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Locally Advanced NSCLC: Radiotherapy Considerations

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Disclosures

Company Name	*Honoraria/ Expenses*	*Consulting/ Advisory Board*	*Funded Research*	*Royalties/ Patent*	*Stock Options*	*Ownership / Equity Position*	*Employee*	*Other (please specify)*
Varian/Siemens Healthineers			x					
Genentech		x						
Merck (RTOG Foundation)	x	x						
Emory University							x	
Castle Biosciences		x						
BioAscend	x							

NCT01993810

PACIFIC: STUDY DESIGN

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

- **Unresectable, Stage III NSCLC without progression and without G2+ toxicity 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

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

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

Placebo
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

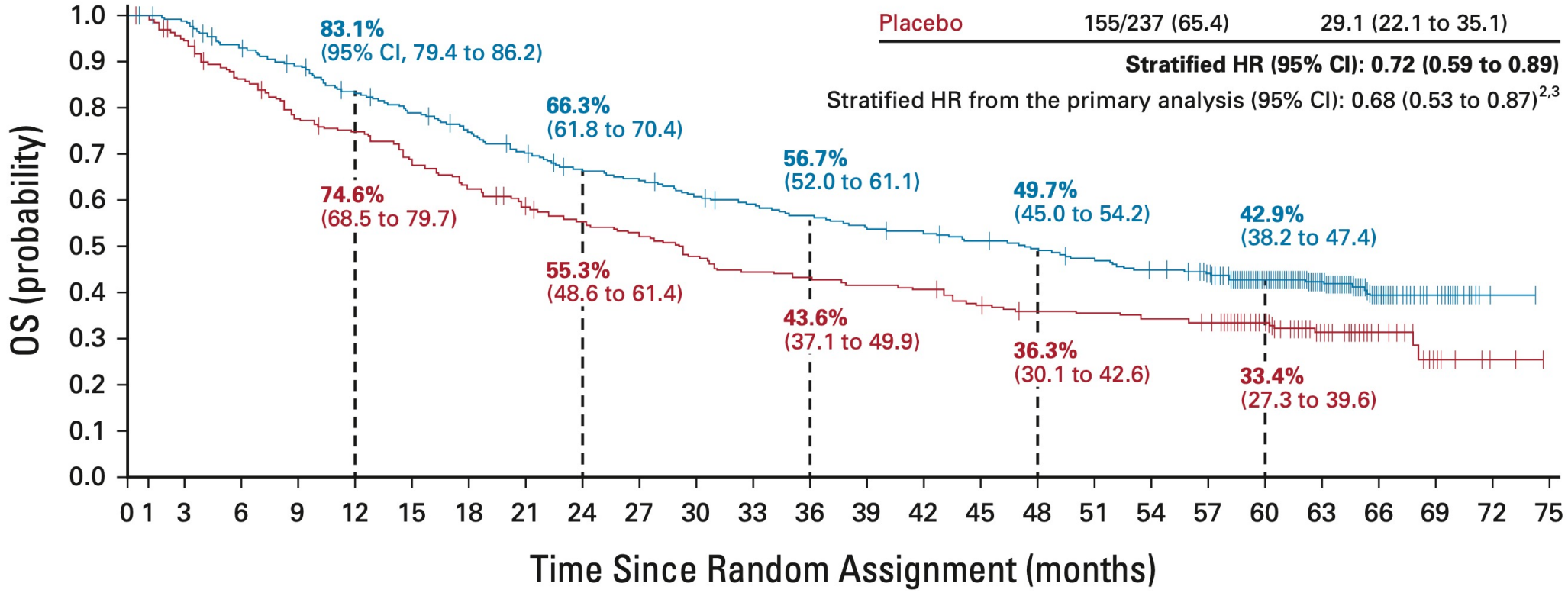
†Defined as the time from randomization until the date of objective disease progression or death by any cause in the absence of progression. BICR, blinded independent central review; cCRT, concurrent CRT; PFS2, time to second progression;
RECIST, Response Evaluation Criteria in Solid Tumors; TTDM, time to death or distant metastasis.

Antonia et al. NEJM 2017 & 2018

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]

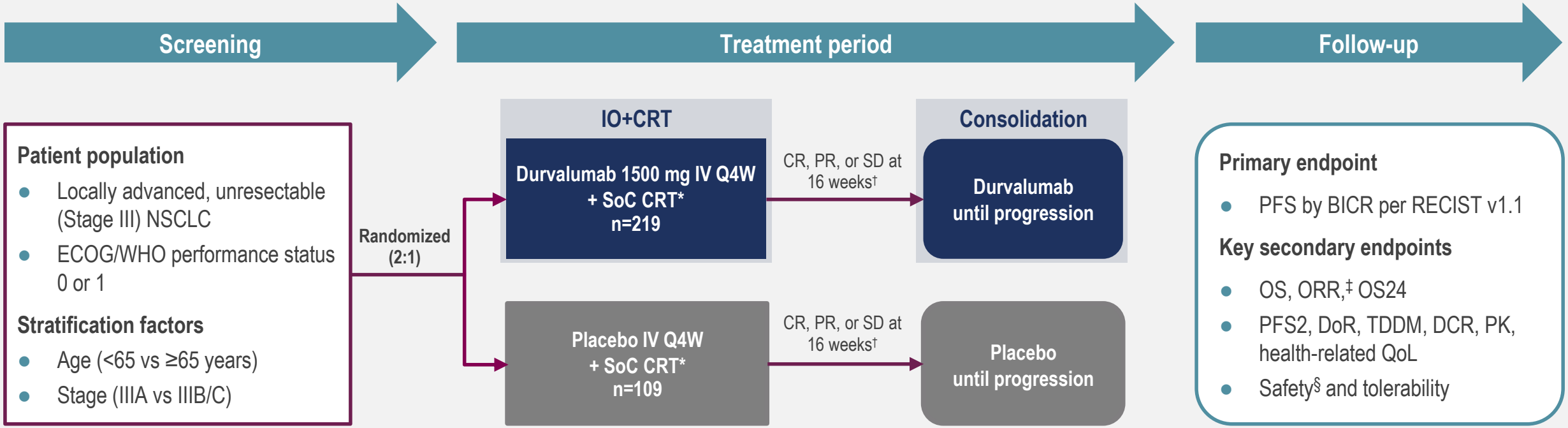


No. at risk:

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

PACIFIC-2

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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Slide courtesy: Jeffrey Bradley

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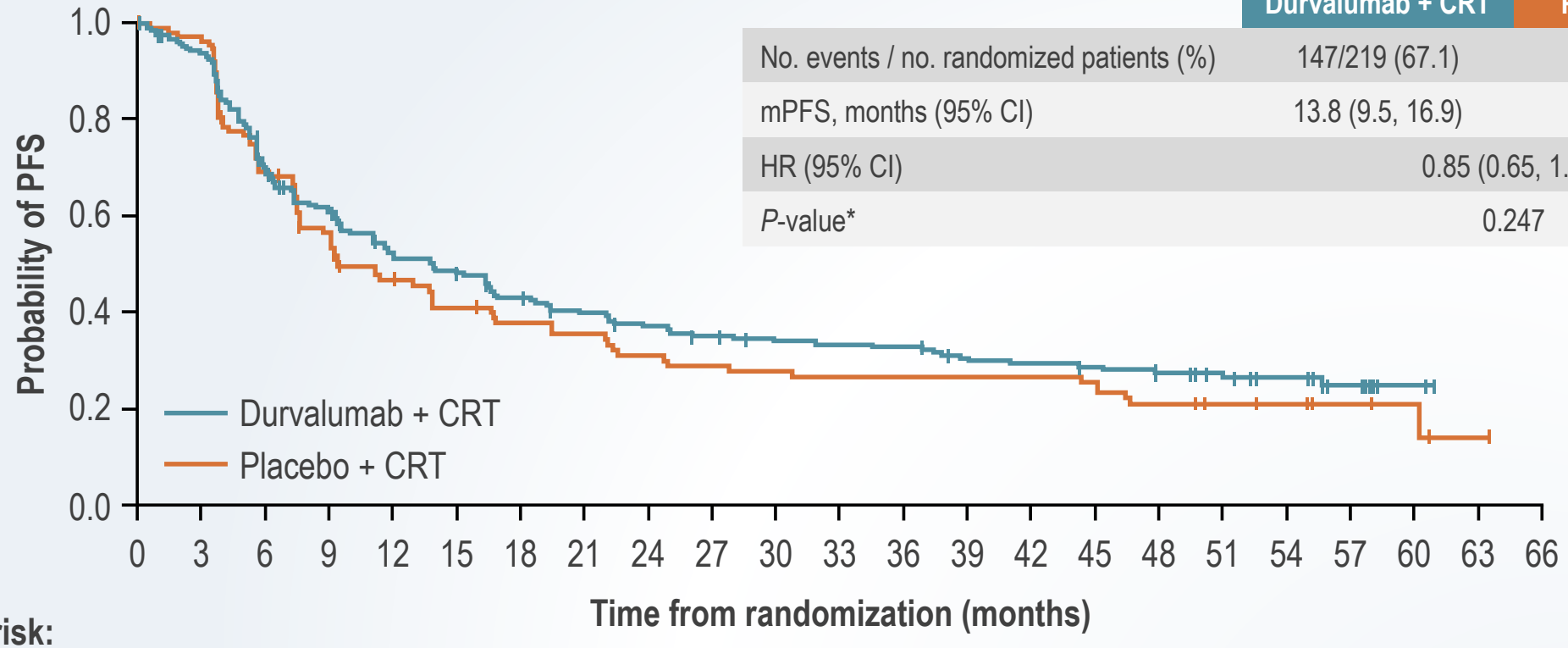
PFS by BICR (ITT population)

	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	



No. at risk:

Durvalumab + CRT	219	199	145	124	102	94	83	75	69	64	60	59	58	50	49	47	43	28	24	10	2	0	0
Placebo + CRT	109	104	72	58	44	38	34	32	28	26	25	24	24	24	24	23	19	15	12	7	3	1	0

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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.

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Summary of Adverse Events (Safety Population)

AE category, n (%)	Durvalumab + CRT (n=219)	Placebo + CRT (n=108)
Any AE	216 (98.6)	108 (100)
Maximum grade 3 or 4*	117 (53.4)	64 (59.3)
Outcome of death	30 (13.7)	11 (10.2)
SAE	103 (47.0)	56 (51.9)
Any AE leading to discontinuation of durvalumab/placebo†	56 (25.6)	13 (12.0)
0 to ≤4 months from start of treatment **(approximates the duration of IO+CRT and ends at the first post-baseline scan)**	31 (14.2)	6 (5.6)
>4 to ≤16 months from start of treatment (approximates the duration of consolidation IO in the SoC PACIFIC regimen)	12 (5.5)	6 (5.6)
>16 months from start of treatment (approximates treatment beyond the duration of consolidation IO in the SoC PACIFIC regimen)	13 (5.9)	1 (0.9)

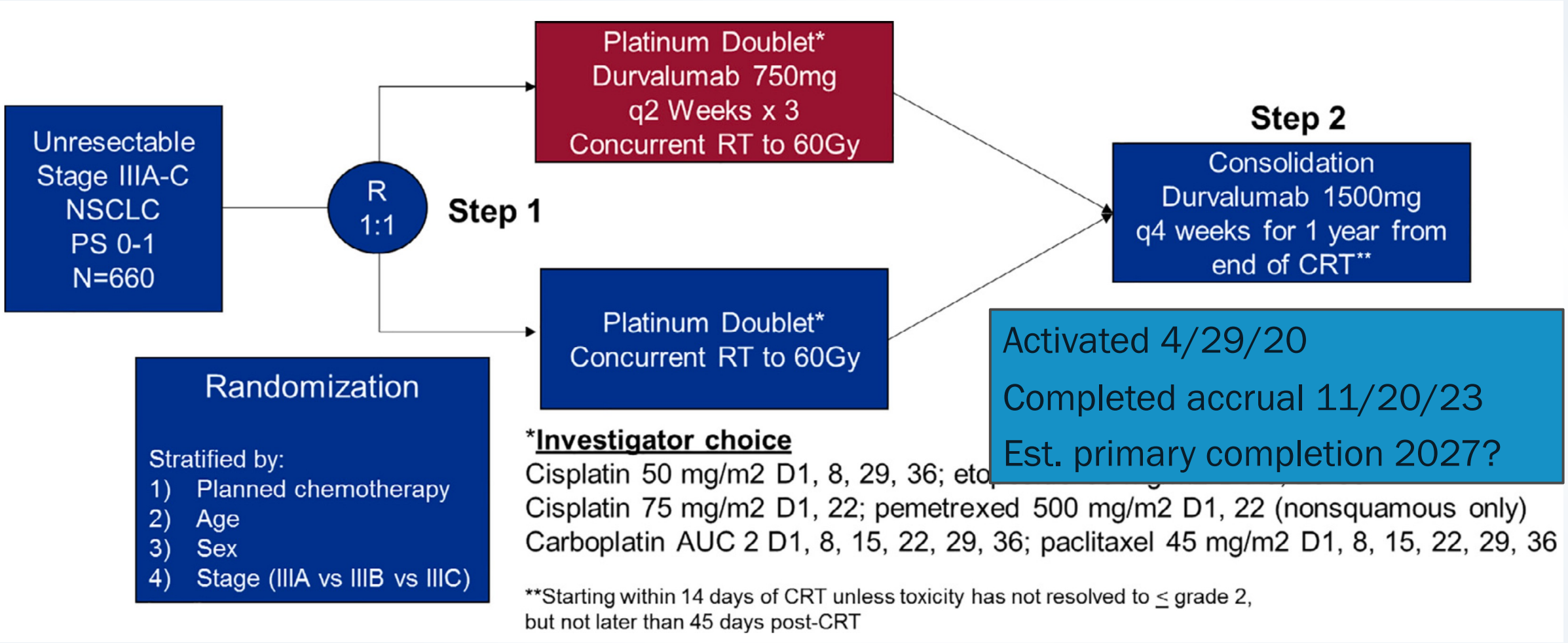
- The most common treatment-emergent AEs with **durvalumab** + SoC CRT were:
  - Anemia (42.0%), pneumonitis or radiation pneumonitis (28.8%), neutropenia (27.4%), and nausea (25.6%)
- The most common treatment-emergent AEs with **placebo** + SoC CRT were:
  - Anemia (38.0%), constipation (28.7%), pneumonitis or radiation pneumonitis (28.7%), and neutropenia (25.9%)
- Combined rates of pneumonitis or radiation pneumonitis were similar in the **durvalumab** arm (28.8%) and **placebo** arm (28.7%)
  - Grade ≥3 pneumonitis or radiation pneumonitis occurred in 10 patients (4.6%) in the **durvalumab** arm and 6 (5.6%) in the **placebo** arm

AE, adverse event; CRT, chemoradiotherapy; CTCAE, Common Terminology Criteria for Adverse Events; IO, immunotherapy; SAE, serious adverse event; SoC, standard of care.

Per CTCAE v5.0.
*Excludes any patients who experienced any AE of maximum CTCAE grade 5.
†At any time, regardless of discontinuation of CRT.

EA5181

Randomized Phase III Trial of MEDI4736 (durvalumab) as Concurrent and Consolidative Therapy or Consolidative Therapy Alone for Unresectable Stage 3 NSCLC



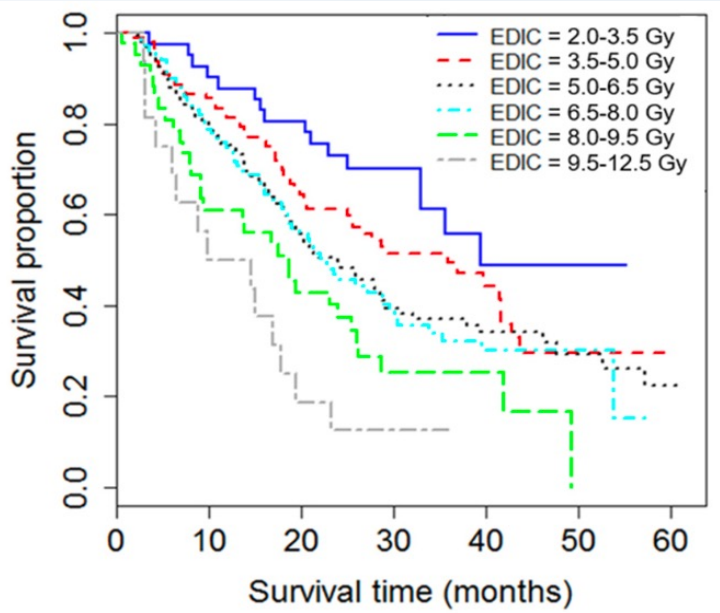
NCT04092283

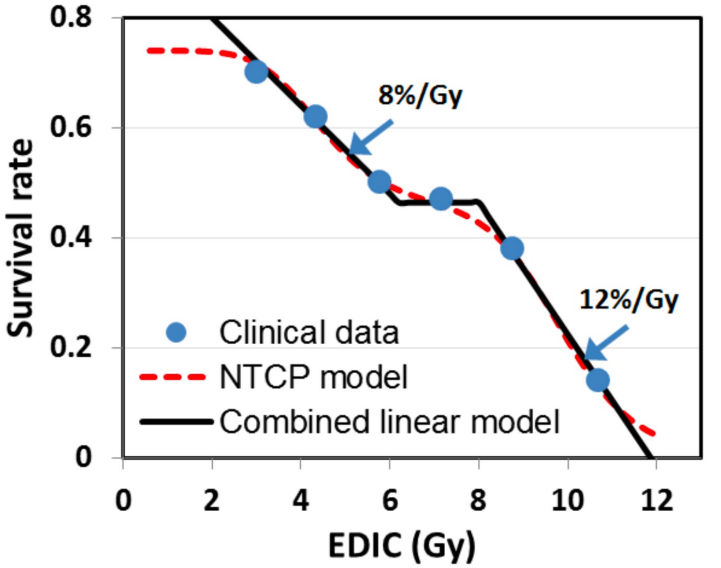
Estimated Dose to Immune Cells (EDIC)

Higher Radiation Dose to the Immune Cells Correlates with Worse Tumor Control and Overall Survival in Patients with Stage III NSCLC: A Secondary Analysis of RTOG0617

- N= 456 (from 544 enrolled) in RTOG 0617
- Motivated by finding that high dose (74 Gy) arm did not have significantly higher rate of lung and heart toxicity despite worse OS
- OS MVA: EDIC HR 1.12 (p = 0.005)
- MVA for PFS (HR 1.05) and LRFS (HR 1.09)
- MLD, MHD, ITD were NS in MV model without EDIC
- Also explored in esophageal, early-stage NSCLC, LS-SCLC, breast cancer

$$EDIC = 12\% * MLD + 8\% * MHD + \left[45\% + 35\% * 0.85 * \left(\frac{n}{45}\right)^{\frac{1}{2}}\right] * ITDV / (61.8 * 10^3)$$





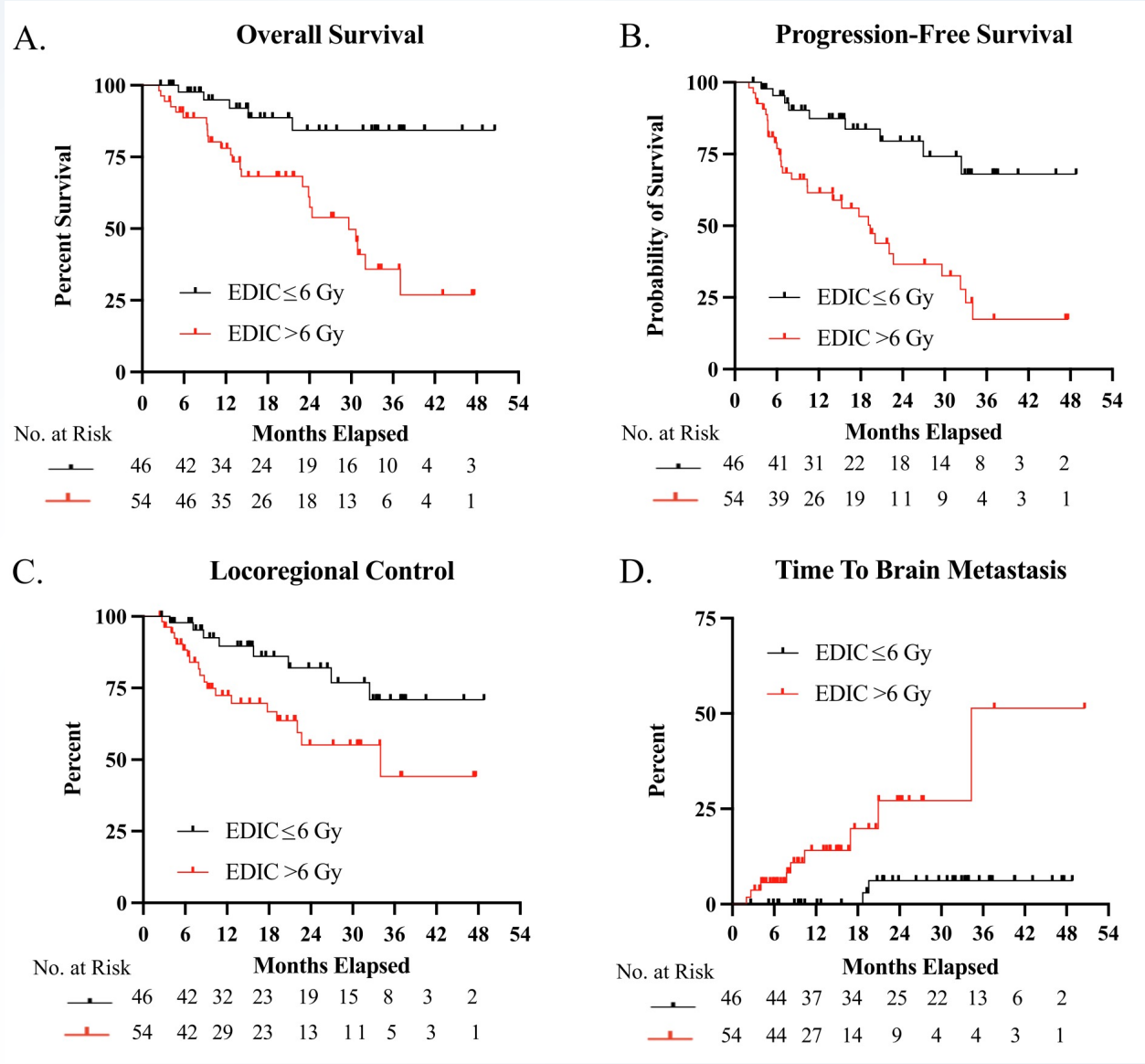
Jin et al. *Cancers (Basel)*. 2021;13(24):6193.

Impact of EDIC in PACIFIC era

Impact of radiation dose to the immune cells in unresectable or stage III non-small cell lung cancer in the durvalumab era

Neal S. McCall [a,*], Hamilton S. McGinnis [a], James R. Janopaul-Naylor [a], Aparna H. Kesarwala [a], Sibo Tian [a], William A. Stokes [a], Joseph W. Shelton [a], Conor E. Steuer [b], Jennifer W. Carlisle [b], Ticiana Leal [b], Suresh S. Ramalingam [b], Jeffrey D. Bradley [a], Kristin A. Higgins [a]

- N = 100 locally-advanced, unresectable stage II/III NSCLC
- Treated with definitive chemoRT -> durvalumab
- OS MVA: EDIC (continuous) HR **1.35**, p <0.001
- OS MVA: EDIC > 6 Gy HR **4.15**, p <0.01
- EDIC was also independent predictor of PFS and LRC, time to BM



McCall et al. *Radiother Oncol*. 2022;174:133-140.

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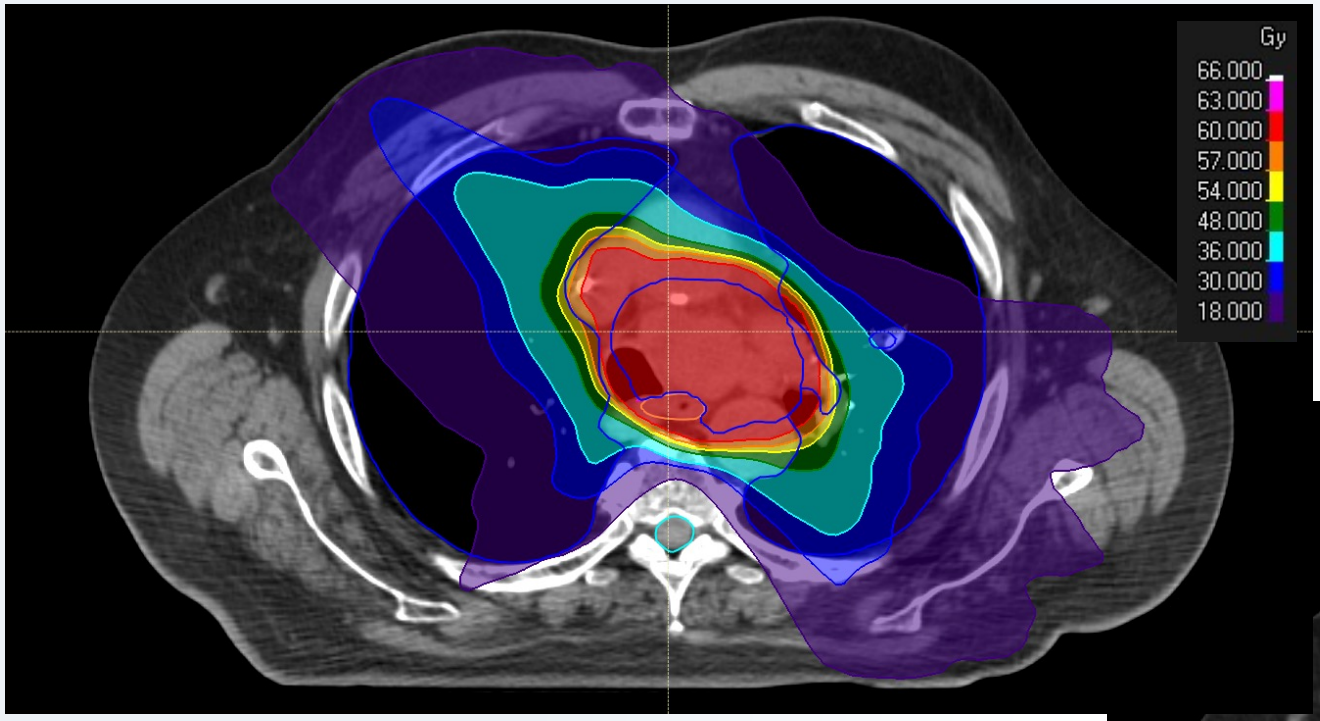
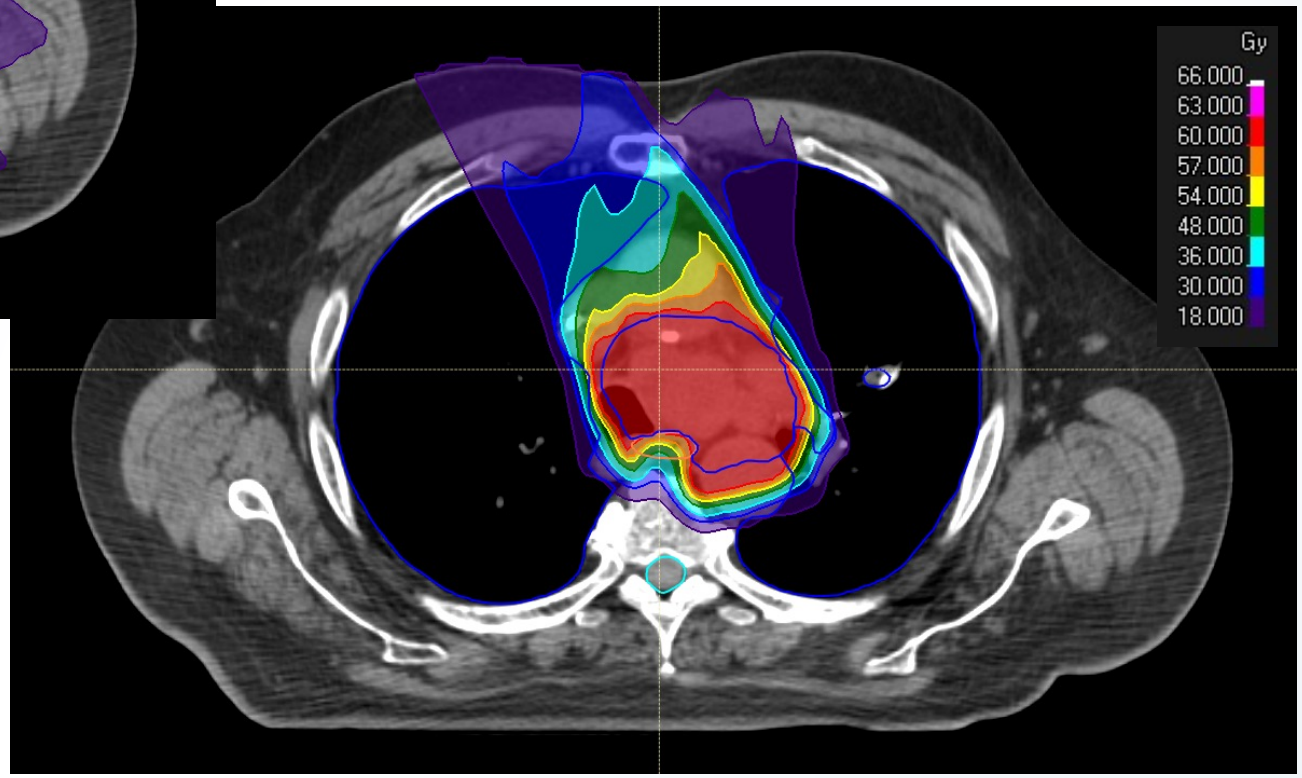


Photons (VMAT)

Protons (IMPT)

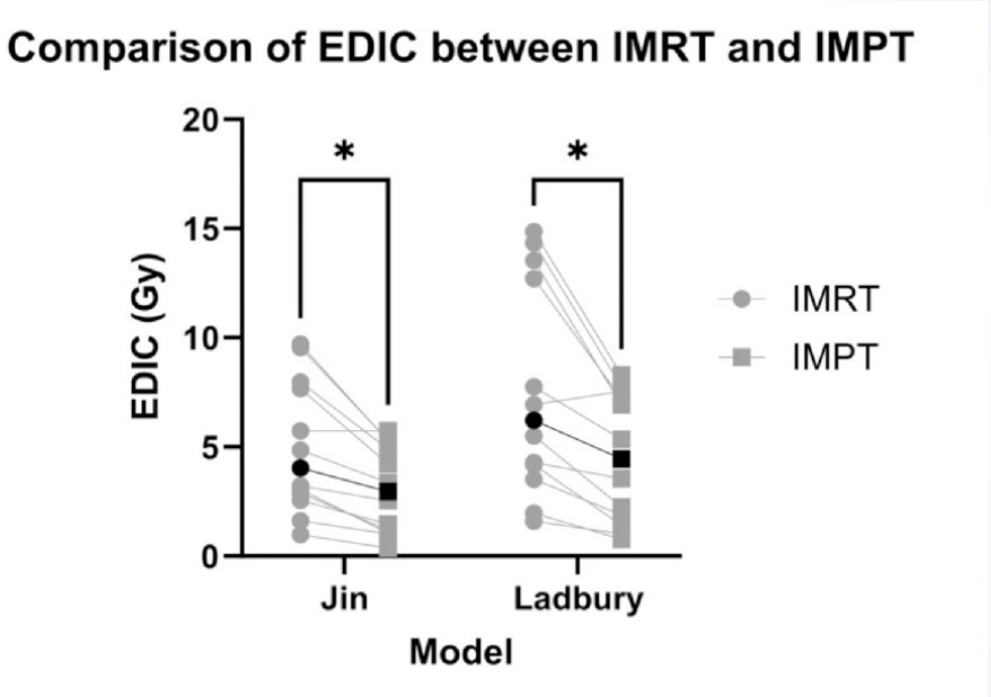


Impact of RT Modality on EDIC

Immune System Dose With Proton Versus Photon Radiotherapy for Treatment of Locally Advanced NSCLC

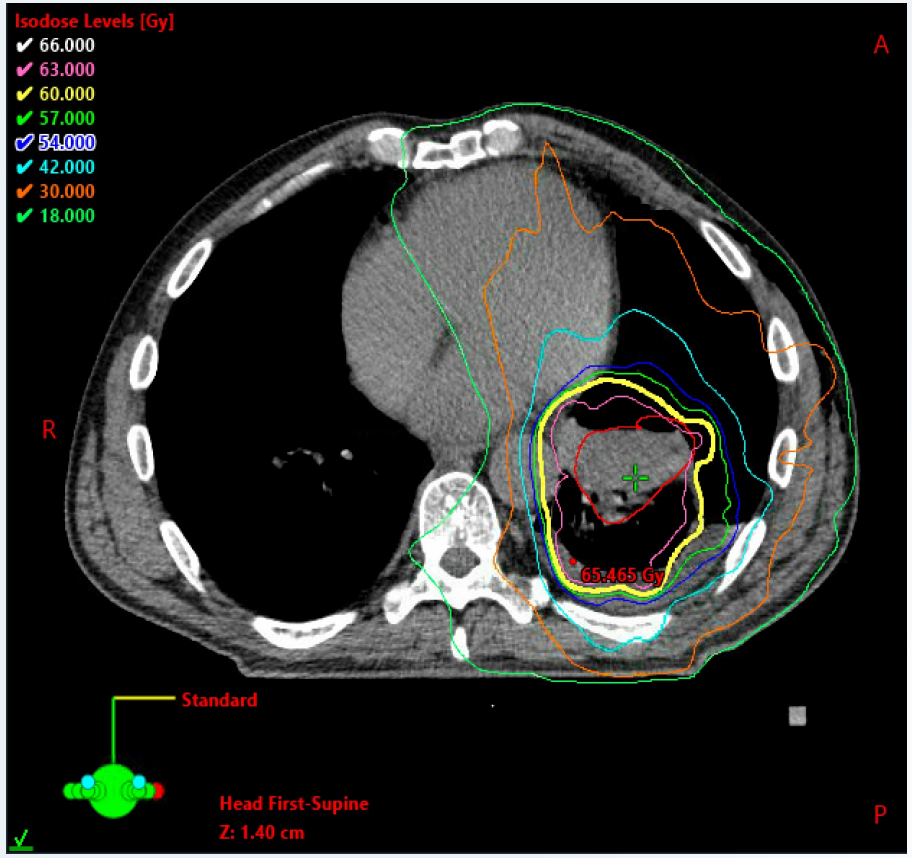
Jimmy S. Patel (MD, PhD)[1], Neal S. McCall (MD)[2], Matthew Thomas (MS)[1], Jun Zhou (PhD)[1], Kristin A. Higgins (MD)[1], Jeffrey D. Bradley (MD)[3], Sibo Tian (MD)[1], Mark W. McDonald (MD)[1], Aparna H. Kesarwala (MD, PhD)[1,*], William A. Stokes (MD)[1,*]

- N=12 patients with treatment-approved IMRT and IMPT plans
- Mean EDIC 4.99 -> 3.04 Gy (IMRT vs IMPT)
  - Mean heart dose 11.4 -> 3.2 Gy
  - Mean lung 15 -> 9.9 Gy
  - Integral dose 203 -> 142.3 Gy·L
- Median 2-yr OS advantage 8% (63% vs 71%, *P* = 0.03; range 0-32%

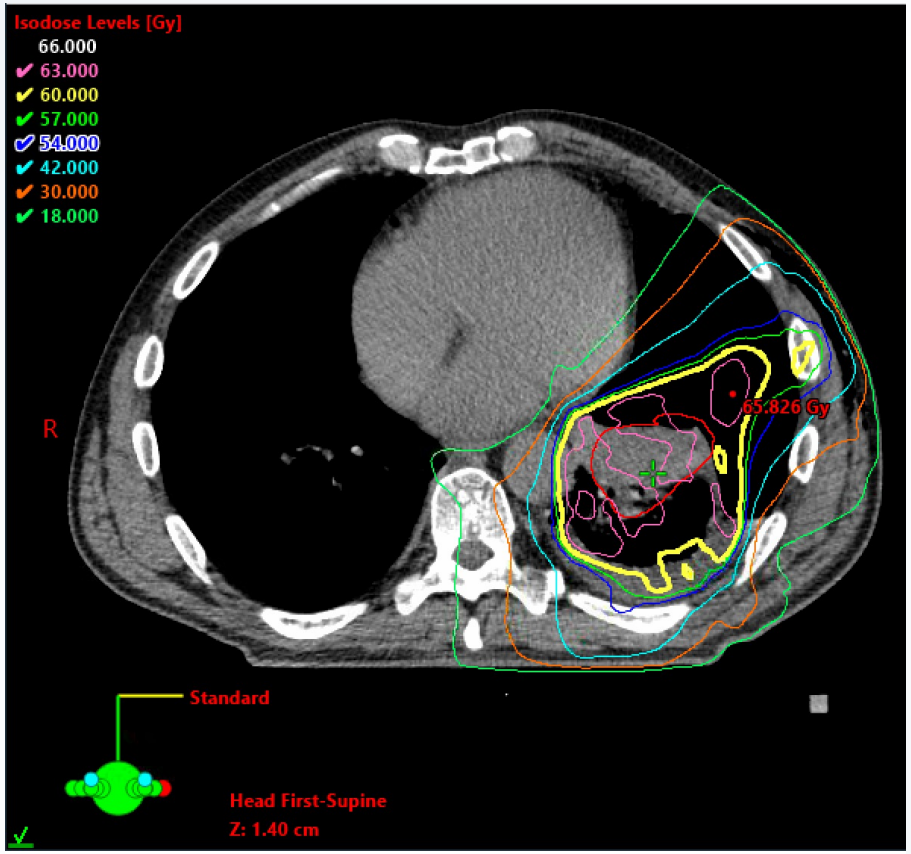


Patel et al. *Int J Part Ther*. 2024;12:100016.

Clinically Delivered Plan



Non-coplanar Oblique Re-plan



N=35, stage III NSCLC treated with CRT

Clinical delivered plans were re-optimized with non-coplanar technique

Mean heart dose
13.5 -> 7.2 Gy

Integral dose
253 -> 215 (Gy·L)

EDIC 5.5 -> 4.9 Gy
($p<0.001$)
HR 1.21, 2-yr OS benefit ~7%

Hopkins et al. *IASLC WCLC.* 2024

NRG RTOG 1308

Phase III Randomized Trial Comparing Overall Survival After Photon vs Proton Chemoradiotherapy for Inoperable Stage II-IIIB NSCLC

STRATIFY	Stage 1.II 2.IIIA 3.IIIB Histology 1.Squamous 2.Non-Squamous Concurrent Chemotherapy Doublet Type 1.Carboplatin/paclitaxel 2.Cisplatin/etoposide 3. carboplatin/ pemetrexed	RANDOMIZE	Arm 1: Photon dose—70 Gy*, at 2 Gy (RBE) once daily plus platinum-based doublet chemotherapy** Arm 2: Proton dose—70 Gy (RBE), at 2 Gy once daily plus platinum-based doublet chemotherapy**	Both Arms: Durvalumab or Consolidation chemotherapy x 2 cycles required for patients who receive concurrent carboplatin and paclitaxel***

Co-Primary: OS, Cardiac AE + lymphocyte reduction

2/3/14 Activated

9/26/23 Closed to accrual

PI Zhongxing Liao

*The highest total prescribed dose will be 70 Gy (Relative Biological Effectiveness (RBE)) **without exceeding tolerance dose-volume limits of all critical normal structures**. The dose range can be 60-70Gy provided the dose constraints of OARs are met.

NCT01993810

RAD5621-22

Proton Beam Radiation Therapy for Resected N2 Non-Small Cell Lung Cancer

Eligibility

resected NSCLC stage III (pN2)

no prior XRT no other recent malignancies

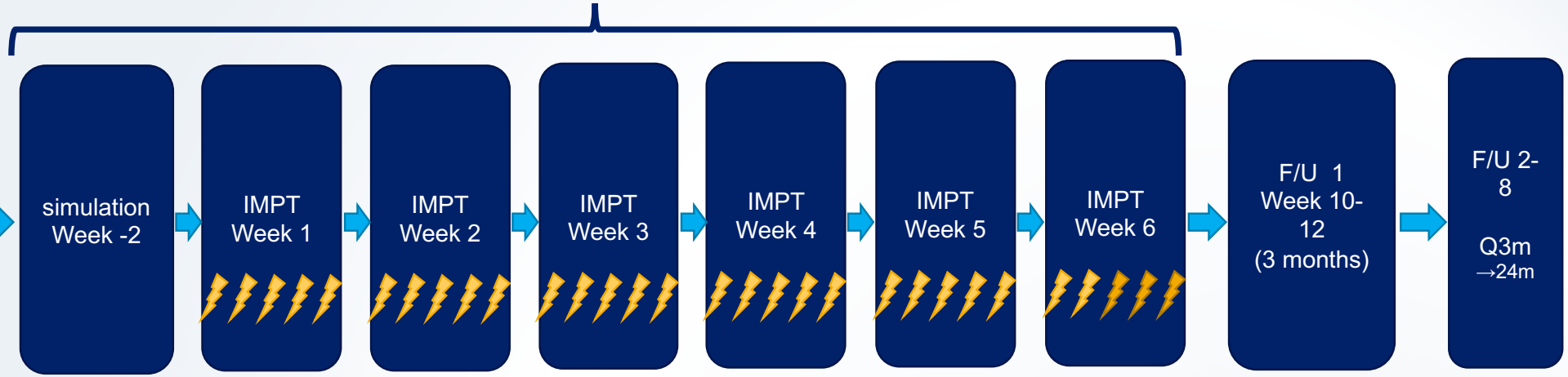
no known sensitizing EGFR or ALK mutations

ECOG PS <2

N = 20

register

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



baseline

mid-treatment (week 3 or 4)

end of treatment (week 6)

follow-up (week 10-12)

Primary endpoint: Safety

Secondary: Radiation dose to circulating immune compartment, Efficacy

PIs: Stokes/Kesarwala/Buchwald; Funding: Winship Invest$

NCT06008730

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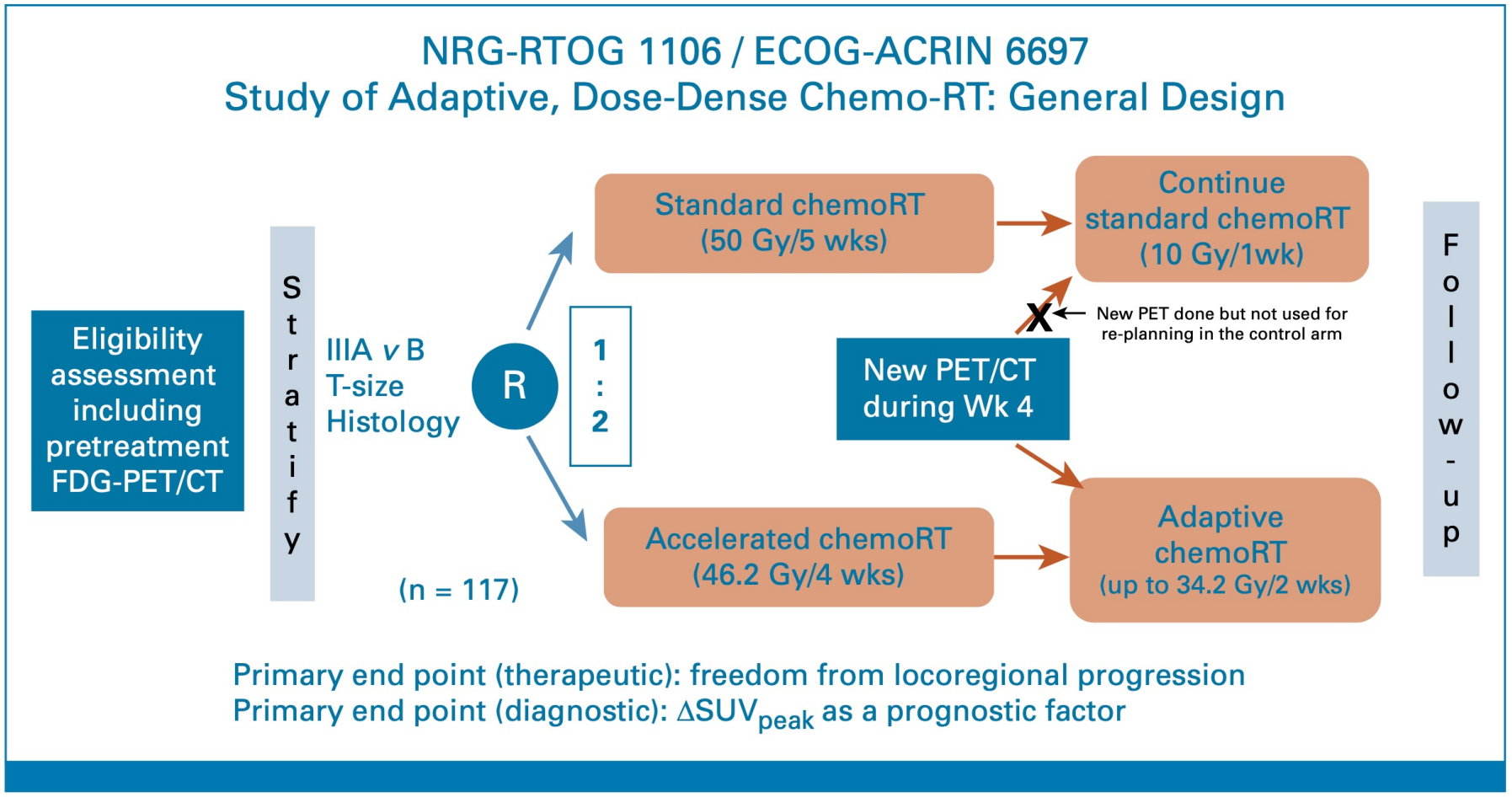
NRG RTOG 1106/EA6697

Randomized Phase II Trial of Individualized Adaptive (chemo) Radiotherapy Using Midtreatment 18F-FDG PET/CT in Stage III NSCLC



2012-2017 (pre-PACIFIC)

All cases required rapid pre-treatment review

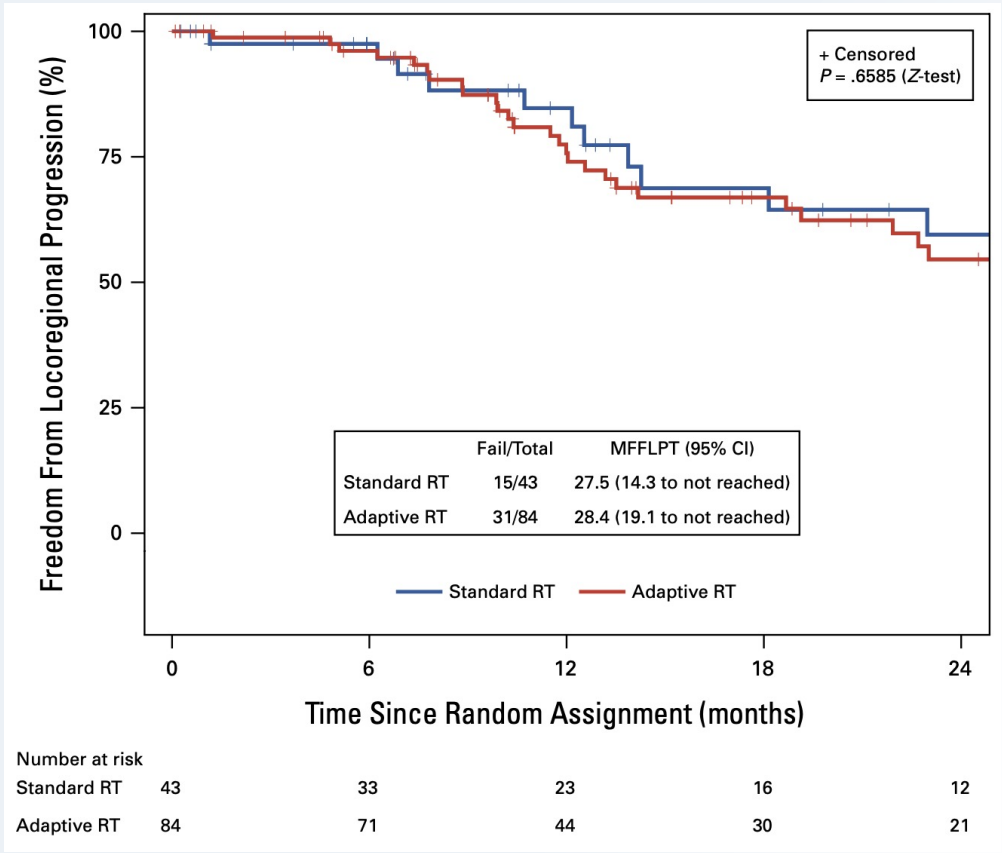
Up to 80.2 Gy in 30 fractions, not exceeding mean lung dose 20 Gy

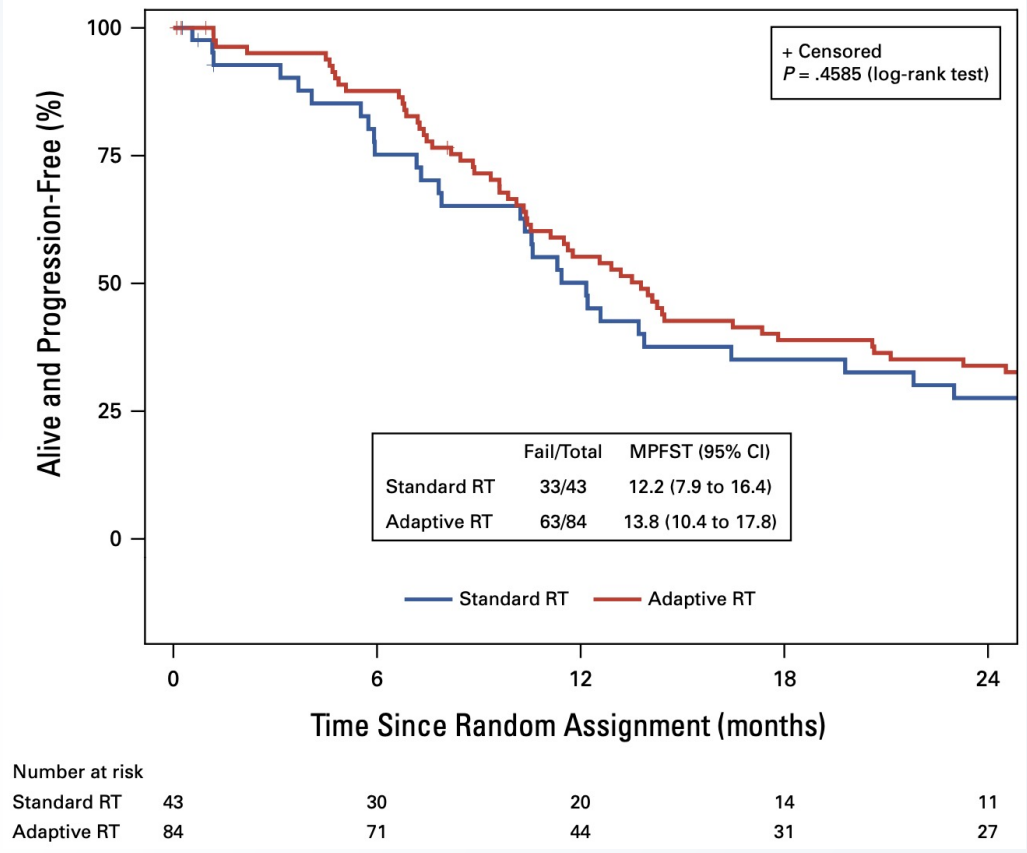
Adaptive fractional dose: 2.2 - 3.8 Gy

Median adaptive dose: 71 Gy

Kong et al. *J Clin Oncol* 2024 PMID 39365957

No improvement in FFLRP or PFS





2-yr FFLRP 54.6 vs 59.5% (Adaptive vs Std)
No significant dosimetric differences

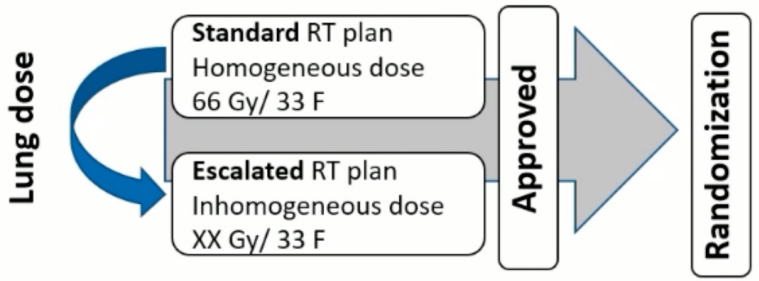
ΔSUV_{peak} and ΔMTV not associated with FFLP
56% reduction in MTV, 33.2% reduction in GTV

Kong et al. *J Clin Oncol* 2024 PMID 39365957

NARLAL 2

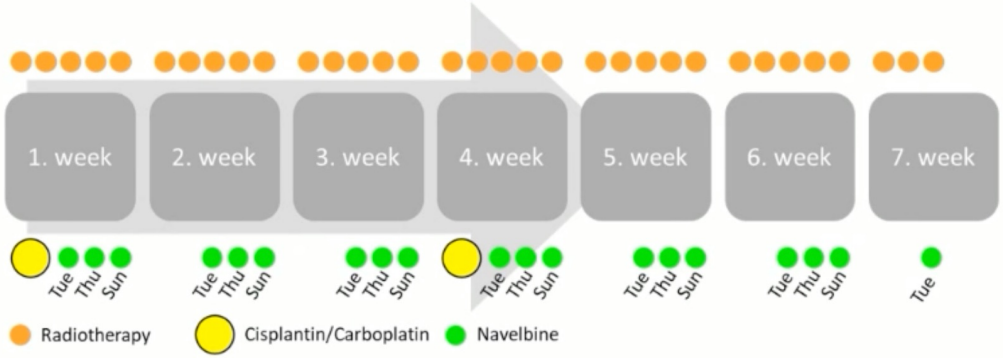
Novel Approach to Radiotherapy for LA-NSCLC - phase III randomized trial on dose escalation

TRIAL DESIGN



Inclusion criteria
- Age>18 years
- NSCLC st. IIB-IIIB
- PS 0-1

Exclusion criteria
- Other active cancer
- Uncontrolled systemic disea



Hansen et al: Radiotherapy & Oncology 2017;

N = 350 randomized

Primary: Locoregional control

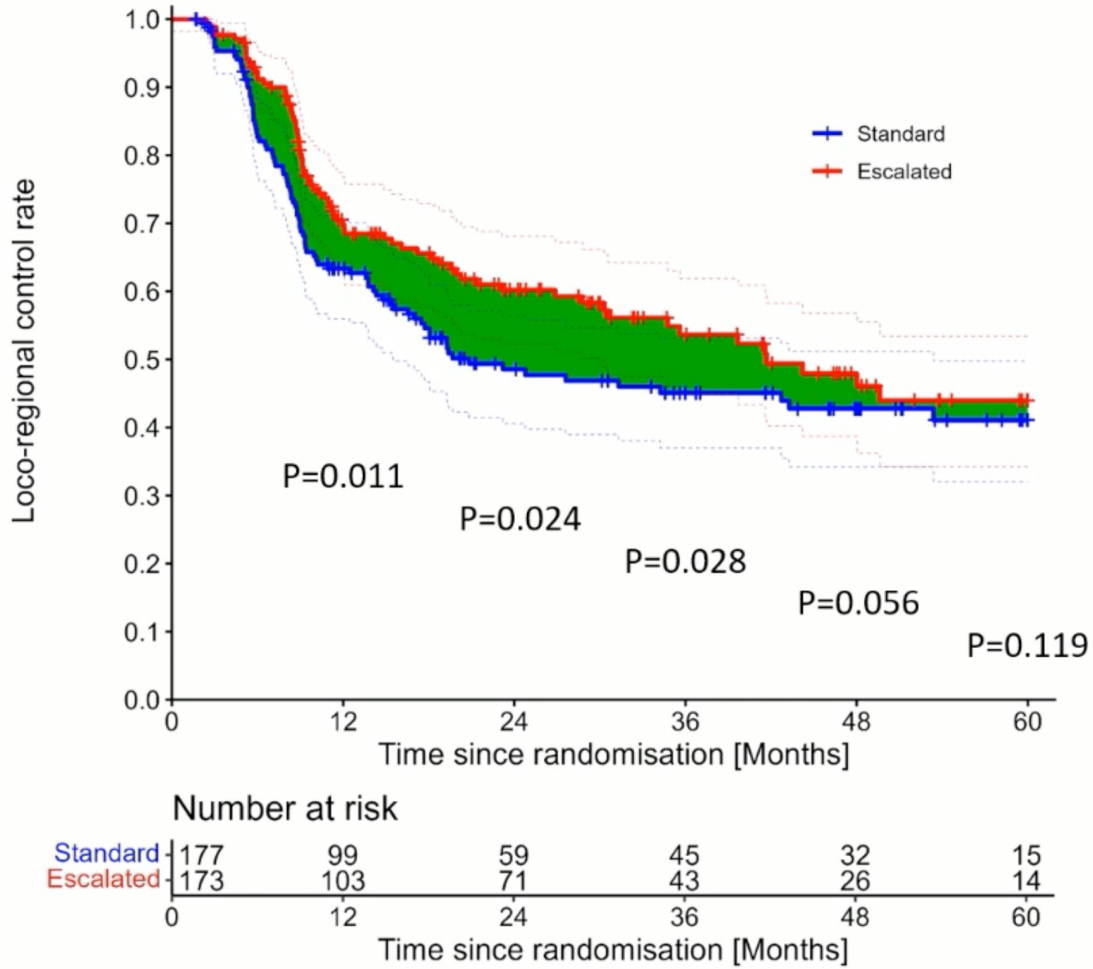
Modern radiotherapy
- 4D-CT
- Daily CBCT
- Adaptive RT

Dose-escalated RT
- Target dose
  - 95 Gy to GTV-p
  - 74 Gy to GTV-n
- 2 plans with equal lung dose created before randomization

NCT02354274

Dose Escalation Improves Locoregional Control

RESULTS



20% received durvalumab

G3 esophagitis
- 9 vs 5.8%

G3 pneumonitis
- 3.4 vs 6.4%

No G4+ acute AEs

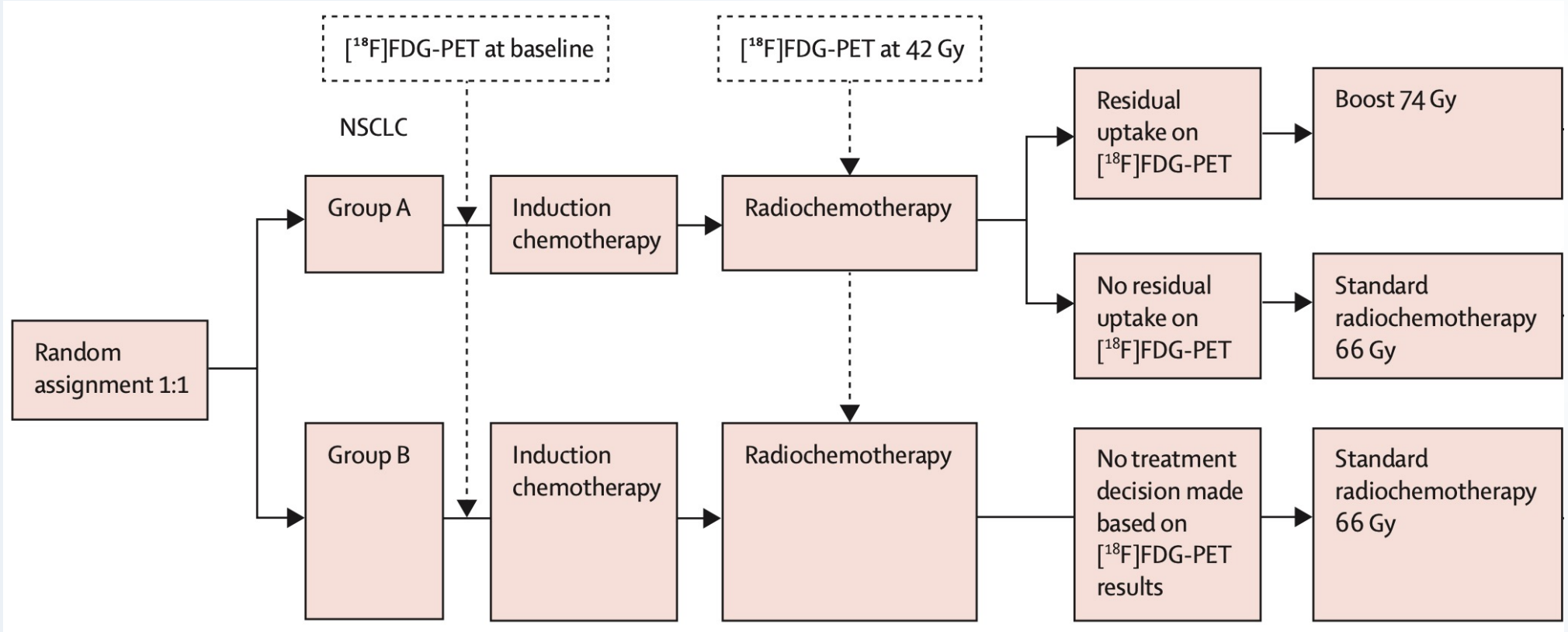
Three G5 events in each arm (1.7%)

OS immature

Schytte et al. Abstract 3531 ESTRO 2024

RTEP7–IFCT-1402

Phase II Adaptive Dose Escalation Trial



71% rcvd boost

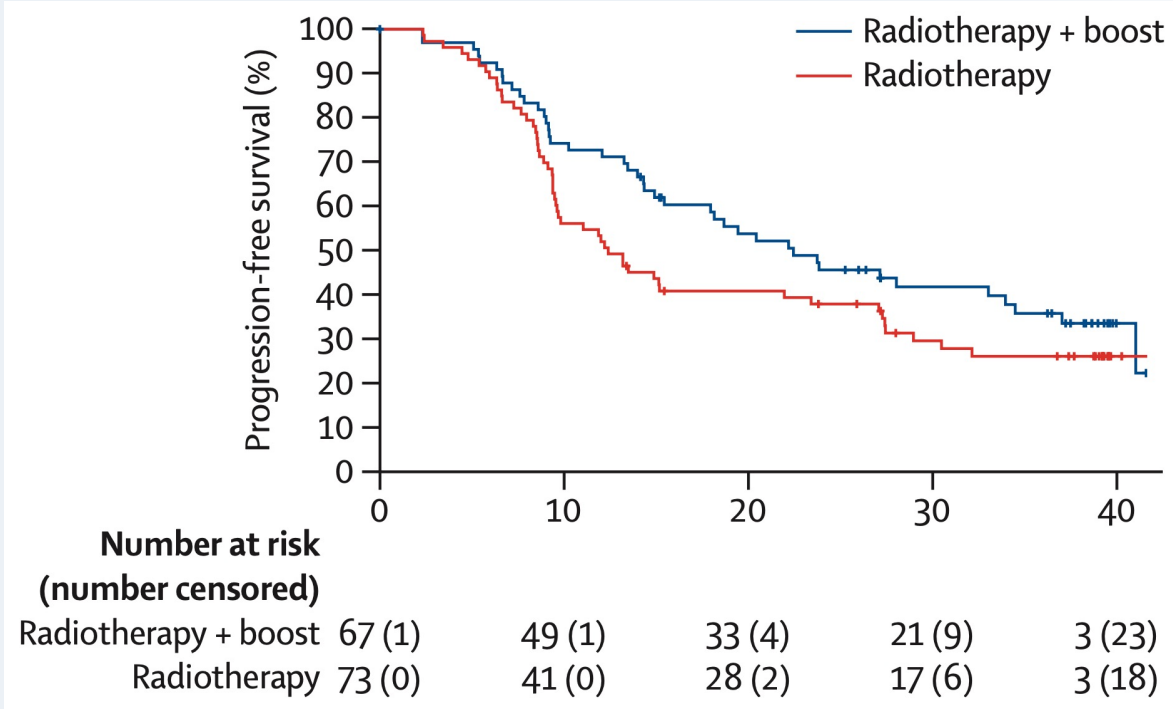
N=158, stage III NSCLC, PS 0-1, EGFR/ALK negative

Stratification: IMRT vs 3D-CRT, center

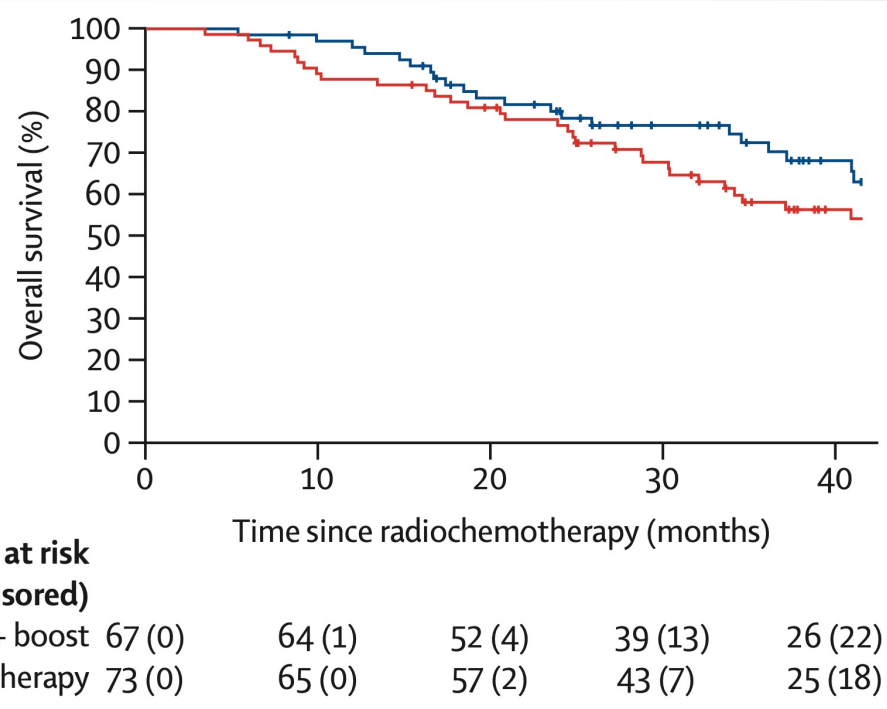
Primary: 15-month local control

2015 to 2021 - Amended for durvalumab (48% rcvd)

Vera et al. *Lancet Oncol* 2024;25(9):1176-1187



Number at risk (number censored)					
Radiotherapy + boost	67 (1)	49 (1)	33 (4)	21 (9)	3 (23)
Radiotherapy	73 (0)	41 (0)	28 (2)	17 (6)	3 (18)



Number at risk (number censored)					
Radiotherapy + boost	67 (0)	64 (1)	52 (4)	39 (13)	26 (22)
Radiotherapy	73 (0)	65 (0)	57 (2)	43 (7)	25 (18)

15-month LC 77.6 vs 71.2% (Boost vs Std dose)

- No durvalumab subgroup: 71.4 vs 61.1%
- Durvalumab subgroup: 82.1 vs 81.1%

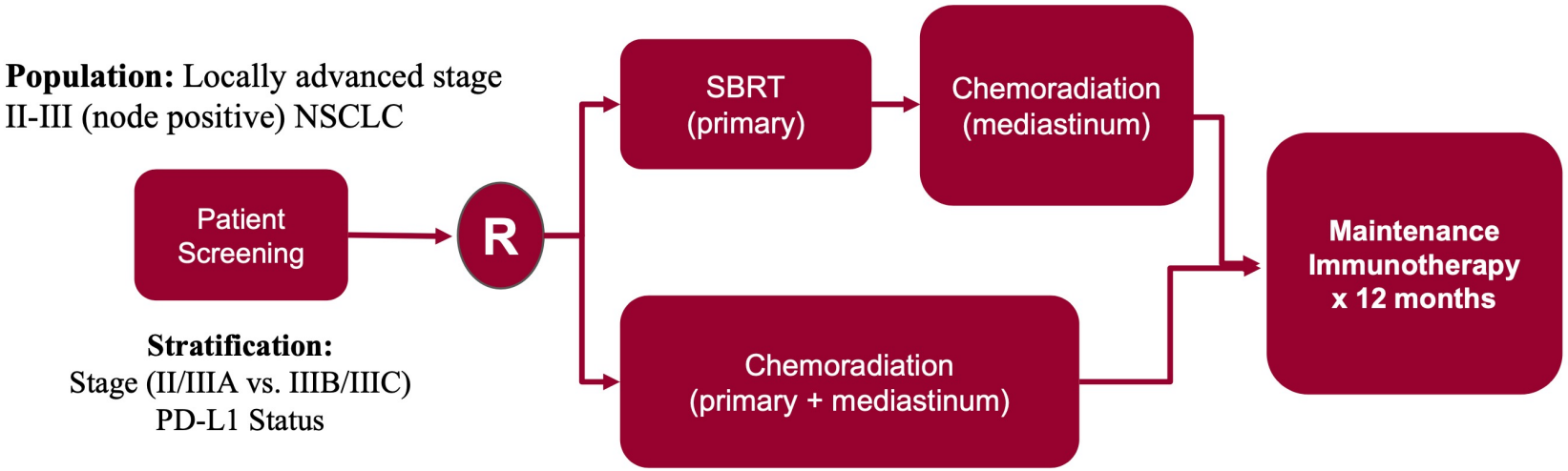
Med PFS 22.3 vs 12.3mo

Acute G3+ AEs: 45 vs 29%
Acute SAEs: 14 vs 7%
Late G3+ AEs: 7 vs 5%

Vera et al. *Lancet Oncol* 2024;25(9):1176-1187

NRG-LU008

Phase III Prospective Randomized Trial of Primary Lung Tumor Stereotactic Body Radiation Therapy Followed by Concurrent Mediastinal Chemoradiation for Locally-Advanced NSCLC



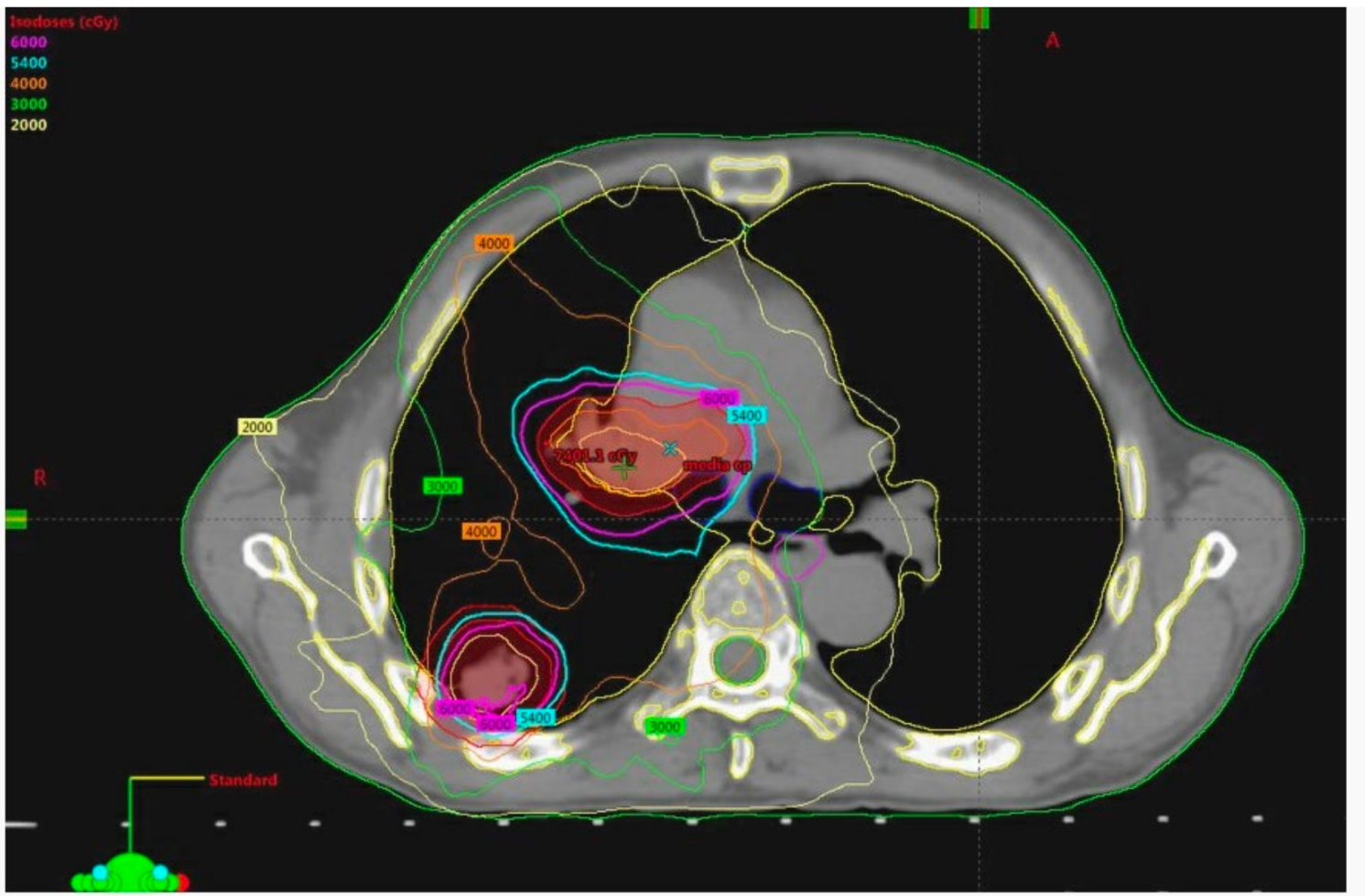
- Control arm: chemoradiation to the primary and mediastinal disease (60 Gy/2 Gy) → immunotherapy maintenance x 12 months
- Experimental arm: SBRT to the primary (standard BED ≥100 Gy dose regimen) → chemoradiation to mediastinal disease (60 Gy/2 Gy) → immunotherapy maintenance x 12 months
  - SBRT to primary tumor:
    - 3 fractions to 54 Gy (BED10 of 151.2 Gy) [peripheral]
    - 4 fractions to 50 Gy (BED10 of 112.5 Gy) [peripheral]
    - 5 fractions to 50 Gy (BED10 of 100 Gy) [peripheral or central]
  - Radiation to involved hilar/mediastinal lymph nodes: 2 Gy x 30 fx to 60 Gy, IMRT or proton therapy
  - Concurrent chemotherapy: carboplatin + paclitaxel, cisplatin + etoposide, cisplatin + pemetrexed, or carboplatin + pemetrexed
  - Maintenance immunotherapy: durvalumab x 12 months [if durvalumab is NOT given, carbo/paclitaxel pts receive 2 cycles of consolidation]

Co-primary: OS and PFS
Activated 5/10/23
N = 97 of 474 planned

NRG ONCOLOGY™

NCT05624996

NRG-LU008 Representative Case



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)

NCT05624996

Takeaway Points

- PACIFIC regimen remains standard of care for locally advanced unresectable NSCLC without driver mutations
- Addition of concurrent immunotherapy to CRT does not appear to confer additional benefit
- Care should be taken to minimize impact of RT on lymphopenia, which may be mitigated by advanced modalities or planning methods
- Dose escalation warrants re-evaluation with modern radiotherapy techniques
- Support ongoing randomized trials in stage III unresectable population