Best Practices for the Continuum of Care: A Multidisciplinary Approach

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Dawn Owen, MD, PhD, Radiation Oncology, Mayo Clinic Rochester

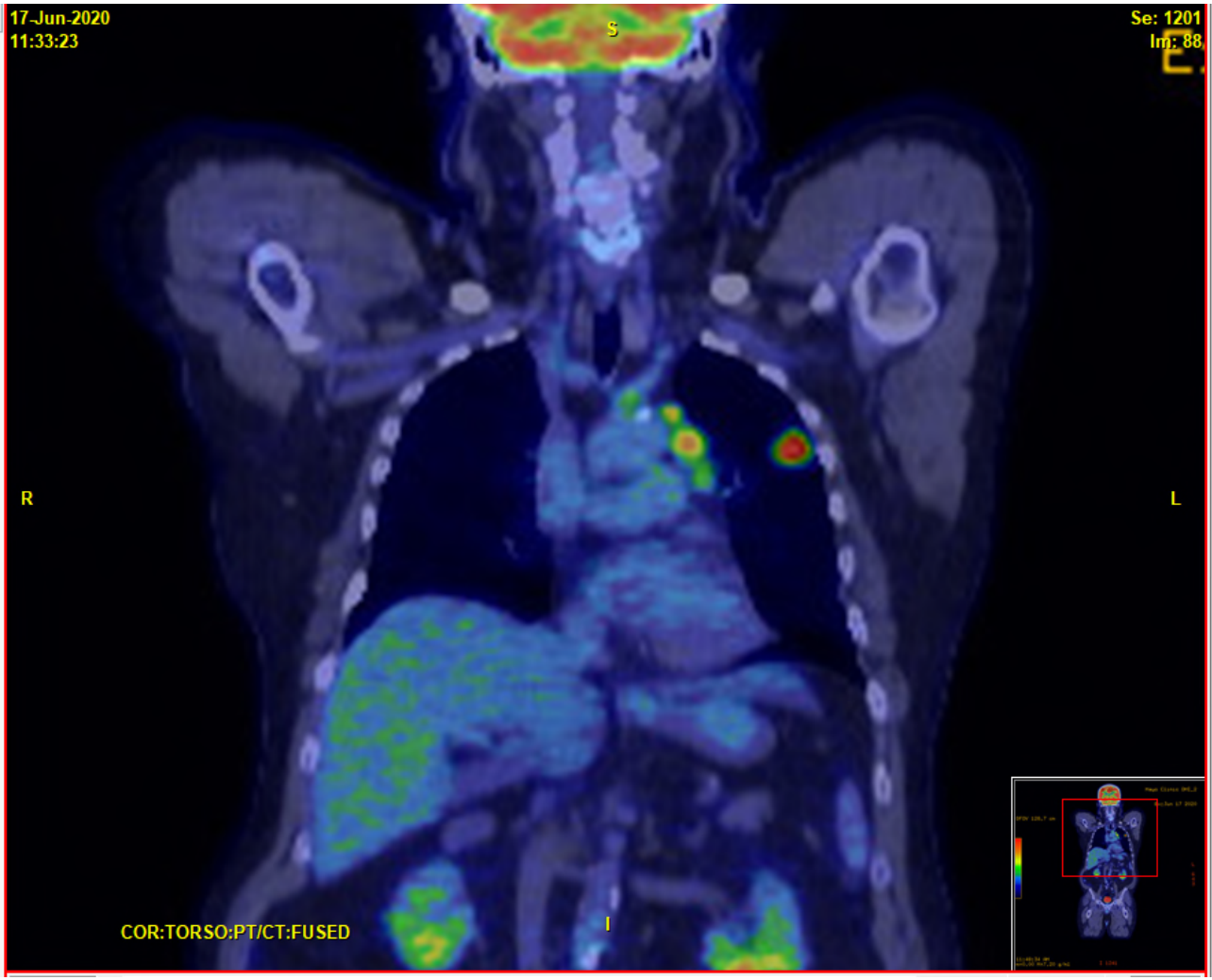
OUTLINE FOR WEBINAR 2

- Multidisciplinary coordination of chemoradiation and durvalumab
- Factors in determining the selection of chemotherapeutic agents
- Radiation considerations
- Diagnosis and management of pneumonitis

CASE 1

72 year old male with history of hypertension, hyperlipidemia, BPH; 14 PYHx quit smoking 25 years ago:

- Presents with back pain for which CT T spine done
- Incidental finding of 2.5 cm LUL nodule
- PET-CT shows FDG avid 2.7 cm LUL nodule, left hilar, AP window, para-aortic, prevascular adenopathy
- MR brain is negative for metastasis
- EBUS shows station 4L positive for adenocarcinoma, TTF1 positive, tumor cells 100% PDL1 expressing
- PFTs → FEV1 1.94 L (75% predicted), FVC 2.77 L (81% predicted), DLCO 81%
- NGS shows KRAS G12C mutation, no other mutations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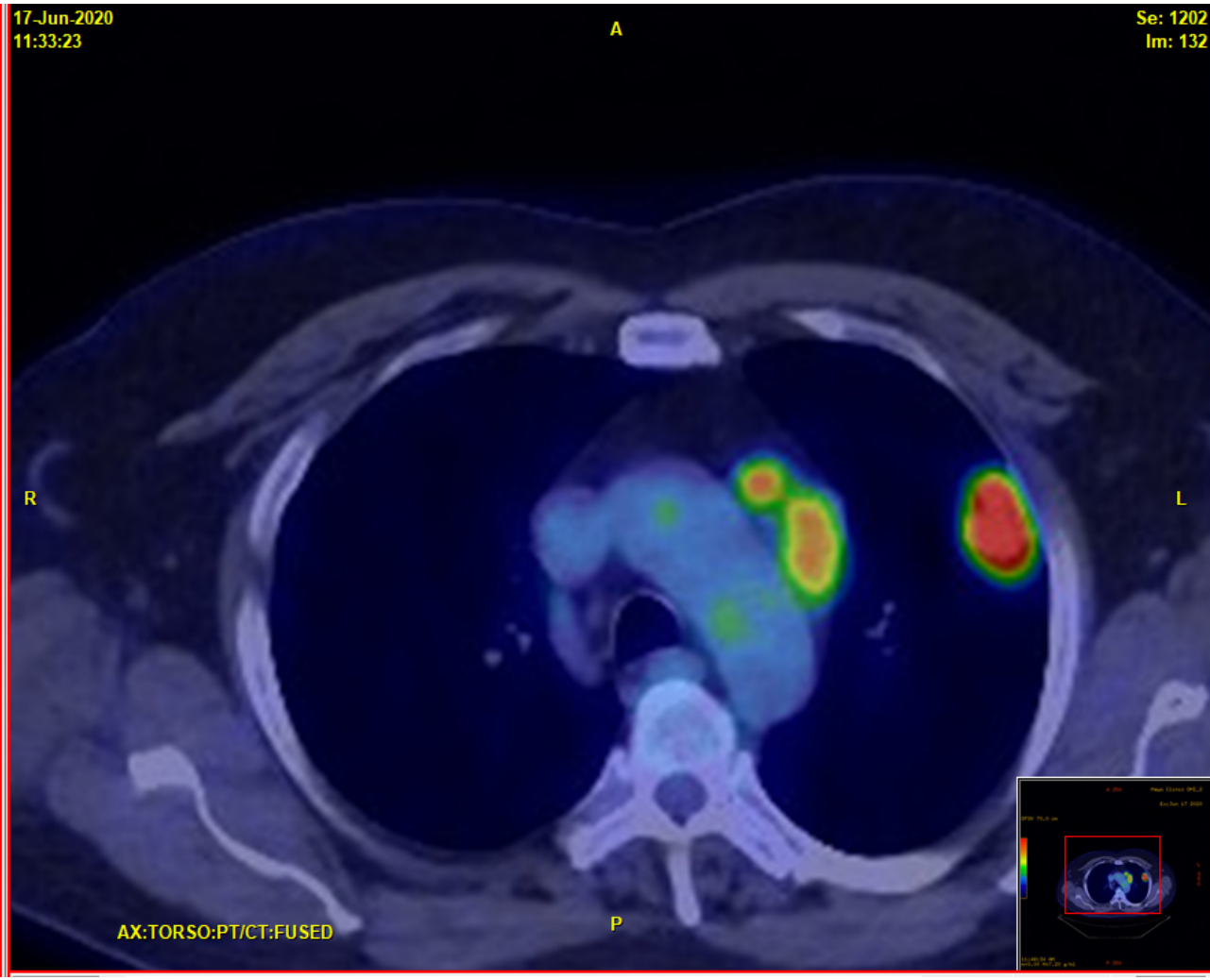
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Radiation Considerations

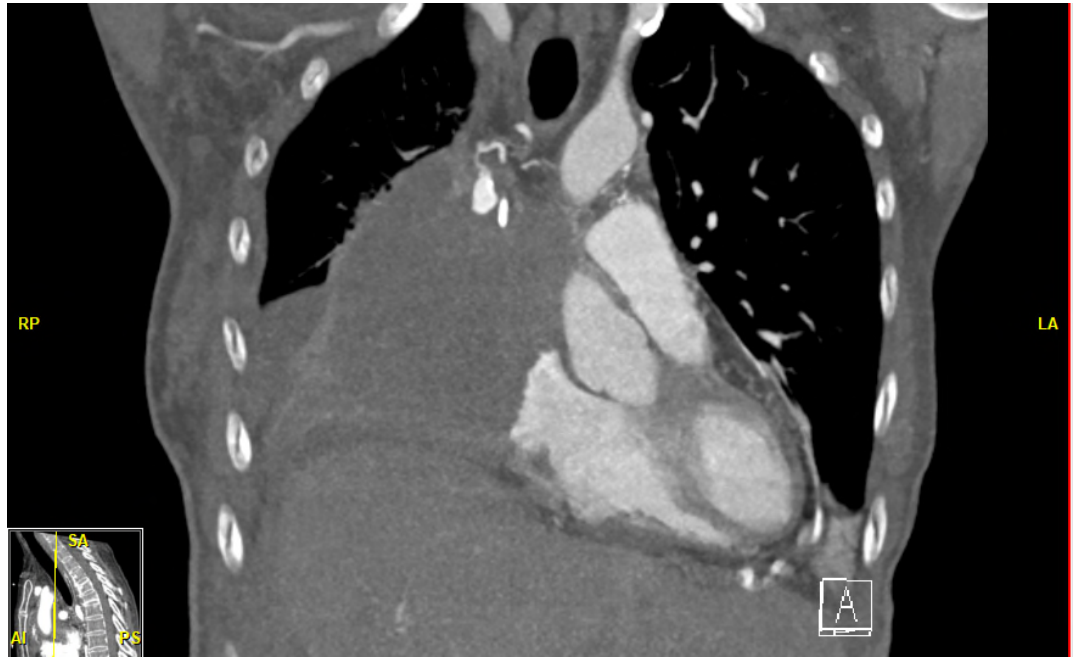
Dawn Owen, MD, PhD

WHAT MAKES A PATIENT TREATABLE?

- First principles:
  - ECOG status
  - Weight stability
  - PFTs (FEV1 > 1 L, DLCO > 40%)
  - Social support
  - Comorbidities
  - “Radioencompassable disease”

WHAT MAKES A TUMOR RADIOENCOMPASSABLE?

- It’s not the tumor, it’s the amount of normal lung that matters!
- Determined at the time of radiation simulation and planning
- Will address strategies to deal with tumors where there is a high tumor to lung ratio in Webinar 3

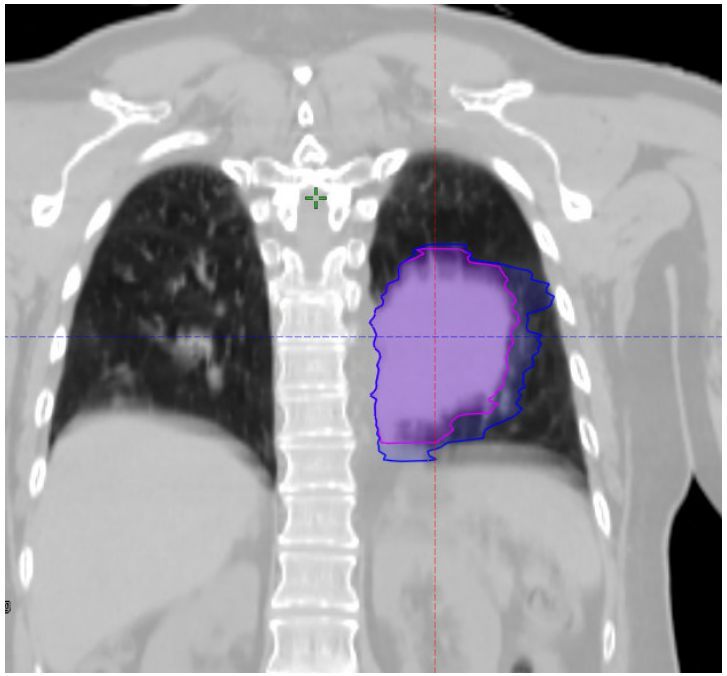


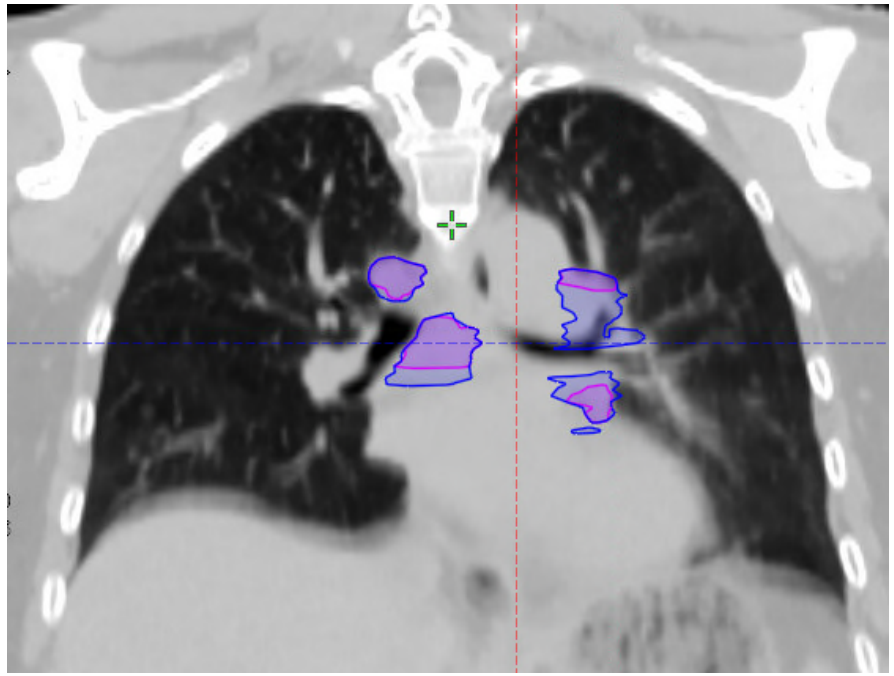
RESTAGE CHEST IF IMAGING IS OLD!

- Really need to time start of RT with chemotherapy
- Want to minimize the time between diagnostic imaging e.g. PET-CT and start of chemoradiation (goal to start of chemoradiation from tissue diagnosis to treatment should be about 1 month)
- If imaging is more than 1 month old, would obtain repeat imaging with diagnostic CT chest with IV contrast
- Ideally want to start CRT for locally advanced NSCLC within a week of simulation due to risk of progression

RADIATION SIMULATION

- It is really important to consider motion management for lung tumors
- Standard of care is a 4DCT scan to assess motion and generation of an IGTV for both nodal volumes and the primary tumor





CONTOURING

- Must contour cord (canal) heart, left and right lung separately, lung total structure (lung – GTV), esophagus at a minimum
- Would also consider contouring liver, stomach for lower lobe tumors and contour plexus for apical tumors
- For volume delineation:
  - GTV
  - IGTV (if free breathing 4DCT)
  - CTV (5-10 mm expansion of IGTV) → do not include structures where cancer is unlikely to have spread e.g. crop from bone, heart, esophagus
  - PTV (5 mm expansion with daily CBCT)

RADIATION PLANNING

- IMRT is preferred (reduces risk of RP compared to 3DCRT – 3.5% vs 7.9%)

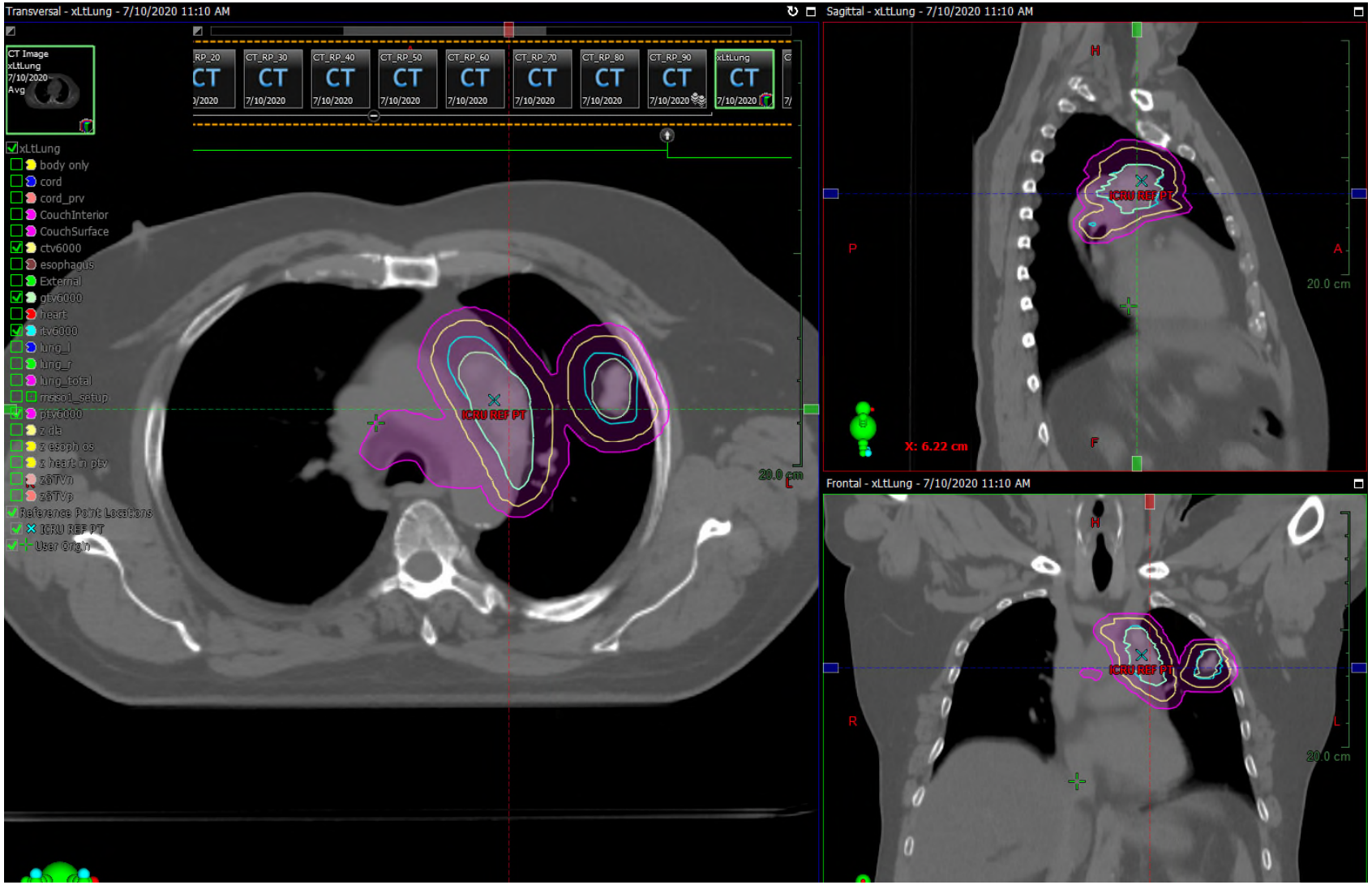
Table A4. Univariate Regression Model for CTCAE Grade 3 or Greater Pneumonitis

Covariate	Comparison	OR (95% CI)	*P*
Radiation therapy technique	3D-CRT (RL) *v* IMRT	0.43 (0.18 to 0.99)	.046
Radiation therapy dose level	60 (RL) *v* 74 Gy	0.64 (0.28 to 1.45)	.284
AJCC stage group	IIIA (RL) *v* IIIB	2.01 (0.93 to 4.32)	.075
PTV volume, mL	Continuous	1.001 (1.000 to 1.002)	.048
Mean lung dose	Continuous	1.097 (0.998 to 1.206)	.056
Lung V5, %	Continuous	1.020 (0.994 to 1.047)	.135
Lung V20, %	Continuous	1.069 (1.012 to 1.129)	.017

NOTE. Results are from respective univariable logistic regression.
Abbreviations: 3D-CRT, three-dimensional conformal external beam radiation therapy; AJCC, American Joint Commission on Cancer; CTCAE, Common Terminology Criteria for Adverse Events (version 3); IMRT, intensity-modulated radiation therapy; OR, odds ratio; PTV, planning treatment volume; RL, reference level; V, volume receiving radiation dose.

Chun et al. , JCO 2017

CASE EXAMPLE



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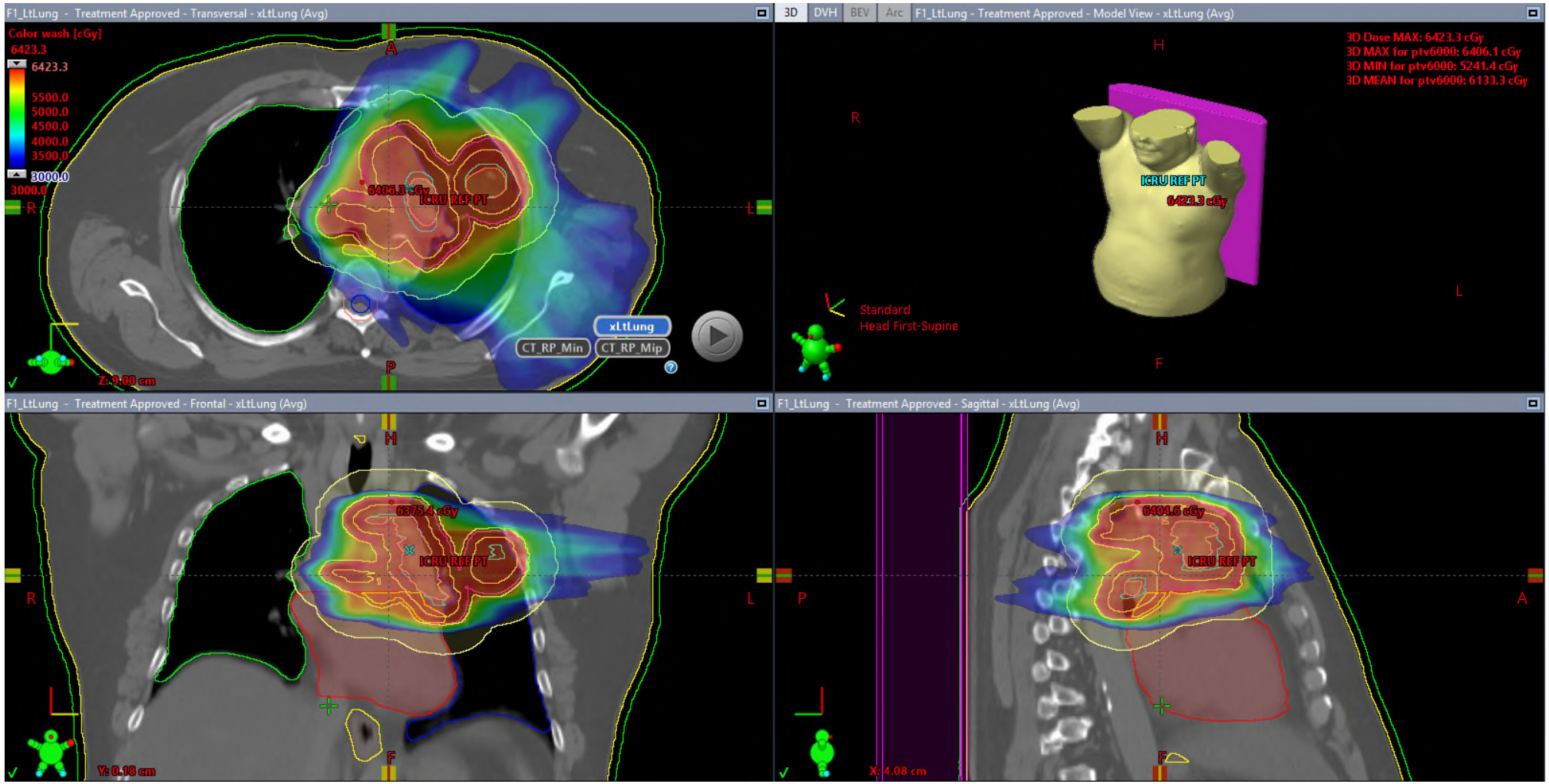

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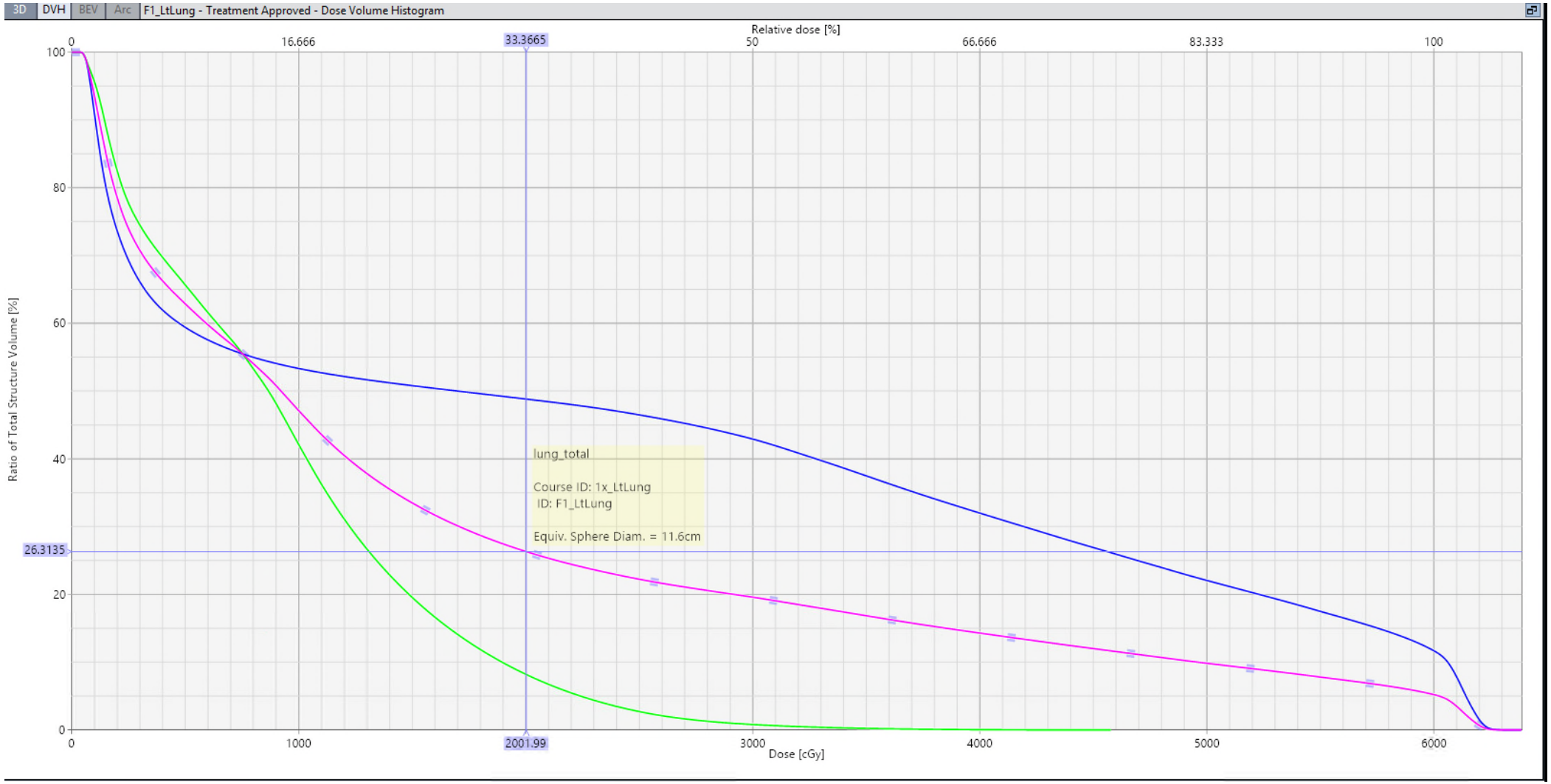
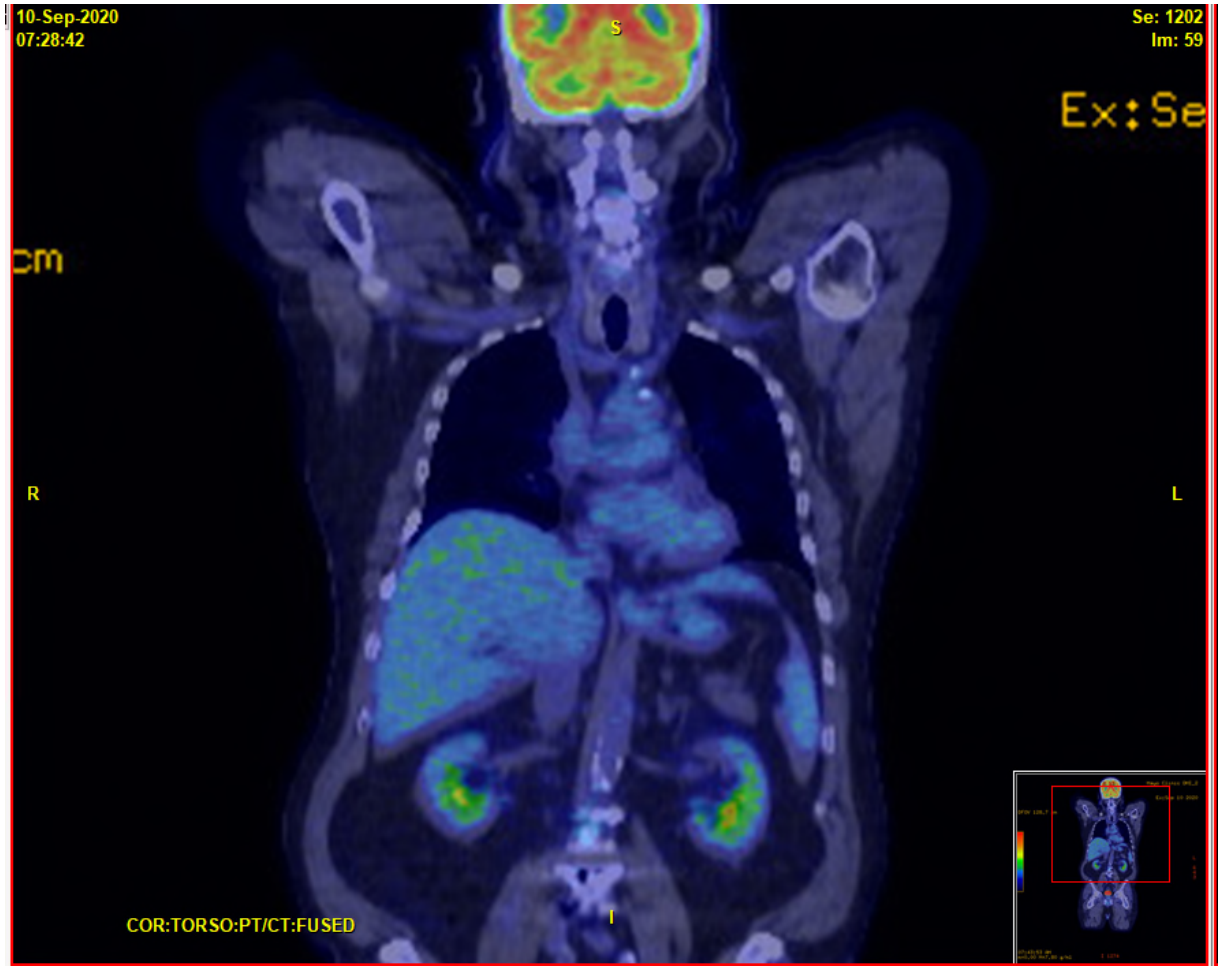
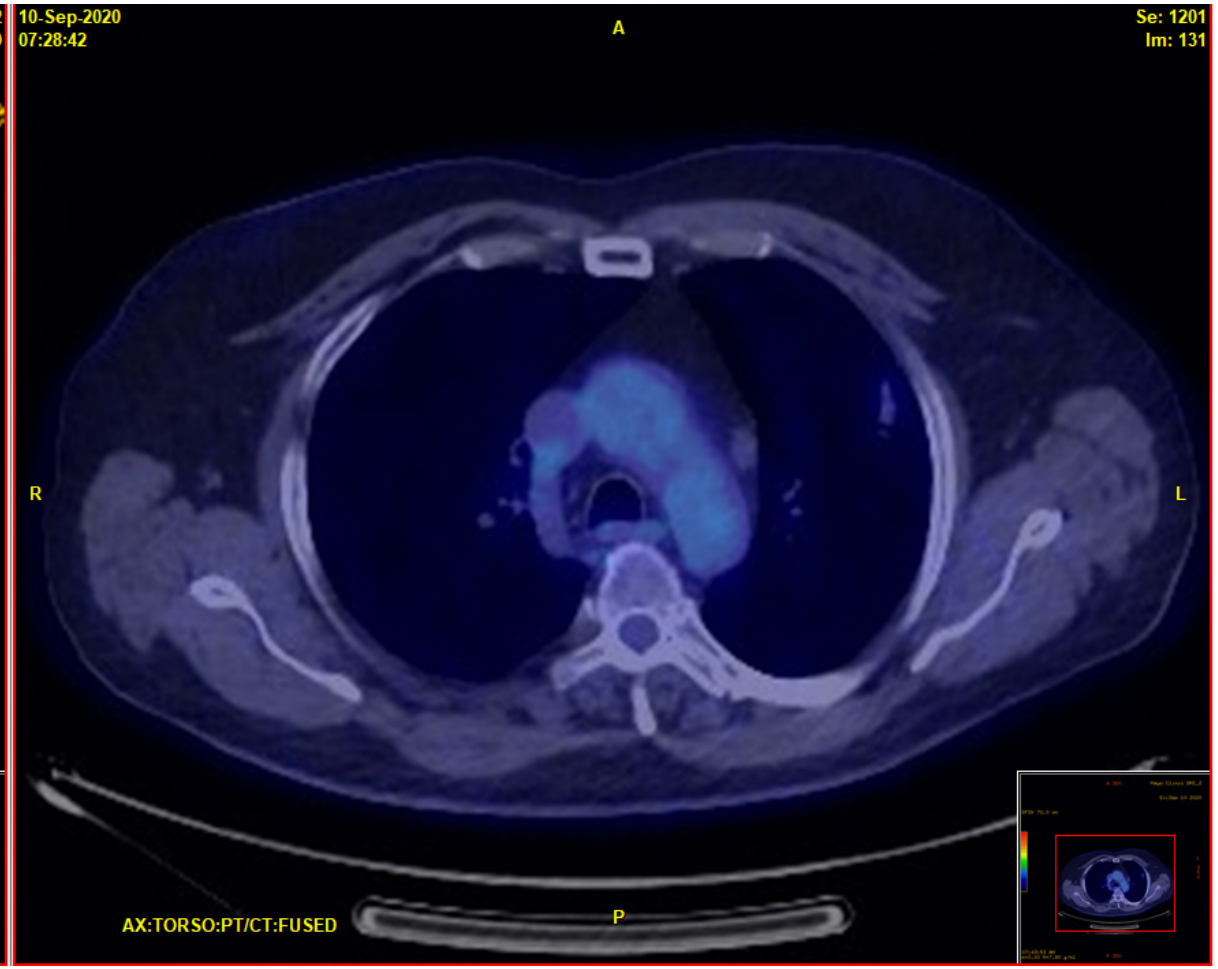


PET CT PRE DURVA POST CRT (3 WEEKS POST)





Systemic Therapy with Radiation for unresectable NSCLC

Jacob Sands, MD

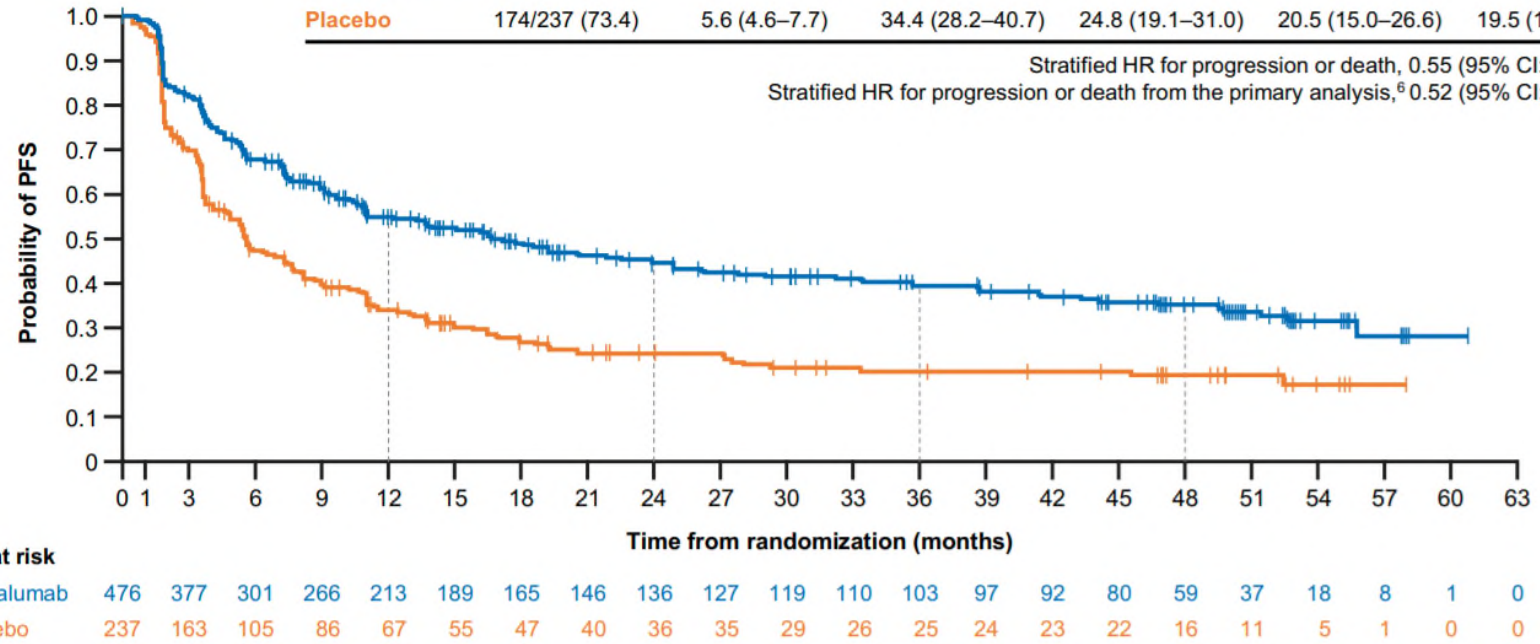
PACIFIC Update

- Durvalumab after completing concurrent chemo and radiation demonstrated ~16% absolute improvement in 4-year PFS.

B

	No. of events/ total no. of patients (%)	Median PFS (95% CI), months	12-month PFS rate (95% CI) %	24-month PFS rate (95% CI) %	36-month PFS rate (95% CI) %	48-month PFS rate (95% CI) %
Durvalumab	266/476 (55.9)	17.2 (12.3–23.8)	55.3 (50.5–59.8)	44.8 (39.8–49.6)	39.8 (34.8–44.8)	35.3 (30.3–40.4)
Placebo	174/237 (73.4)	5.6 (4.6–7.7)	34.4 (28.2–40.7)	24.8 (19.1–31.0)	20.5 (15.0–26.6)	19.5 (14.1–25.7)

Stratified HR for progression or death, 0.55 (95% CI: 0.44–0.67)
Stratified HR for progression or death from the primary analysis,[6] 0.52 (95% CI: 0.42–0.65)



No. at risk																					
Durvalumab	476	377	301	266	213	189	165	146	136	127	119	110	103	97	92	80	59	37	18	8	1	0
Placebo	237	163	105	86	67	55	47	40	36	35	29	26	25	24	23	22	16	11	5	1	0	0

Faivre-Finn JTO 2020

Let’s start with the chemotherapy regimen

- PACIFIC required prior concurrent chemotherapy and radiation for enrollment to randomization: durvalumab vs placebo x1 year

- Eligible chemotherapy regimens included ≥2 cycles platinum-based:
  - Etoposide
  - Vinblastine
  - Vinorelbine
  - Taxane (docetaxel or paclitaxel)
  - Pemetrexed

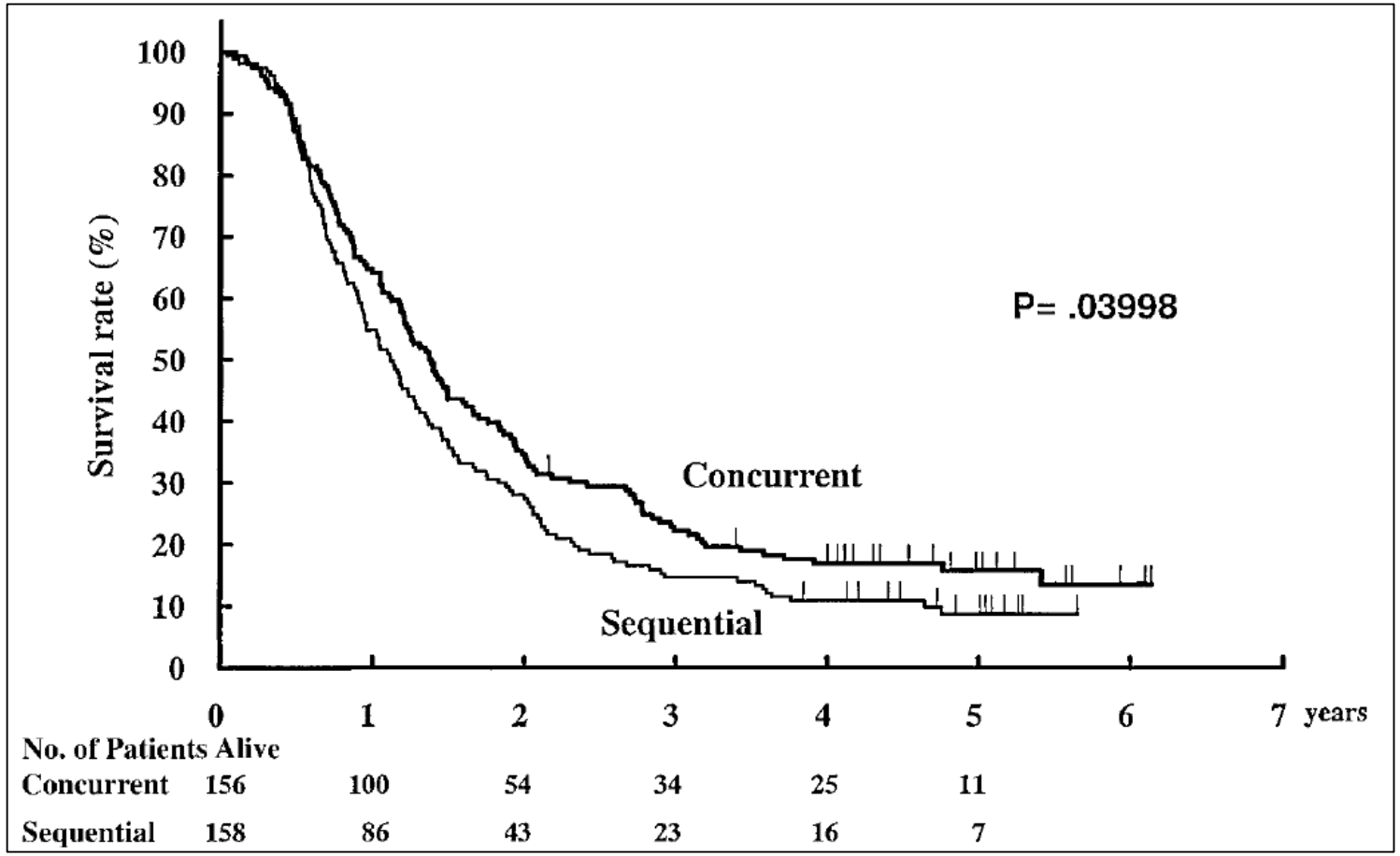
NCCN Guidelines regimens

- Squamous:
  - Carboplatin AUC 2 and Paclitaxel 45-50 mg/m2 weekly
  - Cisplatin 50 mg/m2 days 1, 8, 29, 36 and Etoposide 50 mg/m2 days 1-5 and 29-33

- Non-squamous:
  - Carboplatin AUC 2 and Paclitaxel 45-50 mg/m2 weekly
  - Cisplatin 50 mg/m2 and Etoposide 50 mg/m2
  - Carboplatin AUC 5 and Pemetrexed 500 mg/m2 Q3 weeks
  - Cisplatin 75 mg/m2 and Pemetrexed 500 mg/m2 Q3 weeks

Sequential vs Concurrent Chemo and Radiation

- Chemotherapy in this trial was mitomycin, vindesine, and cisplatin
- Modern chemotherapy regimens are different
- Standard of care is concurrent chemotherapy with radiation
- Sequential strategy is utilized if there is concern about tolerating concurrent chemoradiation



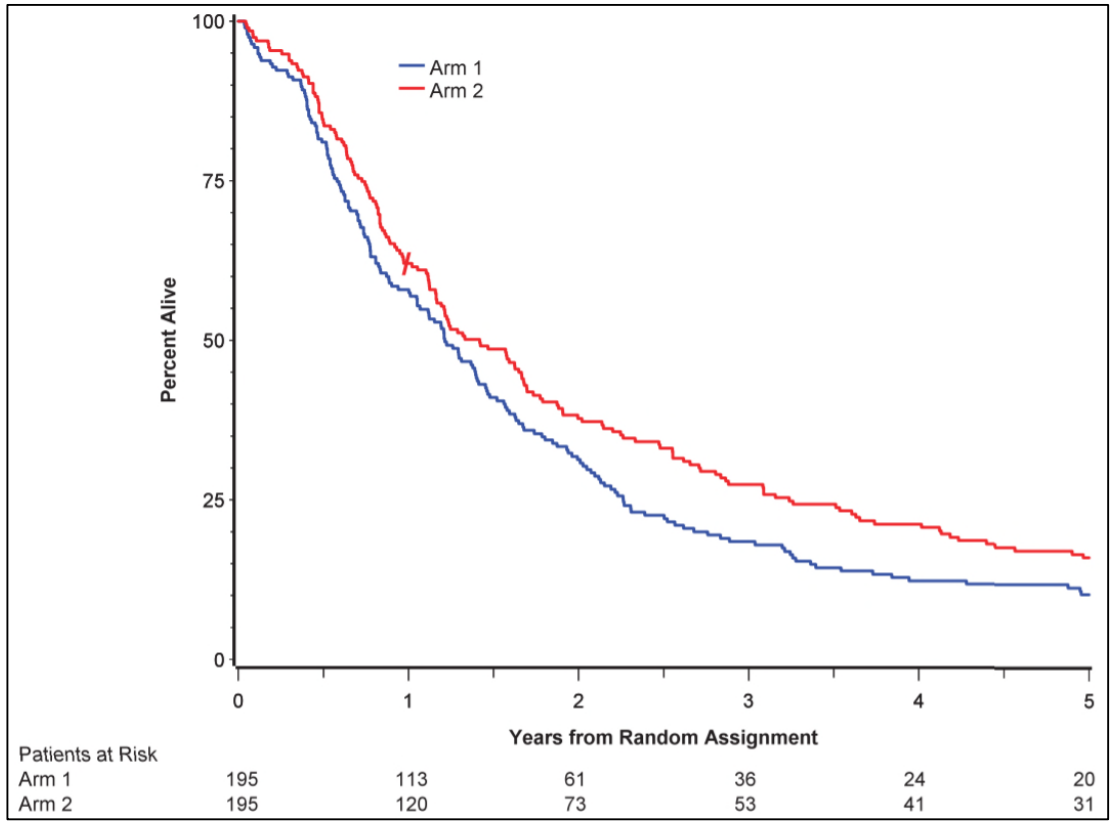
Furuse et al. JCO 1999

Concurrent vs Sequential

Arm 1:
vinblastine 5 mg/m^2 IV bolus weekly first 5 weeks
cisplatin 100 mg/m^2 IV over 30-60 minutes, days 1 & 29
→ (starting day 50) 63 Gy/7 wks/34 daily fractions (1.8 Gy x 25 fx, then 2.0 Gy x 9 fx)

Arm 2:
vinblastine 5 mg/m^2 IV bolus weekly first 5 weeks
cisplatin 100 mg/m^2 IV over 30-60 minutes, days 1 & 29
63 Gy/7 wks/34 daily fractions (1.8 Gy x 25 fx, then 2.0 Gy x 9 fx)

Arm 3:
oral etoposide 50 mg twice daily x 10 only on RT treatment days 1-5, 8-12, 29-33 and 36-40 (75 mg/day if body surface area < 1.7 m^2)
cisplatin 50 mg/m^2 IV over 30-60 minutes on days 1 and 8 and 29 and 36
69.6 Gy/6 wks/58 x 1.2 Gy twice-daily fractions (at least 6 hours apart)



Curran, et al. J Natl Cancer Inst 2011;103:1452-1460

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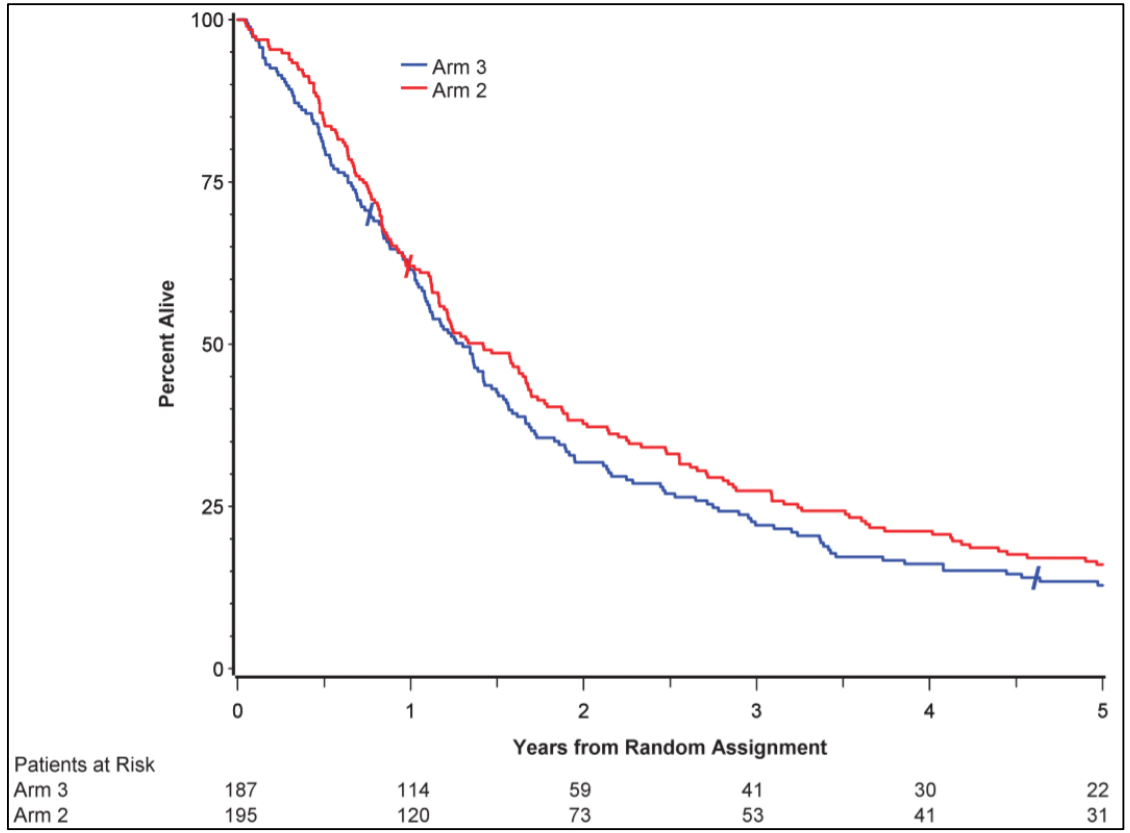


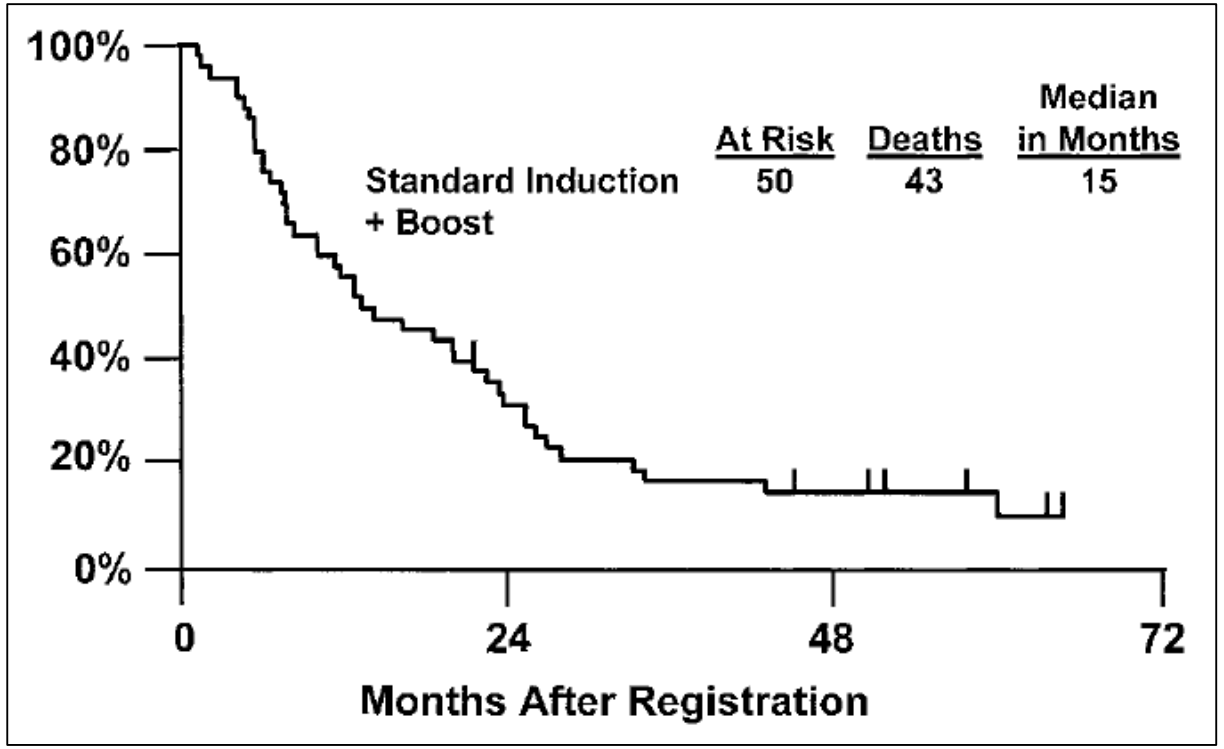
Curran, et al. J Natl Cancer Inst 2011;103:1452-1460

Cisplatin and Etoposide

- Cisplatin 50 mg/m2 days 1, 8, 29, 36
- Etoposide 50 mg/m2 days 1-5, 29-33

- Concurrent Radiation:
  - 2D planning to 61 Gy

- Then 2 additional cycles of chemo



Albain et al. JCO 2002

Cisplatin and Etoposide

Table 1. SWOG 9019: Characteristics of 50 Eligible Patients

Characteristic	No. of Patients	%
Age, years		
Median	58	
Range	36-78	
Female sex	9	18
Race		
Black	5	10
Hispanic	2	4
Asian	3	6
Performance status		
0	23	46
1	27	54
Weight loss*		
< 5%	28	57
5 to < 10%	13	26
10%-20%	6	11
> 20%	3	6
Elevated lactate dehydrogenase	9	18
Squamous histology	24	48
T and N substage		
T4 N0, 1	18	36
T4 N2	12	24
N3	20	40

*Weight loss expressed as percentage of weight 6 months before study entry.

Table 2. SWOG 9019: Major Toxicity

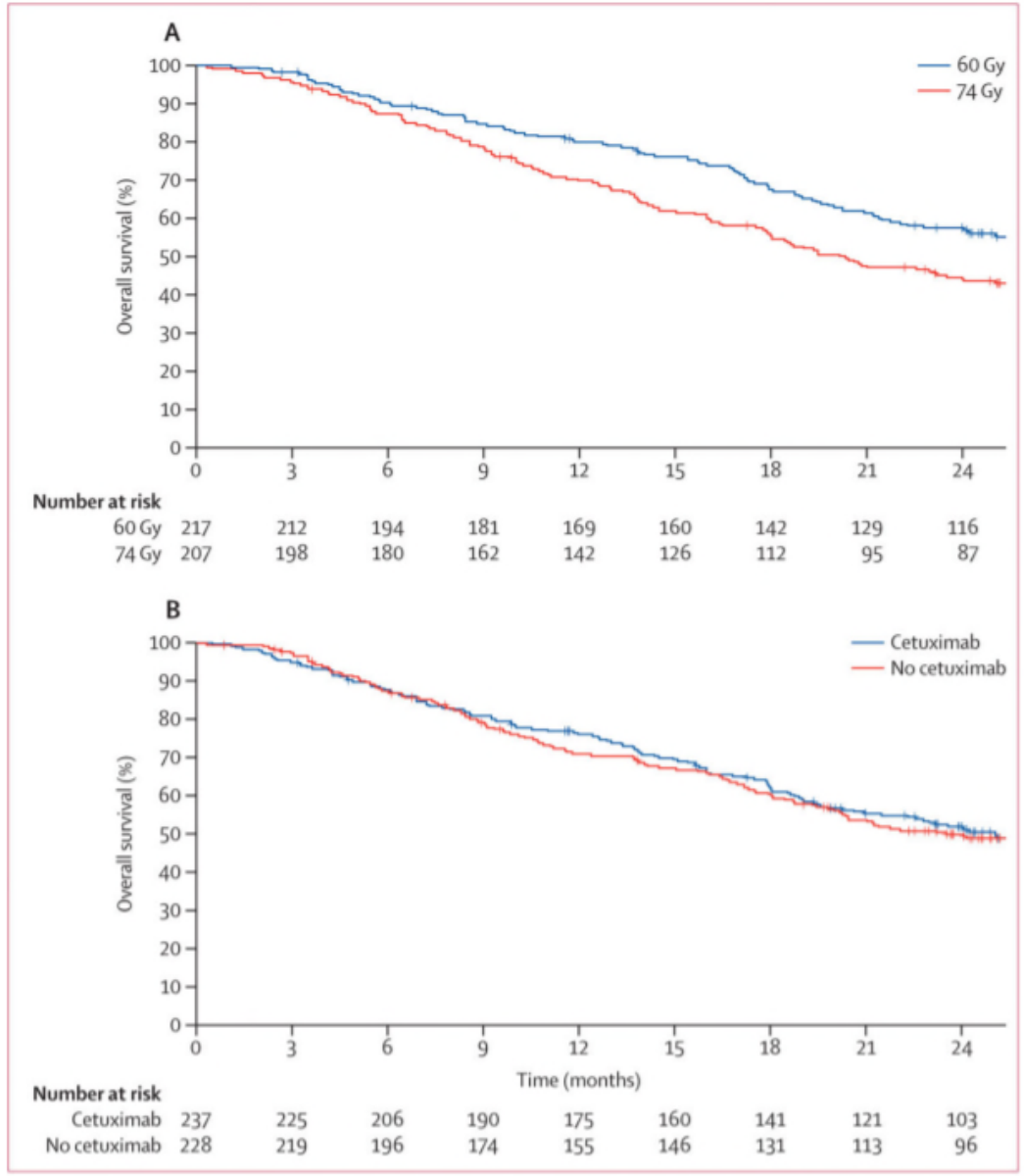
Type of Toxicity*	Frequency (n = 50) No. of Patients	%
Grade 4 neutropenia	16	32
Esophagitis/pharyngitis		
Grade 3	6	12
Grade 4	4	8
Respiratory infection		
Grade 3	3	6
Grade 4	1	2
Grade 3-4 anemia	14	28
Grade 3 malaise/fatigue	6	12
Grade ≥ 3 dehydration	2	4
Grade ≥ 2 radiation pneumonitis	0	

*SWOG standard toxicity criteria (version 1990).

Albain et al. JCO 2002

Carboplatin and Paclitaxel

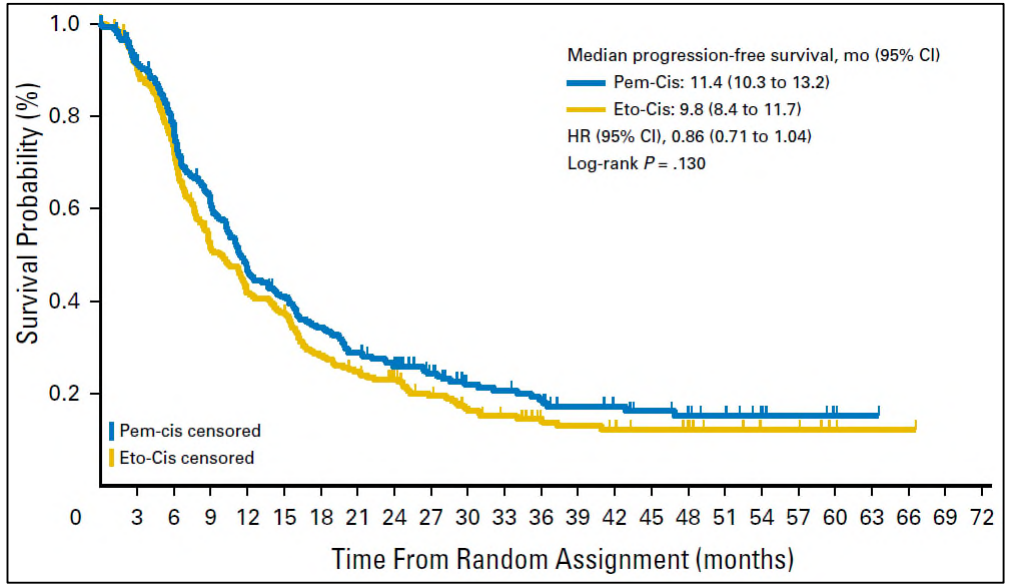
- Carboplatin AUC 2 and Paclitaxel 45 mg/m2 weekly followed by consolidation carboplatin AUC 6 and paclitaxel 200 mg/m2 Q3wks x2



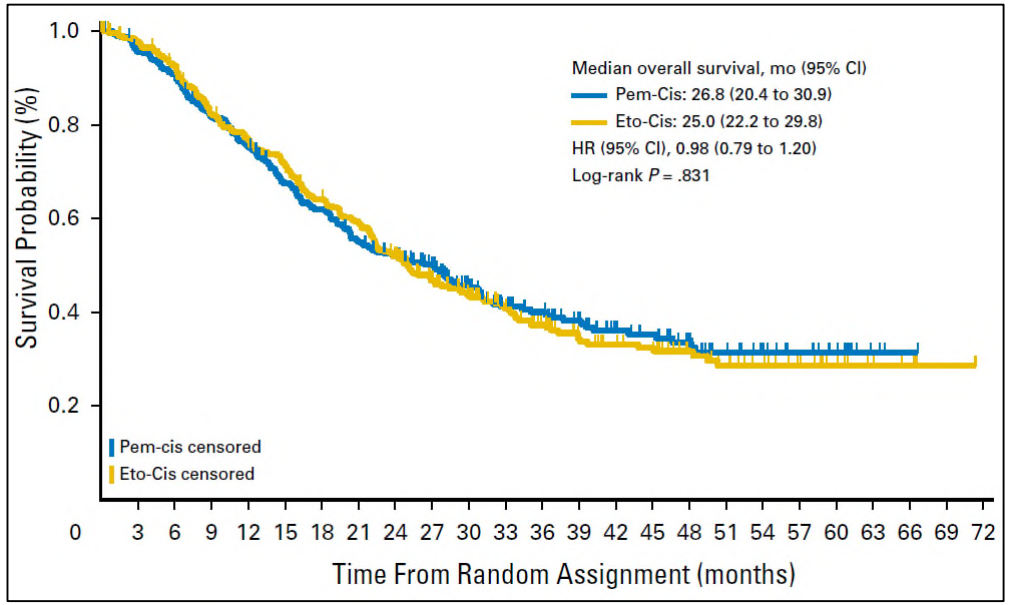
Bradley et al. Lancet Oncol. 2015

Cisplatin Pemetrexed

- Cisplatin 75 mg/m2 and Pemetrexed 500 mg/m2 Q 3wks x3 cycles concurrent with radiation (60-66 Gy) followed by pemetrexed x4 cycles



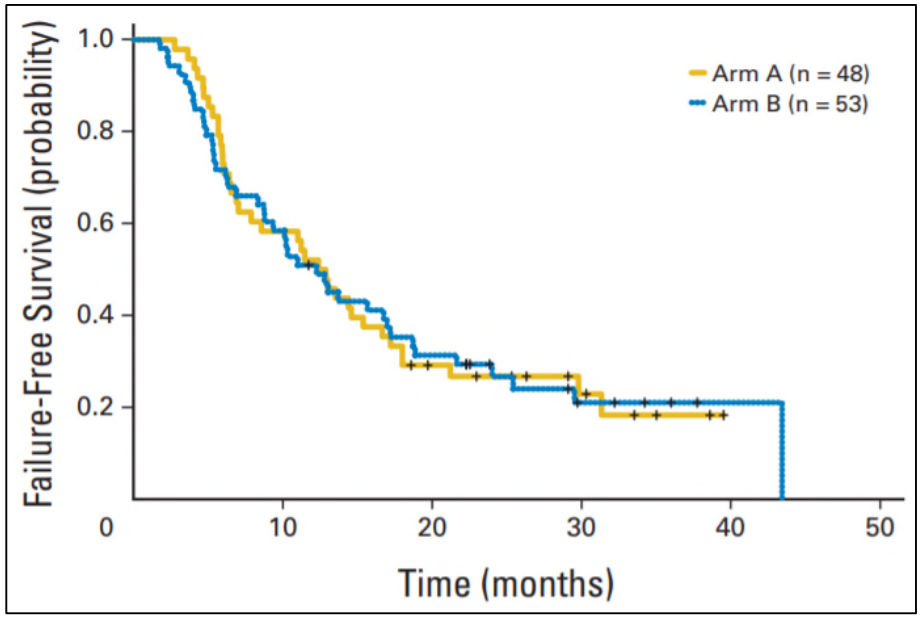
- Superiority study: Negative
- Trend toward improved mPFS
- Improved AE profile with pemetrexed (alopecia, G3 neutropenia / neutropenic fever)

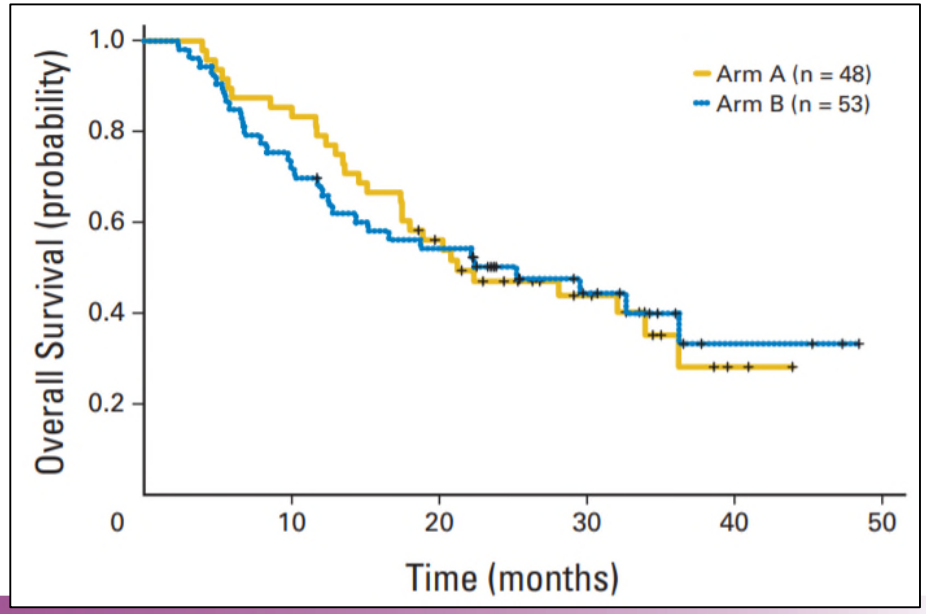


Senan et al. PROCLAIM; JCO 2016

Carboplatin Pemetrexed

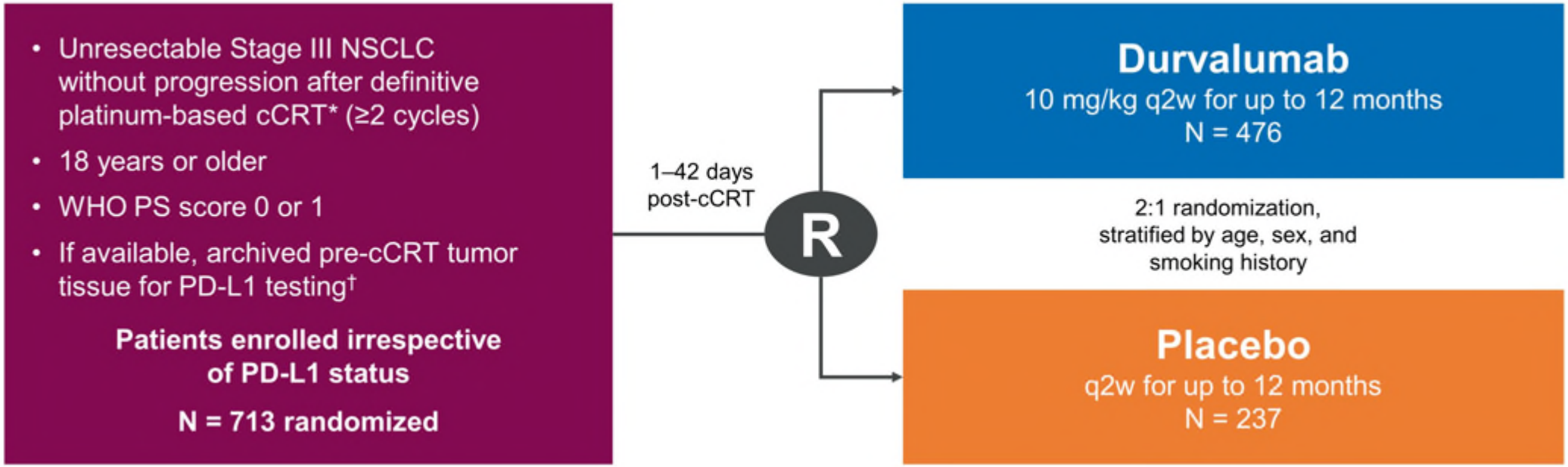
- Arm A: Carboplatin AUC 5 and Pemetrexed 500 mg/m2 Q3 wks x4 cycles concurrent with radiation (70 Gy) followed by pemetrexed x4 cycles
- Arm B: also includes cetuximab
- The limitation of benefit to non-squamous with pemetrexed was not known at the time of this study





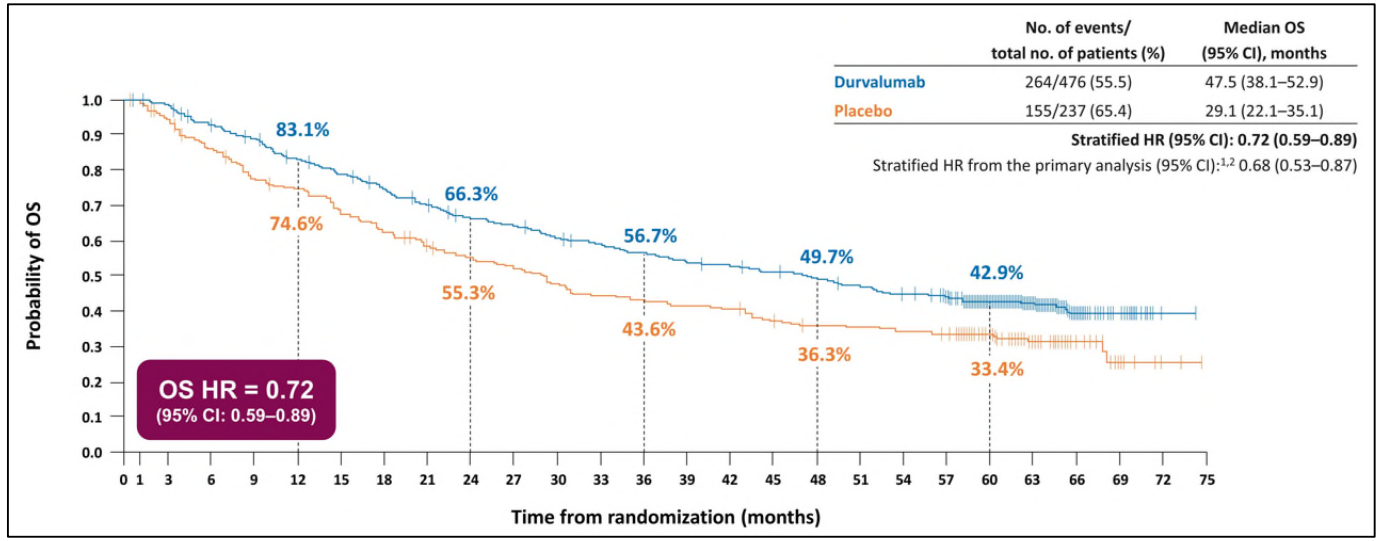
PACIFIC – Durvalumab post-chemoradiation

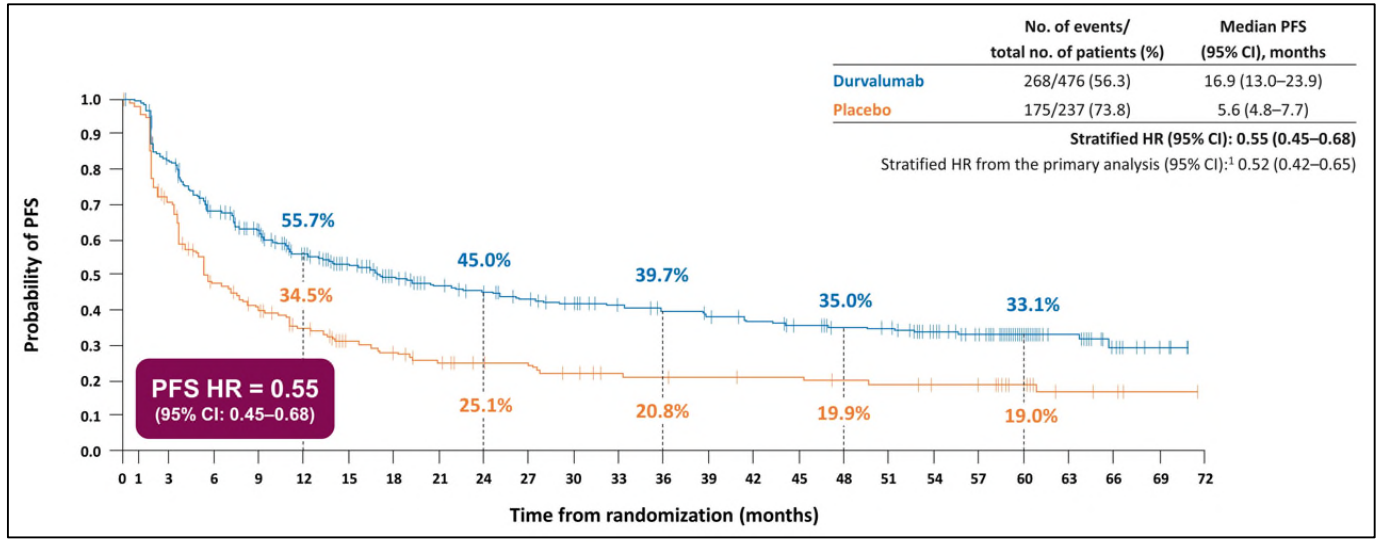
Schema as presented by Dr. Spigel, ASCO 2021



PACIFIC – Durvalumab post-chemoradiation

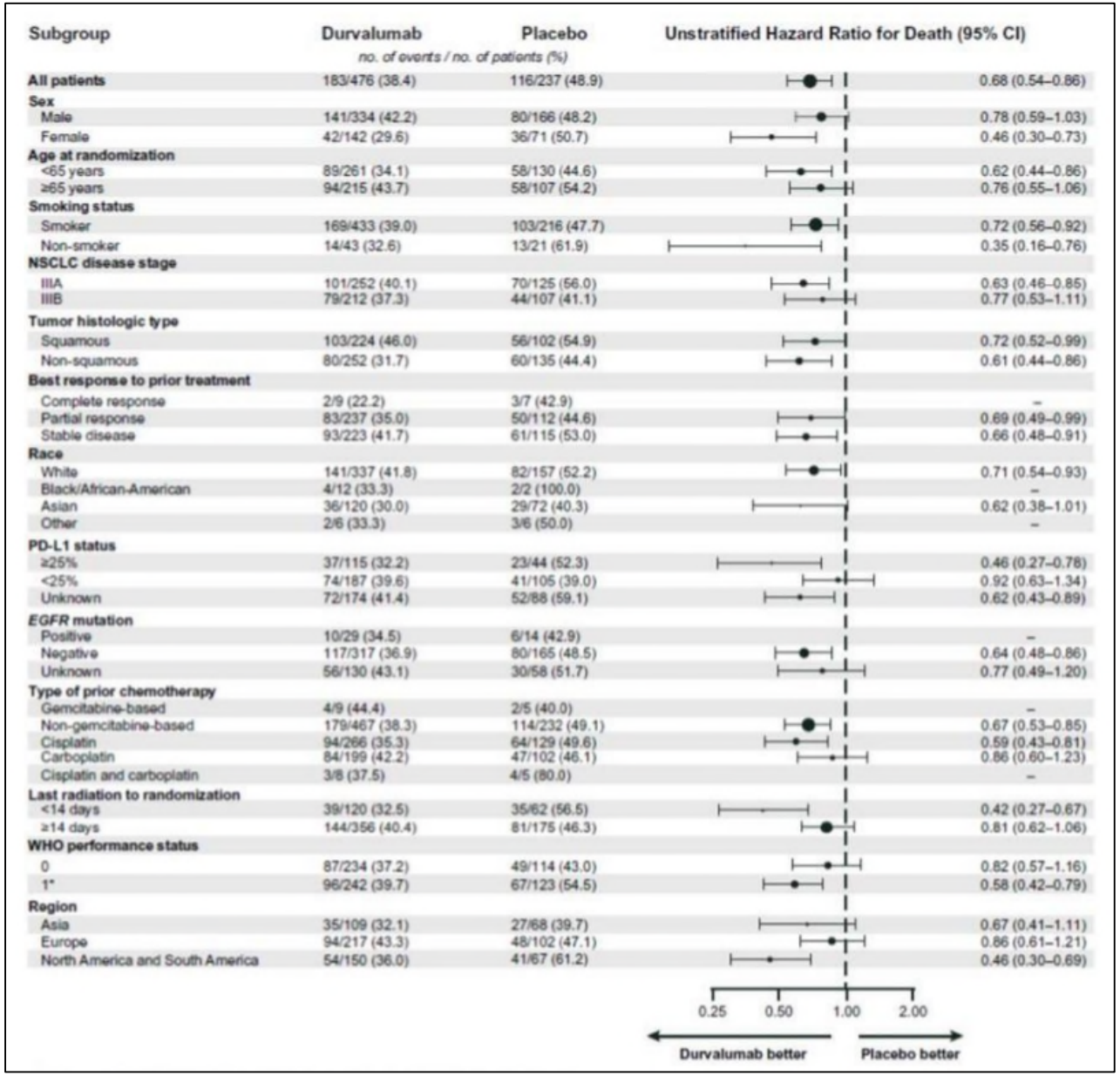
- Durvalumab x1 year after chemoradiation shows a 5-year PFS of 33.1%.
- This raises the question: Does the inclusion of durvalumab increase the rate of cure?



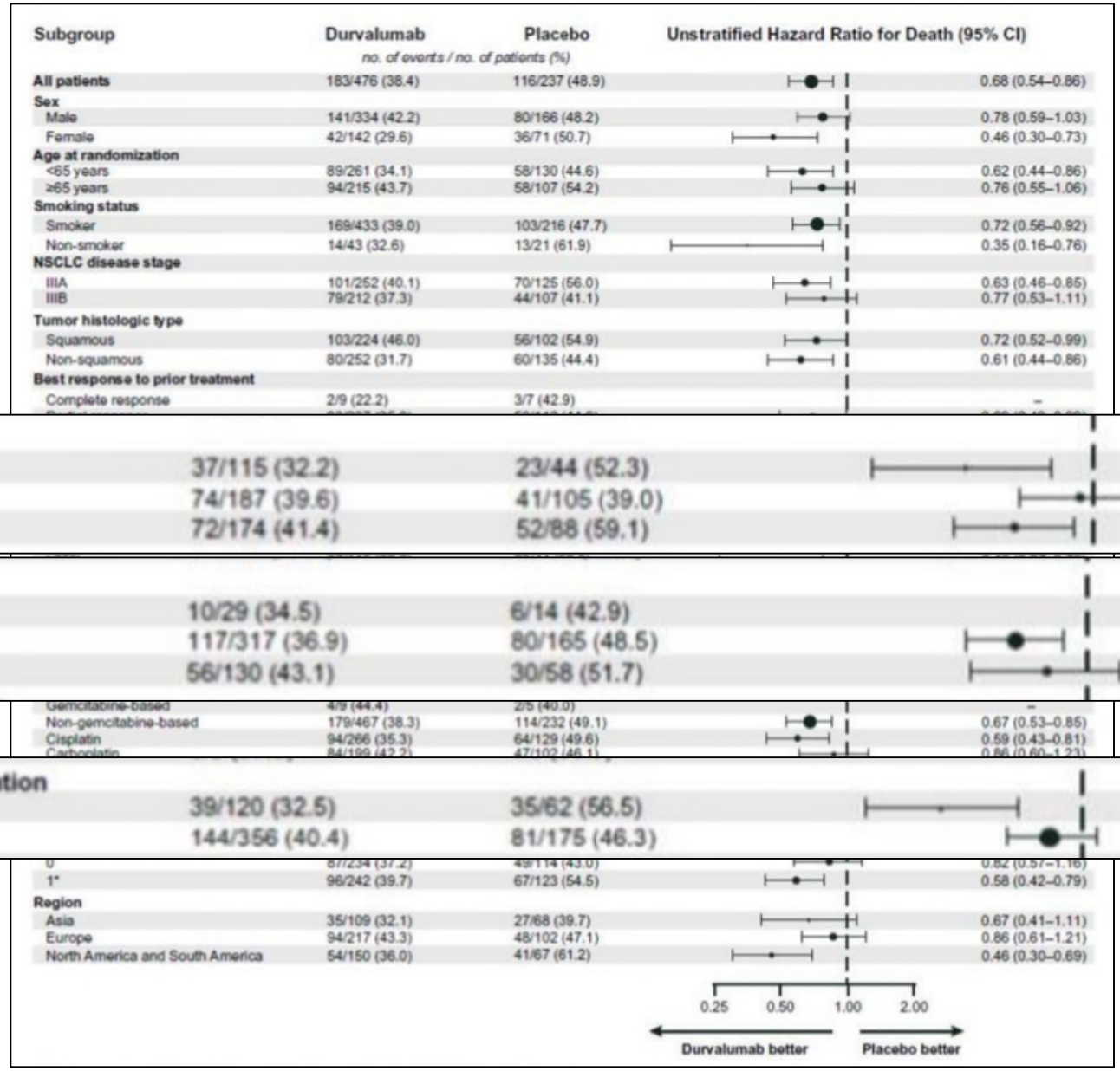


PACIFIC sub-groups

- Does PD-L1 expression impact use of durvalumab?
- What about EGFR mutation + disease?
- Does it matter when durvalumab is started?



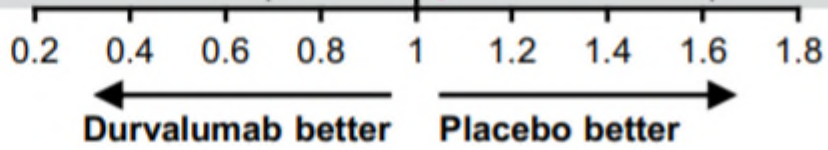
Antonia et al. NEJM 2018 supplement



Antonia et al. NEJM 2018 supplement

PACIFIC Four Year Update

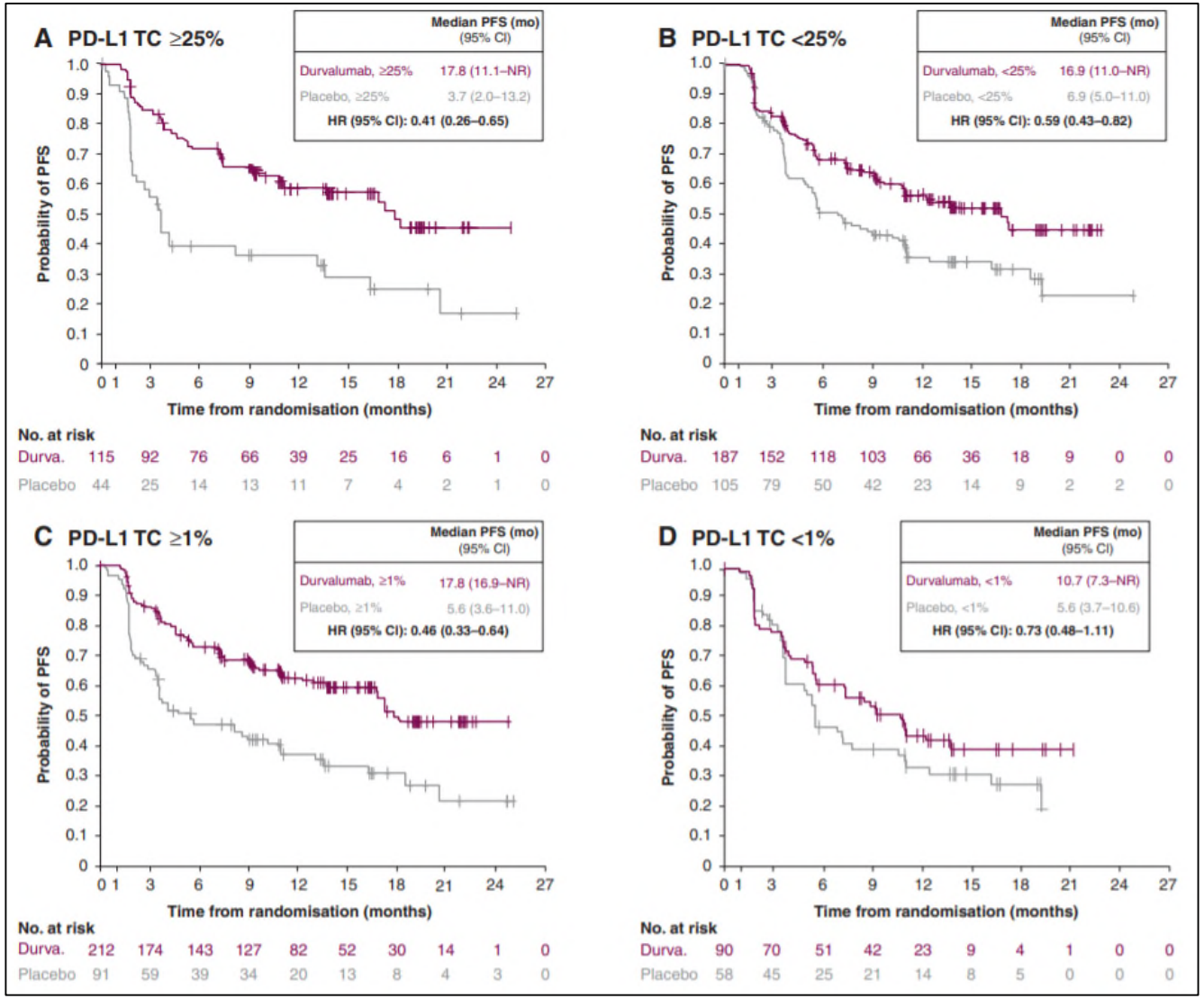
***EGFR* mutation**			
Positive	17/29 (58.6%)	7/14 (50.0%)	0.97 (0.40–2.33)
Negative	156/317 (49.2%)	105/165 (63.6%)	0.64 (0.50–0.83)
Unknown	74/130 (56.9%)	37/58 (63.8%)	0.80 (0.54–1.19)
Last radiation to randomization			
<14 days	59/120 (49.2%)	41/62 (66.1%)	0.53 (0.35–0.79)
≥14 days	188/356 (52.8%)	108/175 (61.7%)	0.78 (0.61–0.99)
PD-L1 status			
≥25%	50/115 (43.5%)	26/44 (59.1%)	0.53 (0.33–0.85)
<25%	102/187 (54.5%)	62/105 (59.0%)	0.85 (0.62–1.17)
Unknown	95/174 (54.6%)	61/88 (69.3%)	0.67 (0.48–0.92)
1–24% (post hoc analysis)	47/97 (48.5%)	28/47 (59.6%)	0.69 (0.43–1.10)
≥1% (post hoc analysis)	97/212 (45.8%)	54/91 (59.3%)	0.60 (0.43–0.84)
<1% (post hoc analysis)	55/90 (61.1%)	34/58 (58.6%)	1.05 (0.69–1.62)



Faivre-Finn et al. JTO 2021

PACIFIC by PD-L1

- Exploratory analyses by PD-L1 cohorts was performed
- Durvalumab was favored over placebo across all analyses except OS in the <1% cohort.



Paz-Ares et al. Annals of Oncology 2020

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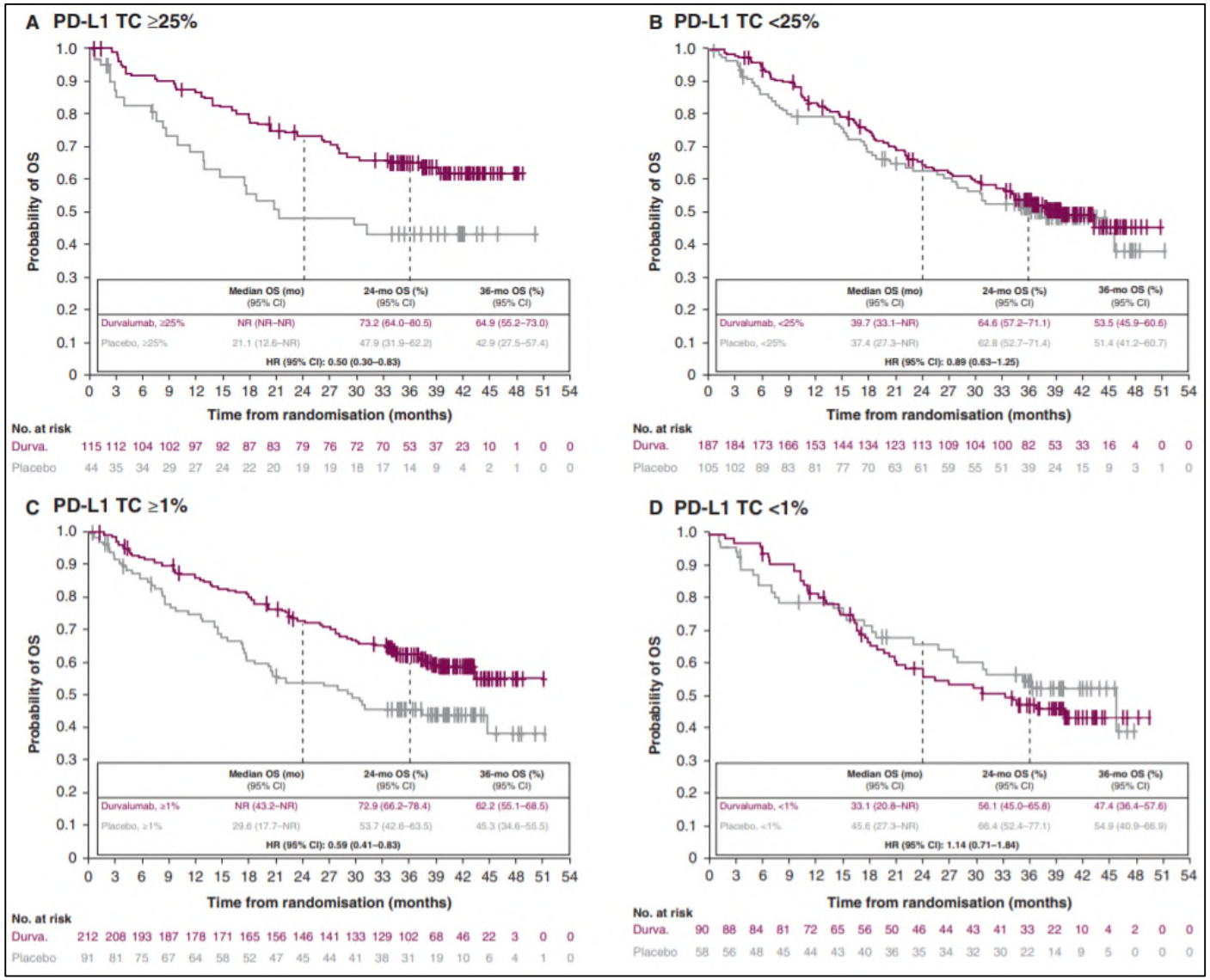
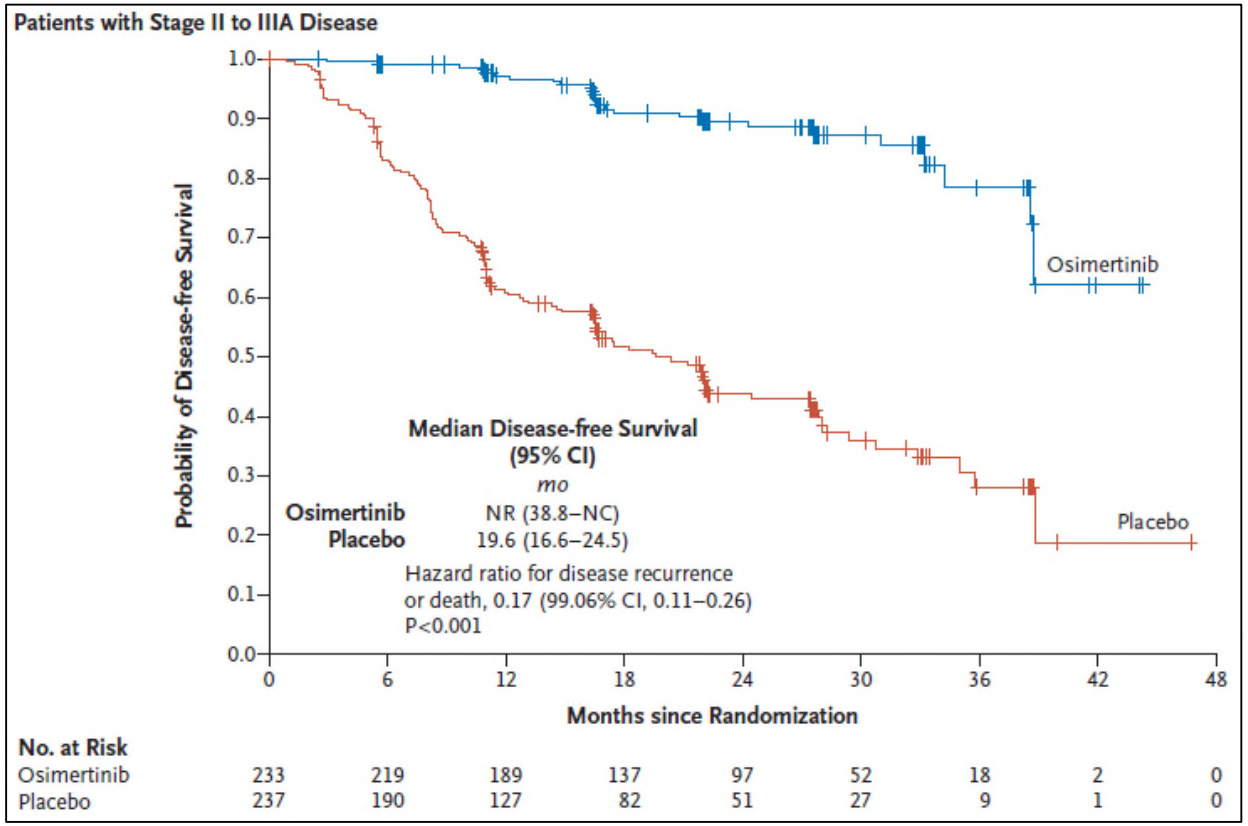
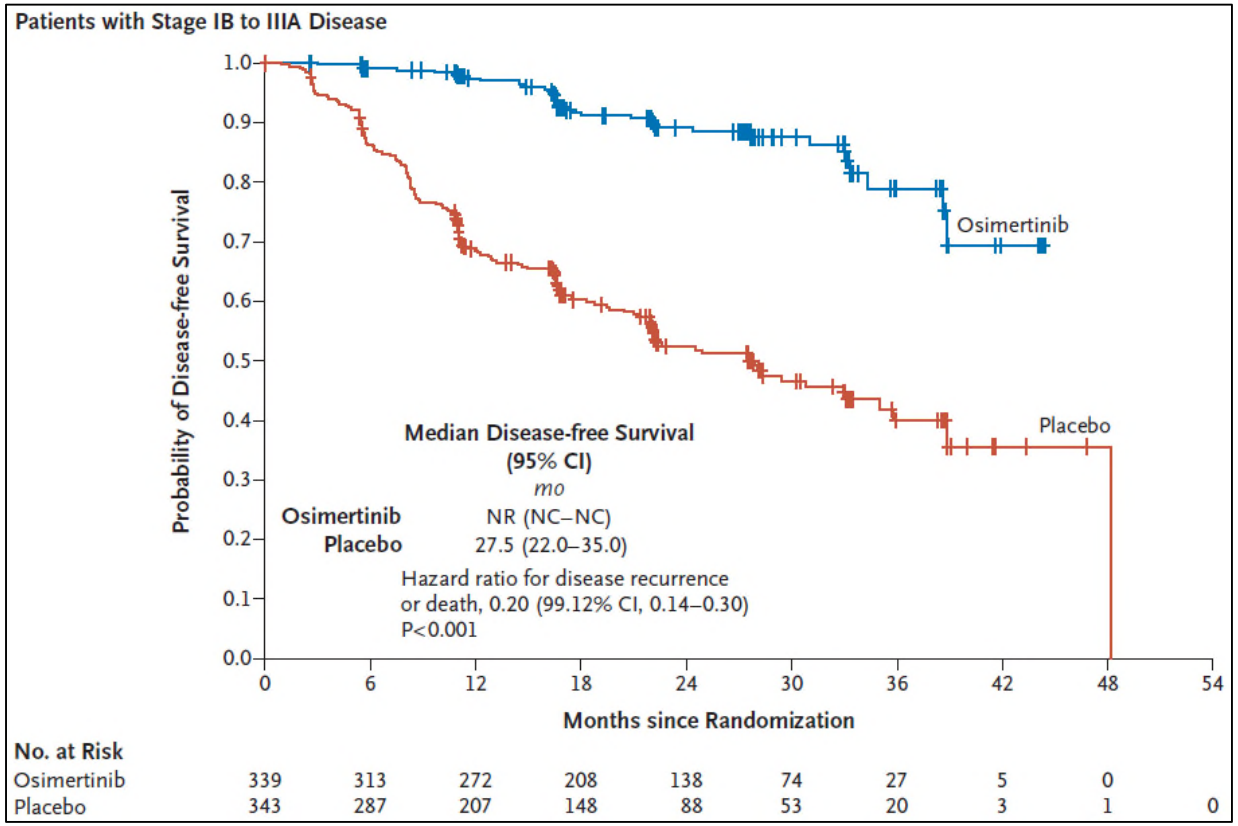


Paz-Ares et al. Annals of Oncology 2020

EGFR in resectable NSCLC





Wu et al. ADAURA. NEJM 2020

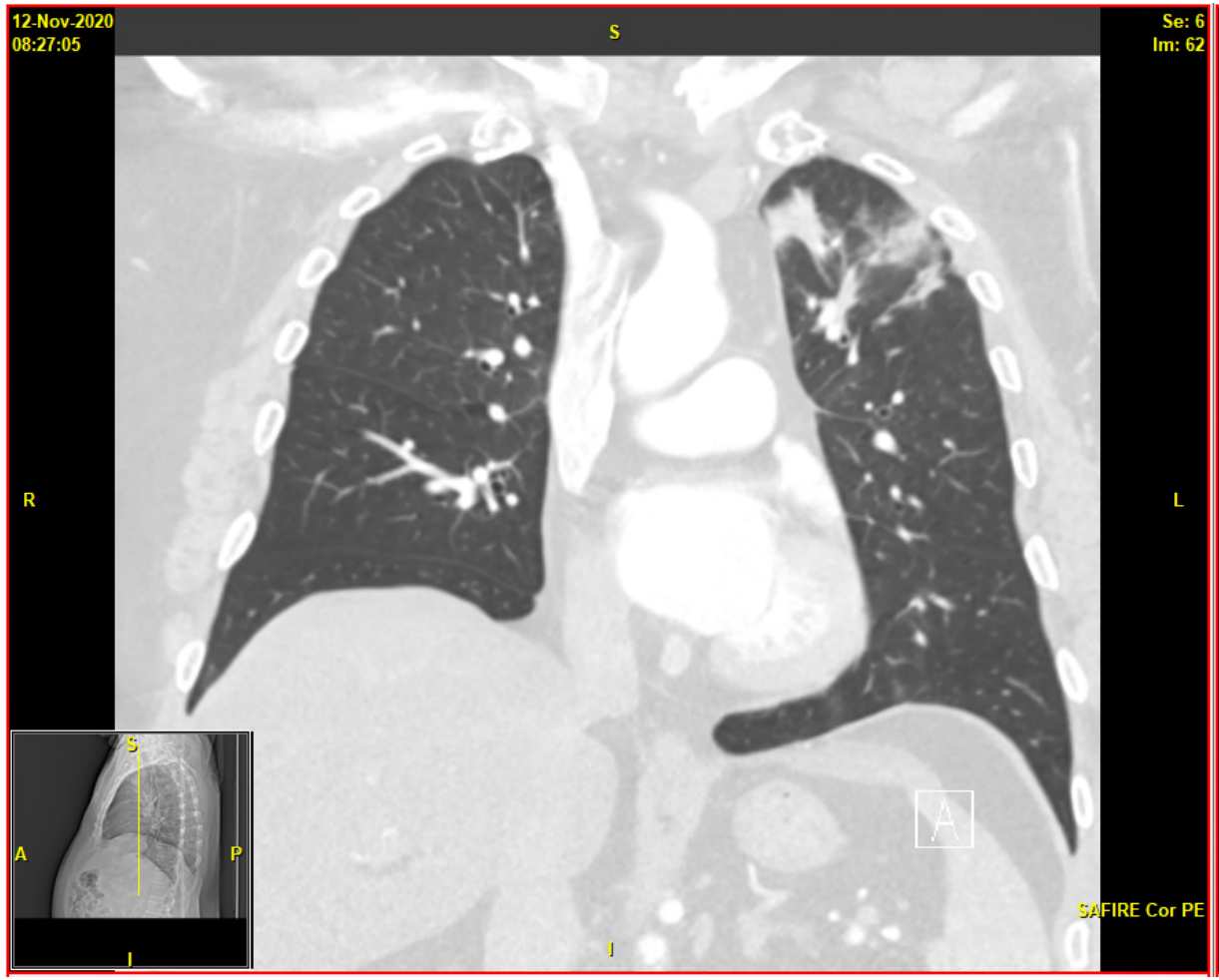
Important Points for Discussion

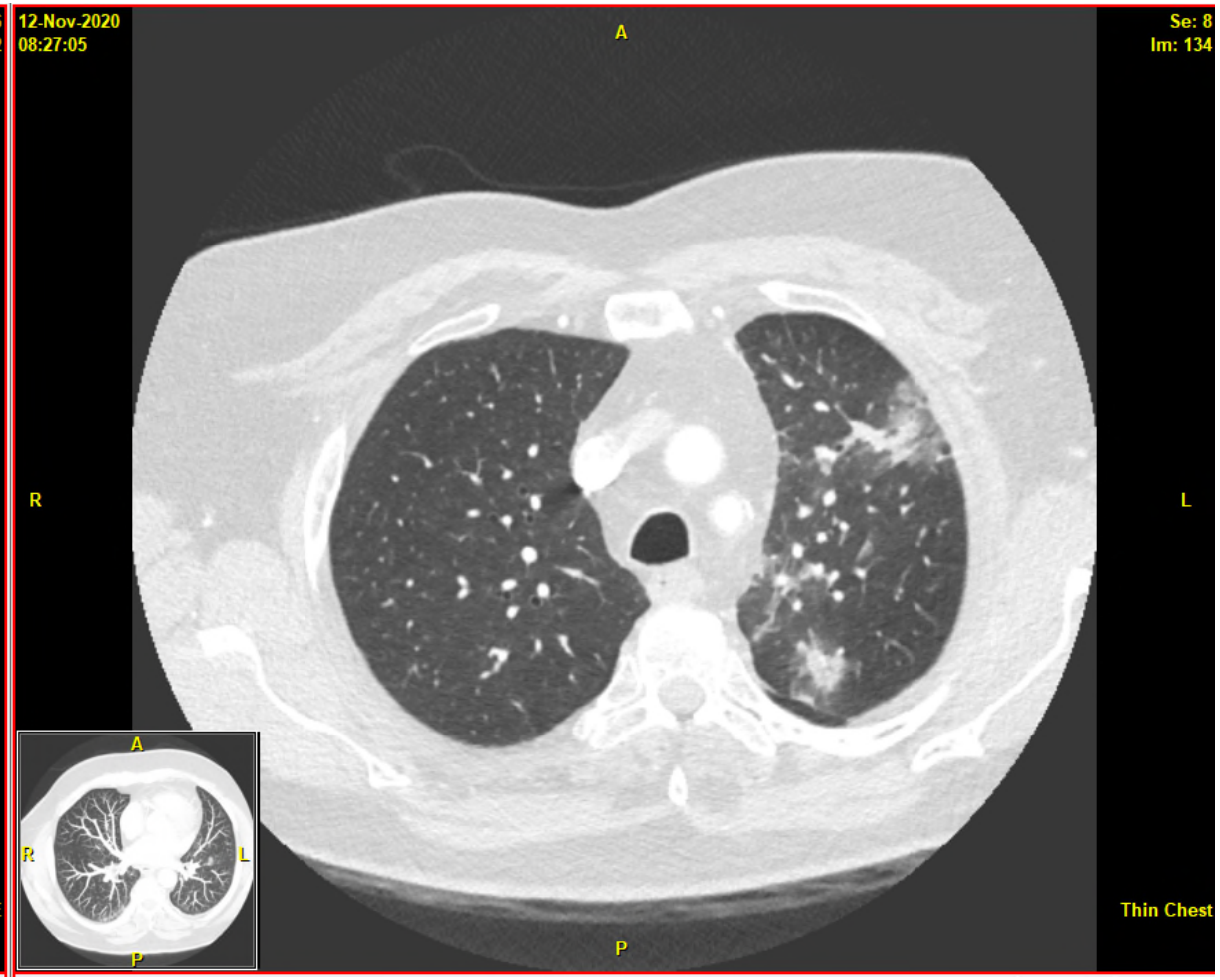
- Does PD-L1 expression impact use of durvalumab?
- What about EGFR mutation + disease?
- Does it matter when durvalumab is started?

Pneumonitis – Radiation vs ICI

Dawn Owen, MD, PhD

PATIENT PRESENTS WITH DYSPNEA 3 MONTHS POST CRT…





COMBINATION CRT AND DURVALUMAB = ???MORE PNEUMONITIS

Table 2. Overview of the results (tolerability) of the PACIFIC study.

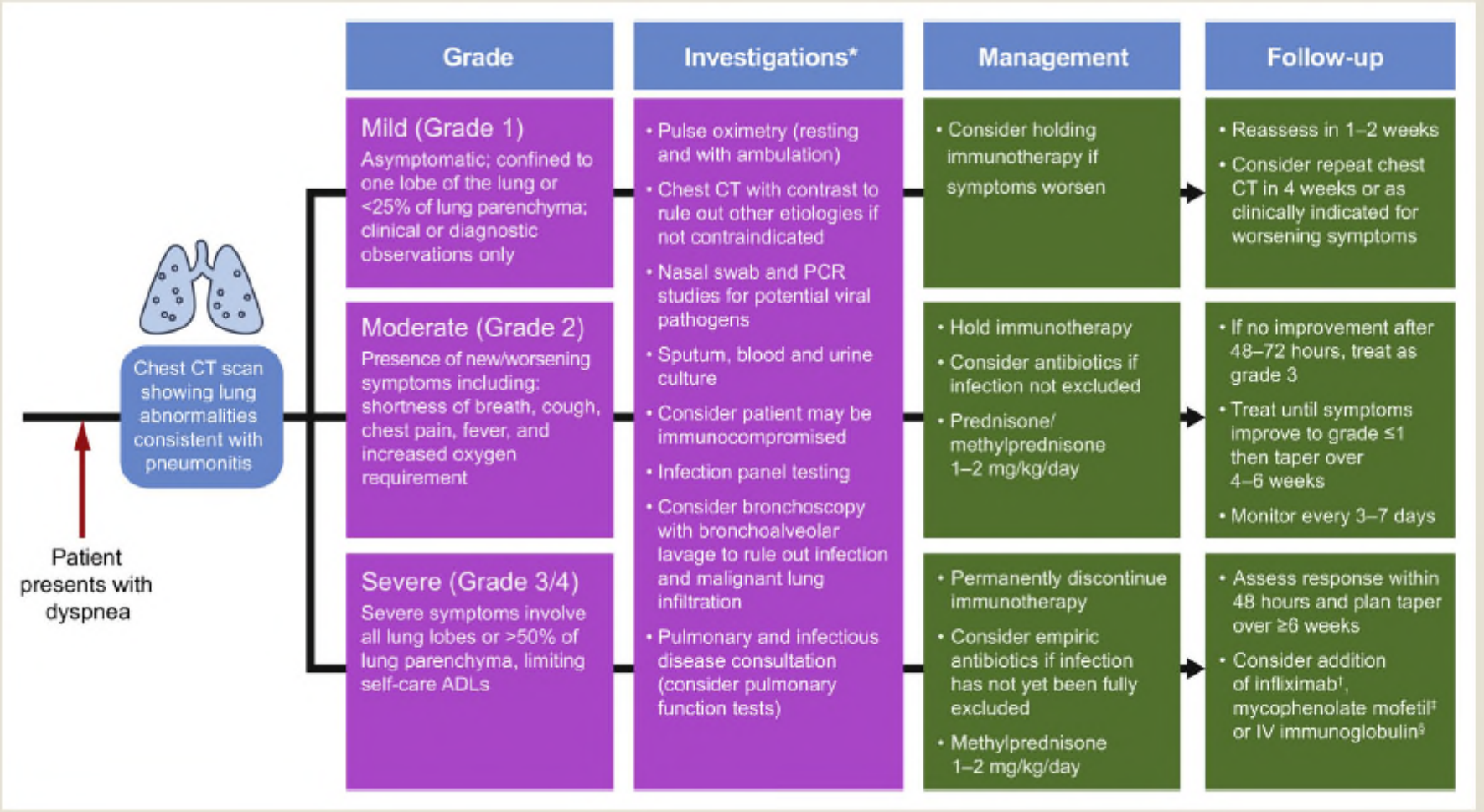
Study	Treatment scheme	All AEs (%)	Most common all grades AEs (%)	G3/4 AEs (%)	Most common G3/4 AEs (%)	Ir-AEs (%)	Discontinuation (%)	Death due to AEs
PACIFIC OS analysis[#]	Durvalumab	96.8%	Cough (35.4%) Pneumonitis or RP* (33.9%) Fatigue (23.8%) Dyspnoea (22.3)	29.9%	Pneumonia (4.4%) Pneumonitis or RP*(3.4%) Anaemia (2.9%)	24.2%	15.4%	4.4%
	Placebo	94.9%	Cough (25.2%) Pneumonitis or RP* (24.8%) Fatigue (20.5%) Dyspnoea (23.9%)	26.1%	Pneumonia (3.8%) Pneumonitis or RP*(2.6%) Anaemia (3.4%)	8.1%	9.8%	5.6%

*Pneumonitis or radiation pneumonitis was assessed by investigators with subsequent review and adjudication by the study sponsor. In addition, pneumonitis is a grouped term that includes acute interstitial pneumonitis, interstitial lung disease, pneumonitis, and pulmonary fibrosis.
[#]Antonia *et al.*[30]
AE, adverse event; Ir, Immune-related; OS, overall survival; RP, radiation pneumonitis.

Botticella et al., Ther Adv Resp Dis 2019
Vansteenkiste et al., ESMO 2019

WORKUP AND MANAGEMENT OF PNEUMONITIS

Figure 3 Patient Management Algorithm



Naidoo et al., Clin Lung Cancer 2020

CLASSIC RISK FACTORS FOR RADIATION PNEUMONITIS (PRE ICI)

TABLE 1 | Dosimetric and biological parameters in radiation-induced lung toxicity.

	Parameters	Risk increase	References
Patients characteristics	Age	over 65	(41–46)
	Gender	female	(44, 47, 48)
	Smoking	non-smokers	(43, 48–53)
	Pre-existing lung diseases	ECOG performance 3–4	(45, 46, 54–62)
	Genetic predisposition	SNPs in various genes	(63–74)
	Tumor location	Base, the upper half of the lung, the region adjacent to the pleura	(51, 70, 75–79)
	Low KPS	Radiation pneumonitis	(41, 48, 77, 78)
Dosimetric parameters	Chemotherapy	Most chemotherapies	(41, 46, 48, 56, 61, 79–90)
	Chemo-XRT schedule:	Sequential > concurrent fraction size >2.67 Gy	(46, 48, 61, 83, 91)
	Targeted therapies	TKI monotherapy and with RT	(92–96)
	Mean Lung Dose (MLD)	Higher MLD	(97–103)
	Dose to the heart	Undetermined	(104, 105)

Patient's characteristics (age, gender, smoking status, pulmonary status, genetic predisposition) and dosimetric parameters (chemotherapy, radiotherapy, tumor location, lung volume, NTCP, MLD) affect the probability of radiation-induced lung toxicity. >, major; NTCP, normal tissue complication probability; MLD, mean lung dose.

Giuranno et al., FONC 2019

PATHOPHYSIOLOGY OF RADIATION PNEUMONITIS

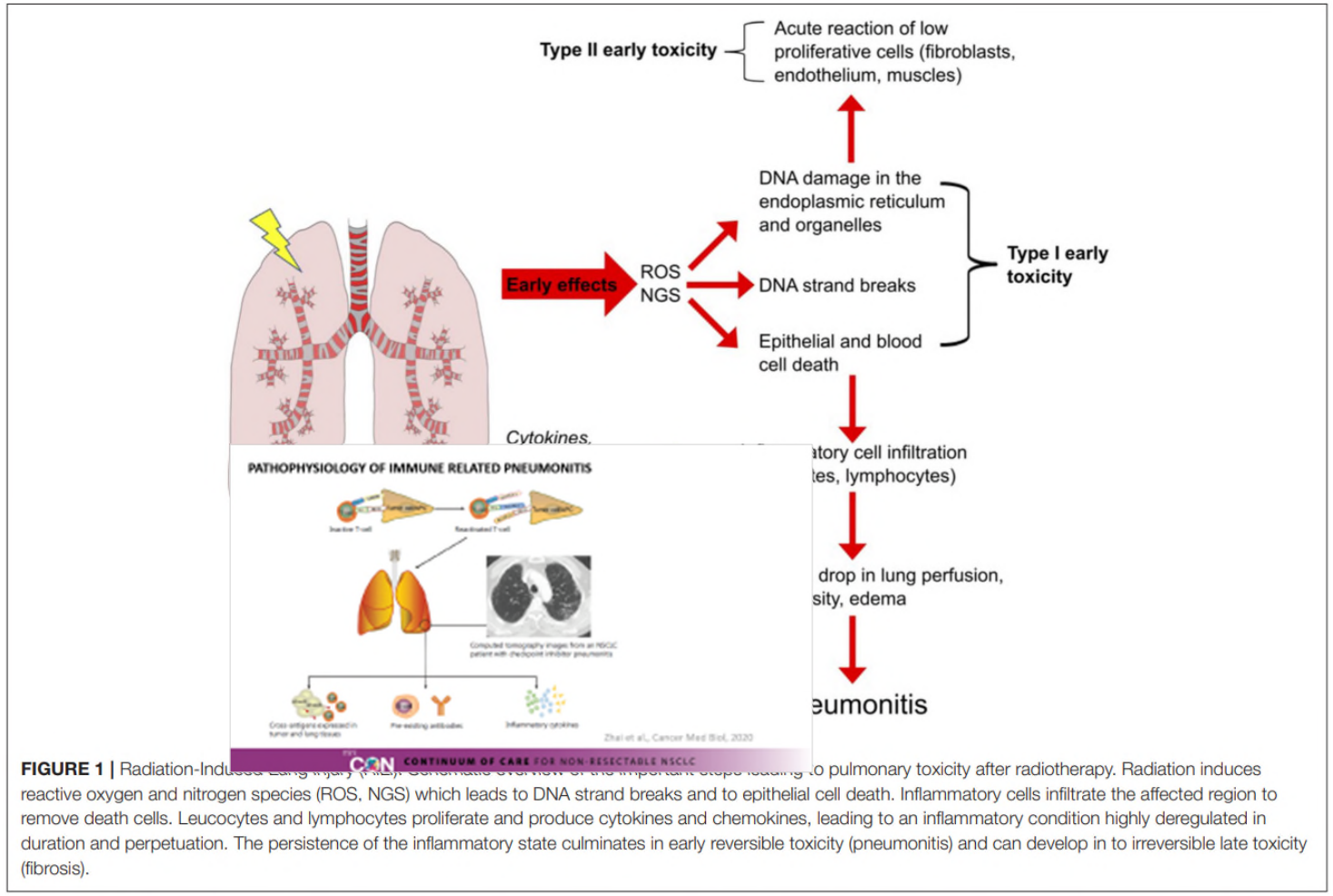
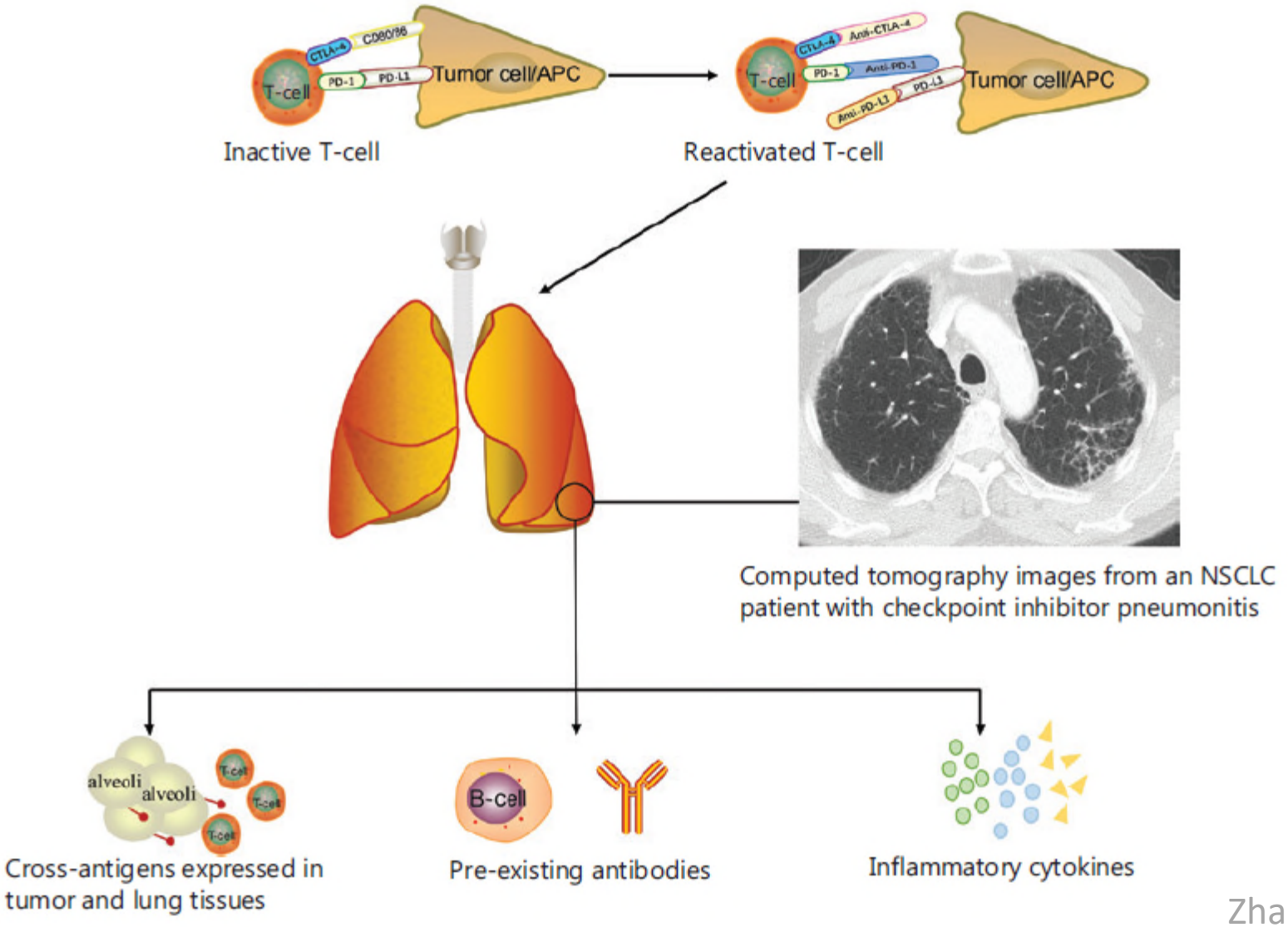


FIGURE 1 | Radiation-Induced Lung Injury (RILI). Schematic overview of the important steps leading to pulmonary toxicity after radiotherapy. Radiation induces reactive oxygen and nitrogen species (ROS, NGS) which leads to DNA strand breaks and to epithelial cell death. Inflammatory cells infiltrate the affected region to remove death cells. Leucocytes and lymphocytes proliferate and produce cytokines and chemokines, leading to an inflammatory condition highly deregulated in duration and perpetuation. The persistence of the inflammatory state culminates in early reversible toxicity (pneumonitis) and can develop in to irreversible late toxicity (fibrosis).

Giuranno et al., FONC 2019

PATHOPHYSIOLOGY OF IMMUNE RELATED PNEUMONITIS



Zhai et al., Cancer Med Biol, 2020

INTERACTION OF RADIATION WITH ICI IN THE LUNG

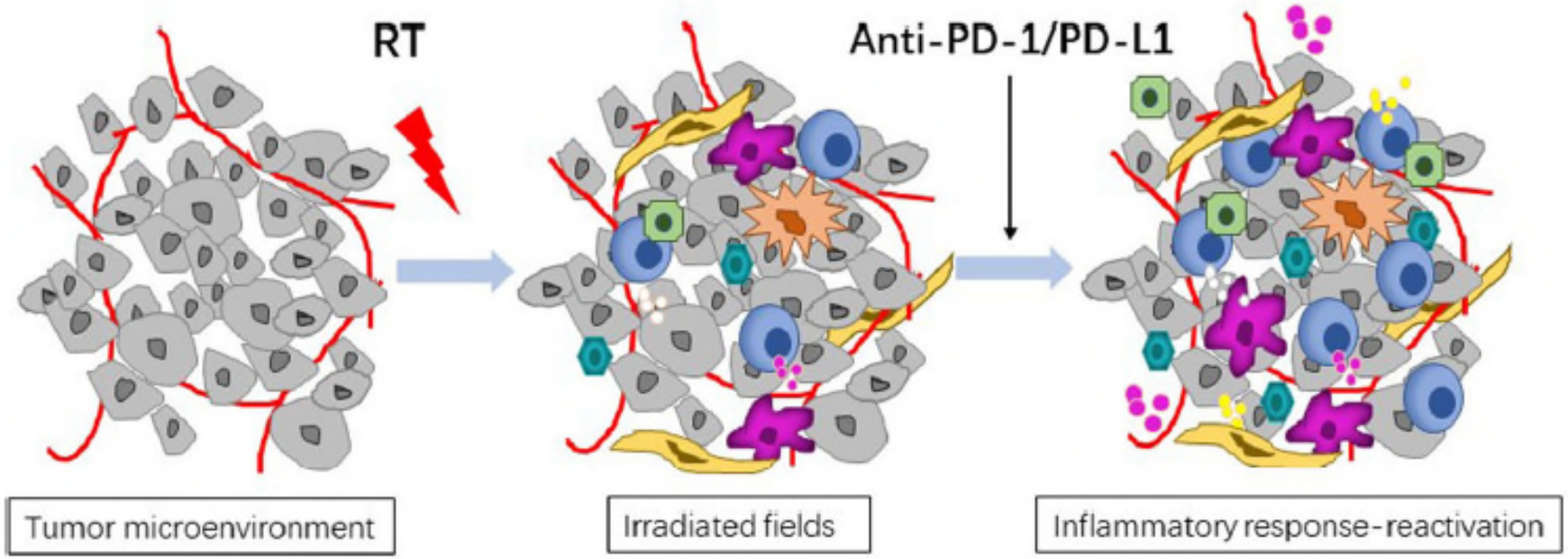


Fig. 2 Immune mechanisms of RRP triggered by anti-PD-1/PD-L1. The immune checkpoint inhibitors evoke an inflammatory reaction in previously irradiated fields

Teng et al., BMC Medicine 2020

ICI after RT may cause a recall phenomenon via an inflammatory response-reactivation to potentiate RP

ARE WE SEEING MORE PNEUMONITIS WITH CRT + DURVALUMAB?

Table 4 Pneumonitis in Asian stage III NSCLC following ICI consolidation therapy

Study	Country (region)	Population	All pneumonitis (%)	G2 pneumonitis (%)	G3–5 pneumonitis (%)
Fukui *et al.*[23]	Japan	108	85	26.0	2.0
Chu *et al.*[24]	China (Taiwan)	31	17.2	NR	6.9
Jung *et al.*[25]	Korea	21	81	42.9	14.3
Sakaguchi *et al.*[33]	Japan	73	73.9	NR	5.5
PACIFIC Japan cohort[14]	Japan	112	54.2	NR	5.6
Current study	China	20	80.0	45.0	0
Pooled data	Asian	365	67.1	31.2	4.4
PACIFIC	Multicountry	476/709	33.9	NR	3.4
LUN14-179	USA	92	NR	10.8	6.5

G2, grade 2; G3–5, grades 3–5; NR, not reported.

Zhang et al., Thor Cancer 2020

Note that Asian descent was an independent risk factor per PACIFIC for RP

DO WE NEED TO REVISIT LUNG CONSTRAINTS IN THE PACIFIC ERA?

Table 2
Relationship between radiation dosage, consolidation treatment and RT pneumonitis by chi-square.

Parameter		No. of patient	RT pneumonitis	*p* value	RT Pneumonitis ≥ Grade 2	*p* value
MLD	<20 Gy	44	19(43.2 %)	0.024	7(15.9 %)	<0.001
	≥20 Gy	17	13(76.5 %)		12(70.6 %)	
Lung V20	<35 %	40	17(42.5 %)	0.058	6(15.0 %)	<0.001
	≥35 %	21	15(71.4 %)		13(61.9 %)	
Consolidation	Observation	40	15(37.5 %)	0.001	8(20.0 %)	0.018
	Durvalumab	21	17(81.0 %)		11(50.0 %)	

RT, radiation; MLD, Mean lung dose; Lung V20, the volume of lung parenchyma that received 20 Gy or more.

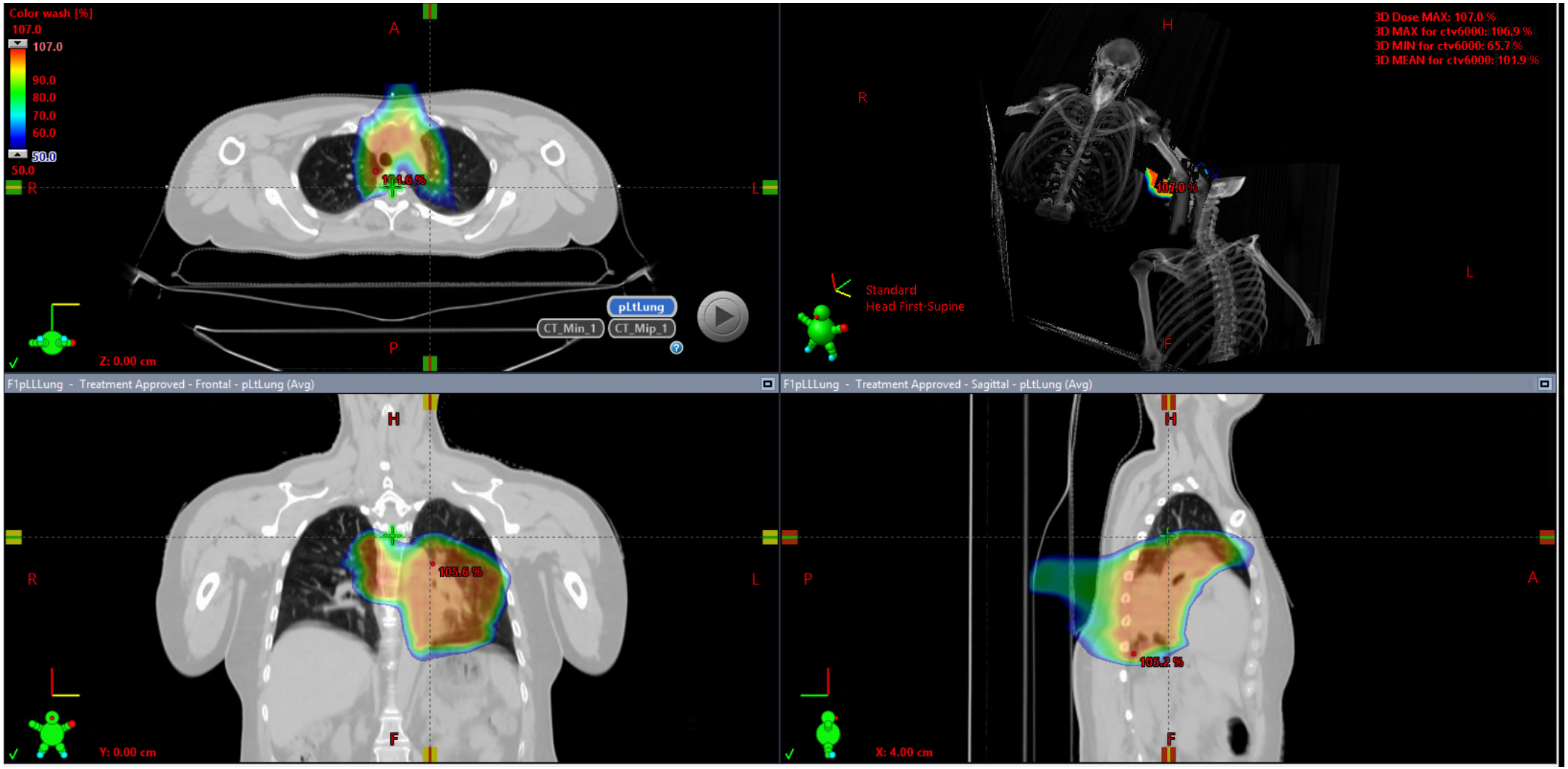
Table 3
Multivariable cox proportional hazards regression analysis for radiation pneumonitis.

		RT pneumonitis			RT pneumonitis ≥ Grade 2		
		HR	95 % CI	*p* value	HR	95 % CI	*p* value
MLD	≥20	2.33	0.21 – 26.04	0.49	5.88	0.45 – 78.04	0.18
Lung V20	≥35 %	1.49	0.17 – 13.46	0.72	2.05	0.17 – 26.27	0.58
Consolidation	Durvalumab	6.13	1.68 – 22.46	0.006	3.58	0.94 – 13.68	0.06

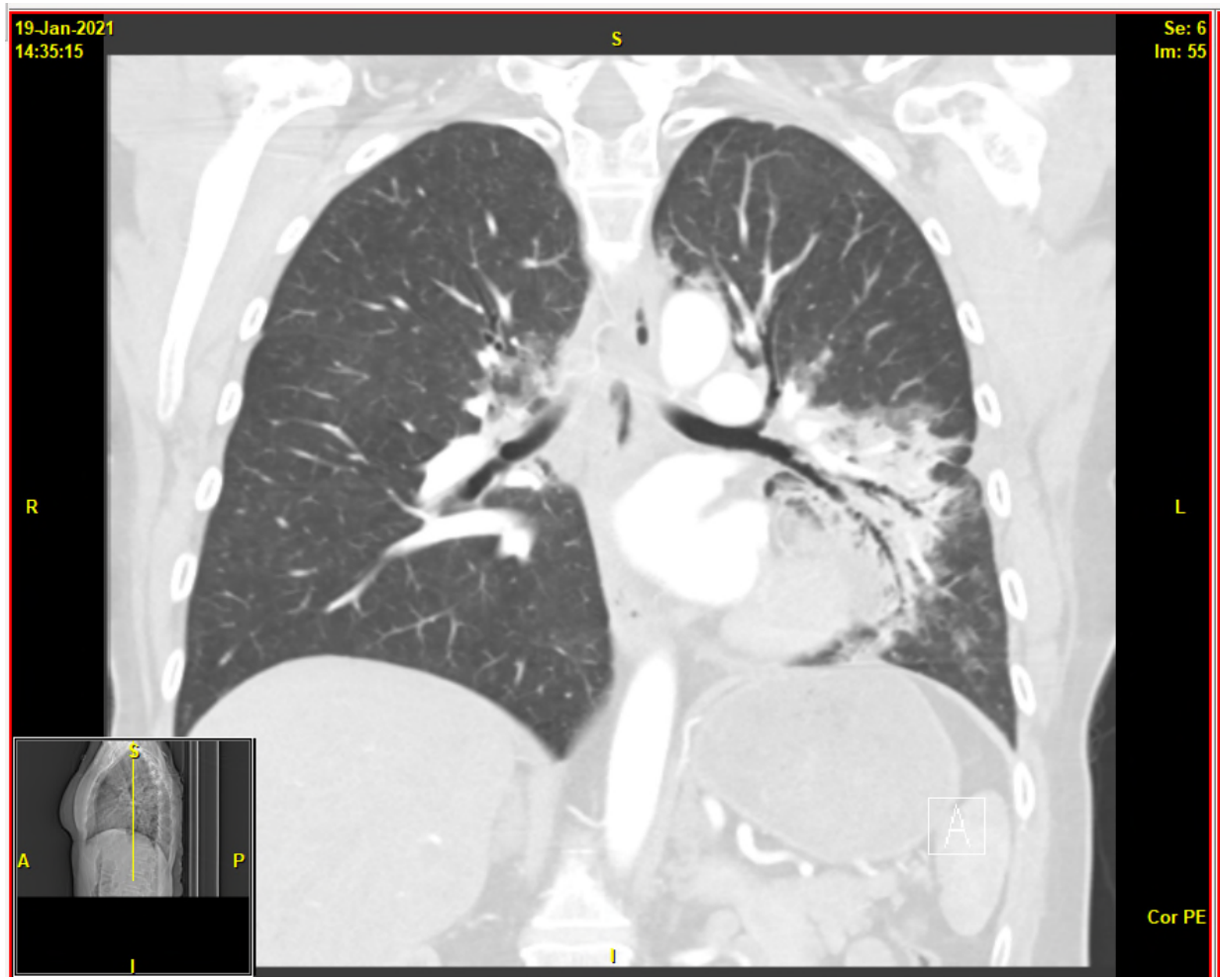
HR, Hazard ratio; CI, Confidence interval; RT, radiation; MLD, Mean lung dose; Lung V20, the volume of lung parenchyma that received 20 Gy or more.

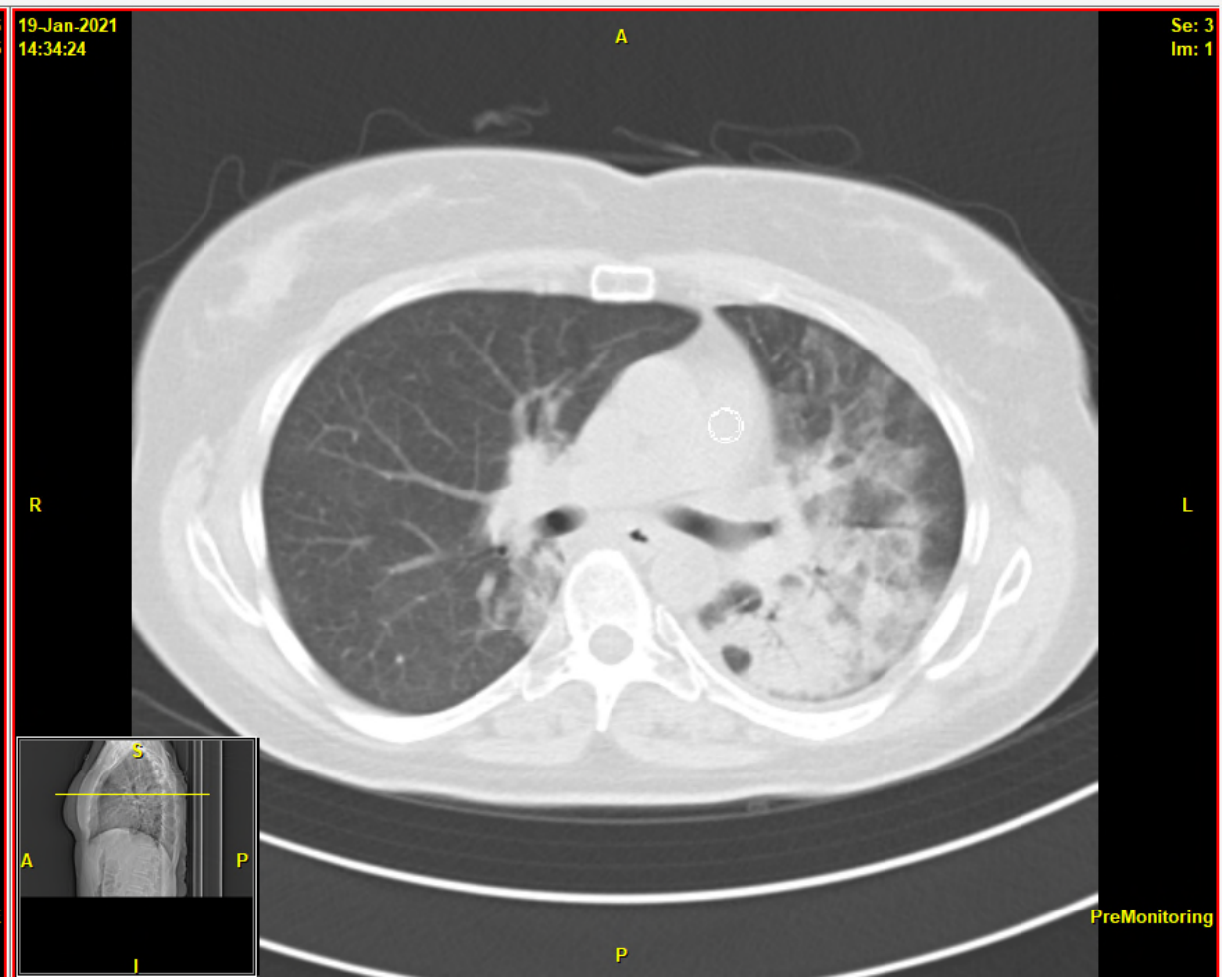
Jung et al., Lung Cancer 2020

CAN WE DISTINGUISH RP FROM ICI-P?

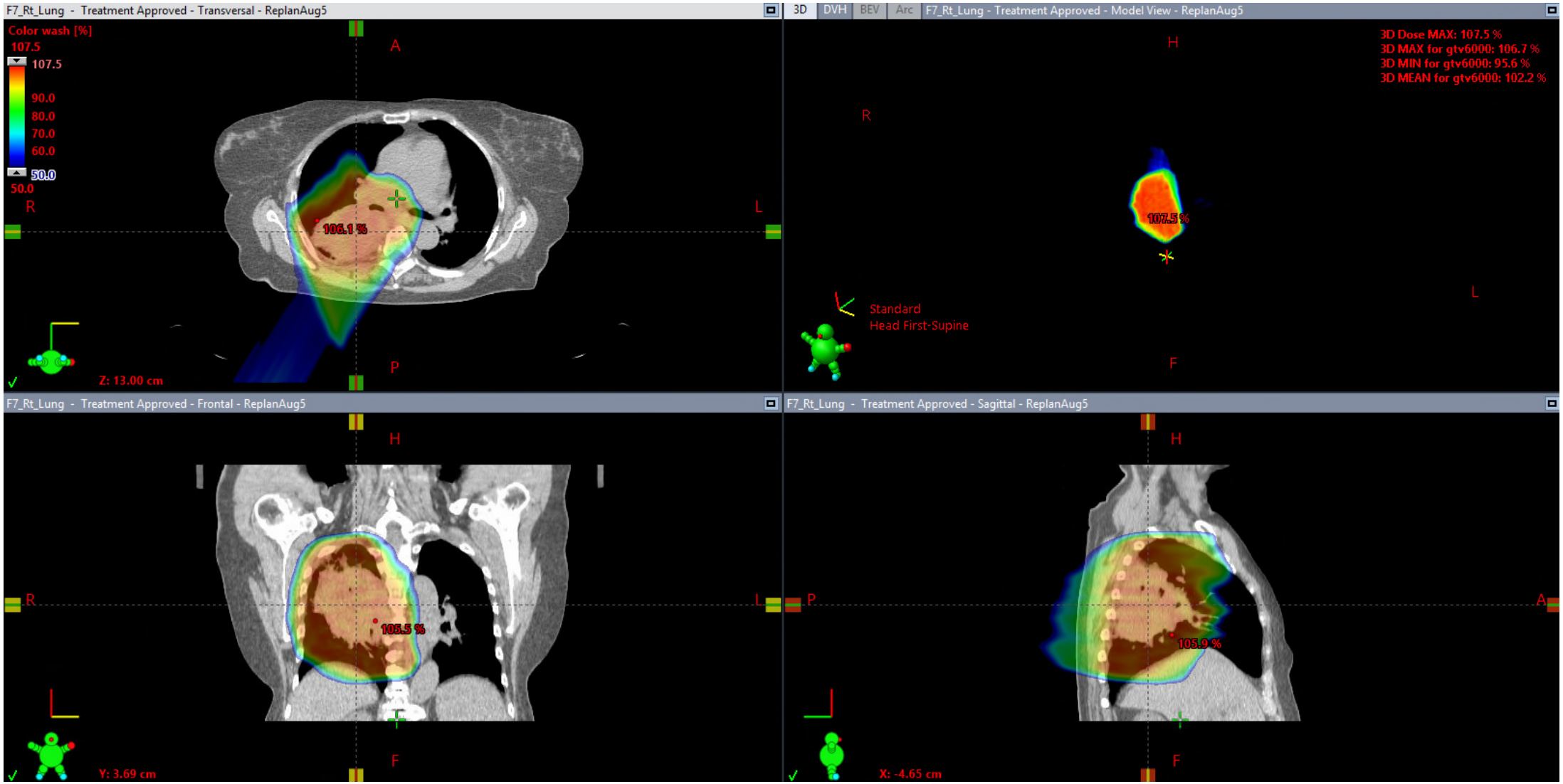


PROBABLE RADIATION PNEUMONITIS

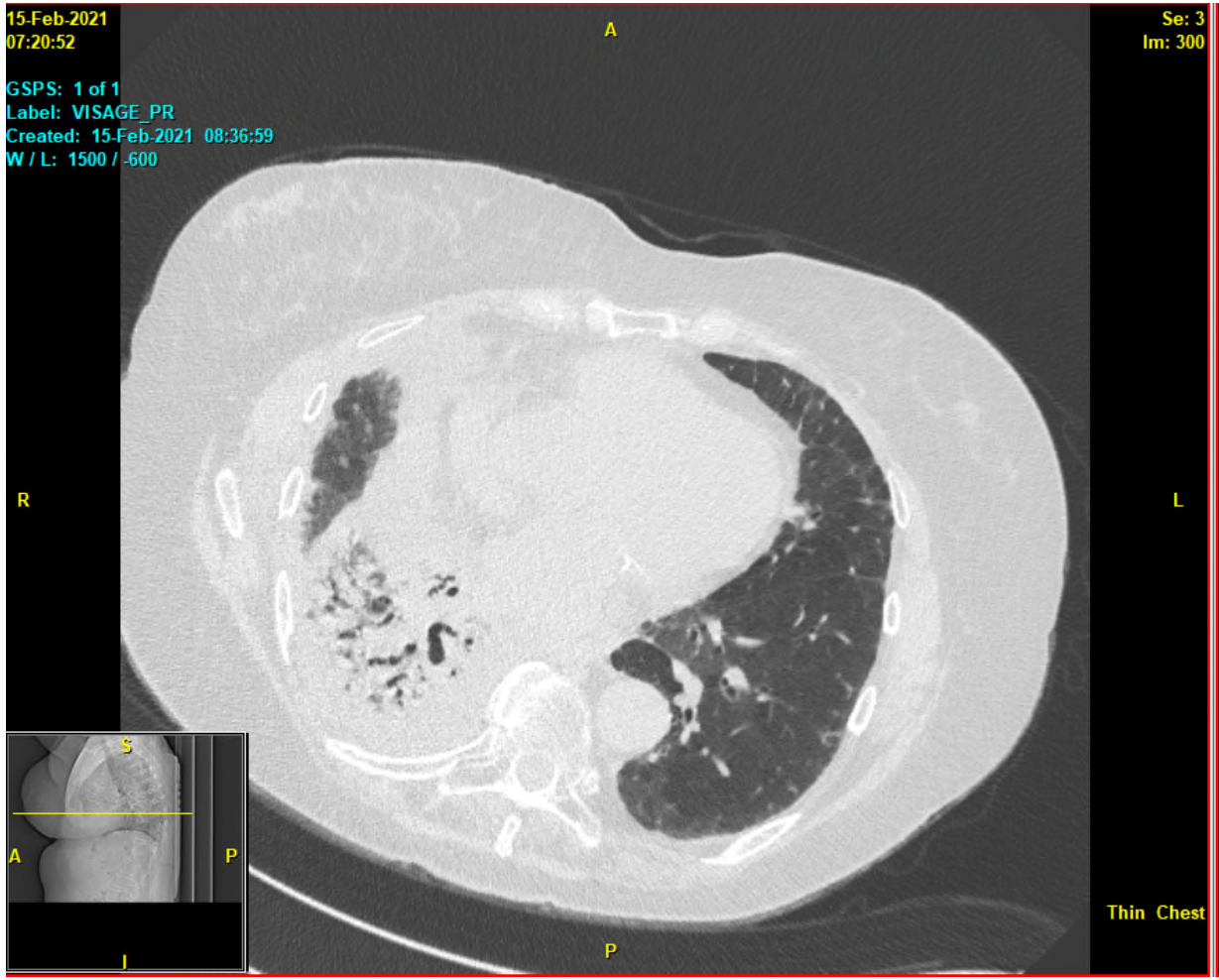


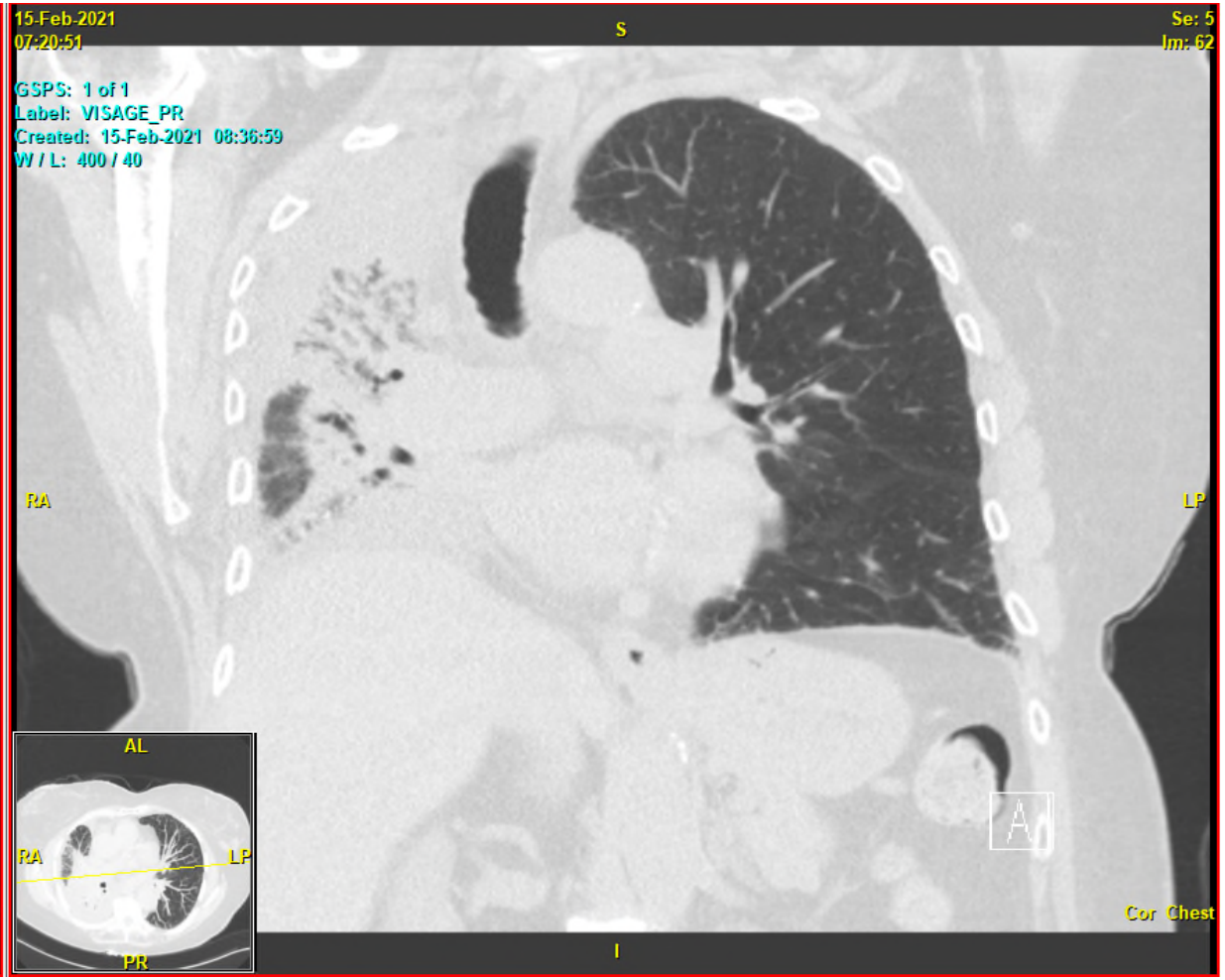


NOTE CHANGES LIMITED MOSTLY TO RT FIELD

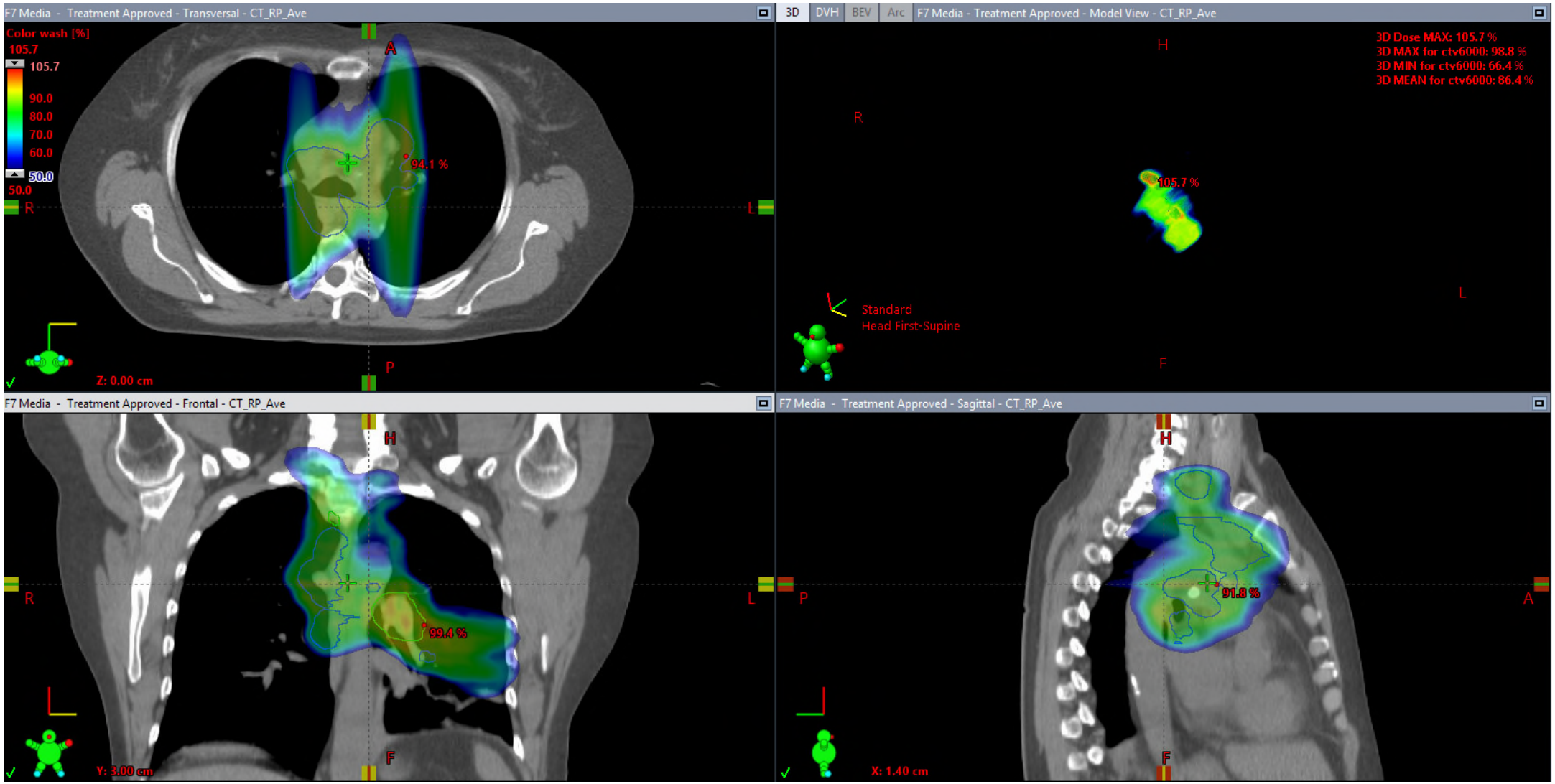


PROBABLE RADIATION PNEUMONITIS

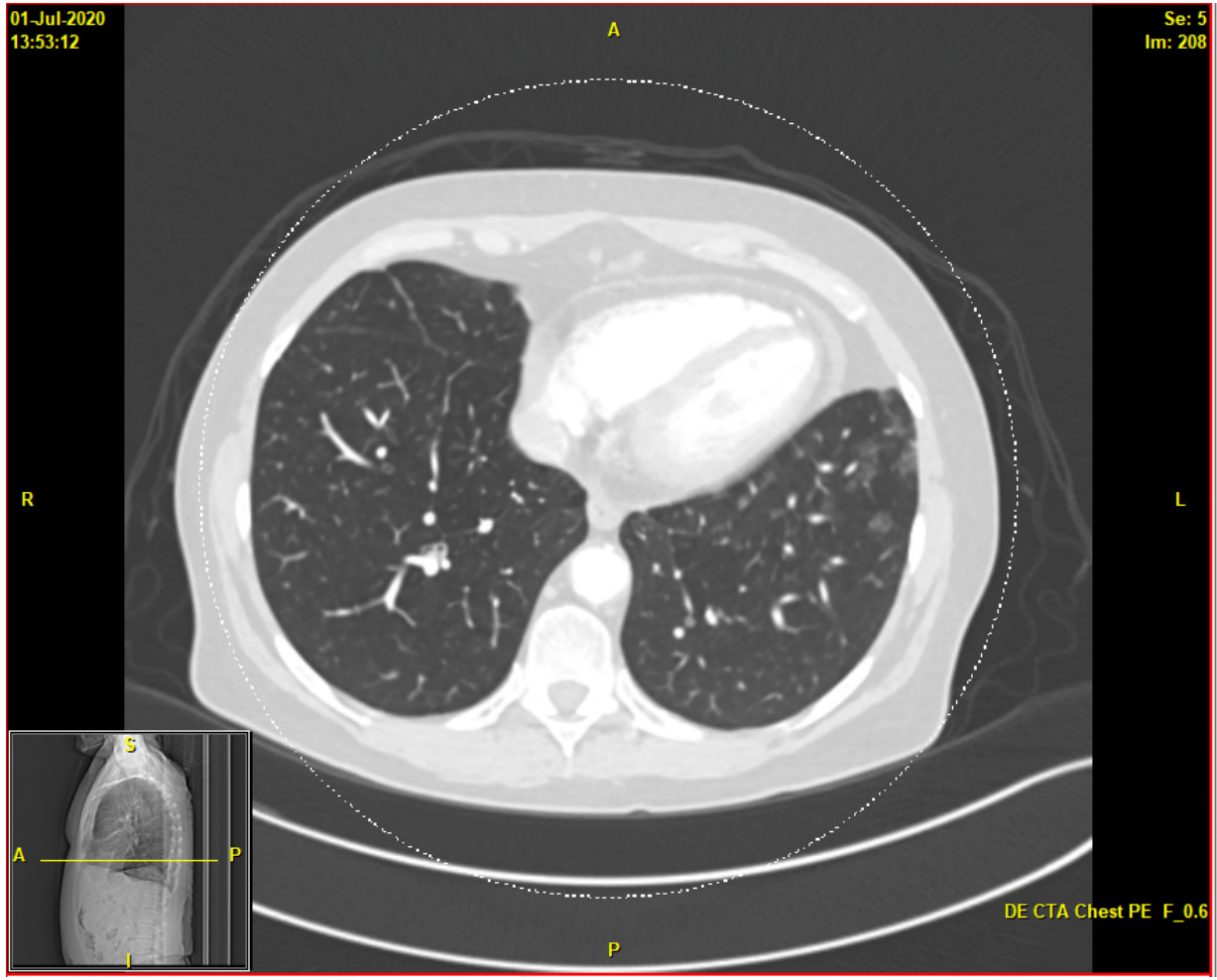


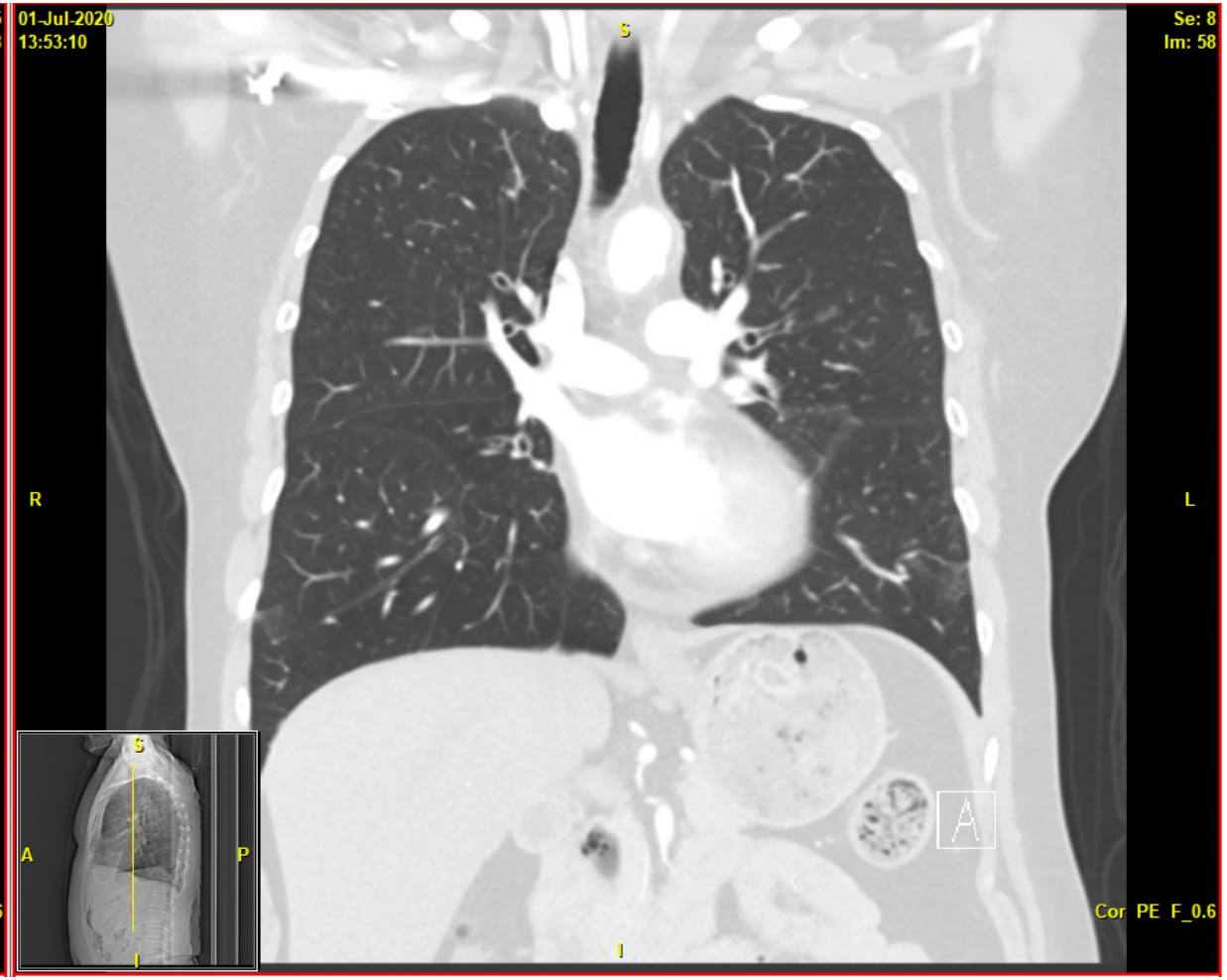


BILATERAL LUNG CHANGES OR MORE DIFFUSE PARENCHYMAL CHANGES

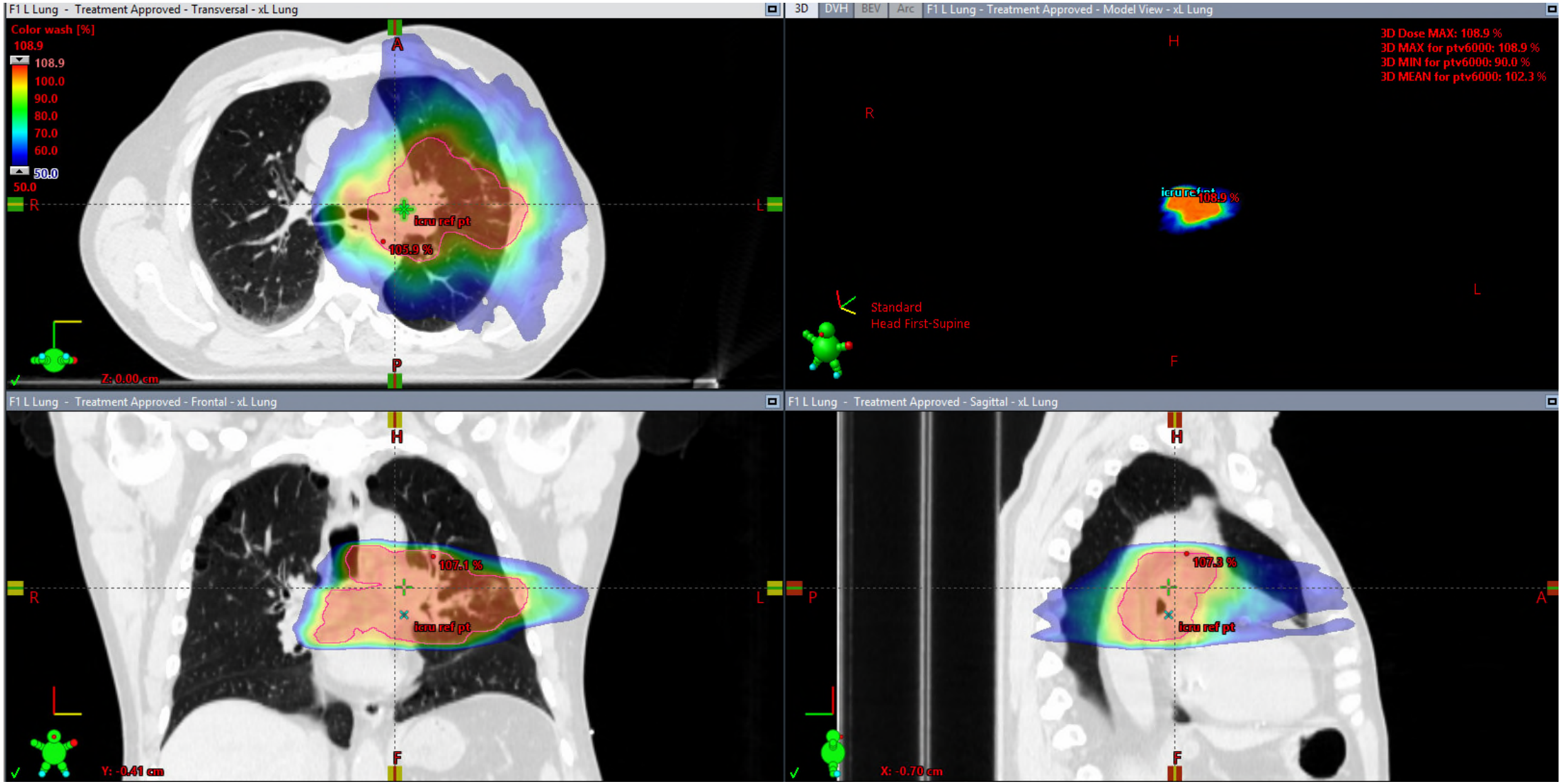


PROBABLE ICI PNEUMONITIS





BUT YOU CAN GET A COMBO OF BOTH!



CHANGES IN BOTH! NOT SURE IF RP OR ICI-P BUT PATIENT SYMPTOMATIC