Penn Medicine
Abramson Cancer Center

Division of Hematology & Oncology

Management of LA-NSCLC in Pts with PD-L1 < 1% or Oncogenic Drivers

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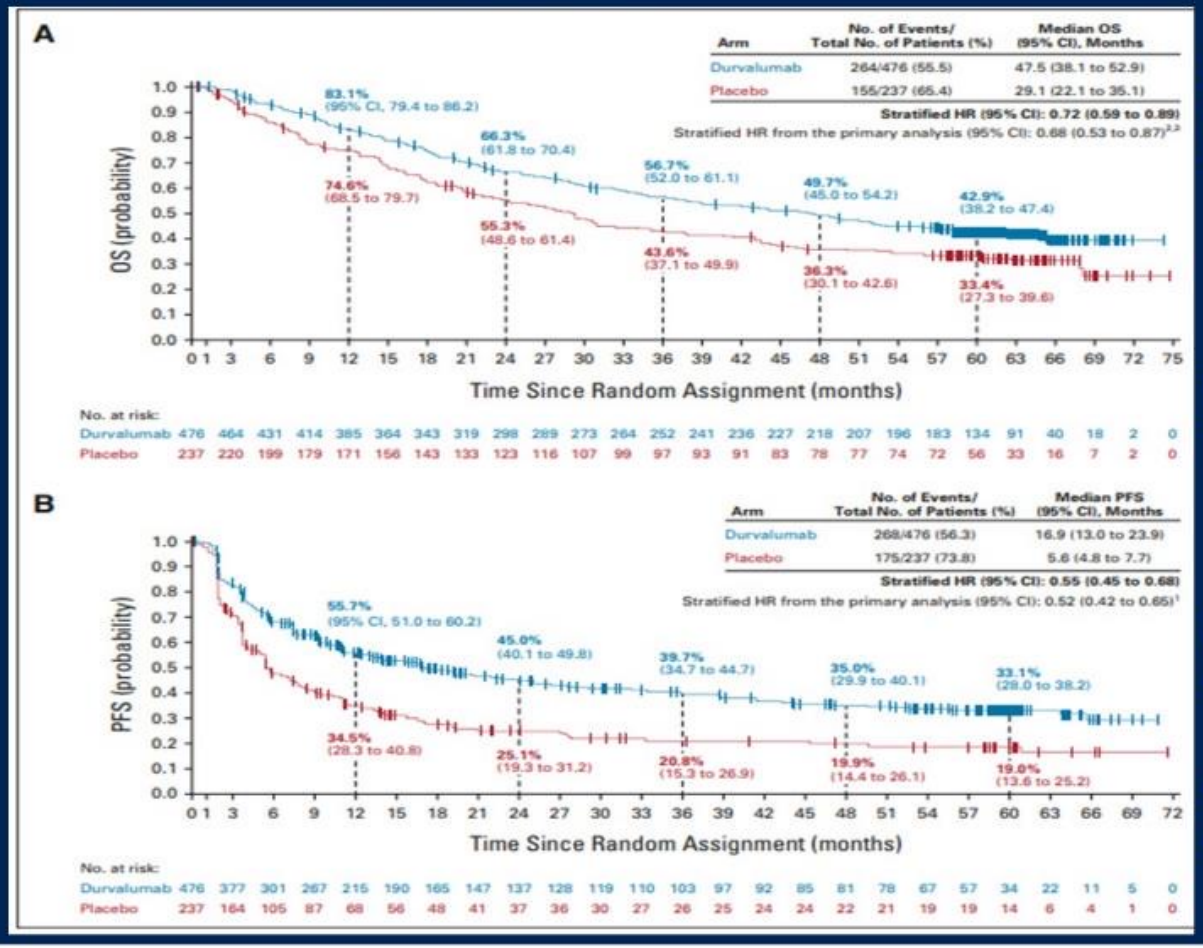
October, 2022

PACIFIC TRIAL



HR = 0.72 OS
Median 47.5 vs 29.1mn

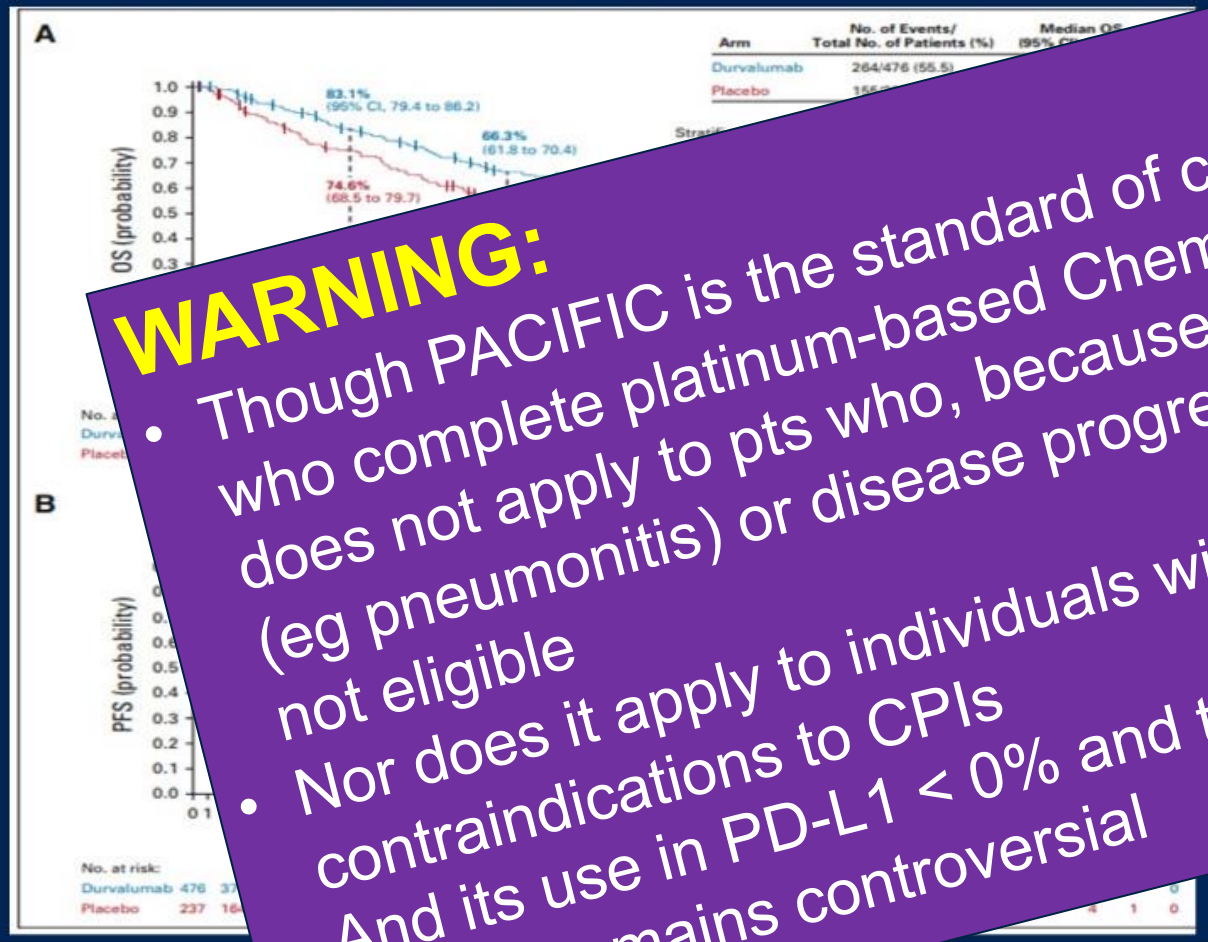
HR = 0.55 PFS
Median 16.9 vs 5.6 mn

Entry Criteria

- No progression during the course of CHEMO/RT
- No unresolved > Grade 2 toxicities
- No Grade ≥ 2 Pneumonitis

PRESENTED BY:
John Michael Varlotto – Chief Radiation Oncology, Marshall University

PACIFIC TRIAL



WARNING:

- Though PACIFIC is the standard of care in LA-NSCLC pts who complete platinum-based Chemo-XRT, this approach does not apply to pts who, because of complications of Tx (eg pneumonitis) or disease progression (~30% total) are not eligible
- Nor does it apply to individuals with AID or other contraindications to CPIs
- And its use in PD-L1 < 0% and those with oncogenic drivers remains controversial

...se of

...ved > Grade 2 toxicities

...Grade ≥ 2 Pneumonitis

2022 ASCO ANNUAL MEETING

...r Varlotto – Chief Radiation Oncology, Marshall University

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

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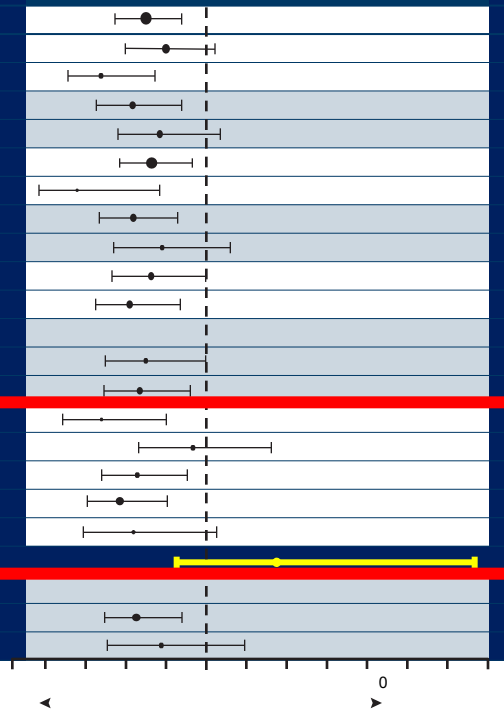
Overall Survival by Subgroup (ITT)

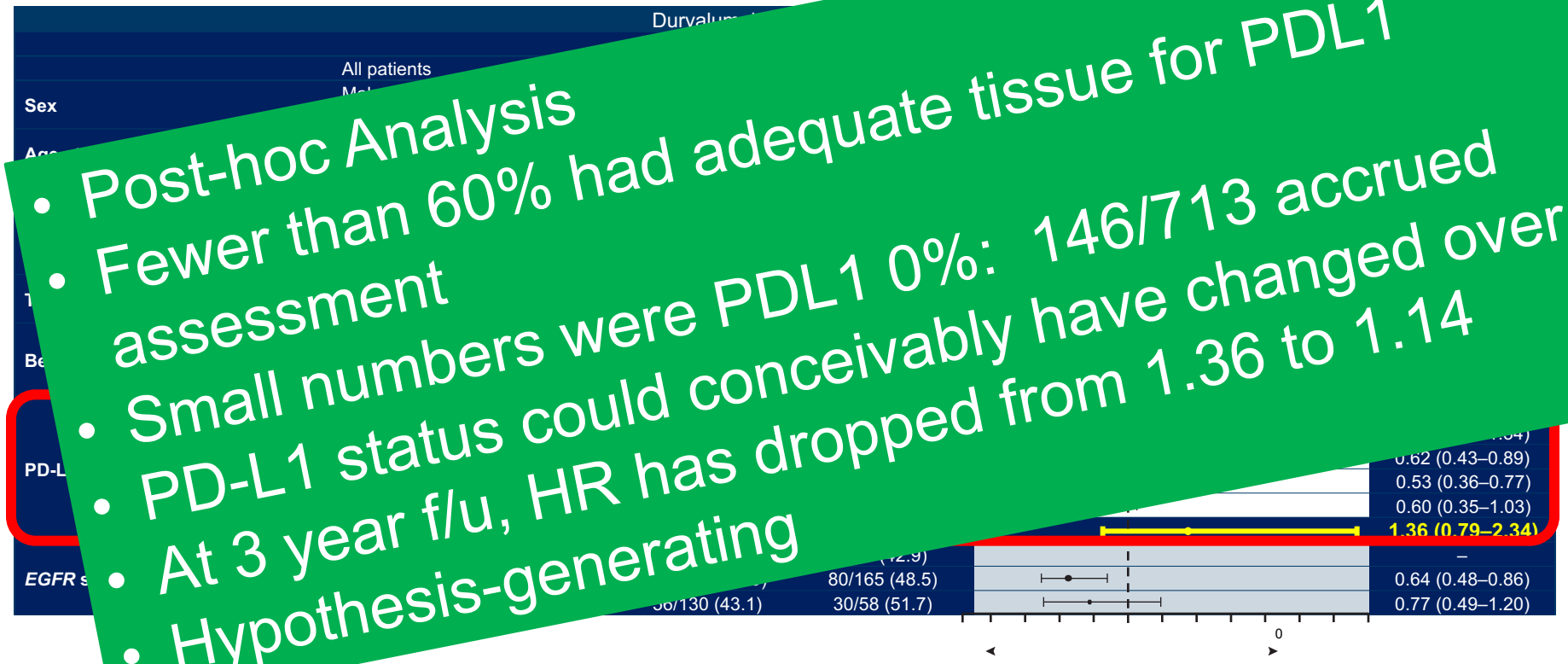
		Durvalumab	Placebo	Unstratified HR* (95% CI)
		No. of events / No. of patients (%)		
	All patients	183/476 (38.4)	116/237 (48.9)	0.68 (0.54–0.86)
Sex	Male	141/334 (42.2)	80/166 (48.2)	0.78 (0.59–1.03)
	Female	42/142 (29.6)	36/71 (50.7)	0.46 (0.30–0.73)
Age at randomization	<65 years	89/261 (34.1)	58/130 (44.6)	0.62 (0.44–0.86)
	≥65 years	94/215 (43.7)	58/107 (54.2)	0.76 (0.55–1.06)
Smoking status	Smoker	169/433 (39.0)	103/216 (47.7)	0.72 (0.56–0.92)
	Non-smoker	14/43 (32.6)	13/21 (61.9)	0.35 (0.16–0.76)
Disease stage	Stage IIIA	101/252 (40.1)	70/125 (56.0)	0.63 (0.46–0.85)
	Stage IIIB	79/212 (37.3)	44/107 (41.1)	0.77 (0.53–1.11)
Tumor histologic type	Squamous	103/224 (46.0)	56/102 (54.9)	0.72 (0.52–0.99)
	Non-squamous	80/252 (31.7)	60/135 (44.4)	0.61 (0.44–0.86)
Best response to prior treatment	CR	2/9 (22.2)	3/7 (42.9)	–
	PR	83/237 (35.0)	50/112 (44.6)	0.69 (0.49–0.99)
	SD	93/223 (41.7)	61/115 (53.0)	0.66 (0.48–0.91)
PD-L1 status	≥25%	37/115 (32.2)	23/44 (52.3)	0.46 (0.27–0.78)
	<25%	74/187 (39.6)	41/105 (39.0)	0.92 (0.63–1.34)
	Unknown	72/174 (41.4)	52/88 (59.1)	0.62 (0.43–0.89)
	≥1%†	70/212 (33.0)	45/91 (49.5)	0.53 (0.36–0.77)
	1–24%†	33/97 (34.0)	22/47 (46.8)	0.60 (0.35–1.03)
	<1%†	**41/90 (45.6)**	**19/58 (32.8)**	**1.36 (0.79–2.34)**
***EGFR* status**	Positive	10/29 (34.5)	6/14 (42.9)	–
	Negative	117/317 (36.9)	80/165 (48.5)	0.64 (0.48–0.86)
	Unknown	56/130 (43.1)	30/58 (51.7)	0.77 (0.49–1.20)



*Not calculated if the subgroup has less than 20 events
†Assessed as part of exploratory post-hoc analyses

[1]Antonia et al. NEJM. 2018

Overall Survival by Subgroup (ITT)



- Post-hoc Analysis
- Fewer than 60% had adequate tissue for PDL1 assessment
- Small numbers were PDL1 0%: 146/713 accrued
- PD-L1 status could conceivably have changed over time
- At 3 year f/u, HR has dropped from 1.36 to 1.14
- Hypothesis-generating

*Not calculat… less than 20 events
†Assessed as … exploratory post-hoc analyses

[1]Antonia et al. NEJM. 2018

ELSEVIER

Journal of Thoracic Oncology

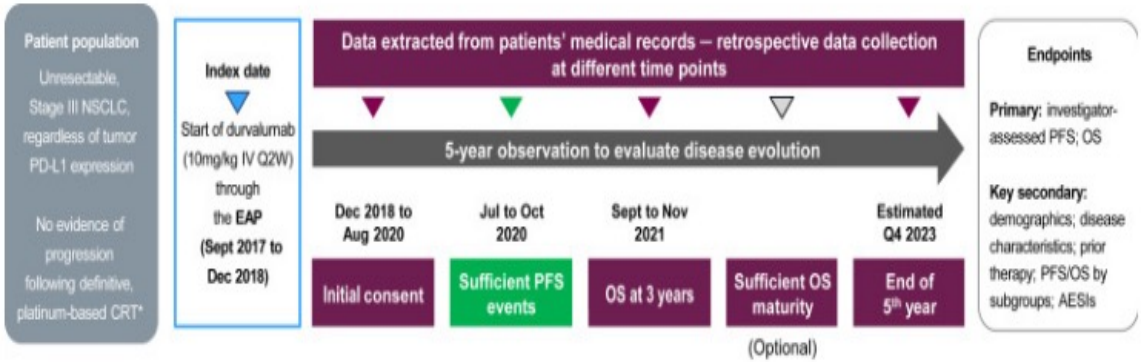
Volume 18, Issue 2, February 2023, Pages 181-193

Original Article

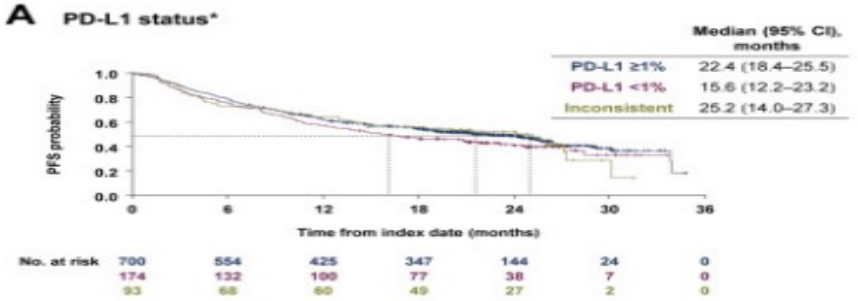
Non-Small Cell Lung Cancer

Treatment Characteristics and Real-World Progression-Free Survival in Patients With Unresectable Stage III NSCLC Who Received Durvalumab After Chemoradiotherapy: Findings From the PACIFIC-R Study

Nicolas Girard MD, PhD [a], Jair Bar MD, PhD [b c], Pilar Garrido MD, PhD [d], Marina C. Garassino MD [e], Fiona McDonald MD, FRCR [f], Françoise Mornex MD, PhD [g], Andrea R. Filippi MD [h], Hans J.M. Smit MD, PhD [i], Solange Peters MD, PhD [j], John K. Field PhD, FRCPath [k], Daniel C. Christoph MD, PhD [l], Anne Sibille MD [m], Rainer Fietkau MD, PhD [n], Vilde D. Haakensen MD, PhD [o], Christos Chouaid MD, PhD [p], Ben Markman MBBS, FRACP [q], T. Jeroen N. Hiltermann MD, PhD [r], Alvaro Taus MD [s], William Sawyer PhD [t], Allison Allen PhD [u]...Benjamin Solomon MBBS, PhD, FRACP [w]



Full analysis set	**N = 1399**
PD-L1 status, n (%)	**n = 967[d]**
≥1%	**700 (72.4)**
<1%	**174 (18.0)**



- No control arm
- Not tested statistically
- No OS data (yet)

Girard JTO 2023

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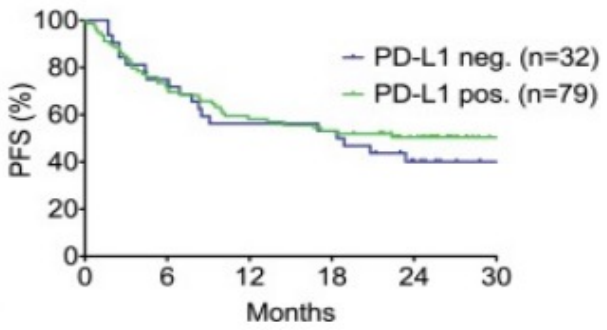
Lung Cancer
Volume 150, December 2020, Pages 114-122

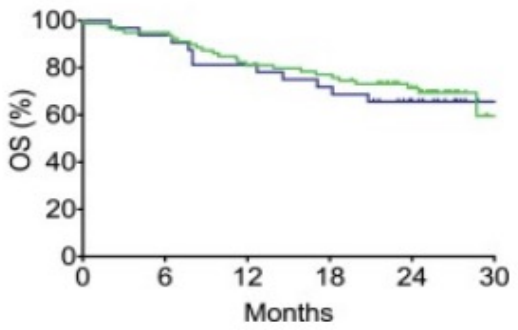
Durvalumab after definitive chemoradiotherapy in locally advanced unresectable non-small cell lung cancer (NSCLC): Real-world data on survival and safety from the German expanded-access program (EAP)

Martin Faehling [a], Christian Schumann [b], Petros Christopoulos [c], Petra Hoffknecht [d], Jürgen Alt [e], Marlitt Horn [f], Stephan Eisenmann [g], Anke Schlenska-Lange [h], Philipp Schütt [i], Felix Steger [j], Wolfgang M. Brückl [k], Daniel C. Christoph [l]

- For 111 patients (88.1 %), the PD-L1 expression level on tumor cells was reported.
  - 71.2 % had a PD-L1-expression level ≥ 1%
  - 49.5 % had PD-L1-expression levels of ≥ 25 %,
  - 28.8 % were PD-L1 negative.
- For comparison, in the PACIFIC trial, the PD-L1-expression level was known for 63.4 % of patients, of whom 67.2 % and 38.1 % had PD-L1-expression levels of ≥ 1 % and ≥ 25 %, respectively.



HR 1.21



HR 1.15

Faehling, M et al Lung Cancer 2020

Efficacy of Consolidation Pembrolizumab vs Durvalumab

Endpoint	LUN 14-179[2] (Pembrolizumab)	PACIFIC[1] (Durvalumab)	PACIFIC[1] (Placebo)
Median Follow-up	23.9 months	14.5 months	14.5 months
Time to Metastatic Disease or Death			
Median	30.7 months	23.2 months	14.6 months
12-month	76.3%	-	-
18-month	60.0%	-	-
Progression Free Survival			
Median	15 months	16.8 months	5.6 months
12-month	60.8%	55.9%	35.3%
18-month	46.9%	44.2%	27.0%
Overall Survival			
Median	NR	NR	28.7
12-month	81.0%	83.1%	75.3%
24-month	61.9%	66.3%	55.6%
36-month	48.5%	57.0%	43.5%

Results in LUN 14-179 appear independent of PD-L1 status

[1]Antonia et al. NEJM. 2017. Nov 16. 1919-1929
[2]Durm et al, ASCO, WCLC 2018.

Implications of PACIFIC and HOG LUN 14-179

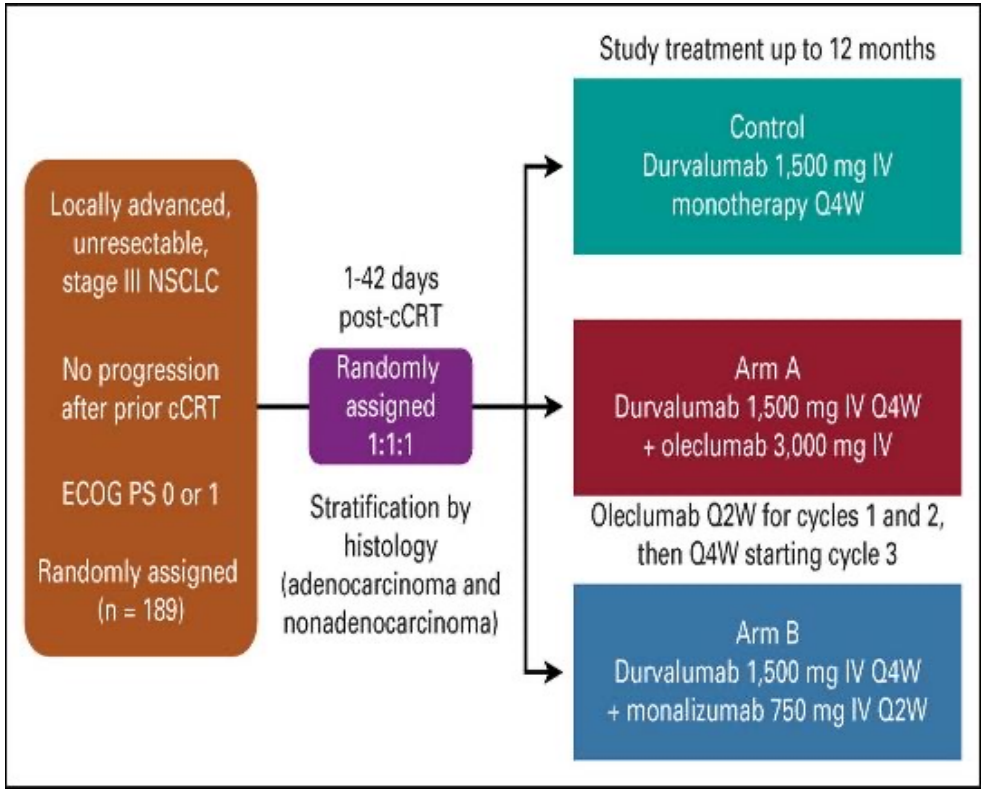
- HOG LUN 14-179
  - PD-L1 status (n=53), No (%)

Negative	11 (20.8)
1-49%	11 (20.8)
< 50%	31 (58.5)

  - No difference in OS between patients with a PD-L1 MPS < 1% and patients with a PD-L1 MPS ≥ 1% (hazard ratio, 0.79; 95% CI, 0.27-2.31; P = .66)
- To date, No trial in LA-NSCLC is currently focused on PD-L1 < 1%
- Most ongoing efforts are “agnostic” to PD-L1 status

Durm et al, ASCO, WCLC 2018.

COAST Phase II Trial: 1^0 Endpoint – ORR

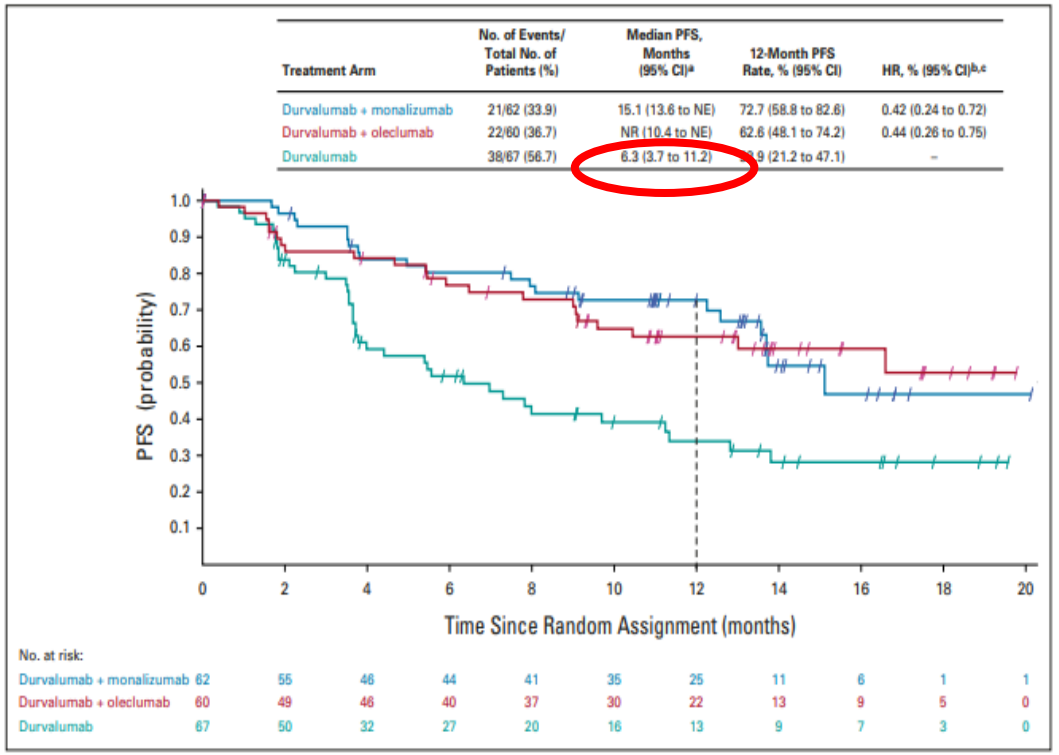


ORR

18%

36%

30%



Treatment Arm	No. of Events/ Total No. of Patients (%)	Median PFS, Months (95% CI)[a]	12-Month PFS Rate, % (95% CI)	HR, % (95% CI)[b,c]
Durvalumab + monalizumab	21/62 (33.9)	15.1 (13.6 to NE)	72.7 (58.8 to 82.6)	0.42 (0.24 to 0.72)
Durvalumab + oleclumab	22/60 (36.7)	NR (10.4 to NE)	62.6 (48.1 to 74.2)	0.44 (0.26 to 0.75)
Durvalumab	38/67 (56.7)	6.3 (3.7 to 11.2)	33.9 (21.2 to 47.1)	–

Oleclumab, inhibits CD73 (adenosine pathway); Monalizumab, blocks NKG2A.

Herbst R, et al. *J Clin Oncol.* 2022;40:3383-3393.

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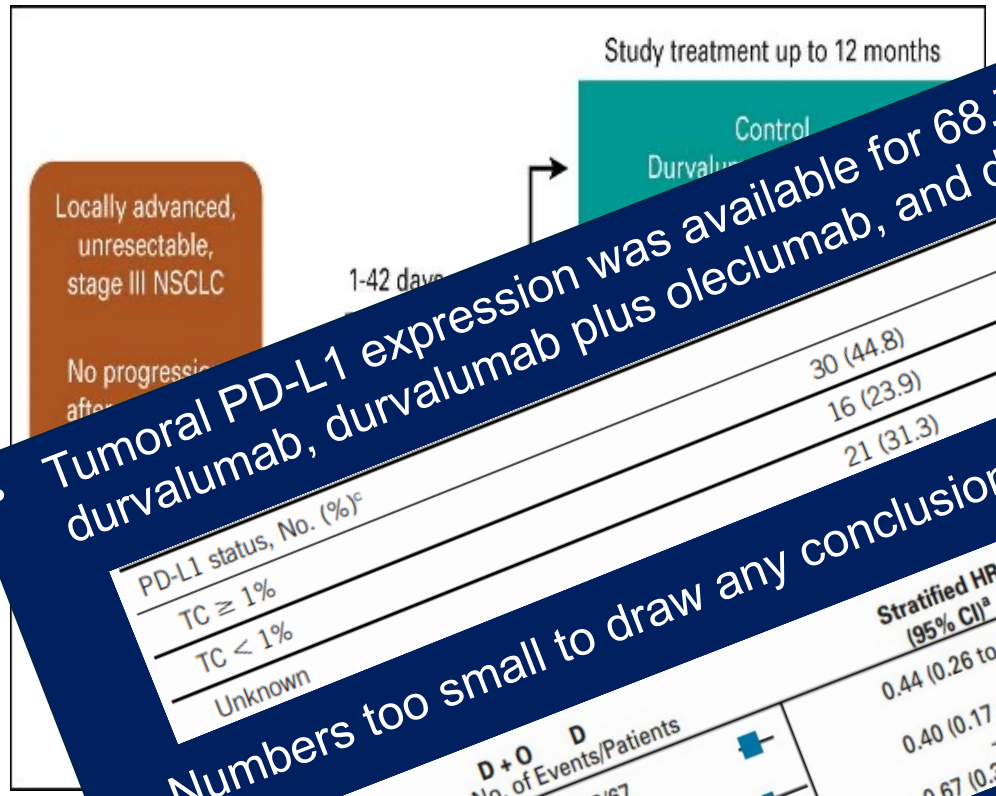
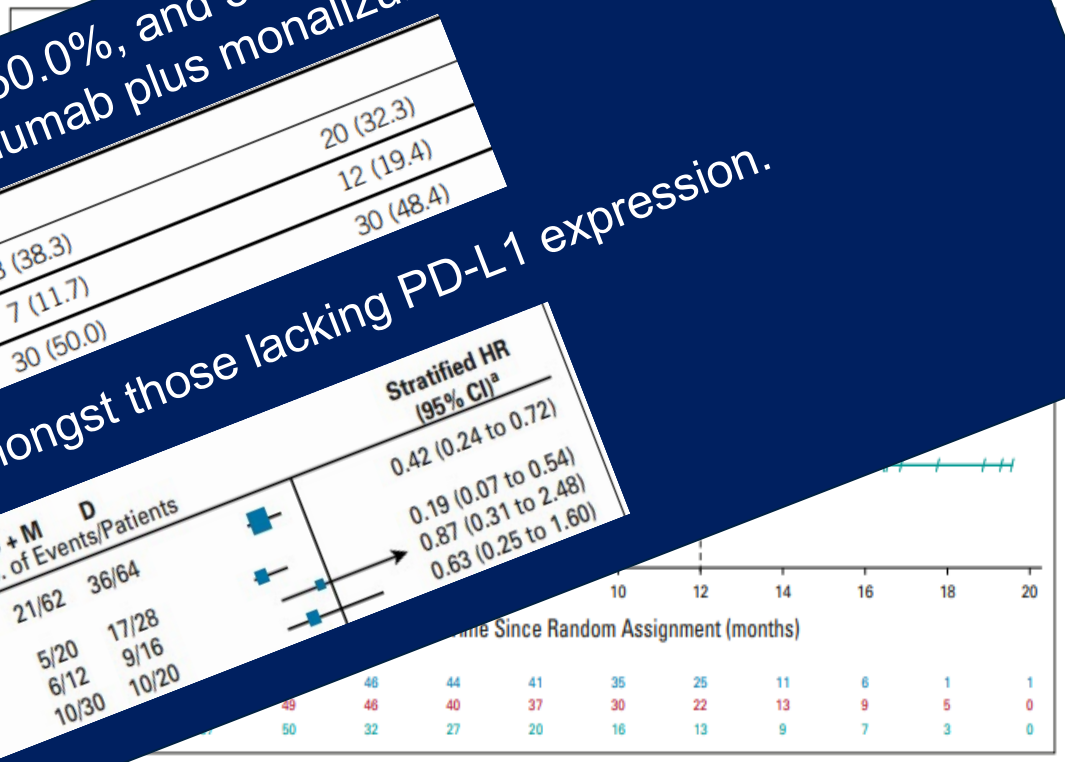
COAST Phase II Trial: 1⁰ Endpoi



PD-L1 status, No. (%)[c]			
TC ≥ 1%	30 (44.8)	23 (38.3)	20 (32.3)
TC < 1%	16 (23.9)	7 (11.7)	12 (19.4)
Unknown	21 (31.3)	30 (50.0)	30 (48.4)



	D + O No. of Events/Patients	D	Stratified HR (95% CI)[a]	D + M No. of Events/Patients	D	Stratified HR (95% CI)[a]
Overall	22/60	38/67	0.44 (0.26 to 0.75)	21/62	36/64	0.42 (0.24 to 0.72)
PD-L1 status						
TC ≥ 1%	8/23	18/30	0.40 (0.17 to 0.94)	5/20	17/28	0.19 (0.07 to 0.54)
TC < 1%	1/7	9/16	—	6/12	9/16	0.87 (0.31 to 2.48)
Unknown	13/30	11/21	0.67 (0.30 to 1.50)	10/30	10/20	0.63 (0.25 to 1.60)

- Tumoral PD-L1 expression was available for 68.7%, 50.0%, and 51.6% of patients in the durvalumab, durvalumab plus oleclumab, and durvalumab plus monalizumab arms, respectively
- Numbers too small to draw any conclusions amongst those lacking PD-L1 expression.

Oleclu… …thway); Monalizumab, blocks NKG2A.
Herbst … …;40:3383-3393.

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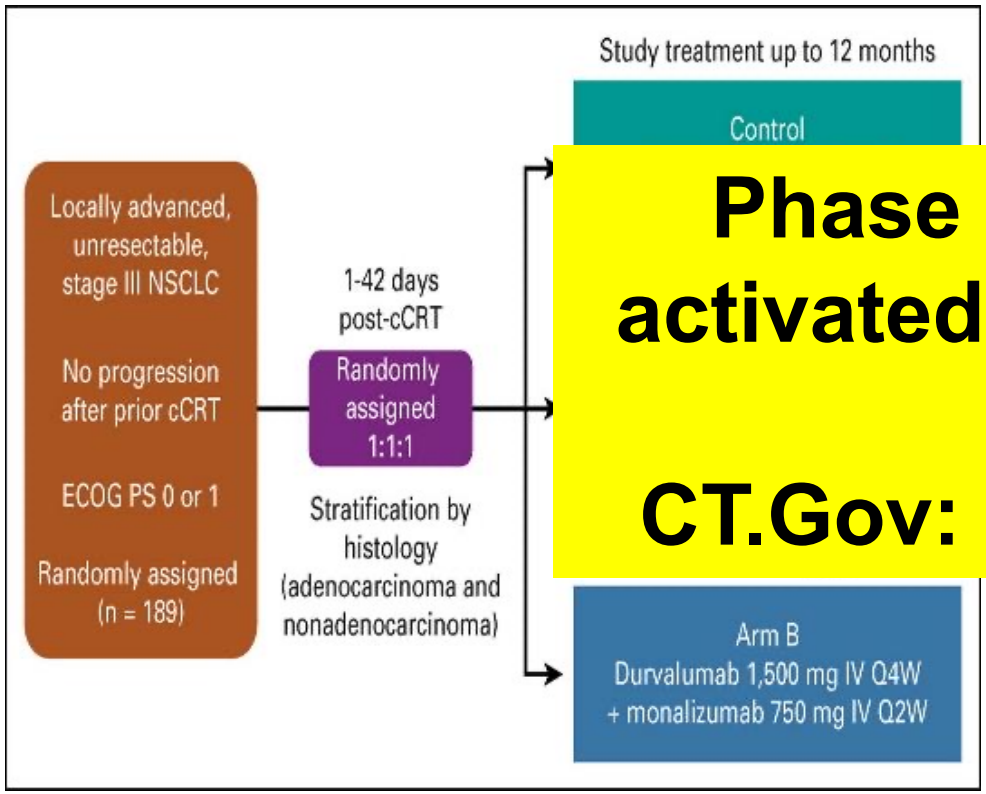
COAST Phase II Trial: 1^0 Endpoint – ORR

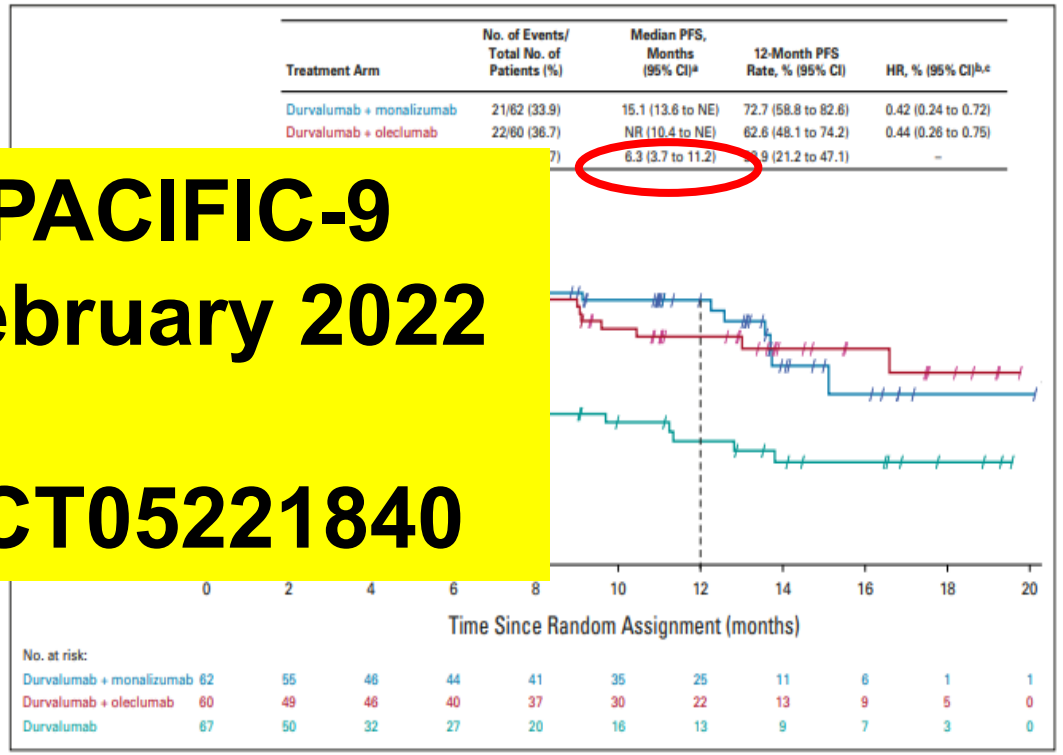


ORR

30%

Phase III PACIFIC-9 activated February 2022

CT.Gov: NCT05221840



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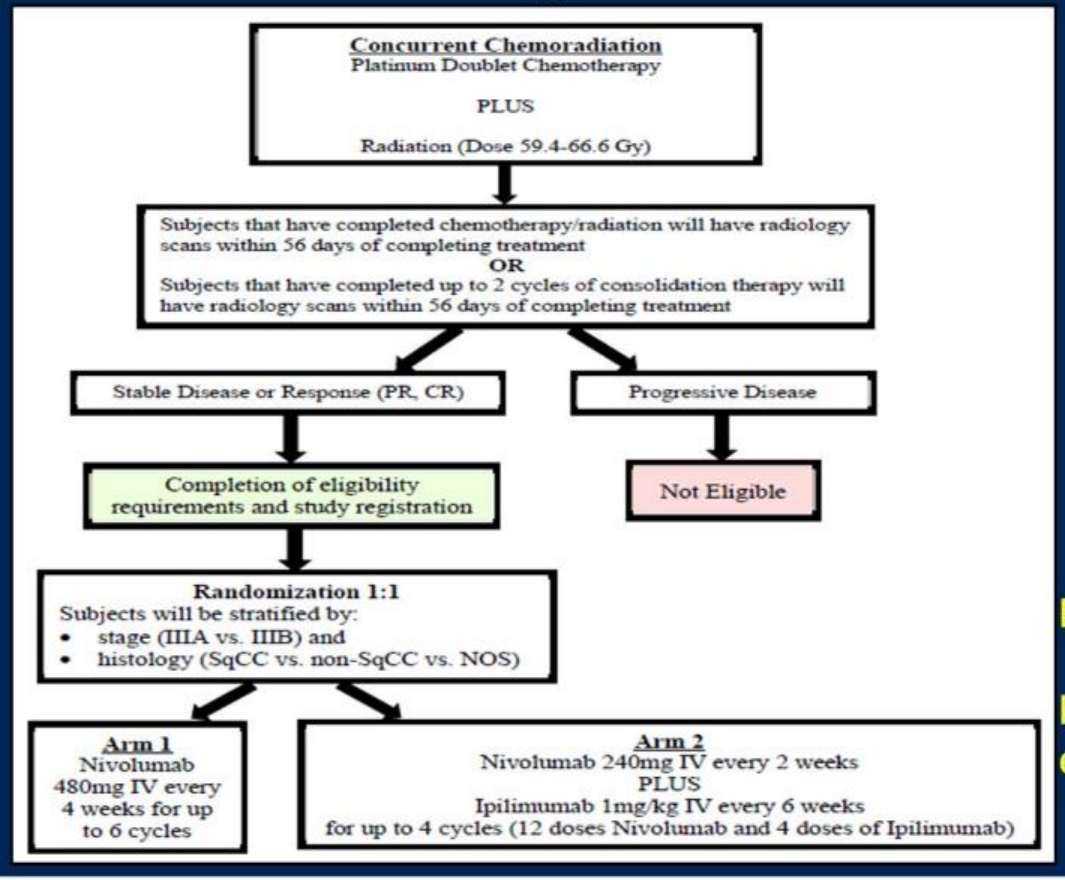
	[illegible]7)	6.3 (3.7 to 11.2)	[illegible].9 (21.2 to 47.1)	–

Oleclumab, inhibits CD73 (adenosine pathway); Monalizumab, blocks NKG2A.

Herbst R, et al. *J Clin Oncol.* 2022;40:3383-3393.

Consolidation Nivolumab Plus Ipilimumab or Nivolumab Alone Following Concurrent Chemoradiation for Patients with Unresectable Stage III Non-Small Cell Lung Cancer. Durm et al



Primary Endpoint-
18- months PFS

1. **Nivo vs historic chemoRT**

2. **Nivo/Ipi vs historic Pacific data**

Big question-

Is 6 months of consolidative immunotherapy enough?

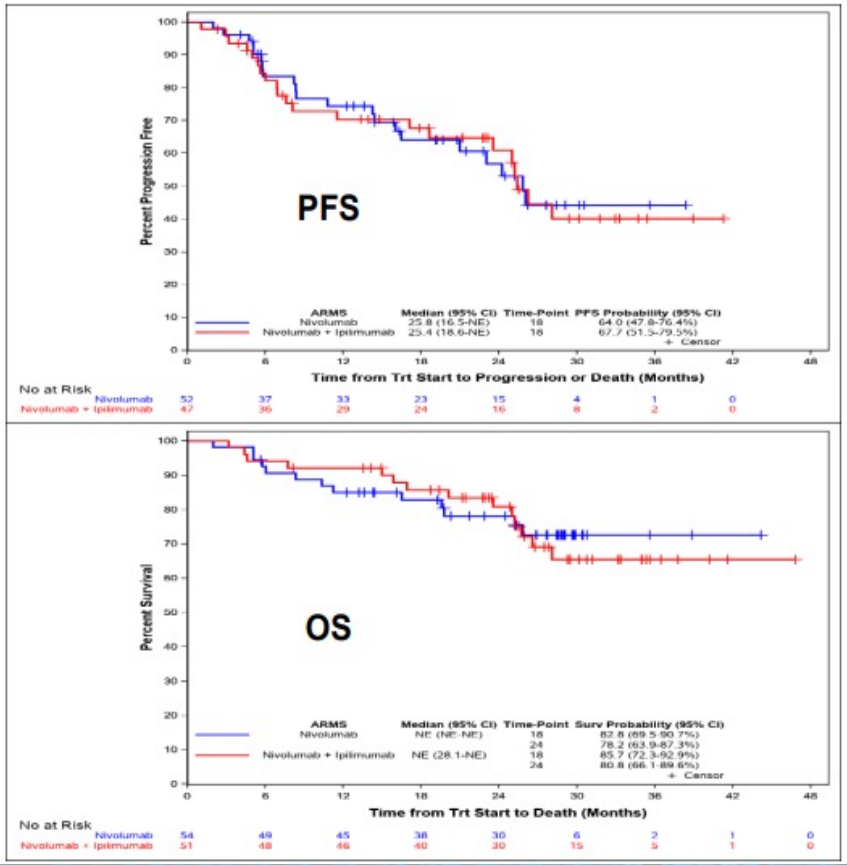
Abstract 8509

PRESENTED BY:
John Michael Varlotto – Chief Radiation Oncology, Marshall University

IASLC 2022 World Conference on Lung Cancer

AUGUST 6-9, 2022 | VIENNA, AUSTRIA

Results

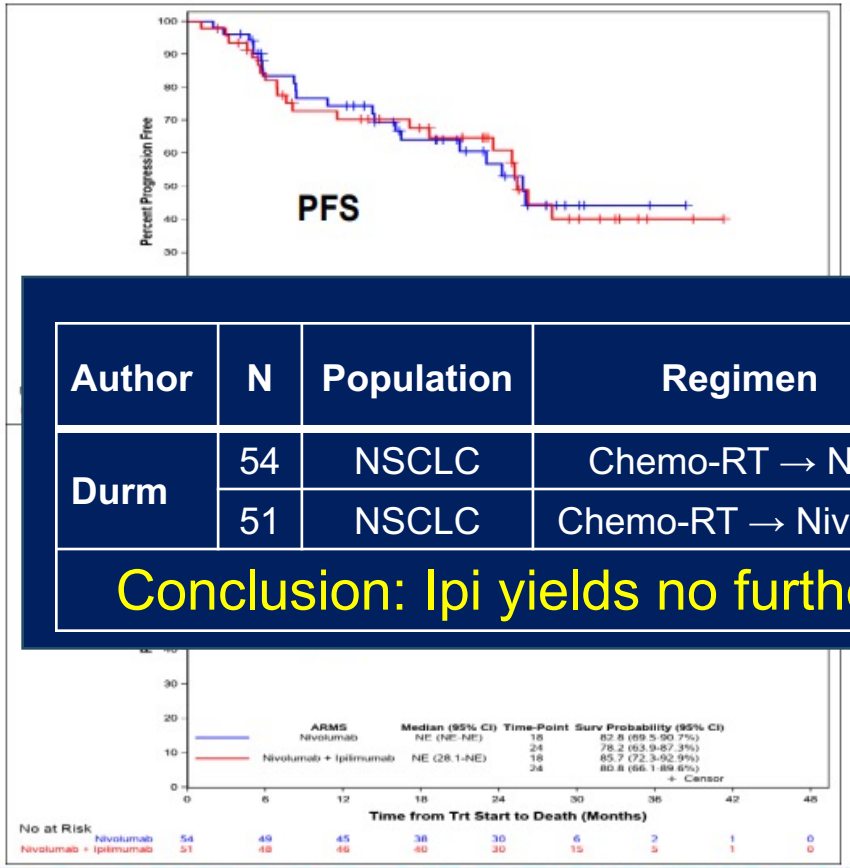


	Nivolumab Alone (N= 52)	Nivolumab/Ipilimumab (N= 47)
Median F/u, months (range)	28.5 (2-44.2)	29.4 (3.2-46.8)
Progression Free Survival*		
18- Month (95% CI)	64.0 (53.8-72.6)	67.7 (57.6-75.9)
P-value	<0.1	<0.1
Median, months (95% CI)	25.8 (23.0-NR)	25.4 (25.0-NR)
Overall Survival		
18- Month (95% CI)	82.8 (69.5-90.7)	85.7 (72.3-92.9)
24- Month (95% CI)	78.2 (63.9-87.3)	80.8 (66.1-89.6)
Median, months (95% CI)	NR (NR-NR)	NR (28.1-NR)

IASLC 2022 World Conference on Lung Cancer

AUGUST 6-9, 2022 | VIENNA, AUSTRIA

Results



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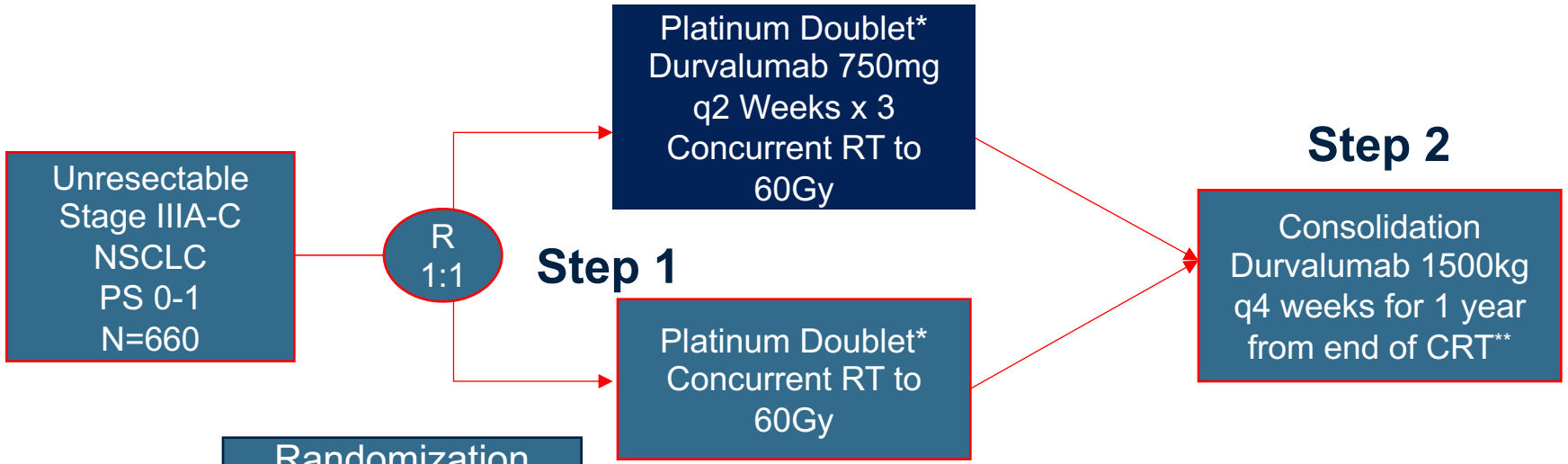
Median F/u, months (range)	28.5 (2-44.2)	29.4 (3.2-46.8)
Progression Free Survival*		
Median, months (95% CI)	NR (NR-NR)	NR (28.1-NR)

Author	N	Population	Regimen	ORR (%)	PFS, med (mo)	Pneumonitis G3+ (%)	trAEs Gr ≥3 (%)
Durm	54	NSCLC	Chemo-RT → Nivo	NR	25.8	9.3	38.5
	51	NSCLC	Chemo-RT → Nivo-Ipi	NR	25.4	15.7	52.9

Conclusion: Ipi yields no further Tx benefit, just heightened toxicity

EA 5181: Trial Schema

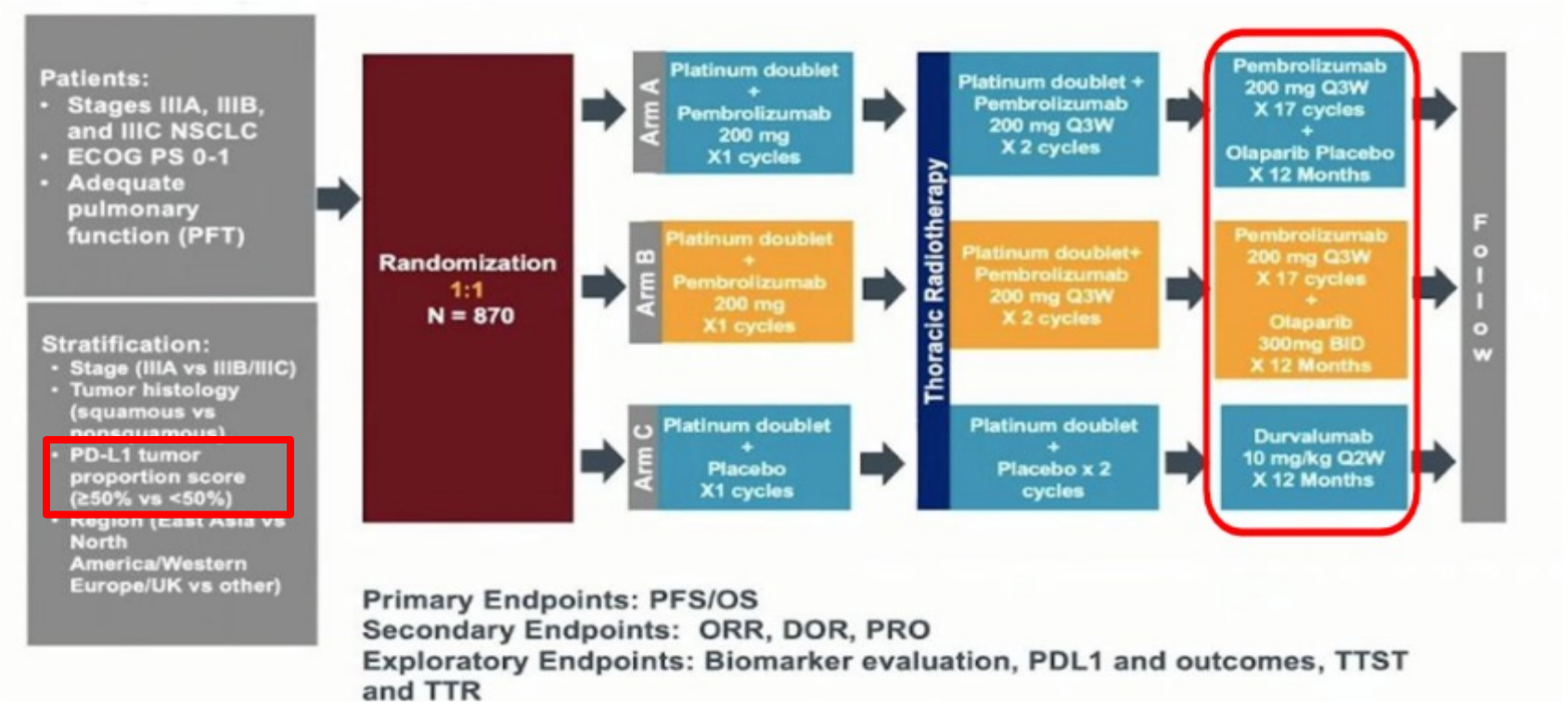


*__Investigator choice__
Cisplatin 50 mg/m2 D1, 8, 29, 36; etoposide 50 mg/m2 D1-5, 29-33
Cisplatin 75 mg/m2 D1, 22; pemetrexed 500 mg/m2 D1, 22 (nonsquamous only)
Carboplatin AUC 2 D1, 8, 15, 22, 29, 36; paclitaxel 45 mg/m2 D1, 8, 15, 22, 29, 36

**Starting within 14 days of CRT unless toxicity has not resolved to ≤ grade 2, but not later than 45 days post-CRT

Ongoing Trials

- KEYLYNK-012 (NCT04380636)
  - ChemoRT +/- Pembro ➔ Pembro +/- Olaparib vs. Durvalumab



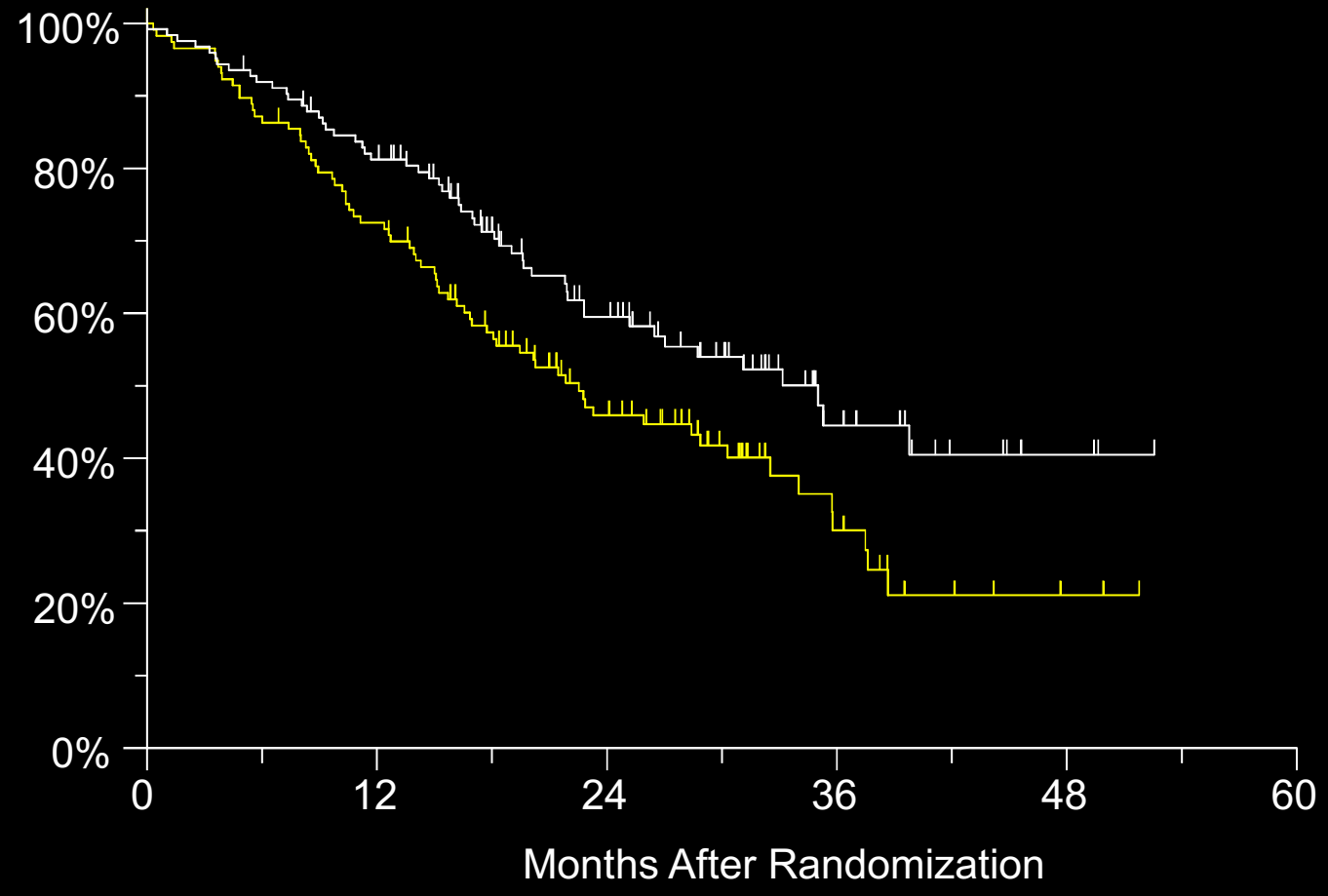
Start date- July 2020

Estimated End- July 2026

Rationale for Consolidation Tx with Targeted Tx in Oncogenic-Driven LA-NSCLC

- Their empiric use, either as consolidation or concurrently with chemoradiation, in absence of clear cut oncogenic drivers, has failed to yield an OS benefit
  - SWOG 0023 and RTOG 0617 are examples

SWOG 0023: Overall Survival from Randomization: Gefitinib vs Placebo after CT-XRT



K, et al. ASCO 2007. Abstract 7513. J Clin Oncol. 2008;26:2450-2456.

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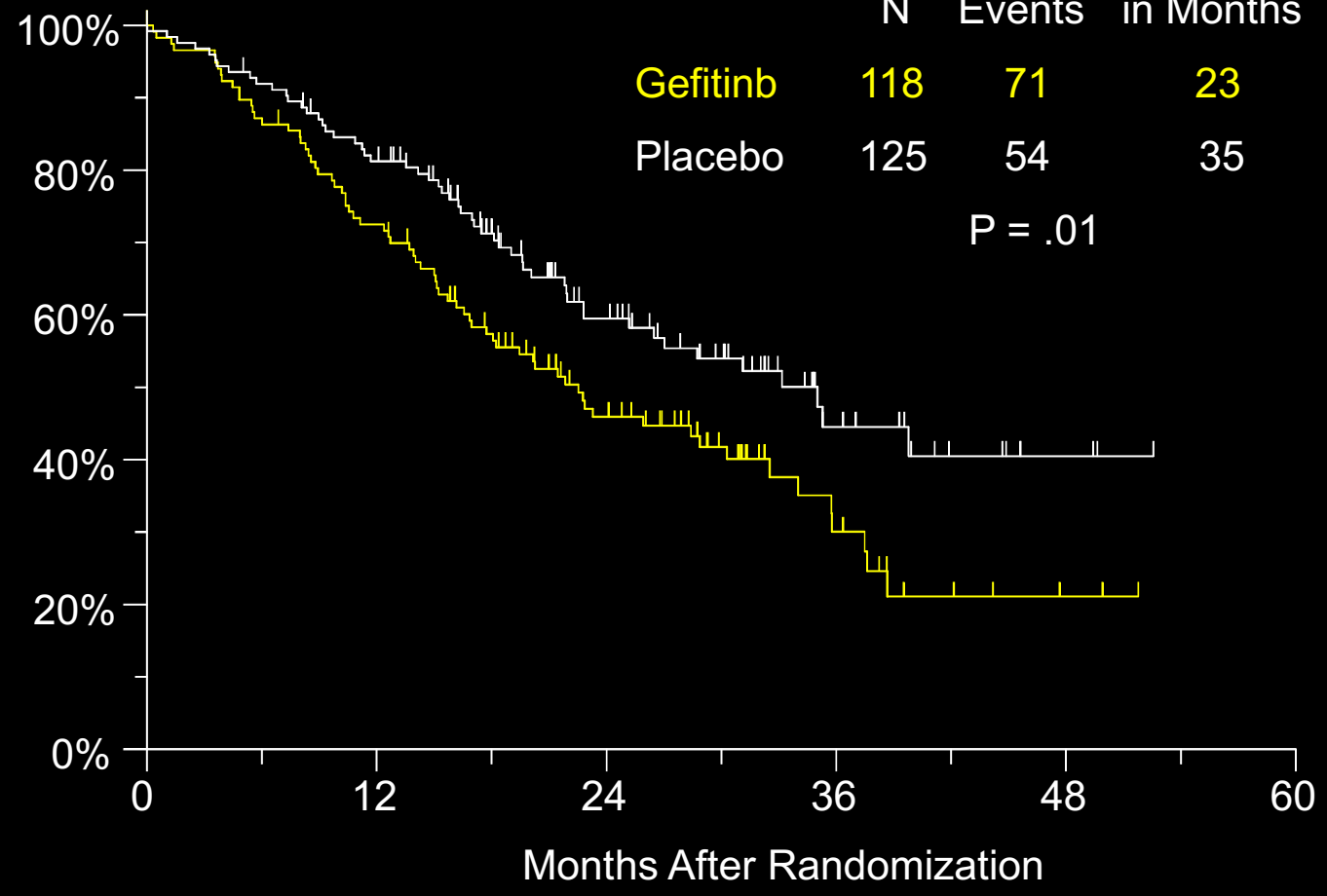
SWOG 0023: Overall Survival from Randomization: Gefitinib vs Placebo after CT-XRT



	N	Events	Median in Months	1 YR OS	2 YR OS
Gefitinb	118	71	23	73%	46%
Placebo	125	54	35	81%	59%

P = .01

K, et al. ASCO 2007. Abstract 7513. J Clin Oncol. 2008;26:2450-2456.

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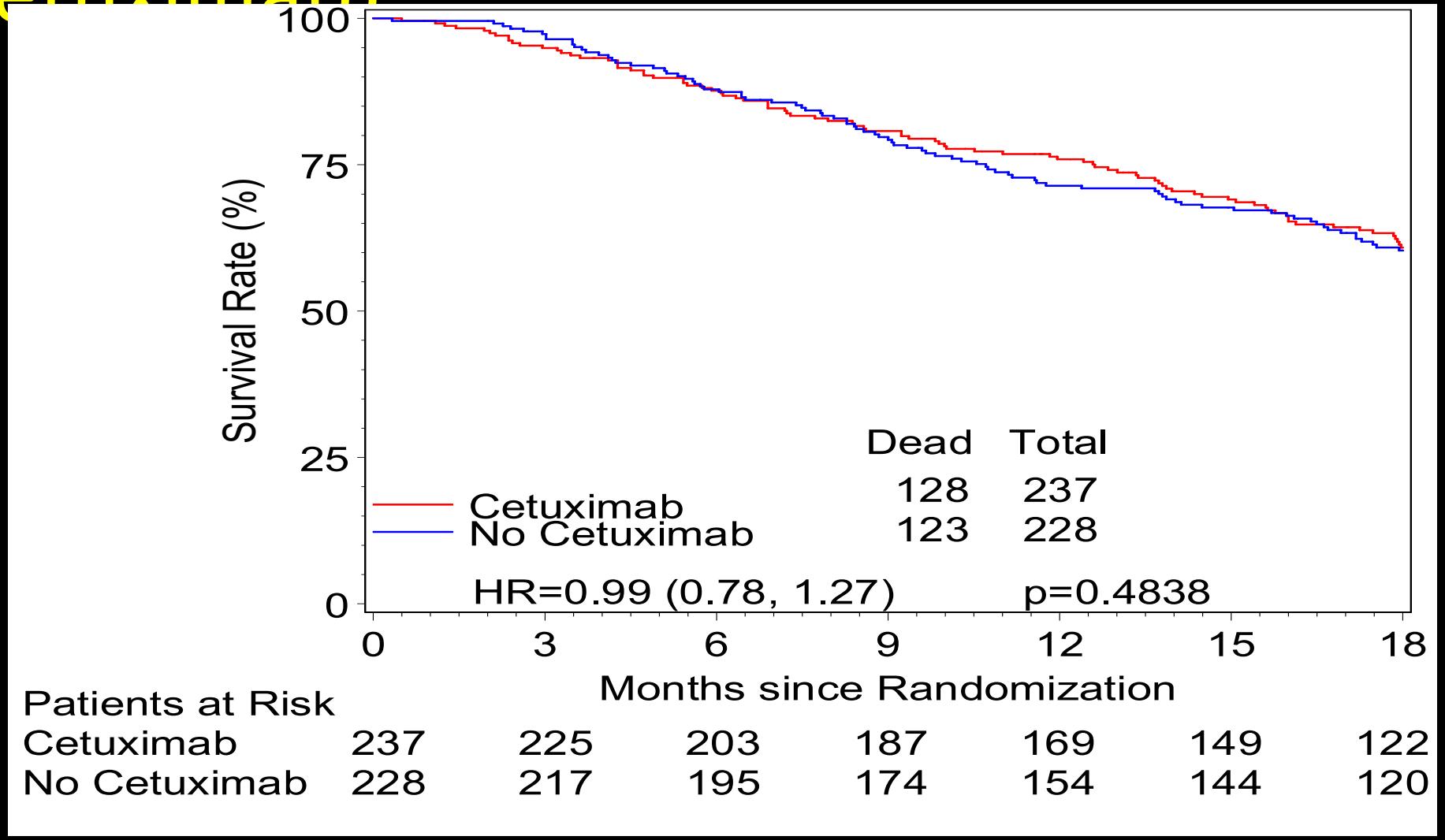
RTOG 0617: Overall Survival (+/- Cetuximab)



Bradley J et al, Lancet Oncol 2015; 16: 187–99

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Rationale for Consolidation Tx with Targeted Tx in Oncogenic-Driven LA-NSCLC

- Their empiric use, either as consolidation or concurrently with chemoradiation, in absence of clear cut oncogenic drivers, has failed to yield an OS benefit
  - SWOG 0023 and RTOG 0617 are examples
- Similarly, Durvalumab in the EGFR mt (+) population in PACIFIC has not resulted in any PFS or OS advantage

Abstract 8541 ASCO 2022: Durvalumab (durva) after chemoradiotherapy (CRT) in unresectable, stage III, EGFR mutation-positive (EGFRm) NSCLC: A post hoc subgroup analysis from PACIFIC.

PACIFIC

- 713 pts enrolled, 35 had EGFR mutations (2/3 exon 19/21, 1/3 “other”)
- For all pts – OS HR 0.68, PFS HR 0.52
- Of 35 EGFR mutation+ pts, 24 rec’d durva, 11 pbo

	Placebo	Durvalumab
Male, %	73	54
IIIA, %	64	46
PS 0, %	64	54
Ind Rx, %	36	8
Asian, %	55	63
PD-L1 <25%	36	67
Med PFS, mo	10.9	11.2*
Med OS, mo	43.0	46.8**
ORR, %	18.2	26.1

* HR 0.91 (0.39,2.13)
** HR 1.02 (0.39, 2.63)

ASCO 2022, A-8541; Naidoo et al., J Thorac Oncol May;18(5):657-663

Penn Medicine Abramson Cancer Center

Rationale for Consolidation Tx with Targeted Tx in Oncogenic-Driven LA-NSCLC

- Their empiric use, either as consolidation or concurrently with chemoradiation, in absence of clear cut oncogenic drivers, has failed to yield an OS benefit
  - SWOG 0023 and RTOG 0617 are examples
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Consolidation EGFR-Tyrosine Kinase Inhibitor vs. Durvalumab vs. Observation in Unresectable *EGFR*-Mutant Stage III NSCLC

A.H. Nassar[#], E. Adib[#], D. Kaldas, J. Feng, T. AbuAli, J. Aredo, B. Fitzgerald, J. Bar, R. Thummalapalli, K. Parikh, R. Whitaker, L. Chen, J. Harris, A. Ayanambakkam, S. Farid, D. Owen, J. Sharp, A.I. Velazquez, M. Ragavan, A. D'aiello, H. Cheng, Z. Piotrowska, M. Wilgucki, J.E. Reuss, T. Patil, Y. Nie, J. Baena Espinar, H. Luders, C. Grohe, K. Sankar, M. Nagasaka, Y.P. Ashara, D.J. Kwiatkowski, R. Mak, A. Amini, A. Lobachov, J.J. Lin, T. Marron, H. Yu, J.W. Neal, H.A. Wakelee, F.A. Shepherd, T.J. Dilling, J.E. Gray, A.R. Naqash*, S.B. Goldberg*, S.Y. Kim*

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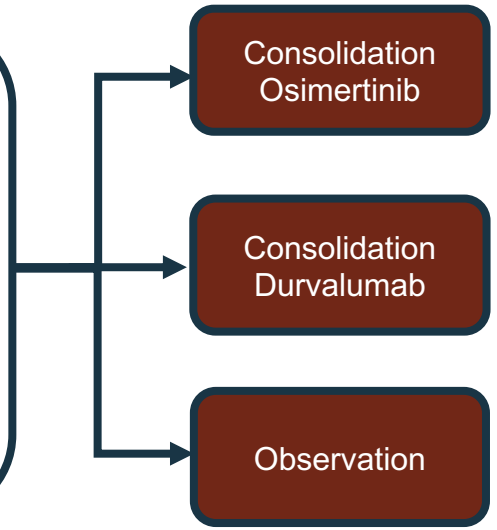
STUDY DESIGN & PATIENT DEMOGRAPHICS

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



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)

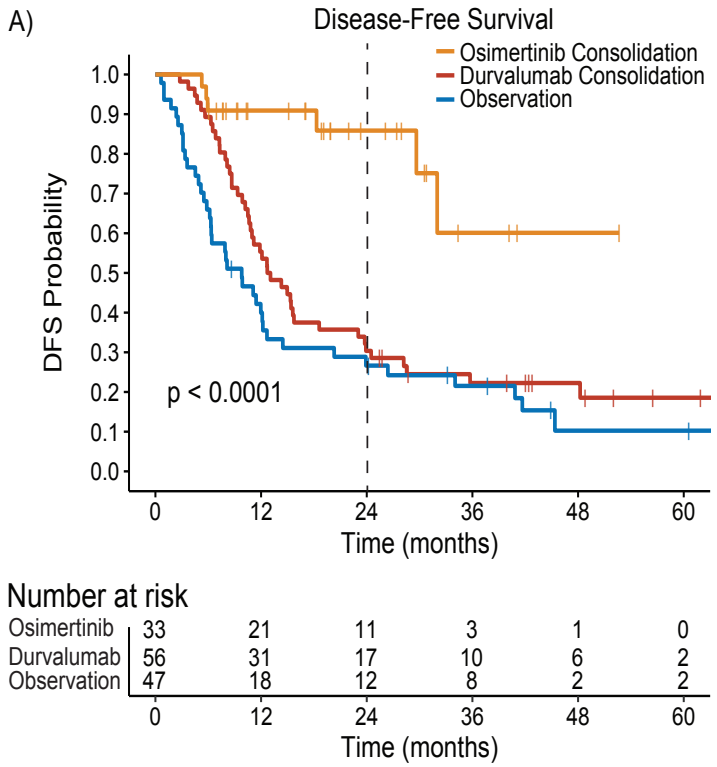
[#]multivariable including nodal status (N stage), stage III A/B/C AJCC 8th, and age

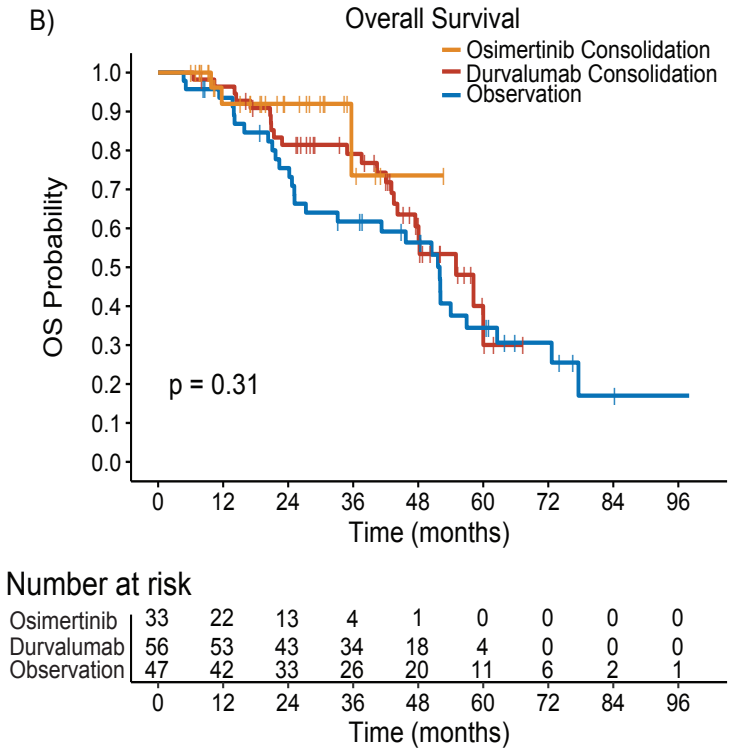
Baseline characteristics

	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 AND OVERALL SURVIVAL





Subsequent systemic therapy after consolidation treatment or observation

Subsequent systemic therapy

Arm	EGFR TKI	IO	Other	Total
Osimertinib	1 (3%)	1 (3%)	1 (3%)	3 (3.7%)
Durvalumab	37 (66%)	1 (1.8%)	3 (5.4%)	41 (51%)
Observation	35 (74%)	1 (2.2%)	1 (2.2%)	37 (46%)
Total	73 (90%)	3 (3.7%)	5 (6.2%)	81

24-month CNS-Relapse: Osimertinib: 6.7% (95% CI, 1.7-32); Durvalumab: 17% (95% CI, 8.1-30); Observation: 11% (95% CI, 3.8-25)

Treatment-related Adverse Events

	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 TKIs → 5 pneumonitis (including 2 ≥grade 3); 5 diarrhea/colitis (including 1 ≥grade 3)

CONCLUSIONS

- This retrospective, multi-center analysis of 136 patients demonstrated superior DFS and CNS control with consolidation osimertinib compared to durvalumab or observation alone following chemoradiation for locally advanced *EGFR*-mutant NSCLC
- Absence of overall survival benefit for osimertinib likely explained by (1) limited numbers, (2) limited follow-up time; and (3) high rate of cross-over in Durva and Observation arms (66-74%)
- No unanticipated safety signals: pneumonitis and grade ≥3 trAE greater with durvalumab vs osimeritinib
- Prospective studies needed to confirm these findings

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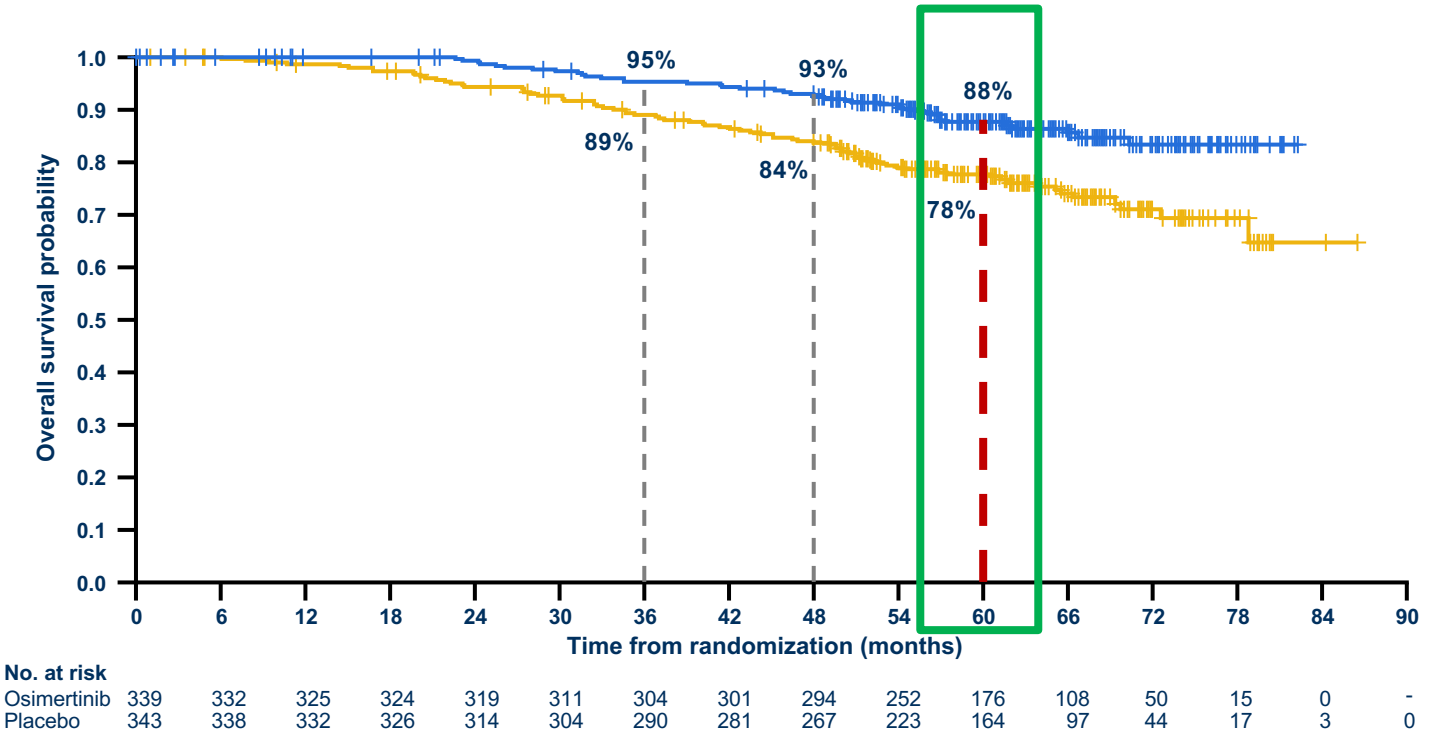
  - SWOG 0023 and RTOG 0617 are examples
- Similarly, Durvalumab in the EGFR mt (+) population in PACIFIC has not resulted in any PFS or OS advantage
- In retrospective analysis, pts with EGFR mt (+) LA-NSCLC receiving an "appropriate" TKI fared better than those receiving CPI or undergoing observation
- Outcome data ADAURA in resectable EFR mt (+) NSCLC and ALINA in resectable ALK (+) NSCLC would suggest a similar approach in LA-NSCLC is worthwhile

ADAURA Overall survival: patients with stage IB / II / IIIA disease

- **Adjuvant osimertinib demonstrated a statistically and clinically significant improvement in OS vs placebo in the overall population of stage IB–IIIA disease**



5-year OS rate, % (95% CI)	
Osimertinib (n=339)	88 (83, 91)
Placebo (n=343)	78 (73, 82)

Overall OS HR (95.03% CI) **0.49 (0.34, 0.70); p<0.0001**

Maturity: 18%
osimertinib 12%, placebo 24%

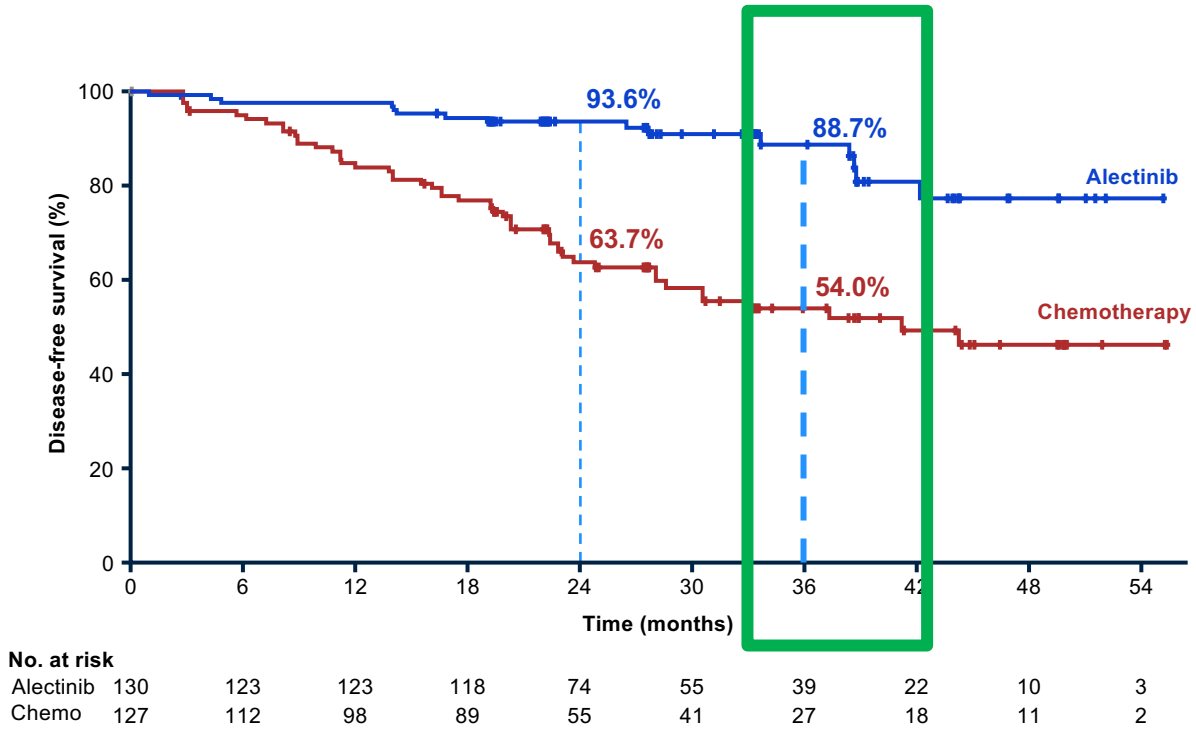
Median follow-up for OS* (censored patients):
osimertinib 61.5 months, placebo 61.5 months

Data cut-off: January 27, 2023.

Tick marks indicate censored data. Alpha allocation of 0.0497. *Median follow-up for OS (all patients): osimertinib 60.4 months, placebo 59.4 months.

CI, confidence interval; HR, hazard ratio; OS, overall survival

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



	Alectinib (N=130)	Chemotherapy (N=127)
Patients with event Death Recurrence	15 (12%) 0 15	50 (39%) 1 49
Median DFS, months (95% CI)	Not reached	41.3 (28.5, NE)
DFS HR (95% CI)	**0.24** (0.13, 0.43) p‡<0.0001	

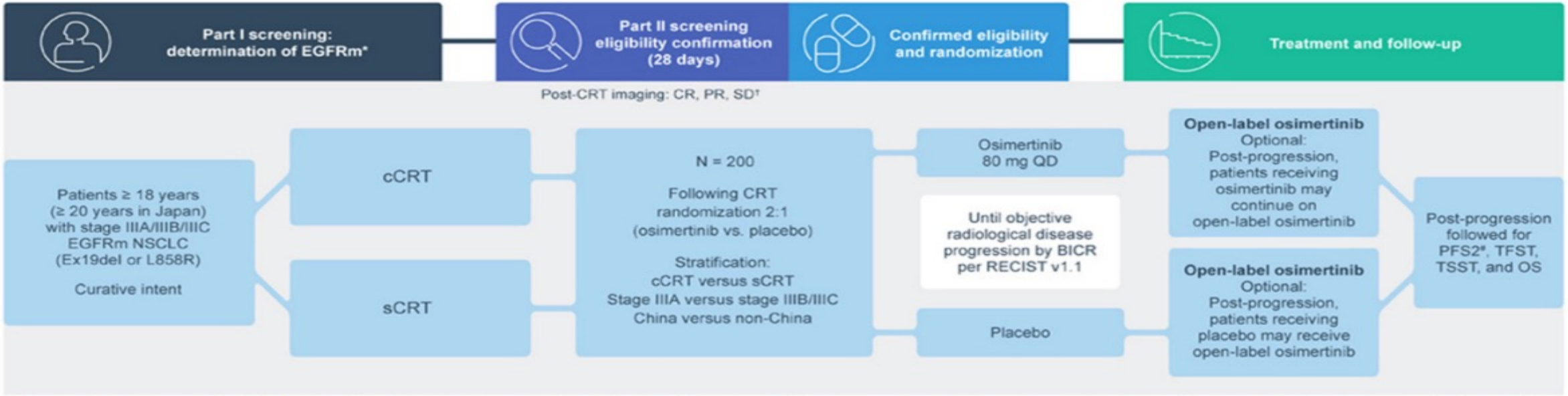
At the data cutoff date, **OS data were immature** with only 6 (2.3%) OS events reported §

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

Data cut-off: 26 June 2023; *Per UICC/AJCC 7th edition; ‡Stratified log rank; §2 events in the alectinib arm, 4 events in the chemo arm; one patient in chemo died but was censored due to incomplete date of death recorded. 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

Ongoing Trials

- **LAURA Trial (NCT03521154)**
  - Osimertinib Maintenance After Definitive Chemoradiation in Unresectable EGFR Mutation+ Stage III NSCLC
  - Primary Endpoint- BICR- confirmed PFS
  - Secondary Endpoints- CNS PFS, OS, PFS by mutation status, safety
  - 1st pt- July 2018
  - Expected results- late 2022



*Patients with a local cobas® EGFR Mutation Test v2 tissue positive result from a CLIA-certified or accredited laboratory do not require part I screening. †Post-CRT imaging performed to assess CR, PR and SD up to 28 days before randomization. #Assessment of PFS2 will not be collected after the primary PFS analysis.

HORIZON 1 STUDY DESIGN

- **BO42777 Phase 1-3 Stage III Unresectable Biomarker-Driven NSCLC**

Key eligibility criteria

- Locally Advanced Stage III NSCLC (UICC/AJCC v8)
- *ALK*+, *ROS1*+, or *RET*+ fusion-positive
- ECOG PS 0–2
- ≥2 prior cycles of platinum-based cCRT or sCRT
- No PD following platinum-based cCRT or sCRT
- PD-L1 TC <1% or ≥1% (per central SP263 on confirmed FFPE tumor specimen; locally on SP263 or 22C3)

Primary Endpoint

- PFS by BICR

***ALK*+ cohort**
Alectinib 600mg BID x 3 years vs Durvalumab 1500 mg IV q4 weeks x 1 year (N=120)

***ROS1*+ cohort**
Entrectinib 600mg QD x 3 years vs Durvalumab 1500 mg IV q4 weeks x 1 year (N=100)

***RET*+ cohort**
Pralsetinib 400mg QD x 3 years vs Durvalumab 1500 mg IV q4 weeks x 1 year (N=100)

Key Secondary Endpoints

- Safety
- QOL
- Time to CNS progression (BICR, Inv)
- ORR (BICR, Inv), DOR, PFS (Inv), OS

ALK=anaplastic lymphoma kinase; BICR=blinded independent central review; BID=twice daily; cCRT=concurrent chemoradiation; CNS=central nervous system; ECOG PS=Eastern Cooperative Oncology Group Performance Status; FFPE=formalin-fixed, paraffin-embedded; Inv=investigator; NSCLC=non-small cell lung cancer; ORR=overall response rate; OS=overall survival; PD-L1=programmed death ligand-1; PFS=progression-free survival; QD=once daily; RET=rearranged during transfection; ROS1=c-ros oncogene-1; sCRT=sequential chemoradiation. NIH. Available at: https://clinicaltrials.gov/ct2/show/NCT05170204. Accessed February 3, 2023.

Conclusions: LA-NSCLC

- PACIFIC remains the SOC
- Optimal approach in PD-L1 0% is uncertain; “default” for now remains Durvalumab post CT-XRT
- Strongly suspect pts with oncogenic driven tumors will benefit from “appropriate” bio-marker specific TKIs

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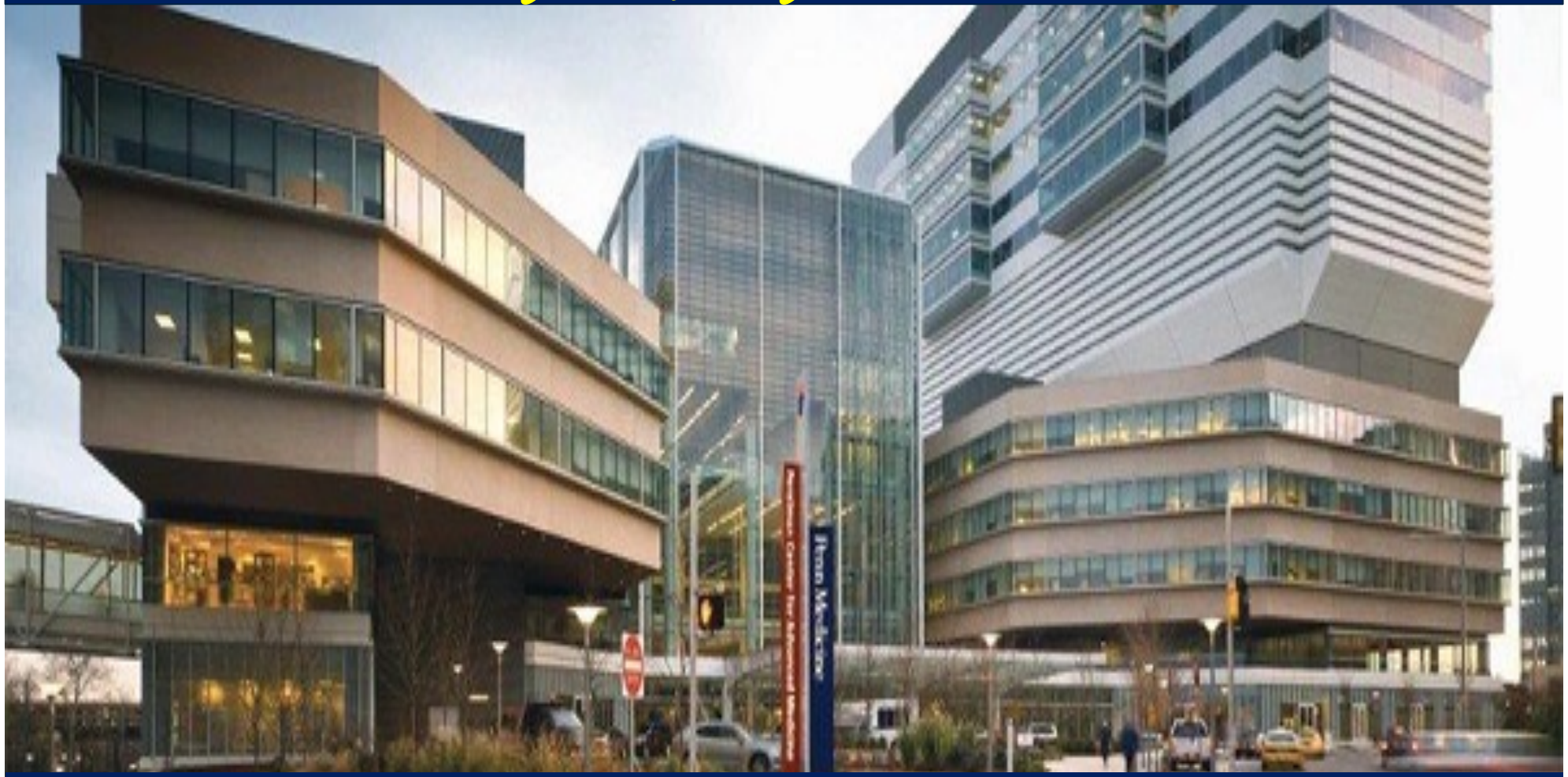
Thank you for your attention



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Thank you!

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