elcc European Lung Cancer Congress

#113P

6th ANNUAL YEAR END REVIEW IN LUNG CANCER 2022

Apollo PROTON Cancer Centres

Proton-therapy and concurrent chemotherapy in stage III NSCLC: Effects on Durvalumab eligibility and safety profile

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INTRODUCTION

RTOG 0617
Median OS- 28.7 months
5-year survival of 32%

PACIFIC TRIAL
Median OS- 47.5 months With 5-year OS-43%

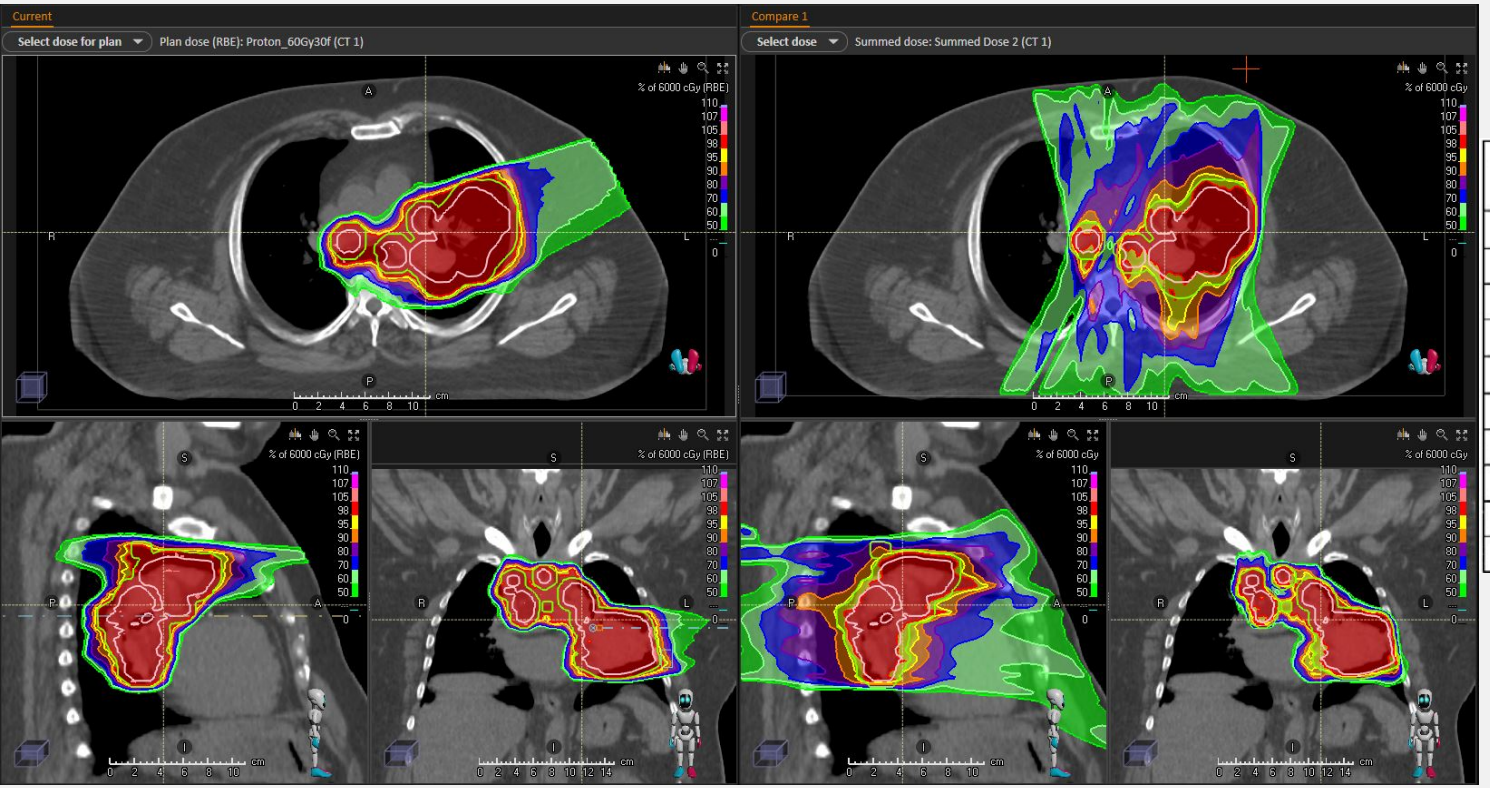
Trial	2 yr OS	2 yr PFS	5yr PFS	5 yr OS
RTOG 0617	60%	31%	20%	32%
PACIFIC	66%	50%	33%	43%

TABLE 2. Maximum Treatment-Related Adverse Events by Arm

	Arm, No. (%)			
Adverse Event	A: 60 Gy (n = 152)	B: 74 Gy (n = 107)	C: 60 Gy + Cetuximab (n = 137)	D: 74 Gy + Cetuximab (n = 100)
No grade ≥ 3 toxicity	42 (27.6)	32 (29.9)	20 (14.6)	10 (10.0)
Grade ≥ 3 toxicity	110 (72.4)	75 (70.1)	117 (85.4)	90 (90.0)
*P**	.0002			

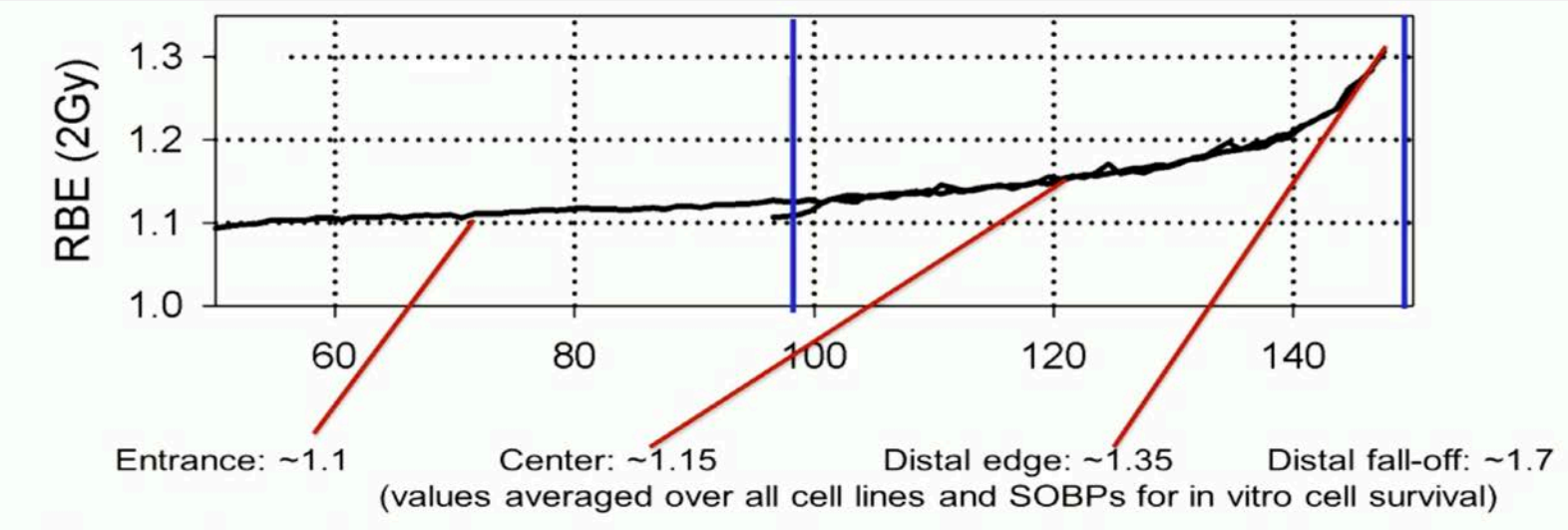
*χ^2 test, 2-sided.

PROTONS- PHYSICAL ADVANTAGE

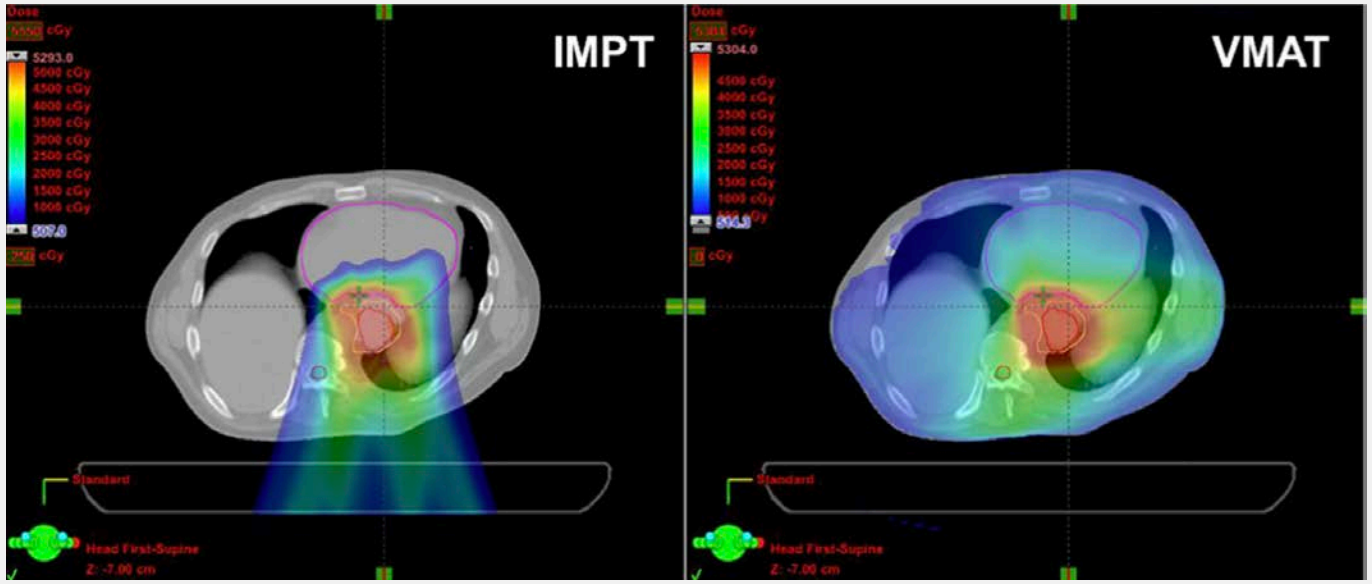


Structure	Dose parameter	Dosimetry achieved with IMRT (as provided)	Dosimetry achieved with IMPT
CTV	D99	57.96 Gy	58.95 Gy
PTV	D95	56.92 Gy	97.9 Gy
Heart	Mean Dose	29.8 Gy	7.2 Gy
Thyroid	Mean Dose	10.6 Gy	5.6 Gy
Total Lung-CTV	Mean Dose	19.7Gy	12 Gy
	V20	36%	22.4%
	V5	61.5%	35.5%
Right Lung-CTV	Mean Dose	9.4 Gy	4 Gy
	V20	14.3%	7%
	V5	39.5%	15%

PROTON THERAPY- BIOLOGICAL ADVANTAGE



IMMUNOLOGICAL ADVANTAGE



- NSCLC is immune hot with increased spatial infiltration of T cells in tumor & microenvironment.
- RT has immune priming effect

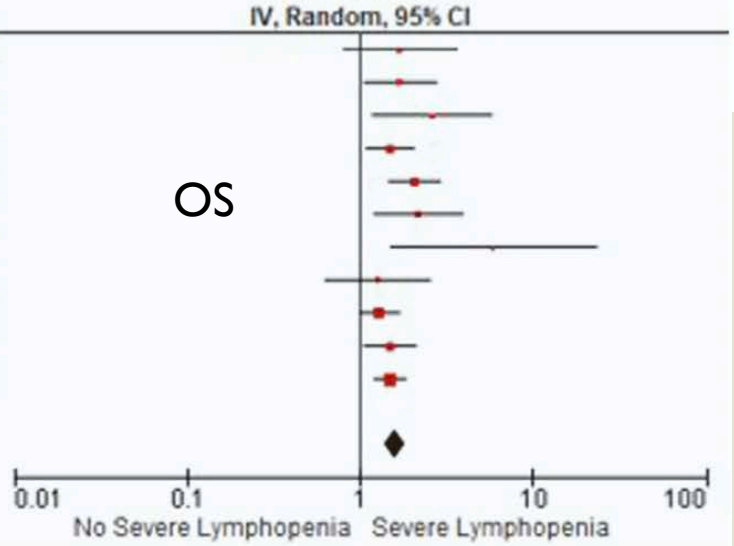
Central Dogma- circulating T Lymphocytes

LD50 of Lymphocytes- 2 Gy
DNA damage can occur at doses as low as 0.5 Gy

Risk and impact of radiation related lymphopenia in lung cancer: A systematic review and meta-analysis

Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Random, 95% CI	Year
Campian 2013	0.5306	0.3846	2.9%	1.70 [0.80, 3.61]	2013
Tang 2014	0.5277	0.2443	6.6%	1.70 [1.05, 2.74]	2014
Cho 2015	0.9632	0.4027	2.6%	2.62 [1.19, 5.77]	2015
Tang 2017	0.4055	0.1582	13.7%	1.50 [1.10, 2.05]	2017
Wang 2019	0.7208	0.1712	12.1%	2.06 [1.47, 2.88]	2019
Zhao 1 2019	0.7701	0.302	4.5%	2.16 [1.20, 3.90]	2019
Zhao 2019	1.7778	0.6988	0.9%	5.92 [1.50, 23.28]	2019
Abravan 1 2020	0.239	0.3577	3.3%	1.27 [0.63, 2.56]	2020
Abravan 2020 SCLC	0.2546	0.1299	18.2%	1.29 [1.00, 1.66]	2020
Chen 2020	0.392	0.1765	11.5%	1.48 [1.05, 2.09]	2020
Abravan 2020 NSCLC	0.4055	0.1054	23.7%	1.50 [1.22, 1.84]	2020
Total (95% CI)			**100.0%**	**1.59 [1.40, 1.81]**	

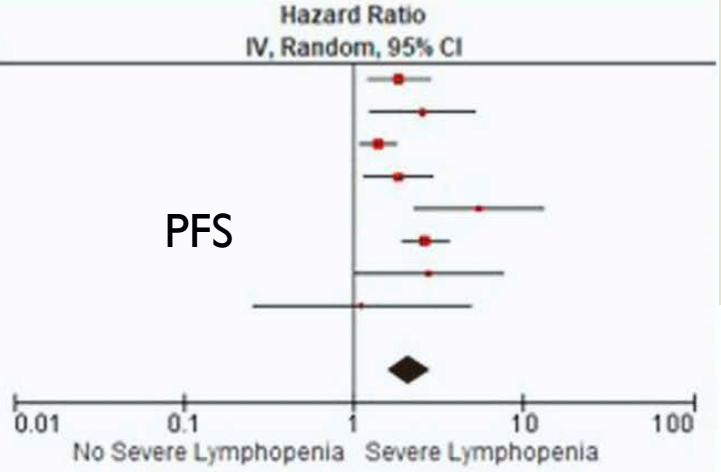
Heterogeneity: Tau² = 0.01; Chi² = 11.98, df = 10 (P = 0.29); I² = 17%
Test for overall effect: Z = 6.94 (P < 0.00001)



C

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI	Year
Tang 2014	0.6152	0.2188	16.3%	1.85 [1.20, 2.84]	2014
Cho 2015	0.9322	0.3618	10.0%	2.54 [1.25, 5.16]	2015
Tang 2017	0.3365	0.123	21.6%	1.40 [1.10, 1.78]	2017
Zhao 1 2019	0.6087	0.2354	15.4%	1.84 [1.16, 2.92]	2019
Zhao 2019	1.6982	0.4488	7.6%	5.46 [2.27, 13.17]	2019
Wang 2019	0.9578	0.1609	19.5%	2.61 [1.90, 3.57]	2019
Chen 2020 Conventional	1.0217	0.5162	6.2%	2.78 [1.01, 7.64]	2020
Chen 2020 SBRT	0.1054	0.7484	3.4%	1.11 [0.26, 4.82]	2020
Total (95% CI)			**100.0%**	**2.10 [1.57, 2.81]**	

Heterogeneity: Tau² = 0.09; Chi² = 17.28, df = 7 (P = 0.02); I² = 59%
Test for overall effect: Z = 5.04 (P < 0.00001)



Significant reduced risk of progression and death in pts without severe lymphopenia during RT.

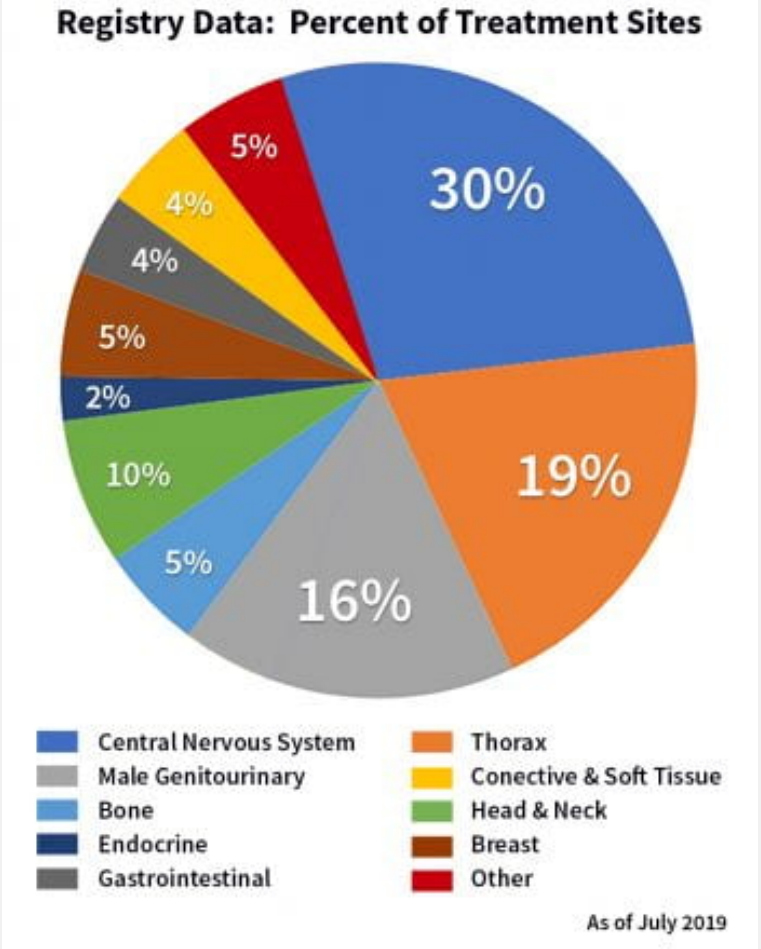
Lung V5, Heart V5 and MLD are surrogate markers to dose received by circulating lymphocytes.

Especially Important in pts with other risk factors like advanced age, lower baseline lymphocyte counts, higher stage and large tumor size.

STUDY QUESTIONS

Can proton therapy in combination with concurrent chemotherapy improve eligibility to receive maintenance immunotherapy ?

Can proton therapy be safely combined with maintenance immunotherapy ?



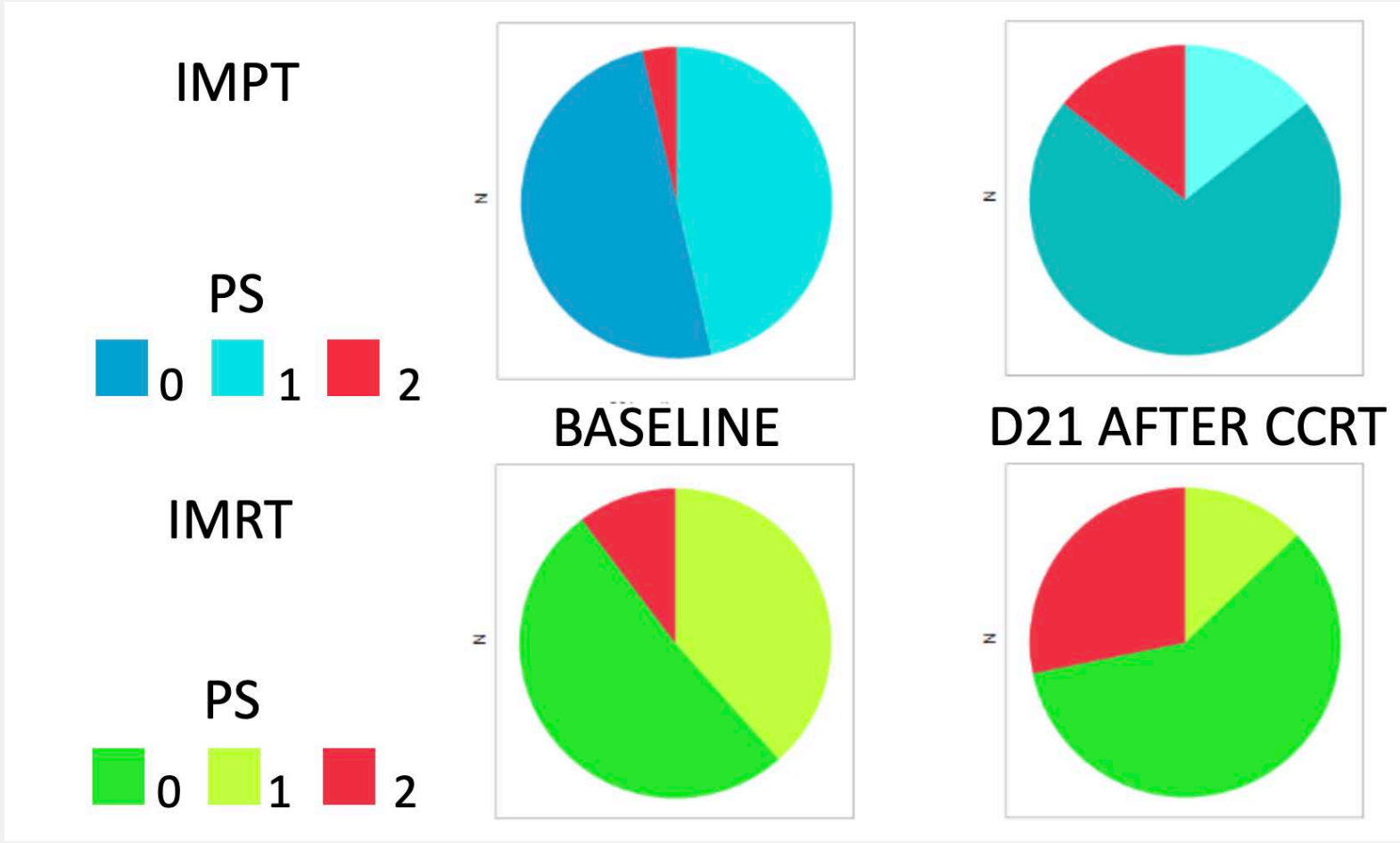
METHOD

- Study design: retrospective data collection froma 2-center prospectively collected lists (226 patients).
- Population: Stage III NSCLC, receiving CCRT between June'16 and Feb'21, staged with FDG-PET and brain imaging.
- Main exclusion criteria: previous cancer diagnosis-within 2 years and previous thoracic RT.

Variable	Overall (n=67)	Protons (n= 28)	Photons (n=39)	p. value
Age – years Median (Range)	66 (35-79)	66 (35-77)	67 (49-79)	0.9
Male (%)	52.2	57.1	48.7	0.49
Tumor Stage - no. (%) IIIA IIIB IIIC	25 (37.3) 38 (56.7) 4 (6)	10 (35.7) 17 (60.7) 1 (3.6)	15 (38.5) 21 (53.8) 3 (7.7)	0.7
PD-L1 % 0-49 ≥ 50% Unknown	31 (46) 20 (30) 16 (24)	10 (35.7) 8 (28.8) 10 (35.7)	21 (53) 13 (33) 5 (12)	0.2
WHO PS after CCRT At day 21 (0-1/≥2)	**80.6%/ 19.4%**	**92.9%/ 7.1%**	**71.8%/ 28.2%**	**0.032**
Immune related adverse events - no. (%) Any grade Grade ≥ 3	18 (26.9) 5 (7.4)	6 (21.4) 3 (10)	12 (30.8) 2 (5)	0.062
Pneumonitis rate during Durvalumab - no. (%) Any grade Grade ≥ 3	16 (26) 4 (6)	7 (25) 2 (7)	9 (23) 2 (5.1)	0.8
Median FU - months	14	9.5	19.5	<0.001

Results

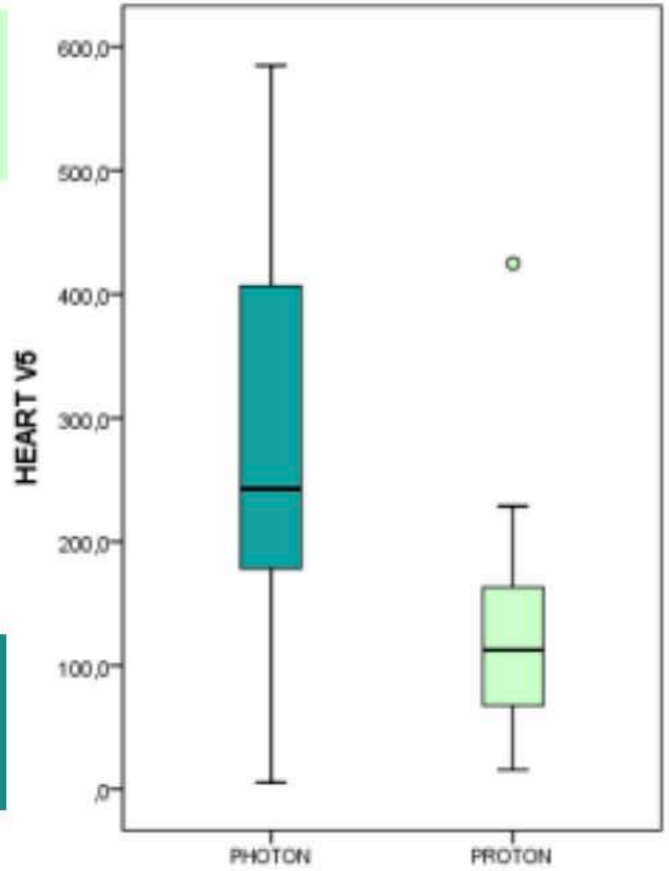
- IRAEs of any grade were reported in 21% vs 31% of pts treated with IMPT and IMRT (NS).
- Hypothyroidism accounted for 44% of IRAEs.
- Pneumonitis during Durvalumab was reported in 25% of IMPT and 23% of IMRT (NS).

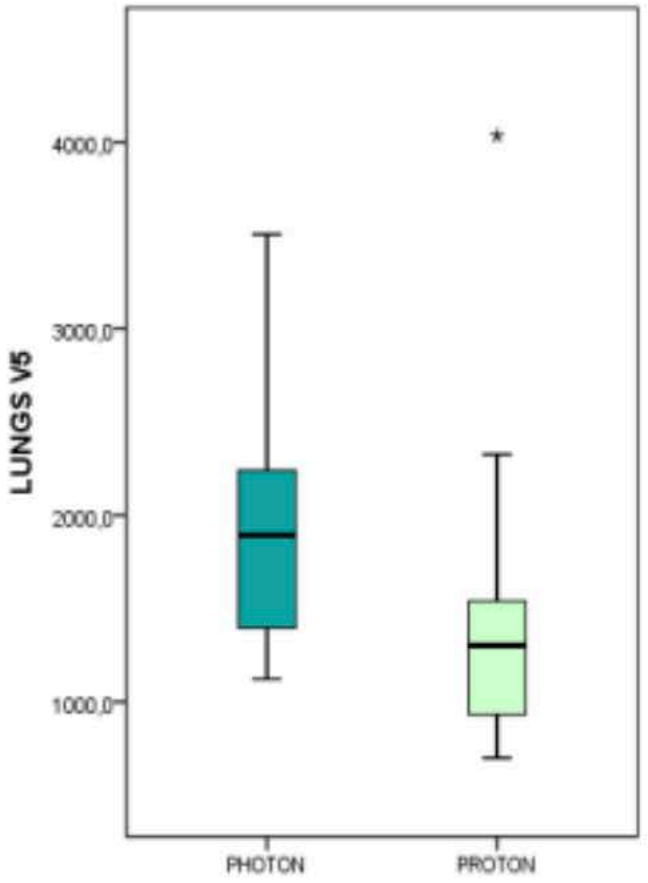


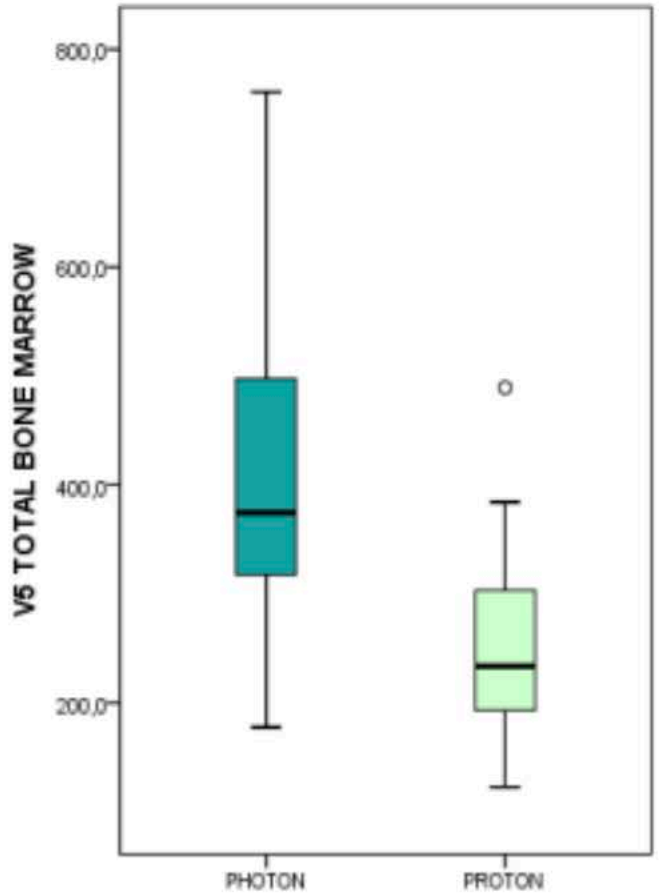
At day 21 after CCRT,
93% (IMPT) vs 72% (IMRT) treated pts had a PS≤1 (OR 0.8, p=0.03).

IMPT

IMRT


HEART V5
600,0
500,0
400,0
300,0
200,0
100,0
,0
PHOTON
PROTON


LUNGS V5
4000,0
3000,0
2000,0
1000,0
PHOTON
PROTON


V5 TOTAL BONE MARROW
800,0
600,0
400,0
200,0
PHOTON
PROTON

CONCLUSION OF THE STUDY

- PS at day 21 after CCRT was better in patients treated with IMPT, thus potentially increasing eligibility for adjuvant Durvalumab.
- The lower Radiotherapy dose delivered with IMPT might explain our findings.
- IMPT appears to be as safe as IMRT regarding IRAEs.

Strength

1. Unique combination of protons with immunotherapy.
2. Several theoretical advantages were being tested.
3. Modern proton therapy used for treatment

Weakness

1. Retrospective data.
2. Small sample size
3. No dosimetry reported yet; neither are detailed acute/late toxicities
4. No outcomes reported

Opportunities

1. Potentially more pts could be eligible for immuno-RT combination.
2. Potential for reducing toxicities during concurrent immune.
3. Reduced pneumonitis & cardiovascular risk
4. Opportunity to improve outcomes especially in challenging situations- LL primaries, N3, multicentric, unhealthy lungs etc.

Threat

1. Financial toxicity due to combining two expensive modalities.