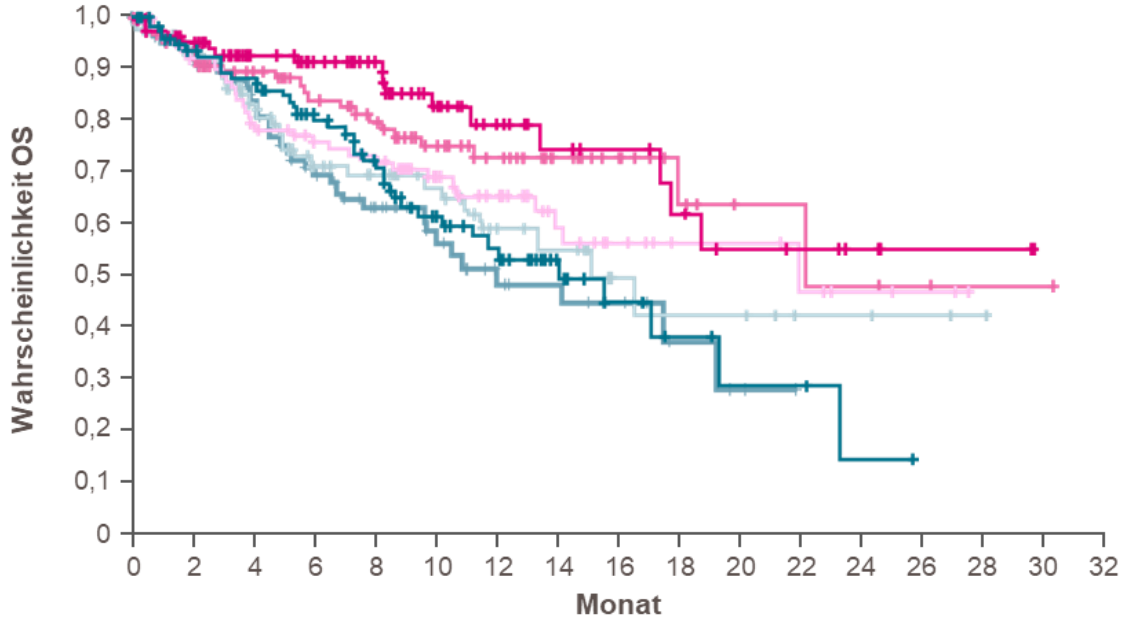


Anzahl Patienten unter Risiko

Cemiplimab	283	244	203	177	154	108	83	55	42	24	18	15	10	6	3	1	0
Chemotherapie	280	239	198	153	125	87	57	41	25	15	11	6	4	2	1	0	0

Mediane Dauer Follow-up:
Cemiplimab → 10,8 Monate (Bereich: 0,1–31,9)
Chemotherapie → 10,9 Monate (Bereich: 0,2–29,5)

OS

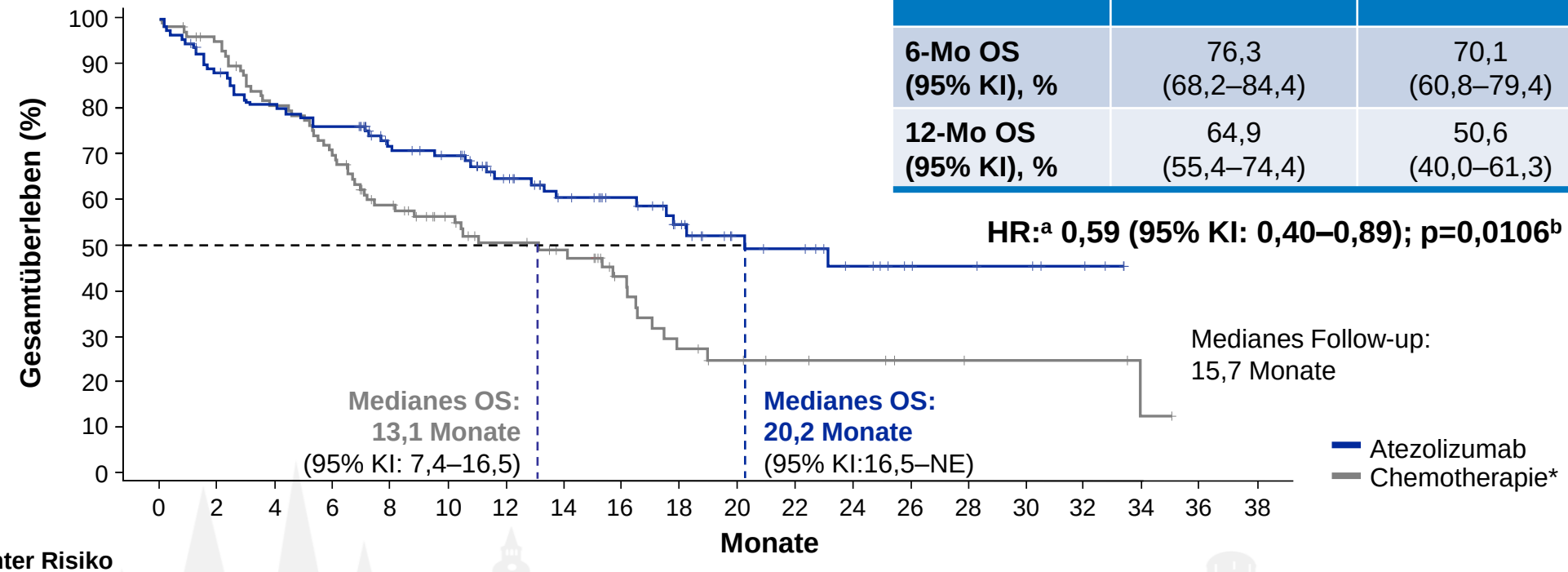


Sezer et al. ESMO 2020. (suppl; Abstr LBA52), Sezer A. et al., . 2021 Feb 13;397(10274):592-604. doi: 10.1016/S0140-6736(21)00228-2

IMpower110 – Gesamtüberleben: TC3 oder IC3 WT: positives CHMP Votum

	Arm A (Atezo) n=107	Arm B (Chemo*) n=98
6-Mo OS (95% KI), %	76,3 (68,2–84,4)	70,1 (60,8–79,4)
12-Mo OS (95% KI), %	64,9 (55,4–74,4)	50,6 (40,0–61,3)

HR:[a] 0,59 (95% KI: 0,40–0,89); p=0,0106[b]



Patienten unter Risiko

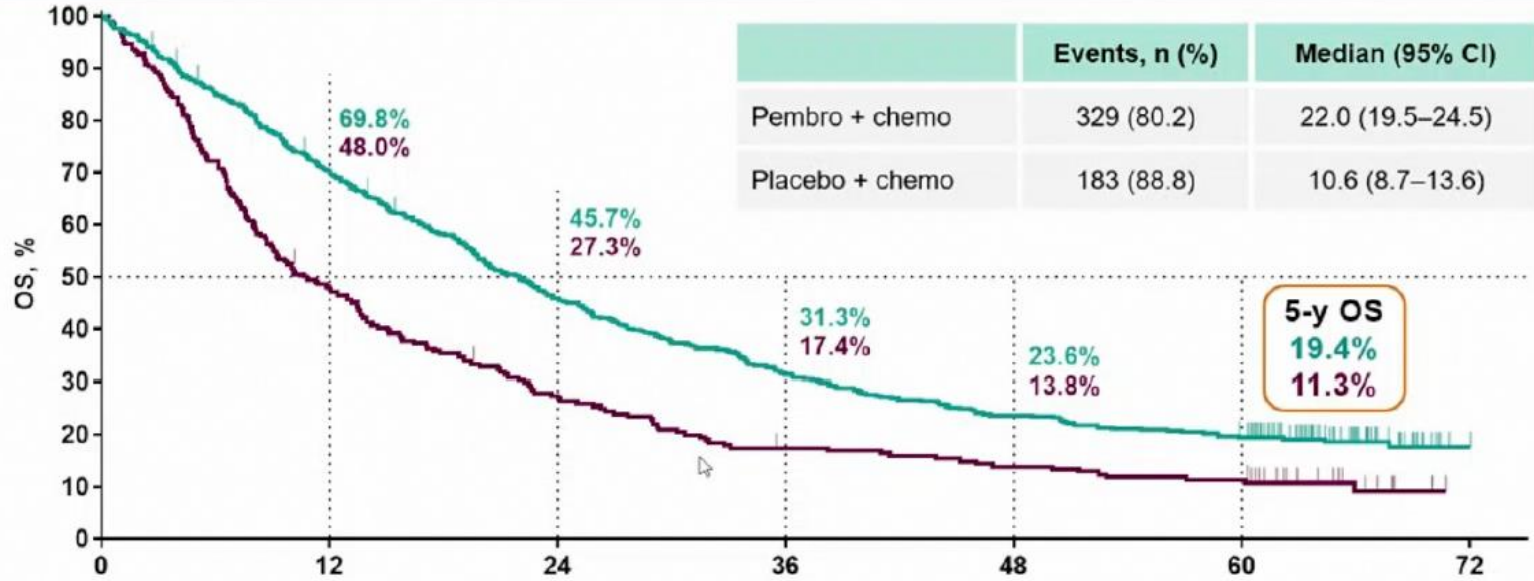
Atezolizumab	107	94	85	80	66	61	48	40	34	25	18	16	11	7	6	5	2	
Chemotherapie*	98	89	75	65	50	40	33	28	19	12	9	7	6	4	3	3	3	1

KI, Konfidenzintervall; OS, Gesamtüberleben (overall survival); NE, nicht evaluierbar. [a]Stratifiziert. [b]Stratifizierter Log-Rank-Test.
*Nsq (Nicht-Plattenepithel): Cisplatin 75 mg/m² oder Carboplatin AUC 6 + Pemetrexed 500 mg/m² IV q3w. Sq (Plattenepithel): Cisplatin 75 mg/m² + Gemcitabin 1250 mg/m² oder Carboplatin AUC 5 + Gemcitabin 1000 mg/m² IV q3w. Datenschnitt: 10. September 2018.

Mod. Spigel D et al. ESMO 2019, Proffered Paper Session 1 – NSCLC, metastatic, Abstract No. LBA78.

KN 189: nicht Platte: OS

OS: ITT Population



	Events, n (%)	Median (95% CI)	HR (95% CI)
Pembro + chemo	329 (80.2)	22.0 (19.5–24.5)	0.60 (0.50–0.72)
Placebo + chemo	183 (88.8)	10.6 (8.7–13.6)	

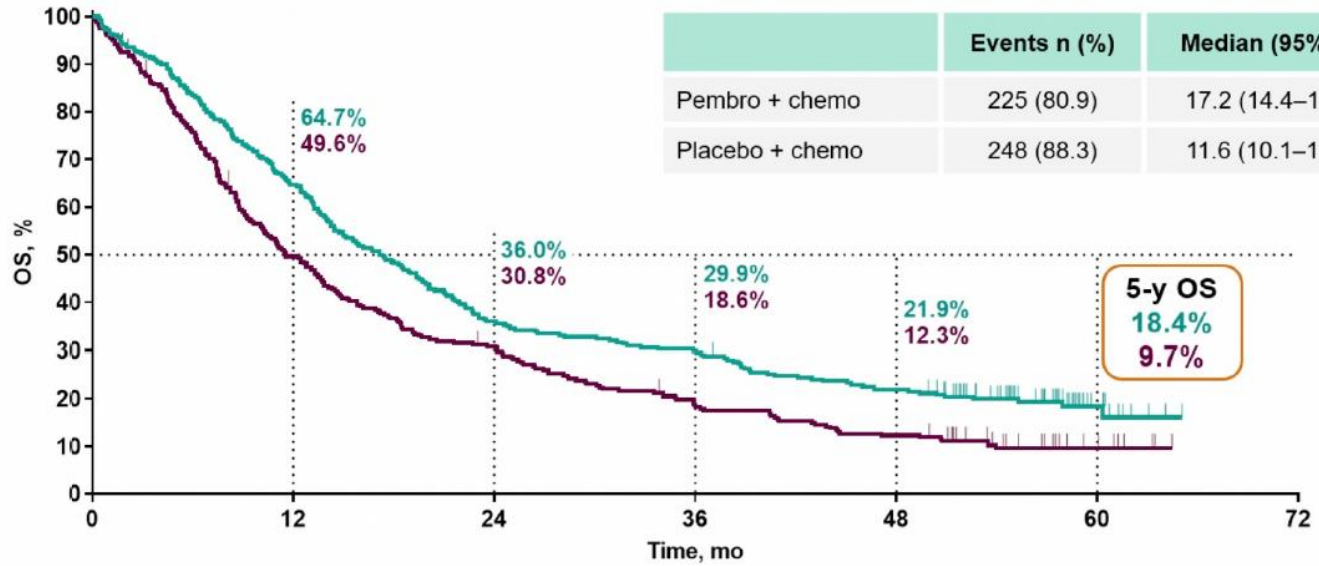
No. at risk							
Pembro + chemo	410	283	184	126	95	77	0
Placebo + chemo	206	98	55	34	27	22	0

	PD-L1 TPS ≥50%		PD-L1 TPS 1%–49%		PD-L1 TPS <1%	
	Pembro + chemo (n = 132)	Placebo + chemo (n = 70)	Pembro + chemo (n = 128)	Placebo + chemo (n = 58)	Pembro + chemo (n = 127)	Placebo + chemo (n = 63)
OS HR (95% CI)	0.68 (0.49–0.96)		0.65 (0.46–0.90)		0.55 (0.39–0.76)	
5-y OS rate,[a] %	29.6	21.4	19.8	7.7	9.6	5.3

[a]Kaplan-Meier estimate. Data cutoff date: March 8, 2022.

KN 407: Platte: OS

OS: ITT Population



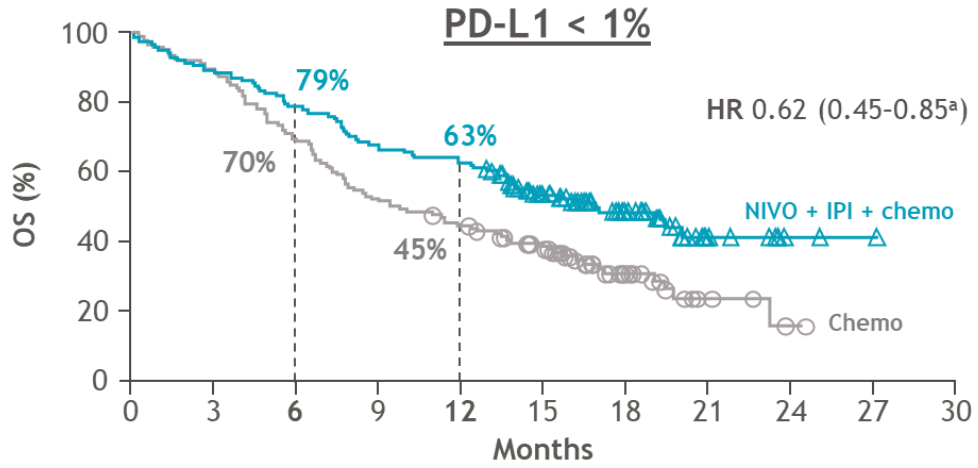
	Events n (%)	Median (95% CI)	HR (95% CI)
Pembro + chemo	225 (80.9)	17.2 (14.4–19.7)	0.71 (0.59–0.85)
Placebo + chemo	248 (88.3)	11.6 (10.1–13.7)	

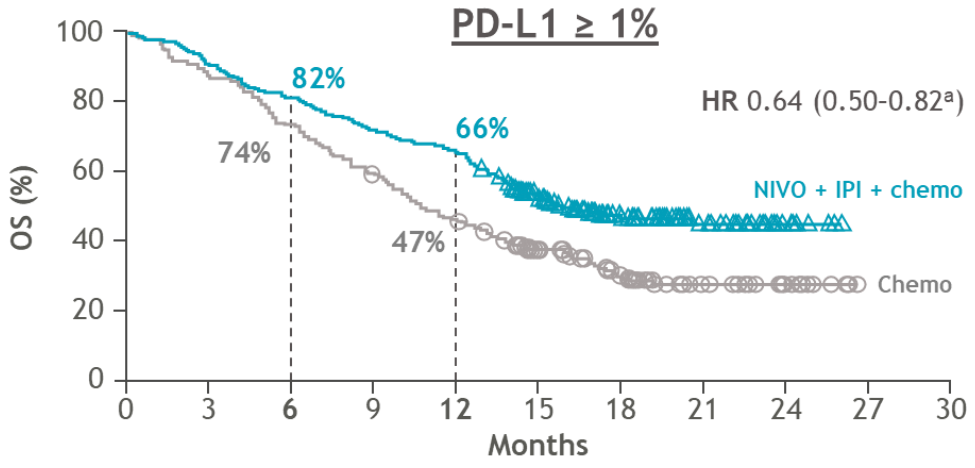
No. at risk							
Pembro + chemo	278	180	100	83	60	10	0
Placebo + chemo	281	137	84	50	33	7	0

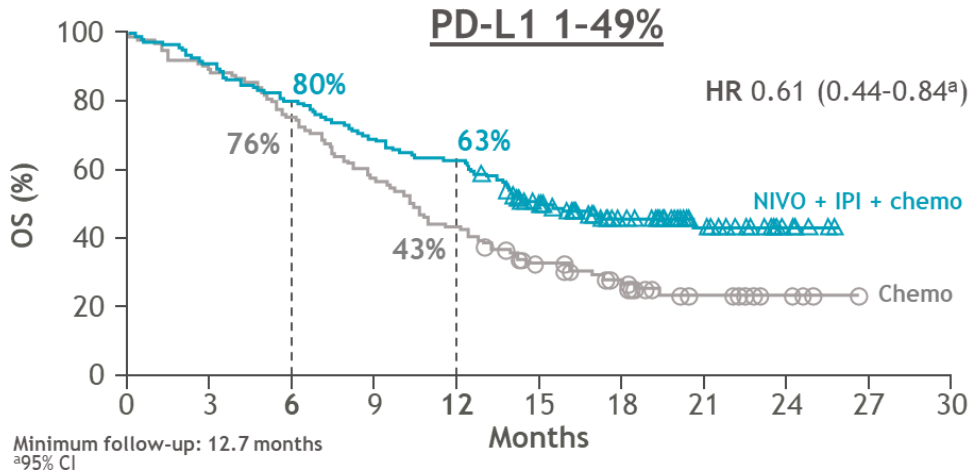
	PD-L1 TPS ≥50%		PD-L1 TPS 1%–49%		PD-L1 TPS <1%	
	Pembro + chemo (n = 73)	Placebo + chemo (n = 73)	Pembro + chemo (n = 103)	Placebo + chemo (n = 104)	Pembro + chemo (n = 95)	Placebo + chemo (n = 99)
OS HR (95% CI)	0.68 (0.47–0.97)		0.61 (0.45–0.83)		0.83 (0.61–1.13)	
5-y OS rate,[a] %	23.3	8.3	20.6	7.6	10.7	13.1

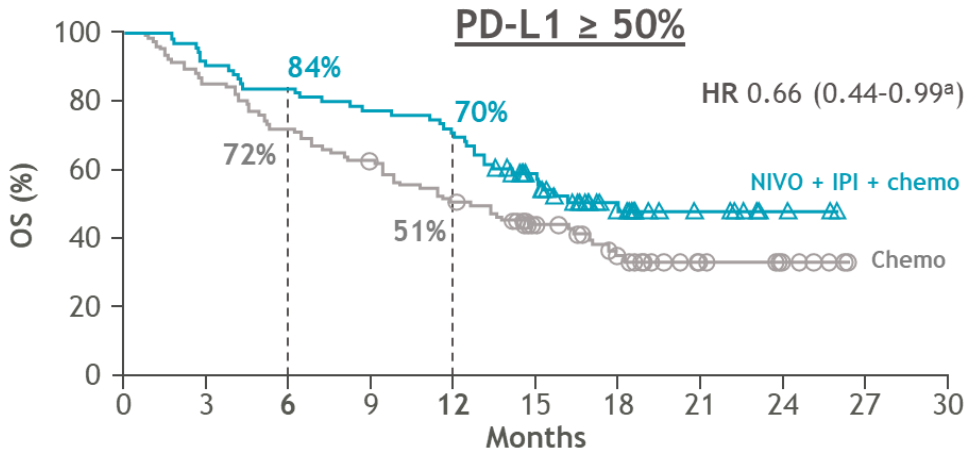
[a]Kaplan-Meier estimate. Data cutoff date: February 23, 2022.

CM 9LA: Chemotherapie vs. CTx 2 Zyklen + Ipi-Nivo: OS









Minimum follow-up: 12.7 months
[a]95% CI

Paz-Arez et al. Lancet Oncol. 2021 Feb;22(2):198-211

POSEIDON Study Design

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

Stage IV NSCLC

N=1013 (randomised)

- *EGFR*/*ALK*wt
- ECOG PS 0 or 1
- Treatment-naïve for metastatic disease
- Tumour biopsy* and baseline plasma sample (for ctDNA)

Stratification factors

- PD-L1 expression (TC ≥50% vs <50%)
- Disease stage (IVA vs IVB)
- Histology (NSQ vs SQ)

R 1:1:1

- **T+D+CT†** q3w 4 cycles → **T (week 16 only) + D q4w until PD**
- **D+CT†** q3w 4 cycles → **D q4w until PD**
- **Platinum-based CT†** q3w up to 6 cycles

Alpha-controlled endpoints

D+CT vs CT:
- PFS‡
- OS

T+D+CT vs CT:
- PFS‡
- OS

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

ctDNA, circulating tumour DNA; D, durvalumab; ECOG, Eastern Cooperative Oncology Group; PD, progressive disease; PS, performance status; q3w, every 3 weeks; q4w, every 4 weeks; T, tremelimumab; TC, tumour cell

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

OS Vorteil: T+D+CT: nicht zugelassen

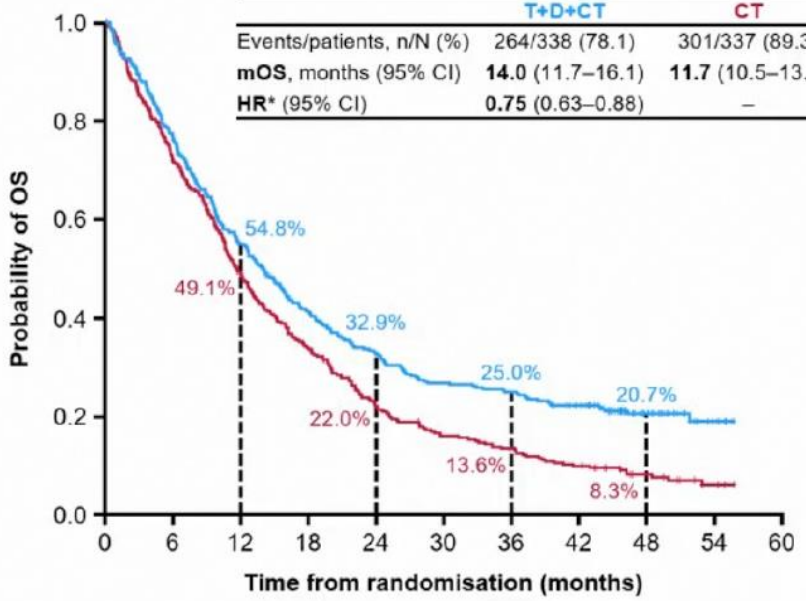
PARIS 2022 ESMO congress

OS Update

Durable long-term OS benefit for T+D+CT vs CT with HR 0.75 and estimated 25.0% alive at 3 yrs vs 13.6%

T+D+CT vs CT

	T+D+CT	CT
Events/patients, n/N (%)	264/338 (78.1)	301/337 (89.3)
mOS, months (95% CI)	**14.0** (11.7–16.1)	**11.7** (10.5–13.1)
HR* (95% CI)	**0.75** (0.63–0.88)	–

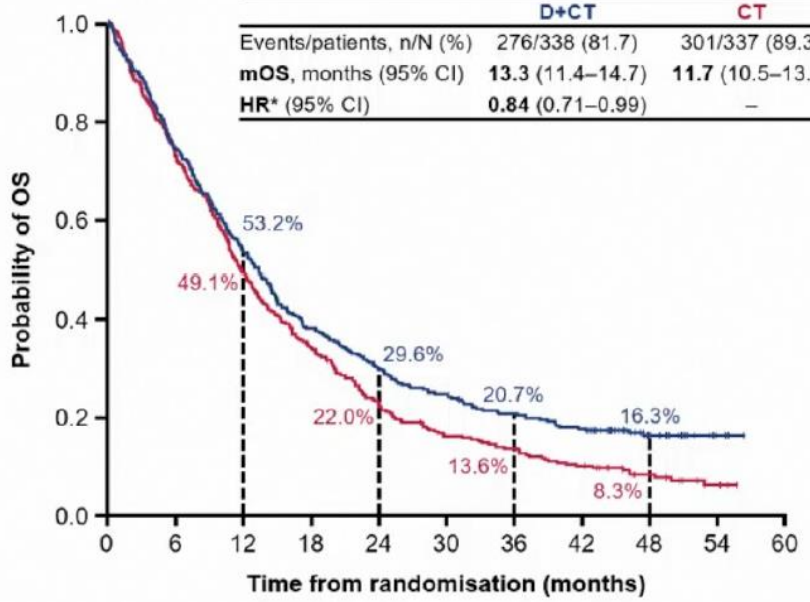


No. at risk

T+D+CT	338	256	183	137	109	89	83	70	32	6	0
CT	337	236	160	111	71	51	42	31	14	5	0

D+CT vs CT

	D+CT	CT
Events/patients, n/N (%)	276/338 (81.7)	301/337 (89.3)
mOS, months (95% CI)	**13.3** (11.4–14.7)	**11.7** (10.5–13.1)
HR* (95% CI)	**0.84** (0.71–0.99)	–



No. at risk

D+CT	338	247	176	126	97	81	67	57	26	5	0
CT	337	236	160	111	71	51	42	31	14	5	0

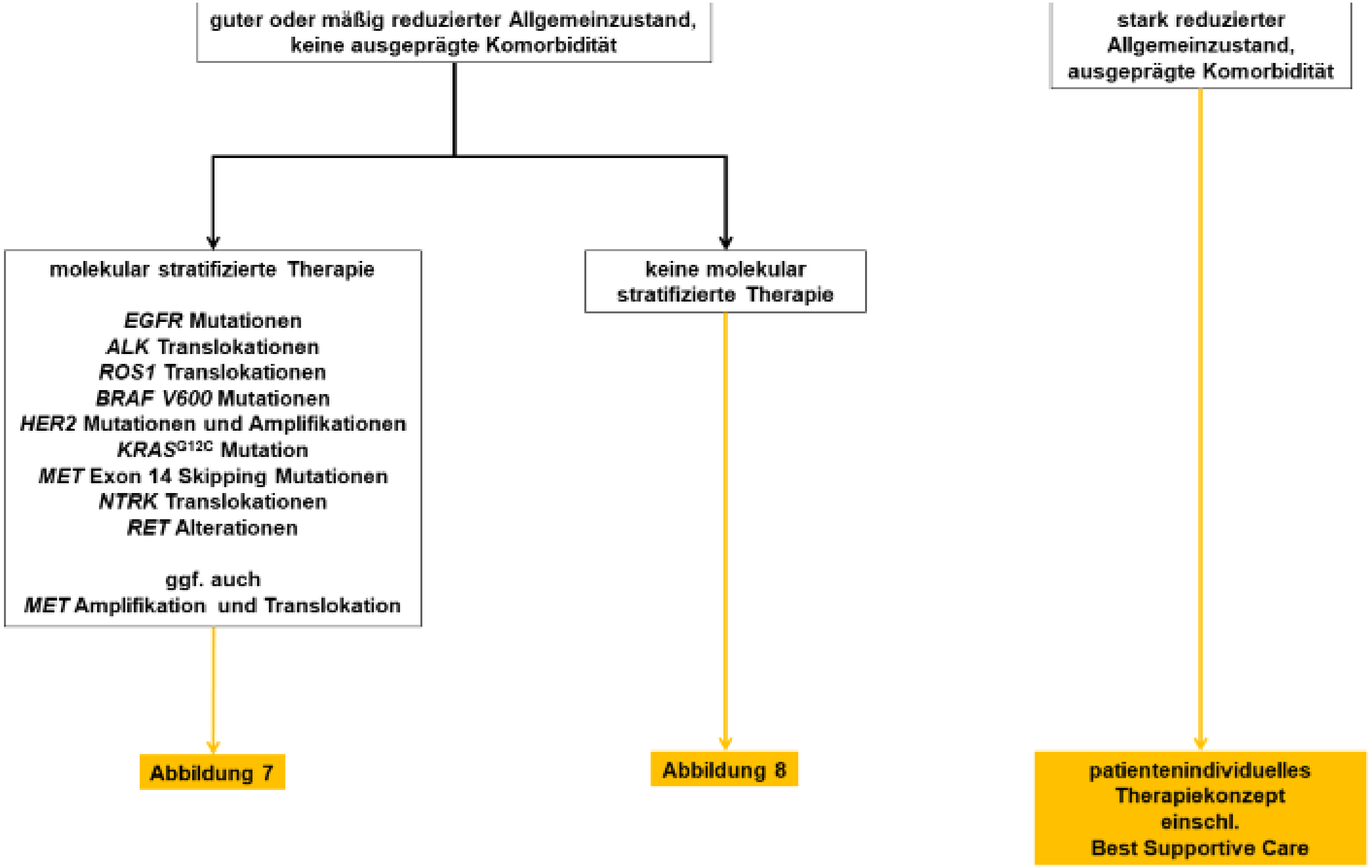
Median follow-up in censored patients at DCO: 46.5 months (range 0.0–56.5)

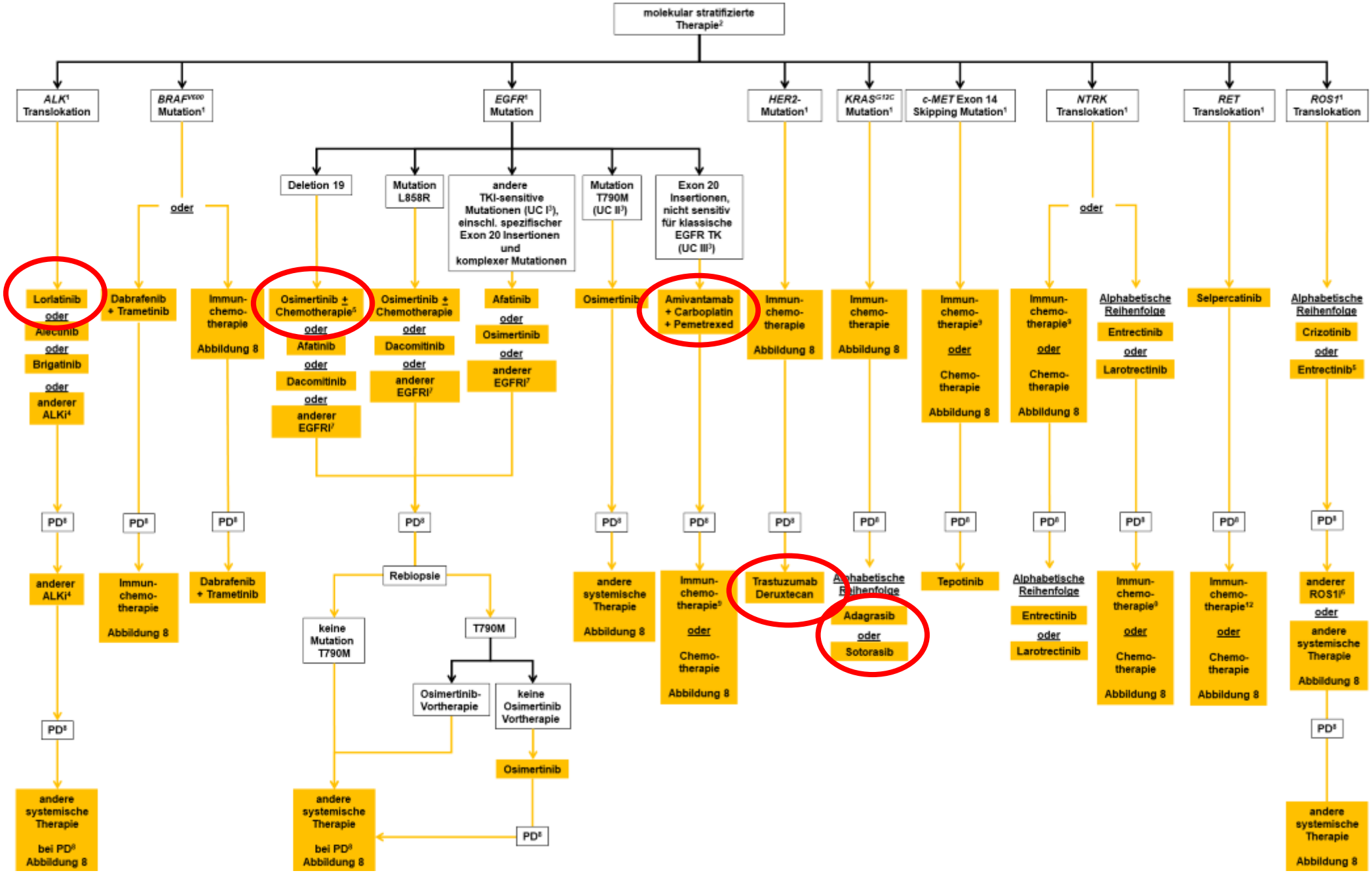
*HR <1 favours D(±T)+CT vs CT (stratified analysis); DCO, 11 Mar 2022

mOS, median OS

Themen

- **EGFR mt + : Osimertinib: bisher Standard: FLAURA2, Mariposa**
- **EGFR Exon 20 ins: Papillon: CTx + Amivantamab**
- **ALK+: Lorlatinib 5 Jahres Daten**
- *ROS + Tumore: keine Änderung (Crizotinib/Entrectinib)*
- *BRAF V600 +: Dabrafenib/Trametinib, neu: Encorafenib und Binimetinib (noch nicht zugelassen)*
- *RET: Selpercatinib 1st line (Pralsetinib vom Markt genommen)*
- *MET-Exon 14 Skipping: Tepotinib 2nd line(Capmatinib vom Markt genommen)*
- *KRAS G12C: Sotorasib, Neu: **Adagrasib**: 2nd line*
- *HER2 mt: Trastuzumab Deruxtecan (vorher off label, jetzt zugelassen)*


guter oder mäßig reduzierter Allgemeinzustand, keine ausgeprägte Komorbidität
stark reduzierter Allgemeinzustand, ausgeprägte Komorbidität
molekular stratifizierte Therapie
EGFR Mutationen
ALK Translokationen
ROS1 Translokationen
BRAF V600 Mutationen
HER2 Mutationen und Amplifikationen
KRASG12C Mutation
MET Exon 14 Skipping Mutationen
NTRK Translokationen
RET Alterationen
ggf. auch
MET Amplifikation und Translokation
keine molekular stratifizierte Therapie
Abbildung 7
Abbildung 8
patientenindividuelles Therapiekonzept einschl. Best Supportive Care


molekular stratifizierte Therapie[2]
ALK[1] Translokation
BRAF[V600] Mutation[1]
EGFR[1] Mutation
HER2-Mutation[1]
KRAS[G12C] Mutation[1]
c-MET Exon 14 Skipping Mutation[1]
NTRK Translokation[1]
RET Translokation[1]
ROS1[1] Translokation
Deletion 19
Mutation L858R
andere TKI-sensitive Mutationen (UC I[3]), einschl. spezifischer Exon 20 Insertionen und komplexer Mutationen
Mutation T790M (UC II[3])
Exon 20 Insertionen, nicht sensitiv für klassische EGFR TK (UC III[3])
oder
Lorlatinib
oder
Alectinib
oder
Brigatinib
oder
anderer ALKi[4]
Dabrafenib + Trametinib
Immun-chemo-therapie
Abbildung 8
Osimertinib ± Chemotherapie[5]
oder
Afatinib
oder
Dacomitinib
oder
anderer EGFRI[7]
Osimertinib ± Chemotherapie
oder
Dacomitinib
oder
anderer EGFRI[7]
Afatinib
oder
Osimertinib
oder
anderer EGFRI[7]
Osimertinib
Amivantamab + Carboplatin + Pemetrexed
Immun-chemo-therapie
Abbildung 8
Immun-chemo-therapie
Abbildung 8
Immun-chemo-therapie[9]
oder
Chemo-therapie
Abbildung 8
Immun-chemo-therapie[9]
oder
Chemo-therapie
Abbildung 8
Alphabetische Reihenfolge
Entrectinib
oder
Larotrectinib
Selpercatinib
Alphabetische Reihenfolge
Crizotinib
oder
Entrectinib[5]
PD[8]
anderer ALKi[4]
Immun-chemo-therapie
Abbildung 8
Dabrafenib + Trametinib
Rebiopsie
keine Mutation T790M
T790M
Osimertinib-Vortherapie
keine Osimertinib Vortherapie
Osimertinib
andere systemische Therapie
bei PD[8]
Abbildung 8
andere systemische Therapie
Abbildung 8
Immun-chemo-therapie[9]
oder
Chemo-therapie
Abbildung 8
Trastuzumab Deruxtecan
Alphabetische Reihenfolge
Adagrasib
oder
Sotorasib
Tepotinib
Alphabetische Reihenfolge
Entrectinib
oder
Larotrectinib
Immun-chemo-therapie[9]
oder
Chemo-therapie
Abbildung 8
Immun-chemo-therapie[12]
oder
Chemo-therapie
Abbildung 8
anderer ROS1i[6]
oder
andere systemische Therapie
Abbildung 8
andere systemische Therapie
Abbildung 8

FLAURA2 Phase III study design

Safety run-in period (N=30)
Published in ESMO Open, 2021[1]

Patients with untreated locally advanced / metastatic EGFRm NSCLC

Key inclusion criteria:

- Aged ≥18 years (Japan: ≥20 years)
- Pathologically confirmed non-squamous NSCLC
- Ex19del / L858R (local / central test)
- WHO PS 0 / 1
- No prior systemic therapy for advanced NSCLC
- Stable CNS metastases were allowed*
- Brain scans at baseline (MRI / CT)

Stratification by:

- **Race** (Chinese Asian / non-Chinese Asian / non-Asian)
- **EGFRm** (local / central test)
- **WHO PS** (0 / 1)

Randomization 1:1 (N=557)

Osimertinib 80 mg (QD) + pemetrexed 500 mg/m² + carboplatin AUC5 or cisplatin 75 mg/m² (Q3W for 4 cycles for platinum-based treatments)

Maintenance osimertinib 80 mg (QD) + pemetrexed (Q3W)†

Osimertinib 80 mg (QD)

Follow-up:

- RECIST 1.1 assessment at 6 and 12 weeks, then every 12 weeks until RECIST 1.1 defined radiological disease progression or other withdrawal criteria were met

- **Primary endpoint:** PFS by investigator assessment per RECIST 1.1‡§
  - **Sensitivity analysis:** PFS by BICR assessment per RECIST 1.1
- **Secondary endpoints:** OS, ORR, DoR, DCR, HRQoL, safety (AEs by CTCAE v5) and PFS2‡

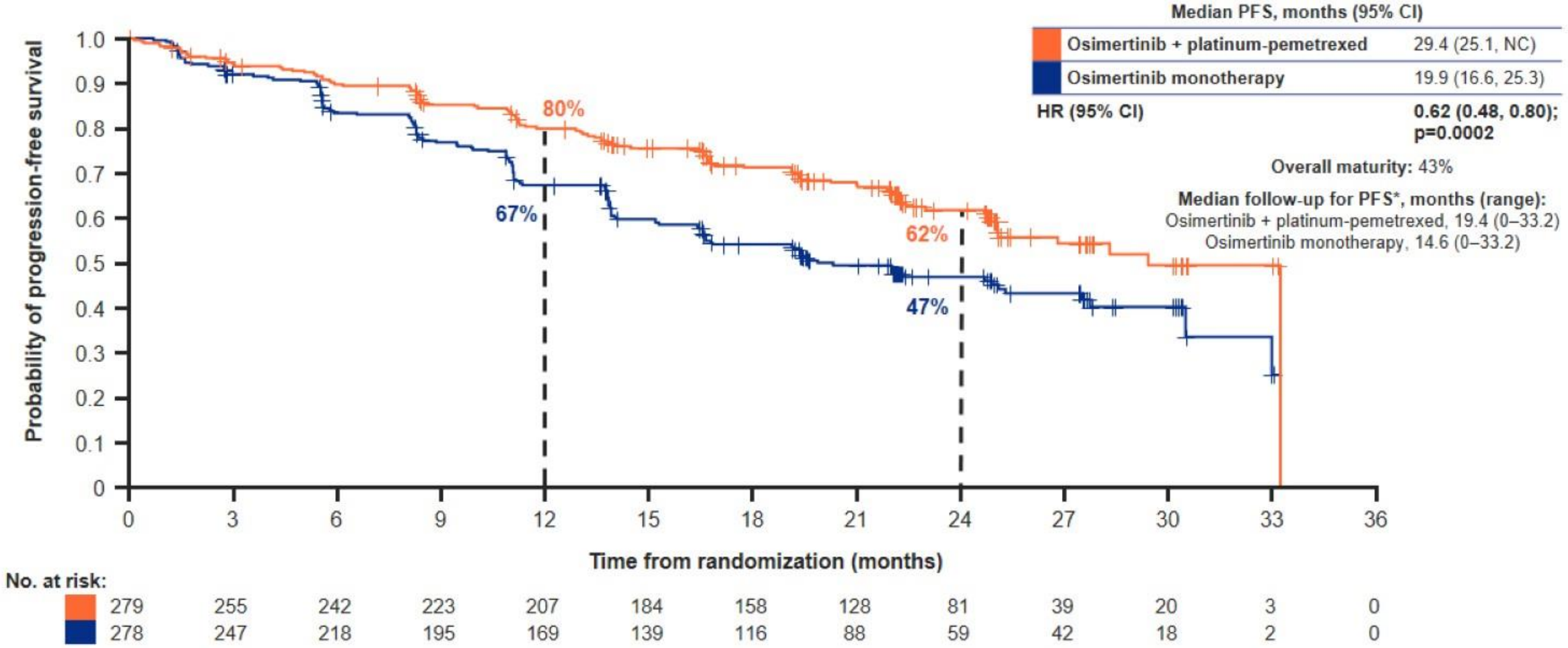
1. Planchard et al. ESMO Open 2021;6:100271

*Not requiring steroids for at least two weeks; †Pemetrexed maintenance continued until a discontinuation criterion was met; ‡Efficacy analyses in the full analysis set, defined as all patients randomized to study treatment regardless of the treatment actually received, and safety analyses in the safety analysis set, defined as all randomized patients who received ≥1 dose of study treatment – one patient who was randomized to osimertinib plus platinum-pemetrexed received only osimertinib and was therefore included in the osimertinib monotherapy safety analysis set; §The study provided 90% power to demonstrate a statistically significant difference in PFS assuming HR=0.68 at 5% two-sided significance level

AE, adverse event; AUC, area under curve; BICR, blinded independent central review; CNS, central nervous system; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; DCR, disease control rate; DoR, duration of response; EGFRm, epidermal growth factor receptor-mutated; EGFR-TKI, EGFR-tyrosine kinase inhibitor; Ex19del, exon 19 deletion; HR, hazard ratio; HRQoL, health-related quality of life; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PFS2, second progression-free survival; QD, once-daily; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; WHO PS, World Health Organization performance status

Progression-free survival per BICR

- Median PFS was improved by ~9.5 months with osimertinib plus platinum-pemetrexed vs osimertinib monotherapy

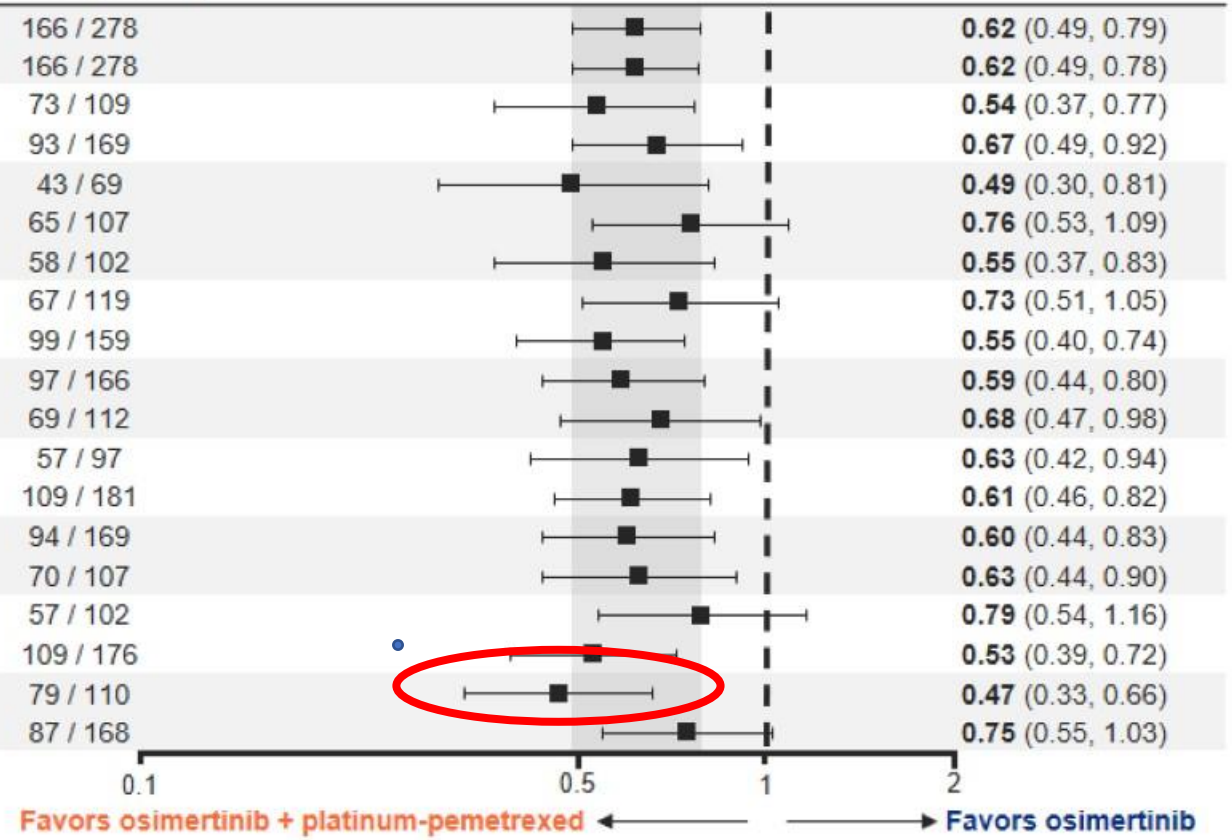


Data cut-off: 03 April 2023
*In all patients
BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; NC, not calculable; PFS, progression-free survival

PFS per investigator across subgroups*

- PFS benefit was consistent across all pre-defined subgroups

Subgroup		Osimertinib + platinum-pemetrexed (Events / patients)	Osimertinib monotherapy (Events / patients)	HR (95% CI)
All patients	Stratified log-rank	120 / 279	166 / 278	**0.62** (0.49, 0.79)
	Unadjusted Cox PH	120 / 279	166 / 278	**0.62** (0.49, 0.78)
Sex	Male	51 / 106	73 / 109	**0.54** (0.37, 0.77)
	Female	69 / 173	93 / 169	**0.67** (0.49, 0.92)
Race	Chinese Asian	26 / 71	43 / 69	**0.49** (0.30, 0.81)
	Non-Chinese Asian	54 / 107	65 / 107	**0.76** (0.53, 1.09)
	Non-Asian	40 / 101	58 / 102	**0.55** (0.37, 0.83)
EGFR mutation test method	Central	52 / 121	67 / 119	**0.73** (0.51, 1.05)
	Local	68 / 158	99 / 159	**0.55** (0.40, 0.74)
Age at screening	<65 years	73 / 174	97 / 166	**0.59** (0.44, 0.80)
	≥65 years	47 / 105	69 / 112	**0.68** (0.47, 0.98)
Smoking history	Yes	43 / 91	57 / 97	**0.63** (0.42, 0.94)
	No	77 / 188	109 / 181	**0.61** (0.46, 0.82)
EGFR mutation type†	Ex19del	65 / 172	94 / 169	**0.60** (0.44, 0.83)
	L858R	55 / 106	70 / 107	**0.63** (0.44, 0.90)
WHO PS	0	48 / 101	57 / 102	**0.79** (0.54, 1.16)
	1	72 / 178	109 / 176	**0.53** (0.39, 0.72)
CNS status at baseline	Yes	52 / 116	79 / 110	**0.47** (0.33, 0.66)
	No	68 / 163	87 / 168	**0.75** (0.55, 1.03)

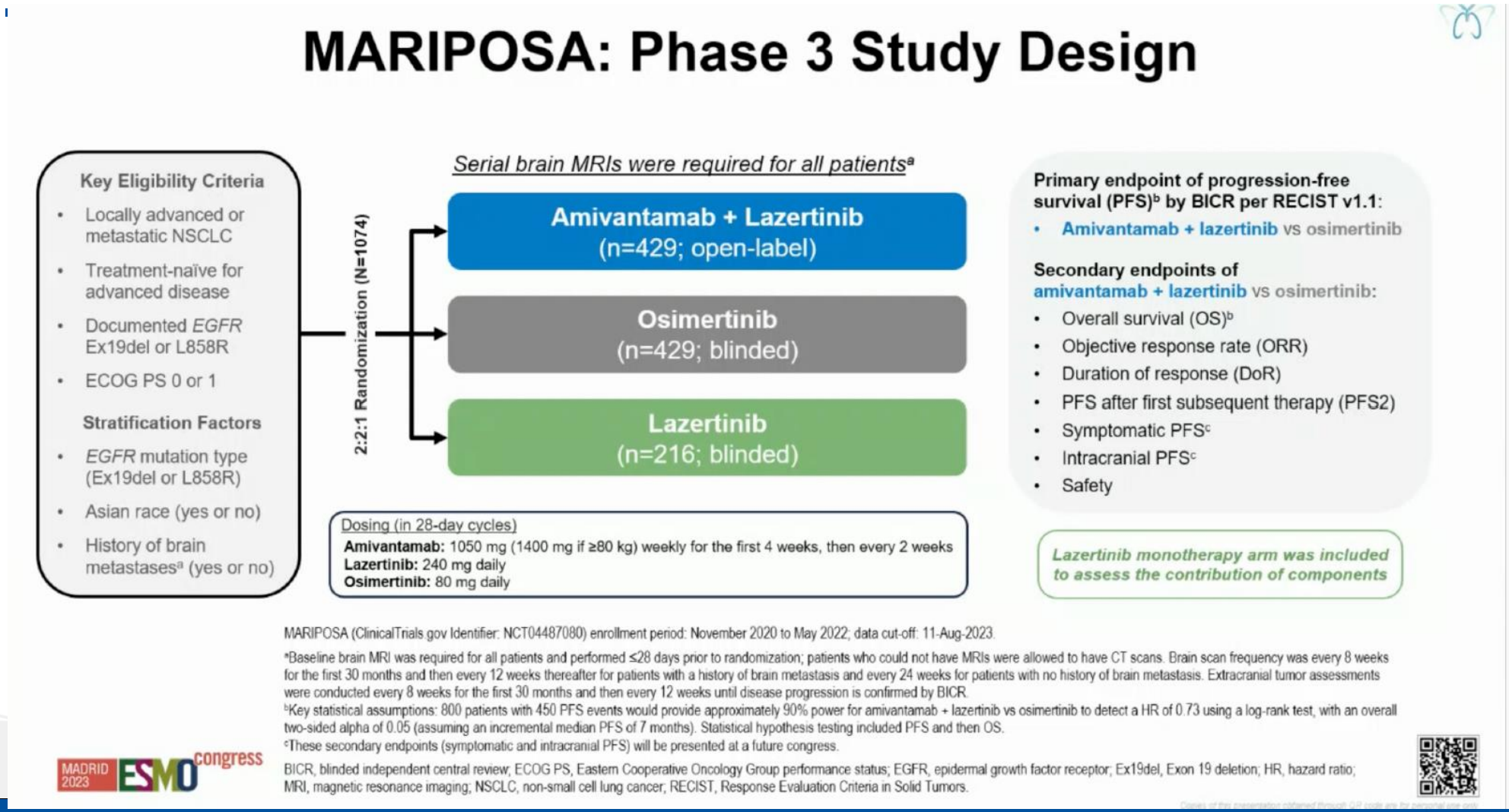


Data cut-off: 03 April 2023

*Two additional subgroups performed to fulfil regulatory requirements for diagnostics are not included: EGFR mutations by central cobas® tissue test and EGFR mutations by central cobas® ctDNA test; †For EGFR mutation type, patients with both Ex19del and L858R were included in the Ex19del group

CI, confidence interval; CNS, central nervous system; EGFR, epidermal growth factor receptor; Ex19del, Exon 19 deletion; HR, hazard ratio; PFS, progression-free survival; PH, proportional hazard; WHO PS, World Health Organization performance status

Marioposa: 1st line EGFR common mutation: Osi vs. Ami + Lazer

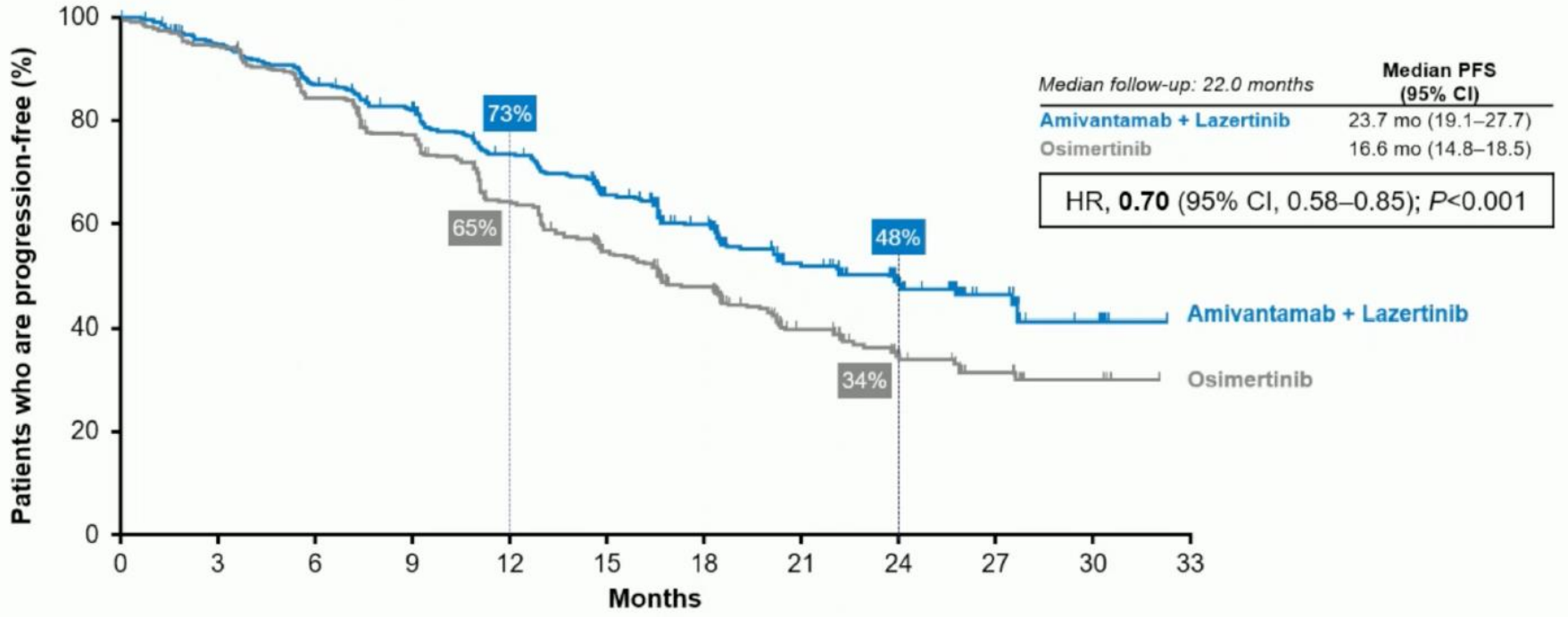


Cho et al., ESMO 2023

Marioposa: 1st line EGFR common mutation: Osi vs. Ami + Lazer

Primary Endpoint: Progression-free Survival by BICR[a]

Amivantamab + lazertinib reduced the risk of progression or death by 30% and improved median PFS by 7.1 months



Median follow-up: 22.0 months	Median PFS (95% CI)
Amivantamab + Lazertinib	23.7 mo (19.1–27.7)
Osimertinib	16.6 mo (14.8–18.5)

HR, **0.70** (95% CI, 0.58–0.85); *P*<0.001

No. at risk												
Amivantamab + Lazertinib	429	391	357	332	291	244	194	106	60	33	8	0
Osimertinib	429	404	358	325	266	205	160	90	48	28	10	0

MADRID 2023 ESMO congress

[a]At time of the prespecified final PFS analysis, there were a total of 444 PFS events in the amivantamab + lazertinib and osimertinib arms combined.

BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; mo, months; PFS, progression-free survival.

Cho et al., ESMO 2023

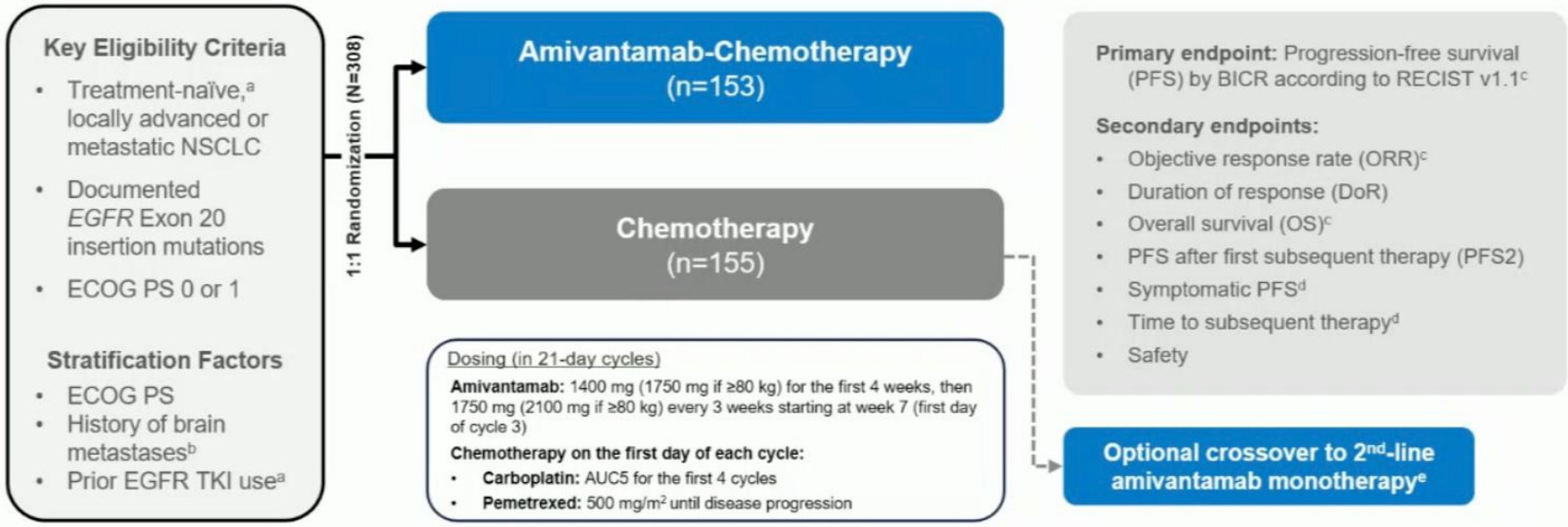
FLAURA2 vs MARIPOSA

FLAURA2		MARIPOSA
25.5m vs 16.7m (inv), HR 0.62	PFS	23.7m vs 16.6m (BICR), HR 0.70
24.9m vs 13.8m (HR 0.47)	PFS in CNS+	18.3m vs 13.0m (HR 0.69)
	PFS in M1 (HEP)	18.2m vs 11m, HR 0.58
HR 0.90 (0.65-1.24, p=0.5238)	**OS**	**0.80 (0.61-1.05, p=0.11)**
64% vs 27%	**G3+ TEAEs**	**75% vs 43%**
Anemia, nausea, neutropenia, thrombocytopenia, appetite		**Infusion reaction, paronychia, rash, hypoalbuminemia, VTE**

Janne, WCLC 2023; Cho, ESMO 2023

Papillon: 1st line Exon 20 ins: CTx vs. CTx + Amivantamab

PAPILLON: Phase 3 Study Design



PAPILLON (ClinicalTrials.gov Identifier: NCT04538664) enrollment period: December 2020 to November 2022; data cut-off: 3-May-2023.

[a]Removed as stratification factor since only 4 patients had prior EGFR TKI use (brief monotherapy with common EGFR TKIs was allowed if lack of response was documented).
[b]Patients with brain metastases were eligible if they received definitive treatment and were asymptomatic, clinically stable, and off corticosteroid treatment for ≥2 weeks prior to randomization.
[c]Key statistical assumption: 300 patients with 200 events needed for 90% power to detect an HR of 0.625 (estimated PFS of 8 vs 5 months). PFS, ORR, and then OS were included in hierarchical testing.
[d]These secondary endpoints (time to subsequent therapy and symptomatic progression-free survival) will be presented at a future congress.
[e]Crossover was only allowed after BICR confirmation of disease progression; amivantamab monotherapy on Q3W dosing per main study.

AUC, area under the curve; BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; HR, hazard ratio; NSCLC, non-small cell lung cancer; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; TKI, tyrosine kinase inhibitor.

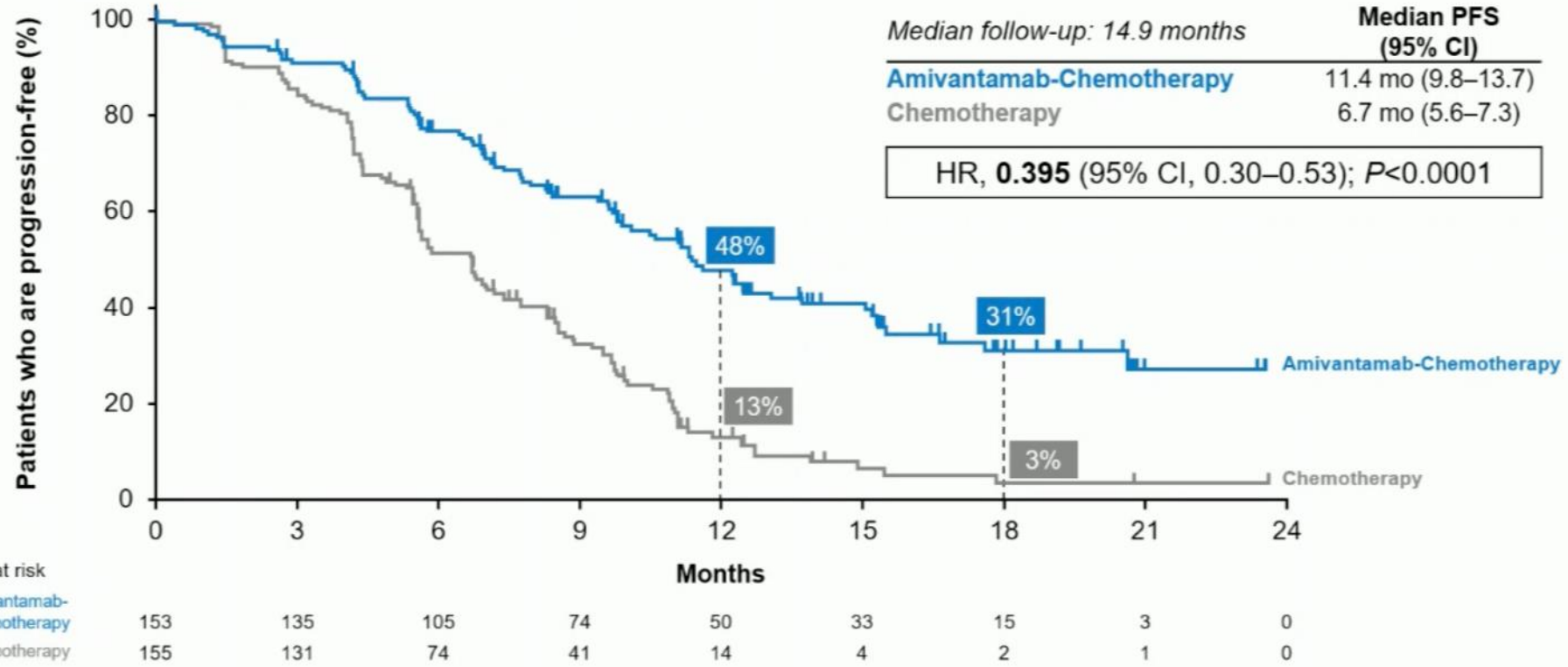
MADRID 2023 ESMO congress

Zhou et al., October 21, 2023, DOI: 10.1056/NEJMoa2306441

Papillon: Exon 20 ins: CTx vs. CTx + Amivantamab

Primary Endpoint: Progression-free Survival by BICR

Amivantamab-chemotherapy reduced risk of progression or death by 60%



MADRID 2023 ESMO congress

Consistent PFS benefit by investigator: 12.9 vs 6.9 mo (HR, 0.38; 95% CI, 0.29–0.51; *P*<0.0001[a])

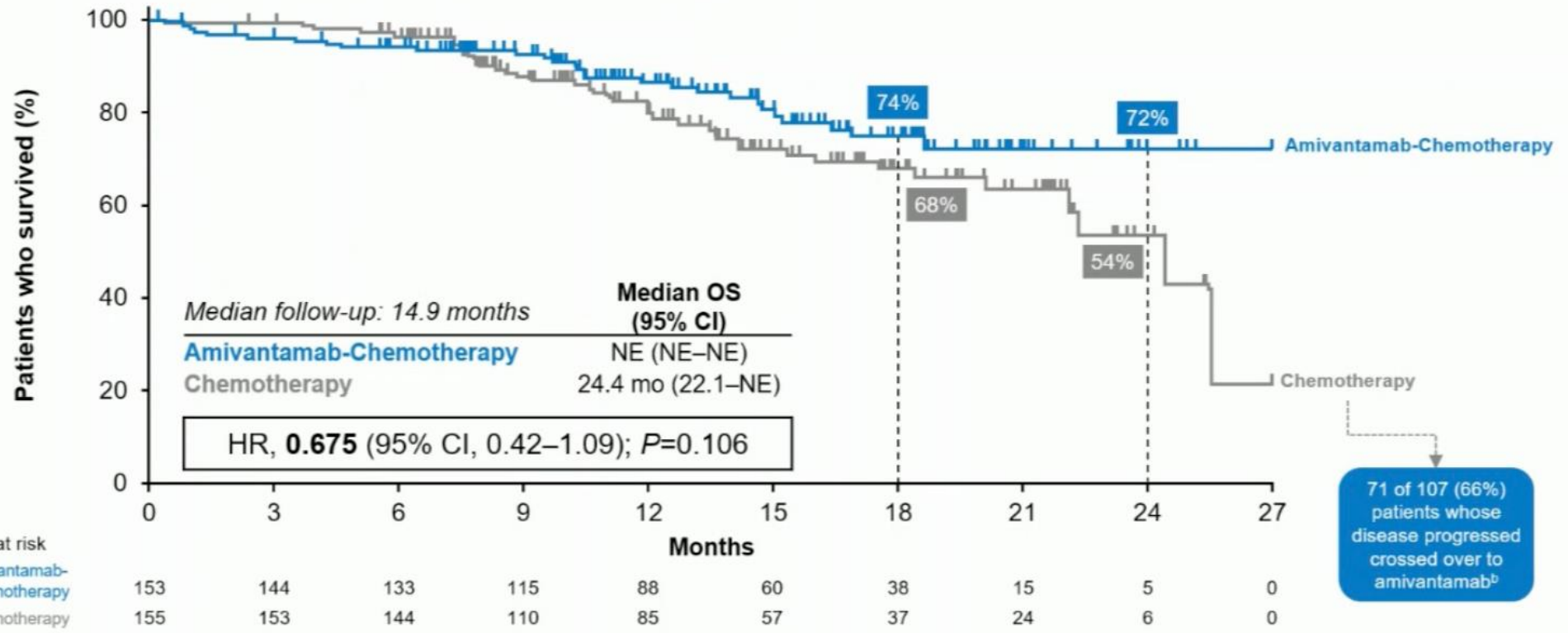
[a]Nominal *P*-value; endpoint not part of hierarchical hypothesis testing. BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; mo, months; PFS, progression-free survival.

Zhou et al., October 21, 2023, DOI: 10.1056/NEJMoa2306441

Papillon: Exon 20 ins: CTx vs. CTx + Amivantamab

Interim Overall Survival[a]

Amivantamab-chemotherapy shows trend in reducing risk of death by over 30%



[a]There were 70 deaths in the study at the time of the prespecified interim OS analysis, which represents 23% of all randomized patients and 33% of the ~210 projected deaths for the final OS analysis.
[b]A total of 71 patients (65 patients as part of the crossover arm plus an additional 6 patients off-protocol) received second-line amivantamab monotherapy out of 107 chemotherapy-randomized patients with disease progression.

CI, confidence interval; HR, hazard ratio; mo, months; NE, not estimable; OS, overall survival.

MADRID 2023 ESMO congress

Zhou et al., October 21, 2023, DOI: 10.1056/NEJMoa2306441

Zusammenfassung

EGFR L858R und Exon19del:

Osimertinib: zugelassener Standard

Osi + CTx: Subgruppen (ZNS, Tumorlast?, L858R?)

Marioposa: keine Zulassung, *Amivantamab sc weniger toxisch als iv*

EGFR Exon 20 ins:

Papillon per KÜ, Zulassung eingereicht

CROWN: A Randomized Global Phase 3 Study

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 QD n=149

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

Crizotinib 250 mg BID n=147

No crossover between treatment arms was permitted

Primary endpoint
- PFS[a] by BICR

Secondary endpoints
- Overall survival
- PFS by investigator
- ORR by BICR and investigator
- DOR, IC ORR, and IC DOR by BICR
- IC TTP by BICR
- TTR and IC TTR by BICR
- Safety
- Quality of life
- Biomarker analyses

- In a subsequent post hoc analysis, at 3 years of follow-up, median PFS by BICR was still not reached (95% CI, NR-NR) with lorlatinib and 9.3 months (95% CI, 7.6-11.1 months) with crizotinib (HR, 0.27; 95% CI, 0.18-0.39)

BICR, blinded independent central review; BID, twice daily; CNS, central nervous system; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; IC, intracranial; NR, not reached; NSCLC, non-small cell lung cancer; ORR, objective response rate; PFS, progression-free survival; PS, performance status; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; TTP, time to tumor progression; TTR, time to tumor response.
[a] Defined as the time from randomization to RECIST-defined progression or death due to any cause.
Solomon BJ, et al. *Lancet Respir Med.* 2023;11:354-366.

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

Current *post hoc* analyses at 5 years

Given that median PFS was still not reached after 3 years, the current analyses aimed to quantify long-term outcomes based on investigator assessment at a clinically meaningful landmark follow-up of 5 years[1]

Endpoint evaluation by BICR stopped after the 3-year analysis[1]

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

Randomised 1:1 N=296[2]

Lorlatinib 100 mg QD n=149[2]

Stratified by:[2]

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

Crizotinib 250 mg BID n=147[2]

No crossover between treatment arms was permitted

Current analyses

Data cutoff: October 31, 2023

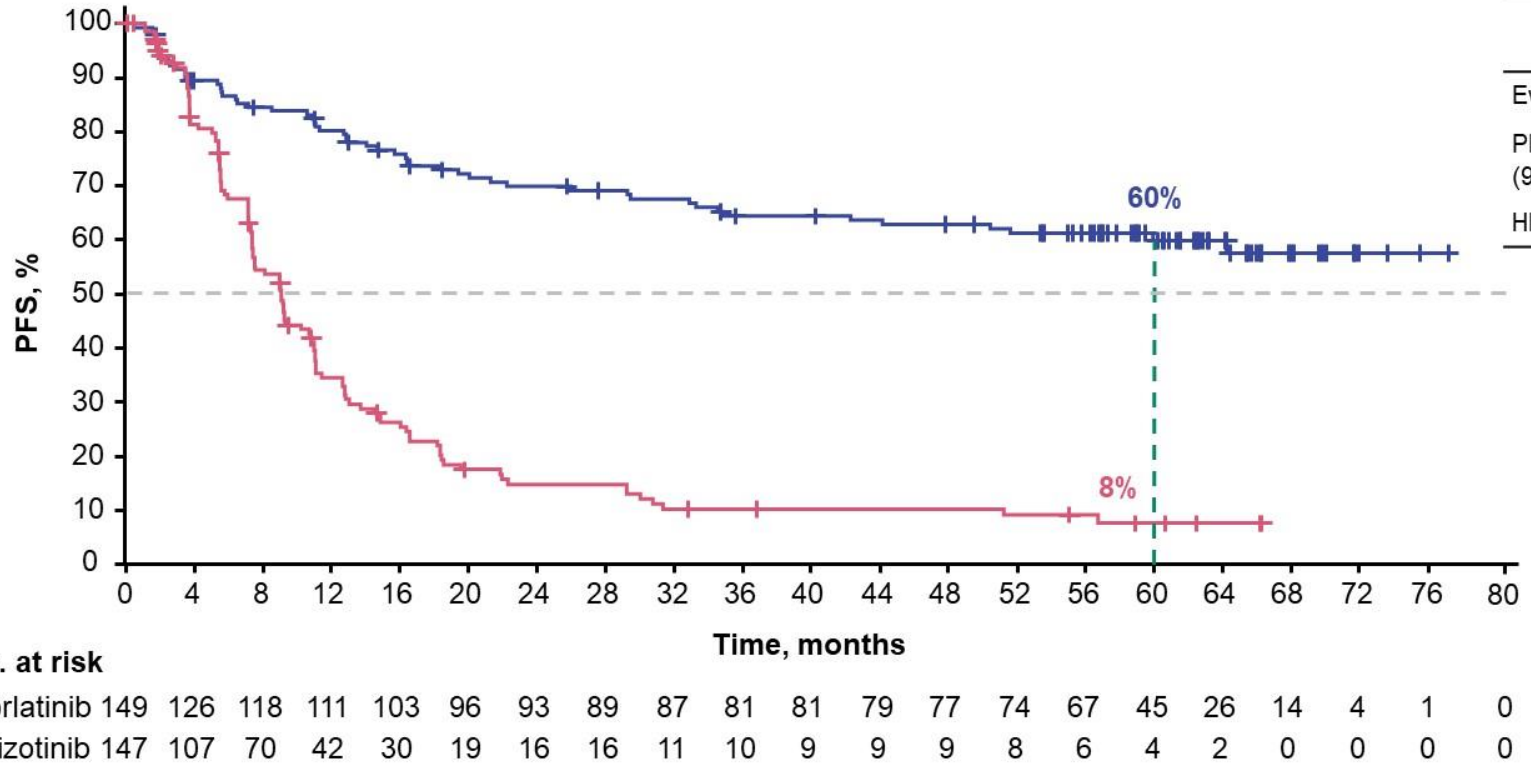
- **Investigator Assessed**
  - PFS[a]
  - ORR and IC ORR
  - DOR and IC DOR
  - IC TTP
- Safety
- Biomarker analyses

[a]Formal statistical testing was not performed; [b]Defined as the time from randomisation to RECIST-defined progression or death due to any cause.

ALK, anaplastic lymphoma kinase; BICR, blinded independent central review; BID, twice daily; CNS, central nervous system; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; IC, intracranial; NSCLC, non-small cell lung cancer; ORR, objective response rate; PFS, progression-free survival; PS, performance status; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumours; TTP, time to tumour progression.

1. Solomon BJ, et al. *J Clin Oncol* 2024 (epub ahead of print) doi: 10.1200/JCO.24.00581; 2. Solomon BJ, et al. *Lancet Respir Med* 2023;11:354–66; 3. NCT03052608. Available at: https://clinicaltrials.gov/study/NCT03052608 (Accessed May 2024).

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)**	

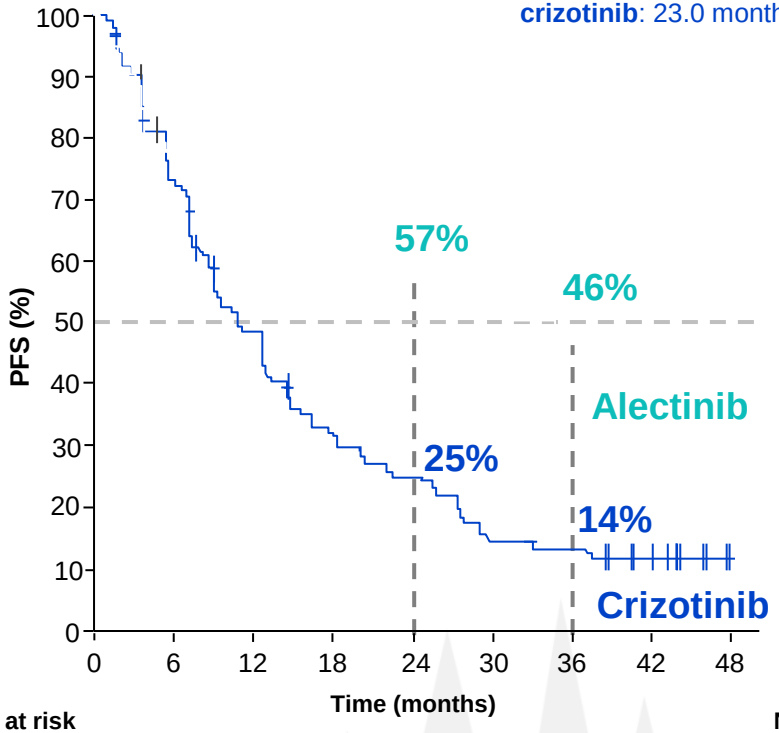
HR, hazard ratio; ITT, intention to treat; NR, not reached; PFS, progression-free survival.

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

Investigator-assessed mPFS for alectinib, brigatinib, and lorlatinib

ALEX (alectinib)[1]

Median duration of follow-up:
crizotinib: 23.0 months

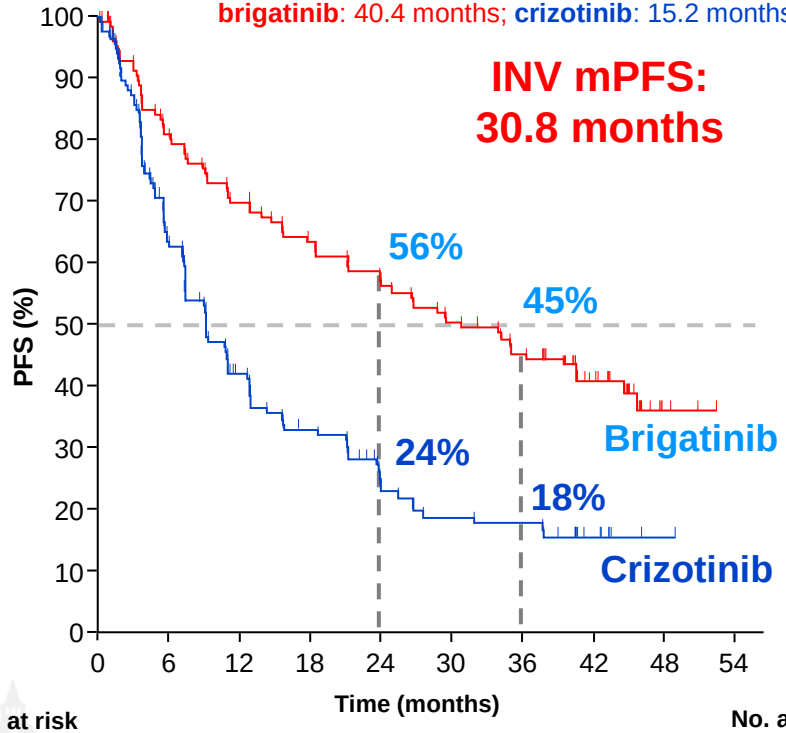


No. at risk

Alectinib	152	113	98	81	79	69	61	39	3
Crizotinib	151	104	65	43	33	19	17	11	NE

ALTA-1L (brigatinib)[2,3]

Median duration of follow-up:
brigatinib: 40.4 months; **crizotinib**: 15.2 months

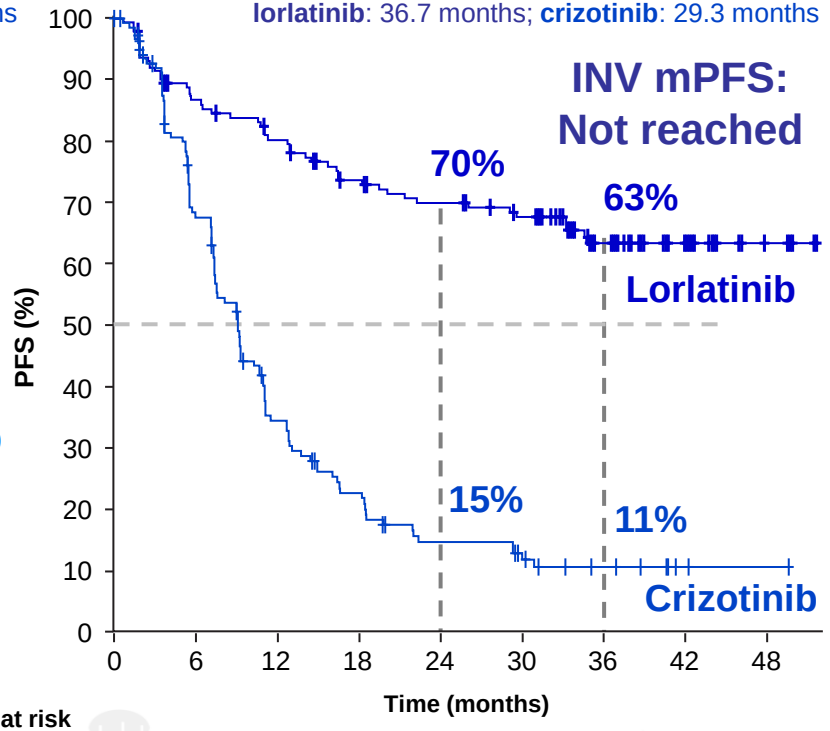


No. at risk

Brigatinib	137	102	88	78	70	60	52	30	3
Crizotinib	138	80	46	35	22	18	17	7	1

CROWN (lorlatinib)[4]

Median duration of follow-up:
lorlatinib: 36.7 months; **crizotinib**: 29.3 months



No. at risk

Lorlatinib	149	122	111	99	93	86	51	22	4
Crizotinib	147	88	42	26	16	12	6	2	1

Cross-trial comparisons have significant limitations. This information is presented in order to generate discussion, not to make comparisons between study results.

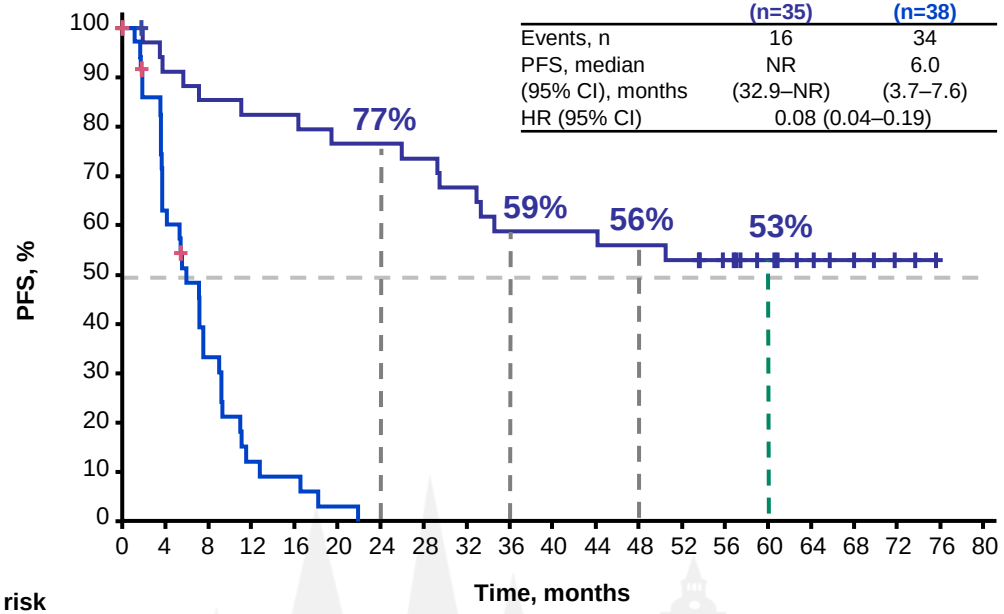
Vertical lines on the graphs indicate censored data.

INV, investigator; mPFS, median progression-free survival; NE, not estimable; PFS, progression-free survival.

1. Mok T, et al. *Ann Oncol* 2020;31:1056–64; 2. Camidge DR, et al. *J Thorac Oncol* 2021;16:2091–108; 3. Camidge DR, et al. *J Clin Oncol* 2020;38:3592–603; 4. Solomon BJ, et al. *Lancet Respir Med* 2023;11:354–66.

Lorlatinib showed superior PFS benefit irrespective of presence or absence of baseline brain metastases

With baseline brain metastases

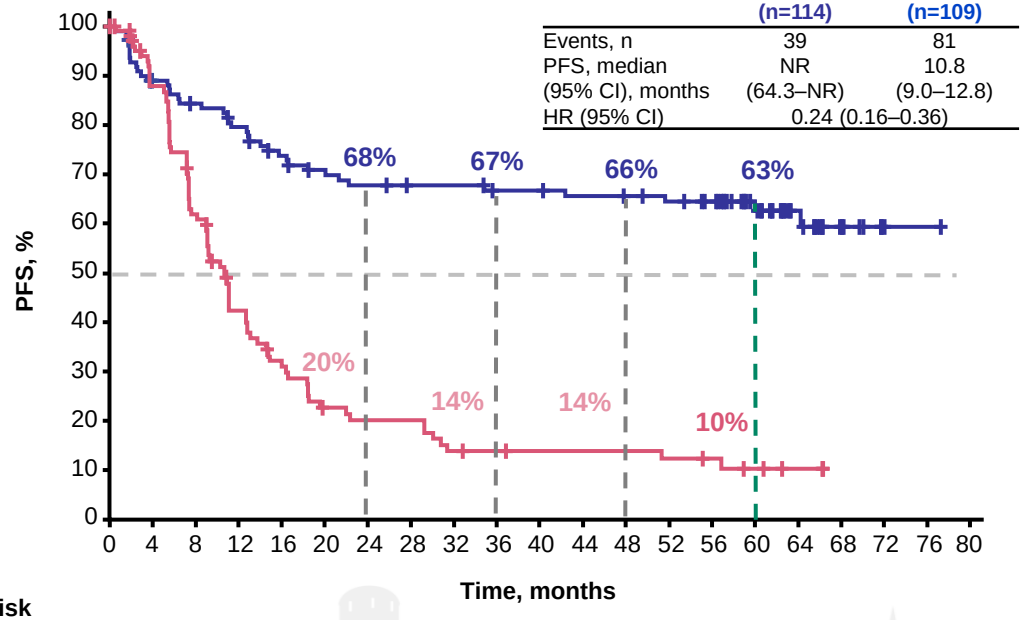


	Lorlatinib (n=35)	Crizotinib (n=38)
Events, n	16	34
PFS, median (95% CI), months	NR (32.9–NR)	6.0 (3.7–7.6)
HR (95% CI)	0.08 (0.04–0.19)	

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

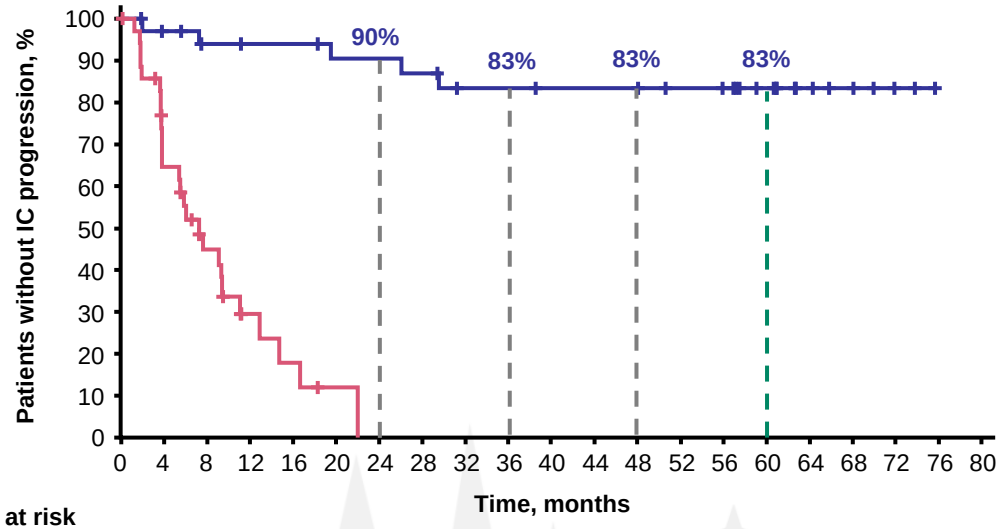
CI, confidence interval; HR, hazard ratio; NR, not reached; PFS, progression-free survival.

Solomon BJ, et al. *J Clin Oncol* 2024 (epub ahead of print) doi: 10.1200/JCO.24.00581.

Time to IC progression was longer with lorlatinib in presence or absence of baseline brain metastases

With baseline brain metastases

	Lorlatinib (n=35)	Crizotinib (n=38)
Events, n	5	26
Time to IC progression, median (95% CI), months	NR (NR–NR)	7.2 (3.7–11.0)
HR (95% CI)	0.03 (0.01–0.13)	

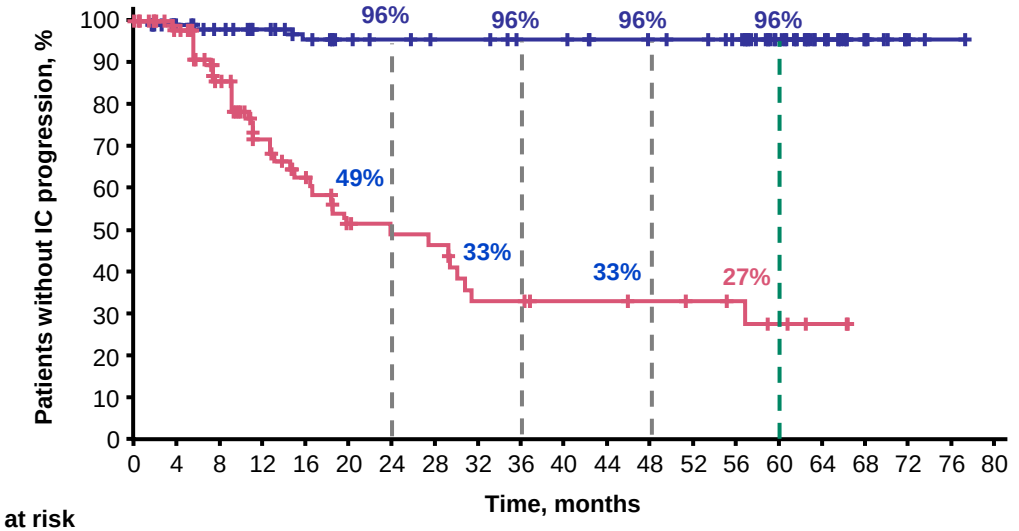


No. at risk

Lorlatinib	35	32	29	28	28	26	26	25	22	22	20	20	19	18	17	12	7	5	2	0	-
Crizotinib	38	21	12	5	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	4	39
Time to IC progression, median (95% CI), months	NR (NR–NR)	23.9 (16.4–30.8)
HR (95% CI)	0.05 (0.02–0.13)	



No. at risk

Lorlatinib	114	96	90	84	77	72	70	67	67	64	64	61	60	59	55	38	22	9	3	1	0
Crizotinib	109	86	63	41	31	21	19	18	12	12	10	10	9	8	6	4	2	0	0	0	0

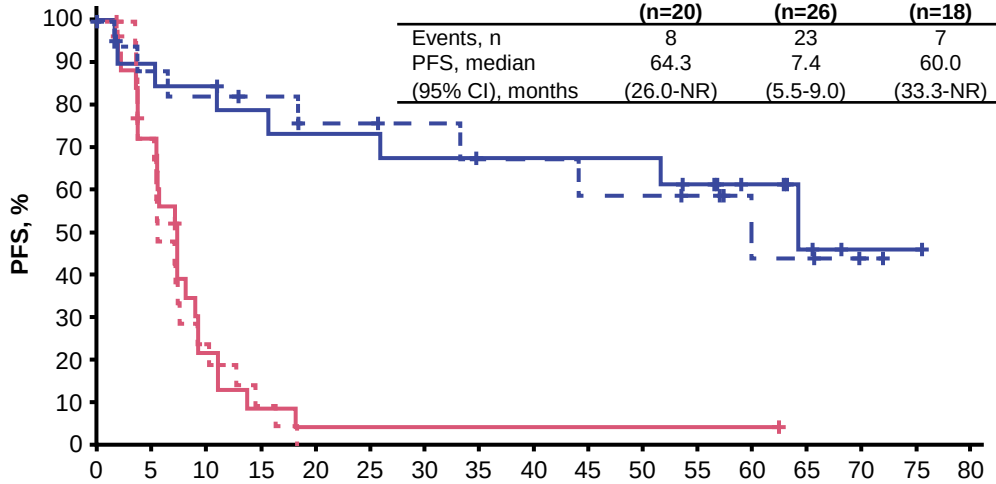
CI, confidence interval; HR, hazard ratio; IC, intracranial; NR, not reached.

Solomon BJ, et al. *J Clin Oncol* 2024 (epub ahead of print) doi: 10.1200/JCO.24.00581.

CROWN: Lorlatinib Treatment Benefited Patients With Poor Prognostic Biomarkers[1,2]

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

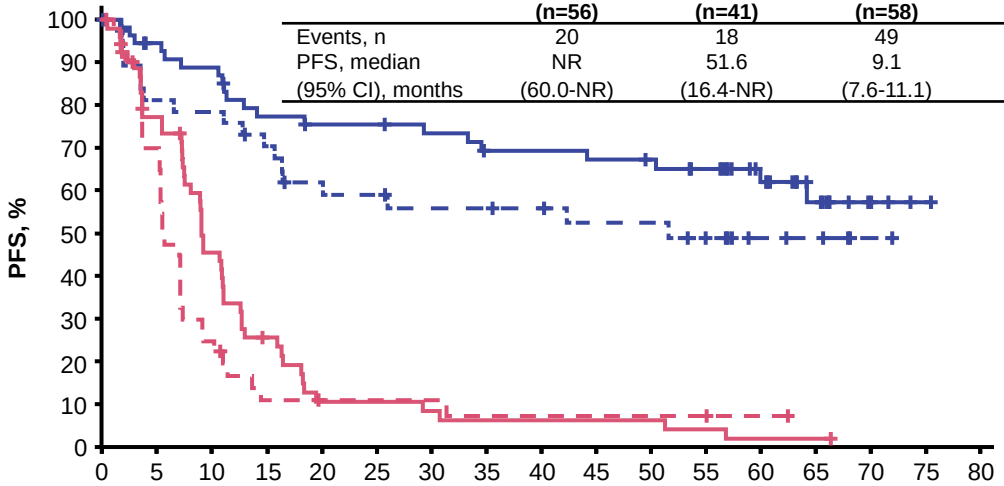
***EML4::ALK* variant 3**

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

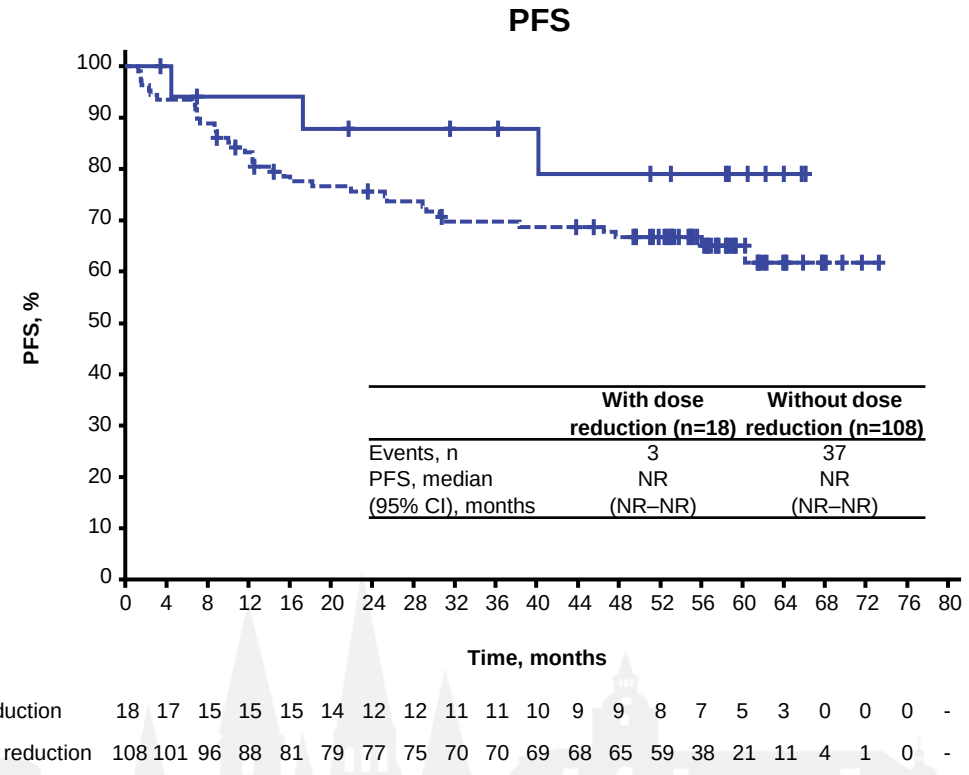
TP53 mut (-)	58	40	23	12	5	5	4	3	3	3	3	2	1	1	0	-	-	
TP53 mut (+)	42	28	10	4	3	3	3	2	2	2	2	2	1	0	0	-	-	

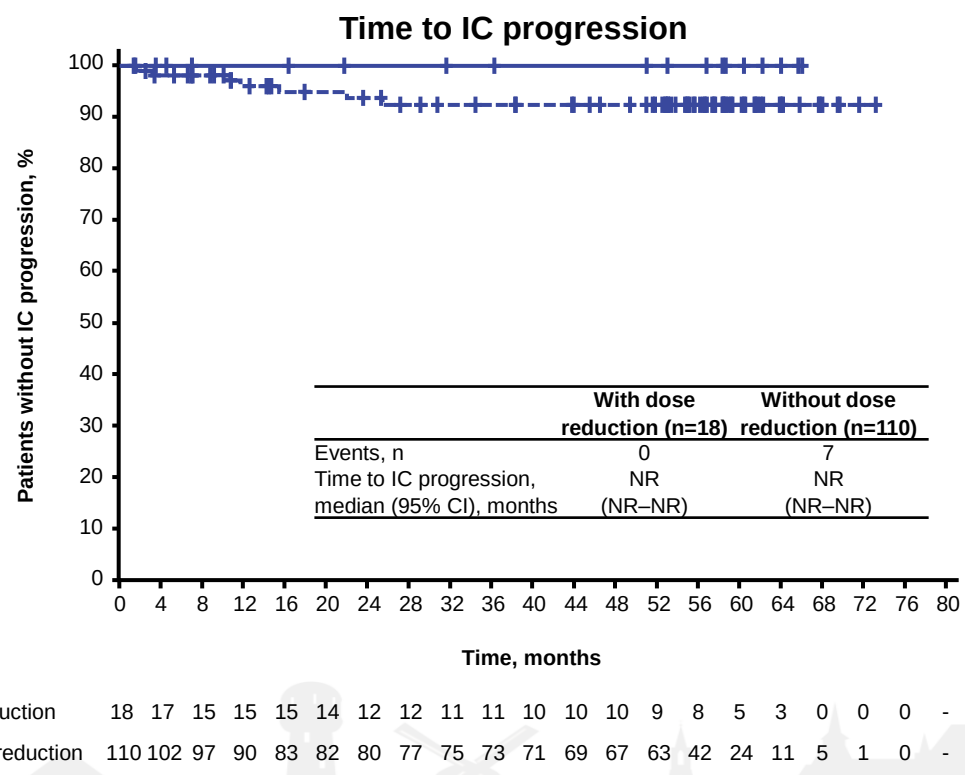
Lorlatinib treatment can benefit patients with poor prognostic biomarkers or difficult-to-treat alterations such as *EMLK4::ALK* variant 3 or *TP53* co-mutation relatively more than crizotinib[3]

ALK, anaplastic lymphoma kinase; CI, confidence interval; mut, mutation; NR, not reached; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

1. Solomon BJ, et al. Presented at: ASCO Annual Meeting; May 31-June 4, 2024; Chicago, IL; 2. Solomon BJ, et al. *J Clin Oncol*. 2024. Supplementary Appendix. doi:10.1200/JCO.24.00581; 3. Solomon BJ, et al. *J Clin Oncol*. 2024. doi:10.1200/JCO.24.00581.

Dose reduction did not impact efficacy of lorlatinib in patients who had dose reduction in the first 16 weeks





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

Solomon BJ, et al. *J Clin Oncol* 2024 (epub ahead of print) doi: 10.1200/JCO.24.00581.

Zusammenfassung

Lorlatinib Standard 1st line, indizierte Dosisreduktion nicht nachteilig, Dosis-reduzierter Beginn bei vulnerablen Gruppen (Definition?)

Therpieauswahl patientenindividuell nach Nebenwirkungsprofil

Aufklärung **inklusive Angehörige**

Tabelle 10: Strukturierte Nachsorge nach kurativer Therapie

Untersuchung	Monate 3	6	12	18	24	36	48	60
Anamnese, körperliche Untersuchung	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
CT Thorax	**X***	**X***	**X**	**X***	**X**	**X**	**X**	**X**
Lungenfunktion	**X**	**X**	**(X)**	**(X)**	**(X)**			

(X) nach Strahlentherapie;

Zusammenfassung

Leitlinie

Was ist neu?

- BreiteTestung bei allen NSCLC unabhängig von Histologie und Raucherstatus
- Testung auf EGFR, BRAF, KRAS, NTRK, HER2 Alterationen, MET exon 14 skipping Mutationen, RET, ALK, ROS, Translokationen
- Induktionstherapie mit I/O als Alternative zur adjuvanten Therapie bei NSCLC Stadium II- IIIB (N2) UICC8
- Adjuvante Therapie mit I/O nach Resektion jetzt bei allen PD-L1 Expressern.
- Osimertinib und Alectinib in der adjuvanten Therapie bei common mutation EGFR bzw. ALK+
- Marktrücknahme von Capmatinib und Pralsetinib
- Zulassung von Adagrasib in der 2nd line bei KRAS G12C
- HER2 mt: Trastuzumab Deruxtecan jetzt in der 2nd line zugelassen
- Exon 20 ins: Amivantamab + Chemotherapie
- ALK+: Lorlatinib als präferierter Standard in der 1st line

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