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ASSOCIAZIONE ITALIANA
GRUPPI ONCOLOGICI MULTIDISCIPLINARI

Congresso Nazionale

CARCINOMA DEL POLMONE:
QUALI NOVITÀ NEL 2024?

V EDIZIONE

28 OTTOBRE 2024
VERONA
Hotel Leon D'Oro

Responsabile Scientifico
STEFANIA GORI

Session IV: Focus on…

Radioterapia integrata con le terapie sistemiche nel NSCLC

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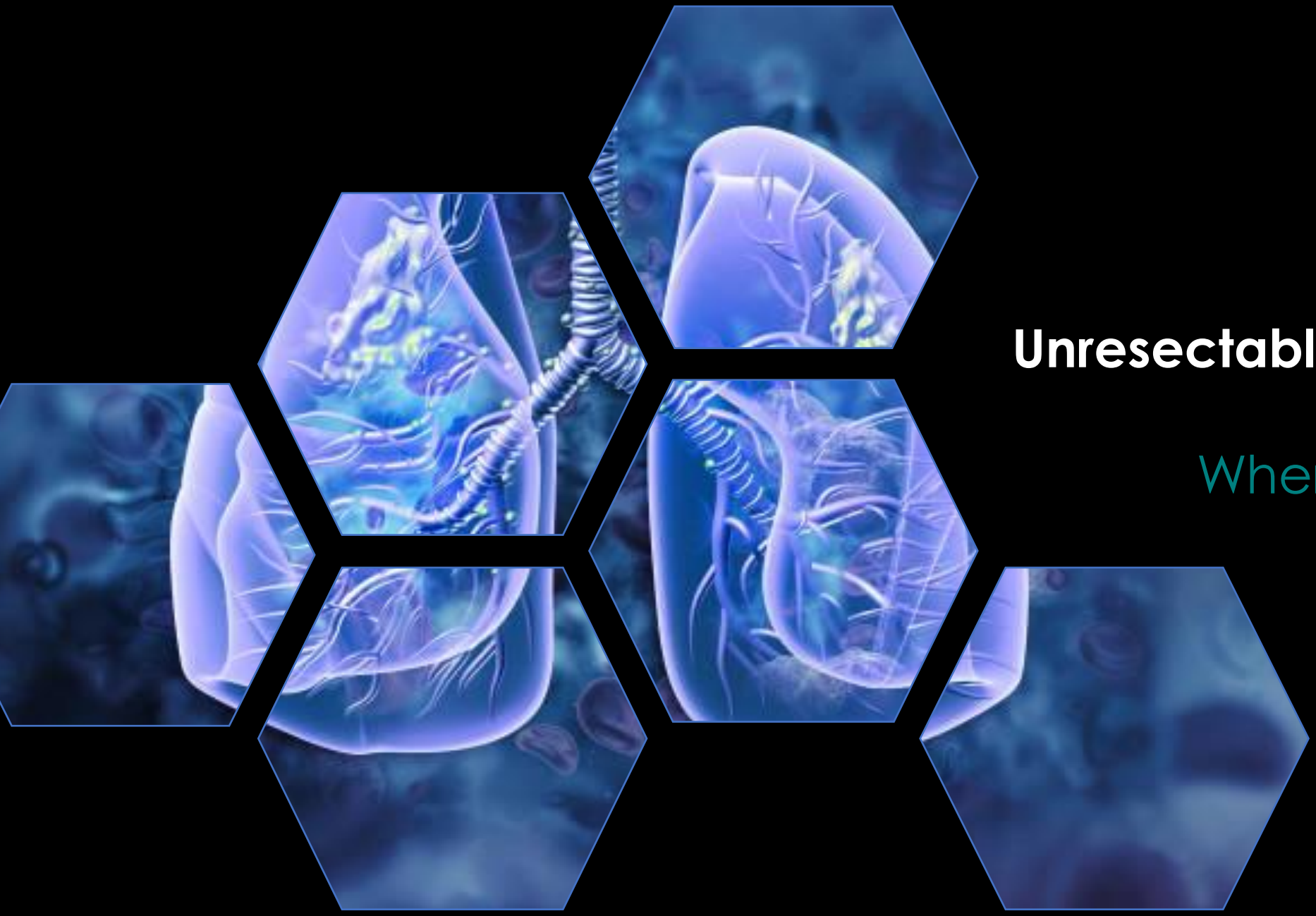
ARO ADVANCED RADIATION ONCOLOGY DEPARTMENT



Unresectable Stage III NSCLC

Where we are!

uIII Stage NSCLC

- Definition
- Standard of care
- Other trials
- Special population
- Conclusions

uIII Stage NSCLC

- **Definition**
- Standard of care
- Other trials
- Special population
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DEFINITION

What is the definition of resectable in NSCLC?

"Resectable" means having a complete resection, but the latter is a post-hoc defined event

R0: complete resection	Run: uncertain resection	R1/R2: incomplete resection
Free margin micrscopically	Free margins/no tumor lefet	No free margins/tumor left
Systematic or lobe-specific systemic LN dissection	Insufficient LN dissection	-
No extracapsular LN extension	No extracapsular LN extension	Extracapsular extension
Highest removed LN negative	Highest removed LN not negative	-

Rami-Porta, et al. Lung Cancer 2005

DEFINITION

New definition of resectability in NSCLC

Technical Resectability: it is mainly determined by the T-descriptor, and it depends on the experience and composition of the surgical team. For instance, patients with tumors invading the spine, may be judged unresectable atone institution, but not at centers where neurosurgeons and orthopedic surgeons closely collaborate in decision making and treatment of such malignancies.

Oncological Resectability: it is mainly determined by lymphatic (N-descriptor) and hematological (M-descriptor) tumor spread. Invasive mediastinal procedures, such as endoscopic ultrasound, endobronchial ultrasound, and mediastinoscopy, are instruments to determine the extent of nodal involvement.

Dickhoff C, et al. J Thorac Oncol 2023

DEFINITION

Delphi Process

Consensus reached

	N0	N1	N2 SINGLE (non-bulky, non-invasive)	N2 MULTI (non-bulky, non-invasive)	N2 BULKY¶	N2 INVASIVE	N3
T1-2	NOT STAGE III DISEASE	NOT STAGE III DISEASE	RESECTABLE	POTENTIALLY RESECTABLE*	UNCLEAR	UNRESECTABLE	UNRESECTABLE
T3 size / satellite / invasion	NOT STAGE III DISEASE	RESECTABLE	RESECTABLE	POTENTIALLY RESECTABLE*	UNRESECTABLE	UNRESECTABLE	UNRESECTABLE
T4 size / satellite	RESECTABLE	RESECTABLE	RESECTABLE	POTENTIALLY RESECTABLE*	UNRESECTABLE	UNRESECTABLE	UNRESECTABLE
T4 invasion	POTENTIALLY RESECTABLE§	POTENTIALLY RESECTABLE§	POTENTIALLY RESECTABLE§	POTENTIALLY RESECTABLE*§	UNRESECTABLE	UNRESECTABLE	UNRESECTABLE

***Multiple station N2**: case-by-case discussion; the exact number of nodes/stations cannot be defined

¶**Bulky N2**: lymph nodes with a short-axis diameter >2.5-3 cm; in specific situations of *highly selected patients*, including those patients in multidisciplinary trials
with surgery as local therapy can be discussed

§Some **T4 tumours by infiltration of major structures** are potentially resectable – see Table 1

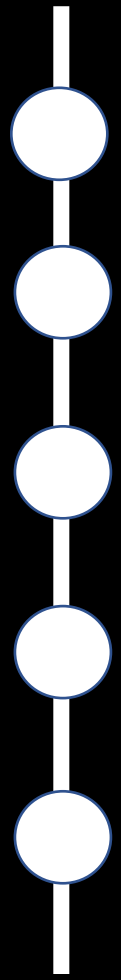
Brandão M. et al. WCLC2023 OA06.05

DEFINITION

			Non-Bulky		Bulky	
	N0	N1	N2 Single	N2 Multi	N2 Single	N2 Multi
T1/T2	Resectable	Resectable	Resectable	Potentially Resectable	Potentially Resectable	Un-Resectable
T3	Resectable	Resectable	Resectable	Potentially Resectable	Potentially Resectable	Un-Resectable
T3 (Pancoast)	Potentially Resectable[+]	Potentially Resectable[+]	Un-Resectable	Un-Resectable	Un-Resectable	Un-Resectable
T4 Size	Potentially Resectable	Potentially Resectable	Un-Resectable	Un-Resectable	Un-Resectable	Un-Resectable
T4 Satellite	Potentially Resectable	Potentially Resectable	Potentially Resectable	Un-Resectable	Un-Resectable	Un-Resectable
T4 Invasion	Potentially Resectable	Potentially Resectable	Un-Resectable	Un-Resectable	Un-Resectable	Un-Resectable

Kim SS. et al. Ann Thorac Surg 2024

uIII Stage NSCLC



- Definition
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- Other trials
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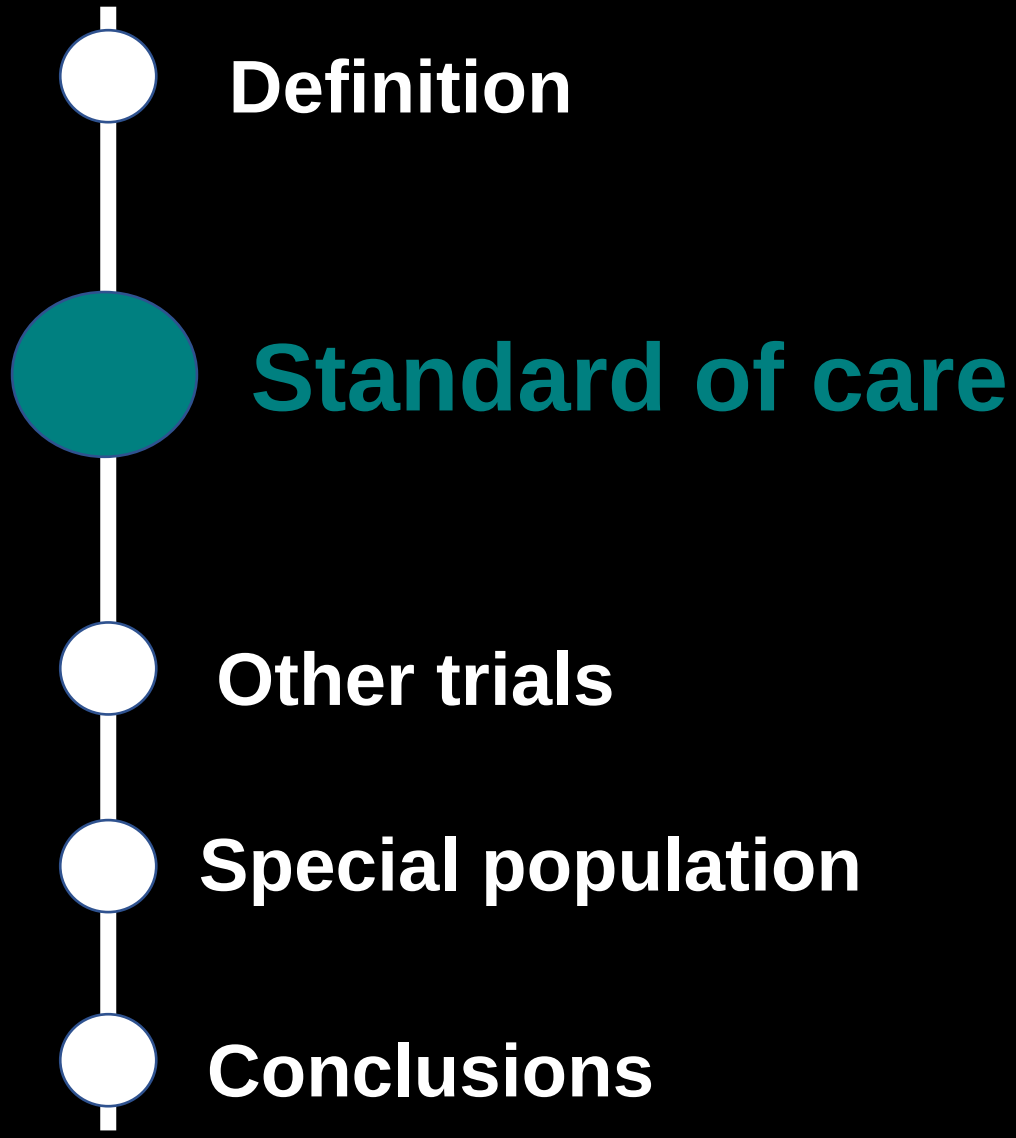
uIII Stage NSCLC



STANDARD OF CARE

Pre- PACIFIC

- Sequential CT-RT vs RT

+ 3% OS at 2y and +2% at 5y (HR 0.90) [*NSCLC Collaborative Group, BMJ 1995]*

- Concurrent CT-RT > Sequential

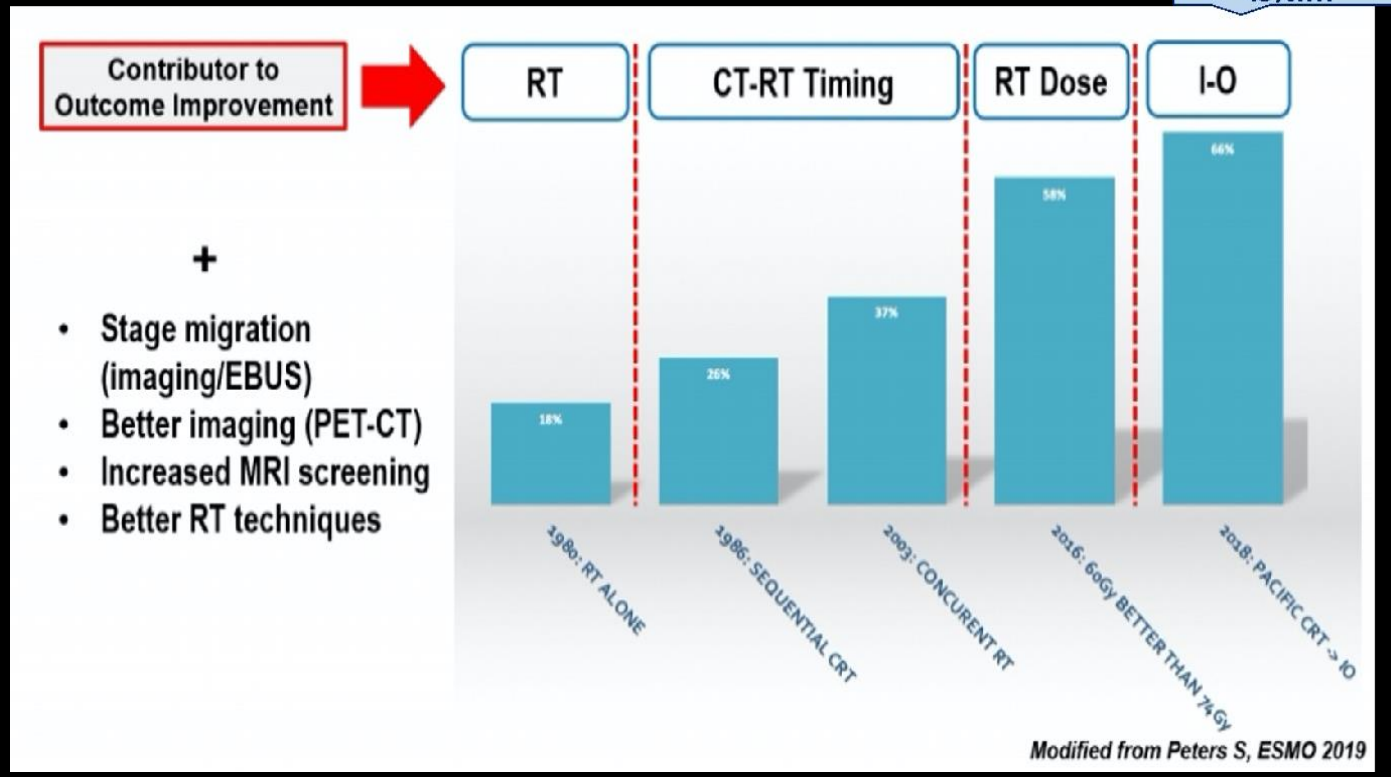
+ 5.7% OS at 3y and **+ 4.5%** at 5y (HR 0.84) *[Auperin et al, JCO 2010]*

- *Concurrent CT-RT OS at 3y* **30-35%**
- **<50%** *fit (PS or 1, <75 years)*

Courtesy by Matteo Sepulcri

STANDARD OF CARE

Pre- PACIFIC

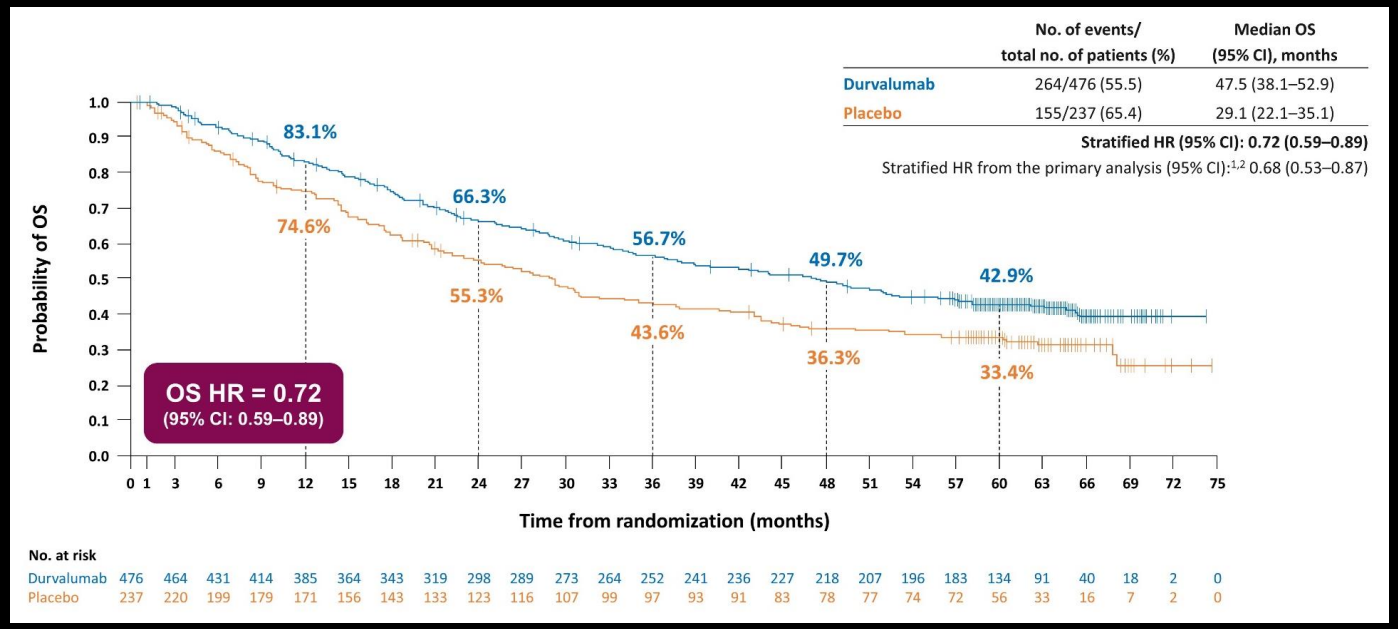


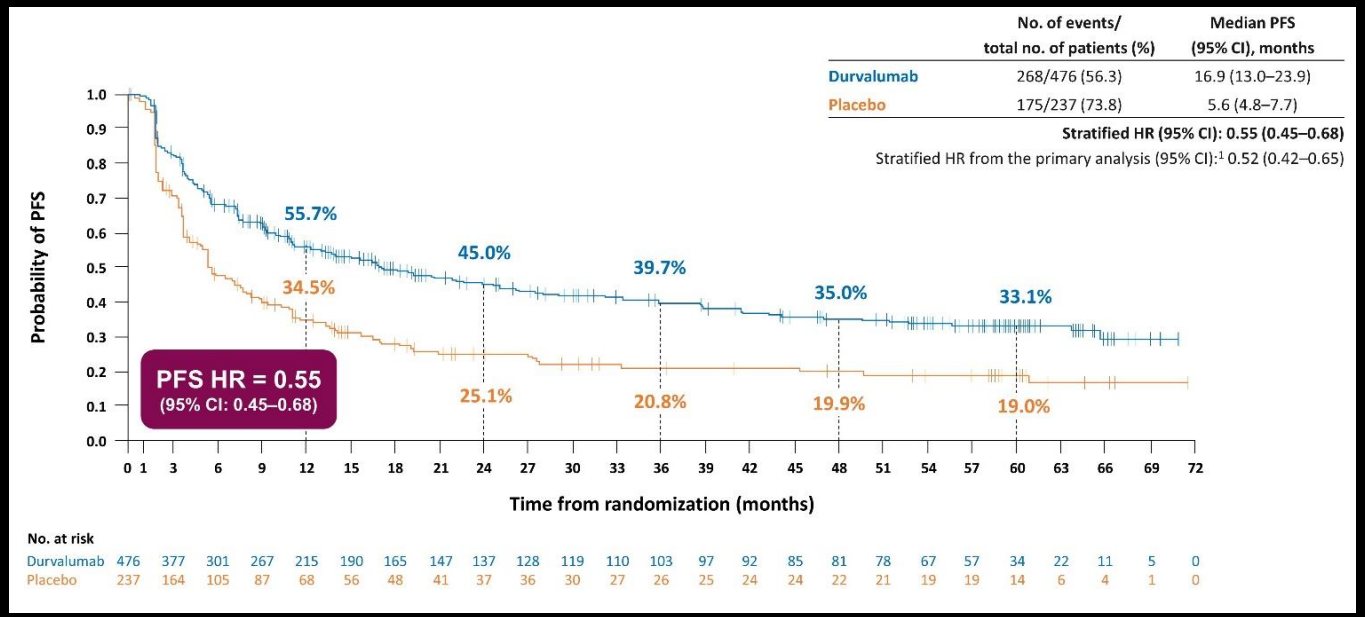
- No OS benefit from high dose RT *[Bradley, Lancet 2015]*
- No OS benefit integrating with biological agents
- No consolidation or maintenance CT after CT/RT

Girard N, ESMO 2021

PACIFIC

STANDARD OF CARE





Pneumonitis or radiation pneumonitis with durvalumab was mostly low grade, and the incidence of G3 or 4 was well balanced between the groups (***3.4% durvalumab vs 2.6% placebo***)

Spigel D, J Thor Oncol 2022

STANDARD OF CARE

PACIFIC

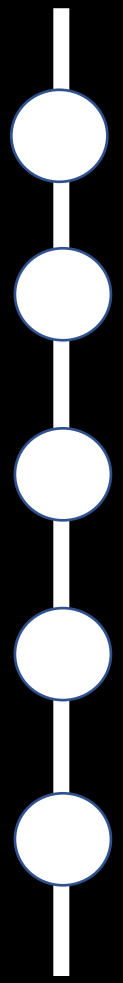
- ✓ **Consolidative durvalumab after CT-RT** is the standard of care with impressive 5-year outcome and safety results
- ✓ PACIFIC trial results brought **light on stage III in clinical practice**

[patients' selection, correct staging, MDT discussion, integration among specialists...]

- More patients candidate to concurrent CT-RT? *[RT technique]*
- What about frailty patients? *[PACIFIC-6; DUART]*
- Adherence to consolidation therapy? *[PACIFIC-R]*
- We need a positive PD-L1 *[diagnostic implications]*
- Is it effective in patients with driver-mutations? *[LAURA]*
- Treatment intensification post CT-RT? *[COAST and PACIFIC-9]*
- IO integration during CT-RT? *[PACIFIC-2; CHECKMATE 73L]*

Courtesy by Matteo Sepulcri

uIII Stage NSCLC



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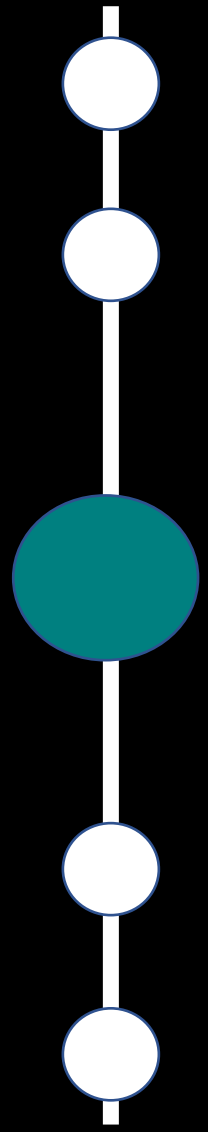
uIII Stage NSCLC



Definition

Standard of care

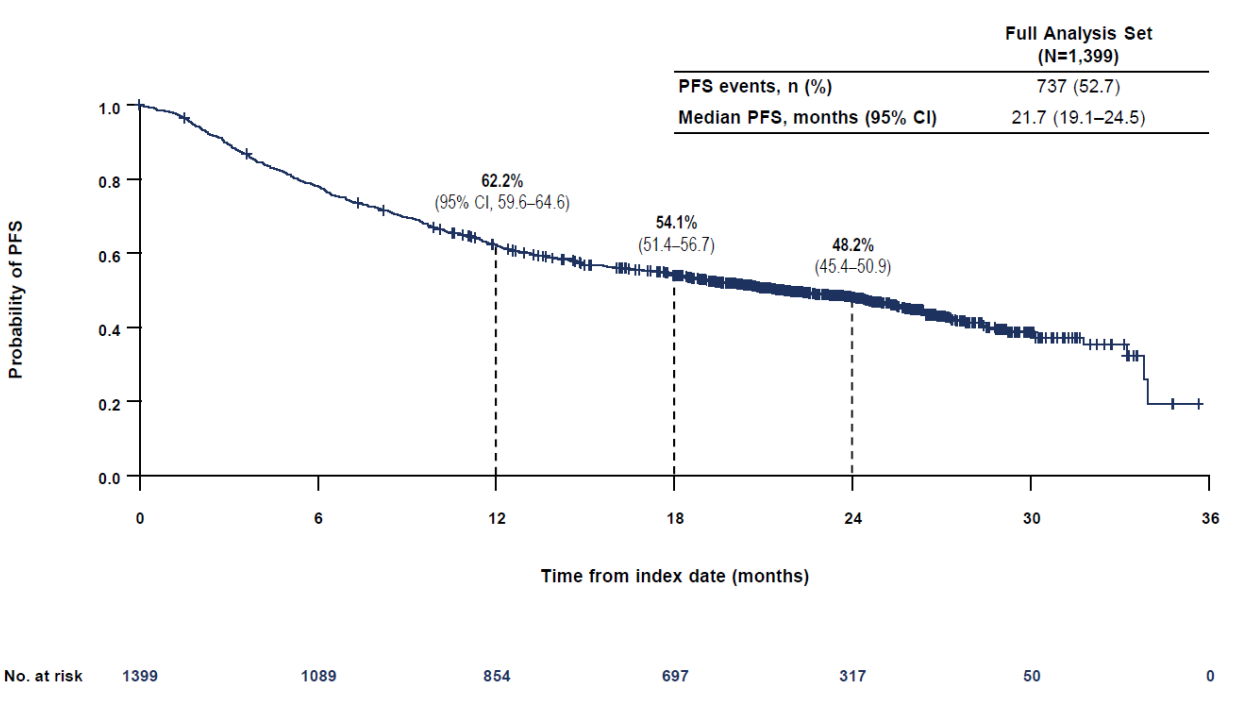
Other trials

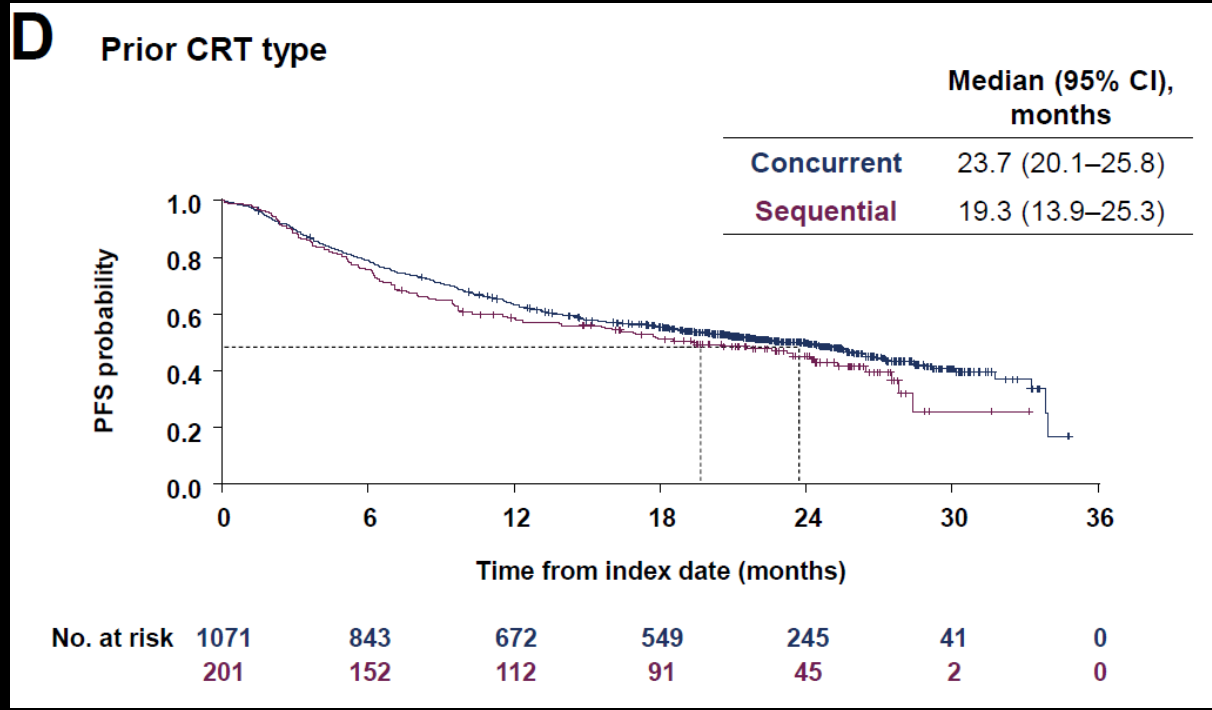
Special population

Conclusions

OTHER TRIALS

PACIFIC - R





Girard N, J Thorac Oncol 2023

OTHER TRIALS

PACIFIC 2

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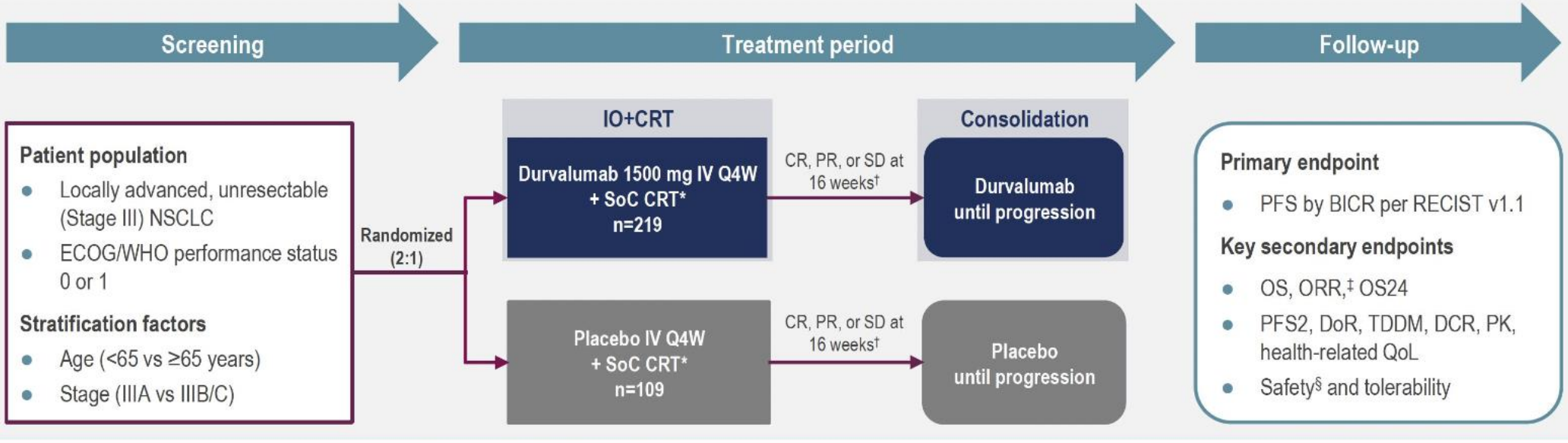
Study design

PACIFIC-2 (NCT03519971) is a phase 3, randomized, double-blind, placebo-controlled, multicenter, global study of durvalumab + CRT followed by durvalumab versus placebo + CRT followed by placebo



Patients were recruited from **29 March 2018** through **24 June 2019** across 106 sites in Asia, Eastern Europe, and the Americas, including: Brazil, Czech Republic, Hungary, India, Japan, Mexico, Peru, Philippines, Poland, Republic of Korea, Russia, Turkey, Thailand, and Vietnam.

OTHER TRIALS

PACIFIC 2

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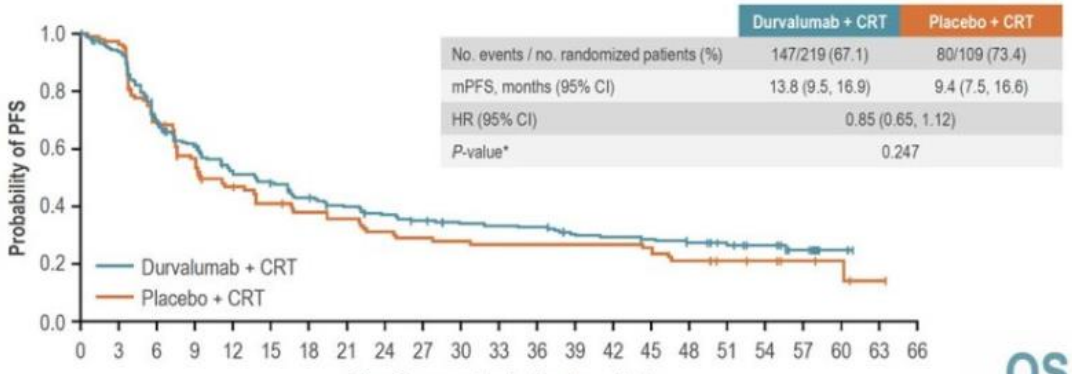
PFS by BICR (ITT population)



	Durvalumab + CRT	Placebo + CRT
No. events / no. randomized patients (%)	147/219 (67.1)	80/109 (73.4)
mPFS, months (95% CI)	13.8 (9.5, 16.9)	9.4 (7.5, 16.6)
HR (95% CI)	0.85 (0.65, 1.12)	
P-value*	0.247	

No. at risk:																							
Durvalumab + CRT	219	199	145	124	102	94	83	75	69	64	60	59	58	50	49	47	43	28	24	10	2	0	0
Placebo + CRT	109	104	72	58	44	38	34	32	28	26	25	24	24	24	24	23	19	15	12	7	3	1	0

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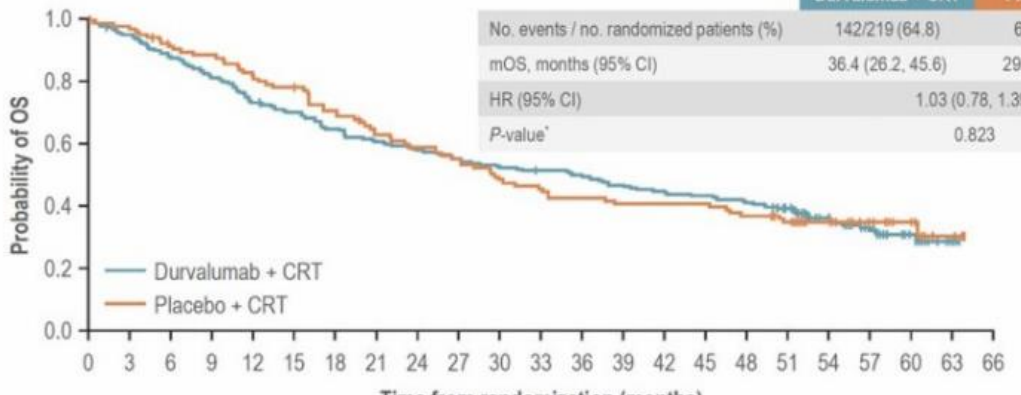
BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; mPFS, median PFS; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

Per RECIST v1.1. Tick marks on the curves indicate ce
*Based on the Lan and DeMets approach that appr
Fleming spending functions; the 2-sided p-value b
statistical significance is 0.0416 for

OS and ORR (ITT population)



	Durvalumab + CRT	Placebo + CRT
No. events / no. randomized patients (%)	142/219 (64.8)	69/109 (63.3)
mOS, months (95% CI)	36.4 (26.2, 45.6)	29.5 (23.2, 45.1)
HR (95% CI)	1.03 (0.78, 1.39)	
P-value*	0.823	

No. at risk:																							
Durvalumab + CRT	219	207	191	177	160	152	141	132	126	120	114	111	107	100	95	94	89	75	49	31	15	1	0
Placebo + CRT	109	106	98	95	87	83	75	66	62	57	51	47	45	43	43	43	39	35	27	17	9	2	0

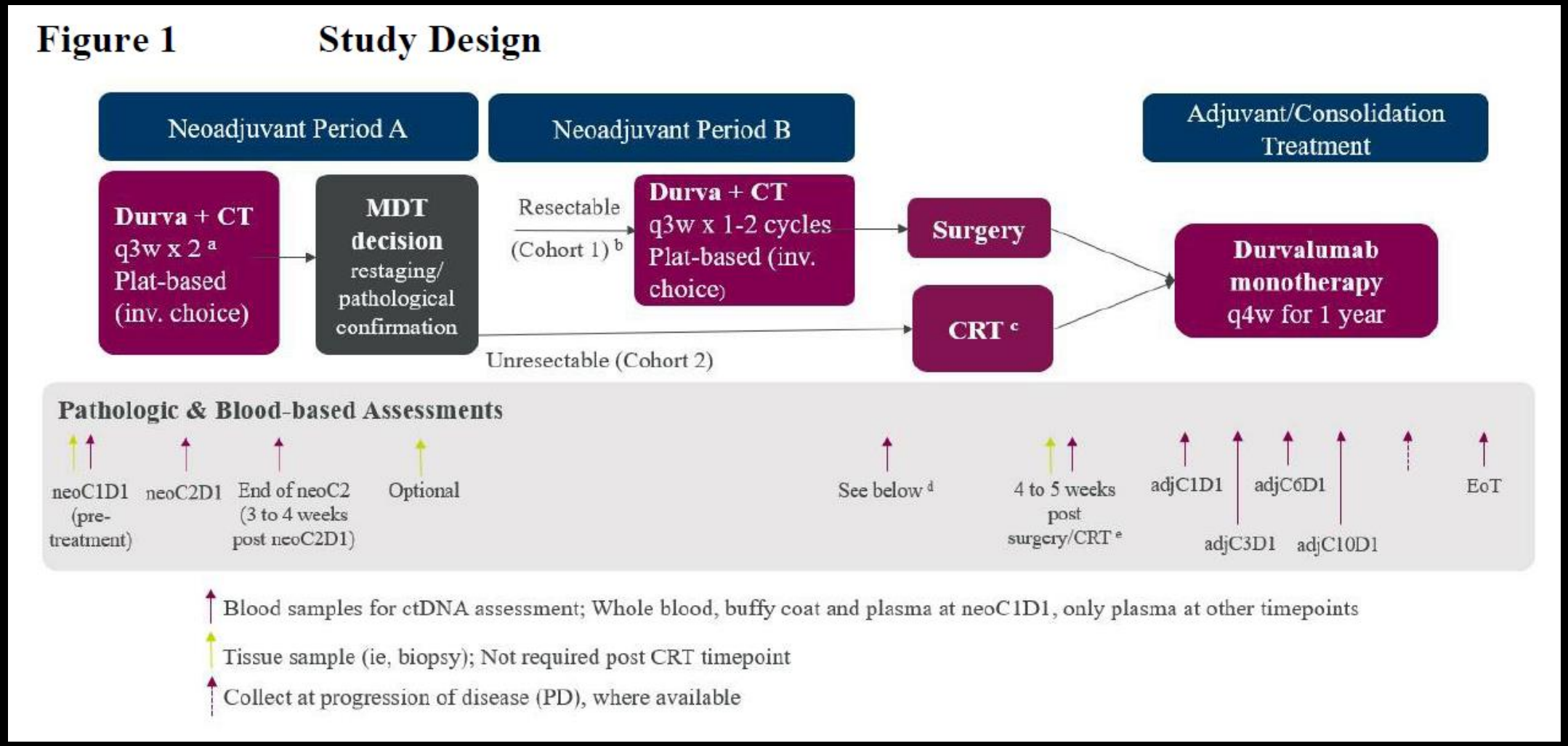
There was no difference in ORR between the durvalumab (60.7%; 95% CI: 53.9, 67.2) and placebo (60.6%; 95% CI: 50.7, 69.8) arms (p=0.976).

OTHER TRIALS

Trial	Phase	Arm I	Arm II	Arm III	Primary End point
BTCRC-LUN 16-081	II	Platinum CCRT → nivolumab	Platinum CCRT → nivo + ipi	NA	PFS
PACIFIC 9	III	Platinum CCRT → durva + oleclumab	Platinum CCRT → durva + monalizumab	Platinum CCRT --> Durva + Placebo	PFS by BICR
PACIFIC 8	III	Platinum CCRT → durva + domvanalimab	Platinum CCRT → durva + placebo	NA	PFS by BICR
KEYLYNK 12	III	Platinum CCRT + pembro → pembro	Platinum CCRT + pembro → pembro + orparib	Platinum CCRT → durva	PFS, OS
Skyscraper-93	III	Platinum CCRT → Tiragolumab plus Atezo	Platinum CCRT → durvalumab	NA	PFS
COAST	II	Platinum CCRT → durva	Platinum CCRT → durva + oleclumab	Platinum CCRT → durva monalizumab	ORR

OTHER TRIALS

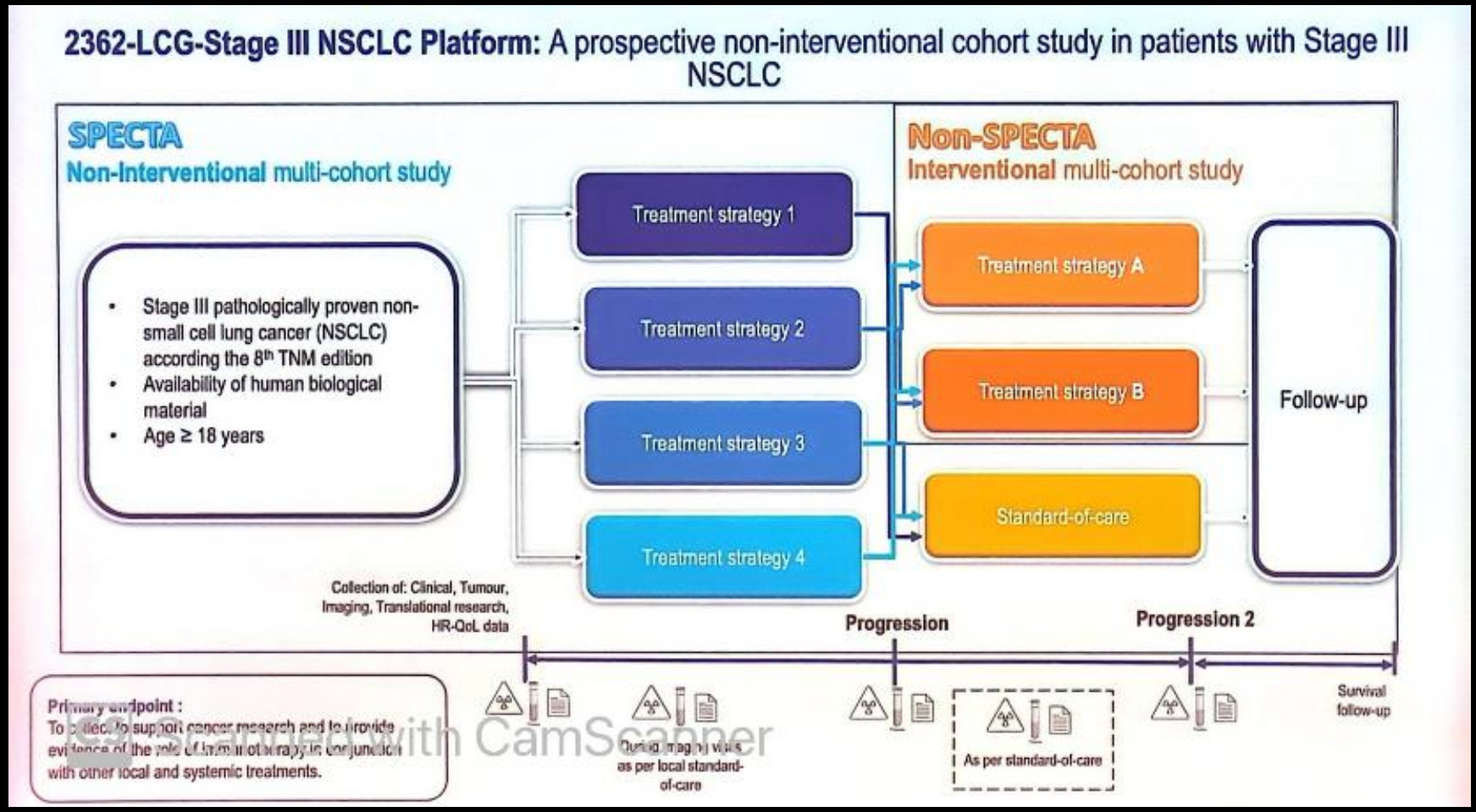
MDT-BRIDGE



Primary end point: resection rate, defined as proportion of all patients who underwent definitive surgery

OTHER TRIALS

SPECTA



Steering Committee

Radiation oncologist

Faivre Finn (Manchester)

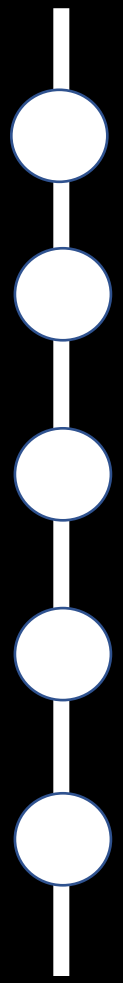
Guckenberger (Zurigo)

Filippi (Milano)

Levy (Parigi)

Giaj Levra (Negrar)

uIII Stage NSCLC



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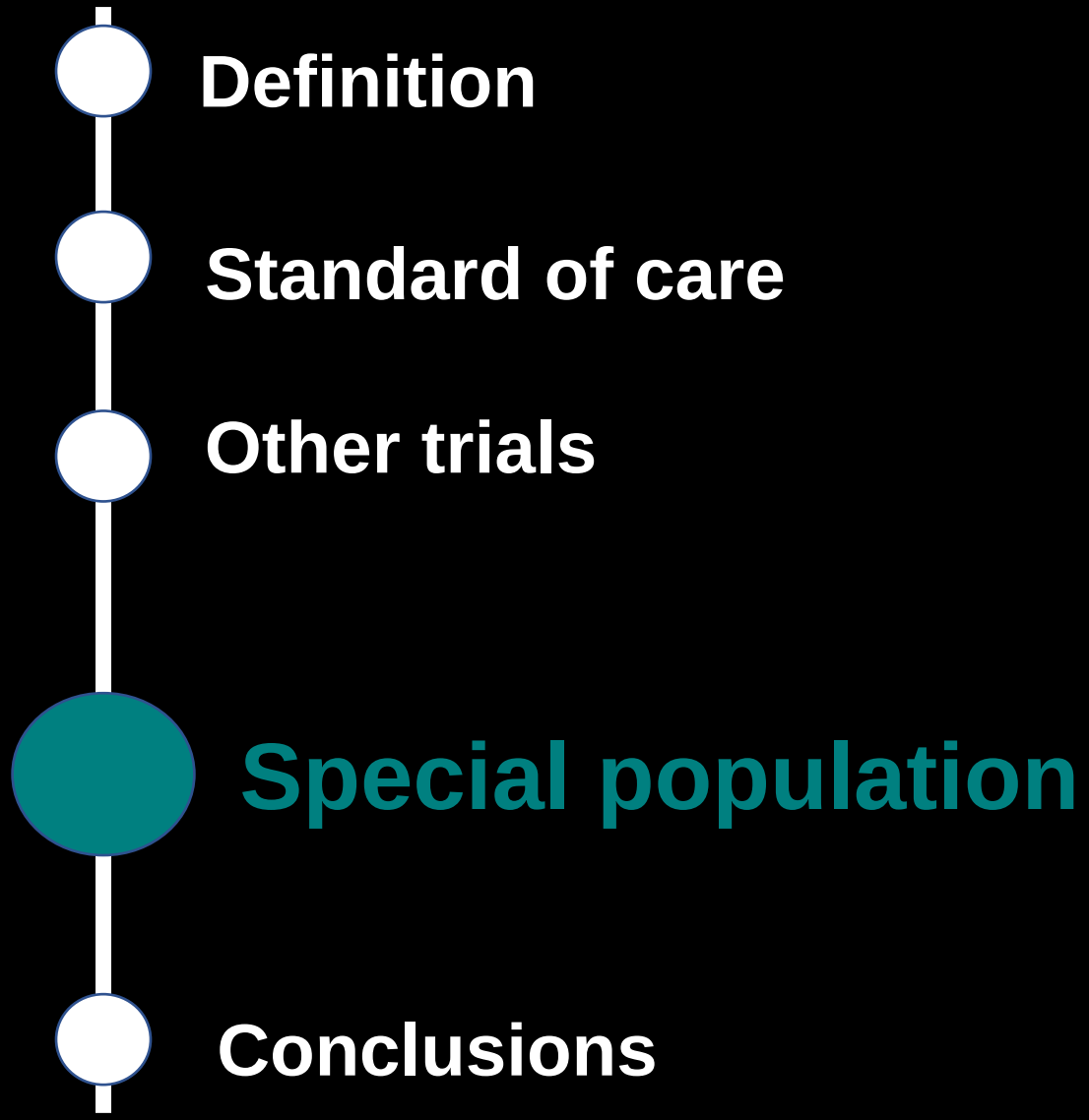
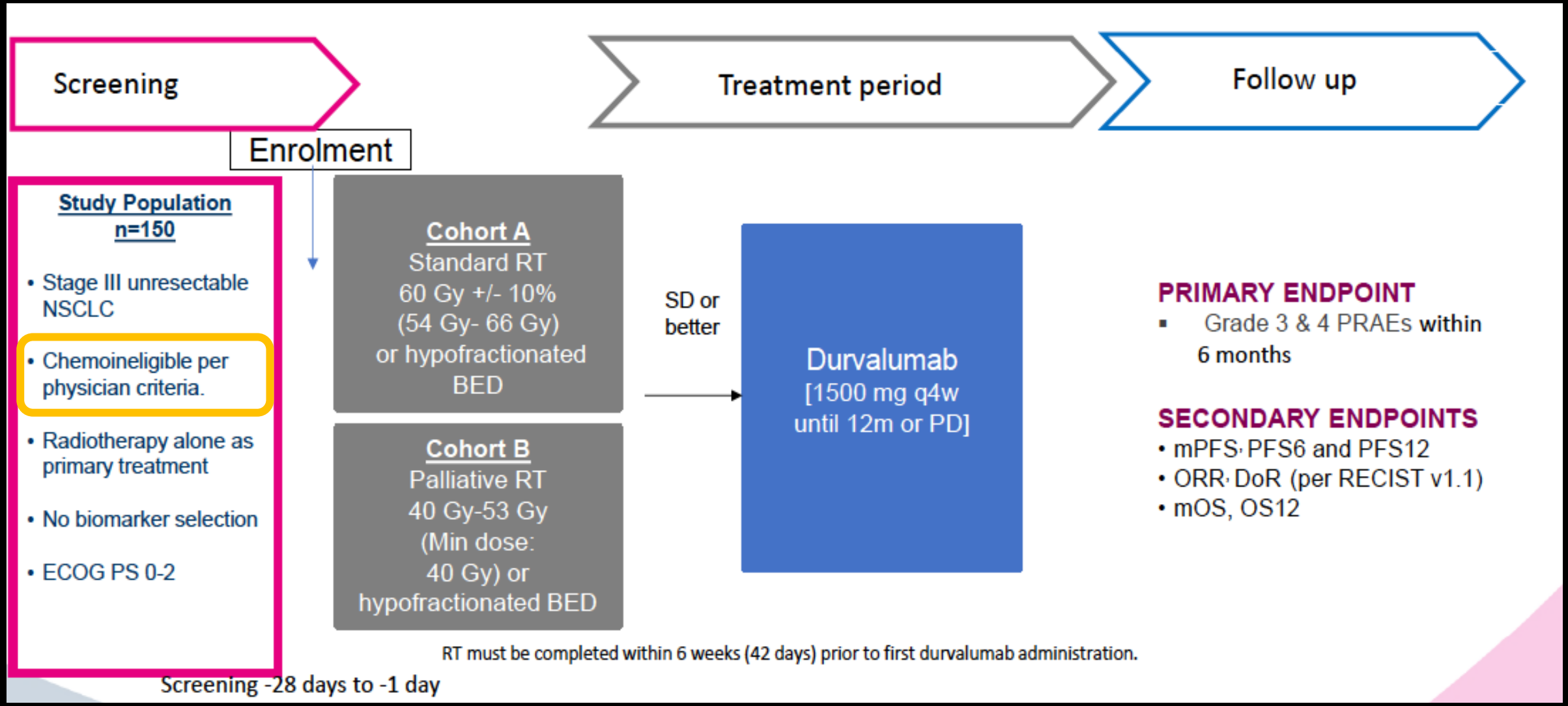


SPECIAL POPULATION

DUART



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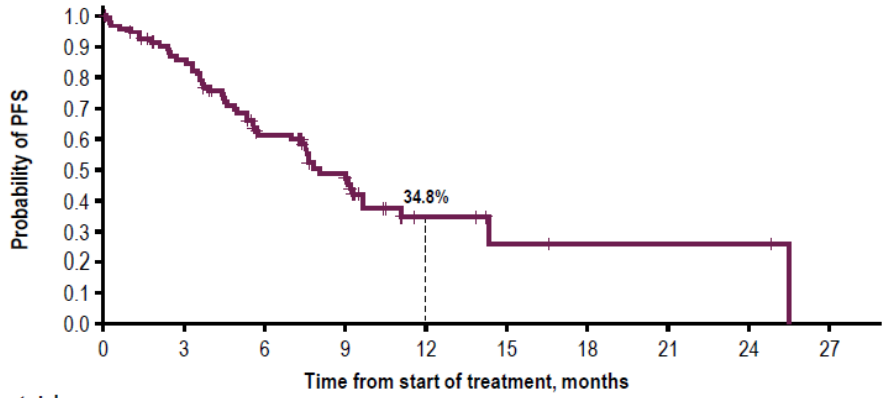
SPECIAL POPULATION

DUART

Efficacy cont'd

PFS

	Cohort A (standard RT)	Cohort B (palliative RT)	Total
No. events / no. patients (%)	26/59 (44.1)	25/43 (58.1)	51/102 (50.0)
Median PFS (95% CI)*, months	9.0 (5.6–NC)	7.6 (5.3–11.0)	8.0 (7.0–9.7)
12-month PFS rate (95% CI)†, %	40.2 (23.6–56.3)	29.3 (13.8–46.7)	34.8 (23.0–46.9)



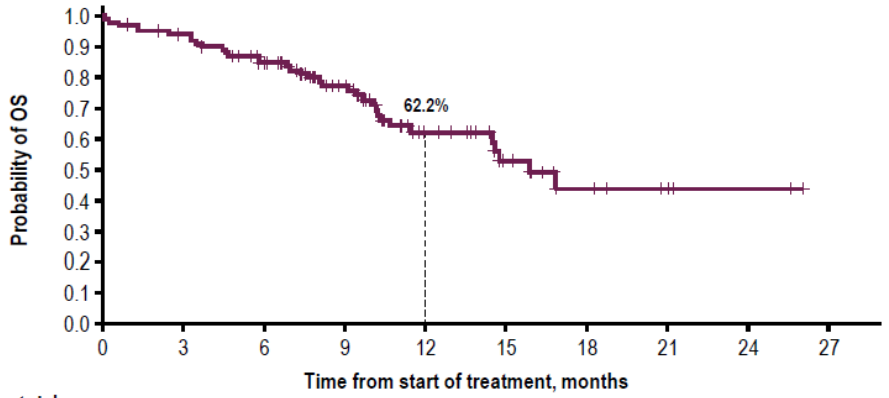
No. at risk:

Total	102	76	47	28	9	3	2	2	2	0

Median follow-up (range) for patients censored for PFS: 7.4 months (0.0–24.9).

OS

	Cohort A (standard RT)	Cohort B (palliative RT)	Total
No. events / no. patients (%)	16/59 (27.1)	19/43 (44.2)	35/102 (34.3)
Median OS (95% CI)*, months	NC (14.5–NC)	14.8 (10.1–NC)	15.9 (11.5–NC)
12-month OS rate (95% CI)†, %	67.0 (50.1–79.2)	56.3 (37.3–71.6)	62.2 (49.8–72.4)



No. at risk:

Total	102	93	78	54	27	15	7	4	2	0

Median follow-up (range) for patients censored for OS: 9.9 months (0.9–26.0).

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CI, confidence interval; NC, not calculable; OS, overall survival; PFS, progression-free survival

*CI calculated using the Brookmeyer-Crowley method.
†CI calculated using the Greenwood method.

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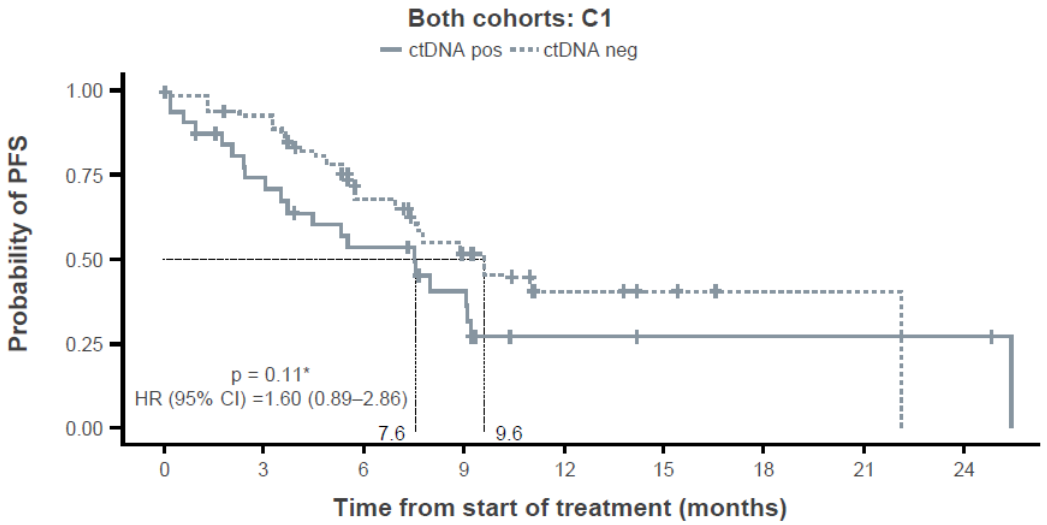
SPECIAL POPULATION

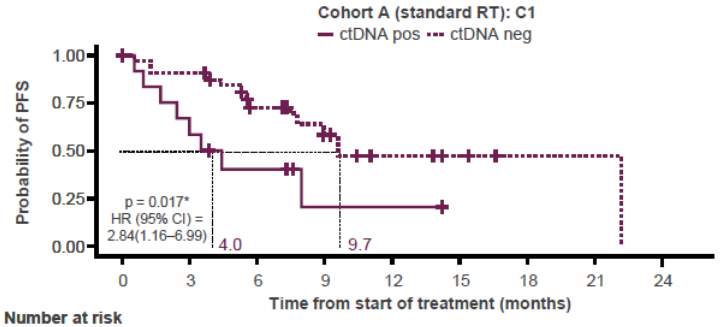
DUART

Detectable ctDNA at C1 (immediately prior to the start of durvalumab) was associated with a trend toward decreased PFS



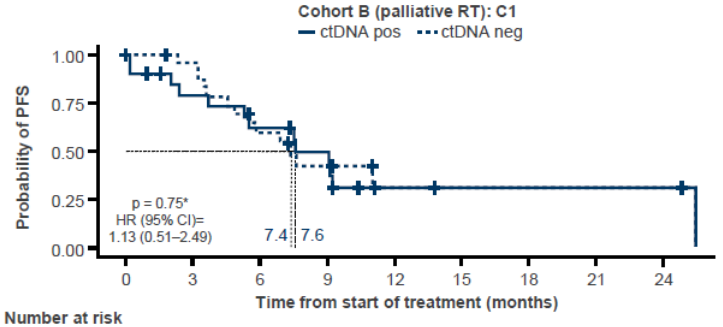
Number at risk

ctDNA pos	32	22	15	9	3	2	2	2	2
ctDNA neg	59	51	31	18	7	3	1	1	0



Number at risk

ctDNA pos	12	8	4	1	1	0	0	0	0
ctDNA neg	34	29	19	11	6	3	1	1	0



Number at risk

ctDNA pos	20	14	11	8	2	2	2	2	2
ctDNA neg	25	22	12	7	1	0	0	0	0

- The proportion of patients with detectable ctDNA at C1 (35.2% †) was numerically higher after palliative (44.4% †) vs standard (26.1% †) RT.

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*Exploratory analysis, nominal p values presented, not adjusted for multiple analysis. HRs calculated with the corresponding ctDNA-negative population as the reference.
†Percentages based on the number of patients with evaluable ctDNA samples at the corresponding timepoint.
Efficacy comparisons were made via Cox proportional hazards model with p-values estimated via log-rank test.
neg, negative; OS, overall survival; pos, positive

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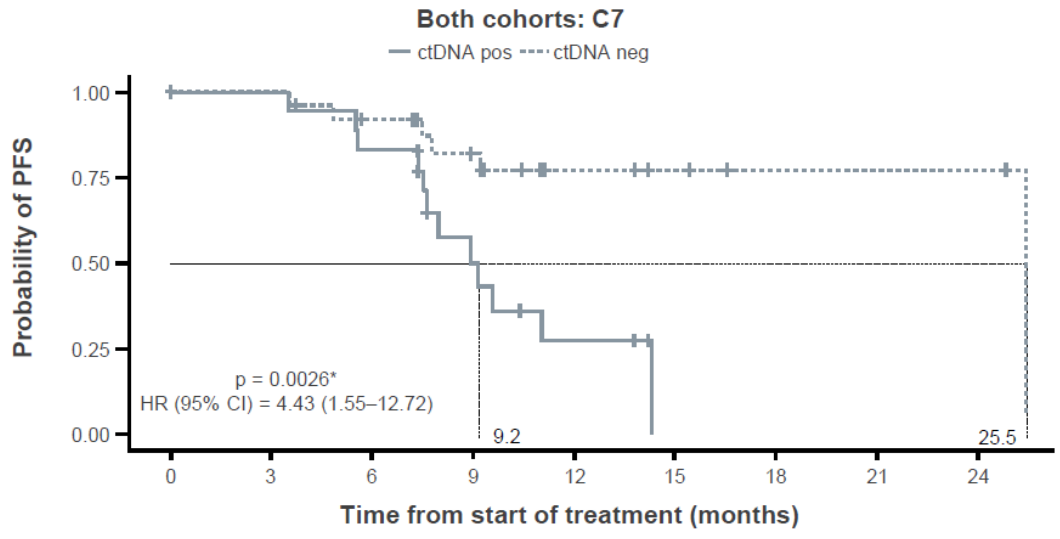
SPECIAL POPULATION

DUART

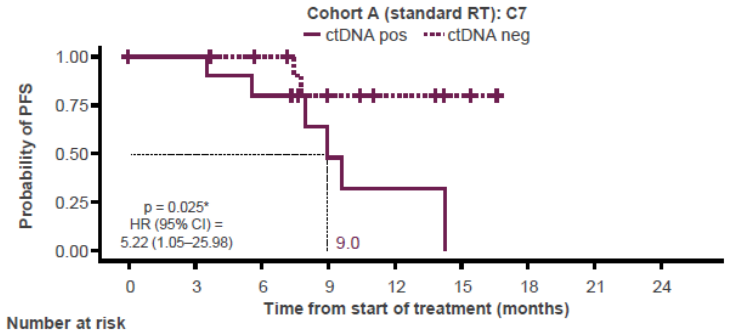
Detectable ctDNA at C7 was associated with shorter PFS



Number at risk

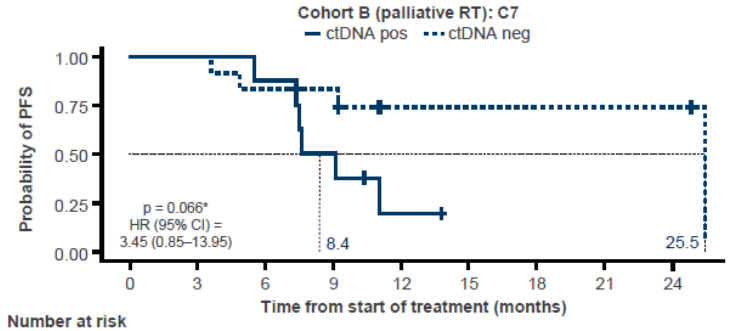
ctDNA pos	18	18	15	7	3	0	0	0	0
ctDNA neg	26	25	21	16	7	4	2	2	2

- The proportion of patients with detectable ctDNA at C7 (40.9%†) was similar after palliative (40.0%†) vs standard (41.7%†) RT.



Number at risk

ctDNA pos	10	10	8	3	2	0	0	0	0
ctDNA neg	14	13	11	7	5	2	0	0	0



Number at risk

ctDNA pos	8	8	7	4	1	0	0	0	0
ctDNA neg	12	12	10	9	2	2	2	2	2

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*Exploratory analysis, nominal p values presented, not adjusted for multiple analysis. HRs calculated with the corresponding ctDNA-negative population as the reference.
†Percentages based on the number of patients with evaluable ctDNA samples at the corresponding timepoint.
Efficacy comparisons were made via Cox proportional hazards model with p-values estimated via log-rank test.

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SPECIAL POPULATION

EGFR – LAURA

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).

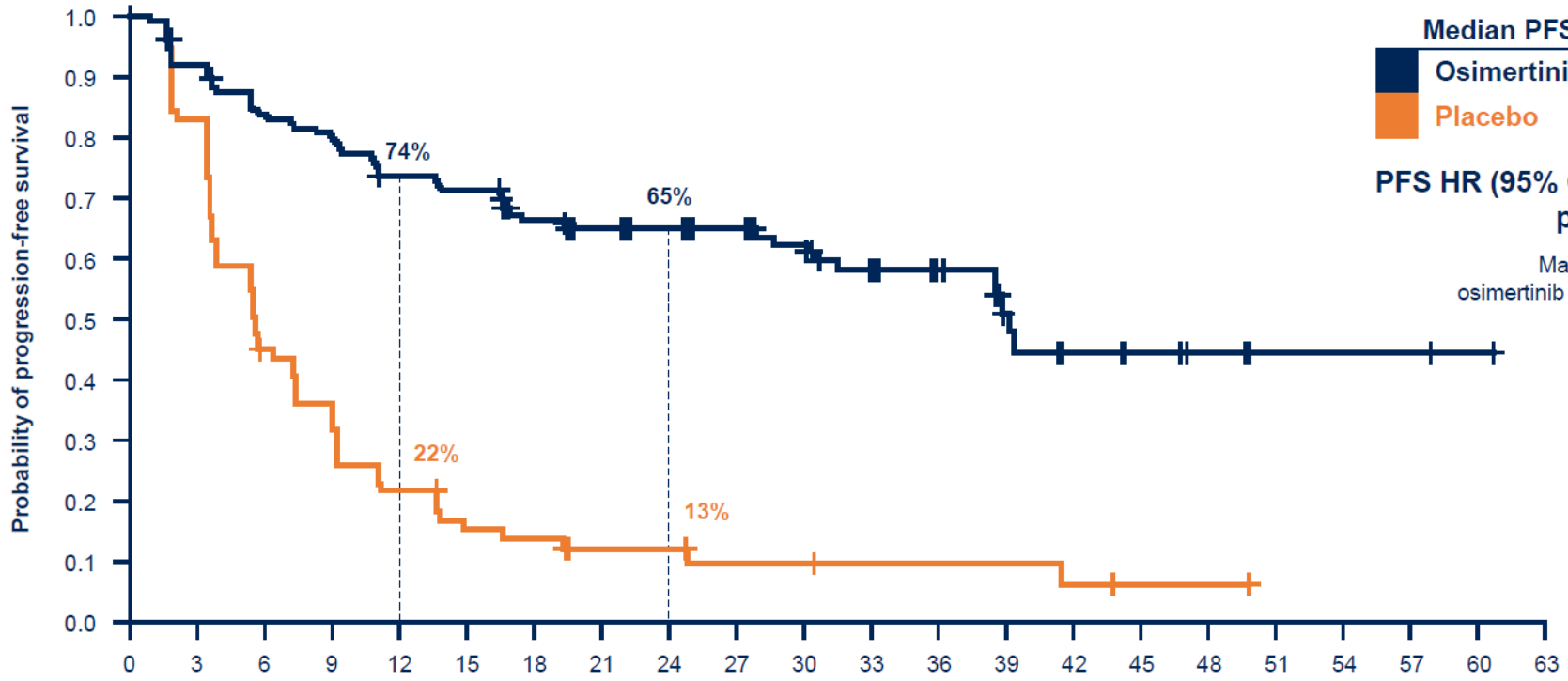
PRESENTED BY: Dr Suresh S. Ramalingam

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

SPECIAL POPULATION

EGFR – LAURA

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

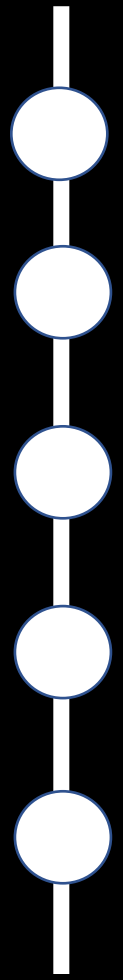
Osimertinib	143	127	114	109	99	96	83	76	69	61	49	37	28	16	9	6	4	2	2	2	1	0
Placebo	73	59	31	25	15	10	9	6	6	4	4	3	3	3	2	1	1	0	0	0	0	0

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

Data cut-off: January 5, 2024.

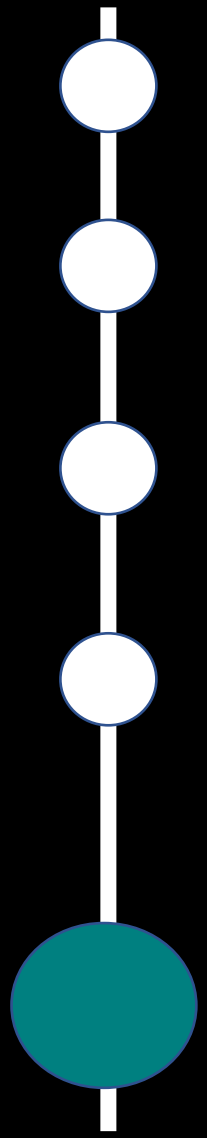
BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; NC, not calculable; PFS, progression-free survival

uIII Stage NSCLC



- Definition
- Standard of care
- Other trials
- Special population
- Conclusions

uIII Stage NSCLC



Definition

Standard of care

Other trials

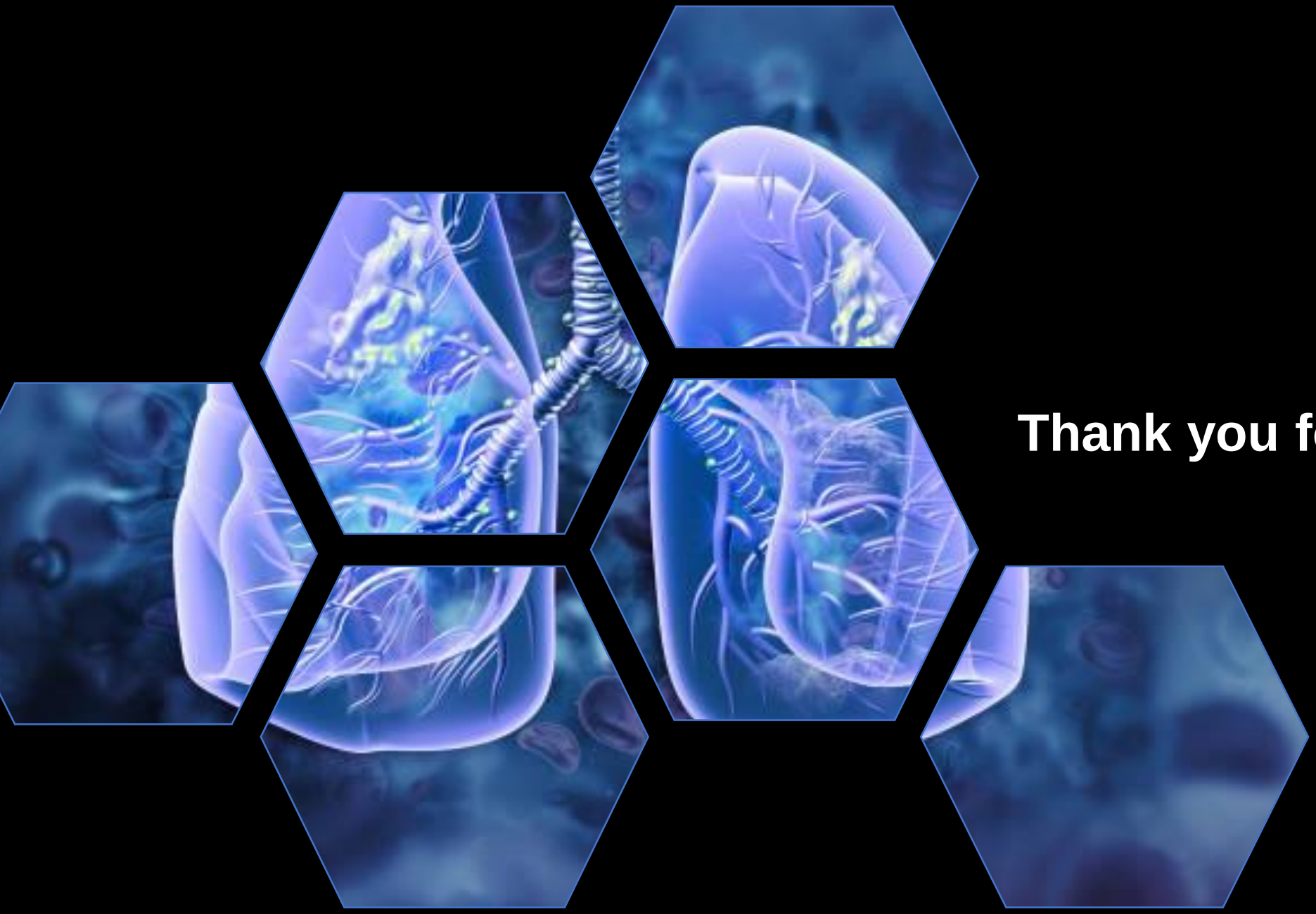
Special population

Conclusions

CONCLUSIONS

uIII Stage NSCLC

- CT and RT with durvalumab is still the standard of care in uIII Stage NSCLC in PD-L1 positive patients
- CT and RT with EGFR will be the next standard of care in uIII Stage NSCLC in EGFR mut patients
- New clinical trials will explore the intentification of IO in uIII Stage NSCLC
- Multidisciplinary discussion is mandatory in order to define at the diagnosis what patients are potentially resectable and how to manage patients not suitable to surgery



Thank you for your attention