Integration of I–O in the management of stage III

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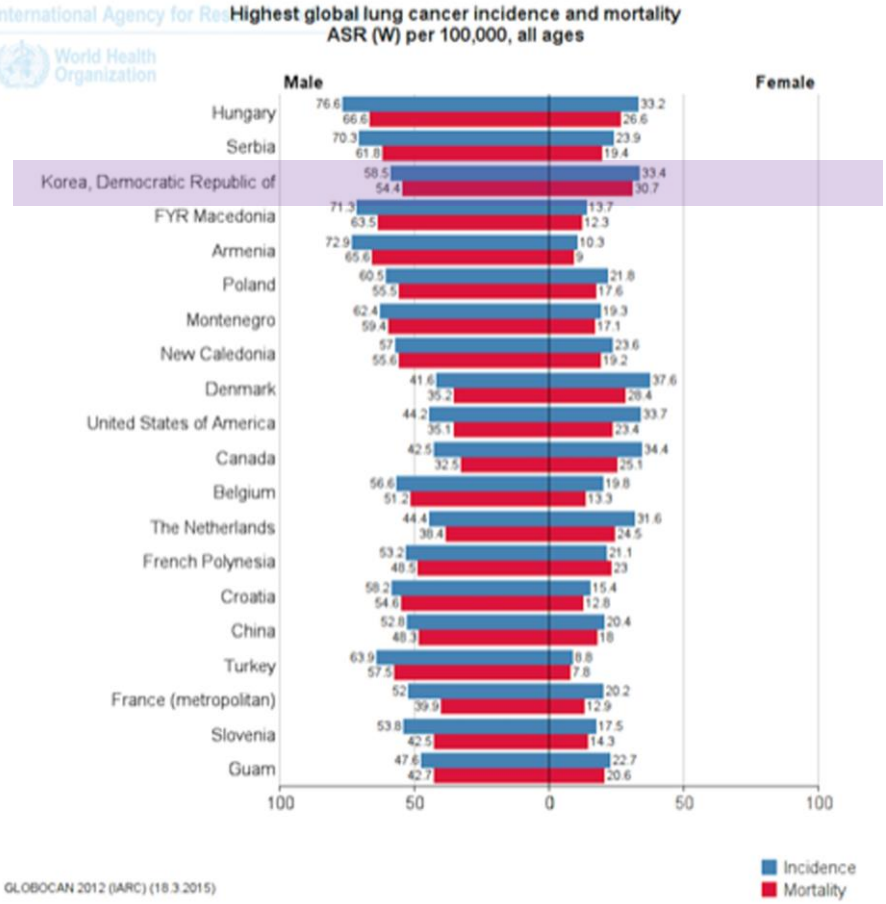
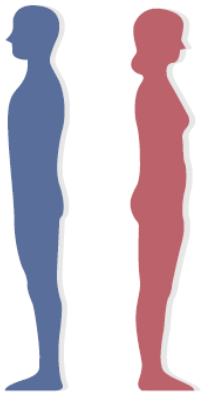
Content

- Epidemiology
- PACIFIC study
- Pembrolizumab / Atezolizumab / Nivolumab
- Surmmary

Epidemiology



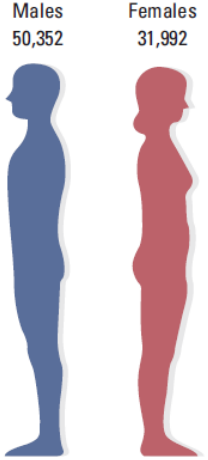
Estimated new cases (n=28,107)



	(%)
Lung	16.4
Stomach	15.0
Colon and rectum	12.0
Prostate	11.1
Liver	9.4
Pancreas	3.4
Gallbladder	3.4
Kidney	3.2
Bladder	3.1
Thyroid	2.6
All sites	100.0

(%)	
23.8	Breast
10.7	Colon and rectum
9.0	Stomach
8.4	Thyroid
8.3	Lung
3.8	Pancreas
3.7	Liver
3.6	Gallbladder
3.0	Cervix corpus
2.8	Cervix uteri
100.0	All sites

Estimated deaths (n=19,488)



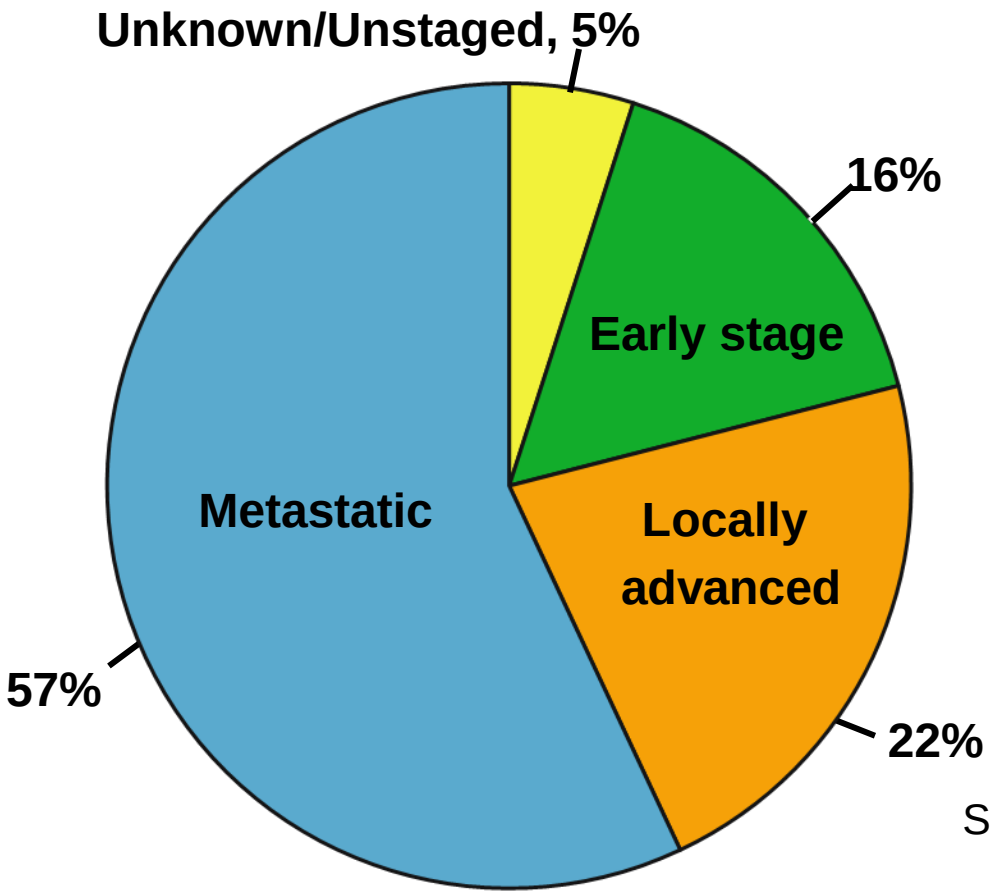
	(%)
Lung	28.3
Liver	15.5
Colon and rectum	9.6
Stomach	8.6
Pancreas	6.7
Gallbladder	4.7
Prostate	4.5
Bladder	2.4
Non-Hodgkin lymphoma	2.3
Esophagus	2.3
All sites	100.0

(%)	
16.4	Lung
12.0	Colon and rectum
10.1	Pancreas
9.1	Liver
8.5	Breast
7.5	Gallbladder
7.4	Stomach
4.0	Ovary
2.7	Non-Hodgkin lymphoma
2.6	Leukemia
100.0	All sites

Annals of Global Health. 2019; 85(1): 8, 1–16

Cancer Res Treat. 2019;51(2):431-437

Percent of Cases by Stage



APPROXIMATELY ONE THIRD OF PATIENTS with non–small-cell lung cancer (NSCLC) have stage III, locally advanced disease at diagnosis.[1] The standard of care for patients with

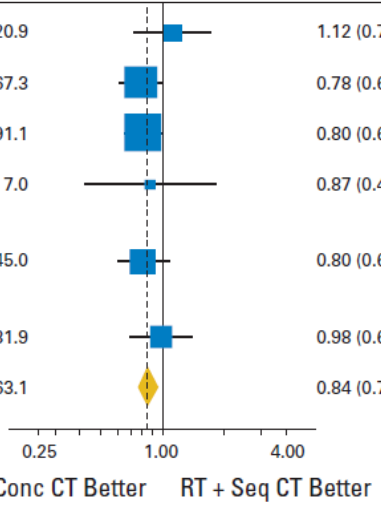
SEER Cancer Statistics Review, 1975-2014.

N Engl J Med 2017;377:1919-29.

Survival

Trial	No. Deaths / No. Entered RT + Conc CT	RT + Seq CT	O-E	Variance	HR (95% CI)
CALGB 8831	45/46	39/45	2.4	20.9	1.12 (0.73 to 1.72)
WJLCG	131/156	142/158	-16.8	67.3	0.78 (0.61 to 0.99)
RTOG 9410	180/204	189/203	-20.5	91.1	0.80 (0.65 to 0.98)
GMMA Ankara 95	15/15	15/15	-1.0	7.0	0.87 (0.41 to 1.82)
GLOT-GFPC NPC	87/102	96/103	-9.9	45.0	0.80 (0.60 to 1.07)
EORTC 08972	63/80	66/78	-0.5	31.9	0.98 (0.69 to 1.39)
Total	521/603	547/602	-46.4	263.1	0.84 (0.74 to 0.95)

Test for heterogeneity:
$\chi^2_5 = 3.24$, $P = .66$, $I^2 = 0\%$

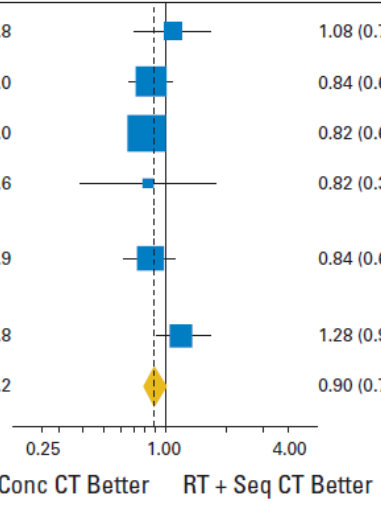


RT + conc CT effect: Log-rank test = 8.19, $P = .004$

Progression free survival

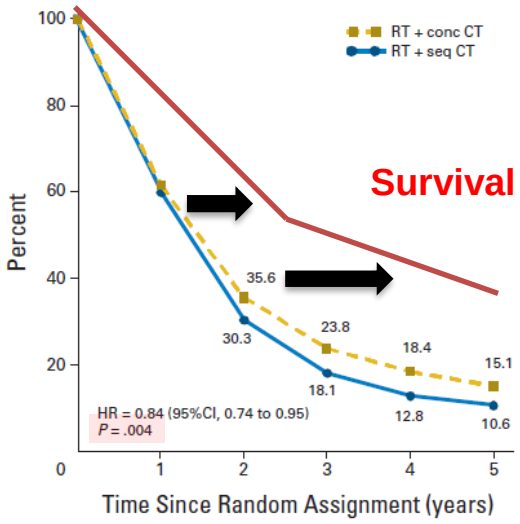
Trial	No. Events / No. Entered RT + Conc CT	RT + Seq CT	O-E	Variance	HR (95% CI)
CALGB 8831	45/46	39/45	1.7	20.8	1.08 (0.70 to 1.66)
WJLCG	128/148	132/145	-11.0	64.0	0.84 (0.66 to 1.08)
RTOG 9410	189/204	192/203	-18.8	94.0	0.82 (0.67 to 1.00)
GMMA Ankara 95	13/15	14/15	-1.3	6.6	0.82 (0.38 to 1.76)
GLOT-GFPC NPC	88/102	97/103	-8.0	44.9	0.84 (0.63 to 1.12)
EORTC 08972	70/80	67/78	8.4	33.8	1.28 (0.92 to 1.80)
Total	533/595	541/589	-29.0	264.2	0.90 (0.79 to 1.01)

Test for heterogeneity:
$\chi^2_5 = 6.37$, $P = .27$, $I^2 = 22\%$

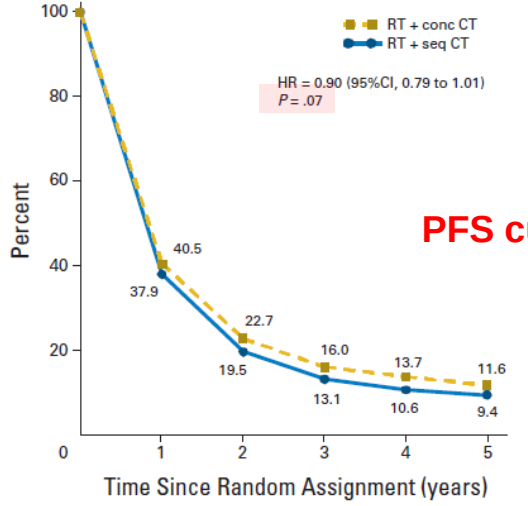


RT + conc CT effect: Log-rank test = 3.18, $P = .07$

J Clin Oncol 28:2181-2190



Survival curve



PFS curve

NCCN National Comprehensive Cancer Network®

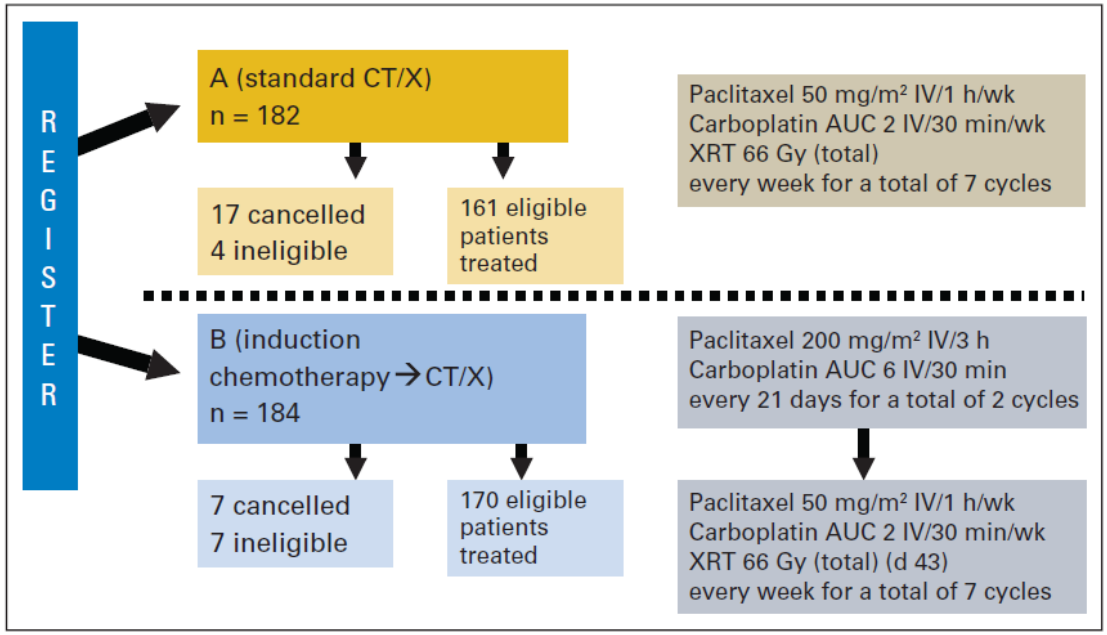
NCCN Guidelines Version 3.2014
Non-Small Cell Lung Cancer

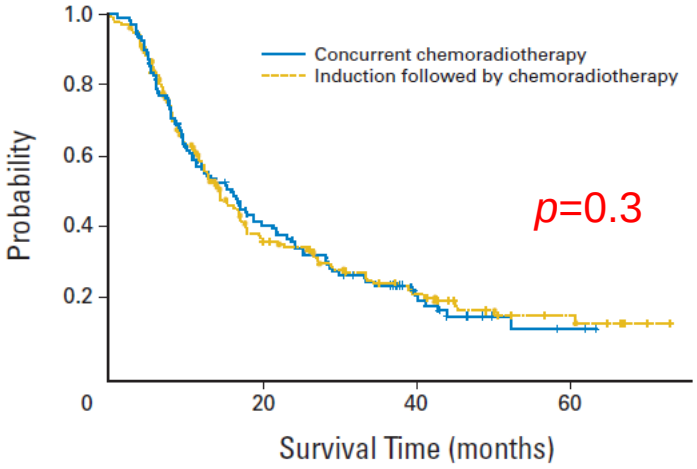
NCCN Guidelines Index
NSCLC Table of Contents
Discussion

CLINICAL ASSESSMENT	PRETREATMENT EVALUATION	INITIAL TREATMENT
Stage IIIB (T1–3, N3)	• PFTs (if not previously done) • PET/CT scan[h] (if not previously done) • Brain MRI • Pathologic confirmation of N3 disease by either: ▸ Mediastinoscopy ▸ Supraclavicular lymph node biopsy ▸ Thoracoscopy ▸ Needle biopsy ▸ Mediastinotomy ▸ EUS biopsy ▸ EBUS biopsy	N3 negative → See Initial treatment for stage I–IIIA (NSCL-8) N3 positive → Definitive concurrent chemoradiation[i,m,q] (category 1) Metastatic disease → See Treatment for Metastasis solitary site (NSCL-13) or distant disease (NSCL-15)

J Clin Oncol 28:2181-2190

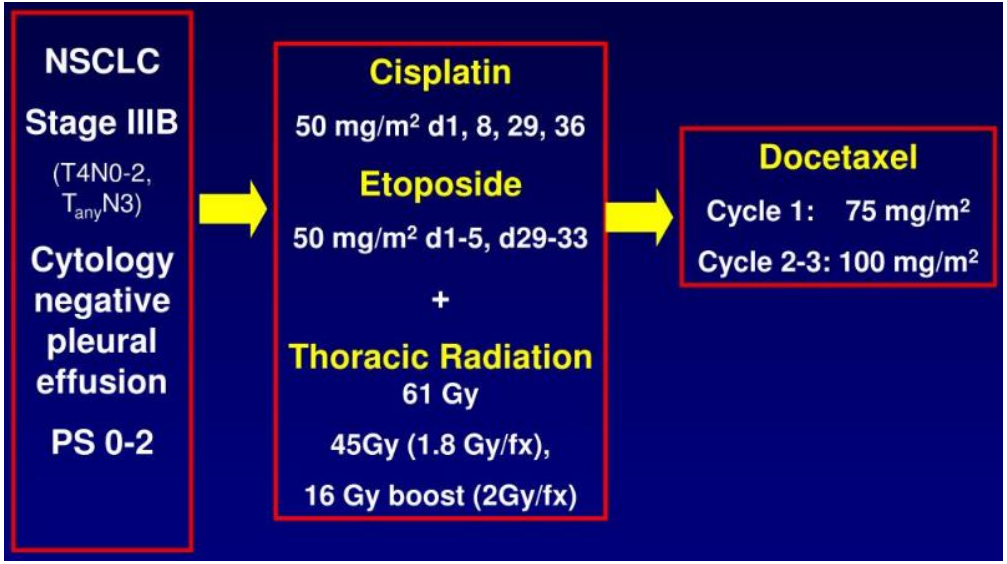
CALGB 39801 study



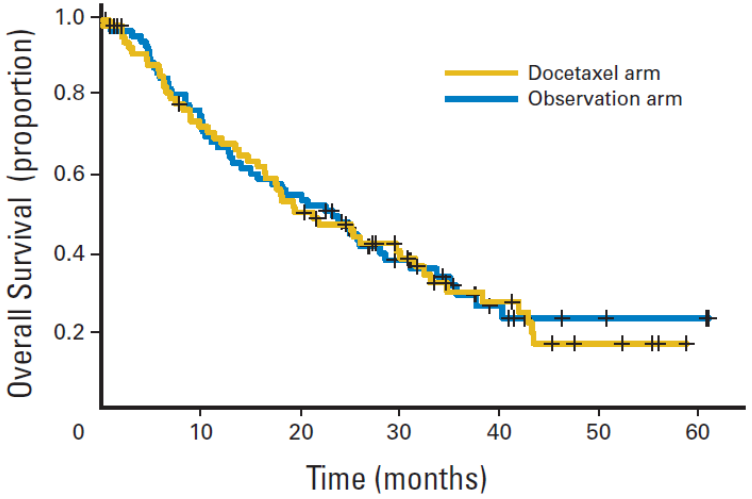


J Clin Oncol 25:1698-1704

SWOG 9504 trial



Phase II, mOS 26months

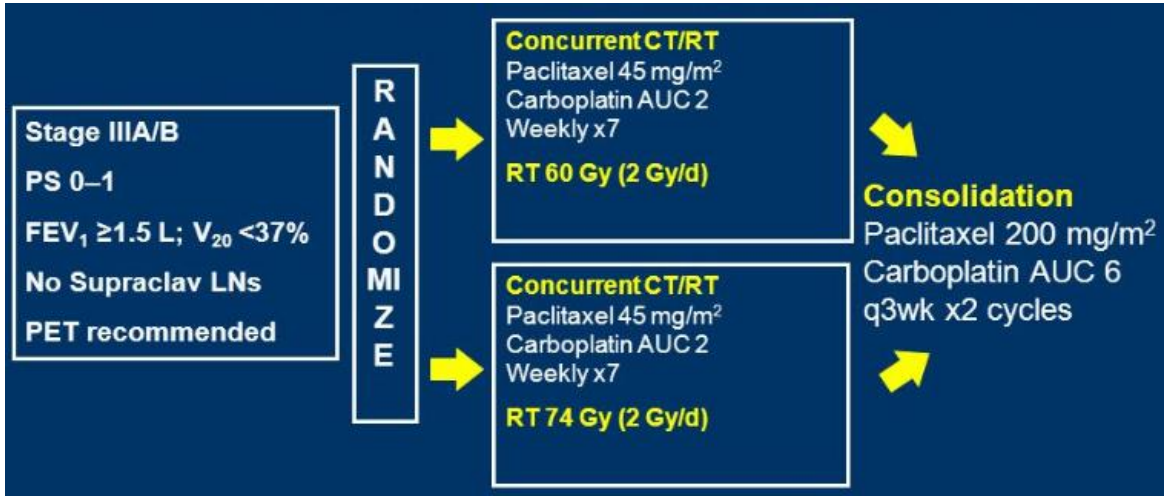


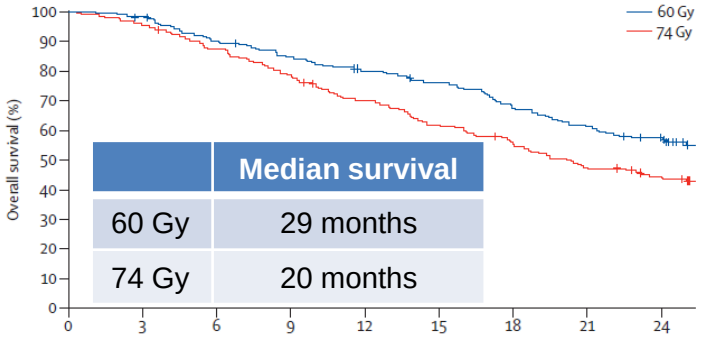
Gr 3 ~ 5

Toxicity	% of Patients PE/XRT	Docetaxel	Observation	*P**
Esophagitis	17.2	—	—	—
Infections	8.9	11.0	0.0	.003
Pneumonitis	—	9.6†	1.4	< .001
Treatment-related death	1.5	5.5	0.0	.058

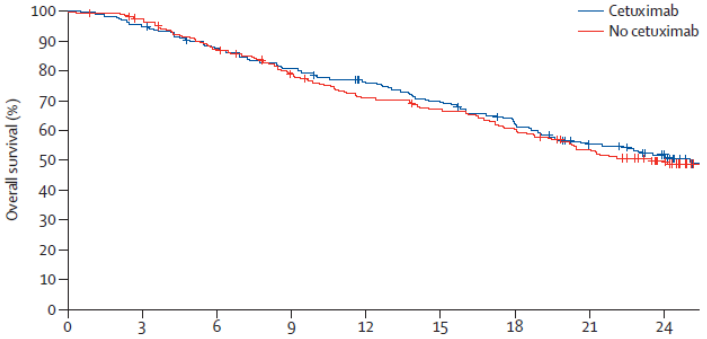
J Clin Oncol 26:5755-5760

RTOG 0617





	Median survival
60 Gy	29 months
74 Gy	20 months



Lancet Oncol 2015; 16: 187–99

Journal of Thoracic Oncology Vol. 12 No. 11: 1687-1695

Boost SBRTx study

Dose Level	Level 1	Level 2	Level 3	Level 4
Dose schema	9 Gy x 2 (2 fractions)	10 Gy x 2 (2 fractions)	6 Gy x 5 (5 fractions)	7 Gy x 5 (5 fractions)
Total Boost Dose	18 Gy	20 Gy	30 Gy	35 Gy
Cumulative BED	87 Gy	92.8 Gy	100.8 Gy	112.3 Gy

5-Year Survival (%)

Type	IA1	IA2	IA3	IB	IIA	IIB	IIIA	IIIB	IIIC	IVA	IVB
Clinical	92	83	77	68	60	53	36	26	13	10	0
Pathologic	90	85	80	73	65	56	41	24	12	-	-

SEER stage	5-year relative survival rate
Localized	61%
Regional	35%
Distant	6%
All SEER stages combined	24%

CHEST 2017; 151(1):193-203

Top 5 Advances in Lung Cancer Immunotherapy Over the Past Decade

1. Immunotherapy demonstrates a significant overall survival benefit in advanced NSCLC
2. Pembrolizumab beats first-line CTx in pts with NSCLC with high tumor PD-L1 expression (>50%) Keynote-24, 2016
3. Chemotherapy-immunotherapy combinations prove reliably superior to chemotherapy doublets alone Keynote-189, Keynote-407, 2018
4. Consolitation durvalumab significantly improves survival and defines a new standard of care in stage III unresectable NSCLC PACIFIC STUDY, 2017
5. Immune checkpoint inhibitor therapy is integrated with CTx as first-line treatment in extensive-stage SCLC

Pacific study

The NEW ENGLAND

ORIGINAL ARTICLE

Overall Survival with Durvalumab

S.J. Antoni
B.C. Cho
G. Os

Patient-re
chemoradi
lung cance

Rina Hui, Mustafa Özgü
Maike de Wit, Byoung Cl

IASLC

BRIEF REPORT

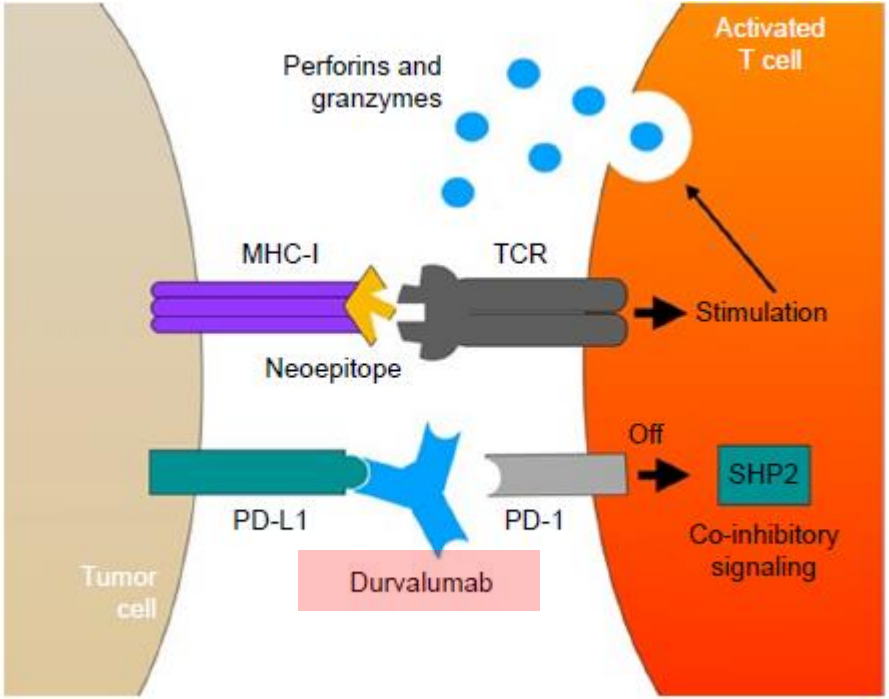
Check for updates

Three-Year Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC—Update from PACIFIC

Jhanelle E. Gray, MD,[a,*] Augusto Villegas, MD,[b] Davey Daniel, MD,[c,d] David Vicente, MD,[e] Shuji Murakami, MD,[f] Rina Hui, MD,[g,h] Takayasu Kurata, MD,[i] Alberto Chiappori, MD,[a] Ki Hyeong Lee, MD,[j] Byoung Chul Cho, MD,[k] David Planchard, MD,[l] Luis Paz-Ares, MD,[m,n] Corinne Faivre-Finn, MD,[o] Johan F. Vansteenkiste, MD,[p] David R. Spigel, MD,[d] Catherine Wadsworth, BVSc,[q] Maria Taboada, MSc,[r] Phillip A. Dennis, MD,[s] Mustafa Özgüroğlu, MD,[t] Scott J. Antonia, MD[a]

Durvalumab

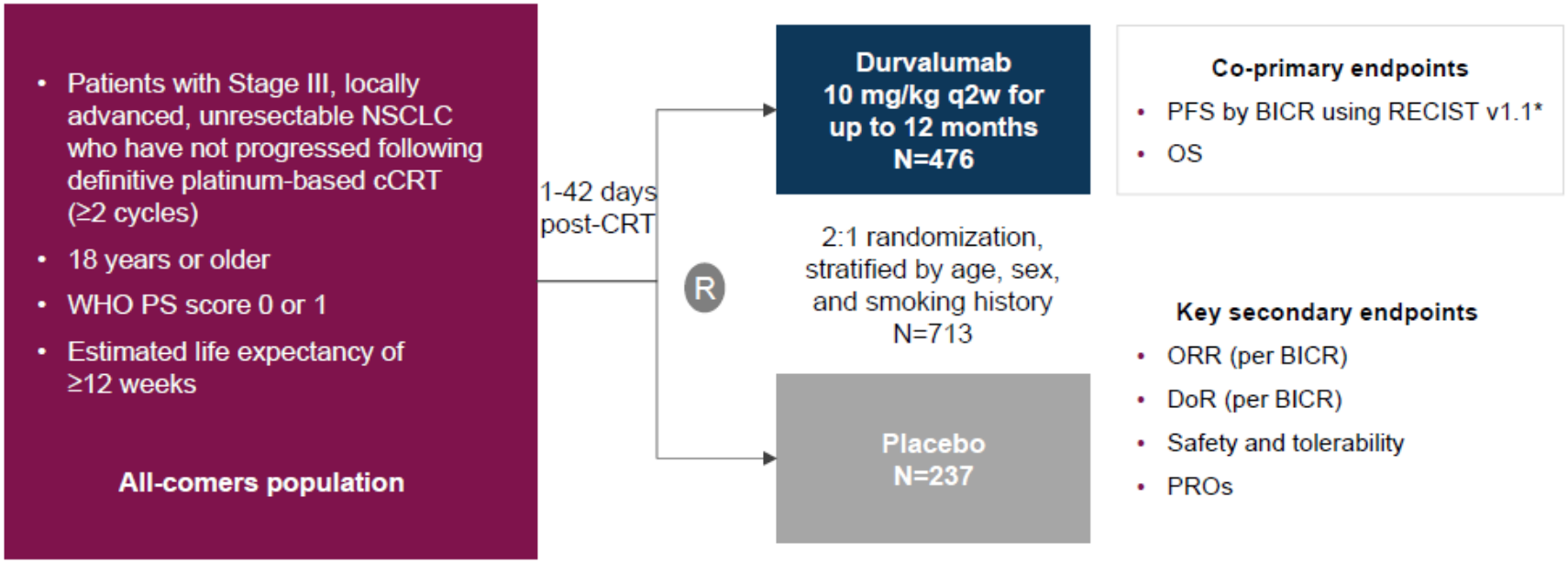
- Selective, high-affinity, human IgG1 monoclonal antibody that blocks programmed death ligand 1 (PD-L1) binding to programmed death 1 (PD-1) and CD80, allowing T cells to recognize and kill tumor cells



Drug Design, Development and Therapy 2018:12 209–215

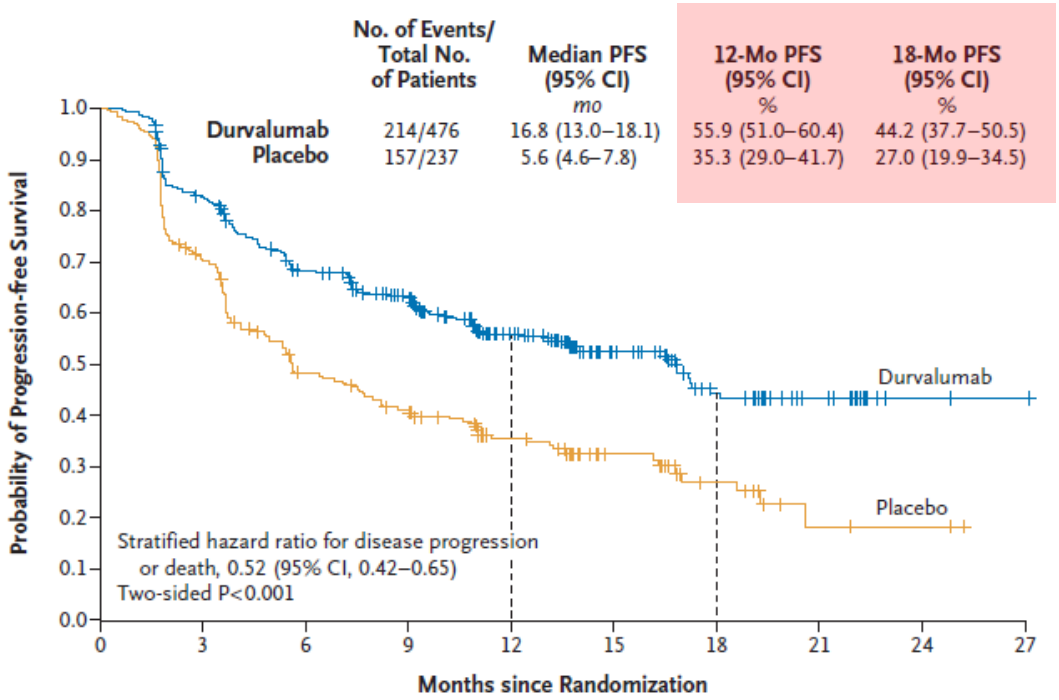
PACIFIC study

Phase III, Randomized, Double-Blind, Placebo-Controlled, Multicenter, International Study



N Engl J Med 2017;377:1919-29.

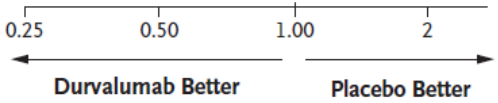
PACIFIC study



N Engl J Med 2017;377:1919-29.

Subgroup Analysis of Prognostic Factors for Progression-free Survival

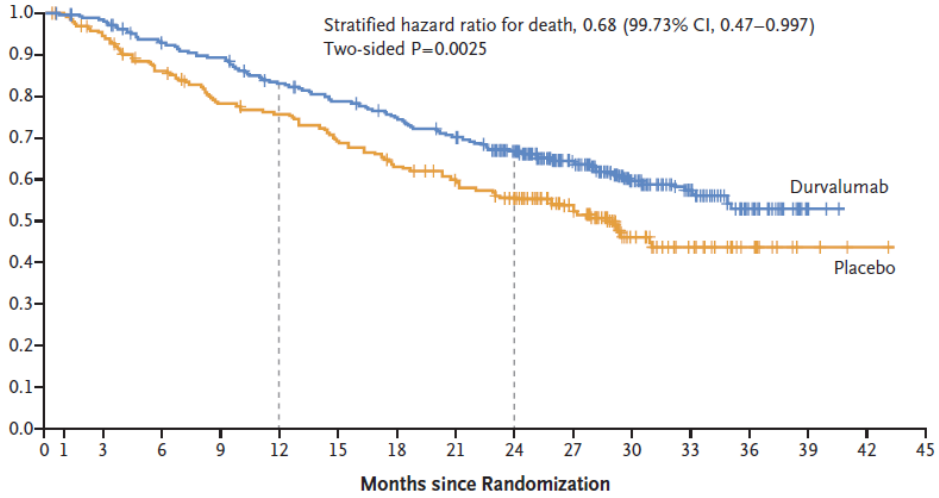
Subgroup	Durvalumab	Placebo	Unstratified Hazard Ratio for Disease Progression or Death (95% CI)
	no. of patients		
All patients	476	237	0.55 (0.45–0.68)
Sex			
Male	334	166	0.56 (0.44–0.71)
Female	142	71	0.54 (0.37–0.79)
Age at randomization			
<65 yr	261	130	0.43 (0.32–0.57)
≥65 yr	215	107	0.74 (0.54–1.01)
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)



N Engl J Med 2017;377:1919-29.

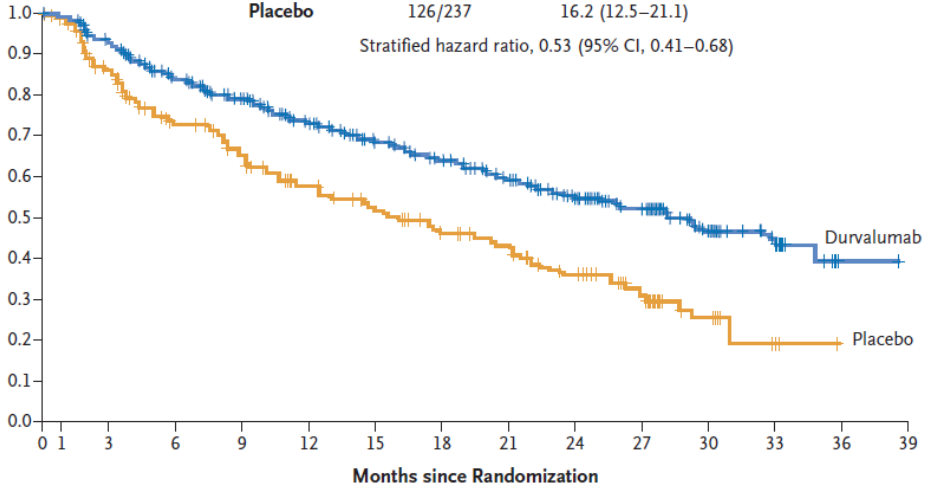
Overall Survival

	No. of Events/ Total No. of Patients	Median Overall Survival (95% CI)	12-Mo Overall Survival Rate (95% CI)	24-Mo Overall Survival Rate (95% CI)
		mo	%	%
Durvalumab	183/476	NR (34.7–NR)	83.1 (79.4–86.2)	66.3 (61.7–70.4)
Placebo	116/237	28.7 (22.9–NR)	75.3 (69.2–80.4)	55.6 (48.9–61.8)



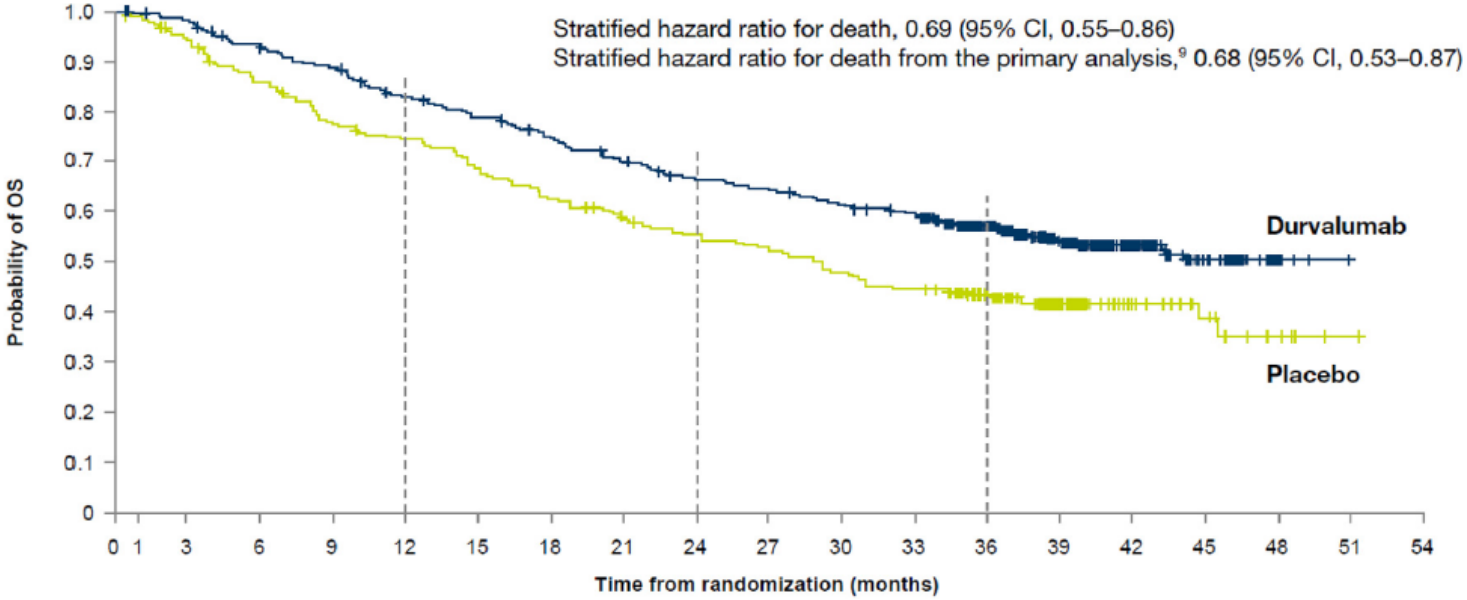
Median Time to Death or Distant Metastasis

	No. of Events/ Total No. of Patients	Median Time to Death or Distant Metastasis (95% CI)
		mo
Durvalumab	182/476	28.3 (24.0–34.9)
Placebo	126/237	16.2 (12.5–21.1)



N Engl J Med 2018;379:2342-50

Updated analysis of overall survival (OS) in the intention-to-treat population

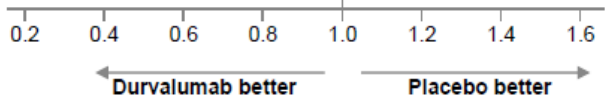


	No. of events/ total no. of patients (%)	Median OS, Months (95% CI)	12-month OS rate (95% CI)	24-month OS rate (95% CI)	36-month OS rate (95% CI)
Durvalumab	210/476 (44.1)	NR (38.4-NR)	83.1 (79.4–86.2)	66.3 (61.8-70.4)	57.0 (52.3-61.4)
Placebo	134/237 (56.5)	29.1 (22.1-35.1)	74.6 (68.5-79.7)	55.3 (48.6-61.4)	43.5 (37.0-49.9)

Journal of Thoracic Oncology Vol. 15 No. 2: 288-293

Overall Survival

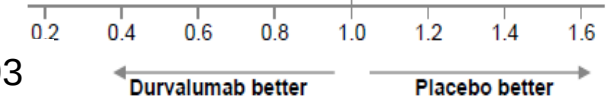
	No. of events / no. of patients (%)		Unstratified hazard ratio for death (95% CI)
	Durvalumab	Placebo	
All patients	210/476 (44.1)	134/237 (56.5)	0.67 (0.54–0.84)
Sex			
Male	159/334 (47.6)	96/166 (57.8)	0.74 (0.57–0.95)
Female	51/142 (35.9)	38/71 (53.5)	0.53 (0.35–0.81)
Age at randomization			
<65 years	102/261 (39.1)	68/130 (52.3)	0.61 (0.45–0.83)
≥65 years	108/215 (50.2)	66/107 (61.7)	0.75 (0.56–1.03)
Smoking status			
Smoker	193/433 (44.6)	121/216 (56.0)	0.70 (0.56–0.88)
Non-smoker	17/43 (39.5)	13/21 (61.9)	0.44 (0.21–0.90)
NSCLC disease stage			
Stage IIIA	114/252 (45.2)	80/125 (64.0)	0.61 (0.46–0.81)
Stage IIIB	90/212 (42.5)	52/107 (48.6)	0.75 (0.53–1.05)
Tumor histologic type			
Squamous histology	114/224 (50.9)	60/102 (58.8)	0.76 (0.55–1.03)
All other histology	96/252 (38.1)	74/135 (54.8)	0.59 (0.43–0.80)
Best response to prior treatment			
Complete response	3/9 (33.3)	3/7 (42.9)	
Partial response	95/237 (40.1)	58/112 (51.8)	0.68 (0.49–0.94)
Stable disease	107/223 (48.0)	71/115 (61.7)	0.65 (0.48–0.88)
Type of prior chemotherapy			
Gemcitabine-based	5/9 (55.6)	2/5 (40.0)	
Non-gemcitabine-based	205/467 (43.9)	132/232 (56.9)	0.66 (0.53–0.82)
Cisplatin	110/266 (41.4)	69/129 (53.5)	0.64 (0.47–0.87)
Carboplatin	94/199 (47.2)	60/102 (58.8)	0.75 (0.54–1.03)
Cisplatin and carboplatin	4/8 (50.0)	4/5 (80.0)	



Journal of Thoracic Oncology Vol. 15 No. 2: 288-293

Overall Survival

	No. of events / no. of patients (%)		Unstratified hazard ratio for death (95% CI)
	Durvalumab	Placebo	
All patients	210/476 (44.1)	134/237 (56.5)	0.67 (0.54–0.84)
Last radiation to randomization			
<14 days	46/120 (38.3)	40/62 (64.5)	0.43 (0.28–0.66)
≥14 days	164/356 (46.1)	94/175 (53.7)	0.79 (0.61–1.02)
WHO performance status			
Normal	95/234 (40.6)	56/114 (49.1)	0.77 (0.55–1.07)
Restricted	115/242 (47.5)	78/123 (63.4)	0.58 (0.44–0.78)
Region			
Asia	43/109 (39.4)	31/68 (45.6)	0.73 (0.46–1.16)
Europe	103/217 (47.5)	55/102 (53.9)	0.83 (0.60–1.15)
North and South America	64/150 (42.7)	48/67 (71.6)	0.44 (0.30–0.64)
Race			
White	160/337 (47.5)	95/157 (60.5)	0.69 (0.54–0.90)
Black/African-American	4/12 (33.3)	2/2 (100.0)	
Asian	44/120 (36.7)	33/72 (45.8)	0.67 (0.42–1.05)
Other	2/6 (33.3)	4/6 (66.7)	
EGFR mutation			
Positive	13/29 (44.8)	6/14 (42.9)	
Negative	136/317 (42.9)	95/165 (57.6)	0.63 (0.49–0.82)
Unknown	61/130 (46.9)	33/58 (56.9)	0.75 (0.49–1.15)
PD-L1 status			
≥25%	41/115 (35.7)	23/44 (52.3)	0.50 (0.30–0.83)
<25%	90/187 (48.1)	53/105 (50.5)	0.89 (0.63–1.25)
1–<24% (posthoc analysis)	43/97 (44.3)	26/47 (55.3)	0.67 (0.41–1.10)
≥1% (posthoc analysis)	84/212 (39.6)	49/91 (53.8)	0.59 (0.41–0.83)
<1% (posthoc analysis)	47/90 (52.2)	27/58 (46.6)	1.14 (0.71–1.84)
Unknown	79/174 (45.4)	58/88 (65.9)	0.60 (0.43–0.84)



Journal of Thoracic Oncology Vol. 15 No. 2: 288-293

Adverse Events

Respiratory Sx

GI Sx

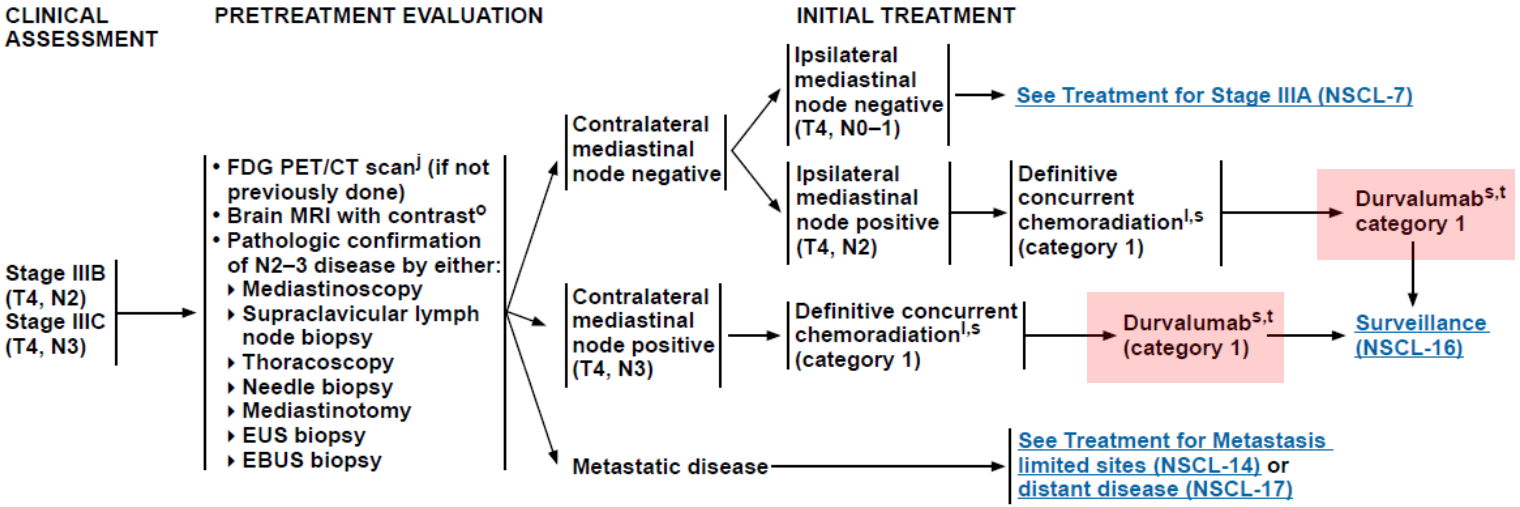
	Durvalumab (N=475)		Placebo (N=234)	
	Any Grade*	Grade 3 or 4	Any Grade*	Grade 3 or 4
	number of patients with event (percent)			
Any event	460 (96.8)	142 (29.9)	222 (94.9)	61 (26.1)
Cough	168 (35.4)	2 (0.4)	59 (25.2)	1 (0.4)
Pneumonitis or radiation pneumonitis†	161 (33.9)	16 (3.4)	58 (24.8)	6 (2.6)
Fatigue	113 (23.8)	1 (0.2)	48 (20.5)	3 (1.3)
Dyspnea	106 (22.3)	7 (1.5)	56 (23.9)	6 (2.6)
Diarrhea	87 (18.3)	3 (0.6)	44 (18.8)	3 (1.3)
Pyrexia	70 (14.7)	1 (0.2)	21 (9.0)	0
Decreased appetite	68 (14.3)	1 (0.2)	30 (12.8)	2 (0.9)
Nausea	66 (13.9)	0	31 (13.2)	0
Pneumonia	62 (13.1)	21 (4.4)	18 (7.7)	9 (3.8)
Arthralgia	59 (12.4)	0	26 (11.1)	0
Pruritus	58 (12.2)	0	11 (4.7)	0
Rash	58 (12.2)	1 (0.2)	17 (7.3)	0
Upper respiratory tract infection	58 (12.2)	1 (0.2)	23 (9.8)	0
Constipation	56 (11.8)	1 (0.2)	20 (8.5)	0
Hypothyroidism	55 (11.6)	1 (0.2)	4 (1.7)	0
Headache	52 (10.9)	1 (0.2)	21 (9.0)	2 (0.9)
Asthenia	51 (10.7)	3 (0.6)	31 (13.2)	1 (0.4)
Back pain	50 (10.5)	1 (0.2)	27 (11.5)	1 (0.4)
Musculoskeletal pain	39 (8.2)	3 (0.6)	24 (10.3)	1 (0.4)
Anemia	36 (7.6)	14 (2.9)	25 (10.7)	8 (3.4)

N Engl J Med 2017;377:1919-29.

National Comprehensive Cancer Network®

NCCN Guidelines Version 5.2020
Non-Small Cell Lung Cancer

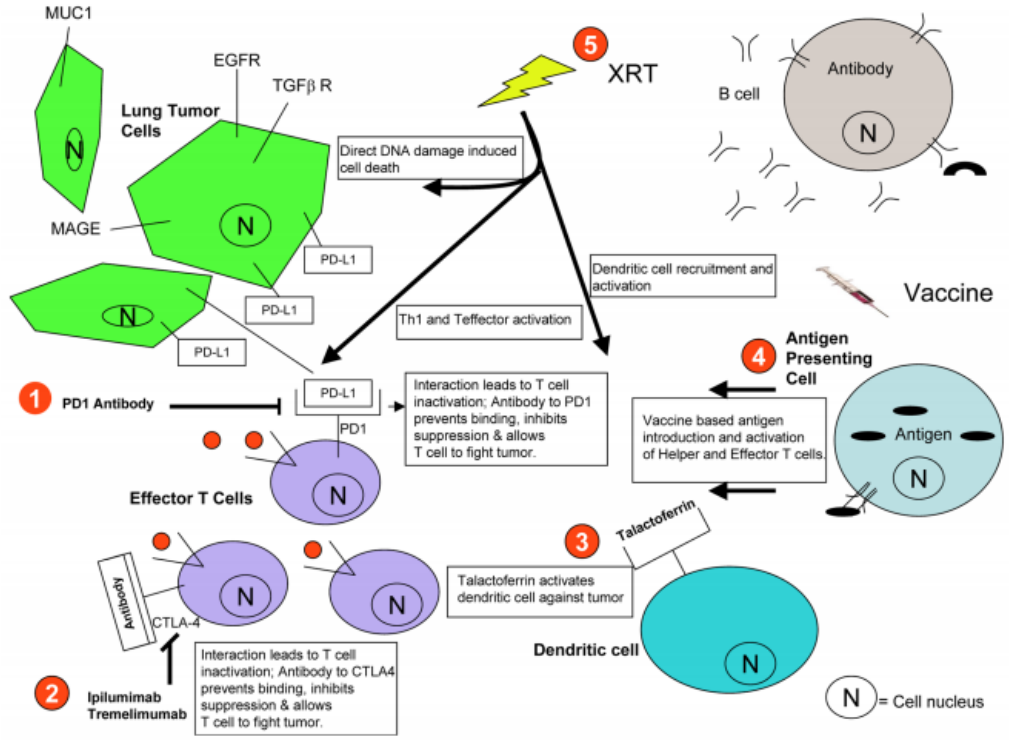
NCCN Guidelines Index
Table of Contents
Discussion

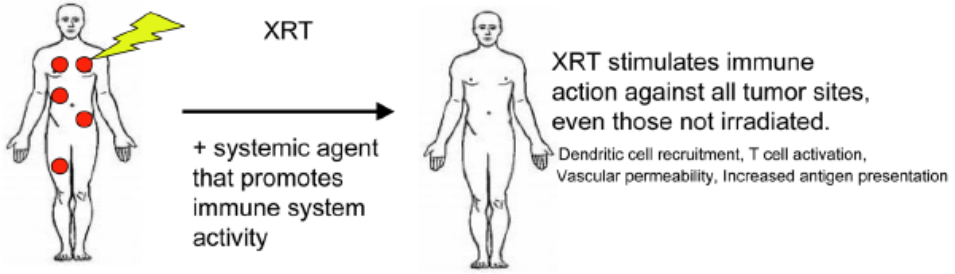


항암요법	투여대상
durvalumab[주1]	PD-L1 발현 양성(발현 비율 ≥ 1%[주5])이면서 백금 기반 동시적 항암화학방사선요법 2주기 이상 투여 후 질병진행이 없는 안정병변 이상의 절제 불가능한 국소 진행성(stage III)으로 CCRT 치료 종료 이후 42일 내에 투여하는 경우 ※급여 인정 기간은 12개월로 함(주1항 최대 2년 적용 불가) ※이전 PD-1 inhibitor 등 면역관문억제제 치료를 받지 않은 경우에 한함
(제2020-81호: 2020.4.1)	

1. 방사선종료일 기준 42일이내
2. 방사선은 54Gy이상 투여
3. Weekly regimen일 경우 4주기 이상 투여
4. Sequential ChemoRTx인 경우 급여 안됨
5. Durvalumab fail -> 다른 약제도 안됨

RTx may promote tumor immunogenicity



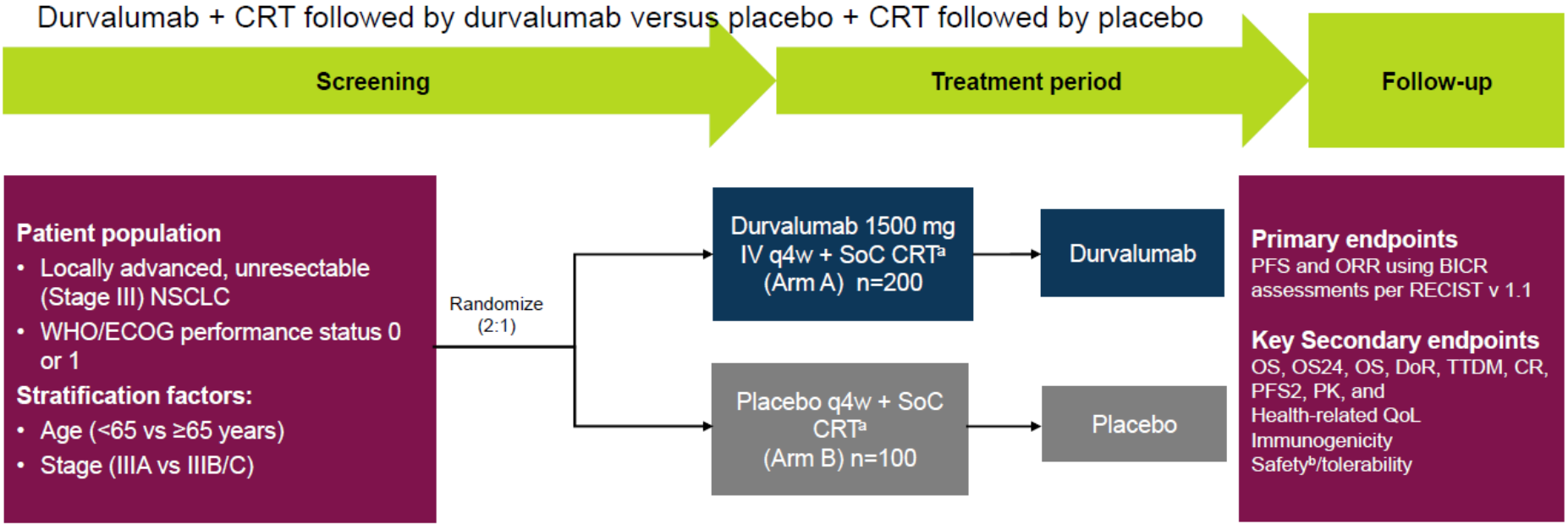


Cancer J. 2013 ; 19(3): 247–262

J Thorac Dis 2018;10(3):1198-1200

PACIFIC 2 study

NCT03519971, 2018.3 ~ 2023.11

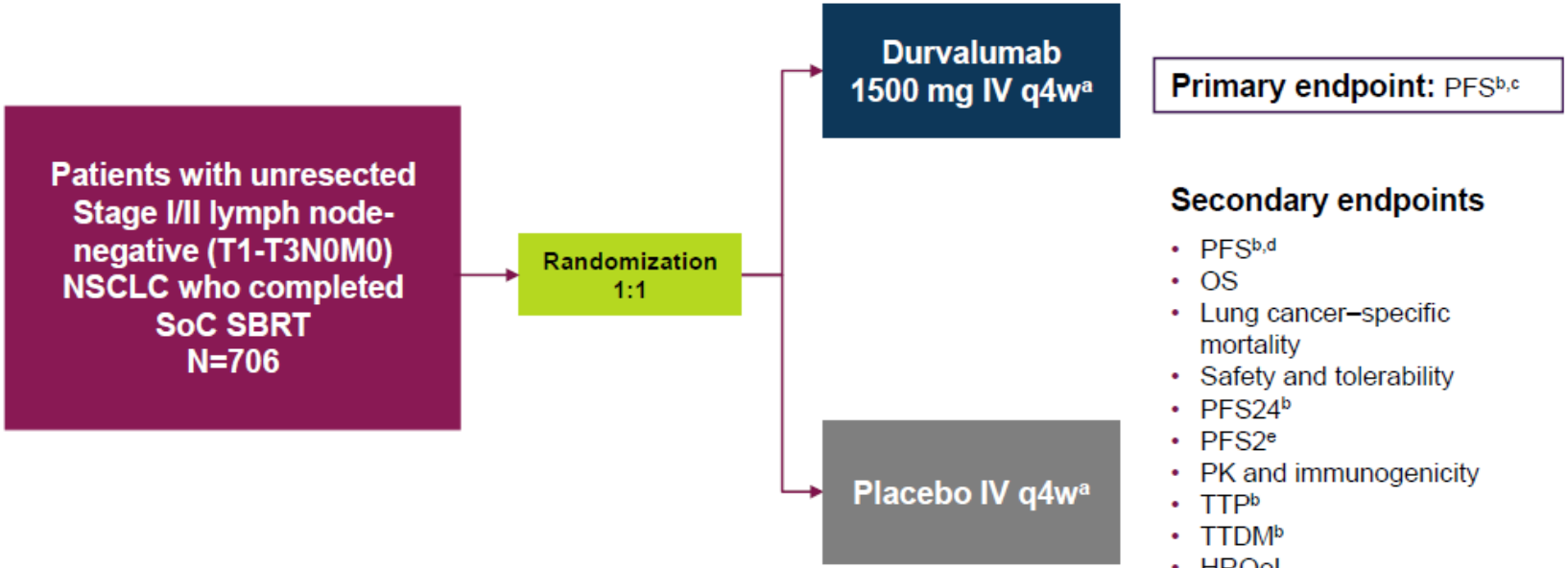


10.1200/JCO.2019.37.15_suppl.TPS8573 Journal of Clinical Oncology 37, no. 15_suppl

PACIFIC 4 study

NCT03833154, 2019.3 ~ 2025.10

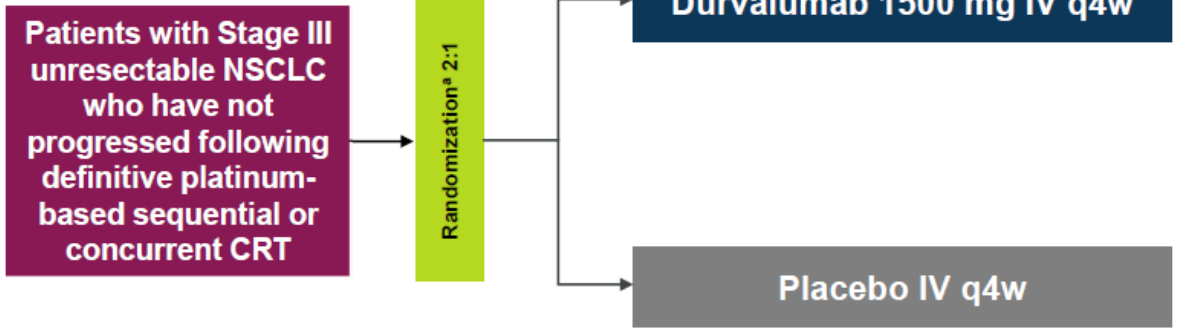
Phase 3, randomized, double-blind, placebo-controlled, multicenter study



PACIFIC 5 study

NCT03706690, 2018.11 ~ 2025.1

Phase 3, randomized, double-blind, placebo-controlled, multicenter study



Treatment until clinical progression/deterioration or confirmed radiological progression

Primary Endpoints

- PFS[b]

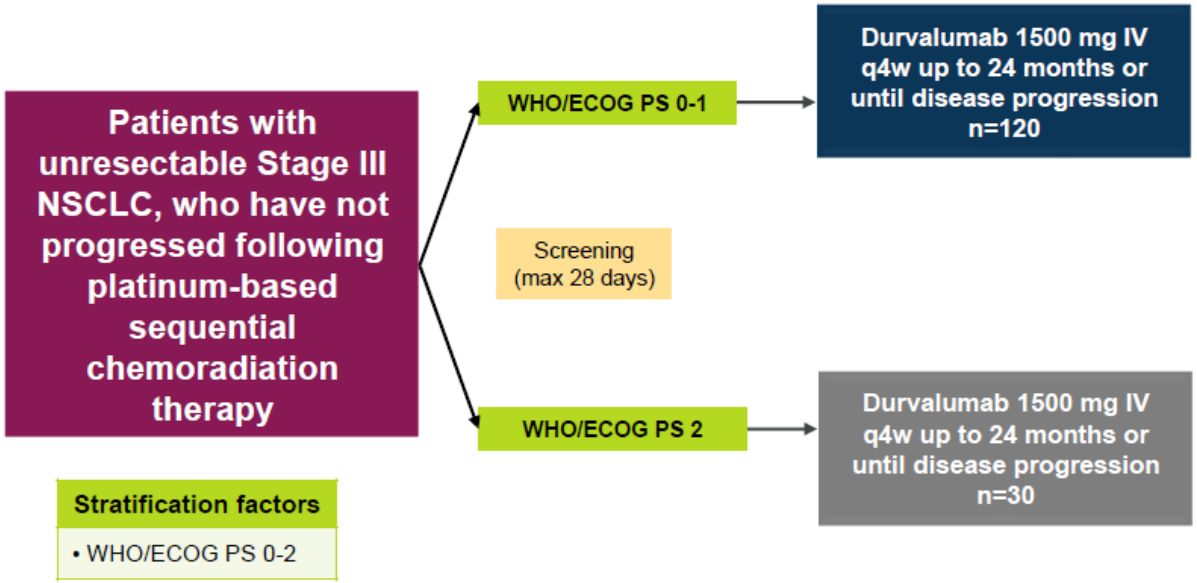
Secondary Endpoints

- OS
- OS24
- ORR[b]
- DoR[b]
- PFS2[c]
- PFS12[b] and PFS18[b]
- TTDM[b]
- Safety and tolerability (assessed by CTCAE version 5.0)
- PK and immunogenicity
- IHC analysis of tumoral PD-L1 expression and spatial distribution within the tumor microenvironment relative to efficacy outcomes (OS, PFS, ORR)

PACIFIC 6 study

NCT03693300, 2019.04 ~ 2023.2

Phase 2, open-label, multicenter study



Primary Endpoints

- Safety and tolerability (occurrence of Grade 3 and Grade 4 TRAEs)

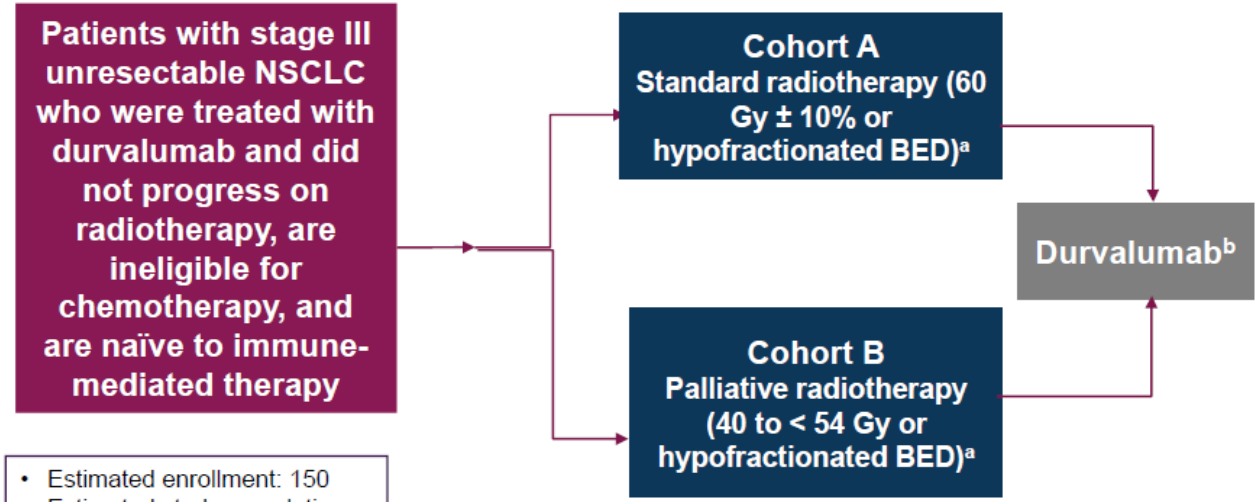
Secondary Endpoints

- mPFS[a], PFS12, PFS24
- mOS, OS12, OS24, OS36
- ORR[a]
- DoR[a]
- Number of patients with AE, SAEs, AESIs, imAEs
- Other safety and tolerability parameters

DUART study

NCT04249362, 2020.09 ~ 2022.6

Phase 2, open-label, single arm, multicenter study, international study



Primary endpoint

Safety and tolerability profile as defined by Grade 3 and Grade 4 PRAEs

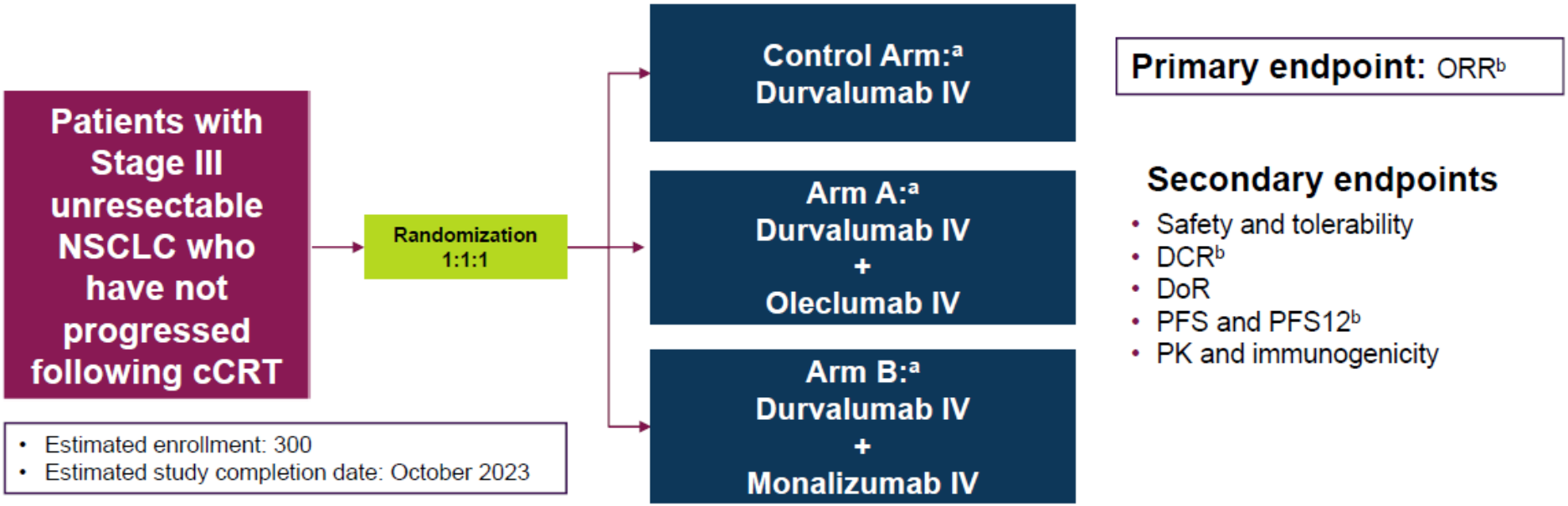
Key secondary endpoints

- Median PFS, PFS at 6 months, PFS at 12 months
- Median OS, OS at 12 months
- ORR
- DoR
- Lung cancer mortality
- Safety and tolerability

COAST study

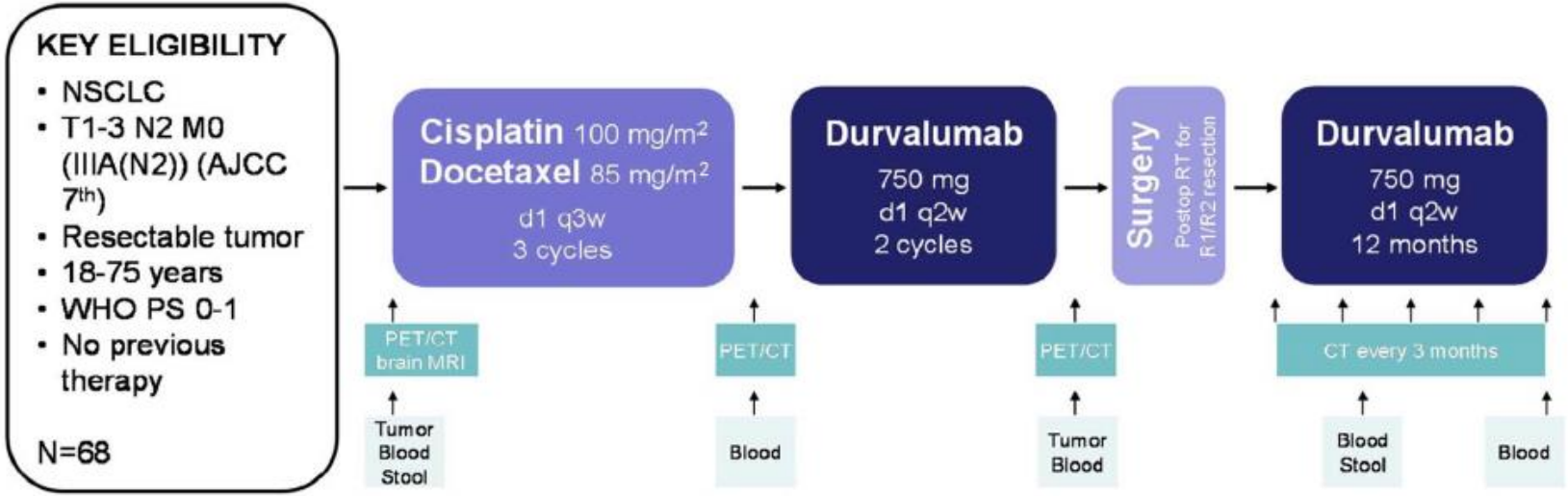
NCT03822351, 2018.12 ~ 2023.10

Phase 2, open-label, randomized, multicenter study, multidrug platform study



SAKK 16/14: Durvalumab + neoadjuvant chemo in patients with stage IIIA(N2) NSCLC

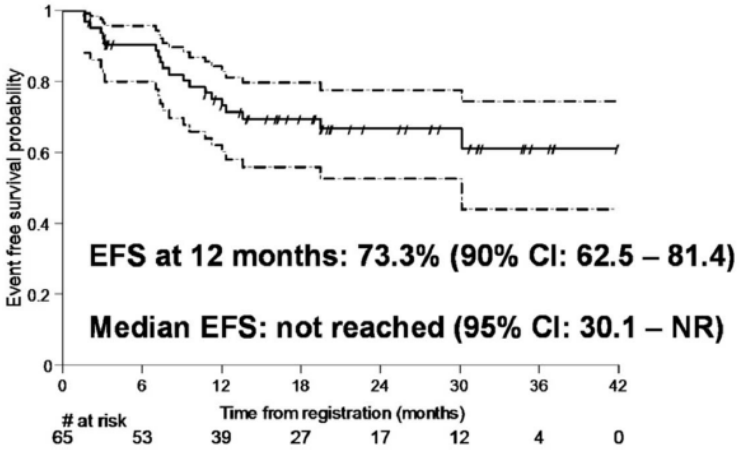
Phase 2, open-label, single arm study

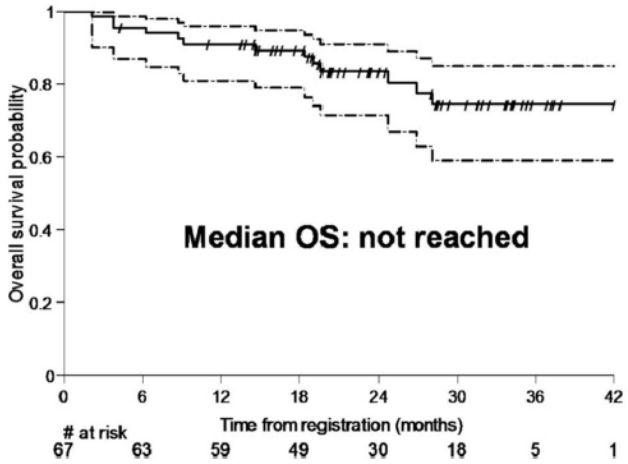


Primary endpoint: Event-free survival at 12 months

Rothschild et al, ASCO 2020, abstract #9016

- 35 males, 32 females
- Median age was 61 yrs
- 52 pts (77.6%) had a WHO PS of 0.
- 95.5% were current or former smokers.
- adenocarcinoma (55.2%), squamous cell histology (32.8%).
- 81.1% of pts underwent resection.
- Pneumonectomy was performed in 5 pts (9.1%), 43 pts underwent lobectomy and 7 pts bilobectomy
- 30-day postoperative mortality was observed in one patient (1.8%)





Rothschild et al, ASCO 2020, abstract #9016

Clinical studies evaluating immunotherapy-radiotherapy combinations in locally advanced NSCLC

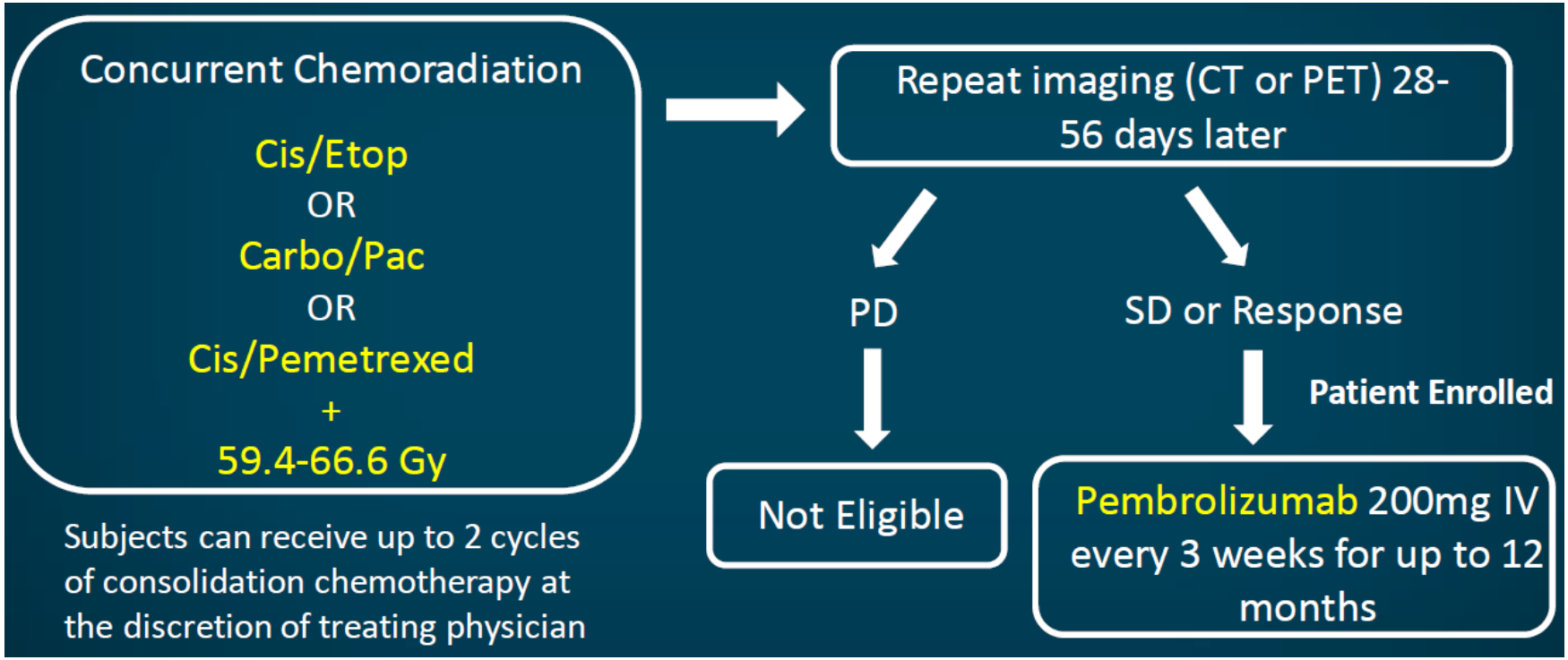
References	Phase	NSCLC setting (accrual)	Immunotherapy	Radiotherapy	Design	Primary outcome
ANTIGEN-SPECIFIC IMMUNOTHERAPY						
Ohyanagi et al. (48)	I	Stage III, unresectable, CR/PR/SD after CRT ($N = 6$)	Tecemotide	≥50 Gy, sequentially or concurrently with CT	CRT > tecemotide[b]	≥1 AE in 83.3% of pts, all G1
Butts et al. (49)	IIB	Stage IIIB, CR/PR/SD after CRT ($N = 65$)[c]	Tecemotide	Dose NS, sequentially or concurrently with CT	• CRT > BSC + tecemotide[b] • CRT > BSC	Median OS 30.6 vs. 13.3 m (HR 0.548, 95% CI 0.301–0.999)[c]
Mitchell et al. (50) (START)	III	Stage III, unresectable, CR/PR/SD after CRT ($N = 1,239$)	Tecemotide	≥50 Gy, sequentially or concurrently with CT	• CRT > tecemotide[b] • CRT > placebo	Median OS 58.7 vs. 57.3 m (HR 0.89; $p = 0.111$)
Patel et al. (51)	II	Stage III, unresectable, non-squamous ($N = 33$)	Tecemotide	66 Gy/33 fx, concurrently with CT	CRT > CT > tecemotide + bevacizumab	≥G3 toxicity in 11 pts, G3 hypertension ($n = 6$)
Brunsvig et al. (52)	II	Stage III, inoperable ($N = 23$)	GV1001 + GM-CSF	60 Gy/30 fx, concurrently with CT	CRT > GV1001 + GM-CSF	No treatment-related SAE
Pujol et al. (53)	I/II	Stage III, unresectable, MAGE A3-positive ($N = 12$)[c]	MAGE-A3 immunotherapeutic	NS	CT > RT > MAGE-A3	Treatment-related AE in 7/12 pts; all <G3. Induced CD4+ and CD8+ T-cell response in 5/6 and 2/6 pts resp.[c]
IMMUNE CHECKPOINT BLOCKADE						
Antonia et al. (31) (PACIFIC)	III	Stage III, unresectable ($N = 713$)	Durva	54–66 Gy, concurrently with CT	• CRT > durva • CRT > placebo	Median OS NR vs. 28.7 m (HR 0.68; $p = 0.0025$); median PFS 17.2 vs. 5.6 m (HR 0.51)
Durm et al. (54)	II	Stage III, unresectable, CR/PR/SD after CRT (N=92)	Pembro	59–66.6 Gy, concurrently with CT	CRT > pembro	Median TMDD 22.4 m (95% CI 17.9-NR)
Lin et al. (55) (DETERRED)	II	Stage III, unresectable ($N = 40$)	Atezo	60–66 Gy/30–33 fx, concurrently with CT	• CRT > CT + atezo • CRT + atezo > CT + atezo	≥G3 atezo-related toxicity in 6 pts; G5 TE fistula ($n = 1$). G3 radiation pneumonitis ($n = 1$)
Peters et al. (56, 57) (NICOLAS)	IA/II	Stage III, unresectable ($N = 79$)	Nivo	• 66 Gy/33 fx, concurrently with CT • 66 Gy/24 fx, sequentially after CT	CRT + nivo > nivo	No ≥G3 post-RT pneumonitis, 1-year PFS 50%

Front. Med. 6:244.

Phase II Study From the Hoosier Cancer Research Network LUN 14-179

Ongoing; Sep, 2021

TMDD, PFS, and OS

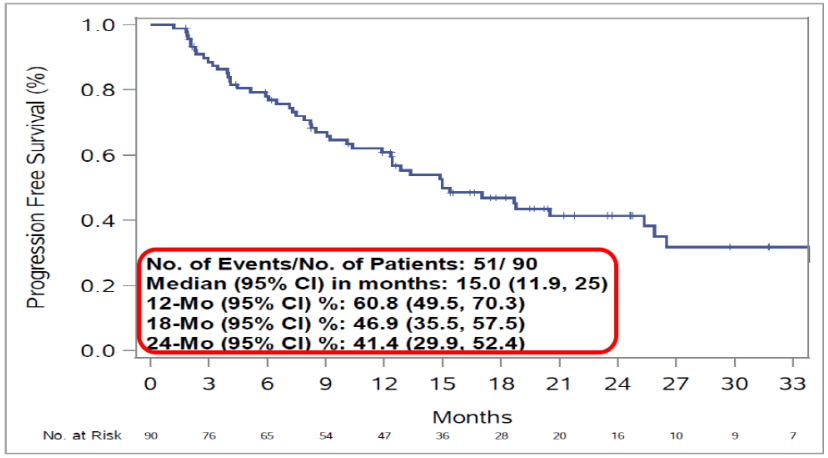


Clinical Lung Cancer, Vol. 21, No. 3, 288-93

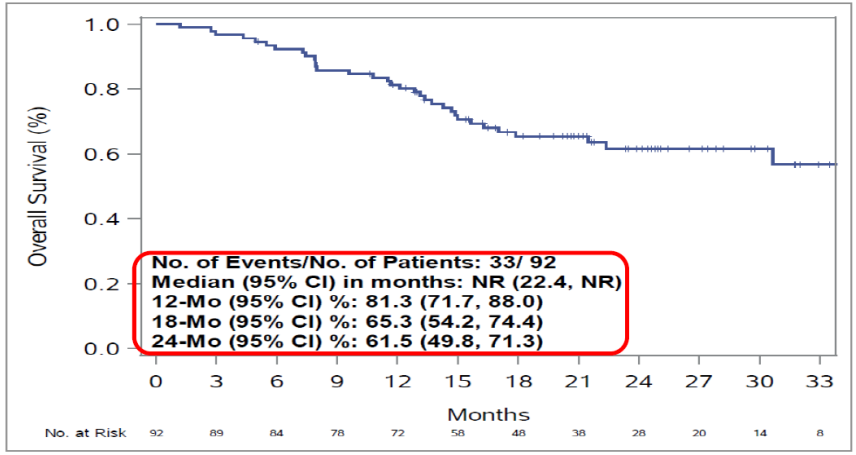
Characteristic	Value
Mean Age (SD), Years	64 (8.6)
Sex	
Male	59 (64)
Female	33 (36)
Stage	
IIIA	55 (60)
IIIB	37 (40)
Histology of NSCLC	
Nonsquamous	51 (55)
Squamous	41 (45)
Distant Metastasis or Death on Follow-up[a]	
Present	40 (43)
Not present	52 (57)

Clinical Lung Cancer, Vol. 21, No. 3, 288-93

Progression free survival



Overall Survival



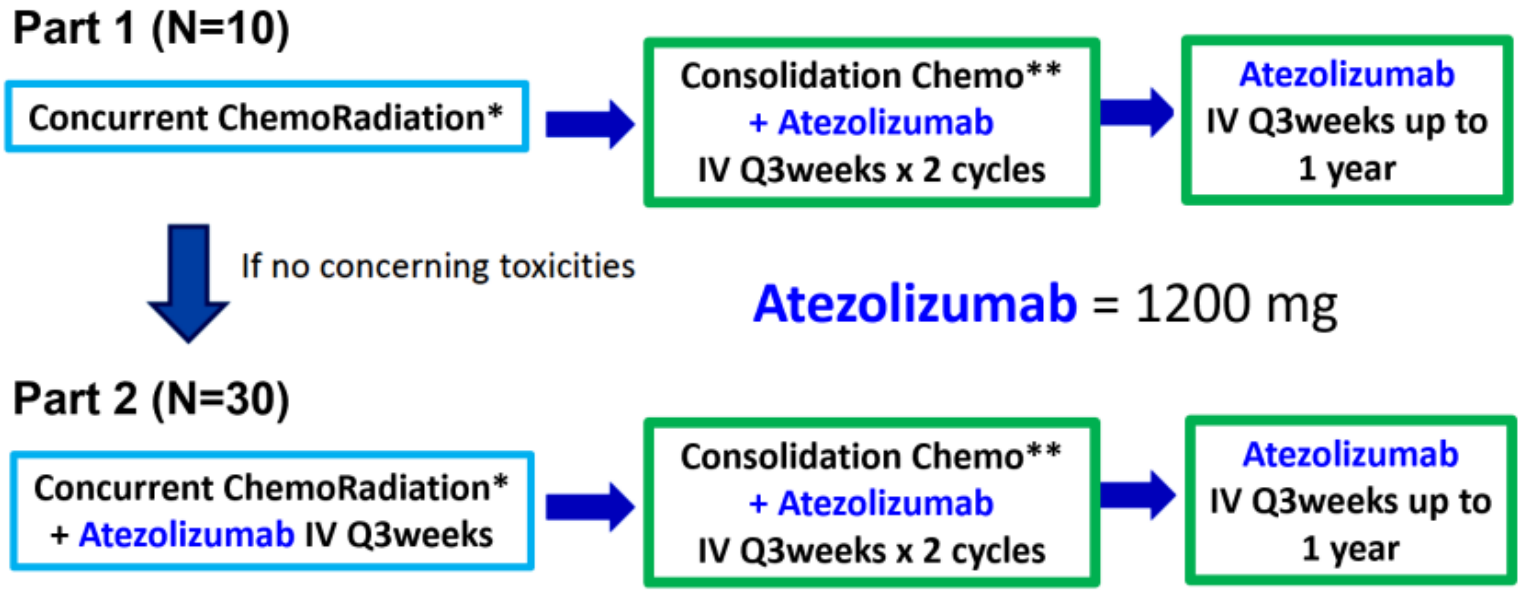
Pembrolizumab vs Durvalumab

Endpoint	LUN 14-179 (Pembrolizumab)	PACIFIC (Durvalumab)	PACIFIC (Placebo)
Median Follow	23.9 months	35.2 months	35.2 months
Time to Metastatic Disease or Death			
Median	22.4 months	28.3 months	16.2 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	29.1 month
12-month	81.0%	83.1%	74.6%
24-month	61.9%	66.3%	55.3%

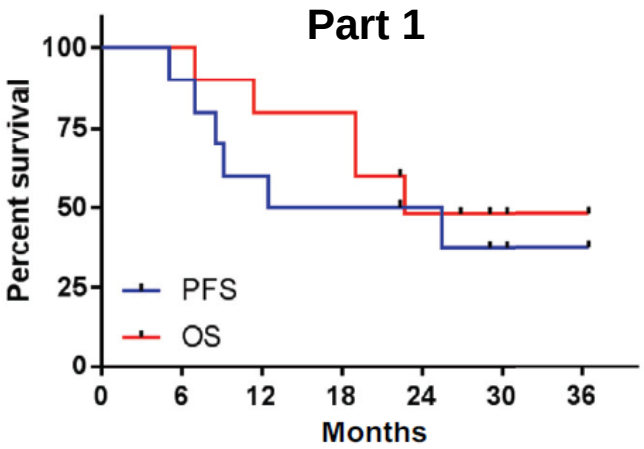
Journal of Thoracic Oncology Vol. 15 No. 2: 288-293. Clinical Lung Cancer, Vol. 21, No. 3, 288-93
N Engl J Med 2017;377:1919-29. N Engl J Med 2018;379:2342-50

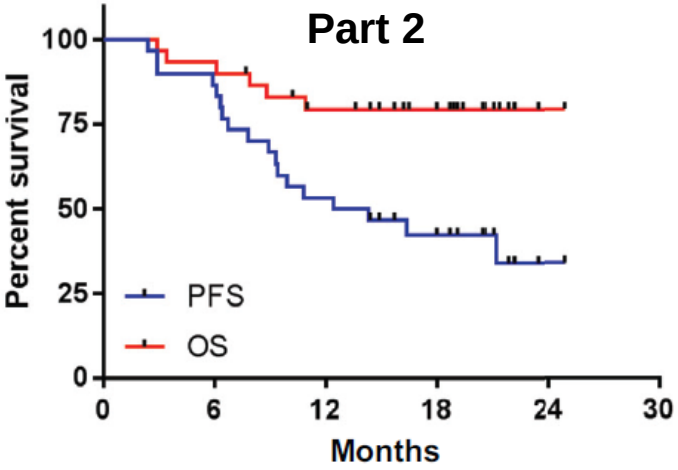
DETERRED trial (Atezolizumab)

Phase II, 2016.2 ~ 2018.4

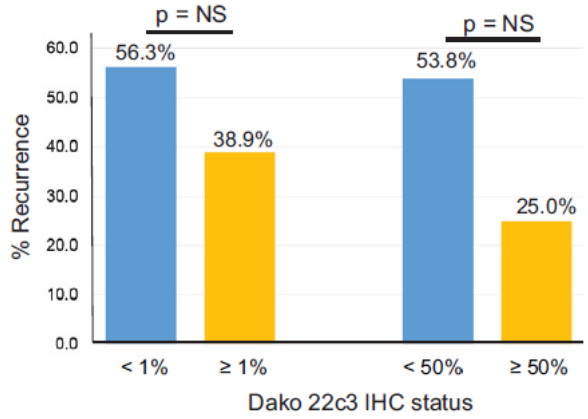


Journal of Thoracic Oncology Vol. 15 No. 2: 248-257





	Part 1	Part 2
mFollow-up (month)	22.5	15.1
mPFS (month)	18.6	13.2
mOS (month)	22.8	NR



Journal of Thoracic Oncology Vol. 15 No. 2: 248-257

DETERRED trial (Atezolizumab)

- Concurrent immunotherapy with atezolizumab and chemoradiation therapy can be administered safely without excessive toxicities
- Grade 3+ pneumonitis rate is low acceptable and does not appear to be enhanced with concurrent atezolizumab, but grade 3 atezo attributable events occurred in ~ 23%
- Early efficacy analysis shows promising results in the concurrent arm with atezolizumab
- Additional follow up is needed to determine longterm efficacy
- Given early results in Part 2, a head-to-head comparison of consolidation vs consolidation and concurrent immunotherapy in setting of standard CRT is mandatory

Pembrolizumab vs Durvalumab vs Atezolizumab

	Phase III	Phase II	Phase II
	PACIFIC (Durvalumab)	**LUN 14-179 (Pembrolizumab)**	**DETERRED (Atezolizumab)**
mPFS	16.8 months	15.0 months	14.6 months

Stage II 15%

	PACIFIC (Durvalumab)	LUN 14-179 (Pembrolizumab)	DETERRED (Atezolizumab)
Any event (Grade 3+)	142/475 (29.9%)	53/92 (57.6%)	32/40 (80%)

NICOLAS trial

Single arm, Phase II

2015.11 ~ 2020.2

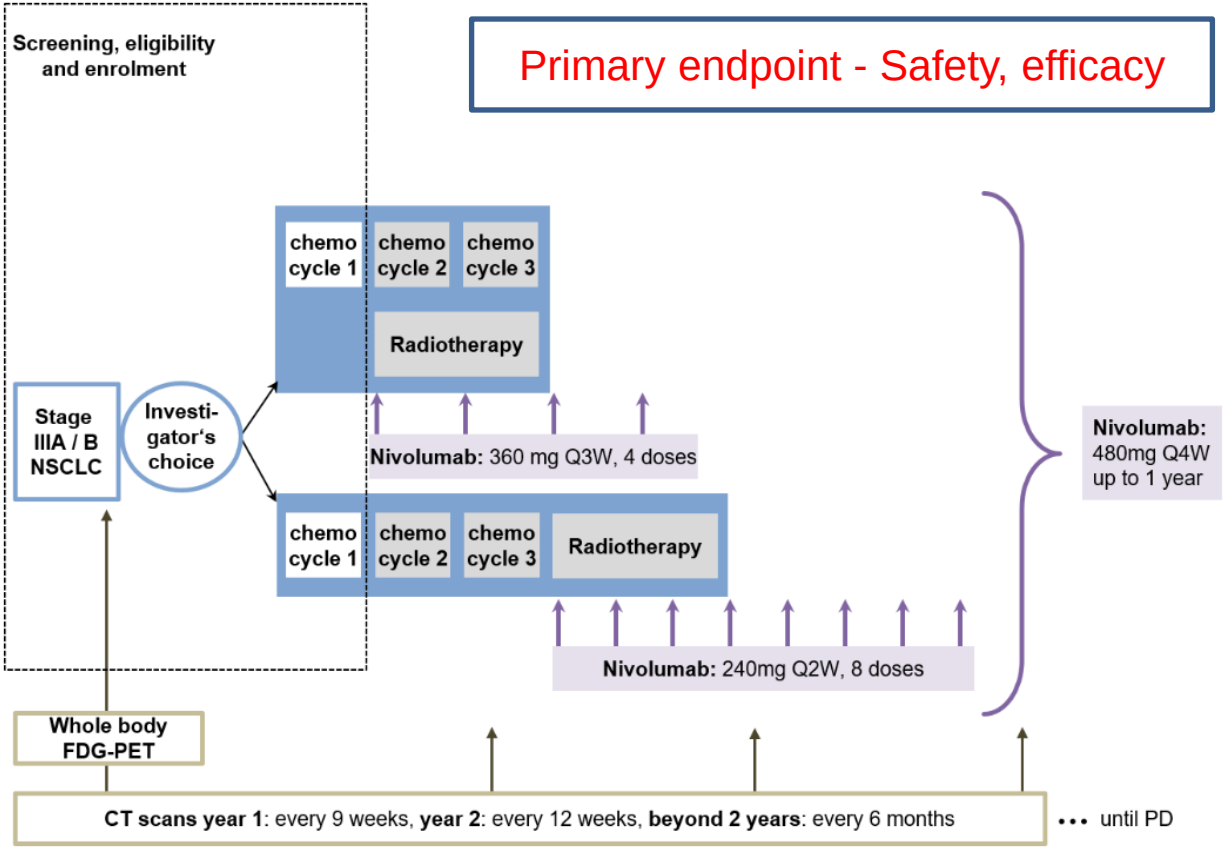
79 patients

67% male

Median age: 62 years

Median f/u: 16.4 months

Stage IIIB (64.0%)



8 pts – pneumonitis (gr 3+)

AE - mild (55%), moderate (30.3%)

severe (10.9%). life-threatening events (2.8%)

Lung Cancer 133 (2019) 83–87

Annals of Oncology 30 (Supplement 5): v591–v601, 2019

Pembrolizumab vs **Durvalumab** vs **Atezolizumab** vs **Nivolumab**

	Phase III	Phase II	Phase II	Phase II
	PACIFIC (Durvalumab)	**LUN 14-179 (Pembrolizumab)**	**DETERRED (Atezolizumab)**	**NICOLAS (Nivolumab)**
mPFS	16.8 months	15.0 months	14.6 months	12.4 months
Stage IIIB	212/476 (44.5%)	37/90 (40%)	14/40 (35%)	50/79 (64%)

Summary

- Consolidation immunotherapy

	Median PFS (month)	Median OS (month)
Durvalumab	16.8	NR
Placebo	5.6	29.1

- Pembrolizumab consolidation performs on par with durvalumab albeit with slightly higher pulmonary toxicity; OS data exceed historic controls
- Atezolizumab/Nivolumab concurrently with CT/RT appears safe; efficacy data VERY preliminary
- Q – Do all PD-1/PD-L1 inhibitors have similar efficacy and toxicity – Optimal duration of consolidation immunotherapy – Consolidation with combination IO agents – Role, if any, of biomarkers


Thank you