Locally Advanced Non-Small Cell Lung Cancer: Systemic Therapy

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Abstracts from WCLC 2023 – Consolidative Therapy

Abstract 1: Peters et al. Real-World Outcomes with Durvalumab after Chemoradiotherapy in Unresectable Stage III *EGFR*-Mutated NSCLC (PACIFIC-R).

Abstract 2: Nassar et al. Consolidation EGFR-Tyrosine Kinase Inhibitor vs. Durvalumab vs. Observation in Unresectable *EGFR*-Mutant Stage III NSCLC.

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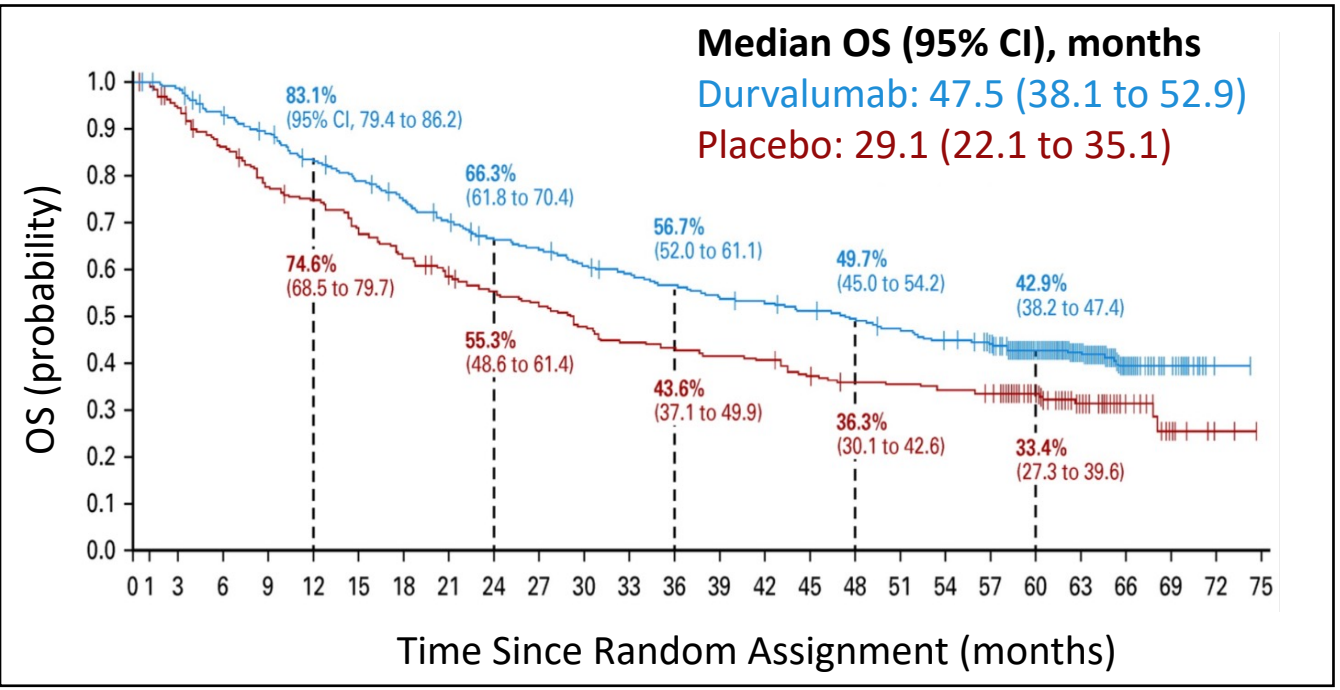
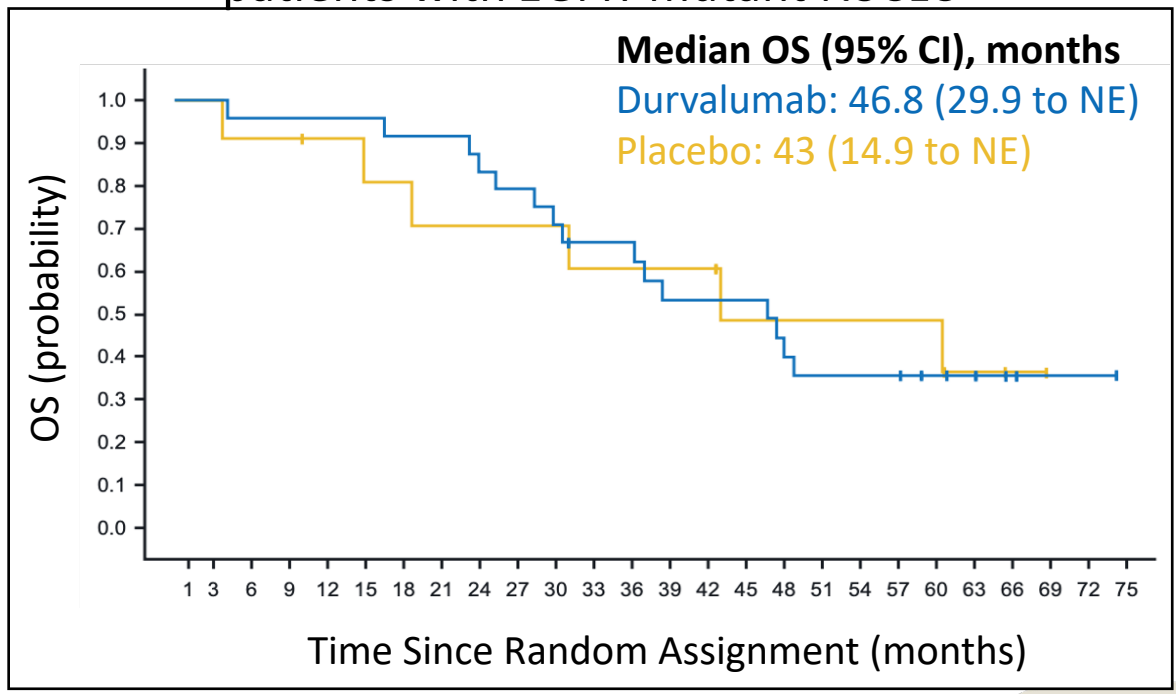
PACIFIC Trial: consolidative durvalumab is the standard of care for patients with unresectable stage III NSCLC and no disease progression after chemoradiation



Spigel et al., JCO, 2022.

PACIFIC Trial Post-Hoc Analysis: this benefit for consolidative durvalumab is less clear among patients with *EGFR*-mutant NSCLC



Naidoo et al., JTO, 2023.

Do patients who have unresectable Stage III *EGFR*-mutant NSCLC benefit from the standard of care consolidative durvalumab after chemoradiation?

PACIFIC-R Study Design

- PACIFIC-R is an ongoing, international, observational study conducted as a retrospective review of established medical records for patients from the PACIFIC EAP (NCT03798535)

≥18 years of age with unresectable, Stage III NSCLC*, regardless of tumour PD-L1 expression

No evidence of progression following platinum-based concurrent or sequential CRT†

Index date

Start of durvalumab (10mg/kg IV Q2W) through the **EAP (Sept 2017 to Dec 2018)**

Data extracted from patients' medical records — retrospective data collection at different time points

5-year observation to evaluate disease evolution

Dec 2018 to Aug 2020	Jul to Oct 2020	Sept to Nov 2021	Estimated late 2023 to 2024
Initial consent	Sufficient PFS events	OS at 3 years	Long-term OS
	(Reported previously[1,2])	(Current analysis[3])	

Endpoints

Primary: investigator-assessed PFS‡; OS

Key secondary: demographics; disease characteristics; prior therapy; PFS/OS by subgroups; AESIs

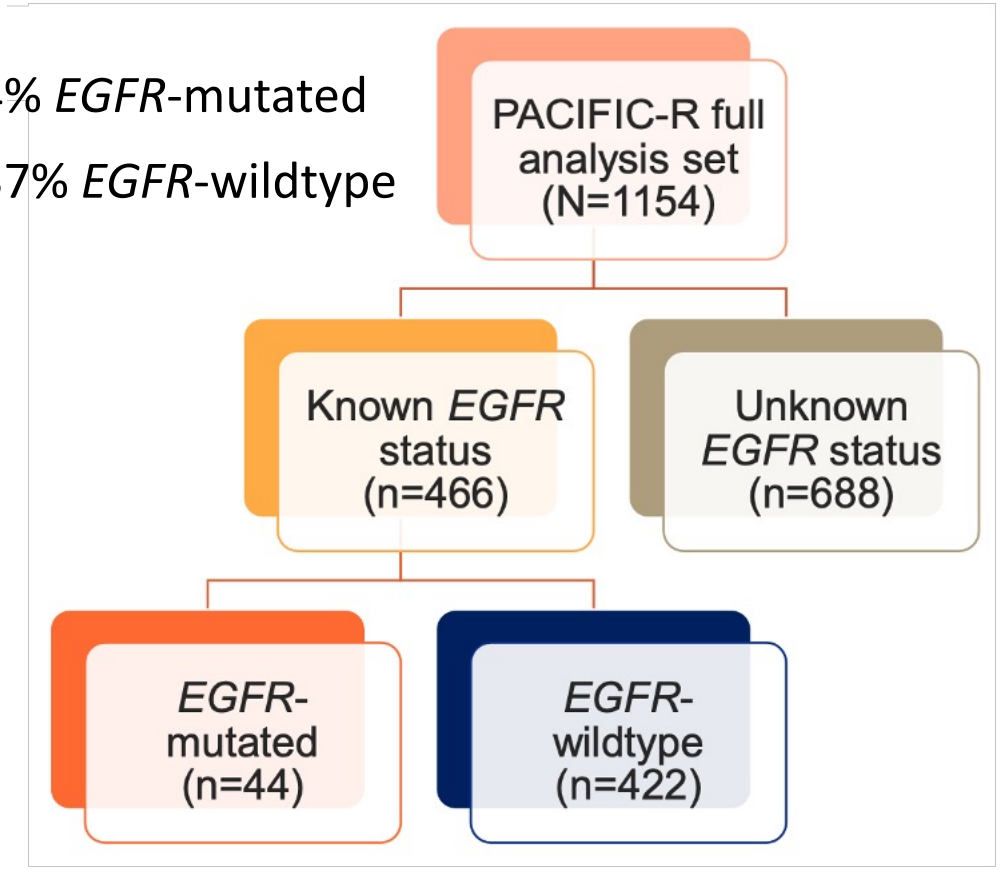
AESI, adverse event of special interest; AJCC, American Joint Committee on Cancer; CRT, chemoradiotherapy; EAP, early access programme; IV, intravenously; NSCLC, non-small-cell lung cancer; OS, overall survival; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; Q2W, every 2 weeks

Study design figure adapted from Girard N et al., J Thorac Oncol 2023;18:181–93. *AJCC 7th or 8th edition. †Patients should have completed platinum-based chemotherapy concurrent or sequential to radiotherapy within the previous 12 weeks without evidence of progression. ‡Because of the real-world nature of PACIFIC-R, progression could be documented by either radiological evaluation (per Response Evaluation Criteria in Solid Tumors [RECIST] v1.1) or the investigator's clinical judgment (depending on local practice). [1]Girard N et al., Ann Oncol 2021;32(suppl_5):S939–48; [2]Girard N et al., J Thorac Oncol 2023;18:181–93; [3]Girard N et al., IOTECH 2022;16:100163

Clinical characteristics by EGFR mutation status

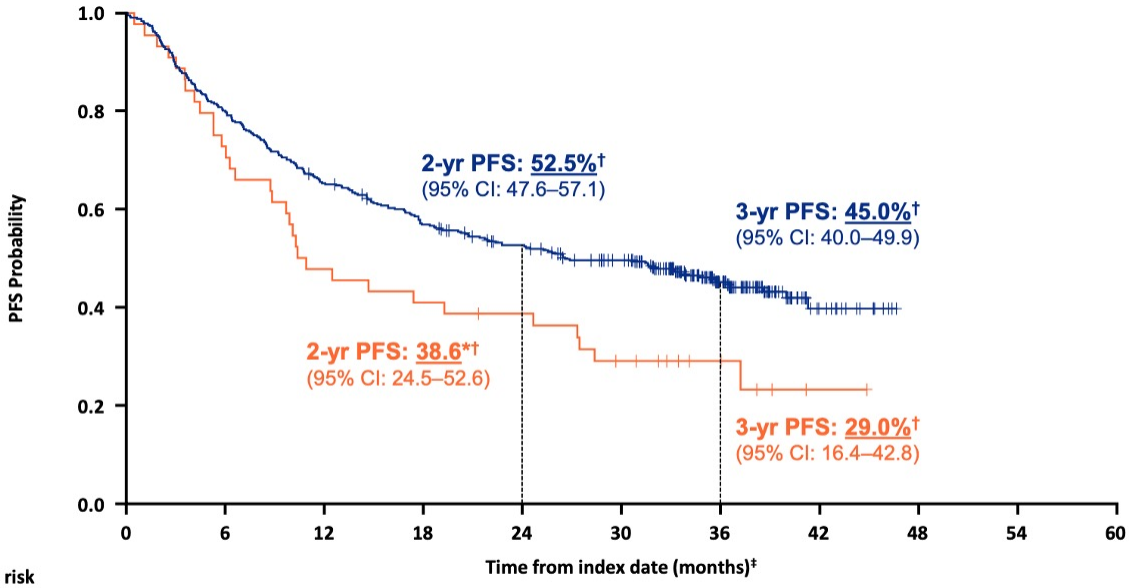
4% *EGFR*-mutated

37% *EGFR*-wildtype



Characteristics*, n (%)		*EGFR*-mutated (n=44)	*EGFR*-wildtype (n=422)
Age	<70 years	26 (59.1)	307 (72.7)
	≥70 years	18 (40.9)	115 (27.3)
Sex	Male	23 (52.3)	248 (58.8)
	Female	21 (47.7)	174 (41.2)
Smoking status	Never	9 (20.5)	46 (10.9)
	Current	11 (25.0)	98 (23.2)
	Former	24 (54.5)	278 (65.9)
ECOG/WHO PS	0	12 (27.3)	156 (37.0)
	1	21 (47.7)	114 (27.0)
	≥2	0	7 (1.7)
	Missing	11 (25.0)	145 (34.4)
Disease histology	Squamous	4 (9.1)	35 (8.3)
	Non-squamous	40 (90.9)	381 (90.3)
	Unknown	0	6 (1.4)
Stage III diagnosis	Initial diagnosis	39 (88.6)	393 (93.1)
	Relapse from early stage	5 (11.4)	29 (6.9)
PD-L1 expression level†	TC ≥1%	29 (76.3)	269 (76.9)
	TC <1%	8 (21.1)	55 (15.7)
	Unknown	1 (2.6)	26 (7.4)
CRT type‡	Concurrent	34 (77.3)	340 (80.6)
	Sequential	8 (18.2)	55 (13.0)
Time from end of RT to durvalumab initiation§	≤42 days	17 (39.5)	148 (36.1)
	>42 days	26 (60.5)	262 (63.9)

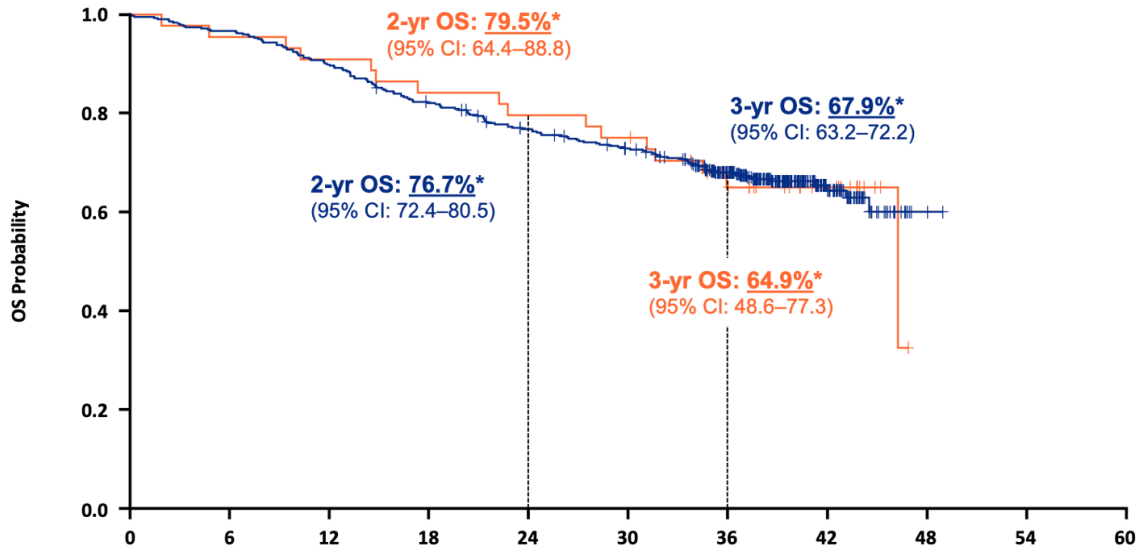
Investigator Assessed PFS



No. at risk											
EGFR-mutated	44	32	21	18	16	11	6	1	0	0	0
EGFR-wildtype	420	336	273	235	209	183	89	15	0	0	0

	Median PFS† (95% CI), months
EGFR-mutated	10.6 (8.7–27.3)
EGFR-wildtype	26.4 (20.5–35.7)

OS



No. at risk											
EGFR-mutated	44	42	40	37	35	33	22	12	0	0	0
EGFR-wildtype	422	408	379	344	316	295	228	61	2	0	0

	Median OS* (95% CI), months
EGFR-mutated	46.3 (46.3–NE)
EGFR-wildtype	NR (NE–NE)

Adverse events of special interest

	EGFR-mutated (n=44)					
	All patients	Required corticosteroids	Required immuno-suppressants	Required endocrine Tx	Durvalumab dose action	
					Temporary stop	*Permanent stop*
Any AESI, n (%)	25 (**56.8**)	16 (**36.4**)	2 (**4.5**)	5 (**11.4**)	6 (**13.6**)	9 (**20.5**)
Pneumonitis	9 (**20.5**)	8 (**18.2**)	2 (**4.5**)	0	4 (**9.1**)	5 (**11.4**)
Endocrinopathies	7 (**15.9**)	0	0	5 (**11.4**)	0	2 (**4.5**)
Rash/dermatitis	4 (**9.1**)	4 (**9.1**)	0	0	1 (**2.3**)	0
GI disorders†	2 (**4.5**)	1 (**2.3**)	0	0	0	1 (**2.3**)
ILD	2 (**4.5**)	1 (**2.3**)	0	0	0	2 (**4.5**)
Other	5 (**11.4**)	3 (**6.8**)	0	0	2 (**4.5**)	0

- Pneumonitis was also the most common AESI (**15.2%**) and AESI leading to discontinuation of durvalumab (**8.1%**) among patients with *EGFR*-wildtype NSCLC (n=422)

PACIFIC-R Conclusions

- Among real world patients with unresectable stage III NSCLC treated with consolidative durvalumab after chemoradiation, those with known *EGFR*-mutated NSCLC had lower PFS than those with known *EGFR*-wildtype NSCLC
- There were no differences detected in OS
- These data should be interpreted cautiously given the small number of patients and the PACIFIC-R study's retrospective nature

What is the optimal treatment for patients with unresectable Stage III *EGFR*-mutated NSCLC after platinum-based chemoradiation?

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Study Design and Patient Characteristics

Multi-institutional retrospective analysis including 24 institutions

Inclusion Criteria:
(1) ≥ age 18 treated years 2015 or later
(2) Stage III, locally advanced, unresectable NSCLC with *EGFR*-sensitizing mutation
(3) Received ≥2 cycles of platinum-based concurrent chemoradiation
(4) No disease progression at time of initiation of consolidation treatments

→ Consolidation Osimertinib
→ Consolidation Durvalumab
→ Observation

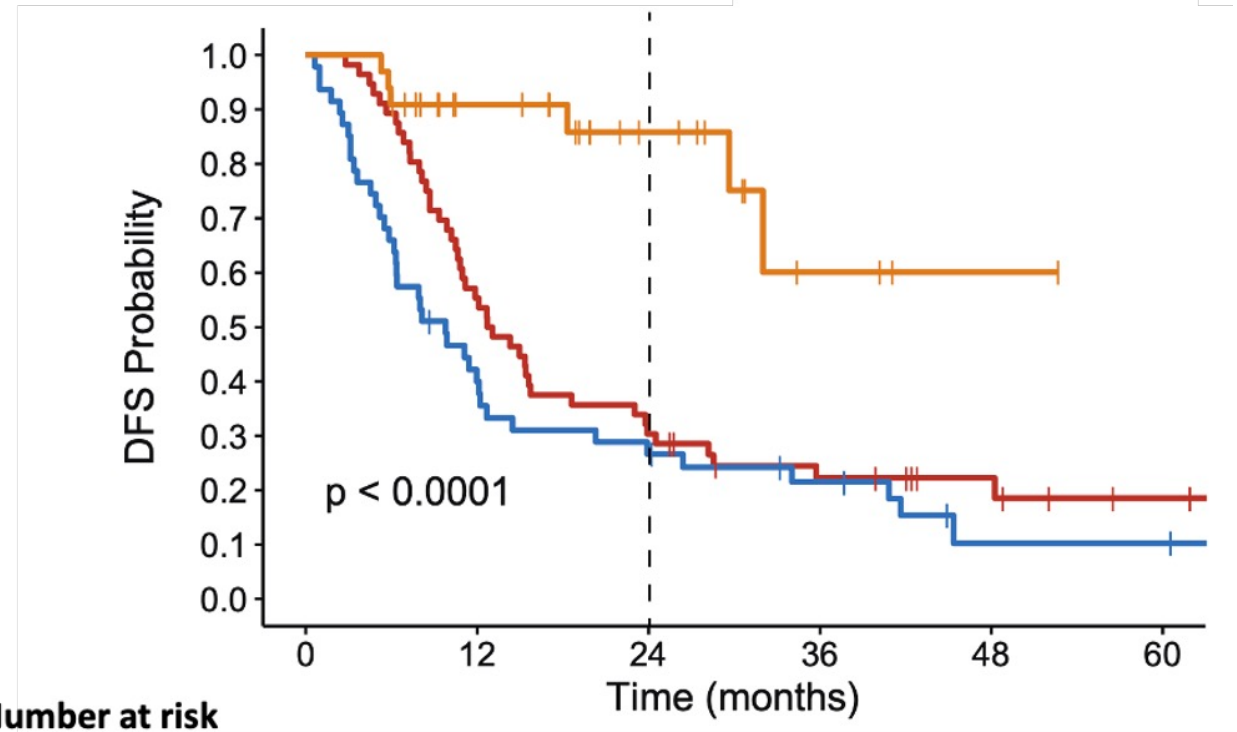
Co-primary endpoints: Disease-free survival (DFS) and overall survival (OS)#
Secondary endpoints: Consolidation treatment-related adverse events (trAE), central nervous system disease-free survival (CNS DFS)

#multivariable including nodal status (N stage), stage III A/B/C AJCC 8th, and age

	Total (N=136)	Osimertinib (N=33)	Durvalumab (N=56)	Observation (N=47)	P-value
Age – Median (IQR)	66 [57, 72]	65 [60, 72]	67 [56, 71]	64 [57, 72]	0.8
Sex – Female	88 (64.7%)	22 (66.7%)	34 (60.7%)	32 (68.1%)	0.7
Race					0.2
White	88 (64.7%)	22 (66.7%)	33 (58.9%)	33 (70.2%)	
Asian	36 (26.5%)	9 (27.3%)	20 (35.7%)	7 (14.9%)	
Black	6 (4.4%)	1 (3.0%)	2 (3.6%)	3 (6.4%)	
Smoking					0.06
Former/Current	55 (40.4%)	10 (30%)	32 (1.8%)	27 (57.4%)	
Never	81 (59.6%)	23 (69.7%)	38 (67.9%)	20 (42.6%)	
PD-L1 TPS*					0.4
<1%	35 (37.2%)	10 (40%)	15 (31.3%)	10 (47.6%)	
≥1%	59 (62.8%)	15 (60%)	33 (68.8%)	11 (52.4%)	
Stage					0.31
IIIA	52 (38.2%)	11 (33.3%)	20 (35.7%)	21 (44.7%)	
IIIB	68 (50.0%)	15 (45.5%)	30 (53.6%)	23 (48.9%)	
IIIC	16 (11.8%)	7 (21.2%)	6 (10.7%)	3 (6.4%)	

*Tumor proportion score

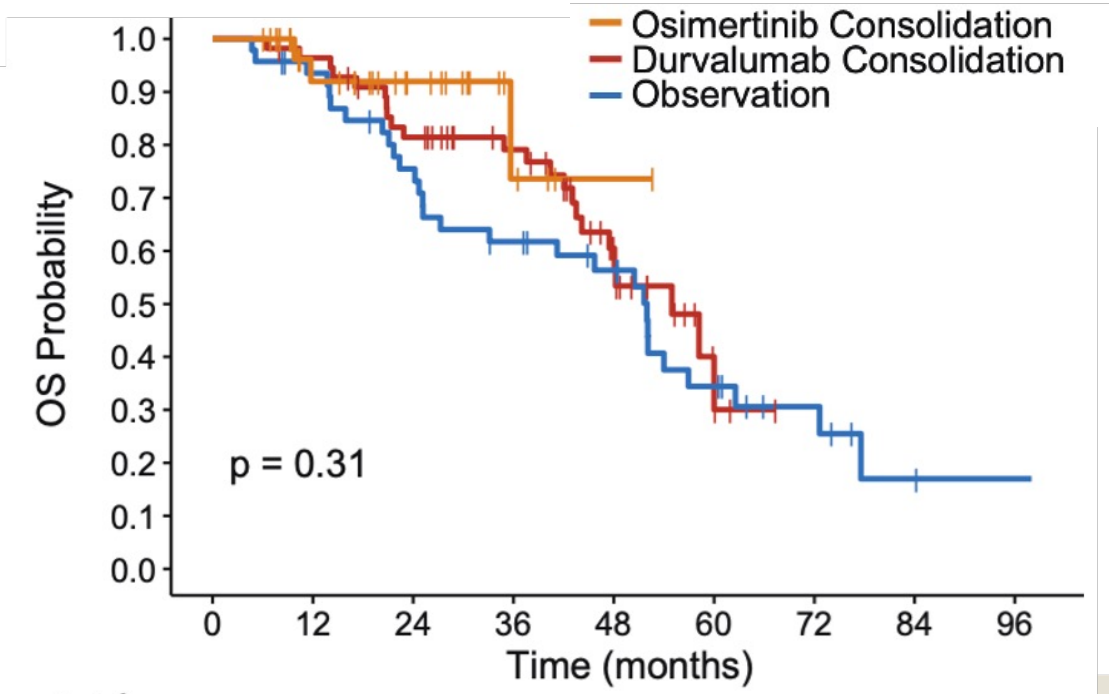
Disease Free Survival



Number at risk

Osimertinib	33	21	11	3	1	0
Durvalumab	56	31	17	10	6	2
Observation	47	18	12	8	2	2

Overall Survival



Number at risk

Osimertinib	33	22	13	4	1	0	0	0	0
Durvalumab	56	53	43	34	18	4	0	0	0
Observation	47	42	33	26	20	11	6	2	1

Treatment-related adverse events (trAE)

	Osimertinib (N=33)		Durvalumab (N=56)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any trAE#	16 (48%)	2 (6.1%)	27 (48%)	10 (18%)
Rash	1 (3.0%)	0 (0%)	1 (1.8%)	0 (0%)
Pneumonitis^	5 (15%)	1 (3.0%)	14 (25%)	7 (13%)
Diarrhea	1 (3.0%)	0 (0%)	2 (3.6%)	1 (1.8%)
Endocrine	0 (0%)	0 (0%)	5 (8.9%)	0 (0%)
AST/ALT elevation	1 (3.0%)	0 (0%)	2 (3.6%)	1 (1.8%)
Other	11 (33%)	1 (3.0%)	3 (5.4%)	1 (1.8%)*
trAE leading to discontinuation	4 (12%)		15 (27%)	
Steroid use	7 (21%)		20 (36%)	

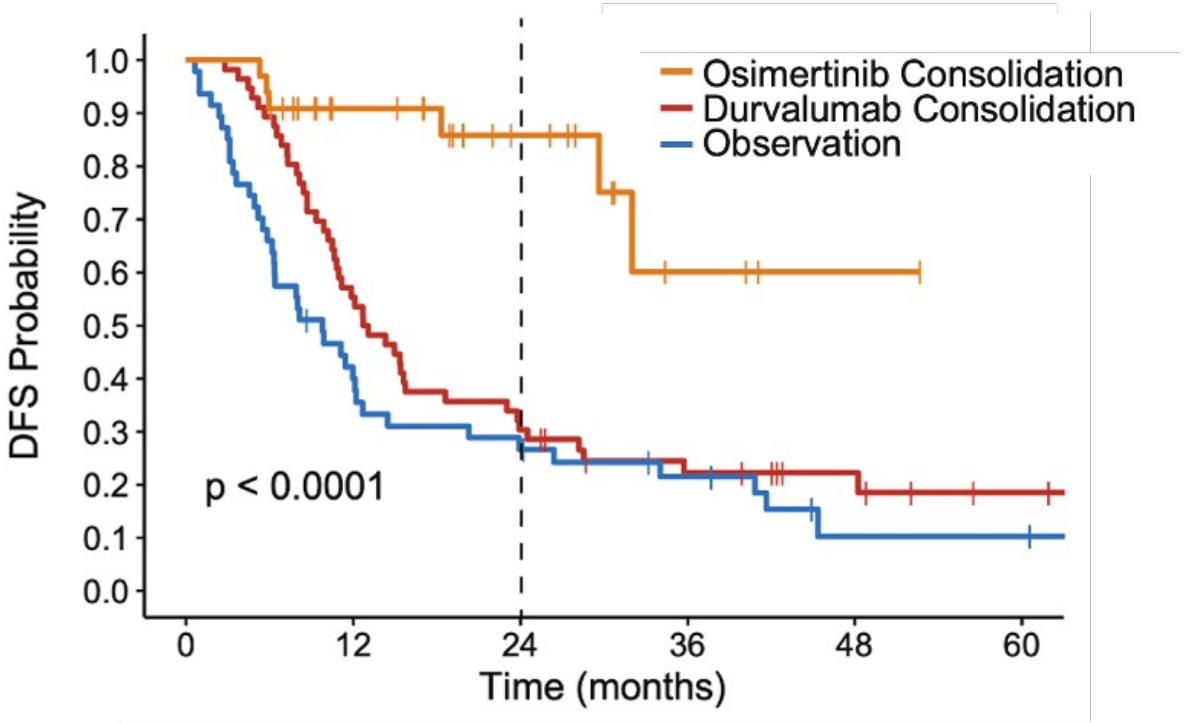
*grade 3 myocarditis
^ Does not include radiation pneumonitis
#Consolidation treatment-related adverse events

14 out of 37 (38%) patients who received EGFR tyrosine kinase inhibitors (TKIs) after durvalumab developed trAE on EGFR TKI, including

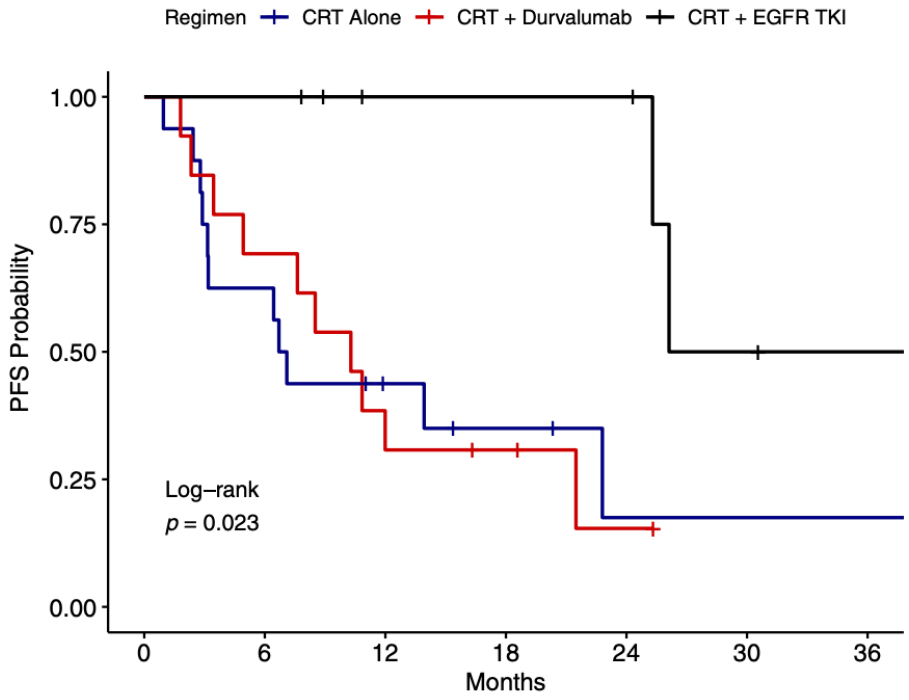
- 5 patients with pneumonitis (2 ≥grade 3)
- 5 patients with colitis (1 ≥grade 3)

These findings are similar to the Stanford experience

DFS
(Nassar et al, WCLC 2023)



PFS
(Aredo et al, JTO 2021)



Nassar et al., Conclusions

- In this retrospective, multi-center analysis of 136 patients, there was a superior DFS with consolidation osimertinib compared to durvalumab or observation alone following chemoradiation for locally advanced *EGFR*-mutant NSCLC
- Lack of difference in overall survival could be explained by subsequent therapies and/or limited follow-up time
- No unanticipated safety signals: pneumonitis and grade ≥3 trAE greater with durvalumab vs osimeritinib

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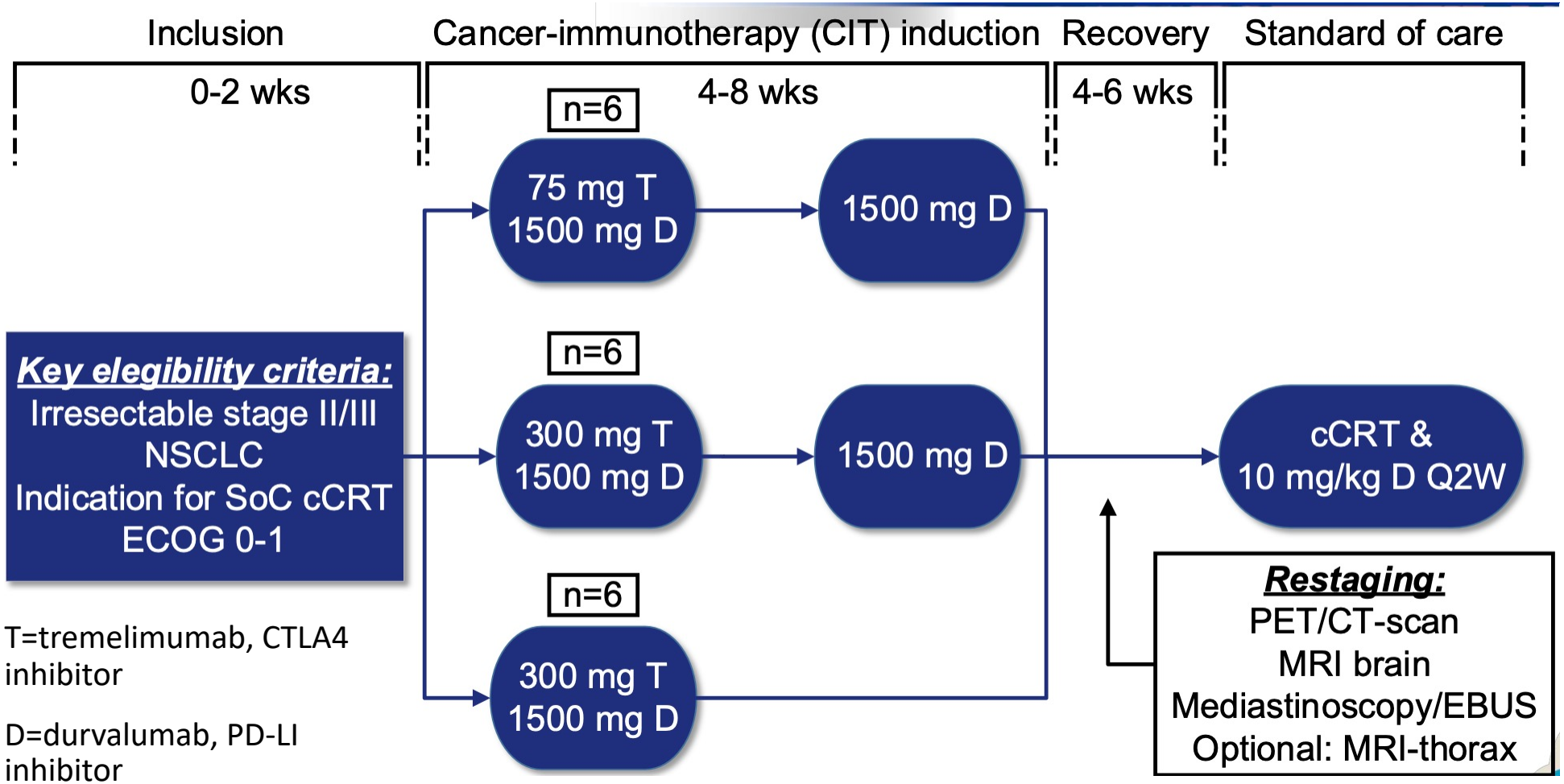

T=tremelimumab, CTLA4 inhibitor

D=durvalumab, PD-LI inhibitor

Primary Endpoint - Safety

Feasibility criteria (≥2/6 patients)

-cCRT impossible due to PD

-Start cCRT impossible <12 weeks

-Failure to complete RTx

Safety criterion (≥3/6 patients)

-Grade III iRAE

Results: Safety

	75T+1500D & 1500D†	300T+1500D & 1500D	300T+1500D†
Feasibility			
cCRT impossible due to PD	0/5	1/6	0/4
Start cCRT impossible <12 weeks	0/5	0/6	0/4
Failure to complete RTx	0/5	0/6	1/4‡
Safety			
Grade III ICI-related AE	1/5	2/6	3/4
Hepatitis	1	0	0
Colitis	0	2	2
Pulmonary abscess	0	0	1
Significant grade II ICI-related AE	0/5	2/6	0/4

†One withdrawal of consent during CIT-induction

‡Due to pulmonary abscess

18 SAEs in 10 patients

4 patients received infliximab due to AE

Results: Efficacy

Response evaluation according to RECIST 1.1

	CR	PR	SD	PD	NA†
Post CIT-induction	0	8	5	2	2
Post cCRT	1	6	1	0	9
Best response	3	7	3	2	2

†Two unavailable due to withdrawal of consent

Restaging post-CIT:

9/12 with multilevel N2/N3 downstaged to N0/1 or single level N2

Post-cCRT:

2 patients trimodality, 1 with pCR

11/13 received Durvalumab post-CCRT

Conclusion

Induction with high dose tremelimumab and durvalumab prior to cCRT was associated with unacceptable toxicity

Induction with dual checkpoint inhibition showed relevant clinical activity indicated by the high numbers of pathological nodal downstaging

Takeaways from WCLC 2023, systemic therapy in locally advanced NSCLC

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Abstract 2: Nassar et al. Consolidation EGFR-Tyrosine Kinase Inhibitor vs. Durvalumab vs. Observation in Unresectable *EGFR*-Mutant Stage III NSCLC.

The role of durvalumab consolidation in patients with unresectable Stage III *EGFR*-mutated NSCLC is extremely limited. More data to come with the ongoing LAURA study.

Abstract 3: Smeenk et al. Tremelimumab plus Durvalumab Prior to Chemoradiotherapy in Unresectable Locally Advanced NSCLC, the Induction Trial

Dual immunotherapy prior to concurrent chemoradiation for locally advanced NSCLC is associated with unacceptable toxicity