OPTIMAL DURATION OF IMMUNOTHERAPY- FINDING THE SWEET SPOT

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Finding the sweet spot!

How did we define the duration of immunotherapy?

How did we define the duration of immunotherapy?

Key contexts to consider today

Neoadjuvant- how many cycles?

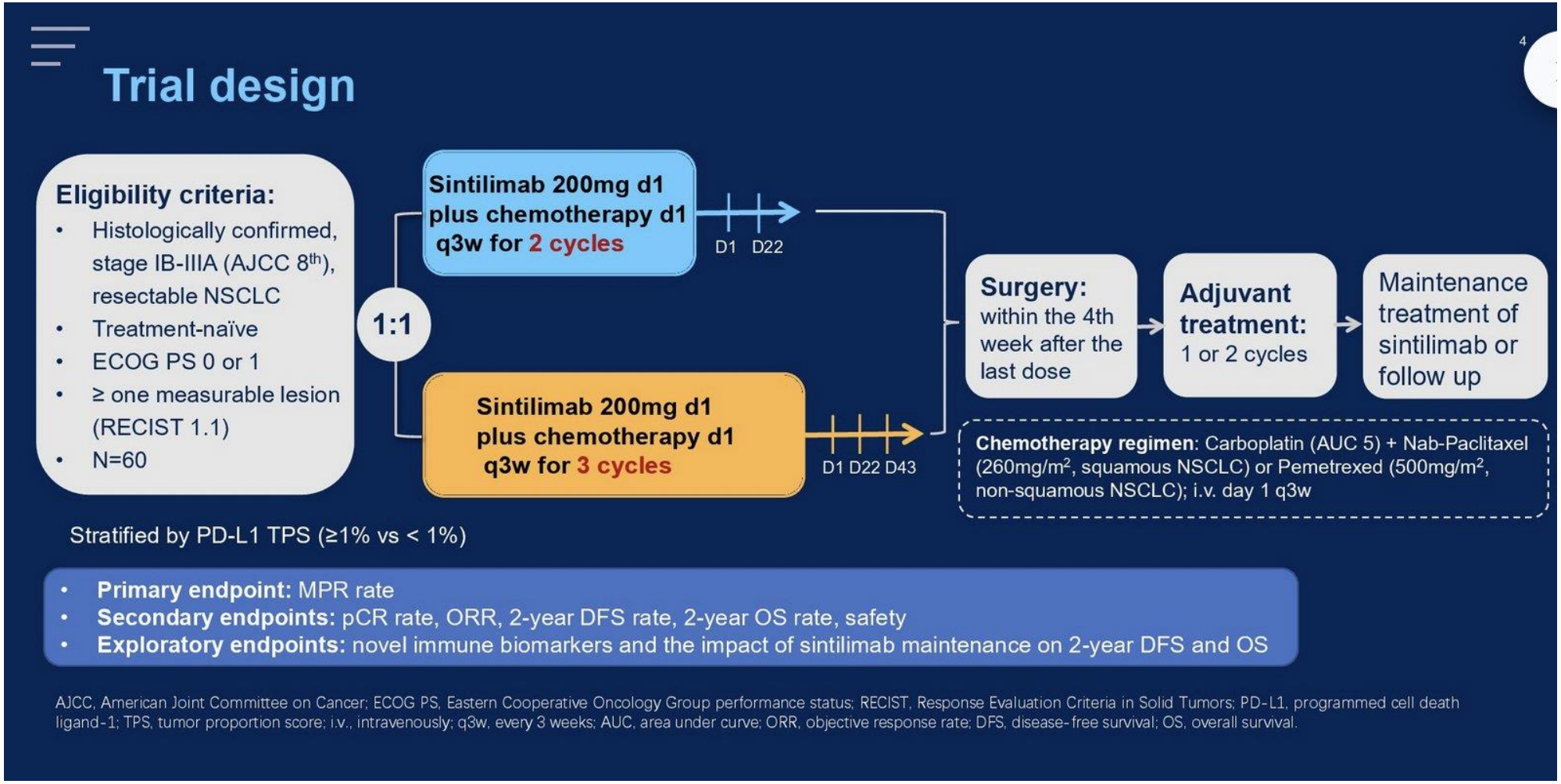
Periop st2/3 NSCLC- adjuvant or no?

Stage 3 unresectable- PACIFIC more or less?

Post SBRT- how much is too much?

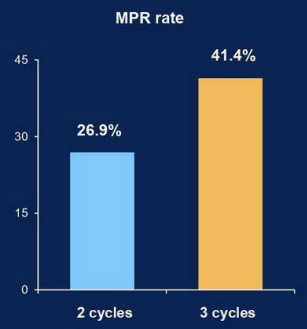
Stage IV – 2 yrs or indefinite? Or can it be less???

How many cycles of neoadjuvant chemo/IO?



Looks like certainly more than 2

Primary endpoint



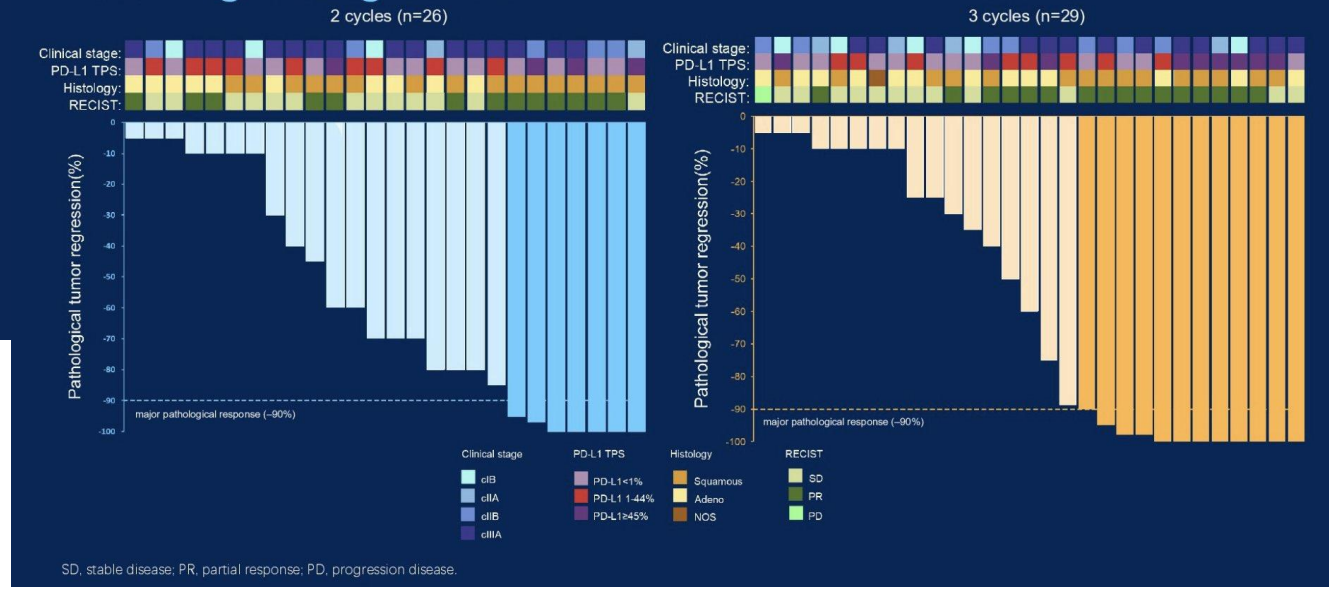
- Three cycles treatment presented a **14.5%** increase in MPR rate in comparison to two cycles

Pathological response, n(%)	Total, n=55	2 cycles, n=26	3 cycles, n=29	*P* value*
MPR	19（34.5%）(95% CI：22.2-48.6%)	7（26.9%）(95% CI：11.6-47.8%)	12（41.4%）(95% CI：23.5-61.1%)	0.260

- Narrow cycle difference of treatment
- Small sample size

*, the two-sided *P* value was from the χ^2 test, the exact two-sided 95% CIs were calculated by use of the Clopper-Pearson method.

Pathological regression



SD, stable disease; PR, partial response; PD, progression disease.

CheckMate 77T[a] study design

Key eligibility criteria
- Resectable, stage IIA (> 4 cm)-IIIB (N2) NSCLC (per AJCC 8th edition)
- No prior systemic anti-cancer treatment
- ECOG PS 0-1
- No *EGFR* mutation/known *ALK* alterations[b]

Stratified by histology (NSQ vs SQ) disease stage (II vs III), and tumor PD-L1[c] (≥ 1% vs < 1% vs not evaluable/indeterminate)

N = 461 (R 1:1)

- NIVO 360 mg Q3W + chemo[d] Q3W (4 cycles) → Radiologic restaging → Surgery (within 6 weeks post-neoadjuvant treatment) → NIVO 480 mg Q4W (1 year)
- PBO Q3W + chemo[d] Q3W (4 cycles) → Radiologic restaging → Surgery (within 6 weeks post-neoadjuvant treatment) → PBO Q4W (1 year)

Follow-up

Follow-up, median (range): 25.4 (15.7-44.2) months

Primary endpoint	Secondary endpoints	Exploratory analyses
• EFS by BICR	• pCR[e] by BIPR • MPR[e] by BIPR • OS • Safety	• EFS by pCR/MPR • EFS by adjuvant treatment

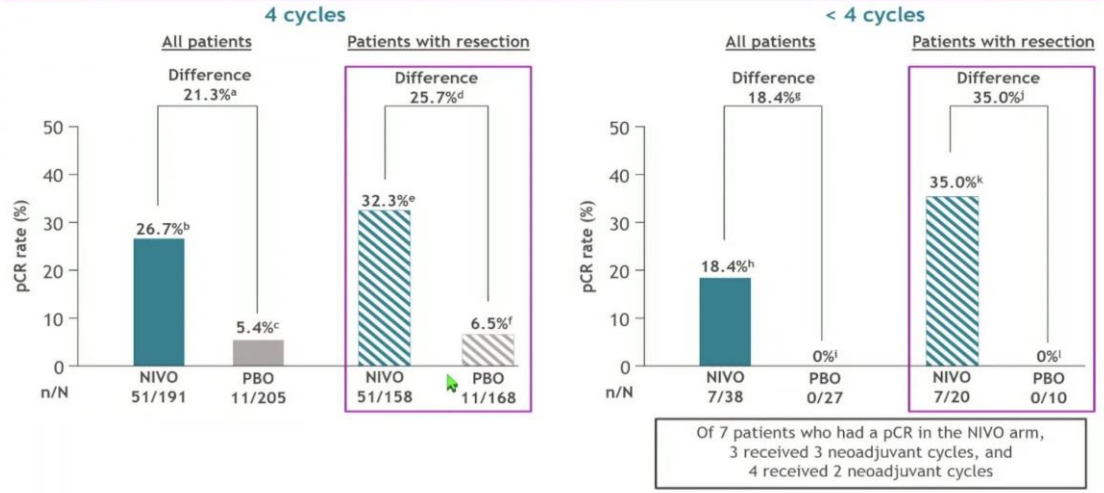
Database lock date: September 6, 2023.

[a]NCT04025879. [b]*EGFR* testing was mandatory in all patients with NSQ histology. *ALK* testing was done in patients with a history of *ALK* alterations. *EGFR*/*ALK* testing done using US FDA/local health authority-approved assays. [c]Determined by the PD-L1 IHC 28-8 pharmDx assay (Dako). [d]NSQ: cisplatin + pemetrexed, carboplatin + pemetrexed, or carboplatin + paclitaxel; SQ: cisplatin + docetaxel or carboplatin + paclitaxel. [e]Assessed per immune-related pathologic response criteria.[1] BICR, blinded independent central review; BIPR, blinded independent pathological review. 1. Cottrell TR, et al. *Ann Oncol* 2018;29:1853-1860.

CM 77T (perioperative NIVO): outcomes by neoadjuvant cycles

CM 77T (perioperative NIVO): outcomes by neoadjuvant cycles

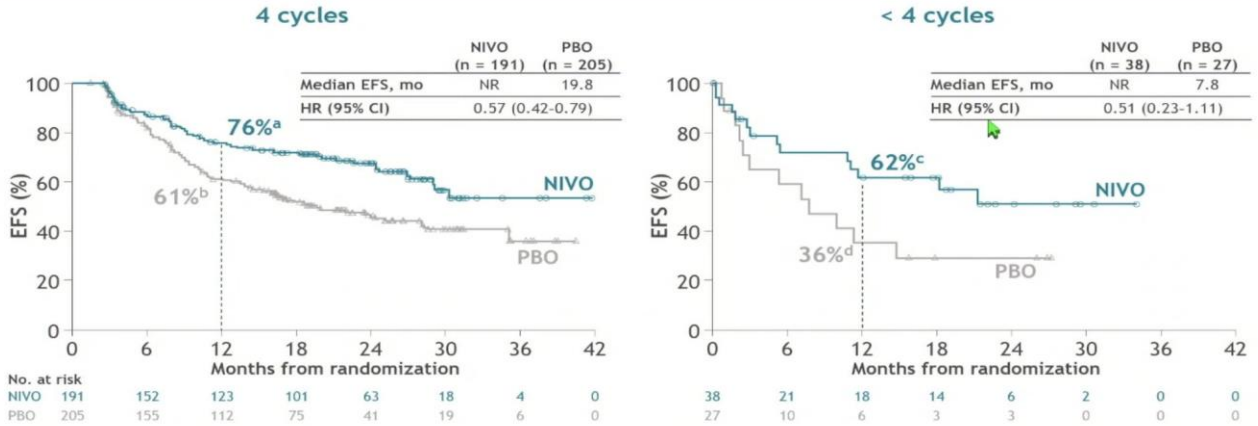
pCR by number of completed neoadjuvant treatment cycles



Of 7 patients who had a pCR in the NIVO arm, 3 received 3 neoadjuvant cycles, and 4 received 2 neoadjuvant cycles

Follow-up, median (range): 25.4 (15.7-44.2) months.
[a]95% CI: [b]14.3-28.4; [c]3.6-33.6; [d]2.7-9.4; [e]17.4-33.9; [f]25.1-40.2; [g]3.3-11.4; [h]2.9-33.4; [i]7.7-34.3; [j]0-12.8; [k]2.5-56.7; [l]15.4-59.2; [m]0-30.8.

EFS by number of completed neoadjuvant treatment cycles



Follow-up, median (range): 25.4 (15.7-44.2) months.
[a]95% CI: [b]68-81; [b]54-[c]42-76; [d]15-57.

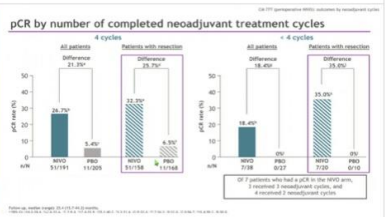
So maybe 3 is the sweet spot here?

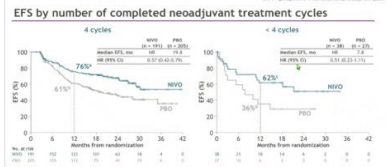
Brendon Stiles @BrendonStilesMD · 2d

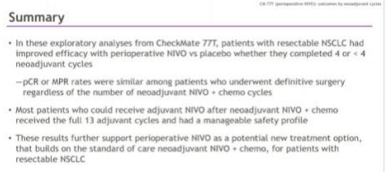
Let's go for 3! Easier on patients and maybe easier on surgery. Also perhaps a faster path to identify nonresponders or those who progress and guide them to other therapy. #ELCC24

Stephen V Liu, MD @StephenVLiu · 2d

Dr. @DrMarkAwad at #ELCC24 with exploratory analysis from CheckMate 77T (perioperative nivolumab + chemotherapy in resectable NSCLC) and shows benefit with IO (pCR, MPR, and EFS) seen in those who completed 4 cycles and those who stopped shy of 4. #ESMOAmbassadors @myESMO



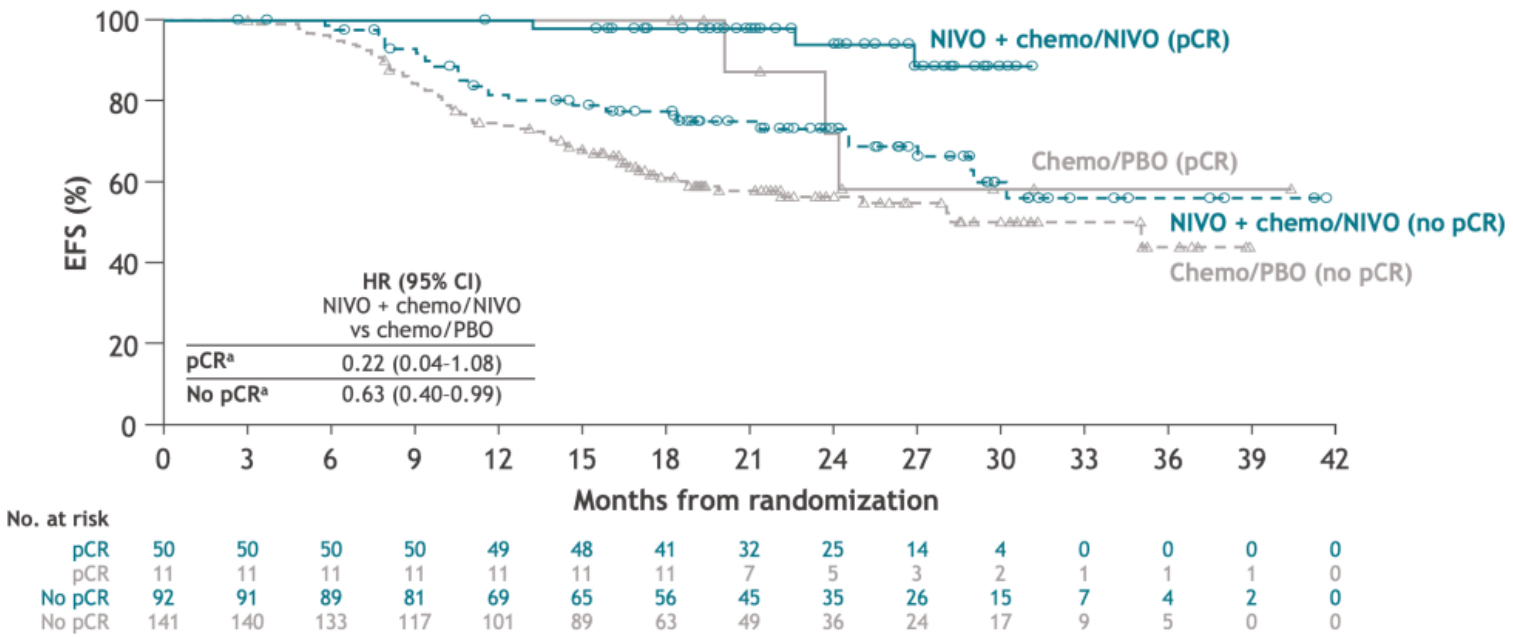




At least some patients with non-pathCR will benefit from adjuvant- who can say no to more sweets?

Exploratory analysis: EFS by pCR status in patients who received adjuvant treatment

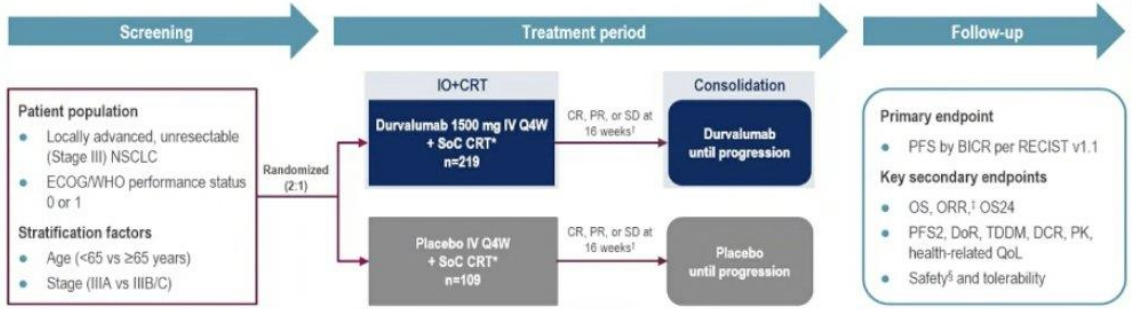
CheckMate 77T: perioperative NIVO in resectable NSCLC



PACIFIC-2- can we extend IO benefit giving it concurrently with chemo-XRT?

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.

BICR, blinded independent central review; CR, complete response; CRT, chemoradiotherapy; DCR, disease control rate; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; Gy, gray; IV, intravenous; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; OS24, overall survival at 24 months; PFS, progression-free survival; PFS2, time from randomization to second progression; PK, pharmacokinetics; PR, partial response; Q4W, once every 4 weeks; QoL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; SoC, standard of care; TDDM, time to death or distant metastasis; WHO, World Health Organization.

*Platinum-based chemotherapy regimens include: cisplatin/etoposide, carboplatin/paclitaxel, pemetrexed/cisplatin (non-squamous only), or pemetrexed/carboplatin (non-squamous only), alongside radiation therapy (5 fractions/week for ~6 weeks [±3 days; total 60 Gy]). †Investigator assessed per RECIST v1.1. ‡Following a protocol amendment, ORR was moved from a primary endpoint to a key secondary endpoint. §Will be reviewed by an independent data monitoring committee in an unblinded manner.

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Key baseline patient characteristics (ITT population)

	Durvalumab + CRT (n=219)	Placebo + CRT (n=109)
Age group (years), n (%)		
<50	18 (8.2)	12 (11.0)
≥50 to <65	107 (48.9)	50 (45.9)
≥65 to <75	75 (34.2)	40 (36.7)
≥75	19 (8.7)	7 (6.4)
Median age (range), years	63.0 (36–84)	63.0 (38–84)
Sex, n (%)		
Male	166 (75.8)	80 (73.4)
Female	53 (24.2)	29 (26.6)
Race, n (%)		
White	141 (64.4)	62 (56.9)
Black or African American	2 (0.9)	0
Asian	65 (29.7)	39 (35.8)
American Indian or Alaska Native	7 (3.2)	7 (6.4)
Other	4 (1.8)	1 (0.9)
ECOG/WHO PS, n (%)		
0 – Normal activity	98 (44.7)	53 (48.6)
1 – Restricted activity	121 (55.3)	56 (51.4)
Histology type, n (%)		
Squamous	121 (55.3)	52 (47.7)
Non-squamous	98 (44.7)	57 (52.3)
PD-L1 status, n (%)*		
<1% (negative)	86 (39.3)	36 (33.0)
≥1% (positive)	113 (51.6)	60 (55.0)
Unknown	20 (9.1)	13 (11.9)

	Durvalumab + CRT (n=219)	Placebo + CRT (n=109)
***EGFR* mutation, n (%)**		
Positive	7 (3.2)	6 (5.5)
Negative	112 (51.1)	60 (55.0)
Unknown	100 (45.7)	43 (39.4)
AJCC stage, n (%)†		
IIIA	76 (34.7)	37 (33.9)
IIIB	109 (49.8)	51 (46.8)
IIIC	33 (15.1)	20 (18.3)
IV	1 (0.5)	1 (0.9)
TNM class at screening, n (%)		
Primary tumour		
TX	2 (0.9)	1 (0.9)
T1	15 (6.8)	10 (9.2)
T2	37 (16.9)	13 (11.9)
T3	39 (17.8)	32 (29.4)
T4	126 (57.5)	53 (48.6)
Regional lymph nodes		
N0	25 (11.4)	7 (6.4)
N1	16 (7.3)	14 (12.8)
N2	124 (56.6)	60 (55.0)
N3	54 (24.7)	28 (25.7)
Distant metastases		
M0	218 (99.5)	108 (99.1)
M1b	1 (0.5)	1 (0.9)

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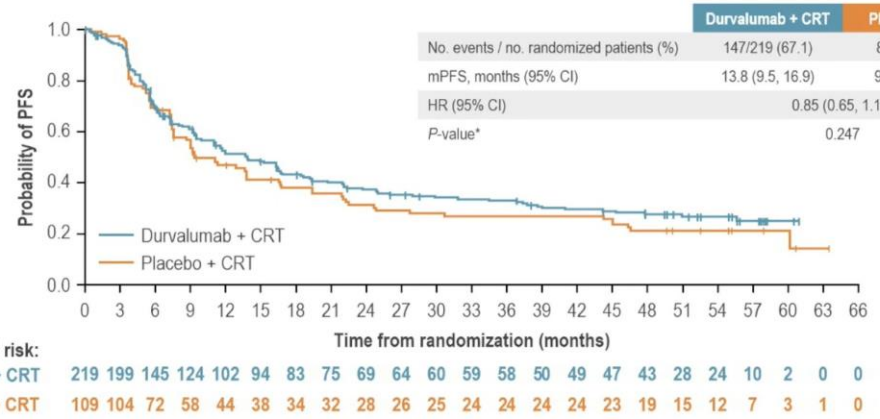
AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; ITT, intention-to-treat; PD-L1, programmed cell death ligand-1; PS, performance status; TNM, tumor, node, metastasis; WHO, World Health Organization.

*PD-L1 testing was retrospective and performed centrally. †Per the 8th edition of the AJCC Cancer Staging Manual.

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	

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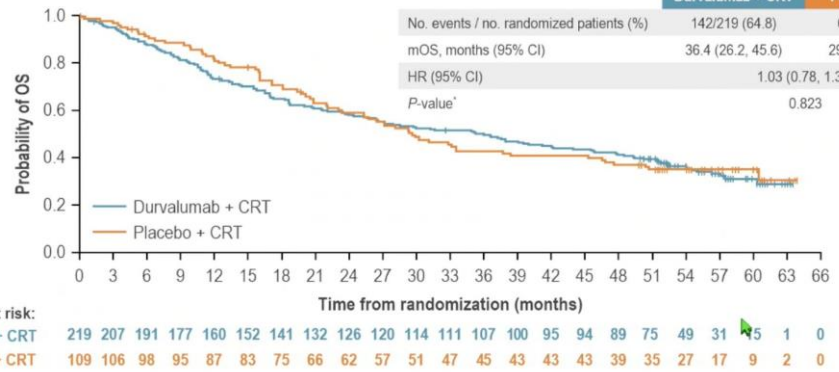
BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; mPFS, median PFS; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

Per RECIST v1.1. Tick marks on the curves indicate censored observations.
*Based on the Lan and DeMets approach that approximates the O'Brien Fleming spending functions; the 2-sided p-value boundary for declaring statistical significance is 0.0416 for an overall 5% alpha.

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	

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).

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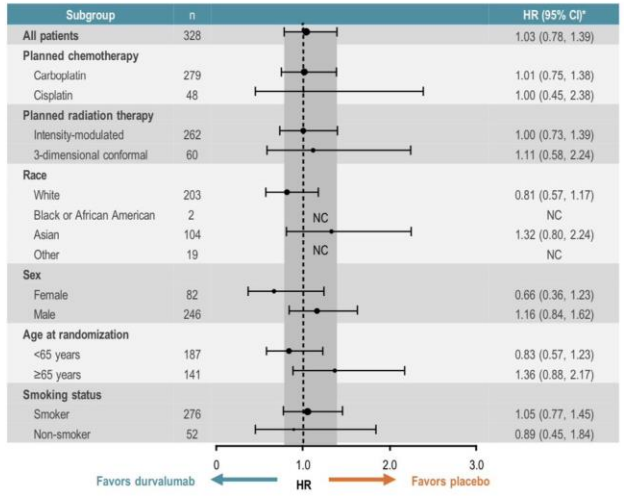
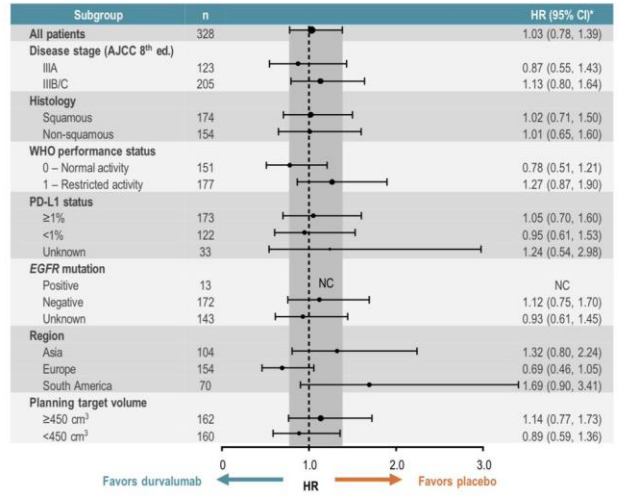
CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; mOS, median OS; OS, overall survival; ORR, objective response rate.

Tick marks on the curves indicate censored observations.
*The 2-sided p value boundary for declaring statistical significance is 4.5% or 5% depending on the previous levels of the multiple testing procedure.

OS (ITT population), subgroup analysis





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CI, confidence interval; ITT, intention to treat; NC, not calculable; HR, hazard ratio; OS, overall survival.

A HR of <1 favors durvalumab and is associated with a longer event-free survival than placebo. The size of circle is proportional to the number of events. The gray band represents the 95% CI for the main OS HR. For all patients, the analysis is based on the main stratified analysis while, for the subgroups, the HR and CI were calculated using an unstratified Cox proportional hazards model, with treatment as the only covariate and ties handled by Efron approach. *HRs and 95% CIs were not calculated if a subgroup had fewer than 5 events in each treatment arm.

PACIFIC-2 hitting the sweet spot

De-escalating adjuvant durvalumab treatment duration in stage III non-small cell lung cancer

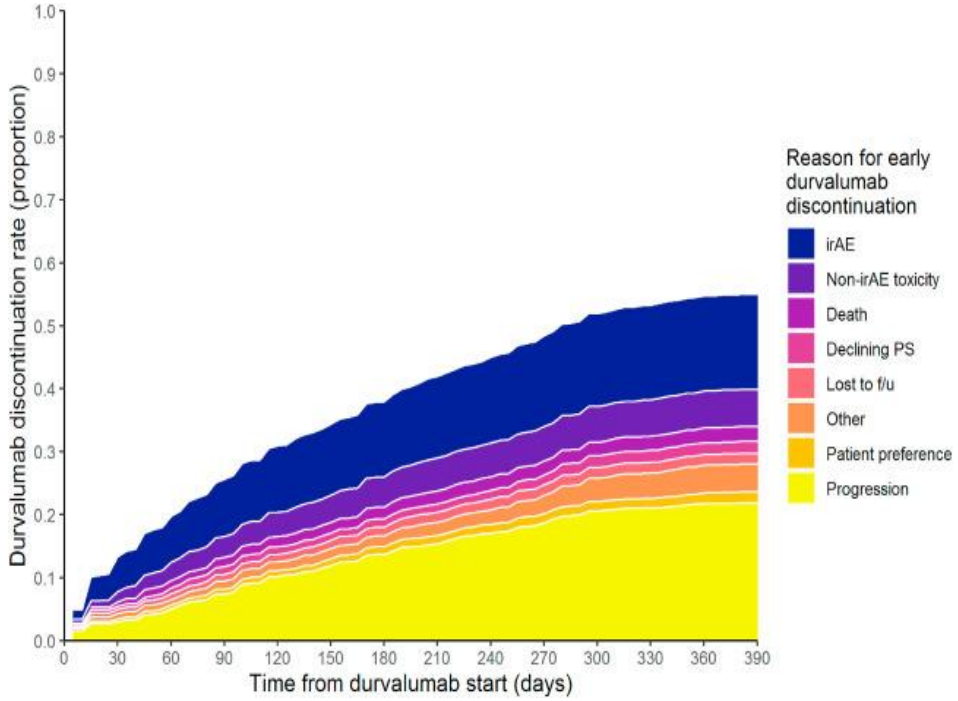
Alex K. Bryant [b d f], Kamya Sankar [a d e], Lili Zhao [c d], Garth W. Strohbehn [d e k], David Elliott [b d f], Drew Moghanaki [g h], Michael J. Kelley [i j], Nithya Ramnath [a e], Michael D. Green [b d f]

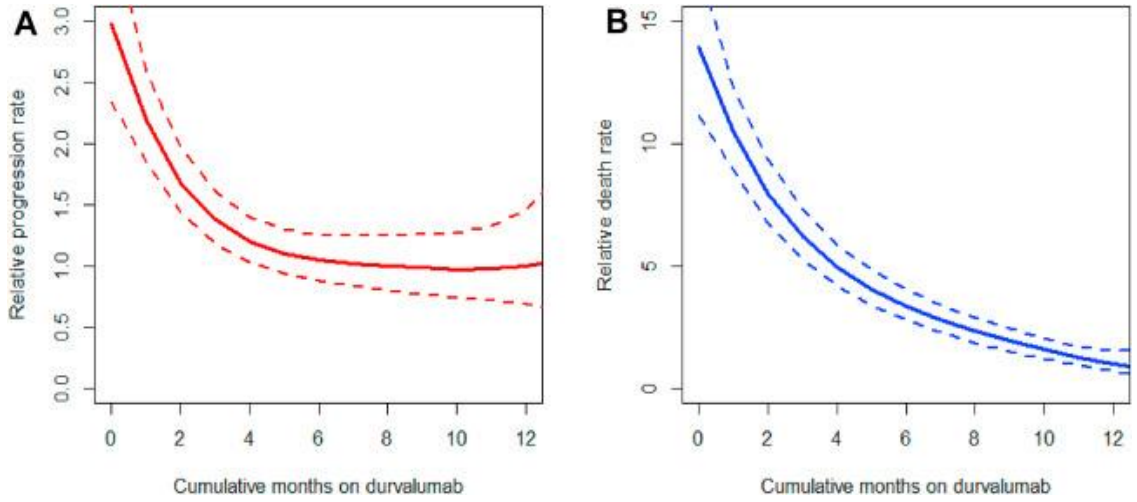
Methods

We identified patients with stage III NSCLC treated with definitive chemoradiation and adjuvant durvalumab from November 2017 to April 2021 from the United States Veterans Affairs system. Predictors of early durvalumab discontinuation were evaluated with Cox proportional hazards regression. The effect of differing durations of durvalumab treatment (up to 6, 9, and 12 months) on PFS and OS were compared with a marginal structural model and time-dependent Cox modelling.

Results

We included 1006 patients with stage III non-small cell lung cancer who received concurrent chemoradiotherapy and at least one dose of adjuvant durvalumab. The median duration of durvalumab treatment was 7 months (interquartile range 2.8–11.5) and 31% completed the intended durvalumab course. The most common reasons for early discontinuation were tumour progression (22%), immune-related adverse events (15%), and non-immune-related toxicity (6.0%), Marginal structural models suggested similar PFS for 9 months versus 12 months of durvalumab treatment and inferior PFS for 6 months versus 12 months.





Personalized Duration of Consolidation Durvalumab Using Circulating Tumor DNA for the Treatment of Inoperable or Unresectable Stage III Non-small Cell Lung Cancer, The Indiana Trial

STATUS: ACTIVE

Open all Close all

Share this clinical trial with your doctor:

Print Email

Description

This phase II trial tests how well the use of circulating tumor DNA testing works to determine the length of durvalumab therapy for patients with stage III non small cell lung cancer that that cannot or is unable to be removed by surgery (inoperable or unresectable). A monoclonal antibody is a type of protein that can bind to certain targets in the body, such as molecules that cause the body to make an immune response (antigens). Immunotherapy with monoclonal antibodies, such as durvalumab, may help the body's immune system attack the cancer, and may interfere with the ability of tumor cells to grow and spread. Circulating tumor DNA (ctDNA) are tiny pieces of cancer DNA in the blood that show how well the body responds to a treatment for a disease or condition. ctDNA may predict the presence or absence of a small number of cancer cells in the body after cancer treatment. Using ctDNA tests to determine when blood is clear of cancer may help determine the optimal cycle to stop treatment with durvalumab for patients with inoperable or unresectable stage III non small cell lung cancer.

PRIMARY OBJECTIVE:

I. Determine if de-escalating the number of durvalumab cycles based on personalized ctDNA clearance guidance to at least 6 cycles after chemoradiation (CRT) in stage III non-resectable non small cell lung cancer (NSCLC) has non-inferior 2-year progression free survival (PFS) rate compared with historical control of empirically treating stage III non-resectable NSCLC for 1 year of durvalumab after CRT.

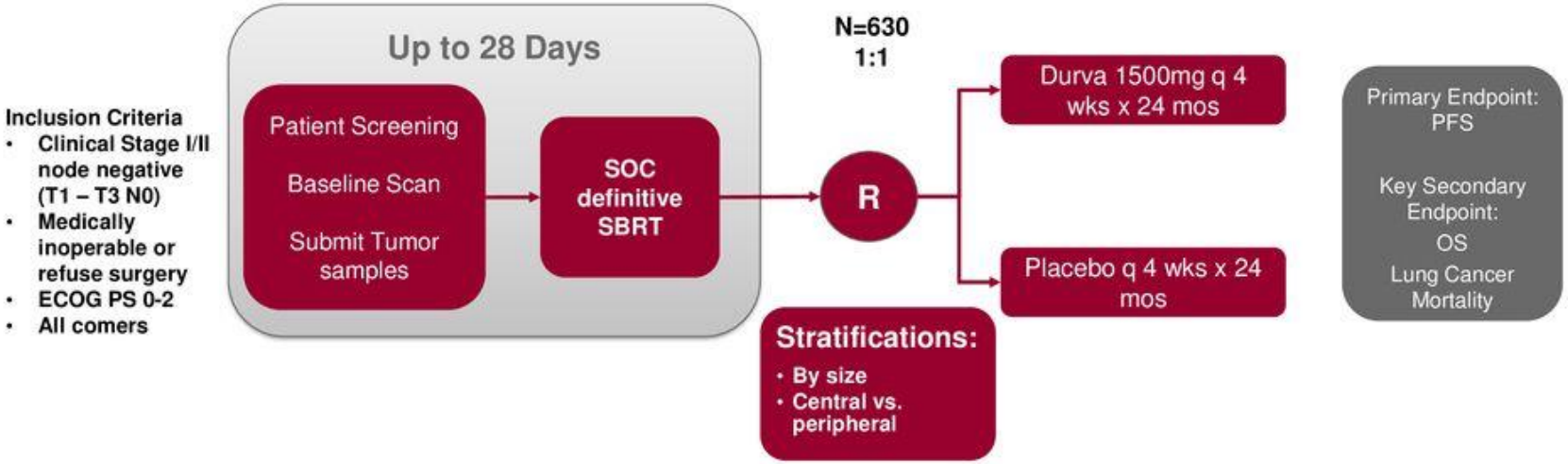
SECONDARY OBJECTIVES:

I. Estimate the 24-month overall survival (OS) of patient treated with consolidation durvalumab based on personalized ctDNA clearance guidance for at least 6 cycles after CRT in stage III non-resectable NSCLC.

II. Estimate the 24-month PFS in patients with persistently detectable ctDNA without radiographic progression of disease after receiving ≥ 6 months of consolidation durvalumab.

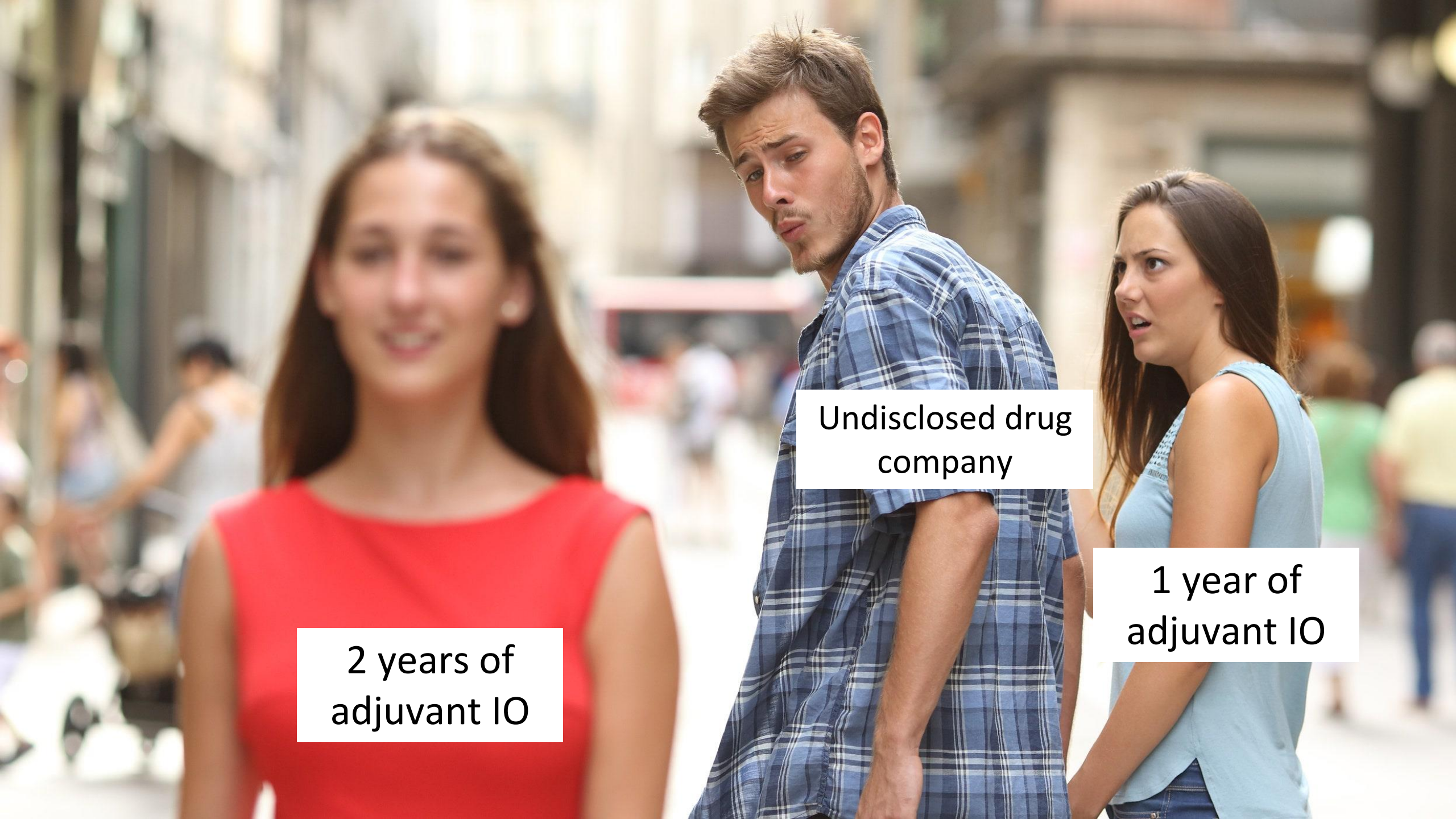
How about IO post-XRT?

PACIFIC 4 / RTOG 3515 Schema

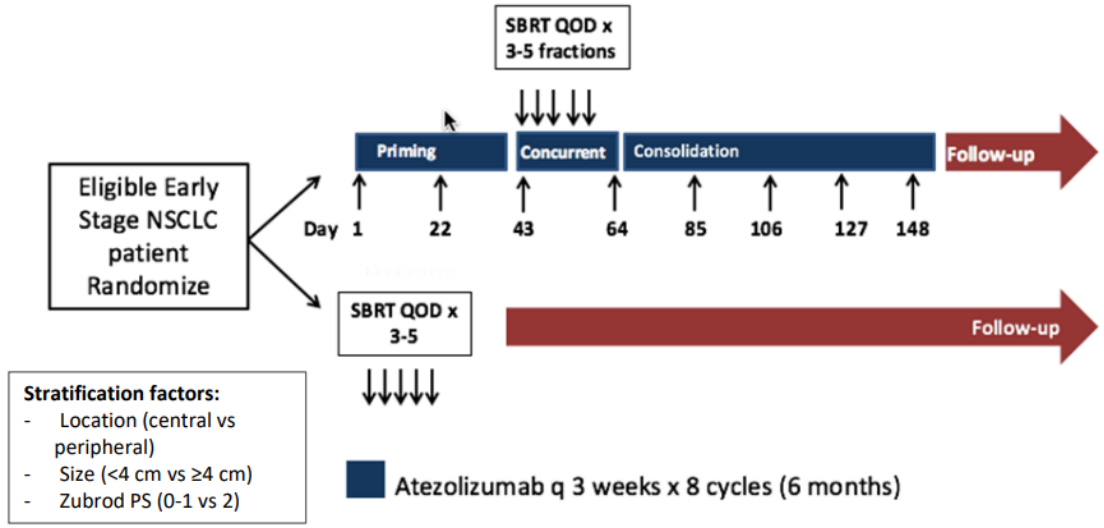


Additional Key points

- NSCLC proven by histology / cytology
- Tissue submission mandated – core preferred but will accept FNA samples for translational analysis
- SOC SBRT taking place during screening. SBRT planning can occur before study enrollment
- Randomization within **7 days of completion of SOC SBRT**


2 years of adjuvant IO
Undisclosed drug company
1 year of adjuvant IO

SWOG/NRG S1914 Schema



Ongoing Phase III Trials of SBRT ± Checkpoint Inhibitors for NSCLC Stage IA-IB

Stage I NSCLC (Inoperable or Refuse Surgery)		
PACIFIC 4	**Keynote 867**	**SWOG 1914**
SBRT ± **durvalumab** (24 months)	SBRT ± **pembrolizumab** (17 cycles)	SBRT ± **atezolizumab** (8 cycles)
Primary Outcome= PFS Secondary Outcome = OS	Primary Outcome= EFS Secondary Outcome = OS	Primary Outcome = OS Secondary Outcome = PFS
Sample Size = 706	Sample Size = 530	Sample Size = 480
Opened March 2019	**Opened June 2019**	**Opened March 2020**
NCT03833154	NCT03924869	NCT04214262

So how about advanced NSCLC? 2 years or indefinite IO?

Clinical Trial	Total of patients completing 2 years of pembro (%)	TRAEs	ORR	PFS (median/ Kaplan-Meier estimated rate)	OS (median/ Kaplan-Meier estimated rate)
KEYNOTE-001[1]	10.9% (60/550) [1]	N/A	86% (Tx naïve) 91% (Tx prior) [1]	PFS rate: N/A	5-year OS rate: 78.6% (Tx naïve) 75.8 (Tx prior) [1]
KEYNOTE-010[2]	11.4% (79/690) [2]	Any TRAEs: 83.5%[2]	95%[2]	2-year PFS rate: 57.7% 1-year PFS rate: 72.5%[2]	2-year OS rate: 86.3% 1-year OS rate: 98.7%[2]
KEYNOTE-024[3]	25.8% (39/154) [3]	Any TRAEs: 87.2%[3]	82.1% ORR • CR: 10.3% • PR: 71.8% • SD: 15.4% • PD: 2.6%[3]	PFS rate: N/A	3 year OS rate: 81.4%[3]
KEYNOTE-042[5]	16.2% (103/637) [5]	N/A	ORR 84.3%[5]	PFS rate: N/A	4-year OS rate: 61.8%[5]
KEYNOTE-189[6]	13.9% (57/410)[7]	Any TRAEs: 100%[6] TRAEs Grade 3/4: 66.7%[6]	ORR: 86.0% • CR: 7.1% • PR: 78.6% [7] • Median DOR was 57.7 mons	3-year PFS rate: 56.2% 1-year PFS rate: 78.5%	3-year OS rate: 71.9% [7]
KEYNOTE-407[8]	19.8% (55/278)[9]	Any TRAES: 100% TRAEs Grade 3/4: 63.6%	90.9% ORR[9] • CR 9.1% • PR 83.6 • SD 7.3%	3-year PFS rate: 58.4% 1-year PFS rate 82.6%	3-year OS rate: 69.5%[9]

CM153 (1yr Nivo continuous vs fixed)

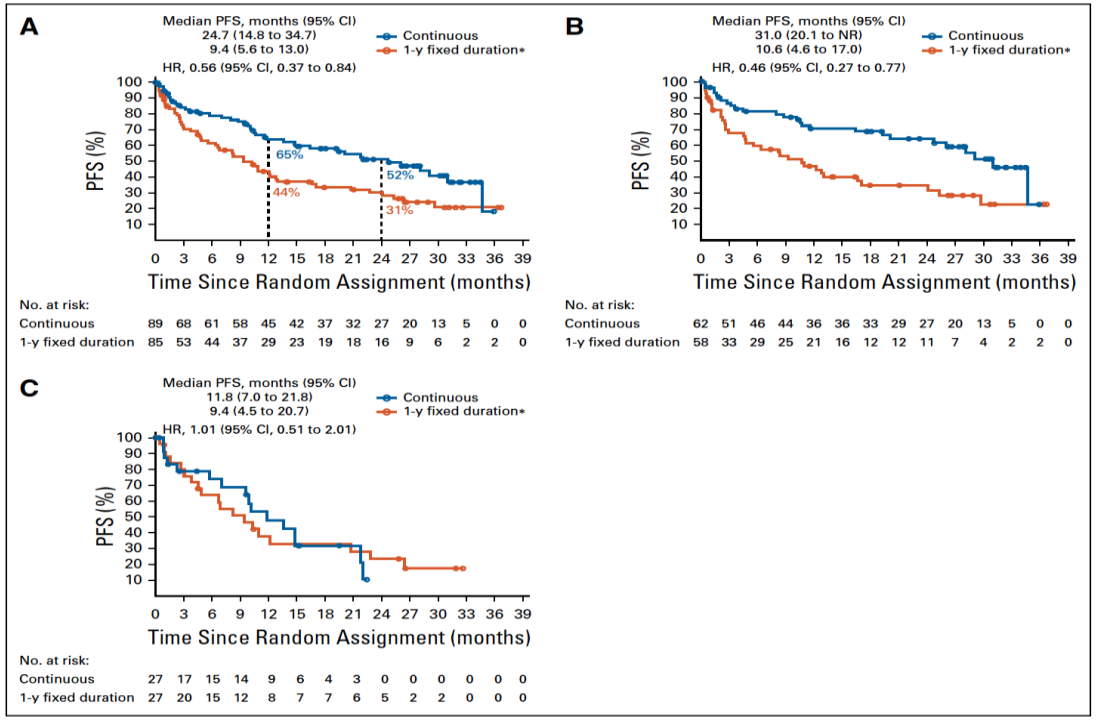


FIG 2. Progression-free survival (PFS) from random assignment (A) in the PFS population, (B) in patients with complete response/partial response, and (C) in patients with stable disease. Random assignment took place after 1 year of treatment with nivolumab; the post–random

	No.	Continuous			1-Year Fixed Duration[a]			
		No. of events (no. of patients)	mPFS (months)	95% CI	No. of events (no. of patients)	mPFS (months)	95% CI	Hazard ratio (95% CI)
Overall	174	42 (89)	24.7	14.8 to 34.7	53 (85)	9.4	5.6 to 13.0	0.56 (0.37 to 0.84)
Sex								
Male	92	20 (47)	28.1	16.4 to NA	29 (45)	8.3	4.5 to 24.1	0.52 (0.29 to 0.92)
Female	82	22 (42)	24.7	10.2 to 34.7	24 (40)	10.9	4.5 to 20.7	0.57 (0.31 to 1.02)
Age, years								
< 70	105	24 (56)	28.1	13.6 to 34.7	32 (49)	10.9	4.8 to 17.0	0.49 (0.29 to 0.83)
≥ 70	69	18 (33)	22.0	8.0 to NA	21 (36)	9.2	4.5 to 25.3	0.67 (0.35 to 1.25)
Smoking status								
Former/current	165	38 (83)	28.1	14.8 to NA	50 (82)	10.6	5.6 to 16.7	0.54 (0.36 to 0.83)
Former	132	31 (65)	26.0	14.8 to 34.7	41 (67)	10.6	4.8 to 17.0	0.57 (0.36 to 0.92)
Current	33	7 (18)	NR	7.0 to NA	9 (15)	9.4	2.1 to 29.7	0.46 (0.17 to 1.23)
Never or unknown	9	4 (6)	1.8	0.8 to NA	3 (3)	4.6	1.2 to 6.7	NA
PD-L1 status, %								
< 1	32	11 (20)	14.8	5.8 to 29.0	9 (12)	4.7	0.4 to NA	0.53 (0.21 to 1.30)
≥ 1	68	13 (30)	28.1	16.4 to NA	23 (38)	8.3	4.8 to 17.0	0.45 (0.23 to 0.90)
≥ 50	24	7 (12)	31.0	10.2 to NA	8 (12)	7.8	0.6 to 20.7	0.28 (0.09 to 0.90)
Not quantifiable/reported	74	18 (39)	24.7	11.6 to NA	21 (35)	12.8	2.9 to 25.3	0.60 (0.32 to 1.13)
Histology								
Squamous	63	13 (28)	24.7	10.6 to NA	24 (35)	8.2	3.8 to 10.9	0.42 (0.21 to 0.84)
Non-squamous	111	29 (61)	26.0	11.8 to 34.7	29 (50)	12.1	6.7 to 22.7	0.67 (0.40 to 1.12)
Performance status								
0-1	166	40 (83)	22.0	13.6 to 31.0	51 (83)	9.4	5.6 to 16.7	0.59 (0.39 to 0.89)
0	65	18 (32)	22.0	11.6 to 29.0	20 (33)	9.2	4.5 to 25.3	0.62 (0.33 to 1.19)
1	101	22 (51)	26.0	10.6 to NA	31 (50)	10.6	4.6 to 17.0	0.58 (0.34 to 1.00)
2	8	2 (6)	34.7	2.7 to 34.7	2 (2)	7.7	4.5 to 10.9	NA
Prior therapies								
1	73	16 (38)	24.7	11.8 to NA	20 (35)	10.2	2.9 to 22.7	0.61 (0.31 to 1.17)
2	49	10 (25)	NR	9.9 to NA	15 (24)	10.6	2.5 to 16.7	0.52 (0.23 to 1.17)
≥ 3 or unknown	52	16 (26)	21.8	10.2 to 31.0	18 (26)	8.2	4.8 to 26.4	0.62 (0.31 to 1.23)
Response at random assignment								
CR/PR	120	26 (62)	31.0	20.1 to NA	34 (58)	10.6	4.6 to 17.0	0.46 (0.27 to 0.77)
SD	54	16 (27)	11.8	7.0 to 21.8	19 (27)	9.4	4.5 to 20.7	1.01 (0.51 to 2.01)

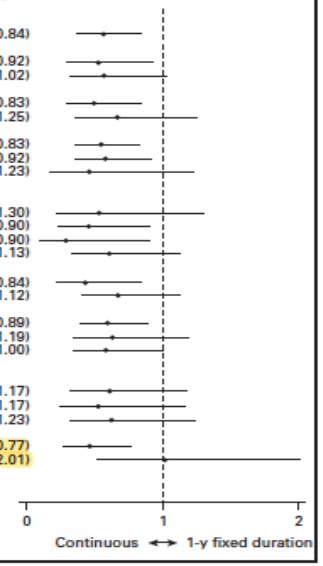


FIG 3. Multivariable analysis of progression-free survival (PFS) since random assignment by subgroup in the PFS population. Random assignment took

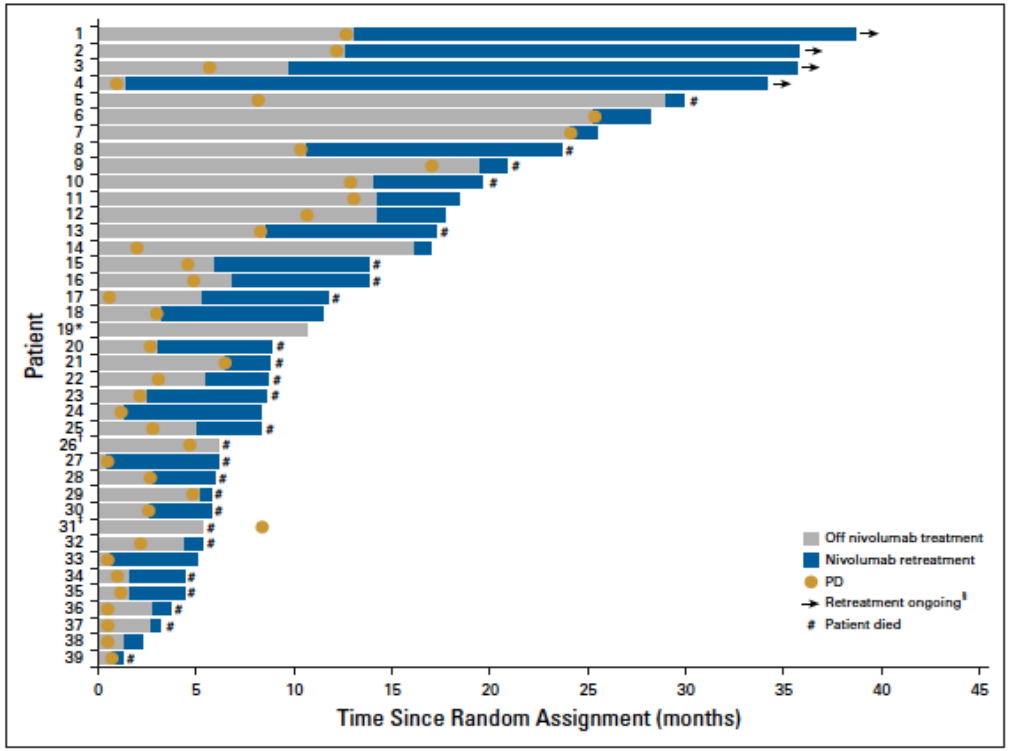
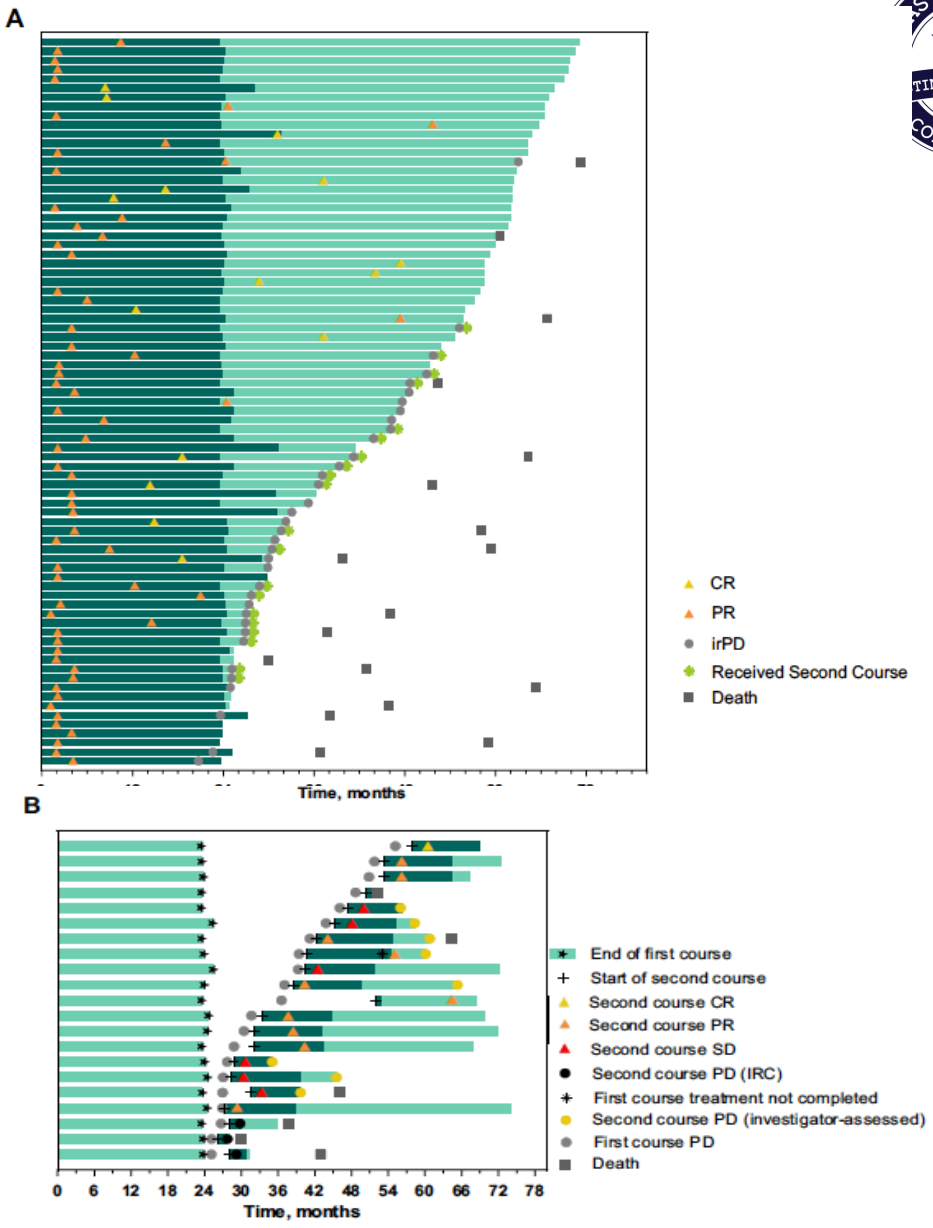


FIG 5. Initiation and duration of nivolumab retreatment in patients in the progression-free survival population who progressed after random assignment. (*) Patient was last reported as progression free and had one dose during retreatment. (†) Patient had one dose during retreatment. (‡) Patient had confirmed disease progression after beginning retreatment; patient had one dose during retreatment. (§) Two additional patients with ongoing retreatment had progressive disease (PD) before random assignment.



KEYNOTE-010 5-year update

- *11.4% completed 35 cycles of pembrolizumab*
- *3-year OS rate: 83.0%*
- *ORR was 98.7%; 19% CR, 79.7% PR, 1.3% SD*
- *Any TRAE 83.5%, Grade 3-5 17.7%*
- *Immune-mediated AEs and infusion reactions (39.2%)*

Figure B

- *14 pts with second course of pembrolizumab*
- *52.3% ORR*

Retrospective data (Sun et al JAMA Onc)

Flatiron database, analyzed cohort n=706
- Fixed duration (700-759 days) (n=113)
- Indefinite duration (≥760 days) (n=593)

Academic: n=90
Fixed 28% (25/90)
Indefinite 72% (65/90)

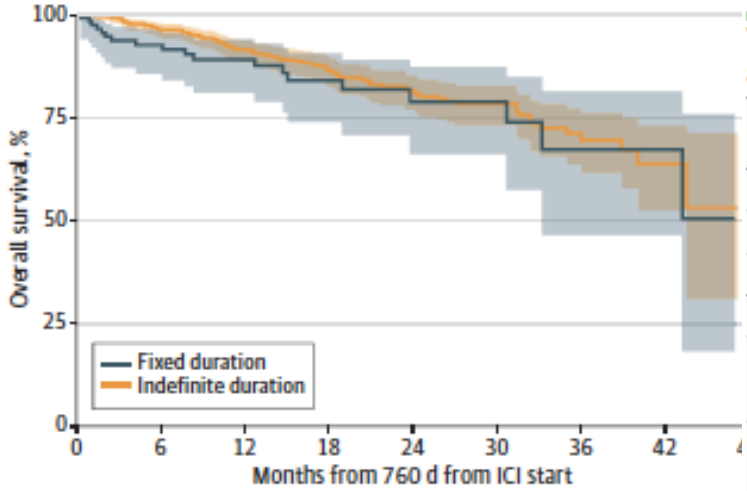
Community: n=616
Fixed 14% (88/616)
Indefinite 86% (528/616)

2-year OS from 760 days
- 79% (fixed-duration) and 81% (indefinite duration), no significant difference

Pts in fixed duration group were more likely to be treated at an academic center (22% (25/113) vs 11% (65/593), p=0.001)

Overall, only ~20% discontinued immunotherapy at 2 yrs

Figure 2. Overall Survival



Kaplan-Meier curve of overall survival from 2 years (760 days) from immune checkpoint inhibitor (ICI) treatment initiation in the fixed-duration cohort (stopped treatment at 2 years; 700-759 days of treatment) and indefinite-duration cohort (at least 760 days of treatment).

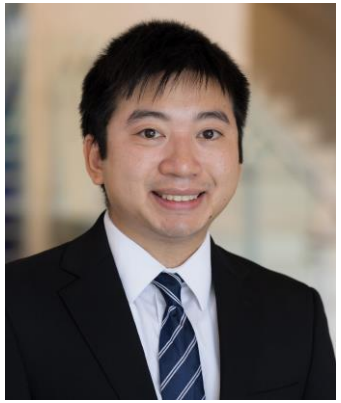
Table 2. Overall Survival in Fixed-Duration Treatment Cohort and Indefinite-Duration Treatment Cohort

Survival Characteristic	Fixed duration (n = 113)	Indefinite duration (n = 593)
Overall survival probability		
3 y (12 mos from 760 d)	0.89 (0.81-0.94)	0.91 (0.88-0.94)
4 y (24 mos from 760 d)	0.79 (0.66-0.87)	0.81 (0.77-0.85)
Hazard ratio for death		
Unadjusted	1.26 (0.77-2.08)	1 [Reference]
P value	.36	
Adjusted[a]	1.33 (0.78-2.25)	1 [Reference]
P value	.29	

[a] Multivariable Cox regression adjusted for age, sex, race, ECOG (Eastern Cooperative Oncology Group) performance status (PS), PD-L1 (programmed death-ligand 1), history of smoking, histologic type, immunotherapy vs chemoimmunotherapy, insurance, and academic vs community site. Multiple imputation by chained equations was used for variables with missing data (race, ECOG PS, PD-L1).

Which biomarkers to use to guide decisions? Flavors galore!

- Baseline tumor biomarkers
- Depth of response
- ctDNA clearance
- irAEs
- ctDNA/MRD- at 2 years
- PET/CT



EONS Study Schema

- Prior 1st line/ maintenance pembro ± optional chemo for 18-24 months ±60 days of pembro
- Baseline CT Chest with additional CT abdomen ± pelvis and MRI brain if known disease involvement ± 28 days of enrollment
- Baseline PROs and questionnaires

Primary endpoint: PFS

Secondary endpoint: OS

R 1:1

Pembrolizumab 200 mg q3wk or 400mg q6wk (up to 24 months or per provider's discretion)

Active surveillance

CT chest and if known disease involvement CT abdomen ± pelvis and MRI brain every 3-6 months

Radiologically confirmed progression per RECIST v1.1

Followup after completion of trial

Optional crossover to treatment arm of pembrolizumab or provider's choice of treatment/SOC

Let’s make sure it will not take EONS eons to find that sweet spot!

So what in thoracic oncology really hits the sweet spot????

So what in thoracic oncology really hits the sweet spot????
TLC does!!!

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