MaTOS™
Masters in Thoracic Oncology Summit
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Stage III Non-surgical NSCLC: Optimal Radiation Therapy Treatment Approach

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MATOS Masters of Thoracic Oncology 2023
Albuquerque, New Mexico

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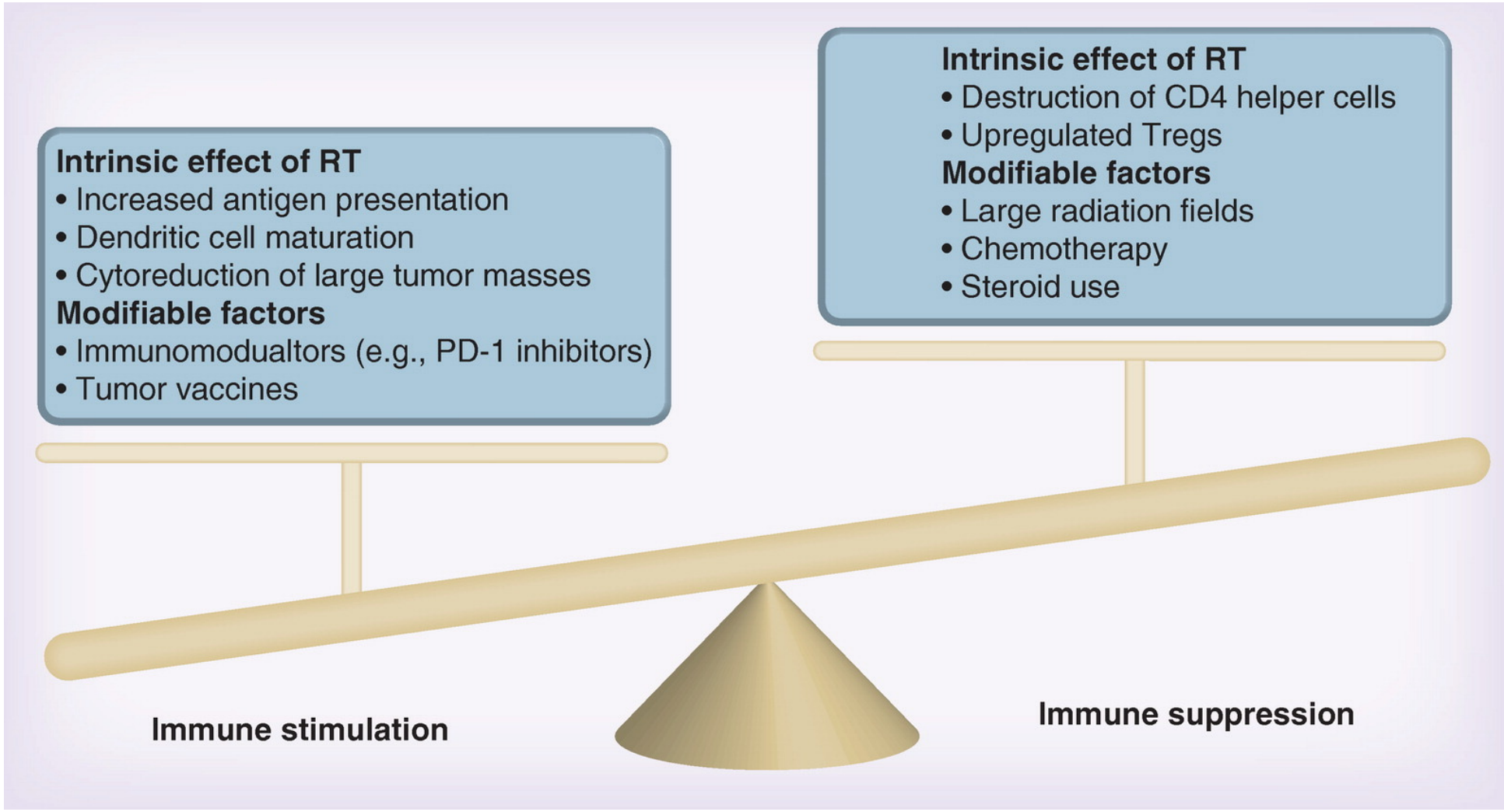
How to integrate radiotherapy in the modern and rapidly-changing era?

- Emphasis on multimodality therapy
- **Sequence and timing of radiation therapy may be critically important**
- Variation may depend on heterogeneity in NSCLC
- Molecular considerations may impact response
- Importance of clinical trials to tease all of this out

Balance immune-stimulatory effects and suppressive effects of RT



Lawrence, Future Medicine 2014

PACIFIC: Study Design

Phase 3, Randomized, Double-blind, Placebo-controlled, Multicenter, International Study

- Unresectable, Stage III NSCLC without progression after definitive platinum-based cCRT (≥2 cycles)
- 18 years or older
- WHO PS score 0 or 1
- If available, archived pre-cCRT tumor tissue for PD-L1 testing*

All-comers population (i.e. irrespective of PD-L1 status)

N=713 randomized

1–42 days post-cCRT

R

2:1 randomization, stratified by age, sex, and smoking history

Durvalumab
10 mg/kg q2w for up to 12 months
N=476

Placebo
10 mg/kg q2w for up to 12 months
N=237

Primary endpoints

- PFS by BICR using RECIST v1.1†
- OS

Key secondary endpoints

- ORR, DoR and TTDM by BICR
- PFS2 by investigator
- Safety
- PROs

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Adjuvant Therapy with Single Agent

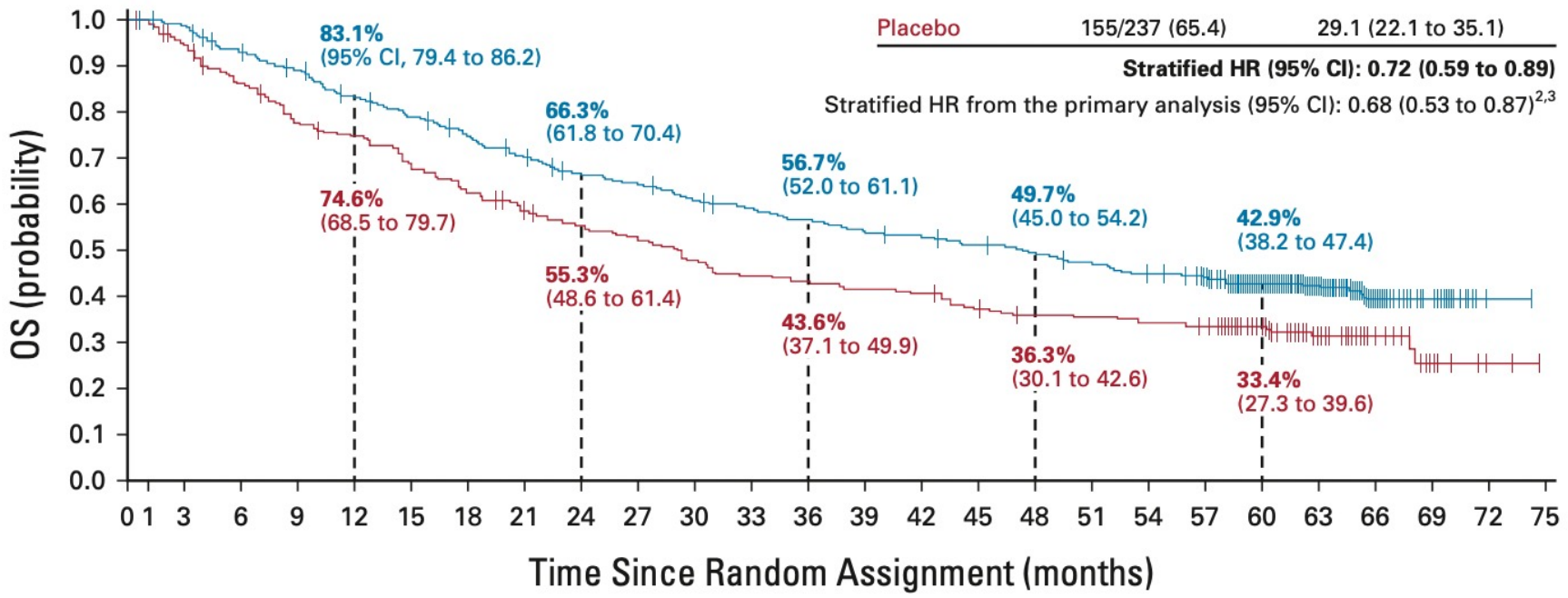
PACIFIC: Updated OVERALL SURVIVAL (ITT)

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

Spigel D, JCO, December 2021.

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Safety & tolerability of consolidation durvalumab

PACIFIC: Updated Safety Summary

DCO: March 22, 2018

	Durvalumab (N=475)	Placebo (N=234)
Any-grade all-causality AEs, n (%)	460 (96.8)	222 (94.9)
Grade 3/4	145 (30.5)	61 (26.1)
Outcome of death	21 (4.4)	15 (6.4)
Leading to discontinuation	73 (15.4)	23 (9.8)
Serious AEs, n (%)	138 (29.1)	54 (23.1)
Any-grade pneumonitis/radiation pneumonitis, n (%)	161 (33.9)	58 (24.8)
Grade 3/4	17 (3.6)	7 (3.0)
Outcome of death	5 (1.1)	5 (2.1)
Leading to discontinuation	30 (6.3)	10 (4.3)

Exploratory Subgroup Analysis in Pneumonitis: Time to Onset (WCLC 2018)

	Durvalumab	Placebo
Time to onset from 1st dose, median days (range) [N]	55.0 (1–406) [161]	55.0 (1–255) [58]
Time to onset from radiotherapy, median days (range) [N]	73.0 (20–433) [161]	76.5 (24–280) [58]
Duration, median days (range) [N]*	64.0 (3–568) [79]	57.0 (5–187) [23]

Antonia SA…, Gray JE et al. NEJM. 2018.
Vansteenkiste JF, et al. WCLC. 2018.

PACIFIC: Exploratory Analyses Summary

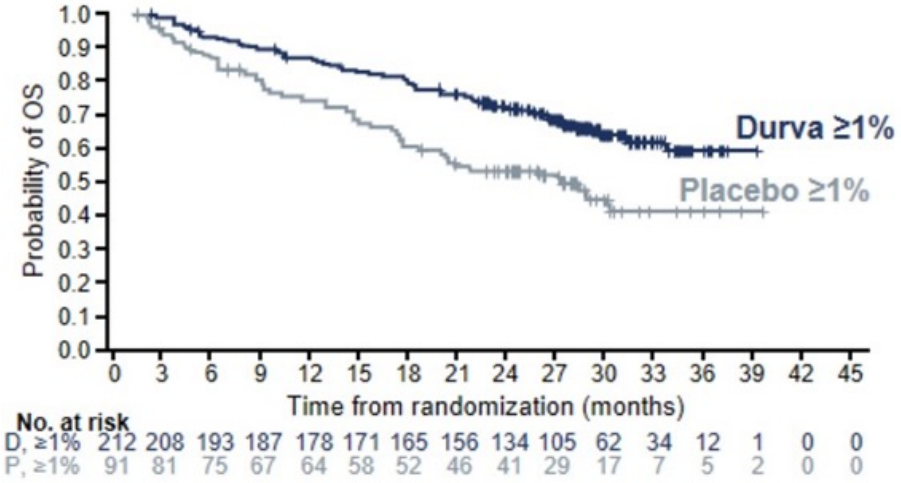
- **PD-L1 testing was not mandatory, and status was unknown for 37% of patients**

- **Definitive conclusions on outcomes by PD-L1 status cannot be drawn due to limitations around post-hoc exploratory subgroup analyses**

Conclusions on Outcomes by PD-L1 Status is not definitive due to limitations

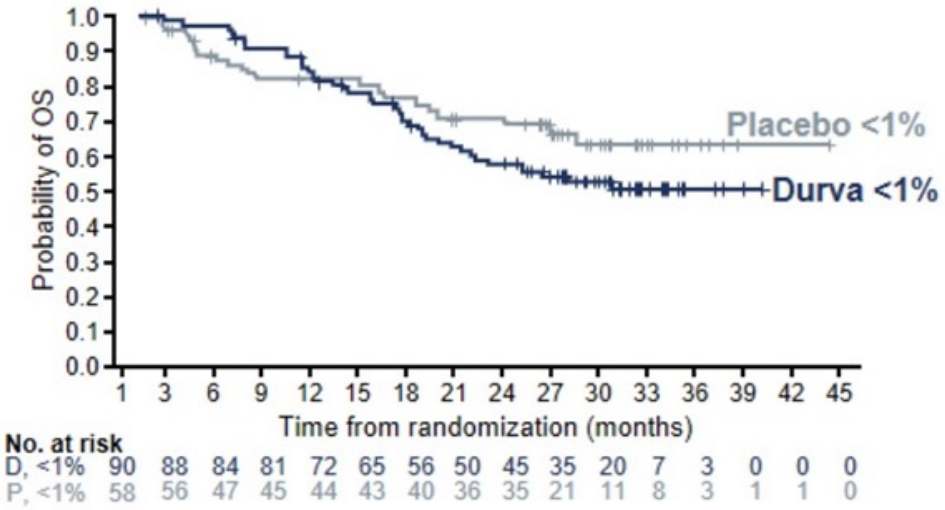
OS (BICR) by PD-L1 TC ≥1%

	No. events / no. patients (%)	Median OS (95% CI), mo
Durvalumab, ≥1%	70/212 (33.0)	NR (NR, NR)
Placebo, ≥1%	45/91 (49.5)	29.1 (17.7, NR)
	≥1% OS HR 0.53 (95% CI 0.36, 0.77)	



OS (BICR) by PD-L1 TC <1%

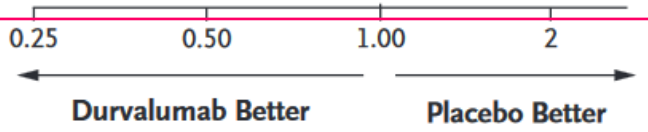
	No. events / no. patients (%)	Median OS (95% CI), mo
Durvalumab, <1%	41/90 (45.6)	NR (20.8, NR)
Placebo, <1%	19/58 (32.8)	NR (27.3, NR)
	≥1% OS HR 1.36 (95% CI 0.79, 2.34)	



- In the PD-L1 TC <1% subgroup, imbalances exist in baseline characteristics.
- Placebo arm: > more males, SQCLC, and Stage IIIB.

DFS by EGFR status

Subgroup	Durvalumab	Placebo	Unstratified Hazard Ratio for Disease Progression or Death (95% CI)
	no. of patients		
All patients	476	237	0.55 (0.45–0.68)
Sex			
Male	334	166	0.56 (0.44–0.71)
Female	142	71	0.54 (0.37–0.79)
Age at randomization			
<65 yr	261	130	0.43 (0.32–0.57)
≥65 yr	215	107	0.74 (0.54–1.01)
Smoking status			
Smoker	433	216	0.59 (0.47–0.73)
Nonsmoker	43	21	0.29 (0.15–0.57)
NSCLC disease stage			
IIIA	252	125	0.53 (0.40–0.71)
IIIB	212	107	0.59 (0.44–0.80)
Tumor histologic type			
Squamous	224	102	0.68 (0.50–0.92)
Nonsquamous	252	135	0.45 (0.33–0.59)
Best response			
Complete response	9	7	—
Partial response	232	111	0.55 (0.41–0.75)
Stable disease	222	114	0.55 (0.41–0.74)
PD-L1 status			
≥25%	115	44	0.41 (0.26–0.65)
<25%	187	105	0.59 (0.43–0.82)
Unknown	174	88	0.59 (0.42–0.83)
EGFR mutation			
Positive	29	14	0.76 (0.35–1.64)
Negative	315	165	0.47 (0.36–0.60)
Unknown	132	58	0.79 (0.52–1.20)



Antonia SJ et al. N Engl J Med 2017.

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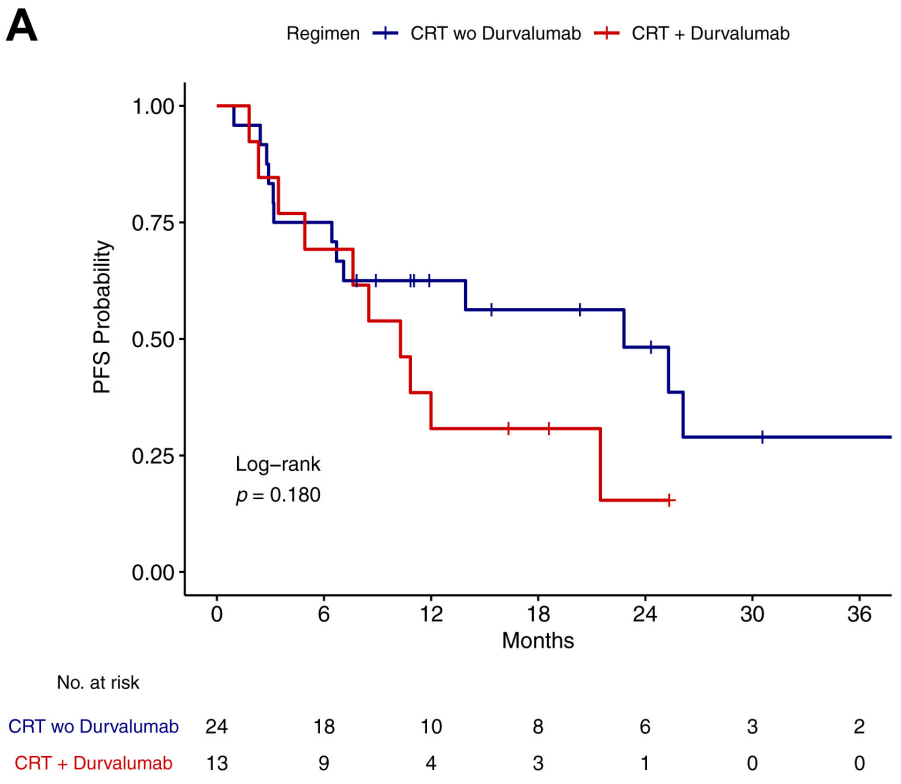
Consolidation Durvalumab for Stage III EGFRmut NSCLC – Stanford, City of Hope, UCSF, UC Davis



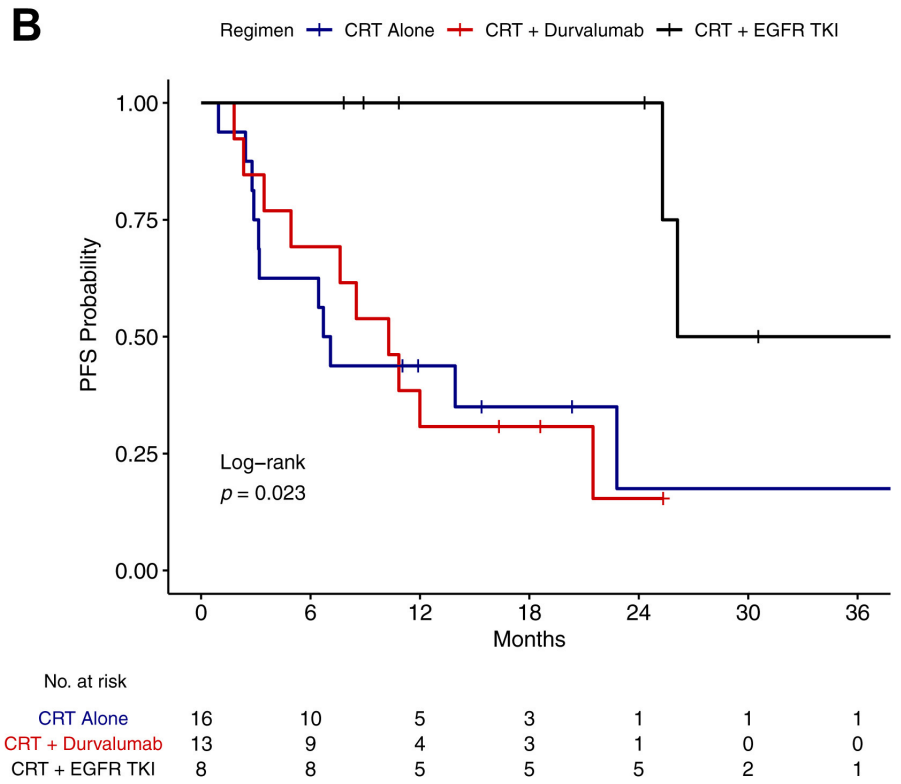


Figure 3: PFS after chemoXRT +/- Durva
(*A*) Median PFS CRT + durvalumab versus CRT wo durvalumab
10.3 months versus 22.8 months (log-rank $p = 0.180$).
(*B*) Median PFS CRT alone versus CRT durvalumab versus CRT + EGFR TKI :
6.9 mo vs 10.3 mo vs 26.1 mon (log-rank $p = 0.023$).

Aredo JTO 2021

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PACIFIC Real-World Study: ESMO 2021

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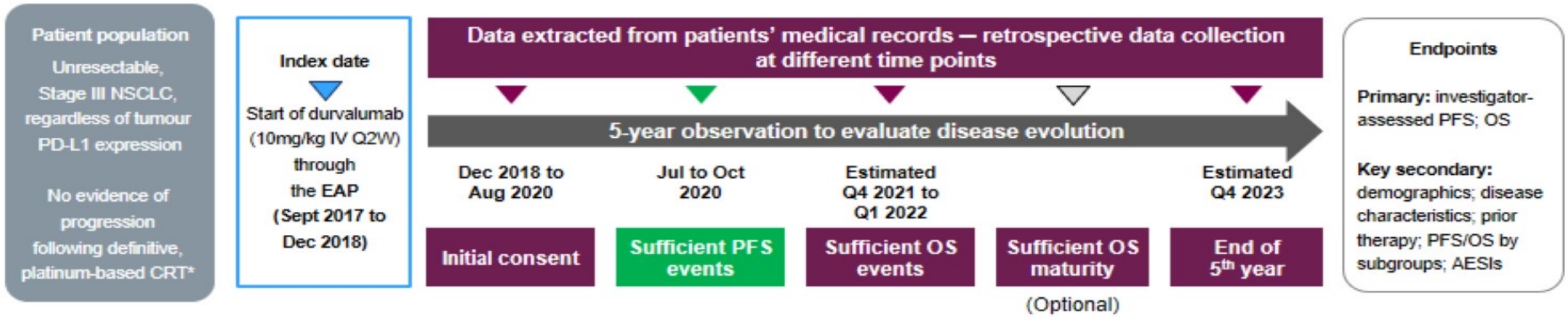
Study Design & Status (NCT03798535)

PACIFIC-R: An International, Observational Study



- **1,399 patients** included in the **full analysis set (FAS)** from **290 active sites** in **11 participating countries**
  - France (n=342), Spain (244)†, Australia (165), Netherlands (155), Belgium (118), Italy (116), Israel (92), Germany (62), UK (54), Norway (36), and Switzerland (15)

*Patients had completed platinum-based chemotherapy concurrent or sequential to radiotherapy within the previous 12 weeks without evidence of disease progression; †Spanish data are from an externally sponsored study integrated in April 2021
AESI, adverse event of special interest; CRT, chemoradiotherapy; EAP, expanded 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

Girard N, et al ESMO congress 2021. 1171 MO.

PACIFIC-R DATA

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Patient Characteristics & Durvalumab Treatment

Characteristics		FAS (N=1,399)
Age at EAP inclusion (years)	Median (range)	66.0 (26–88)
Age categories, %	≤75 years / >75 years	89.6 / 10.4
Sex, %	Male / Female	67.5 / 32.5
Smoking status at EAP inclusion, %	Never / Current / Former	7.9 / 32.6 / 59.5
Stage at diagnosis, %*[A]	Stage IIIA	43.2
	Stage IIIB/C	51.0
Histological subtype, %*[B]	Squamous	35.5
	Non-squamous	63.1
	Unknown	1.4
ECOG/WHO PS at EAP inclusion, %	0 / 1 / 2 / 3	51.4 / 46.6 / 1.9 / 0.1
CRT type, %*[C]	Concurrent	76.6
	Sequential	14.3
	Other	9.1
PD-L1 expression, %*[D] (Based on n=967 tested patients)	≥1%	72.5
	<1%	17.9
	Inconsistent†	9.6

- **Median time to durvalumab initiation** from the end of RT = **56 days**
- Overall **median durvalumab treatment duration** = 335 days (**~11 months**)
  - >12 months' treatment: 20.1%
  - >14 months' treatment: 4.4%
- Patients received a **median of 22 durvalumab infusions**
  - 7.1% received >26 infusions

Cut-off date for data extraction: 8 April 2021

*Percentages based on patients for whom the data were available; †PD-L1 expression tested but not clearly reported.

[A]Disease stage was missing for n=7 and n=74 had were diagnosed at a stage <III; [B]Histology was missing for n=2; [C]CRT type was missing for n=2; [D]PD-L1 was not tested for n=432

CRT, chemoradiotherapy; EAP, expanded access programme; ECOG/WHO PS, Eastern Cooperative Oncology Group/World Health Organization performance status; FAS, full analysis set; PD-L1, programmed cell death-ligand 1; RT, radiotherapy

	PACIFIC-R FAS	PACIFIC trial (durva. arm)[1]
PFS	N=1,399	N=476
Total events, N (%)	737 (52.7)	268 (56.3)†
Progression per RECIST	456 (32.6)	
Progression per physician assessment	170 (12.2)	
Progression, assessment unknown	30 (2.1)	
Deaths in absence of progression	81 (5.8)	
Median PFS, months	**21.7**	**16.9**
95% CI	19.2–24.5	13.0–23.9
PFS rate, %		
12 months	62.4	55.7
24 months	48.2	45.0

Girard N, et al ESMO congress 2021. 1171 MO.

PACIFIC-R Toxicity Data

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Durvalumab Treatment Discontinuation

FAS (N=1,399)	Discontinuation reason, n (%)*	Median time from durva. start to discontinuation
Patient decision	20 (1.4)	6.1 months
AE	233 (16.7)	2.8 months
Completed treatment†	659 (47.1)	12.0 months
Disease progression	377 (26.9)	5.1 months
Death	21 (1.5)	1.9 months

- **Pneumonitis/interstitial lung disease (ILD)** was the most common AE leading to (% of FAS):
  - **Permanent** discontinuation: 133 (**9.5%**)‡
  - **Temporary** interruption: 73 (**5.2%**)‡

Pneumonitis/ILD

	FAS (N=1,399)
Patients with any pneumonitis/ILD, n (%)§	250 (17.9)
Mild event¶	56 (4.0)
Moderate event¶	118 (8.4)
Severe event¶	41 (2.9)
Life-threatening or fatal event¶	5 (0.4)

- Median **time to onset** of pneumonitis/ILD from durvalumab initiation: **2.5 months**
- **Corticosteroid** administration was required in **71.3%** of events#

*Other discontinuation reason: missing (n=2), 'other' reasons (n=68), lost to follow-up (n=3), and ongoing durvalumab at time of data extraction (n=16); †Investigator's decision per country protocol and, where applicable, was after >12 months' treatment; ‡Categories are not mutually exclusive (i.e. a single patient could both interrupt and permanently discontinue durvalumab due to pneumonitis/ILD); §37/1,399 patients (2.6%) had pneumonitis/ILD events of unknown severity; ¶Categories are not mutually exclusive – patients experiencing ≥2 events of different severity can be counted under both categories. #A total of 279 pneumonitis/ILD events were reported among the 250 patients who experienced pneumonitis/ILD
AE, adverse event; FAS, full analysis set; ILD, interstitial lung disease

Girard N, et al ESMO congress 2021. 1171 MO.

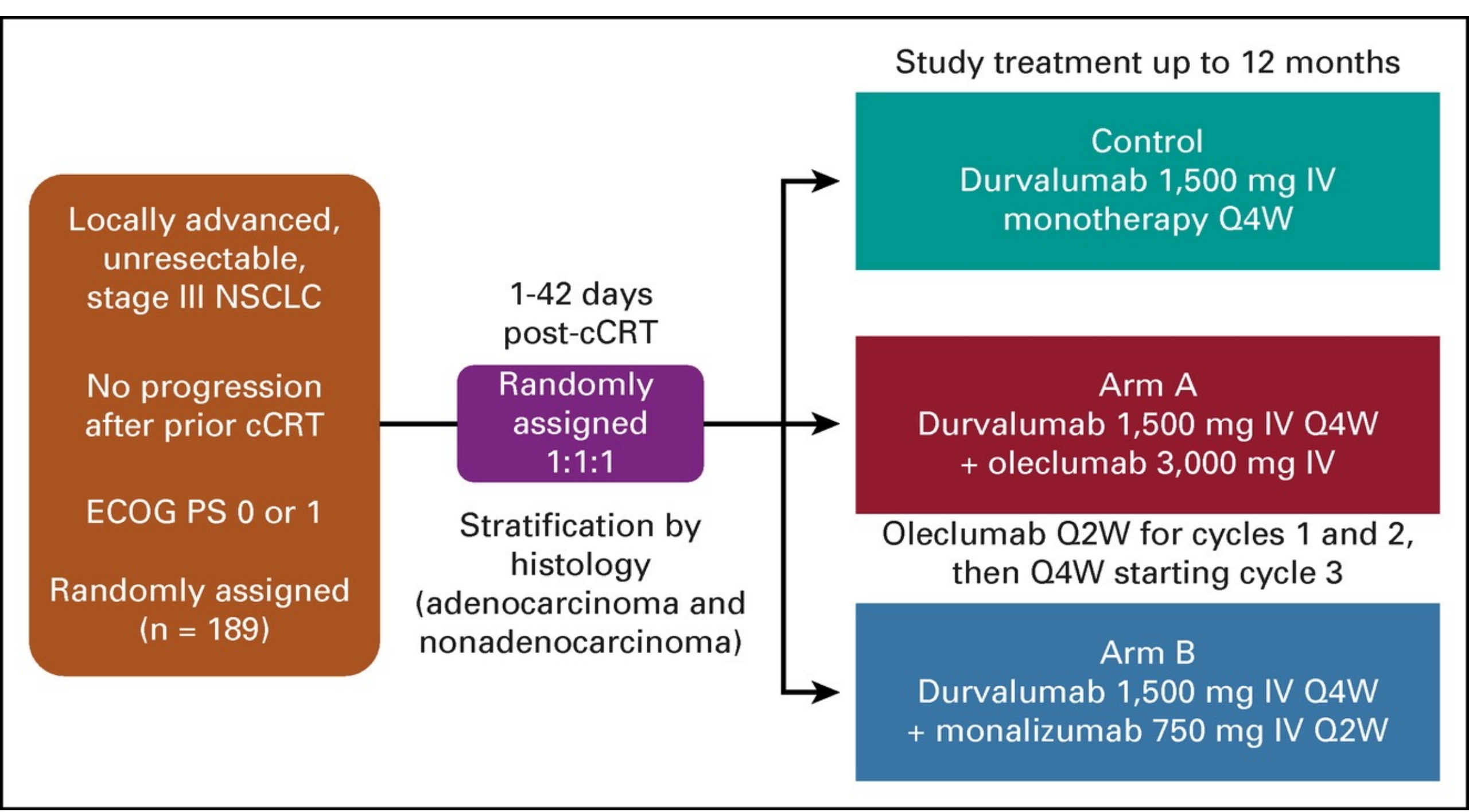
Combination IO therapy as consolidation after CRT in patients with stage III unresectable NSCLC

COAST: an open label, randomized, phase II platform study of durvalumab alone or in combination with novel agents in patients with locally advanced unresectable, stage III NSCLC

Herbst et al, JCO 2022 doi.org/10.1200/JCO.22.00227

- Oleclumab:
  - Targets CD73 results in increased activity of CD8-positive effector cells, activates macrophages, reduces myeloid-derived suppressor cells, and regulatory T-lymphocytes
  - Reduces inhibitory effects on immune system and enhances cytotoxic T-cell immune responses
  - Also decreases the migration of cancer cells (prevents metastases)

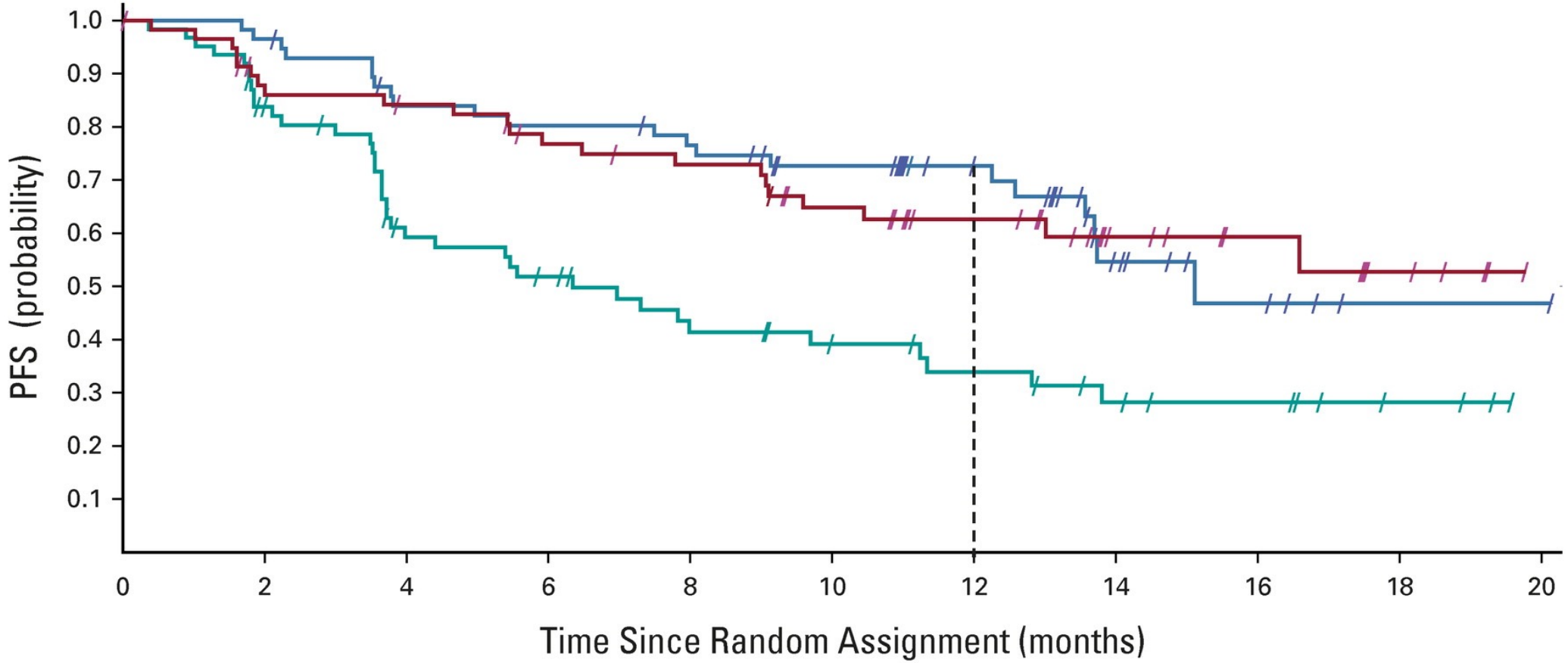
- Monolizumab:
  - Rescue NK cell exhaustion resulting in anti-tumor effect and enhances T cell antitumor activity


Study treatment up to 12 months
Locally advanced, unresectable, stage III NSCLC
No progression after prior cCRT
ECOG PS 0 or 1
Randomly assigned (n = 189)
1-42 days post-cCRT
Randomly assigned 1:1:1
Stratification by histology (adenocarcinoma and nonadenocarcinoma)
Control
Durvalumab 1,500 mg IV monotherapy Q4W
Arm A
Durvalumab 1,500 mg IV Q4W + oleclumab 3,000 mg IV
Oleclumab Q2W for cycles 1 and 2, then Q4W starting cycle 3
Arm B
Durvalumab 1,500 mg IV Q4W + monalizumab 750 mg IV Q2W

Overall Response Rate:

D	25.4%
D+O	38.4%
D+M	37.1%

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)	–



No. at risk:

Durvalumab + monalizumab	62	55	46	44	41	35	25	11	6	1	1
Durvalumab + oleclumab	60	49	46	40	37	30	22	13	9	5	0
Durvalumab	67	50	32	27	20	16	13	9	7	3	0

TABLE A1. Durvalumab-Related TEAEs Occurring in ≥10% of Patients in Any Arm (as-treated population)

	Durvalumab (n = 66)		Durvalumab + Oleclumab (n = 59)		Durvalumab + Monalizumab (n = 61)	
Preferred Term, No. (%)	**Any Grade**	**Grade 3/4**	**Any Grade**	**Grade 3/4**	**Any Grade**	**Grade 3/4**
Patients with at least one durvalumab-related TEAE	49 (74.2)	5 (7.6)	45 (76.3)	2 (3.4)	47 (77.0)	7 (11.5)
Asthenia	6 (9.1)	0	7 (11.9)	0	7 (11.5)	0
Pneumonitis[a]	7 (10.6)	0	10 (16.9)	0	6 (9.8)	1 (1.6)
Pruritus	6 (9.1)	0	10 (16.9)	0	10 (16.4)	0
Hypothyroidism	10 (15.2)	0	8 (13.6)	0	11 (18.0)	0
Diarrhea	2 (3.0)	1 (1.5)	3 (5.1)	0	8 (13.1)	0
Rash	4 (6.1)	0	7 (11.9)	0	6 (9.8)	0

NOTE. Data cutoff: May 17, 2021.

Abbreviation: TEAE, treatment-emergent adverse event.

[a]In addition, radiation pneumonitis of any grade (grade 3/4) occurred in two (1) patients in the durvalumab arm.

Conclusions

- ORR is incredibly difficult to interpret in patients with stage III disease treated with CRT and consolidation IO therapy!
- PFS is also challenging, unless the patient has clear metastatic disease
  - Having said that, it is encouraging to see improvement in mPFS
- Encouraging to see no increased AE's, especially pneumonitis
- "Worthy of further exploration"

PACIFIC 2

Study Design Go to

Study Type :	Interventional (Clinical Trial)
Actual Enrollment :	328 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	Double (Participant, Care Provider)
Primary Purpose:	Treatment
Official Title:	A Phase III, Randomized, Placebo-controlled, Double-blind, Multi-center, International Study of Durvalumab Given Concurrently With Platinum-based Chemoradiation Therapy in Patients With Locally Advanced, Unresectable NSCLC (Stage III) (PACIFIC2)
Actual Study Start Date :	March 29, 2018
Estimated Primary Completion Date :	April 28, 2023
Estimated Study Completion Date :	October 17, 2024

IO Concurrent with Chemoradiation

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Dropping the Chemo in Chemoradiation and Replacing with IO

JAMA Oncology | Original Investigation

Durvalumab Plus Concurrent Radiotherapy for Treatment of Locally Advanced Non-Small Cell Lung Cancer
The DOLPHIN Phase 2 Nonrandomized Controlled Trial

Motoko Tachihara, MD, PhD; Kayoko Tsujino, MD, PhD; Takeaki Ishihara, MD, PhD; Hidetoshi Hayashi, MD, PhD; Yuki Sato, MD; Takayasu Kurata, MD, PhD; Shunichi Sugawara, MD, PhD; Yoshimasa Shiraishi, MD; Shunsuke Teraoka, MD; Koichi Azuma, MD, PhD; Haruko Daga, MD, PhD; Masafumi Yamaguchi, MD, PhD; Takeshi Kodaira, MD, PhD; Miyako Satouchi, MD, PhD; Mototsugu Shimokawa, PhD; Nobuyuki Yamamoto, MD, PhD; Kazuhiko Nakagawa, MD, PhD; for the West Japan Oncology Group (WJOG)

Supplemental content

IMPORTANCE Administration of durvalumab after concurrent chemoradiotherapy is the standard treatment of unresectable, locally advanced non-small cell lung cancer (NSCLC); however, 20% to 30% of patients do not receive durvalumab because of adverse events (AEs) during concurrent chemoradiotherapy. In addition, radiotherapy and immunotherapy have a synergistic effect.

OBJECTIVE To investigate the efficacy and safety of durvalumab immunotherapy plus concurrent radiotherapy followed by maintenance with durvalumab therapy for treatment of locally advanced NSCLC without chemotherapy.

DESIGN, SETTING, AND PARTICIPANTS The multicenter, single-arm DOLPHIN (Phase II Study of Durvalumab [MEDI4736] Plus Concurrent Radiation Therapy in Advanced Localized NSCLC Patients) nonrandomized controlled trial was performed by 12 institutions in Japan from September 13, 2019, to May 31, 2022. Participants in the primary registration phase included 74 patients with programmed cell death ligand 1 (PD-L1)-positive, unresectable, locally advanced NSCLC. The current analyses were conducted from June 1, 2022, to October 31, 2022.

INTERVENTIONS Patients received radiotherapy (60 Gy) in combination with concurrent and maintenance durvalumab immunotherapy, 10 mg/kg every 2 weeks, for up to 1 year.

MAIN OUTCOMES AND MEASURES The primary end point of the rate of 12-month progression-free survival (PFS), as assessed by an independent central review, was estimated using the Kaplan-Meier method and evaluated with 90% CIs calculated using the Greenwood formula. The key secondary end points were PFS, objective response rate, treatment completion rate, and AEs.

RESULTS Data from 35 patients (median [range] age, 72 [44-83] years; 31 [88.6%] men) were included in the full analysis set of the evaluable population. The 12-month PFS rate was 72.1% (90% CI, 59.1%-85.1%), and the median PFS was 25.6 months (95% CI, 13.1 months to not estimable) at a median follow-up of 22.8 months (range, 4.3-31.8 months). Scheduled radiation therapy was completed in 97.1% of patients. The confirmed objective response rate was 90.9% (95% CI, 75.7%-98.1%), and the treatment completion rate was 57.6% (95% CI, 39.2%-74.5%). Among 34 patients evaluated in the safety analysis set, AEs of grade 3 or 4 occurred in 18 patients (52.9%), and of grade 5 in 2 patients (5.9%). Pneumonitis or radiation pneumonitis of any grade occurred in 23 patients (67.6%), and of grades 3 or 4 in 4 patients (11.8%).

CONCLUSIONS AND RELEVANCE Findings from this phase 2 nonrandomized controlled trial indicate that durvalumab immunotherapy combined with curative radiotherapy for patients with PD-L1-positive, unresectable, locally advanced NSCLC is a promising treatment with tolerable AEs and is appropriate as a study treatment for phase 3 clinical trials.

TRIAL REGISTRATION Japan Registry of Clinical Trials ID: jRCT2080224763

JAMA Oncol. doi:10.1001/jamaoncol.2023.3309

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UTSW study closed early, all 10 patients had toxicity 10/10 with 0% PD-L1 expression

MSKCC study if nearly 50 patients in single arm Ph2 just completed enrollment

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IO + xrt single arm Ph2, no concurrent chemo

UTSW study

But MSK study ok – nearly done with 50 patient enrollment

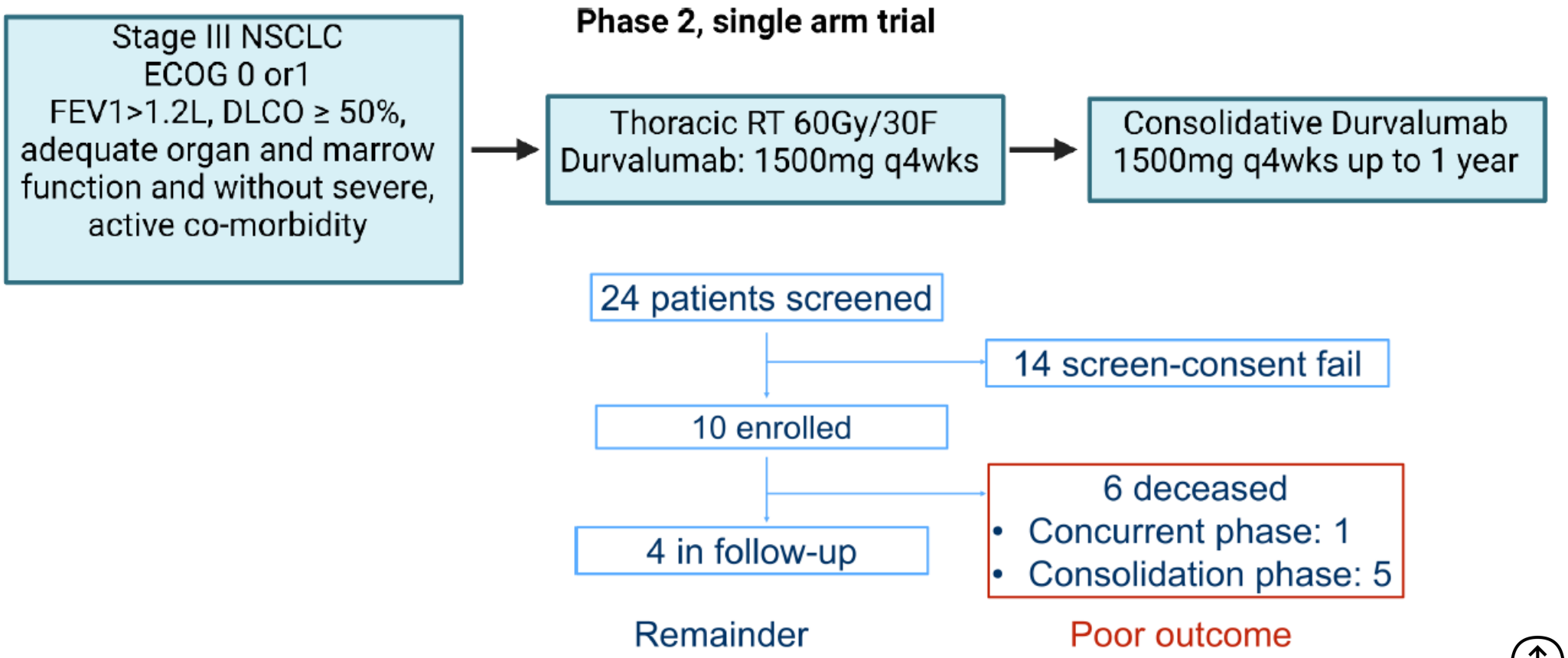


Table 1. Patient and tumor characteristics

	Total (n = 10)	Poor outcome (n = 6)	Remainder (n = 4)
Mean age, years (range)	65 (56-74)	66.7 (61-74)	62.5 (56-67)
Race			
White	9	6	3
Black/African American	1	0	1
Ethnicity			
Non-Hispanic	7	4	2
Hispanic	3	1	2
Gender			
Male	6	3	3
Female	4	3	1
Performance Status			
0	2	1	1
1	8	5	3
Smoking status			
Current smoker	2	1	1
Former smoker	8	5	3
Mean FEV1, liter (range)	2.0(1.5-3.4)	2.3(1.5-3.4)	1.6 (1.5-1.9)
Mean DLCO, % pred (range)	61.8(10.4-99.2)	54.4(10.4-99.2)	72.9 (59.0-81.0)
Baseline tumor size, mm (range)	80.7 (27.0-162.3)	84.8 (32.2-151.4)	75.5 (27.0-162.3)
Histology			
Adenocarcinoma	6	3	3
Squamous	4	3	1
T stage			
T1	2	0	2
T2	1	1	0
T3	4	3	1
T4	3	2	1
N stage			
N1	1	1	0
N2	6	4	2
N3	3	1	2
PDL1 <1%	8	4	4
PDL1 non-contributory	2	2	0

Table 2. Grade 3 or higher toxicities

ID	Adverse Event	Grade	Attribution to RT	Attribution to Durvalumab
1	Esophageal fistula	3	Possible	Possible
	Lung infection	3	Possible	Possible
	Sepsis	3	Possible	Possible
	Anemia	3	Not related	Not related
	Non cardiac chest pain	3	Possible	Not related
	Lung infection	3	Possible	Possible
	Esophageal fistula	3	Possible	Possible
	Dyspnea	3	Possible	Possible
	Aspiration	3	Possible	Unlikely
	Covid19 pneumonia (death)	5	Not related	Not related
2	Hypercalcemia	4	Not related	Not related
	Anemia	3	Not related	Not related
	Acute kidney injury	4	Not related	Possible
	Sepsis	3	Not related	Not related
	Disease progression (death)	5	Not related	Not related
4	Lung infection	3	Possible	Possible
	Hemorrhoidal hemorrhage	3	Not related	Not related
	Pleural effusion	3	Unlikely	Unlikely
	Hypoxia	3	Not related	Not related
	Disease progression (death)	5	Not related	Not related
5	Bone pain	3	Not related	Not related
	Disease progression (death)	5	Not related	Not related
9	Syncope	3	Not related	Not related
	Pneumonitis	3	Possible	Probable
	Lung infection	3	Not related	Not related
	Hypoxemic respiratory failure	3	Possible	Possible
10	Pneumonitis	3	Possible	Possible
	Respiratory failure (death)	5	Possible	Possible

Table 3. Patterns of failure

ID	Site of disease progression
2	Liver metastasis after 7 cycles of Durvalumab
4	Pleural metastasis after 9 cycles of Durvalumab
5	Multiple bone metastasis after 4 cycles of Durvalumab

Table 4. Radiation treatments and dosimetry parameters

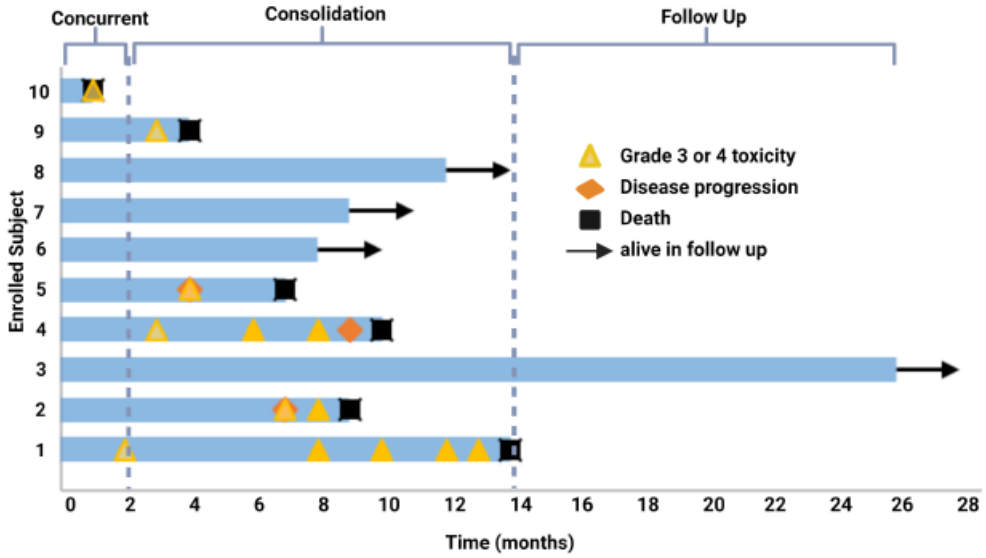
	Total (n = 10)	Poor outcome (n = 6)	Remainder (n = 4)
Radiation			
Did not complete	1	1	0
Complete	9	5	4
Radiation Dose			
	60Gy	5	4
	12Gy	1	0
PTV volume, cc (range)	874.7 (79.3-3099.2)	623.0 (79.3-1153.3)	1138.2. (415.8-3099.2)
Protocol deviation	4	2	2
Criteria Lung V5Gy≤70%		Subject#2 70.1 Subject #9 85.7	Subject #3 91 Subject #8 74.5
	Total (n = 9)	**Poor outcome (n = 5)***	**Remainder (n = 4)**
Radiation eclipsed days	43 (41-55)	44.4 (41-55)	41.5 (41-42)
Mean Lung dose, Gy (range)	15.3 (5.8-20.9)	13.2(5.8-20.9)	18.0 (14.4-20.5)
Lung, V20, % (range)	26.3 (6.5-37.1)	22.5 (6.5-34.0)	31.0(21.9-37.1)
Lung, V5, % (range)	62.3 (30.4-91.0)	54.5 (30.4-85.7)	72.2 (55.3-91.0)
Mean heart dose, Gy (range)	10.7 (0.9-31.3)	8.7 (0.9-31.3)	13.2 (2.0-27.4)
Heart, V30, % (range)	13.9 (0-59.8)	13.9 (0-59.8)	13.9 (0.1-38.9)
Heart, V45, % (range)	3.8 (0-13.2)	3.1 (0-13.2)	4.7 (0-11.6)
Mean esophageal Dose	21.4 (5.6-36.8)	20.3 (5.6-36.8)	22.9(9.9-30.6)
Max Spinal cord point dose	35.7 (23.5-50.4)	36.1 (23.5-50.4)	35.2 (26.0-41.7)

Steroids with chemo dampens tox

ILD

Chemo dampens IO and xrt effect on lungs

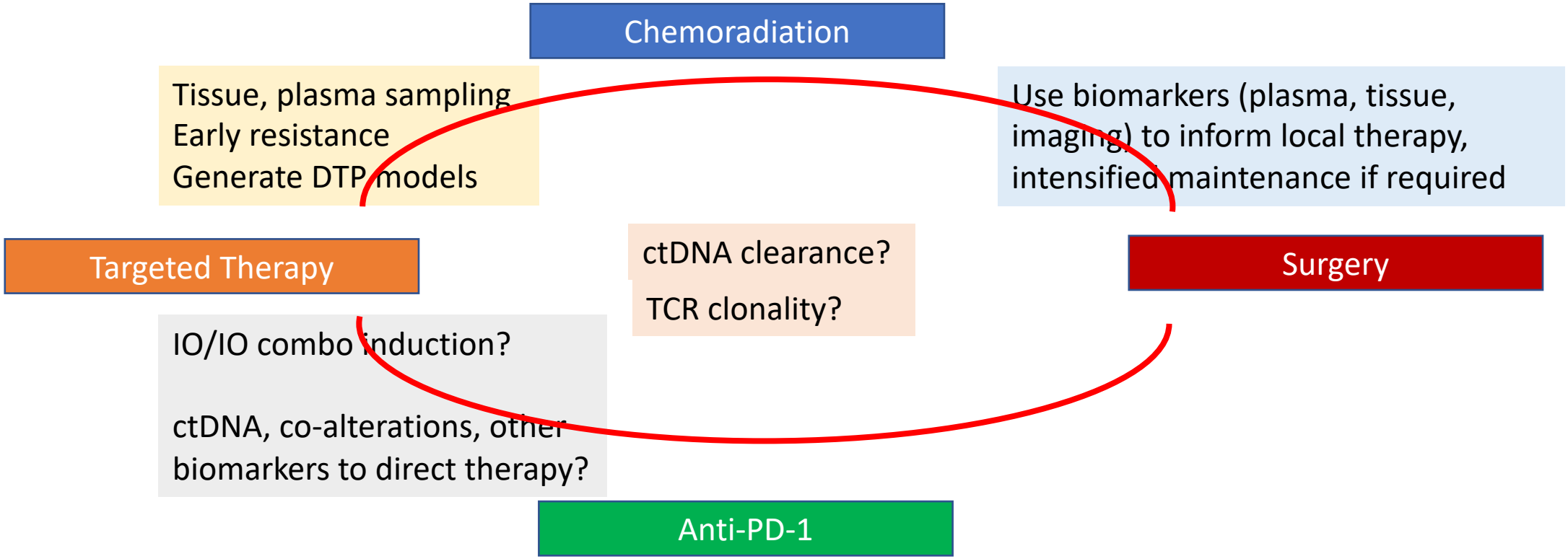
Figure 1.Swimmer plot since the initiation of treatment



Summary

- Six of the ten patients experienced grade 3 or higher adverse events including one with esophageal fistula, three with lung infections and two with pneumonitis (including one grade 5 event during the concurrent phase).
- Three patients experienced regional and/or distant disease progression during consolidation.
- Patients with higher-grade toxicities were more likely to be older, ECOG 1 (vs. 0), have higher T stage and squamous histology.
- Baseline pulmonary function, tumor size, nodal stage, smoking status, planning tumor volume (PTV), and dose to normal structures were not associated with high-grade toxicities or disease progression.

Where to from here?



Modify Checkpoint Inhibitors with ADCs and Bispecifics

Memorial Sloan Kettering Cancer Center

Summary

- Which pts for neoadj CI?
  - Adequate PFTs, PS
  - Large, centrally located, Stage IIIA NSCLC
  - PD-L1 ≥ 1%, EGFR/Alk neg?
  - Time to quit smoking, pulm rehab?
  - World-wide variation
  - Need to streamline upfront genomic assessment
- Which pts for adjuvant therapy?
  - ctDna +, No Path CR?
  - What type adj therapy?
- How do we identify Novel Neoadjuvant Therapies?
  - Surrogate endpoints: Path CR or MPR?
  - Can we utilize surrogate endpoints for other therapies – (ie targeted therapy)