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Evolving Landscape of Stage III NSCLC

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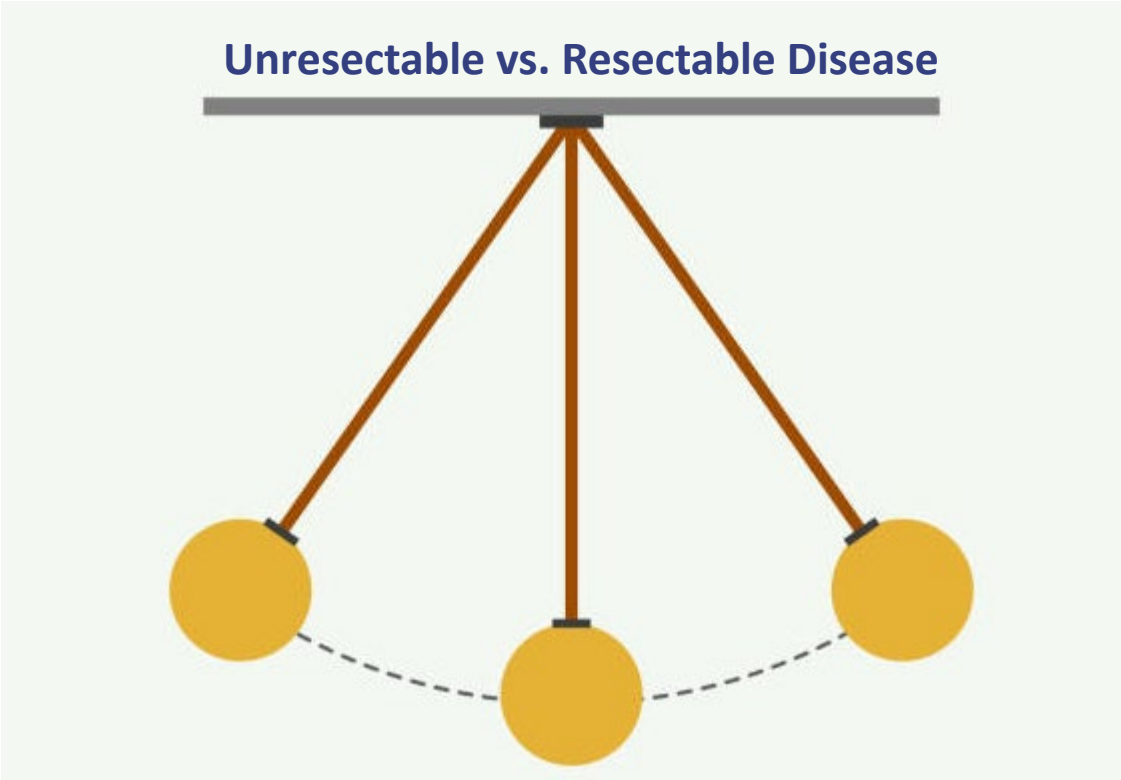
Shifting Paradigms in Stage III NSCLC?

CRT + consolidative Immunotherapy



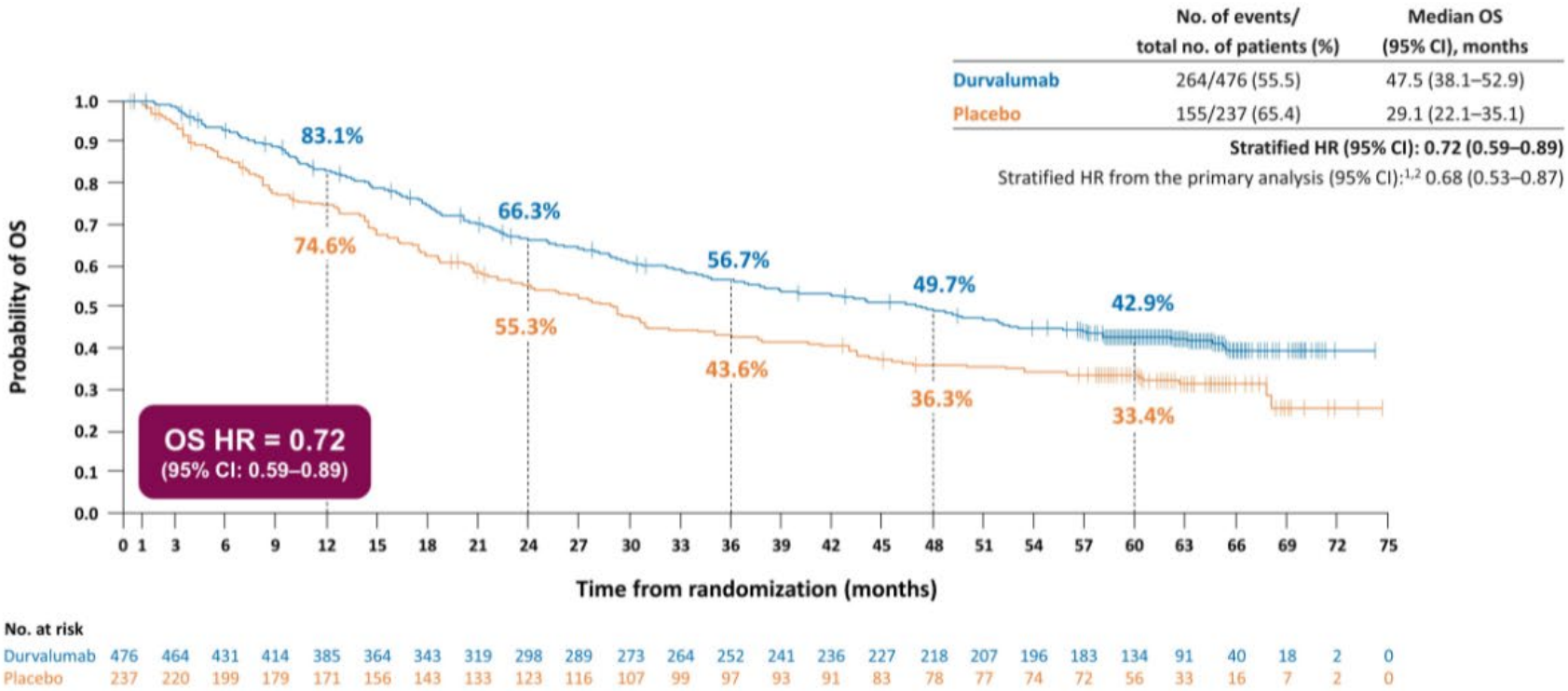
Neoadj Chemo IO + Surgery

2017- First PACIFIC publication

2022 – Checkmate 816

5 yr PACIFIC Overall Survival Data

Updated OS (ITT)



CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival

Data cutoff: 11 January 2021 (median follow-up: all patients, 34.2 months [range, 0.2–74.7]; censored patients, 61.6 months [range, 0.4–74.7]).
1. Antonia SJ, et al. New Engl J Med 2018;379:2342–50; 2. European Medicines Agency. Durvalumab (Imfinzi). Summary of product characteristics 2020. Available from: https://www.ema.europa.eu/en/documents/product-information/imfinzi-epar-product-information_en.pdf 5. [Accessed April 2021]

Spigel DR et al. 2021 ASCO Annual Meeting. Abstract 8511. Spigel DR et al. *J Clin Oncol*. 2022;40(12):1301-1311.

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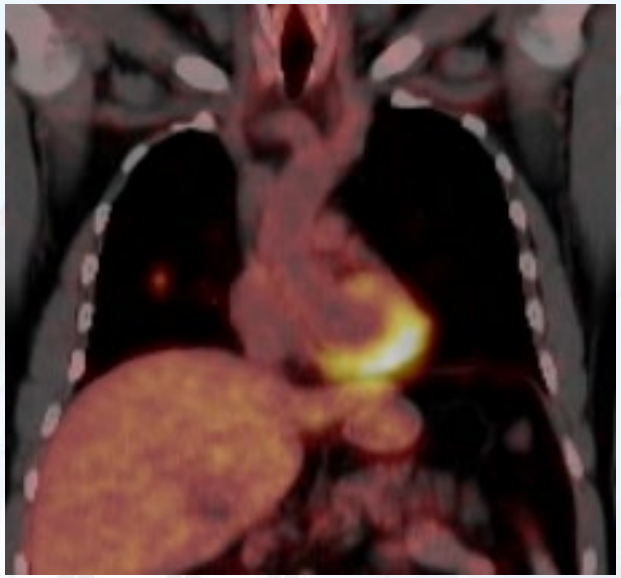
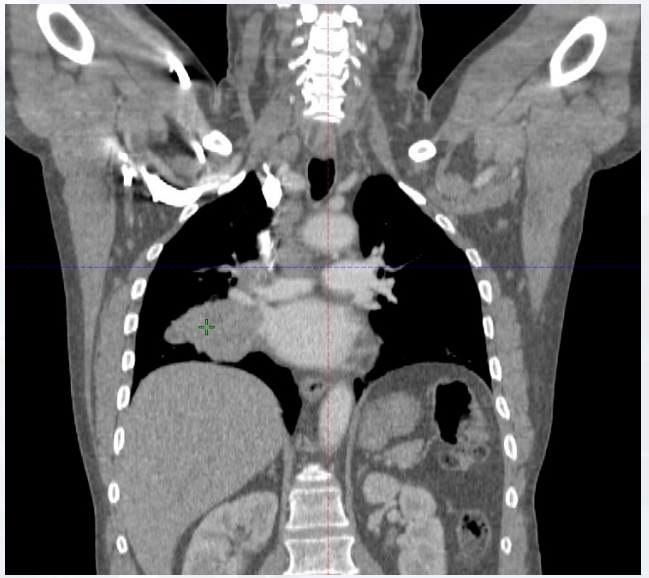
Resectable vs. Unresectable?





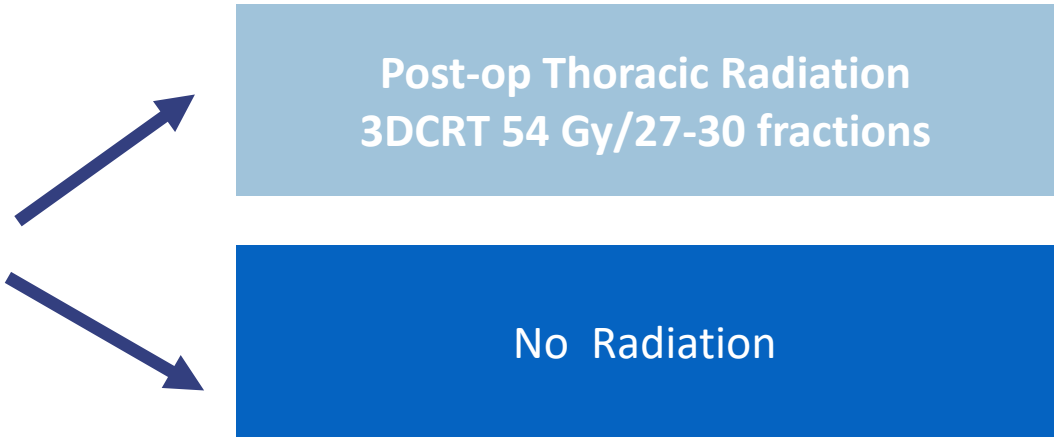
LUNG-ART Trial Schema

- Randomized phase III trial comparing post-operative RT to no post-op RT in patients with completely resected NSCLC and N2 involvement

Stratified by treating site, administration of chemotherapy (pre-op chemo vs. post-op chemo vs. none), # of N2 lymph nodes involved (1 vs. 2+), Histology (SCC vs. other), use of pre-treatment PET (yes vs. no)

Patients with completely resected NSCLC with mediastinal exploration, pathologically confirmed N2, adequate post-op FEV1 > 1 L
WHO PS 0/1
(N = 501)

RT to begin 2-8 weeks after surgery



- Primary endpoints: DFS
- Secondary endpoints including toxicity (cardiopulmonary), local control, OS, patterns of recurrence, second cancers

LUNG-ART Disease Free Survival

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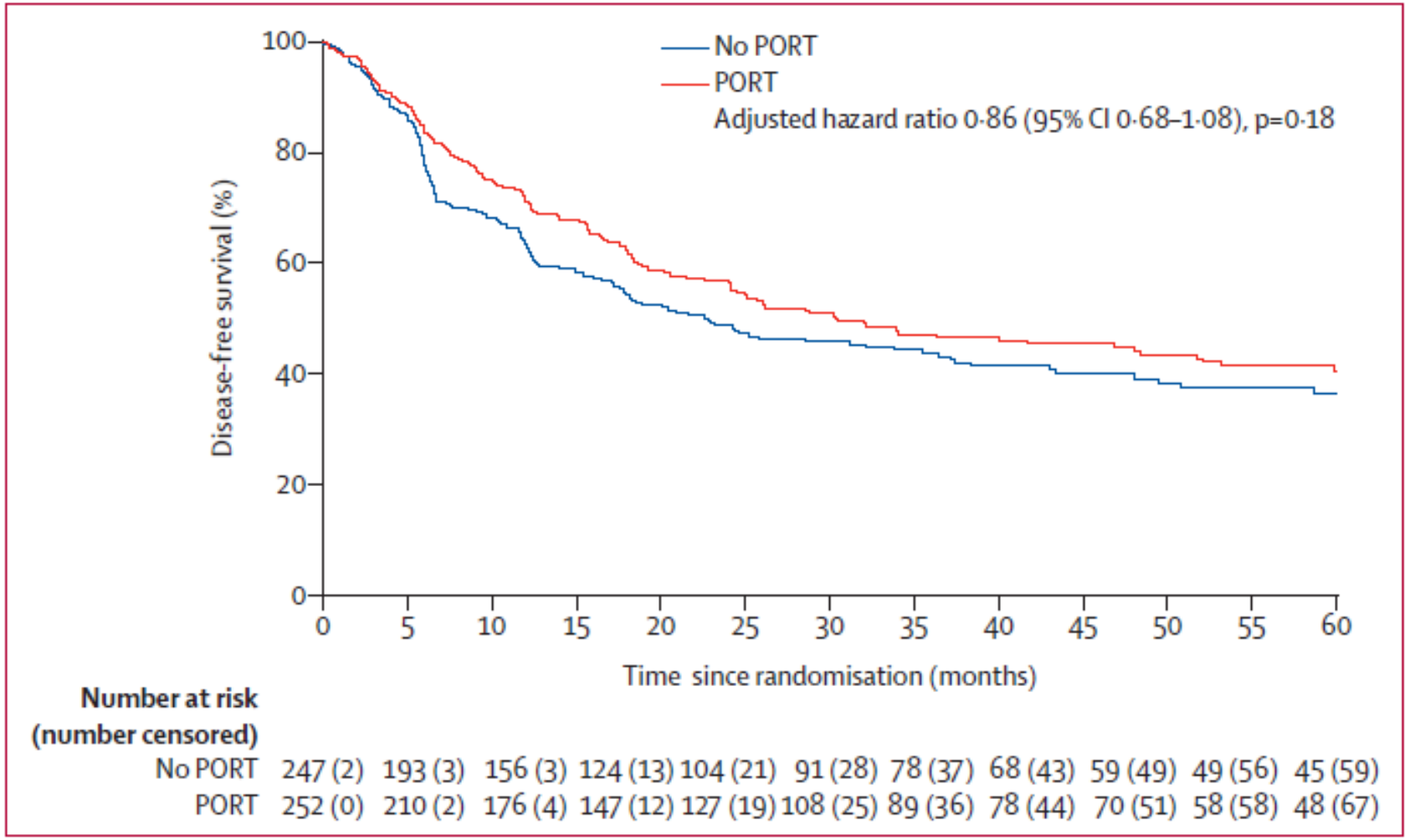


Number at risk (number censored)												
No PORT	247 (2)	193 (3)	156 (3)	124 (13)	104 (21)	91 (28)	78 (37)	68 (43)	59 (49)	49 (56)	45 (59)
PORT	252 (0)	210 (2)	176 (4)	147 (12)	127 (19)	108 (25)	89 (36)	78 (44)	70 (51)	58 (58)	48 (67)

Le Pechoux et al, Lancet Oncol. 2022 Jan;23(1):104-114.

LUNG-ART DFS Components

	PORT group (n=252)	Control group (n=249)
All disease-free survival events	144	152
Relapses and metastases	123 (85%)	144 (95%)
Mediastinal relapse	36 (25%)	70 (46%)
Brain metastasis	34 (24%)	27 (18%)
Extracranial metastasis	71 (49%)	71 (47%)
Death	21 (15%)	8 (5%)
Causes of death		
Cardiopulmonary	11 (8%)	0
Non-cancer related	0	1 (1%)
PORT toxicity	2 (1%)	0
Progression	1 (1%)	0
Second primary cancer	4 (3%)	2 (1%)
Vascular	0	1 (1%)
Unknown	3 (2%)	4 (3%)

Data are n (%), regarding the number of patients with event. Patients can have several different events at the same time. PORT=postoperative radiotherapy.

Table 3: **Disease-free survival events**

Le Pechoux et al, Lancet Oncol. 2022 Jan;23(1):104-114.

Proton Beam Radiation Therapy in Patients with Resected N2 Non-Small Cell Lung Cancer

Intensity-Modulated Proton Therapy (54 GyE in 27 or 30 fractions)

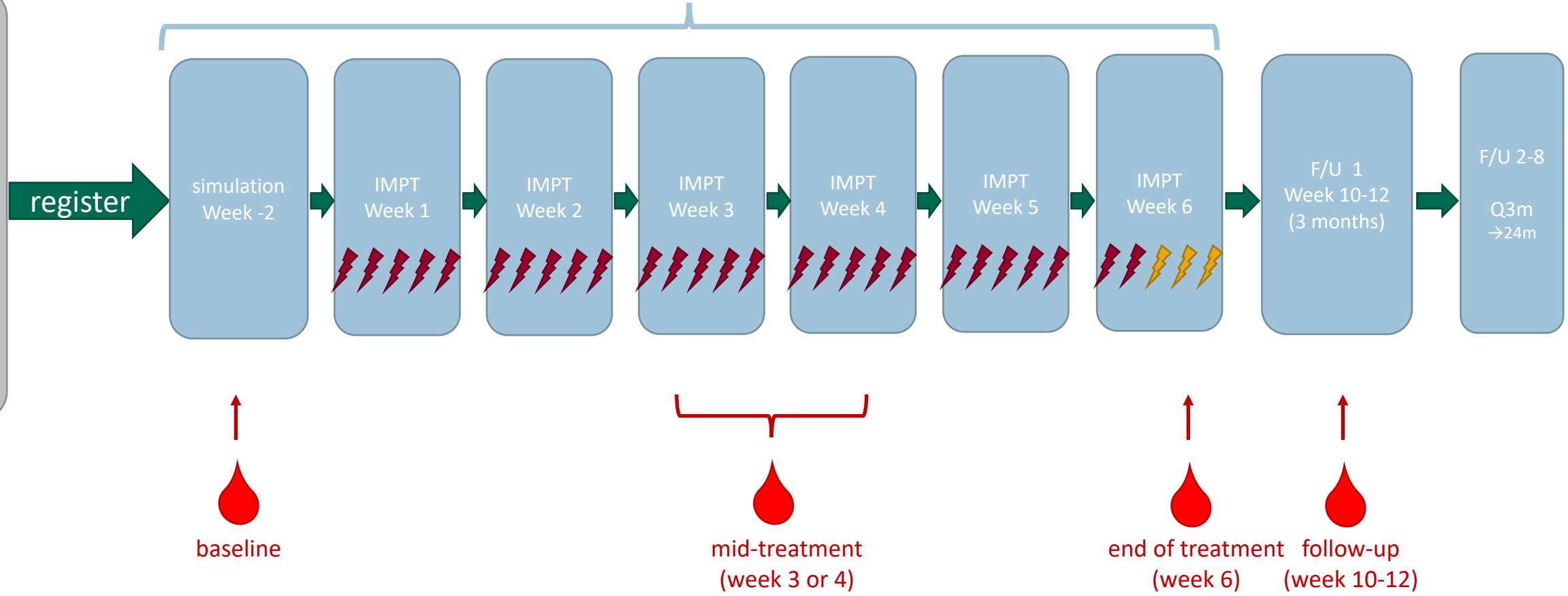
Eligibility

resected NSCLC stage III (pN2)

no prior XRT no other recent malignancies

no known sensitizing EGFR or ALK mutations

ECOG PS <2



Winship Trial RAD5621-22; PIs: Kesarwala/Stokes/Buchwald; Funding: Winship Invest$

Surgery vs. ChemoRT for Multi-Station N2

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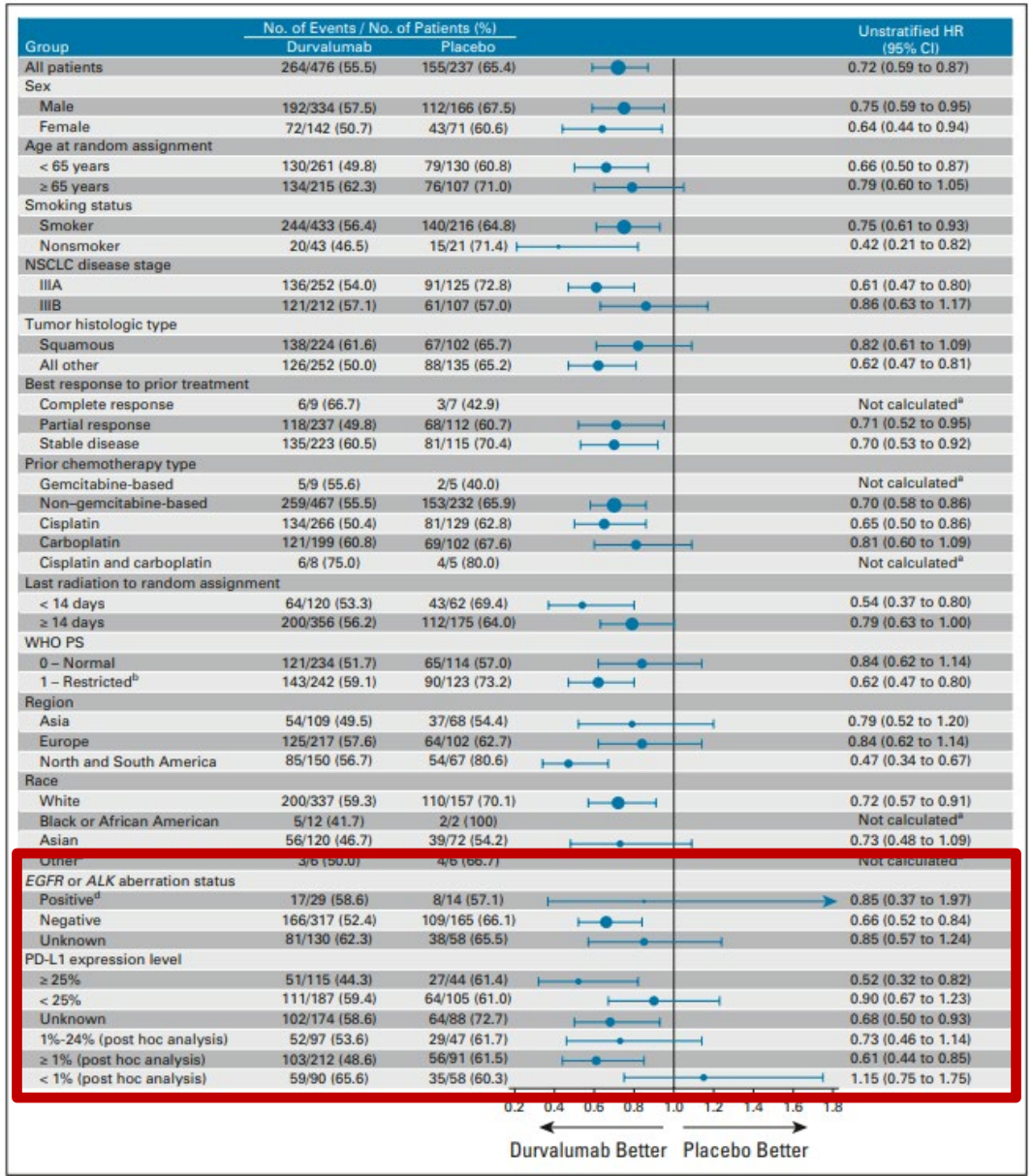
- Multi-station N2 and stage IIIB included in many preop chemo IO studies
- Do these pts benefit from surgery?
- ~20% of pts don't make it to resection → what is ultimate clinical outcome for these patients?

Controversies in Unresectable Stage III NSCLC

- Immunotherapy in patients with PD-L1 negative tumors?
- Immunotherapy in patients with driver mutations?
- Treatment strategy for ECOG PS 2 patients?
- Best treatment for recurrent disease?
  - Distant recurrence post-Pacific
  - Local only recurrence



Group	No. of Events / No. of Patients (%) Durvalumab	Placebo	Unstratified HR (95% CI)
All patients	264/476 (55.5)	155/237 (65.4)	0.72 (0.59 to 0.87)
Sex			
Male	192/334 (57.5)	112/166 (67.5)	0.75 (0.59 to 0.95)
Female	72/142 (50.7)	43/71 (60.6)	0.64 (0.44 to 0.94)
Age at random assignment			
< 65 years	130/261 (49.8)	79/130 (60.8)	0.66 (0.50 to 0.87)
≥ 65 years	134/215 (62.3)	76/107 (71.0)	0.79 (0.60 to 1.05)
Smoking status			
Smoker	244/433 (56.4)	140/216 (64.8)	0.75 (0.61 to 0.93)
Nonsmoker	20/43 (46.5)	15/21 (71.4)	0.42 (0.21 to 0.82)
NSCLC disease stage			
IIIA	136/252 (54.0)	91/125 (72.8)	0.61 (0.47 to 0.80)
IIIB	121/212 (57.1)	61/107 (57.0)	0.86 (0.63 to 1.17)
Tumor histologic type			
Squamous	138/224 (61.6)	67/102 (65.7)	0.82 (0.61 to 1.09)
All other	126/252 (50.0)	88/135 (65.2)	0.62 (0.47 to 0.81)
Best response to prior treatment			
Complete response	6/9 (66.7)	3/7 (42.9)	Not calculated[a]
Partial response	118/237 (49.8)	68/112 (60.7)	0.71 (0.52 to 0.95)
Stable disease	135/223 (60.5)	81/115 (70.4)	0.70 (0.53 to 0.92)
Prior chemotherapy type			
Gemcitabine-based	5/9 (55.6)	2/5 (40.0)	Not calculated[a]
Non–gemcitabine-based	259/467 (55.5)	153/232 (65.9)	0.70 (0.58 to 0.86)
Cisplatin	134/266 (50.4)	81/129 (62.8)	0.65 (0.50 to 0.86)
Carboplatin	121/199 (60.8)	69/102 (67.6)	0.81 (0.60 to 1.09)
Cisplatin and carboplatin	6/8 (75.0)	4/5 (80.0)	Not calculated[a]
Last radiation to random assignment			
< 14 days	64/120 (53.3)	43/62 (69.4)	0.54 (0.37 to 0.80)
≥ 14 days	200/356 (56.2)	112/175 (64.0)	0.79 (0.63 to 1.00)
WHO PS			
0 – Normal	121/234 (51.7)	65/114 (57.0)	0.84 (0.62 to 1.14)
1 – Restricted[b]	143/242 (59.1)	90/123 (73.2)	0.62 (0.47 to 0.80)
Region			
Asia	54/109 (49.5)	37/68 (54.4)	0.79 (0.52 to 1.20)
Europe	125/217 (57.6)	64/102 (62.7)	0.84 (0.62 to 1.14)
North and South America	85/150 (56.7)	54/67 (80.6)	0.47 (0.34 to 0.67)
Race			
White	200/337 (59.3)	110/157 (70.1)	0.72 (0.57 to 0.91)
Black or African American	5/12 (41.7)	2/2 (100)	Not calculated[a]
Asian	56/120 (46.7)	39/72 (54.2)	0.73 (0.48 to 1.09)
Other	3/6 (50.0)	4/6 (66.7)	Not calculated[a]
EGFR or *ALK* aberration status			
Positive[d]	17/29 (58.6)	8/14 (57.1)	0.85 (0.37 to 1.97)
Negative	166/317 (52.4)	109/165 (66.1)	0.66 (0.52 to 0.84)
Unknown	81/130 (62.3)	38/58 (65.5)	0.85 (0.57 to 1.24)
PD-L1 expression level			
≥ 25%	51/115 (44.3)	27/44 (61.4)	0.52 (0.32 to 0.82)
< 25%	111/187 (59.4)	64/105 (61.0)	0.90 (0.67 to 1.23)
Unknown	102/174 (58.6)	64/88 (72.7)	0.68 (0.50 to 0.93)
1%-24% (post hoc analysis)	52/97 (53.6)	29/47 (61.7)	0.73 (0.46 to 1.14)
≥ 1% (post hoc analysis)	103/212 (48.6)	56/91 (61.5)	0.61 (0.44 to 0.85)
< 1% (post hoc analysis)	59/90 (65.6)	35/58 (60.3)	1.15 (0.75 to 1.75)

Spigel et al, J Clin Oncol. 2022 Apr 20; 40(12): 1301–1311

LAURA

Phase III, double-blind, randomized, placebo-controlled trial

Osimertinib (EGFR)

Patients with locally advanced, unresectable (Stage III) *EGFR*m[a] NSCLC whose disease has not progressed during or following definitive platinum-based CRT

N=216[b]

Concurrent chemoradiation

or

sequential chemoradiation

R[c] 2:1

- **Osimertinib[d]**
- **Placebo**

Open-label osimertinib Optional:[e] Patients from either arm may receive open-label osimertinib post-progression

Primary endpoint

- PFS

Secondary endpoints

- PFS in patients with EGFR Ex19del or L858R mutation
- PFS in patients with EGFR mutations Ex19del or L858R detectable in plasma-derived ctDNA
- Time to CNS PFS
- OS, ORR, DoR, DCR, tumor shrinkage, TTDM, TTD, PFS2, TFST, TSST
- Patients reported disease-related symptoms and HRQoL
- Incidence of adverse events
- PK

[a]Ex19del or L858R either alone or in combination with other EGFR mutations; [b] Actual enrollment; [c]Randomized within 6 weeks of completion of chemoradiation; [d]Osimertinib dosing schedule: 80 mg PO QD; [e]A protocol amendment has been made in the Clinical Study Protocol version 2 (February 18, 2020).

CNS = central nervous system; CRT = chemoradiation therapy; ctDNA = circulating tumor DNA; DCR = disease control rate; DoR = duration of response; EGFR = epidermal growth factor receptor; *EGFR*m = epidermal growth factor receptor mutation-positive; Ex19del = exon 19 deletion; HRQoL = health-related quality of life; NSCLC = non-small-cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PFS2 = second progression-free survival on a subsequent treatment; PK = pharmacokinetic; PO = orally; QD = once daily; R = randomize; TFST = time to first subsequent therapy; TSST = time to second subsequent therapy; TTD = time to treatment discontinuation; TTDM = time to death or distant metastases.

Study NCT03521154. ClinicalTrials.gov website.

Immunotherapy Strategy for Stage III PS 2

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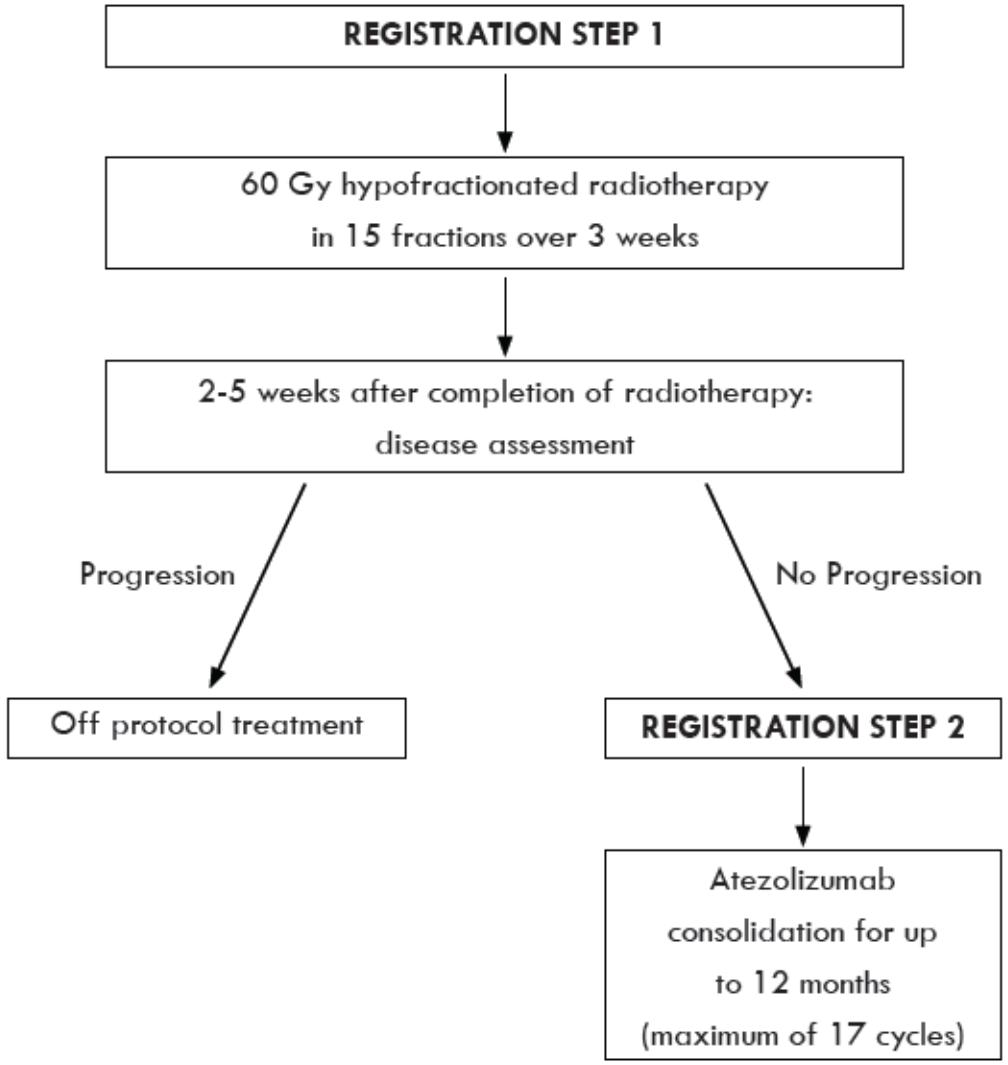
S1933

SWOG CANCER RESEARCH NETWORK

SCHEMA



Study Chairs:

Raid Aljumaily, MD, Medical Oncology
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Timur Mitin, MD, PhD, Radiation Oncology
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Oregon Health and Science University
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Co-Chairs:

Roy H. Decker, MD, PhD – Radiation Oncology,
Department of Therapeutic Radiology,
Yale School of Medicine

Antoinette Wozniak, MD – Medical Oncology
Hillman Cancer Center, University of Pittsburgh Medical Center

ADDING to the PACIFIC Regimen

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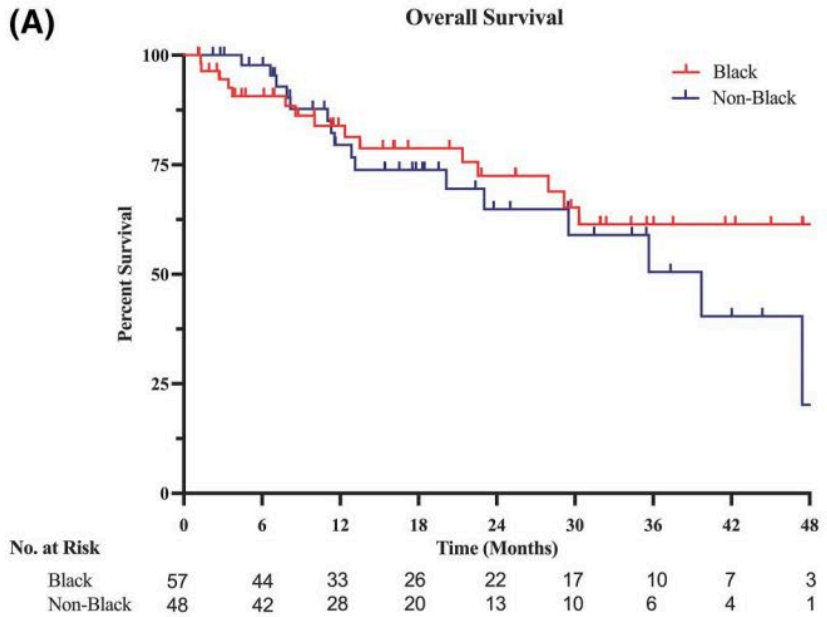
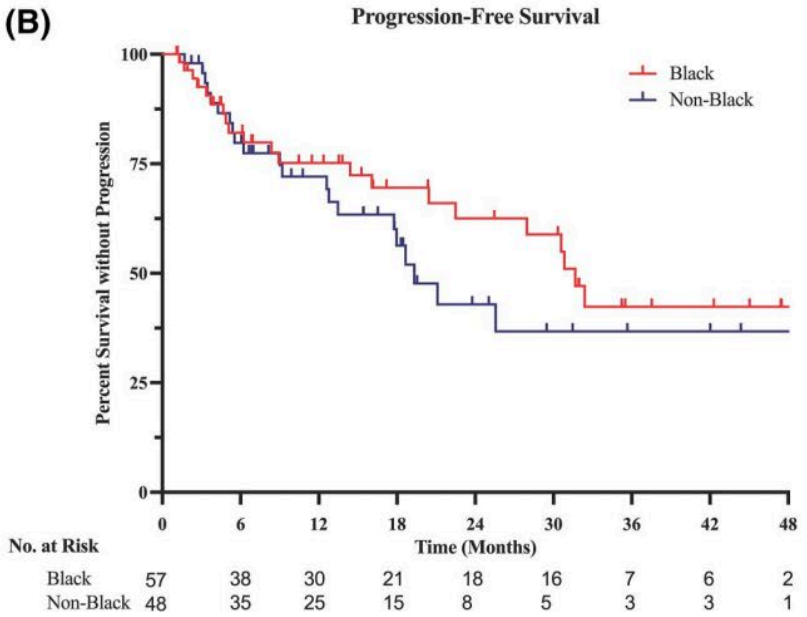
- Can we continue to reduce distant recurrence with IO combos?
- Will timing of IO impact survival?
- How to best optimize RT component?
  - Management of isolated local recurrence

Consolidative Durvalumab and Race

PACIFIC Trial: 14 African Americans (2%)
Emory Experience: 57 African Americans, 2017-2021



Race	Median OS	18-Month OS	36-Month OS
Black	Not Reached	78.8%	61.4%
Non-Black	39.7 Months	73.4%	50.5%



Race	Median PFS	18-Month PFS	36-Month PFS
Black	31.7 Months	69.5%	42.4%
Non-Black	19.3 Months	56.3%	36.8%

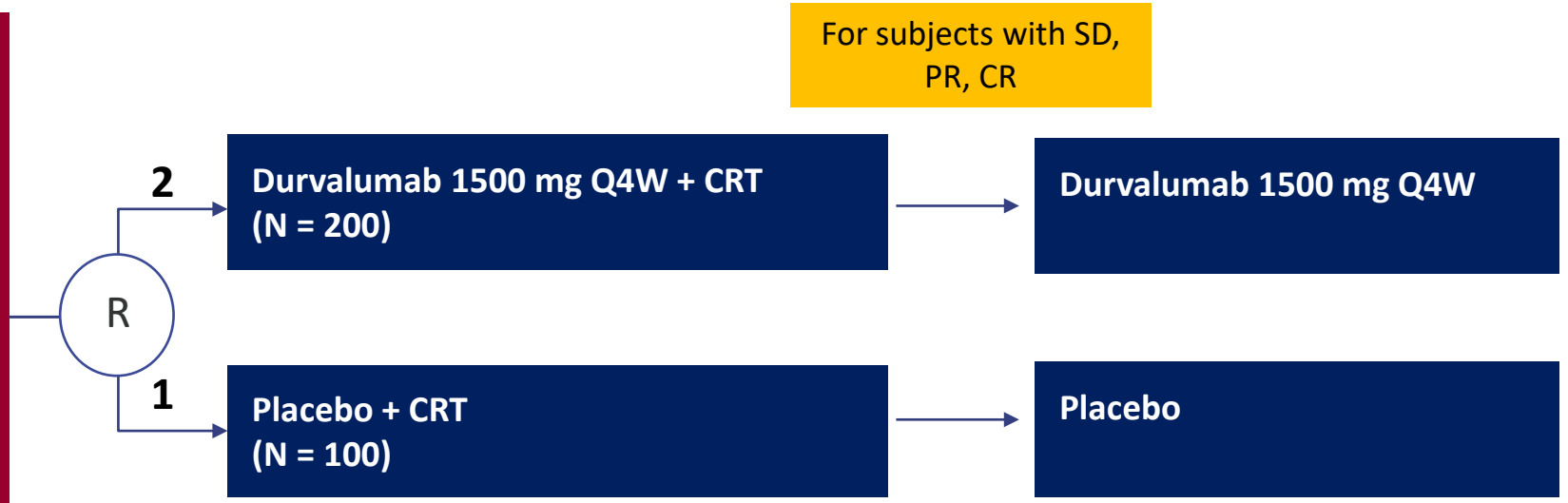
McCall/Higgins et al, Cancer. 2023 Jun 24

PACIFIC-2: Study Design

Study Population

- Patients with unresectable, Stage III NSCLC
- All-comers (PD-L1 expression-agnostic)
- ECOG PS 0-1

Randomised N = 300 patients



- Early IDMC safety assessment in first 15 and 60 TOTAL subjects (CRT+28 days)
- In Japan, assessment after first 9 TOTAL subjects (CRT+28 days)

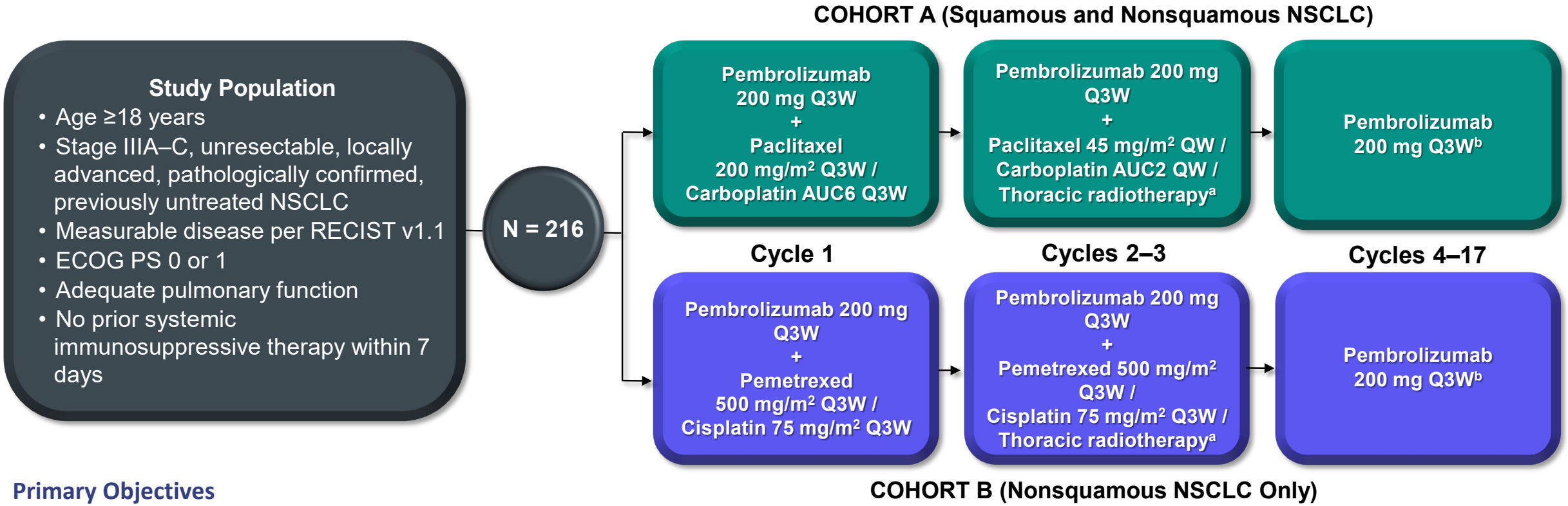
Stratification

- Age (≤65, >65)
- Stage (IIIA vs IIIB/C)

- **Primary Endpoints: ORR, PFS**
- **Key Secondary Endpoints:** OS, OS24
- **Treat to progression**

NCT03519971. Updated October 13, 2022. https://clinicaltrials.gov/ct2/show/NCT03519971

KEYNOTE-799 (NCT03631784) Study Design



Primary Objectives

- ORR per RECIST v1.1 by BICR
- Proportion of patients with grade ≥3 pneumonitis[c]

Secondary Objectives

- PFS per RECIST v1.1 by BICR, OS, and safety

Statistical Analysis Details

- Efficacy and safety assessed in all patients as-treated

BICR, blinded independent central review.

[a]60 Gy in 30 daily 2-Gy fractions 5 days per week. [b]Treatment continued until cycle 17 was completed or until documented disease progression, unacceptable AEs, intercurrent illness that prevented further administration of treatment, or study withdrawal. Pembrolizumab therapy was discontinued permanently in patients who developed grade ≥3 or recurrent grade 2 pneumonitis. [c]Per National Cancer Institute Common Terminology Criteria for Adverse Events v4.0; includes immune-mediated AE of "pneumonitis" and the Medical Dictionary for Regulatory Activities (MedDRA) preferred term of "radiation pneumonitis."

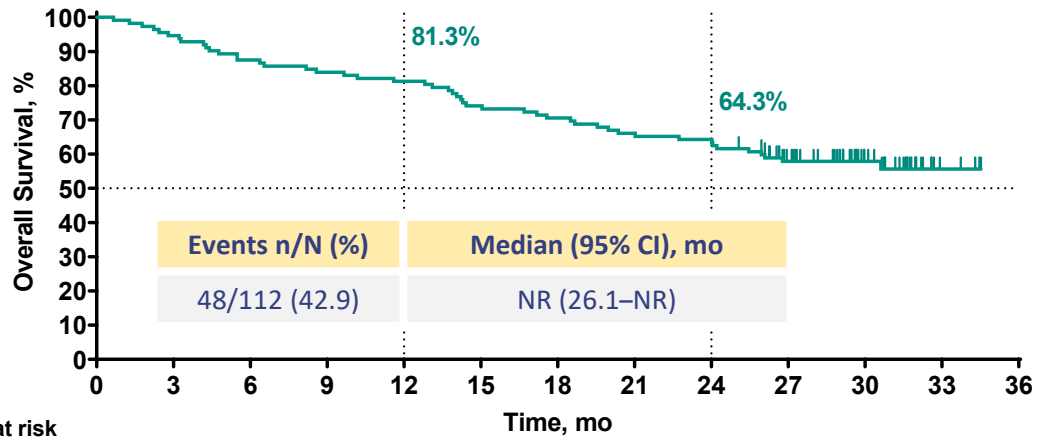
KEYNOTE-799
2-year update

N	Population	Regimen	ORR (%)	PFS, med (mos)	Pneumonitis G3+/Gr5
112	NSCLC	Ind CbP + Pembro Conc chemoRT + Pembro Consolidation Pembro	**71.4**	**30.6 mos** (55.3% 2 yr)	**8/3.6**
102	ns-NSCLC	Ind Cis/Pem + Pembro Conc Cis/Pem/RT + Pembro Consolidation Pembro	**75.5**	**60.6% 2 yr**	**6.9/1.0**

Reck M et al. ASCO Annual Meeting 2022. Abstract 8508.

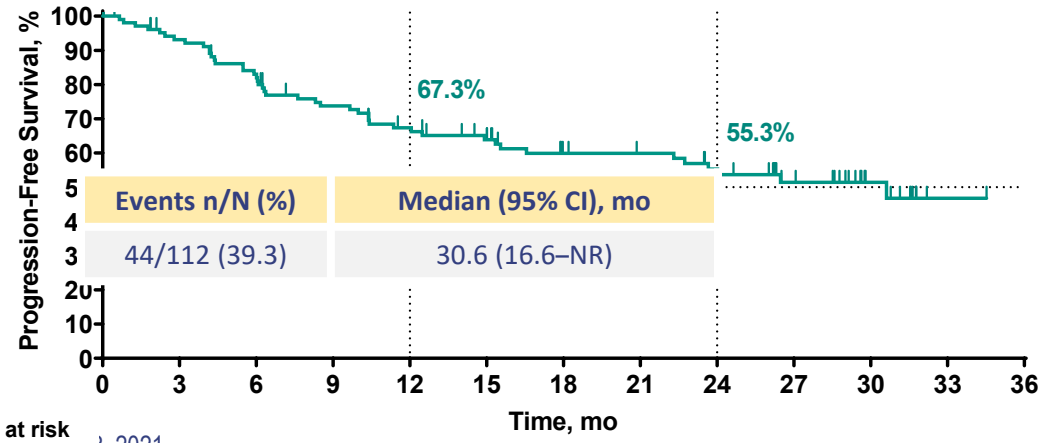
Progression-Free Survival and Overall Survival

Cohort A
(squamous and nonsquamous histology)



No. at risk

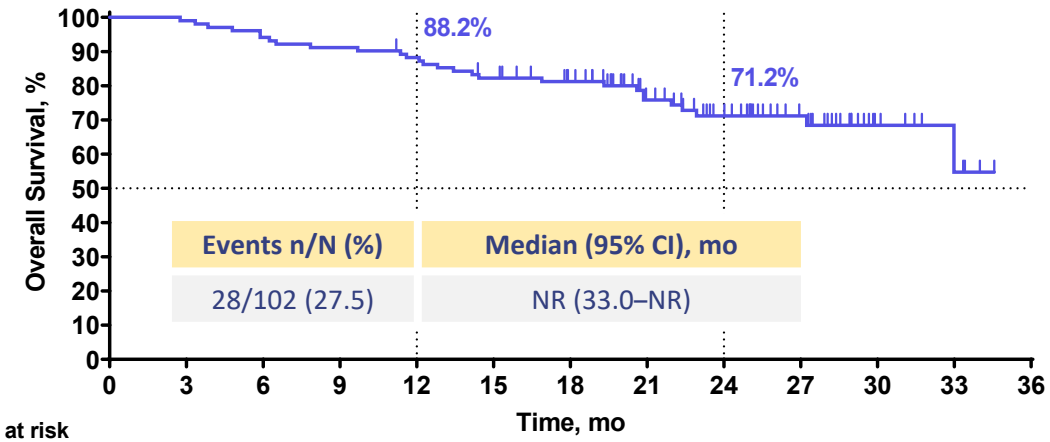
Cohort A	112	106	98	94	91	83	79	74	72	54	28	4	0



No. at risk

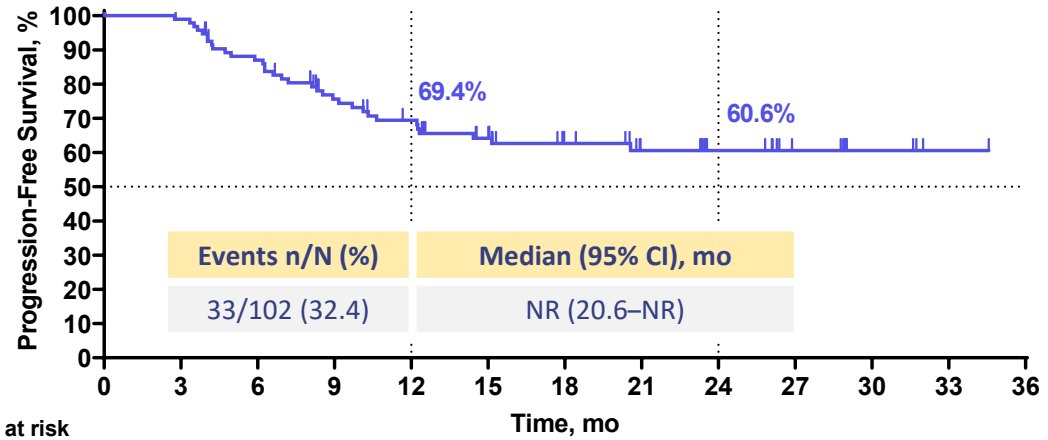
Cohort A	112	93	82	70	60	53	42	40	34	22	11	1	0

Cohort B
(nonsquamous histology only)



No. at risk

Cohort B	102	101	96	93	89	82	73	53	40	26	9	4	0



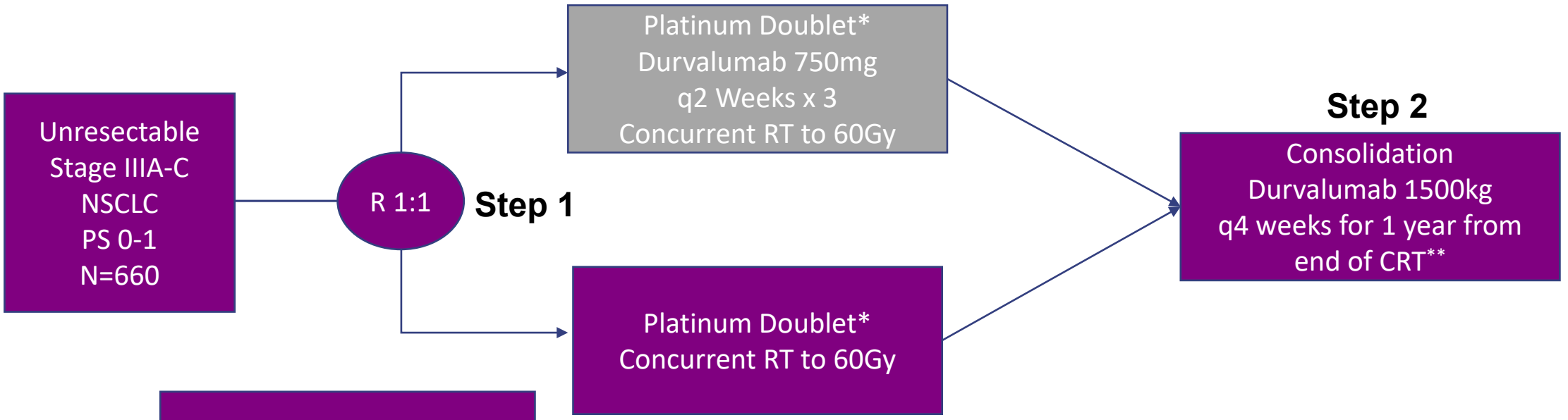
No. at risk

Cohort B	102	93	79	62	54	44	33	26	19	13	4	1	0

Data cut[illegible] 2021

Jabbour et al, ASTRO annual meeting 2022

EA 5181: Trial Schema



Randomization

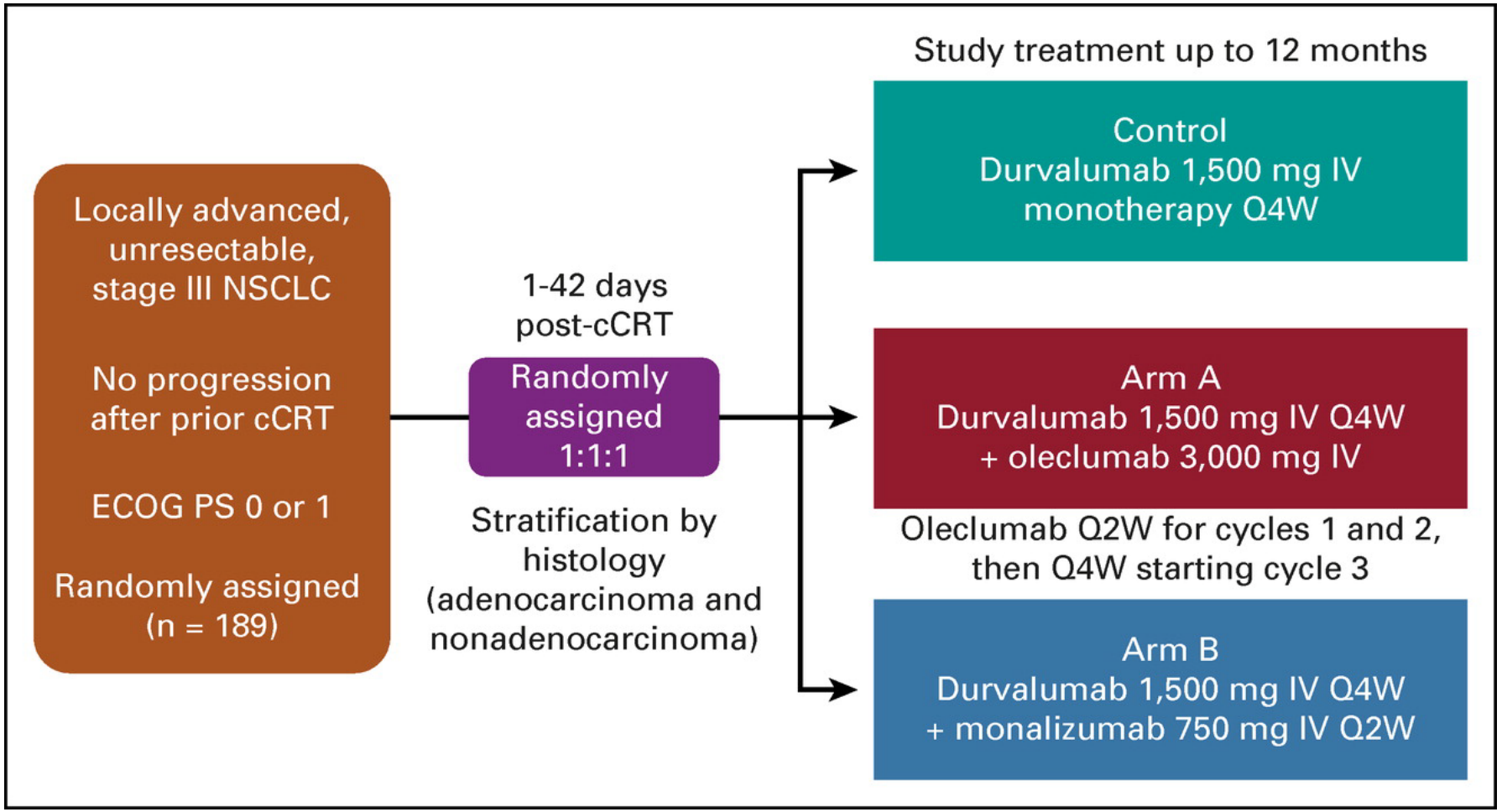
Stratified by:
1) Planned chemotherapy
2) Age
3) Sex
4) Stage (IIIA vs IIIB vs IIIC)

*__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

NCT04092283. Updated October 19, 2022. https://clinicaltrials.gov/ct2/show/NCT04092283

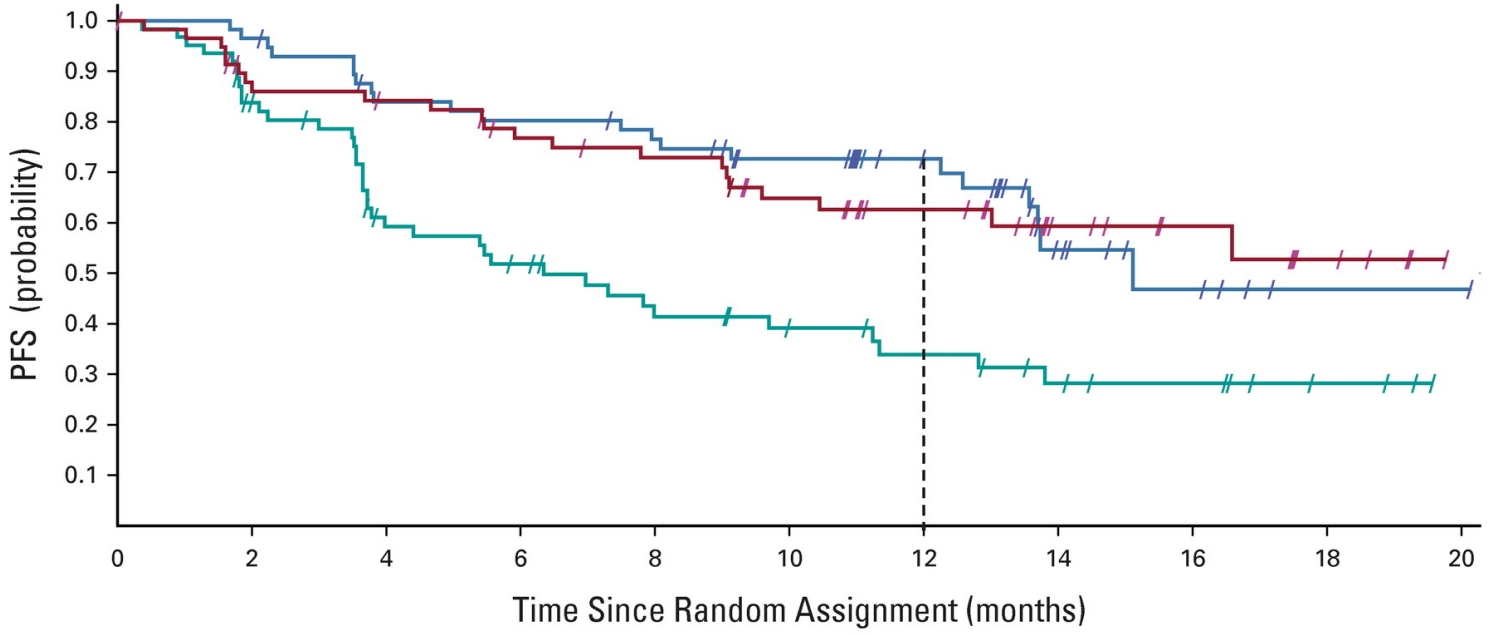
IO Combos: COAST Randomized Phase II



Herbst RS et al. *J Clin Oncol*. 2022;40(29):3383-3393.

IO Combos: COAST Randomized Phase II

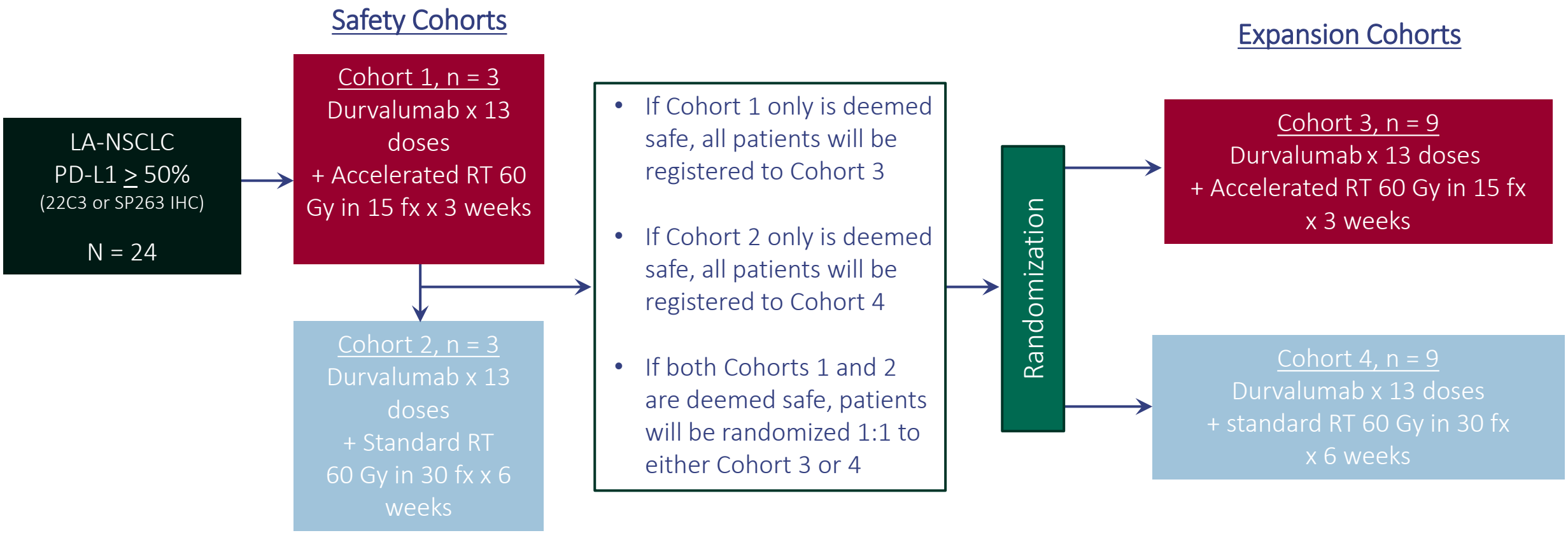
Treatment Arm	No. of Events/ Total No. of Patients (%)	Median PFS, Months (95% CI)[a]	12-Month PFS Rate, % (95% CI)	HR, % (95% CI)[b,c]
Durvalumab + monalizumab	21/62 (33.9)	15.1 (13.6 to NE)	72.7 (58.8 to 82.6)	0.42 (0.24 to 0.72)
Durvalumab + oleclumab	22/60 (36.7)	NR (10.4 to NE)	62.6 (48.1 to 74.2)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

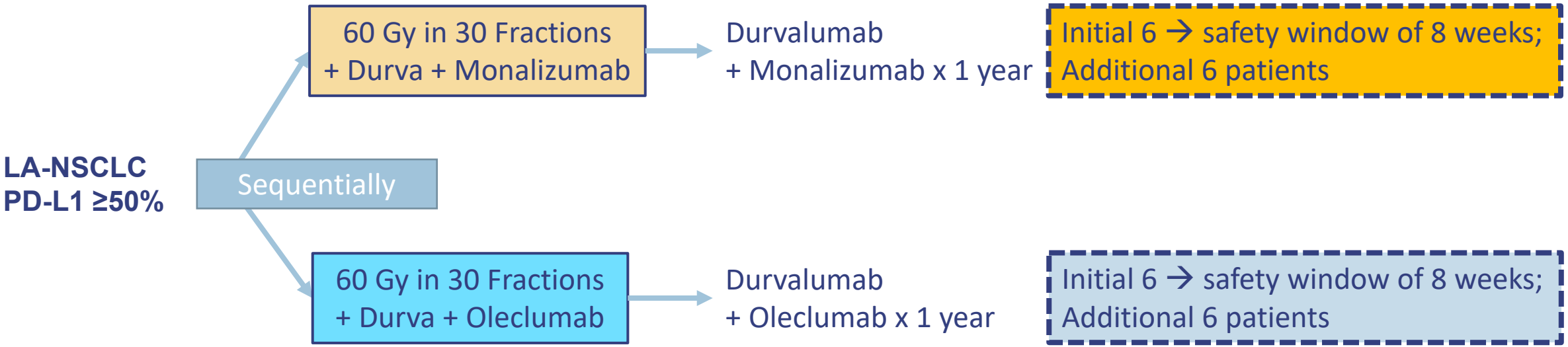
Herbst RS et al. *J Clin Oncol*. 2022; 40(29):3383-3393.

NRG-LU004: Phase I Trial of Accelerated or Conventionally Fractionated Radiotherapy Combined With MEDI4736 (durvalumab) in PD-L1 High Locally Advanced Non-Small Cell Lung Cancer (NSCLC) (ARCHON-1)



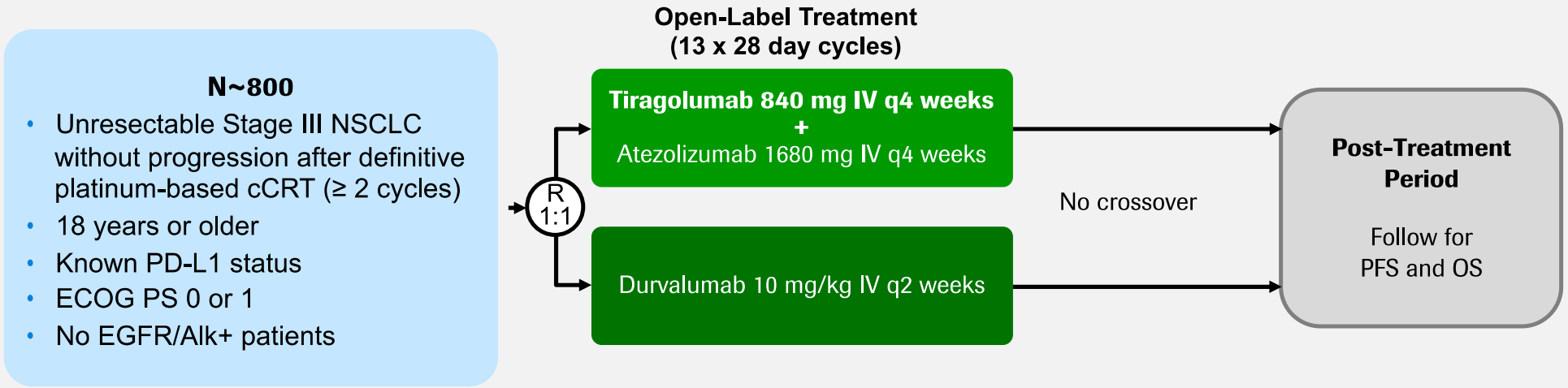
Primary: safety of adding durvalumab to 2 schedules of RT (60 Gy in 30 fx or 15 fx)
Secondary: feasibility, toxicities, PFS
Exploratory: tumor tissue/blood biomarkers, microbiome, TMB, PD-L1 IHC

Amendment for LU004
(Approved by CTEP June 2023)



SKYSCRAPER-03:Tiragolumab + Atezolizumab in Stage III NSCLC

Study Schema



Stratification Factors:

- PD-L1 expression (<1% vs ≥1%)
- Staging (IIIA vs IIIB vs IIIC)
- Histology (Squamous vs Non-Squamous)
- ECOG PS (0 vs 1)

Safety Run-in:

- iDMC review after a minimum of 24 patients (approximately 12 patients per arm) have completed 2 cycles of study treatment
- Enrollment will not be paused

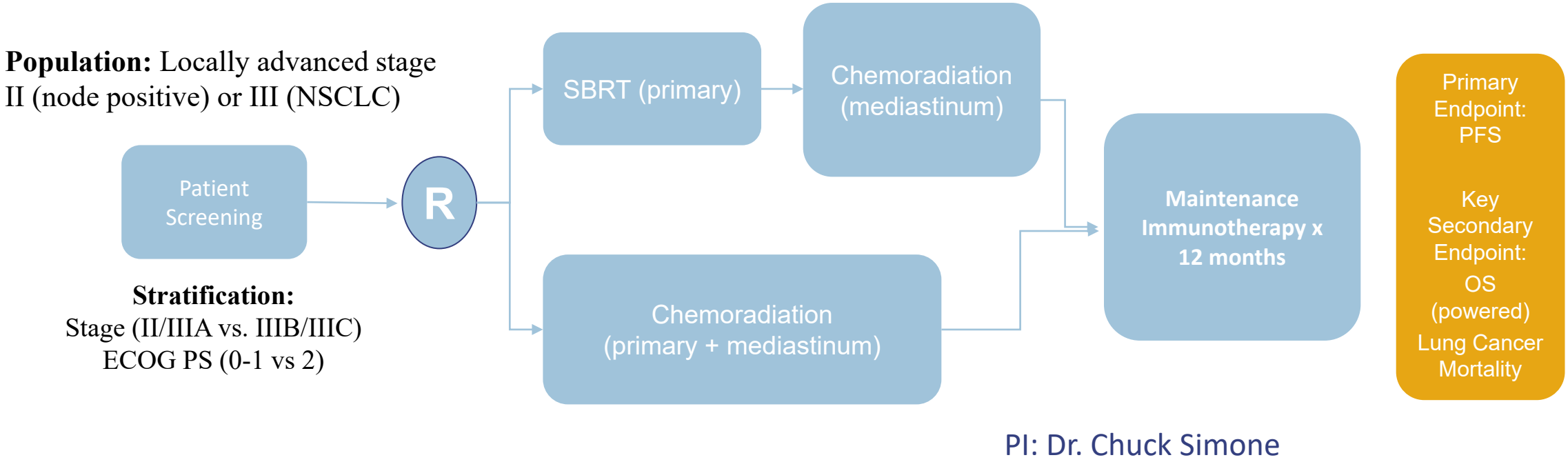
Co-Primary Endpoints:

IRF-assessed PFS in the

- PD-L1 positive population
- ITT population

https://clinicaltrials.gov/ct2/show/NCT04513925

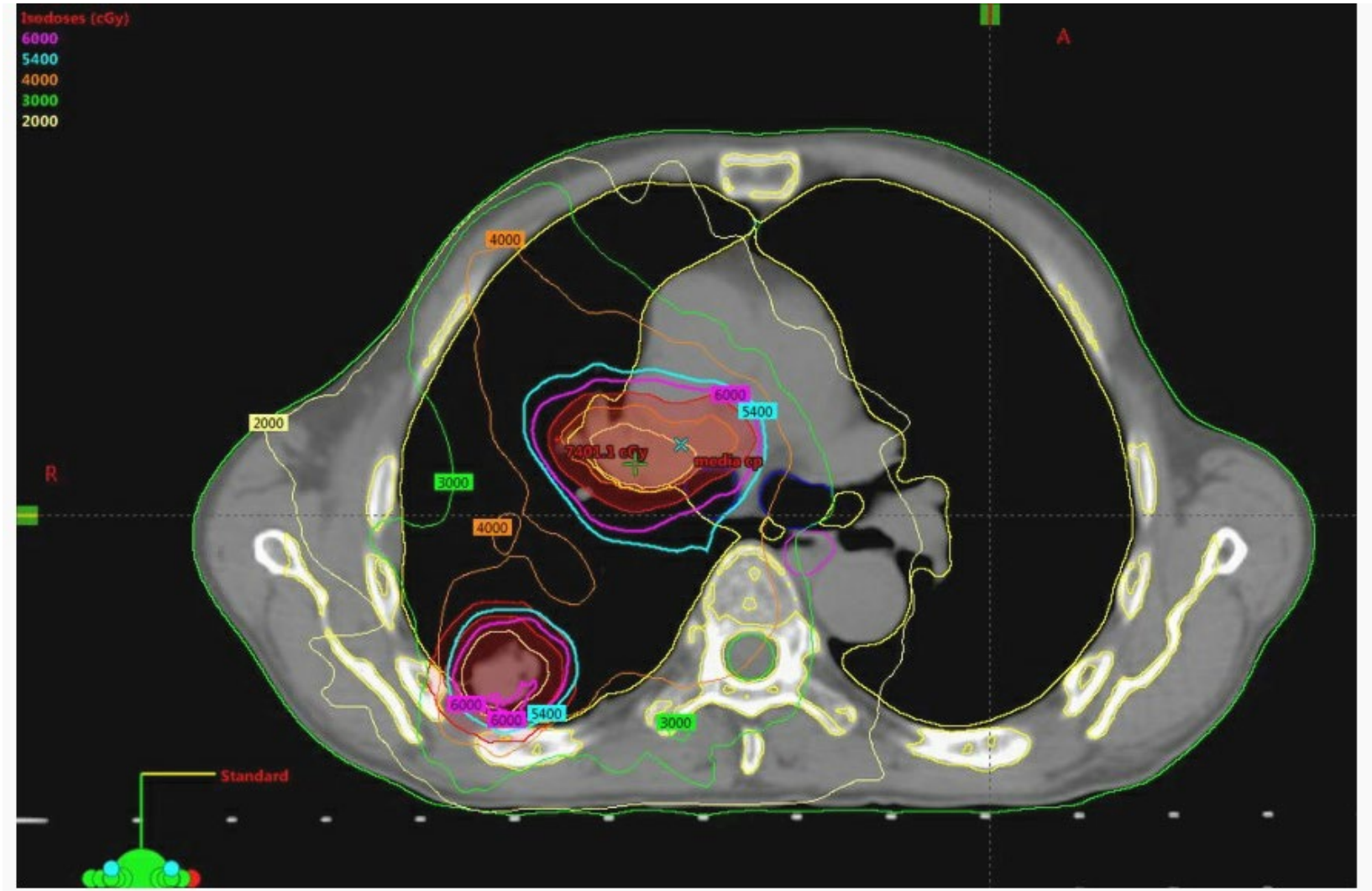
LU008 Schema: Phase III



PI: Dr. Chuck Simone

- Control arm: chemoradiation to the primary and mediastinal disease (60 Gy/2 Gy) → immunotherapy maintenance x 12 months
- Experimental arm: SBRT to the primary (standard BED ≥100 Gy dose regimen) → chemoradiation to mediastinal disease (60 Gy/2 Gy) → immunotherapy maintenance x 12 months
  - **SBRT to primary tumor**:
    - 3 fractions to 54 Gy (BED10 of 151.2 Gy) [peripheral]
    - 4 fractions to 50 Gy (BED10 of 112.5 Gy) [peripheral or central]
    - 5 fractions to 50 Gy (BED10 of 100 Gy) [central] or to 60 Gy (BED10 of 132 Gy) [peripheral or central]

NRG LU008 – SBRT to primary



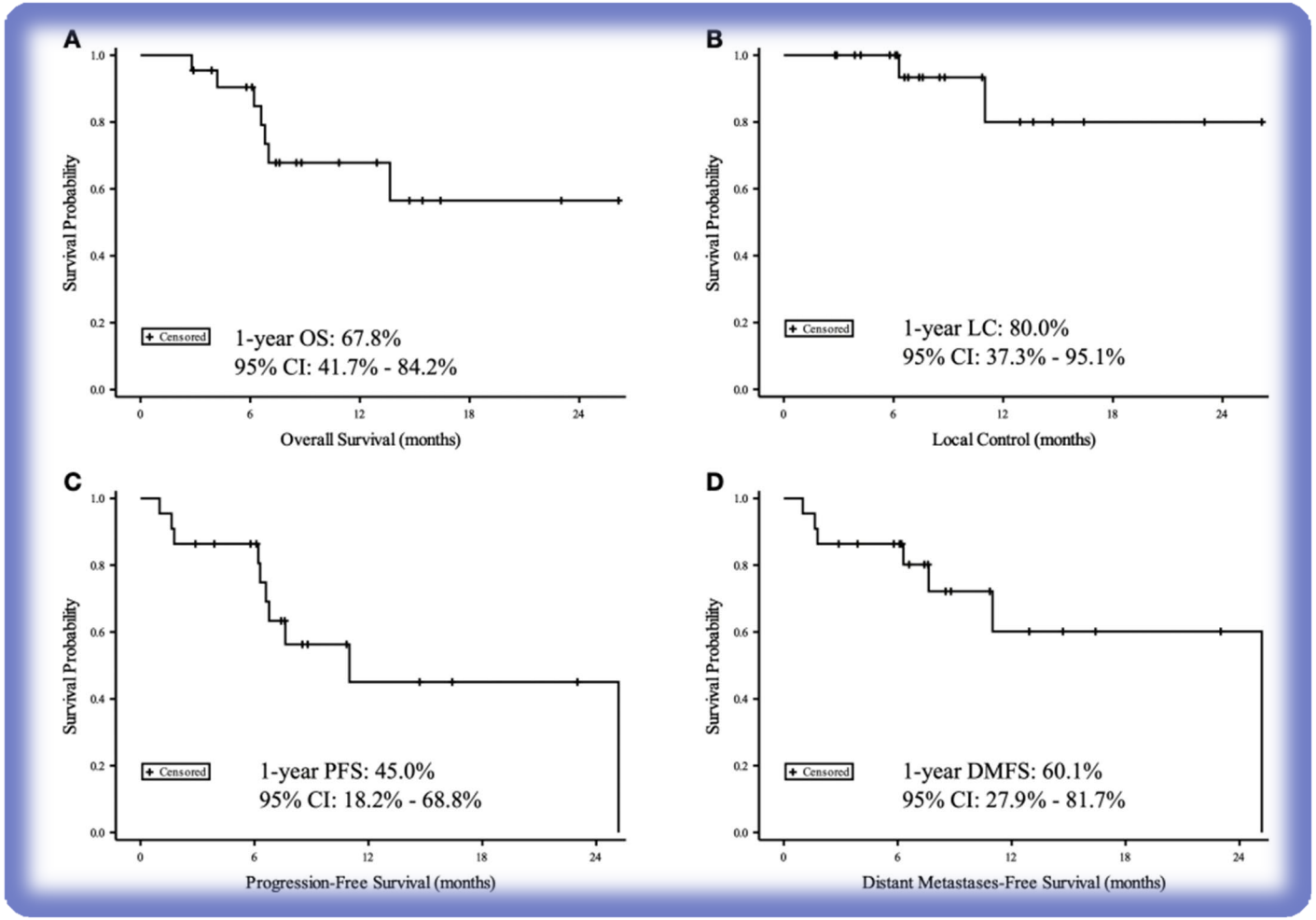
Total volume of lung receiving 40 Gy= 332 cc (compared to 590 cc, 44% reduction)
Total volume of lung receiving 20 Gy=922 cc (compared to1300 cc, 29% reduction)
Total volume of lung receiving 10 Gy=2168 cc (compared to 2360, 8% reduction)

Local Recurrence Post-PACIFIC: Re-irradiation with Proton Therapy

- 22 patients, 2019-2021 with in-field disease recurrence or second primary after definitive chemoradiation (45% received consolidative immunotherapy)

- Median time to re-treatment: 28 months
- 36% received concurrent chemotherapy with proton therapy, 18% received immunotherapy following proton therapy (median dose 60 Gy)

- Grade 3 toxicity 14% (2 pneumonitis, one dermatitis), No grade 4 or 5 toxicities



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Re-irradiation with Proton Therapy

Variable	Initial Course Median (Range)	Initial Course BED for α/β = 3 (Range)	IMPT Median (Range)	IMPT BED for α/β = 3 (Range)	Cumulative Median (Range)
Prescription Dose	60 Gy (45-70 Gy)		60 GyE (44-60 GyE)		120 GyE (89-130 GyE)
Lung V20 Gy (or GyE)	19% (1%-3%)		8% (2%-26%)		22% (7%-54%)
Lung V5 Gy (or GyE)	51% (4%-96%)		17% (3%-46%)		55% (13%-99%)
Mean Lung dose	12 Gy (1-20 Gy)	14 Gy (1-26 Gy)	4 GyE (1-14 GyE)	5 GyE (1-17 GyE)	17 GyE (5-33 GyE)
Heart V10 Gy (or GyE)	17% (0%-89%)		3% (0%-51%)		22% (4%-89%)
Mean Heart dose	6 Gy (1-25 Gy)	6 Gy (1-33 Gy)	1 GyE (0-24 GyE)	1 GyE (0-31 GyE)	9 GyE (2-54 GyE)
Max Spinal Cord dose	29 Gy (5-46 Gy)	40 Gy (5-86 Gy)	10 GyE (0-35 GyE)	11 GyE (0-50 GyE)	41 GyE (5-58 GyE)
Mean Esophagus dose	18 Gy (2-50 Gy)	21 Gy (2-72 Gy)	4 GyE (0-24 GyE)	4 GyE (0-31 GyE)	31 GyE (2-62 GyE)
Max Aorta dose	59 Gy (17-72 Gy)	107 Gy (36-130 Gy)	47 GyE (0-63 GyE)	93 GyE (0-147 GyE)	92 GyE (24-133 GyE)
Max Pulmonary Artery dose	57 Gy (0-69 Gy)	102 Gy (0-122 Gy)	47 GyE (0-62 GyE)	90 GyE (0-120 GyE)	87 GyE (0-127 GyE)
Max Proximal Bronchial Tree dose	64 Gy (8-70 Gy)	110 Gy (9-124 Gy)	63 GyE (6-64 GyE)	105 GyE (0-155 GyE)	110 GyE (13-129 GyE)
Max Brachial Plexus dose	34 Gy (0-71 Gy)	49 Gy (0-127 Gy)	7 GyE (0-62 GyE)	8 GyE (0-147 GyE)	37 GyE (0-132 GyE)

BED, biologically equivalent dose; IMPT, intensity modulated proton therapy.

Janpaul-Naylor/Higgins et al, Front Oncol. 2023 Jan 17;12:1074675

Conclusions

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- Cure rates for locally advanced NSCLC are improving
- Innovation in this space is strong
- Enroll patients in clinical trials testing these novel therapies
- As new therapies come on-line, our practice patterns will need to evolve