How protons make fitter patients – focus on unresectable stage III NSCLC

MAASTRO proton symposium

Lizza Hendriks, MD, PhD
Pulmonologist
Maastricht UMC+, the Netherlands

@HendriksLizza

Francesco Cortiula, MD
Medical Oncologist
University Hospital Udine, Italy
PhD candidate Maastricht University

@FCortiula

Disclosures L Hendriks

Interest	Company/organisation
Grants/research support	Roche Genentech, AstraZeneca, Boehringer Ingelheim, Takeda, Merck, Pfizer, Novartis, Gilead (all to institution)
Honoraria or consultation fees	Advisory boards: Abbvie, Amgen, Anhearth, AstraZeneca, Bayer, BMS, Boehringer Ingelheim, Daiichi, GSK, Janssen, Lilly, Merck, MSD, Novartis, Pfizer, Pierre Fabre, Roche, Sanofi, Summit Therapeutics, Takeda (all to institution)
Participation in a company sponsored bureau	Not applicable
Stock shareholder	Not applicable
Spouse/partner	Not applicable
Other support/potential conflict of interest	Speaker educationals/webinars: AstraZeneca, Bayer, Lilly, MSD, high5oncology, Takeda, Janssen, GSK, Sanofi, Pfizer (Inst), Medtalks, Benecke, VJOncology, Medimix (self). Member guideline committees: Dutch guidelines on NSCLC, brain metastases and leptomeningeal metastases (payment to self), ESMO guidelines on metastatic NSCLC, non-metastatic NSCLC and SCLC (non-financial). Other (non-financial): secretary NVALT studies foundation, subchair EORTC metastatic NSCLC systemic therapy, vice-chair scientific committee Dutch Thoracic Group. local PI of clinical trials: AstraZeneca, GSK, Novartis, Merck, Roche, Takeda, Blueprint, Mirati, Abbvie, Gilead, MSD, Merck, Amgen, Boehringer Ingelheim, Pfizer

Disclosures F Cortiula

Interest	Company/organisation
Grants/research support	None
Honoraria or consultation fees	Advisory boards: MSD, Regeneron
Participation in a company sponsored bureau	None
Stock shareholder	None
Spouse/partner	None
Other support/potential conflict of interest	Speaker educationals/webinars: AstraZeneca, johnson & johnson, Roche Member guideline committees: ESMO living guidelines on metastatic NSCLC (non-financial). PI of clinical trials: AstraZeneca, MSD (non-financial).

Overview

Where do we come from in unresectable stage III NSCLC?

Current standard of care

New immunotherapy based treatments

Why protons make fitter patients and why this matters

Take home messages

Evolution of the treatment for patients with unresectable stage III NSCLC

RTOG73-01
60Gy/30fr
>superior control vs several other Rtx regimens

CALGB 8433
Seq CRT > OS vs Rtx alone

RTOG94-10
Conc CRT > OS vs seq CRT

PROCLAIM
Pem-cis = eto-cis conc CRT
SWOG S0023
No benefit maintenance gefitinib
Etc….

RTOG0716
No benefit 74Gy vs 60Gy, no benefit adding cetuximab

PACIFIC
Adj durvalumab > OS vs placebo after conc CRT

1980s
RTx only
2y OS 18%

1996
Seq CRT
5y OS 17%

2011
Conc CRT*
5y OS 16%

2020
Conc CRT
5y OS 32%

2022
PACIFIC
5y OS 43%

Survival improvement due to: better staging – better treatment and supportive care – immunotherapy

>40% of patients with unresectable stage III NSCLC still ineligible for conc CRT

Maastricht UMC+

Perez Cancer 1982; Dillman JNCI 1996; Curran JNCI 2011; Bradley JCO 2020; Senan JCO 2016; Kelly JCO 2008; Spigel JCO 2022; De Ruysscher Ann Oncol 2009; Hanna JCO 2008. *median and 2y OS superior for CCRT

PACIFIC: adjuvant durva, the standard of care for unresectable stage III NSCLC

270/983 NOT randomized

- Unresectable, Stage III NSCLC without progression 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

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

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

Placebo 10 mg/kg q2w for up to 12 months N=237

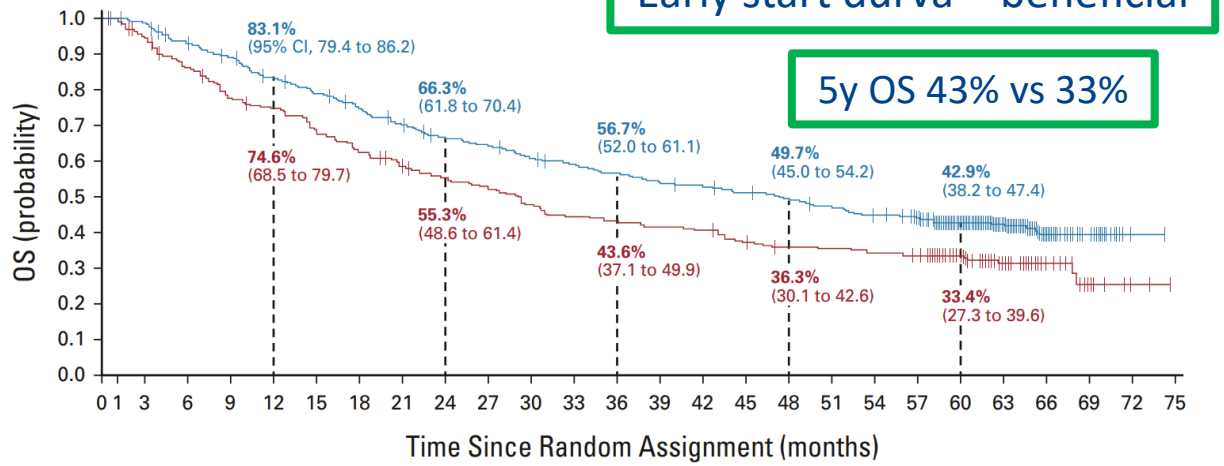
Unresectable stage III (TNM7)
Loosely defined and based on site's criteria

Primary endpoints
PFS (BICR)
OS

No data about use of protons

Early start durva = beneficial

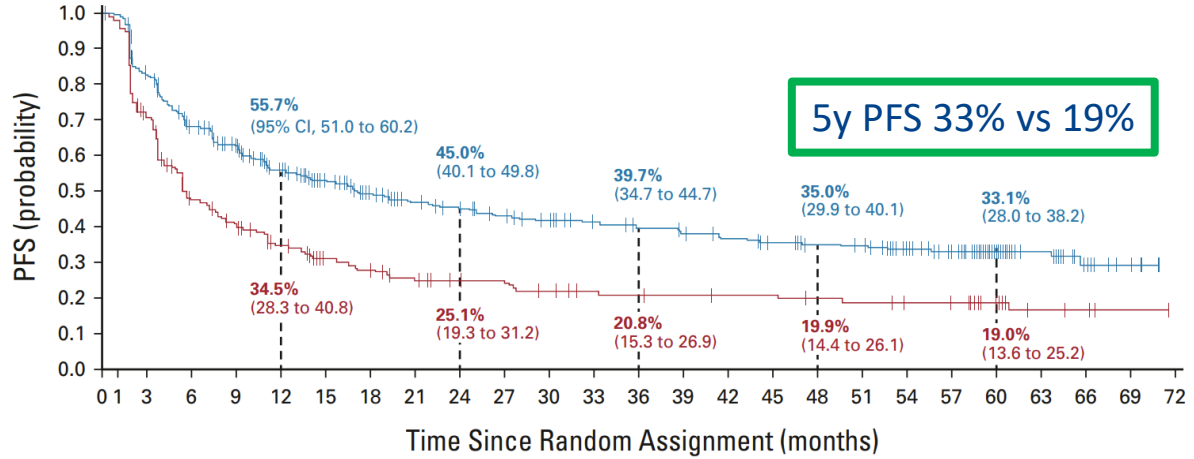
5y OS 43% vs 33%



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

5y PFS 33% vs 19%



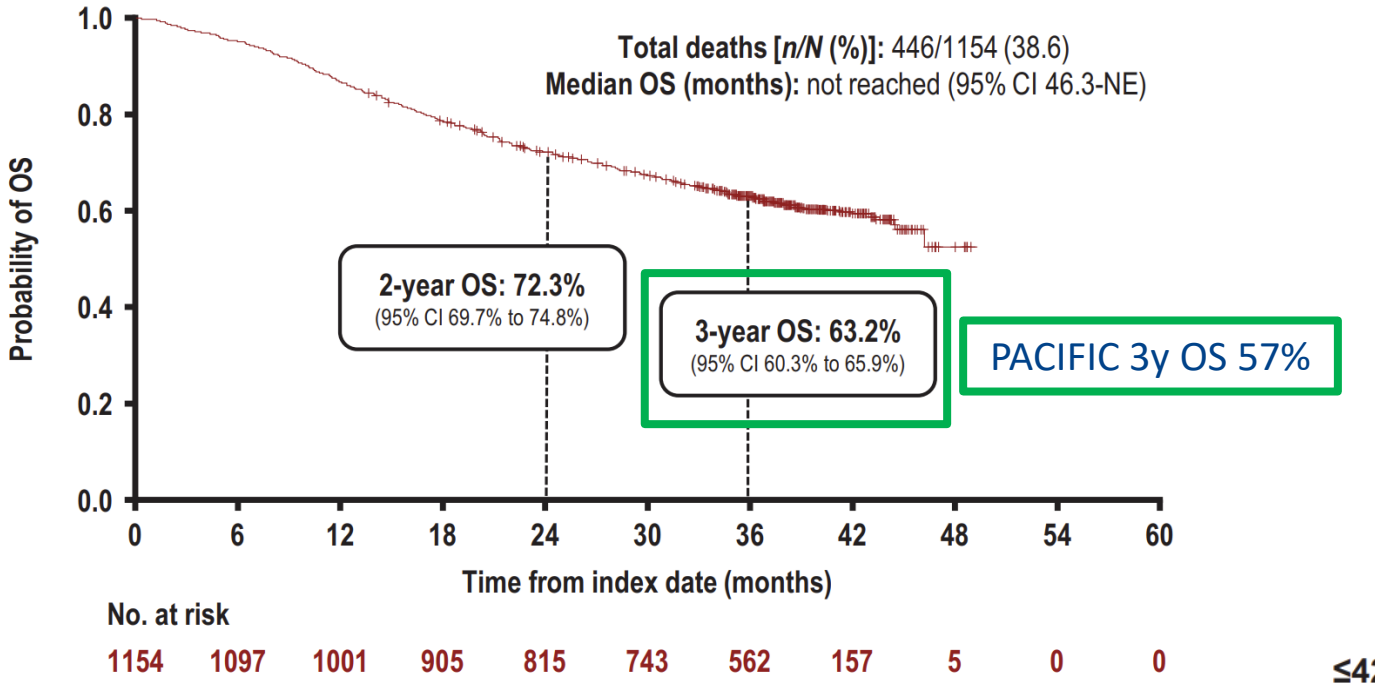
No. at risk:

Durvalumab	476	377	301	267	215	190	165	147	137	128	119	110	103	97	92	85	81	78	67	57	34	22	11	5	0
Placebo	237	164	105	87	68	56	48	41	37	36	30	27	26	25	24	24	22	21	19	19	14	6	4	1	0

Maastricht UMC+

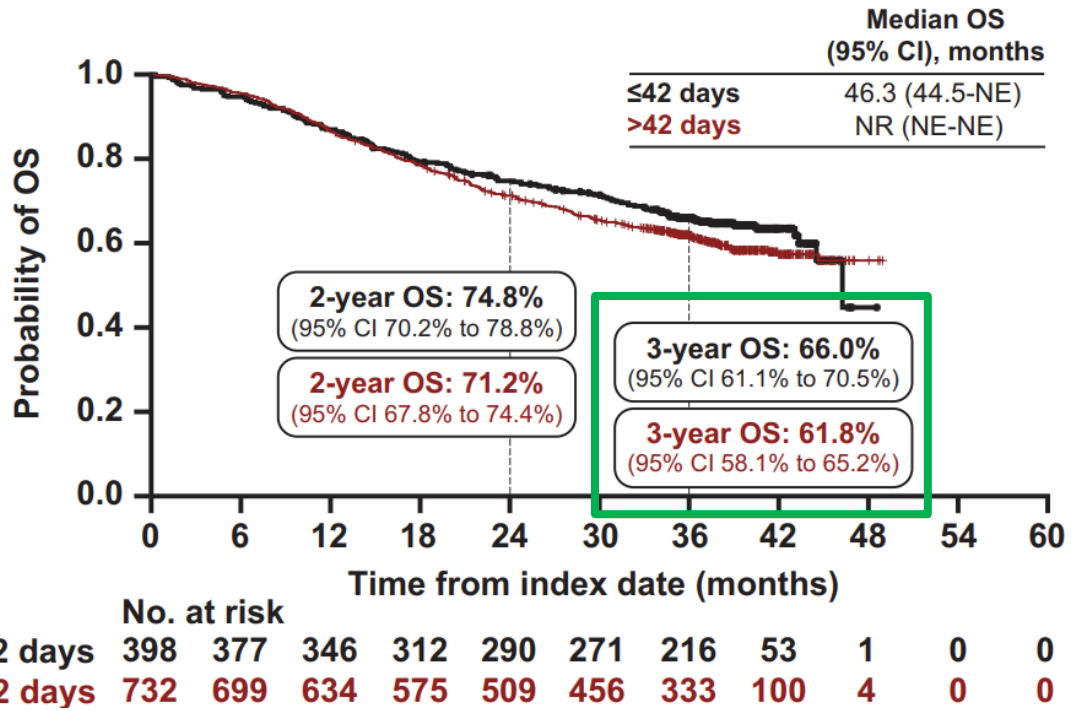
Spigel JCO 2022

Does the benefit extend to a “real-world” population? PACIFIC-R interim OS data



PACIFIC 3y OS 57%

Early start durva = beneficial

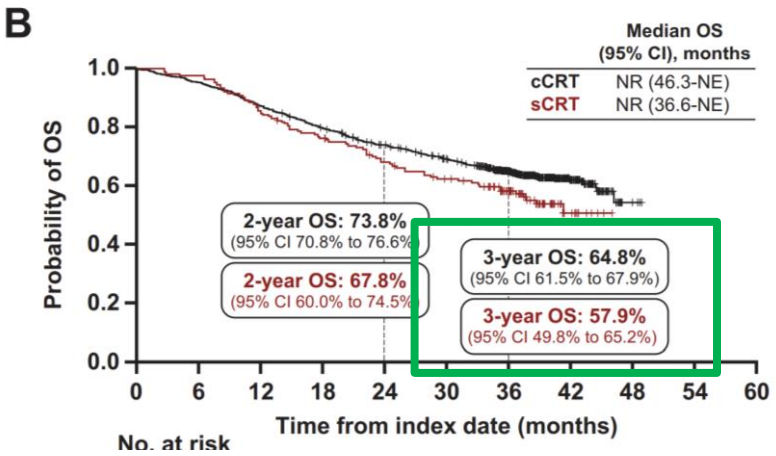


N = 1154 - **type of RTx?** - Median time to start durva: 56d; **64% >42 days**
30% 70+ years old; 2% PS 2; 15% seq CRT

Maastricht UMC+

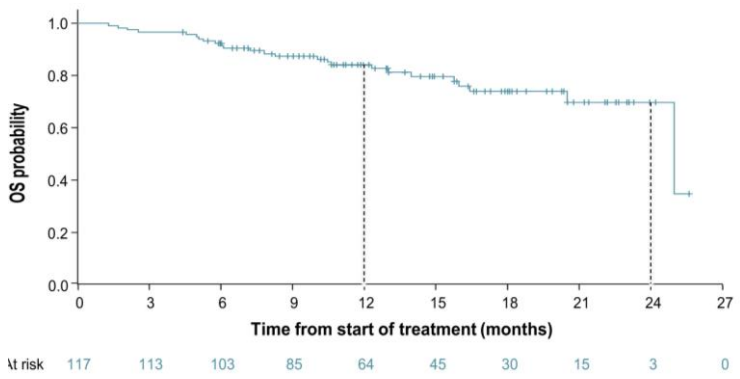
Adjuvant immunotherapy after sequential chemoradiotherapy?

PACIFIC-R sCRT vs cCRT



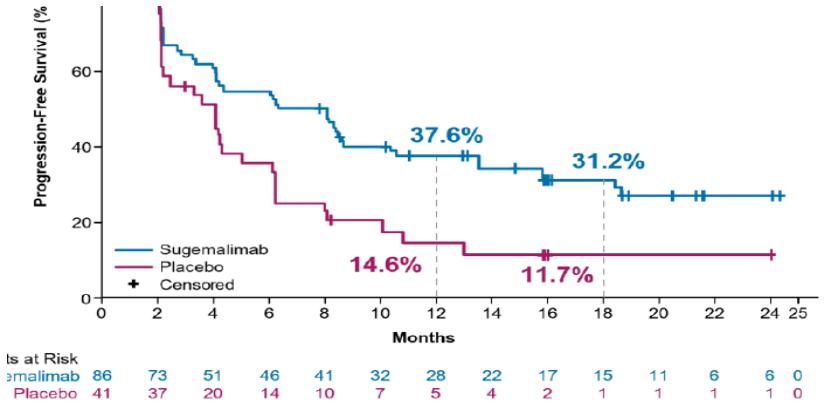
3 years OS 57.9%

PACIFIC-6 adj durva 2 years, N=117
2.6% PS2 – no data type of Rtx



2-year OS 69.8%

GEMSTONE 301 seq CRT subgroup
Adj sugemalimab 2y vs placebo
Eligible only PS 0-1, **no data about type of Rtx**



mPFS 8.1 vs 4.1
18 months PFS 31.2% vs 11.8%

Daily practice sCRT = frail patient

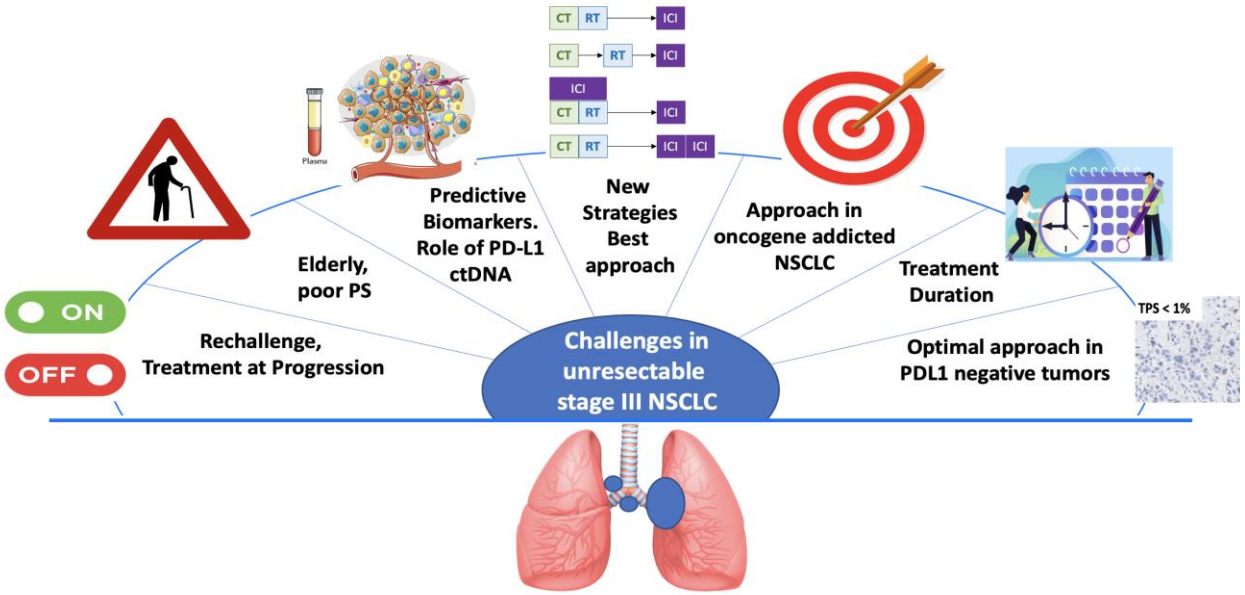
Maastricht UMC+

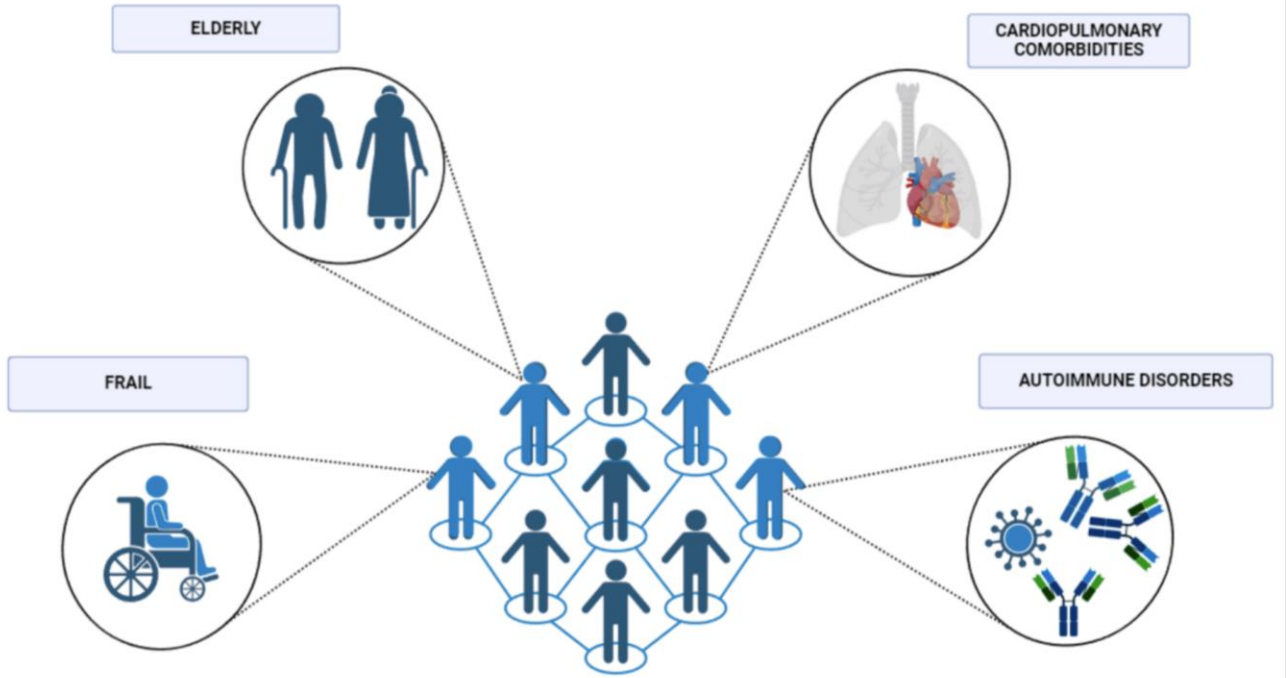
Fillippi ESMO Open 2024; Garassino JTO 2022; Zhou Lancet 2022

Multiple challenges remain in unresectable stage III NSCLC

New strategies needed to improve survival

We need to ↓ tox for those with ↑risk



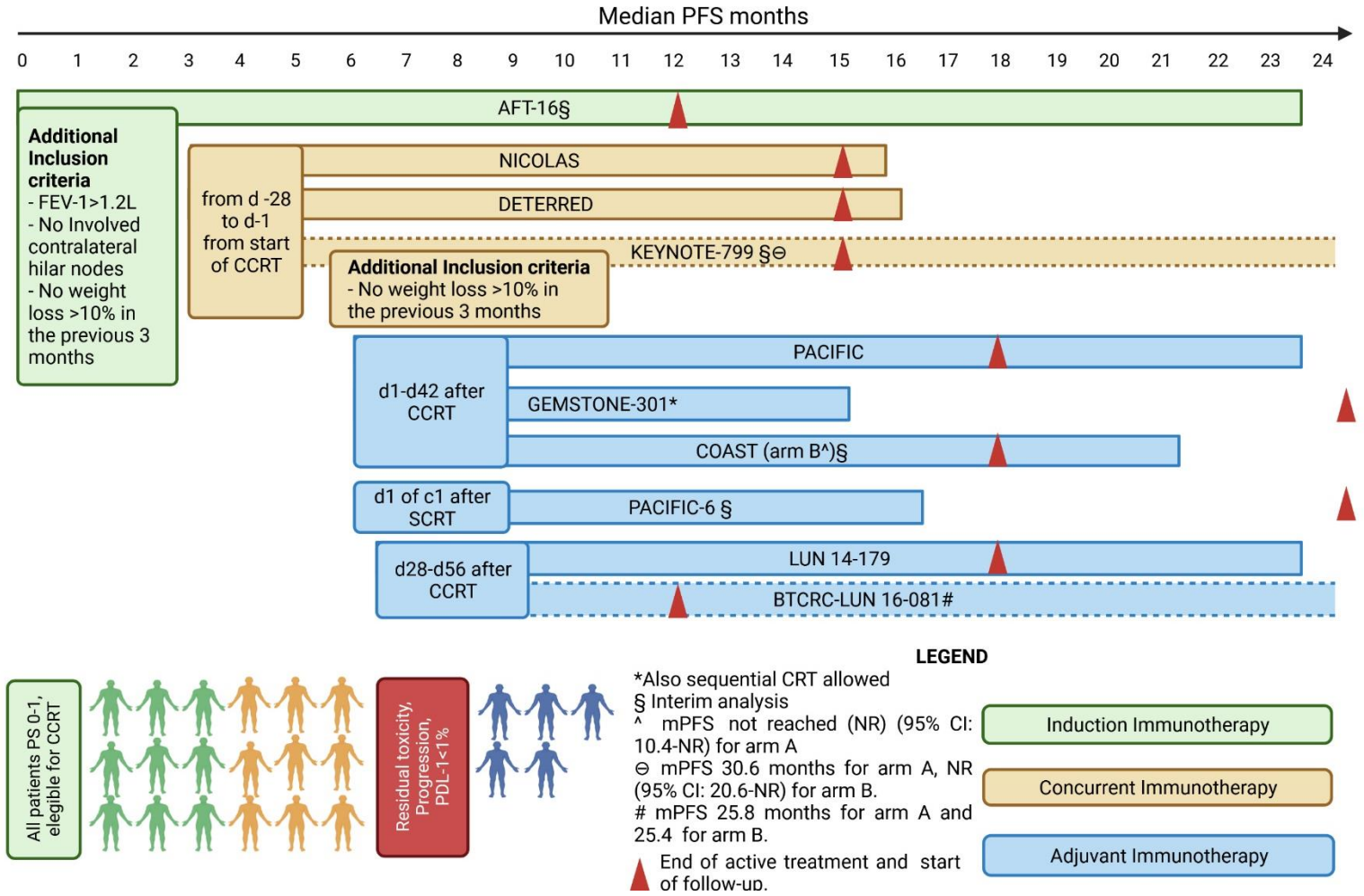


We need FIT patients for enrollment in trial

Maastricht UMC+

Remon Ther Adv Med Oncol 2022; Bortolot CTR 2024

Radiotherapy – immunotherapy strategies evaluated in stage III NSCLC



Comparing outcomes with different strategies not possible!

All patients eligible for CCRT

Healthy immune system

All patients eligible for CCRT

CT/ICI synergism

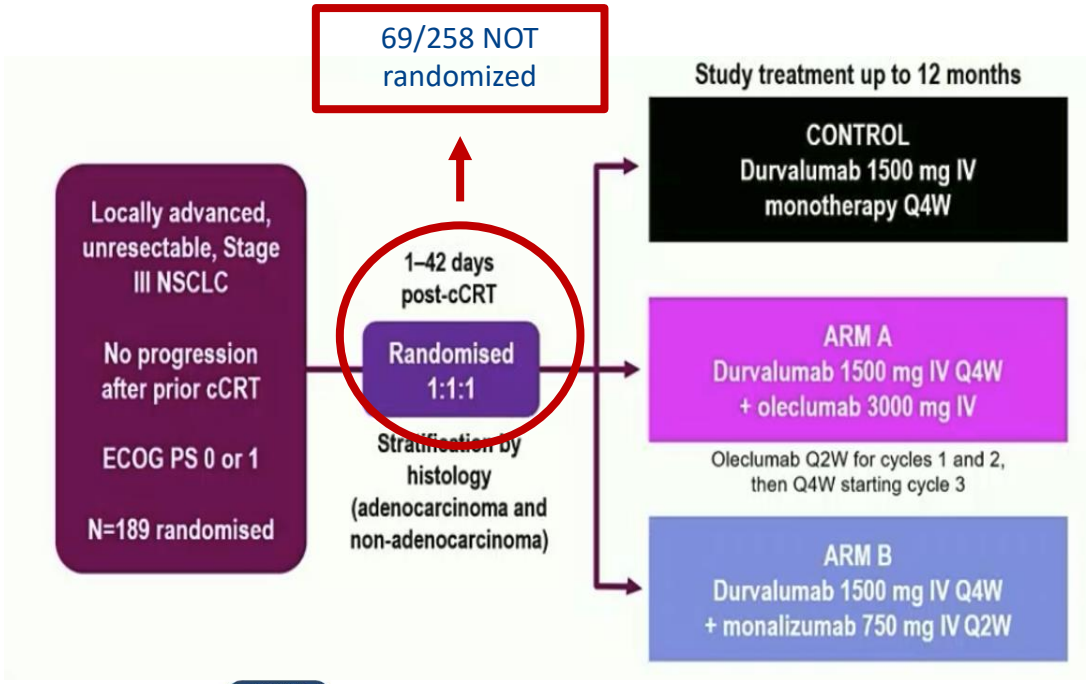
Less toxic vs concurrent?

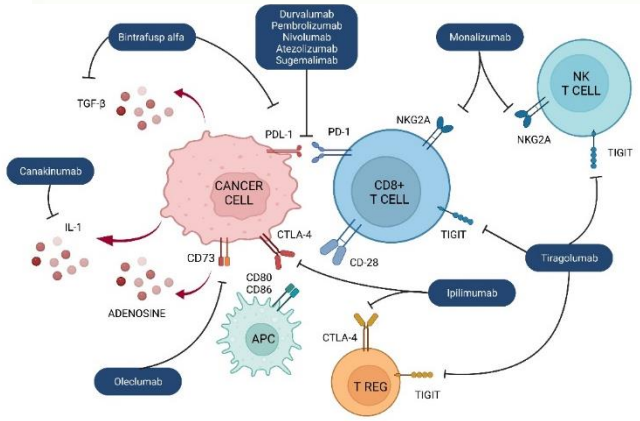
Early PD not eligible (but would they have progressed with ICI?)

WHAT ABOUT PROTONS?

(Modified from) Cortiula et al, *Ann Onc* , 2022

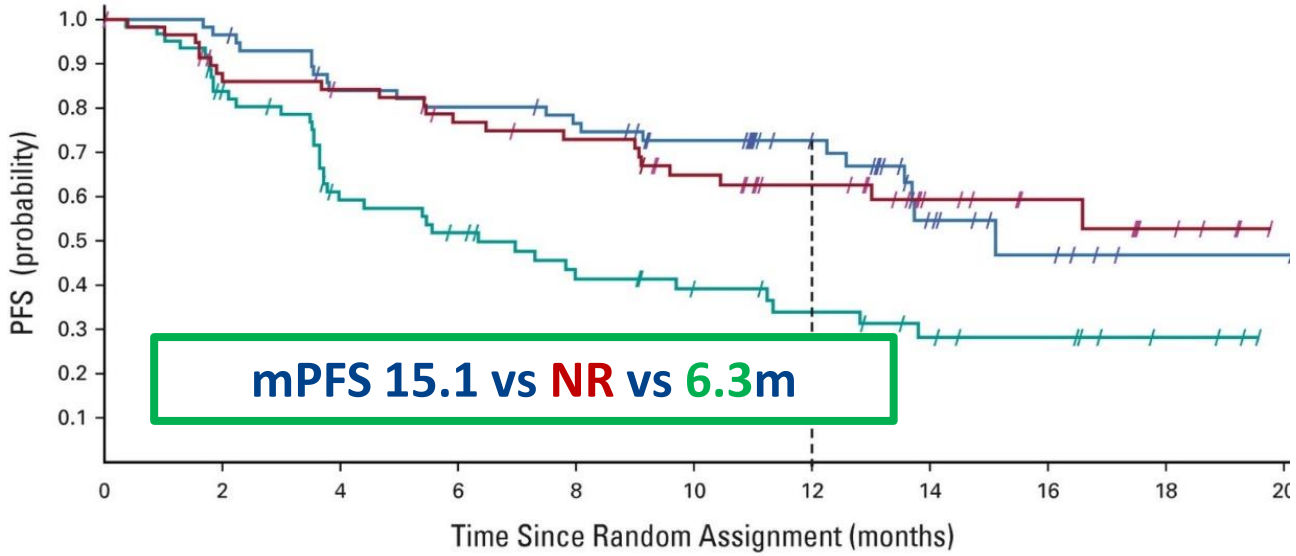
Novel approaches – combination immunotherapy - COAST





Durvalumab arm underperforms: patient characteristics?
<2% gr 3+ pneumonitis

No data about use of protons



mPFS 15.1 vs NR vs 6.3m

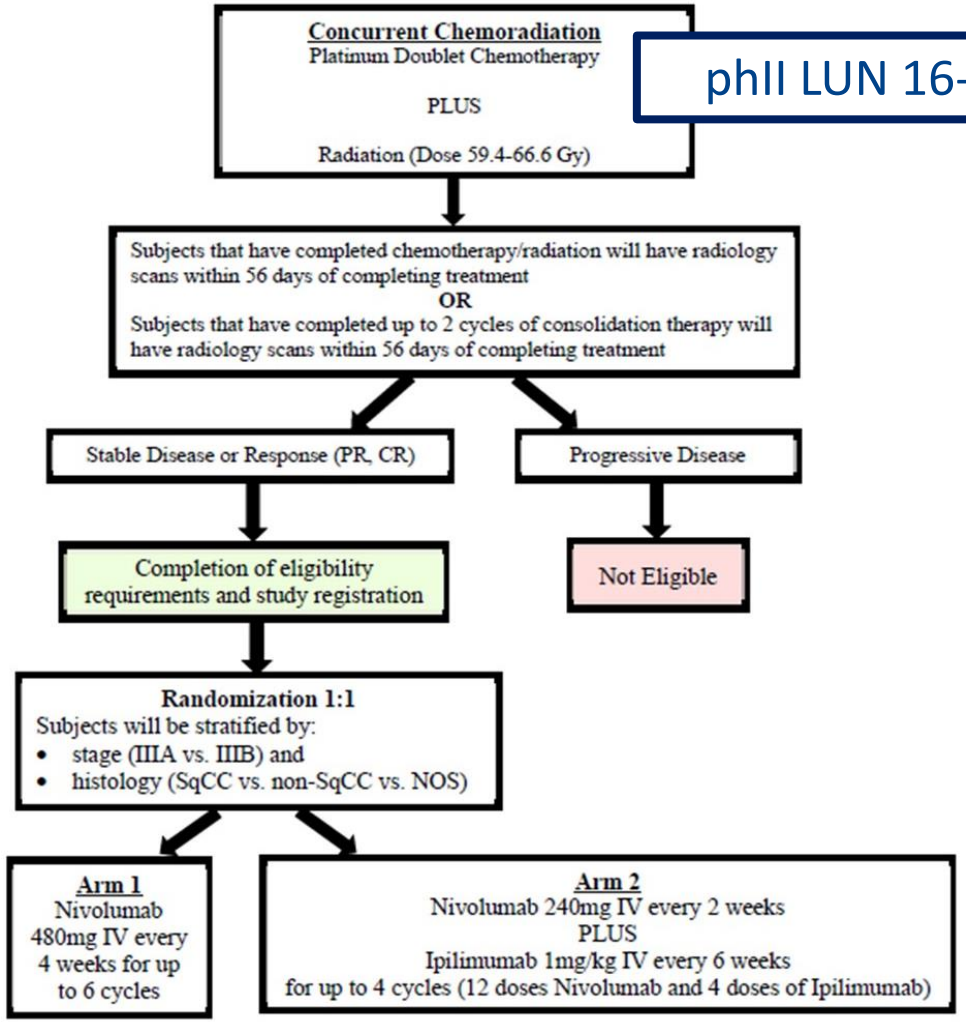
No. at risk:

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

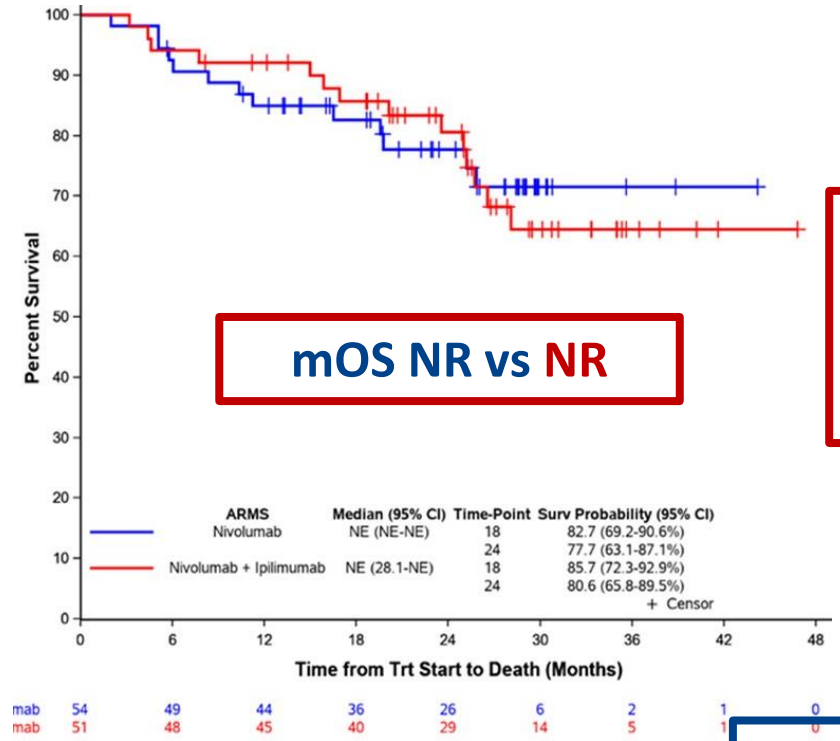
Phase III PACIFIC-9 ongoing

Herbst JCO 22; Cortiula Ann Oncol 2022

Novel combinations: dual immunotherapy



phII LUN 16-081



mOS NR vs NR

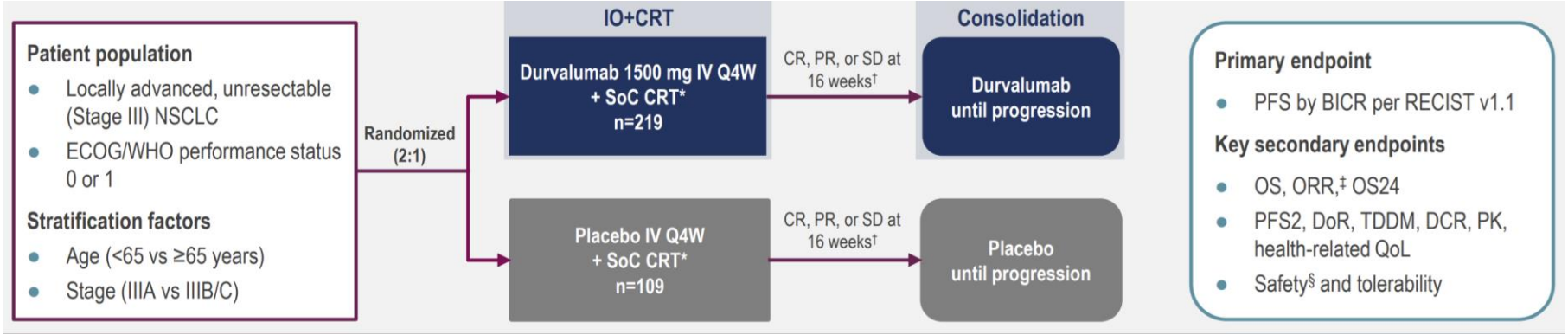
Grade 3+ pneumonitis 9% (nivo) vs 18% (nivo/ipi)
↑grade 3+ tox with combination (19 vs 28%)

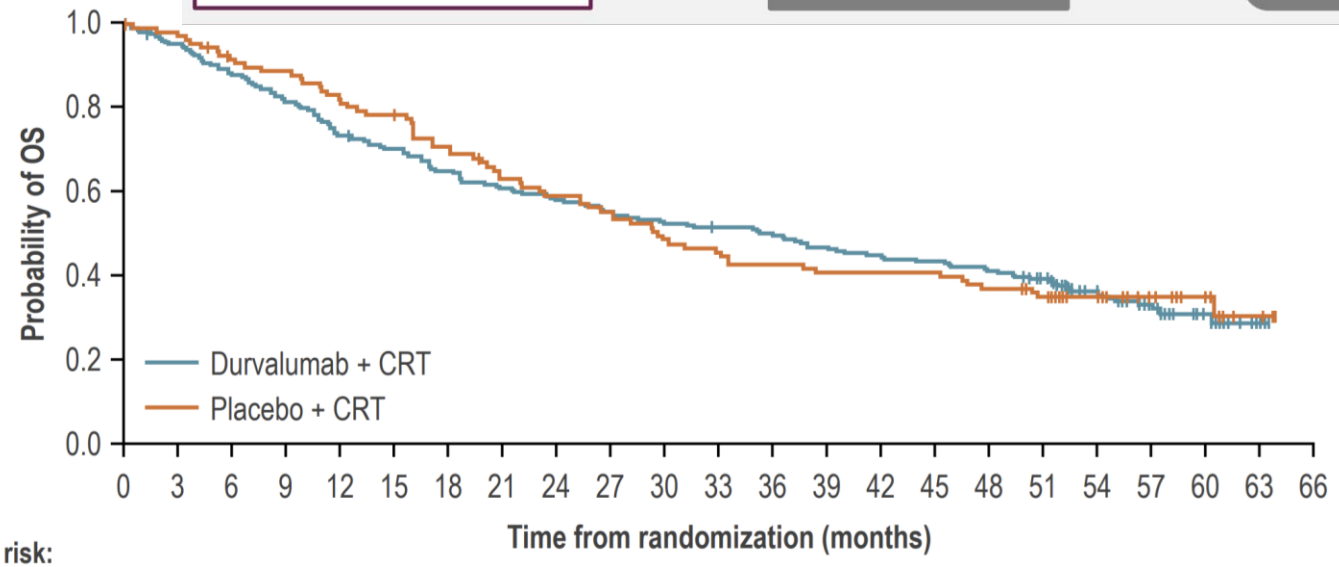
PHASE III CHECKMATE 73LA PRESS RELEASE: NEGATIVE STUDY

Durm ASCO 22; De Ruysscher Clin Lung Cancer 2022

Novel approaches – concurrent immunotherapy?

After promising phII data (NICOLAS, DETERRED) ph III PACIFIC-2 negative for OS





mOS 36.4m vs 29.5m, HR 1.03

+ ↑ toxicity

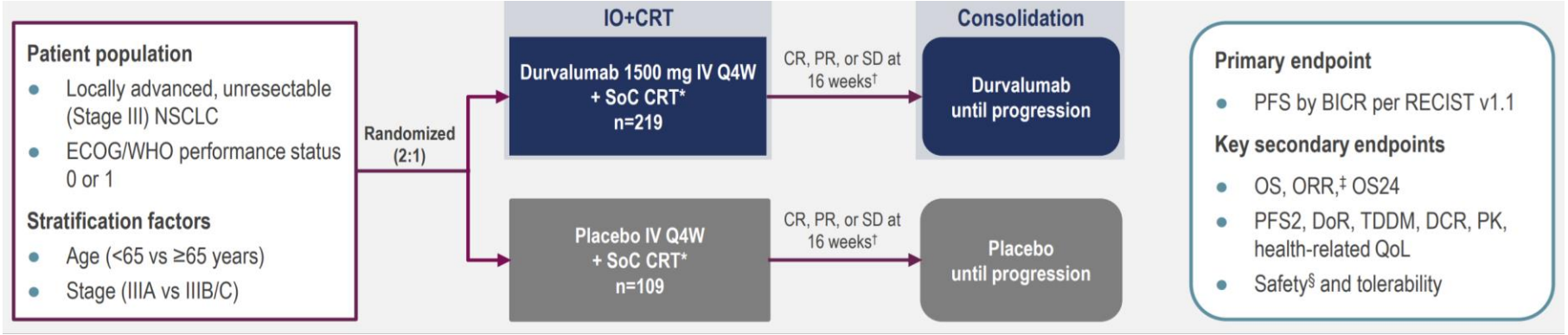
No data about use of protons

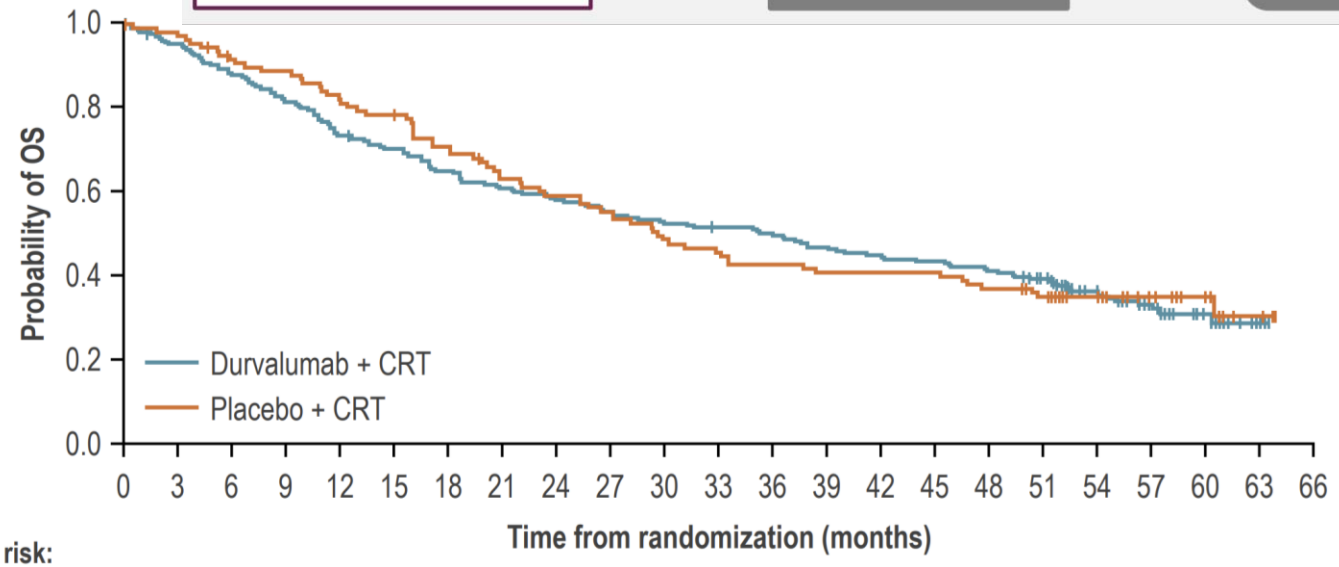
Maastricht UMC+

Peters JTO 2021; Lin JTO 2020: Liu Lung Cancer 2022; Bradley ELCC 2024

Novel approaches – concurrent immunotherapy?

After promising phII data (NICOLAS, DETERRED) ph III PACIFIC-2 negative for OS



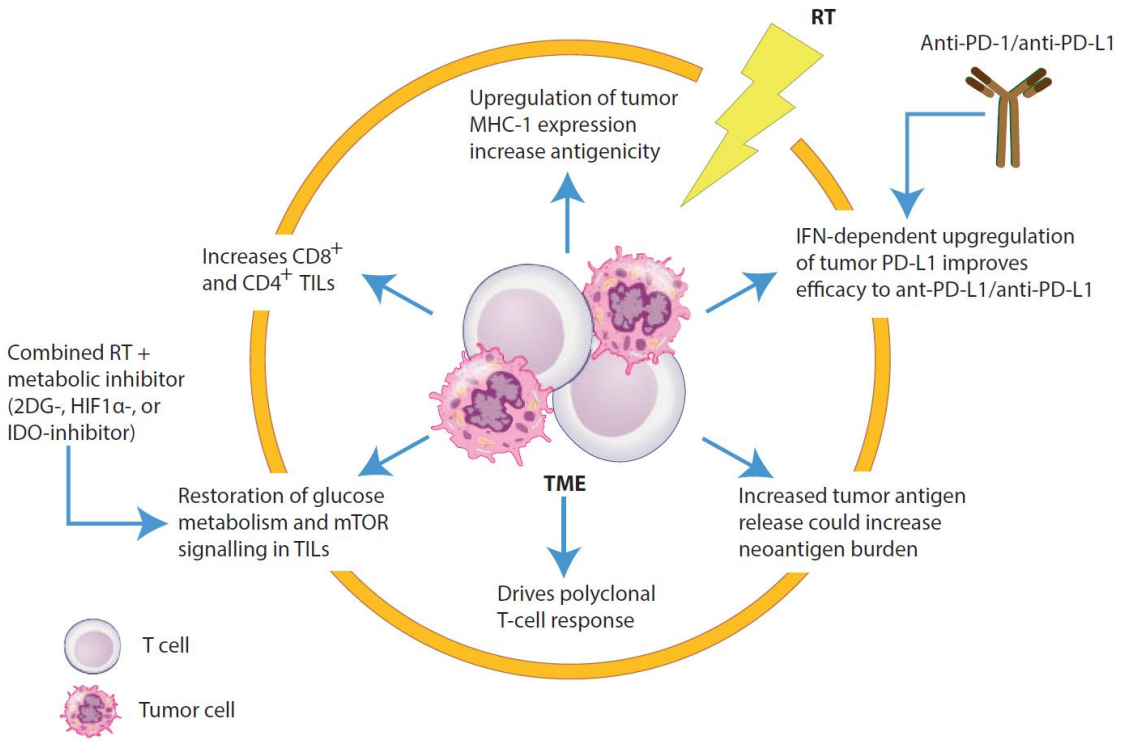


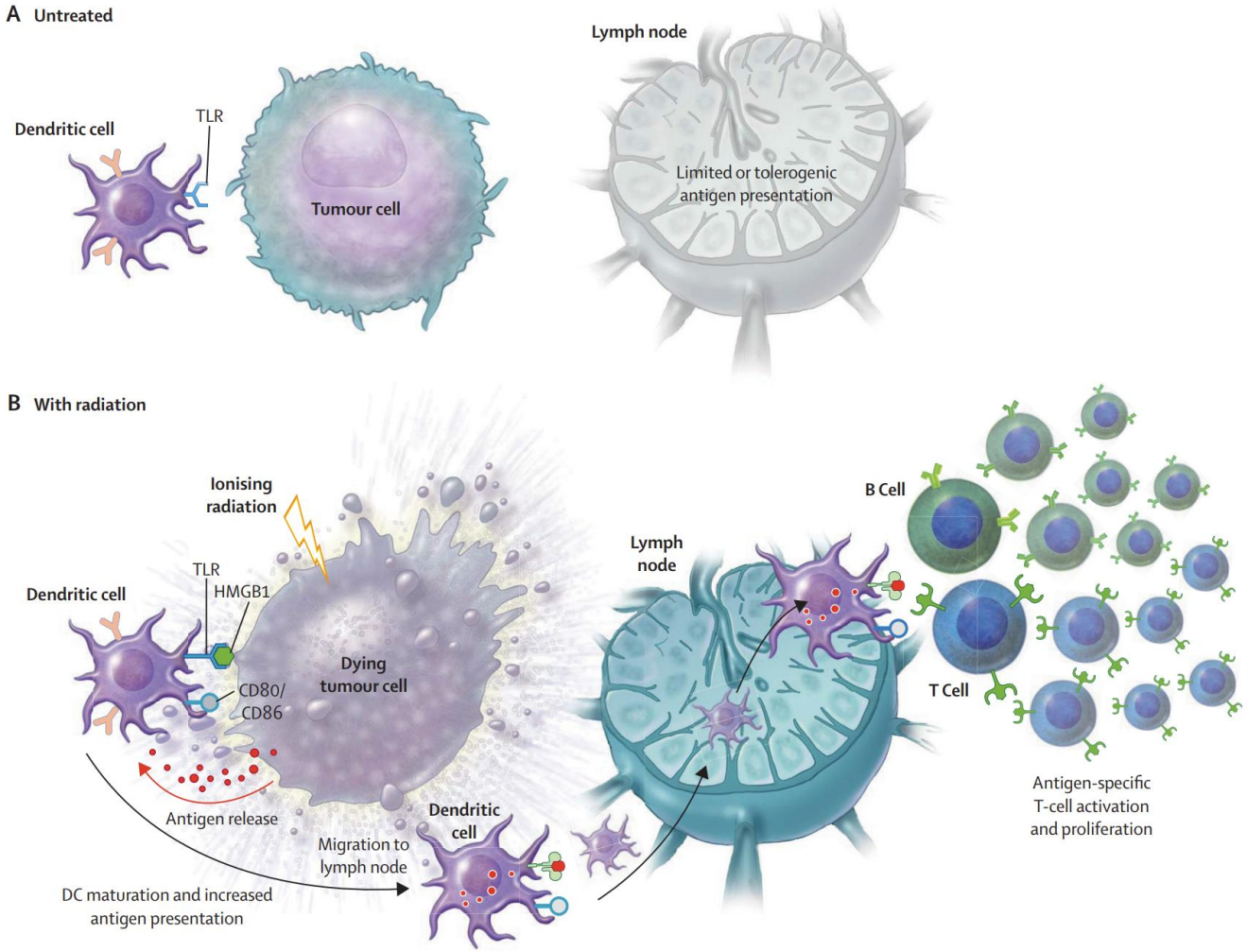
Is this due to the immunosuppressive effect of concurrent RT?

Maastricht UMC+

Rationale to combine immunotherapy and radiotherapy

RTx and ICI can act synergistically

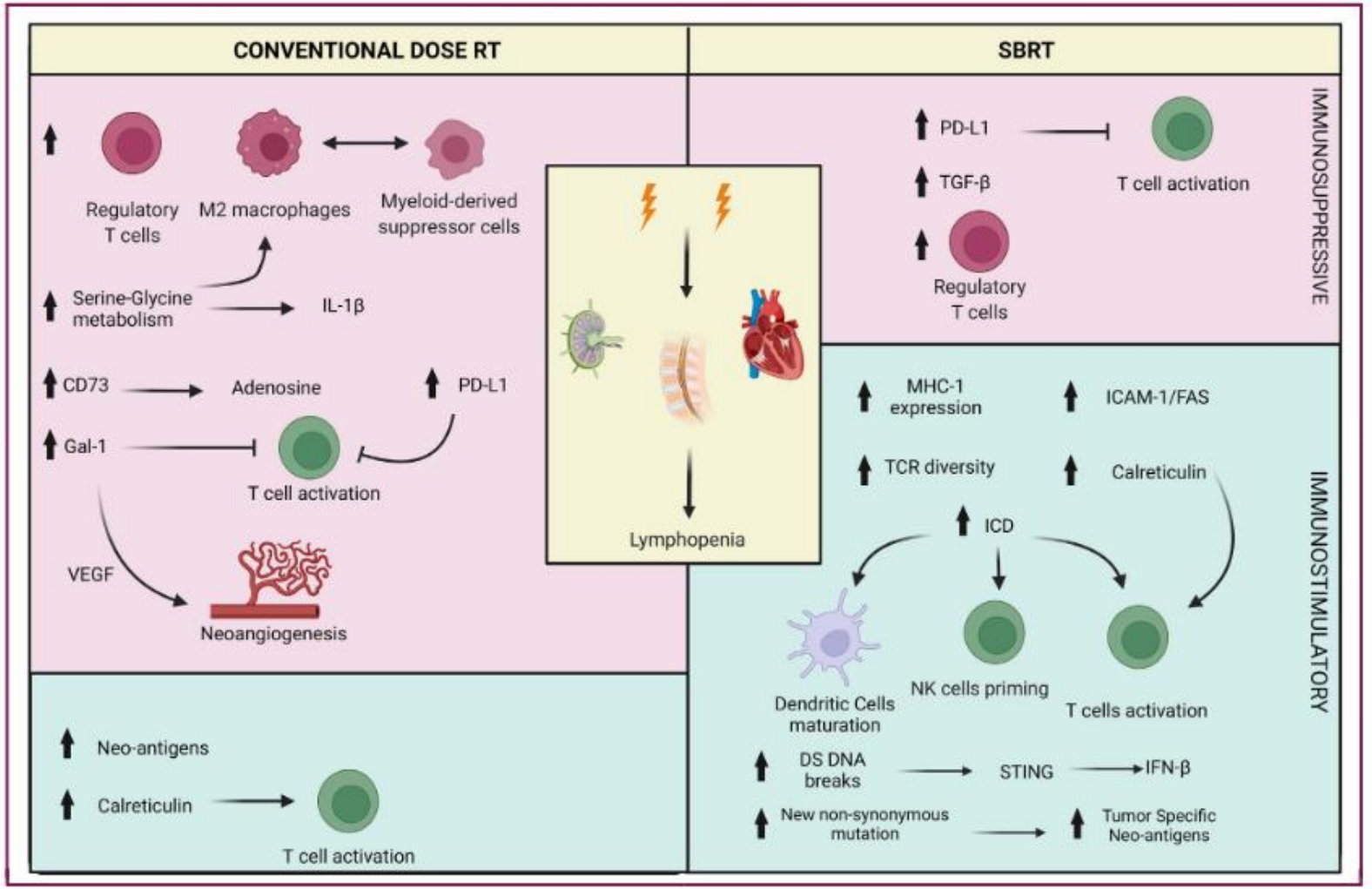




Maastricht UMC+

Kordbacheh Ann Oncol 2018; Sharabi Lancet Oncol 2015

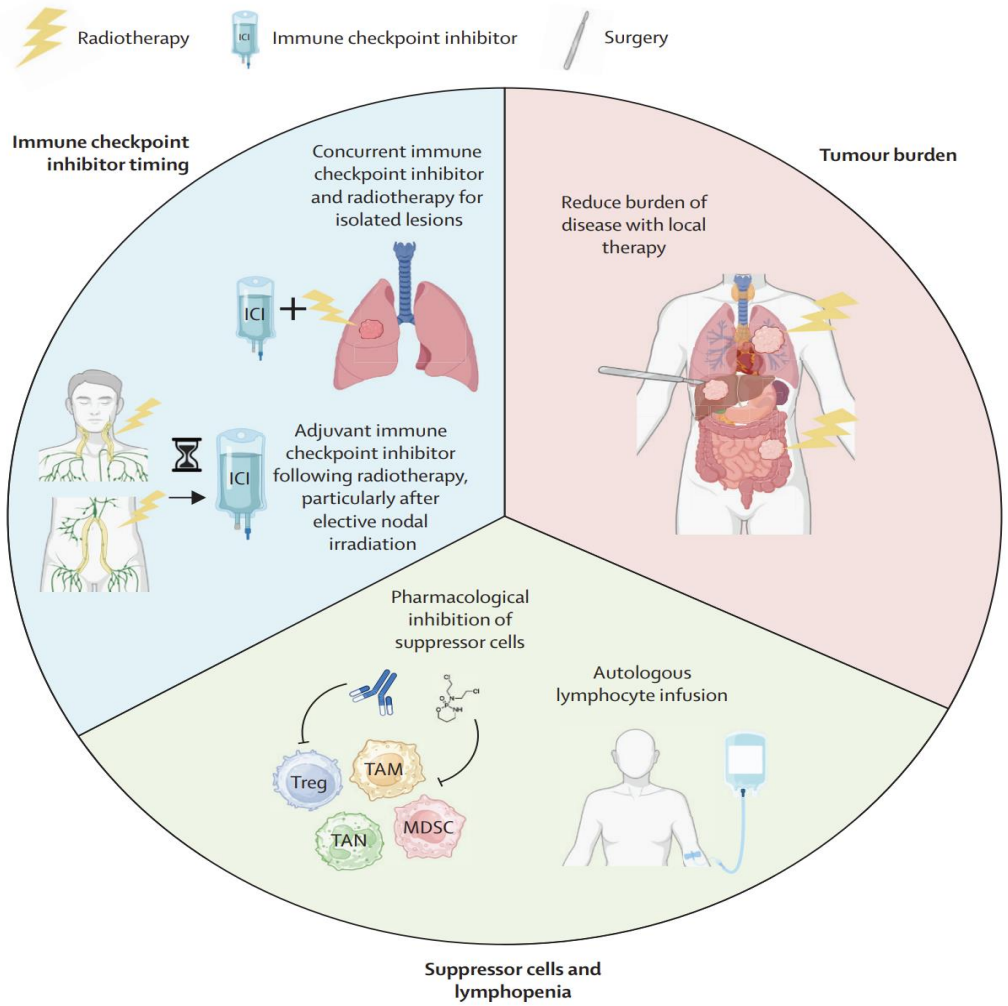
But radiotherapy can also be immunosuppressive



Maastricht UMC+

Cortiula, Ann Onc 2022

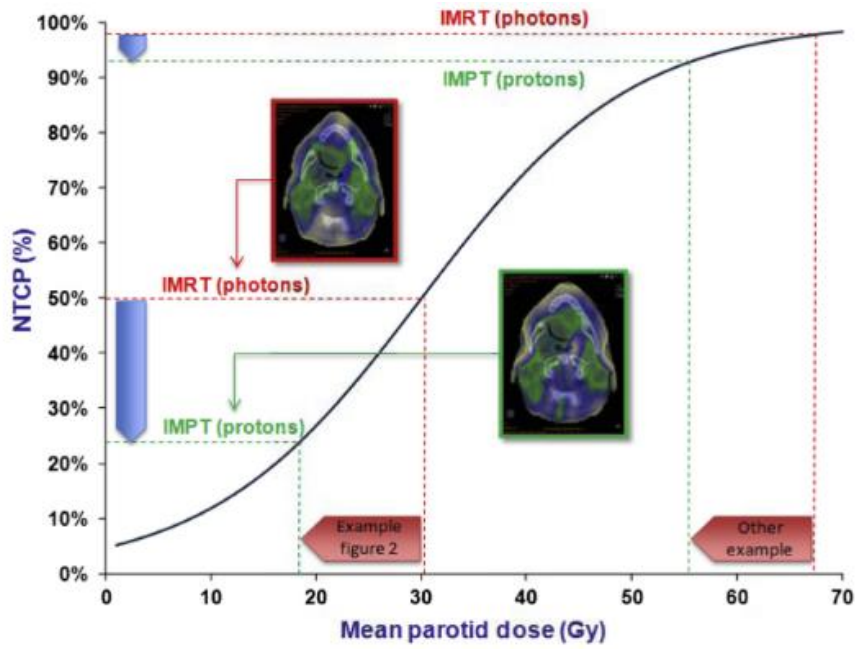
How to minimize the immunosuppressive effects of Rtx?

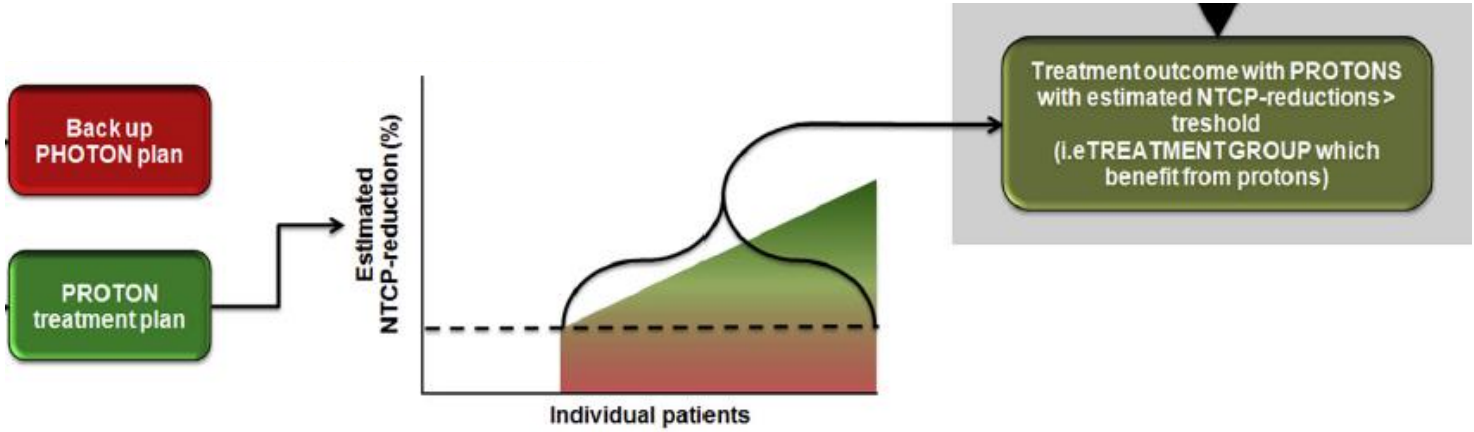


Proton therapy?

Lynch Lancet Oncol 2024

Patients' selection for proton therapy – decision process





Patients are selected for PROTONS through Normal Tissue Complication Probability models.

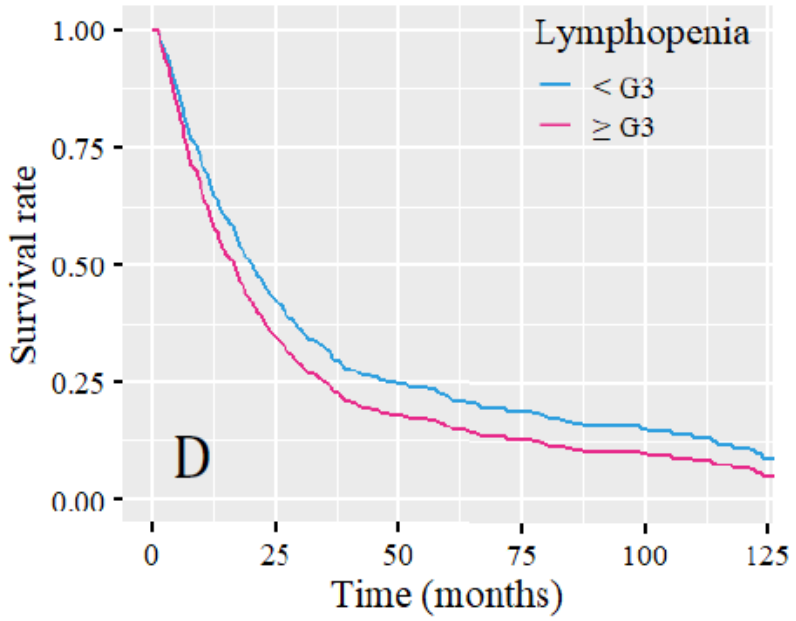
- ⬇10% grade ≥2 pneumonitis @ 6 months
- ⬇10% grade ≥2 esophagitis @3 months
- ⬇ 2% all-cause mortality @ 2yrs
- ⬇ 15% esophagitis+pneumonitis grade ≥2

Langendijk et al, 2013

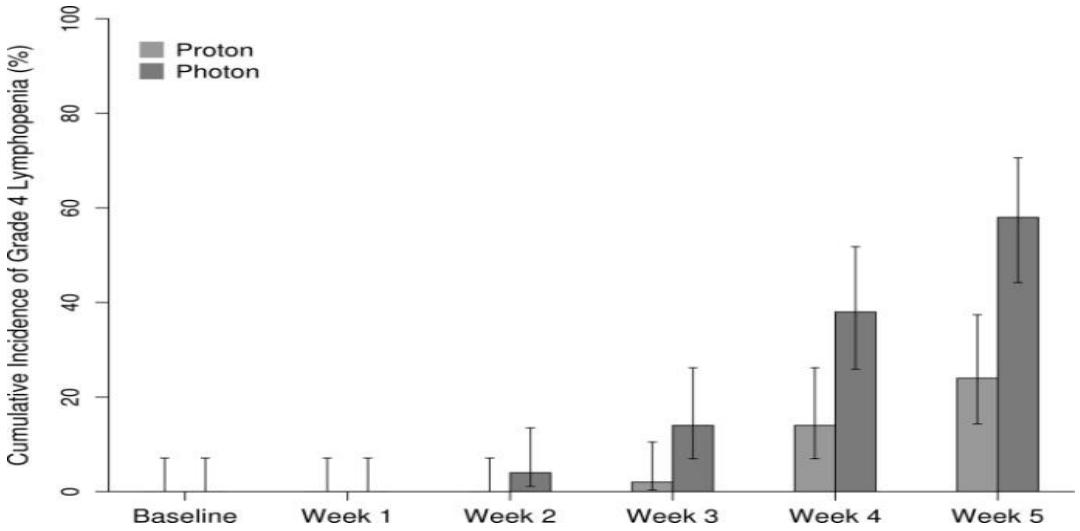
How protons can make a fitter immune system?

- RT volumes to bone marrow, thymus and lymph nodes
- RT volumes to circulating immune cells.

Pts with locally advanced NSCLC treated with RT



Lymphopenia Grade 4 (esophageal cancer)

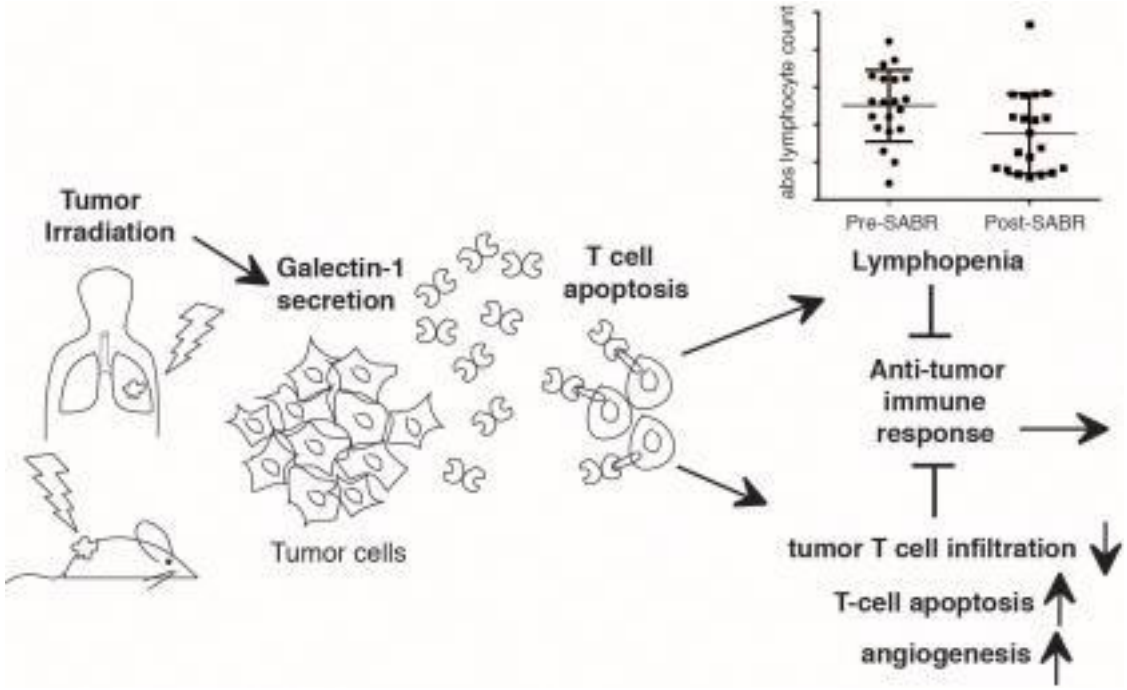


0.5-2 Gy is already lethal for stem cells and lymphocytes.

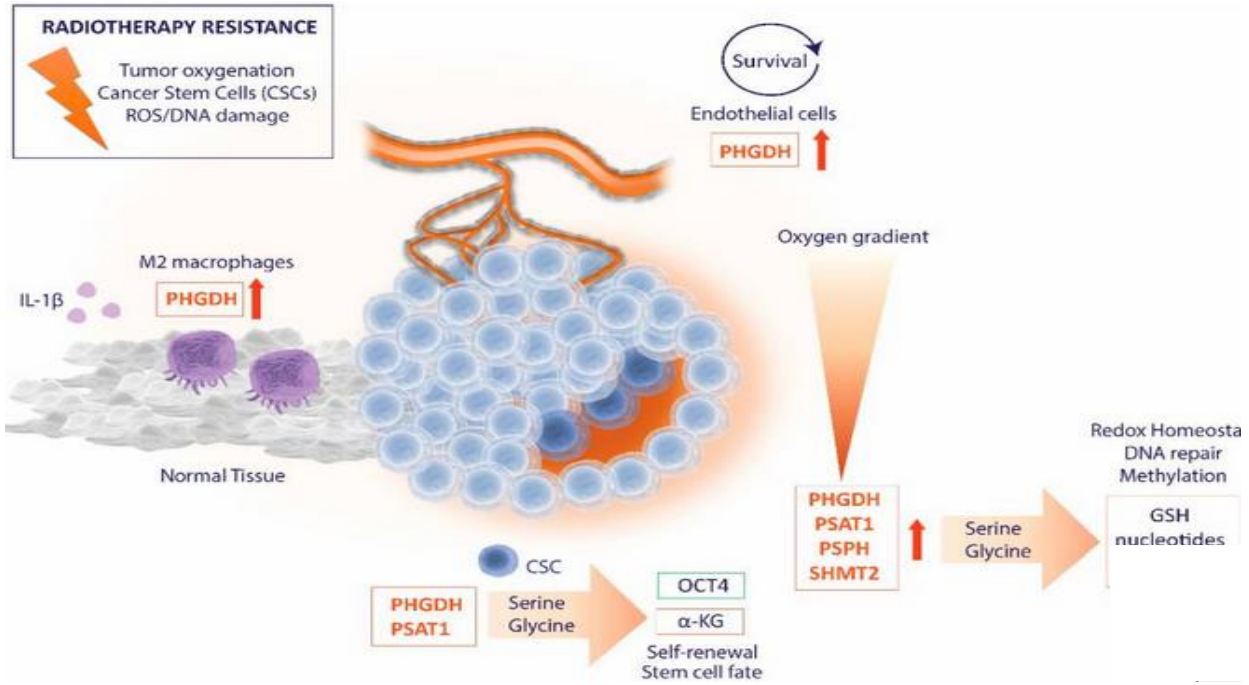
Maastricht UMC+

1.Wennerberg et al, 2017
2.Abravan et al, 2020

How protons can make a fitter immune system?



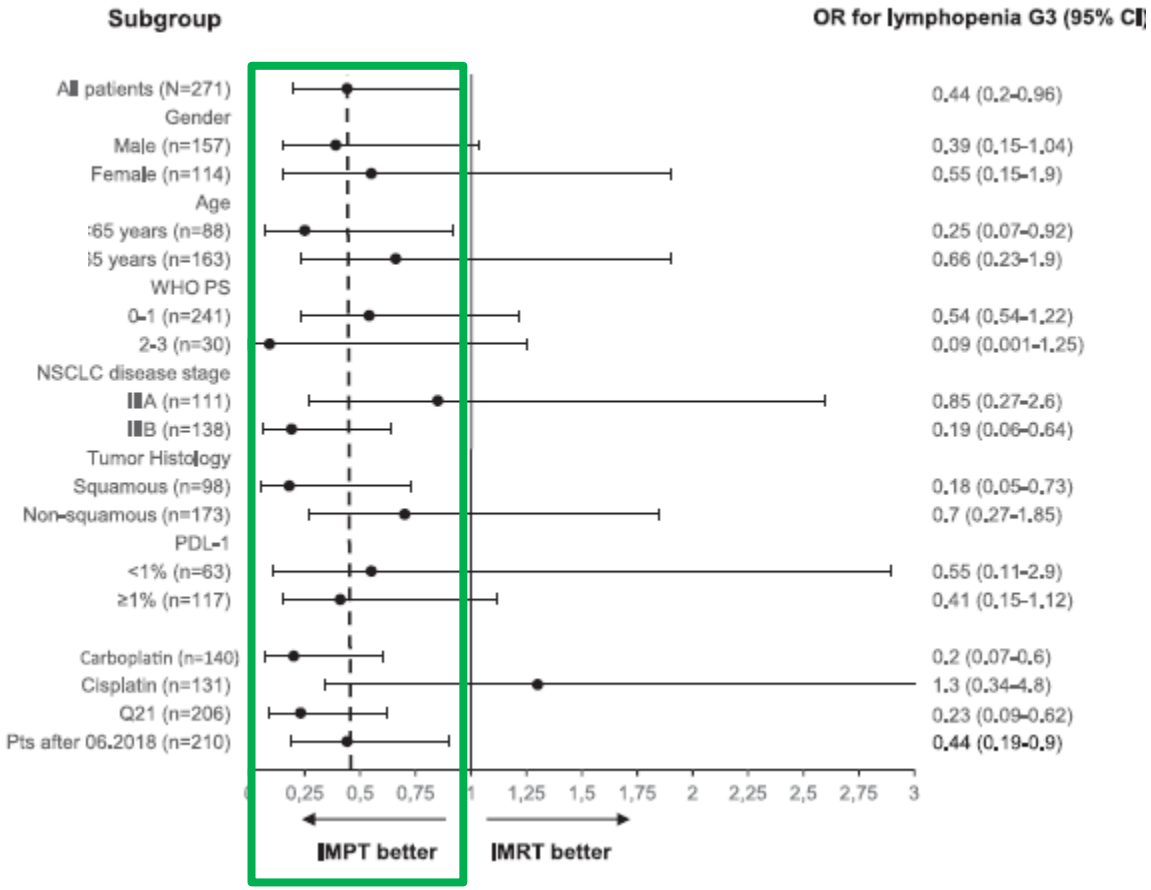
Healthy tissues inflammation generated by RT might impair the immune system

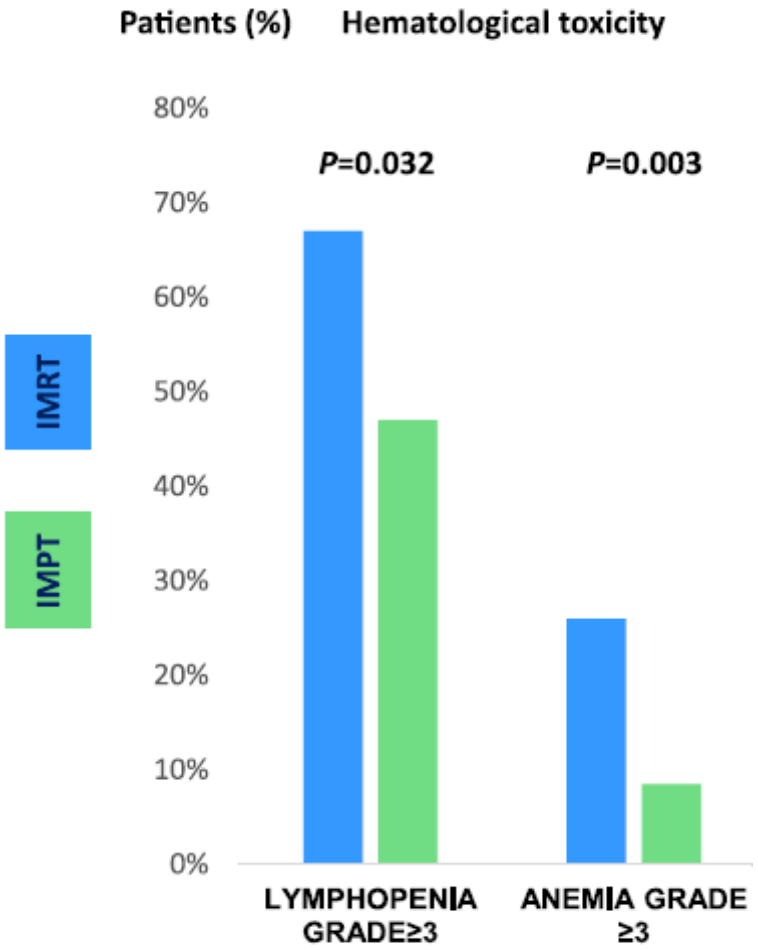


Kuo et al, 2014
Sanchez-Castillo et al, 2020

How protons can make a fitter immune system?

Can we prevent lymphopenia?
Retrospective multicenter series N = 228 protons vs photons

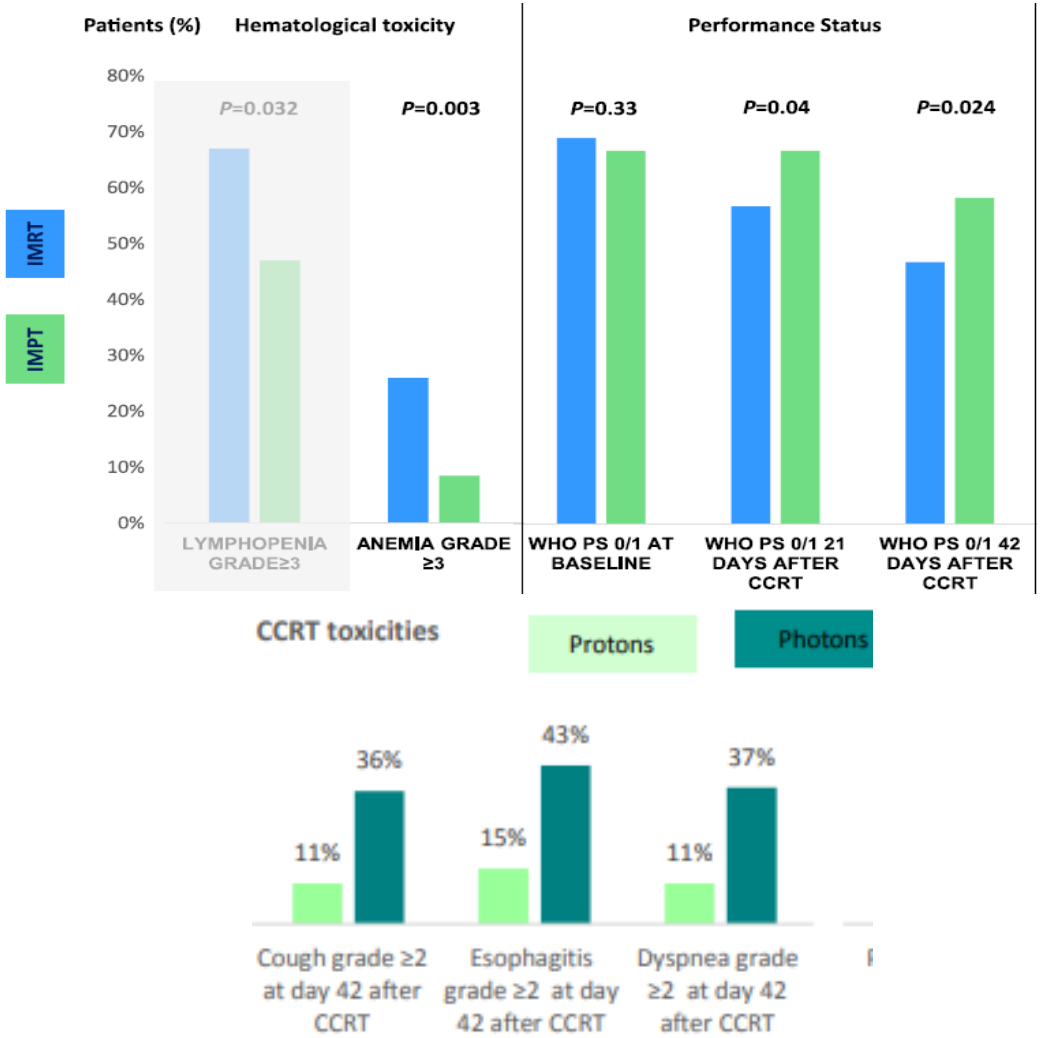


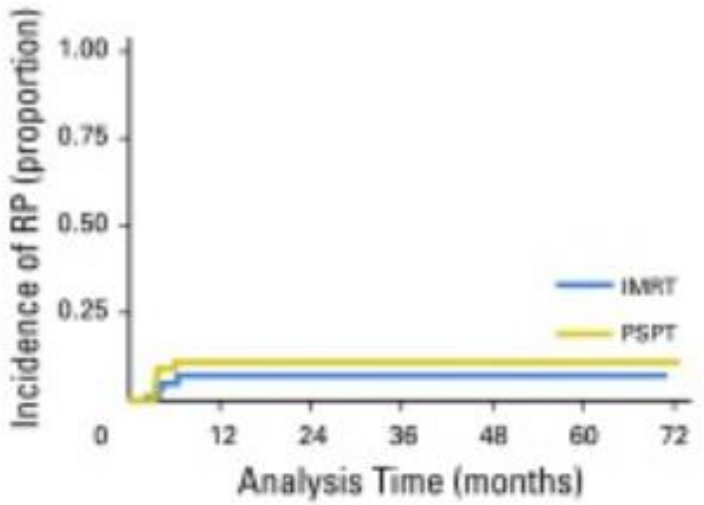


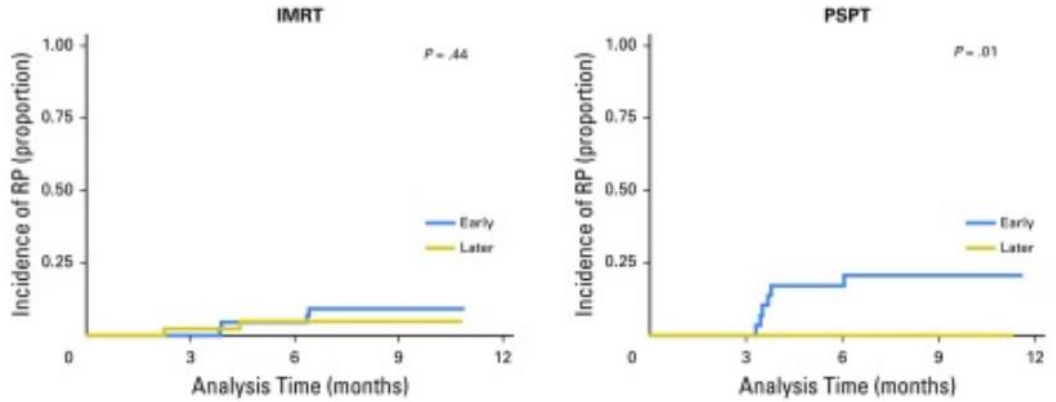
Maastricht UMC+

Cortiula et al, Radiotherapy and Oncology 2023

How protons can make fitter patients?







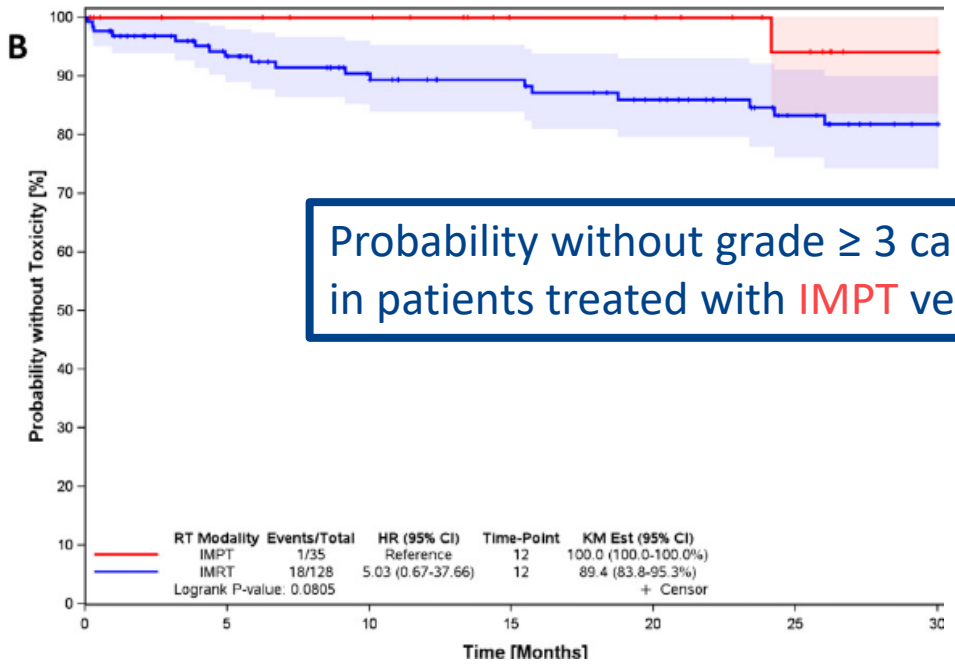
Maastricht UMC+

Cortiula et al, Radiotherapy and Oncology 2023; Liao et al, JCO, 2018

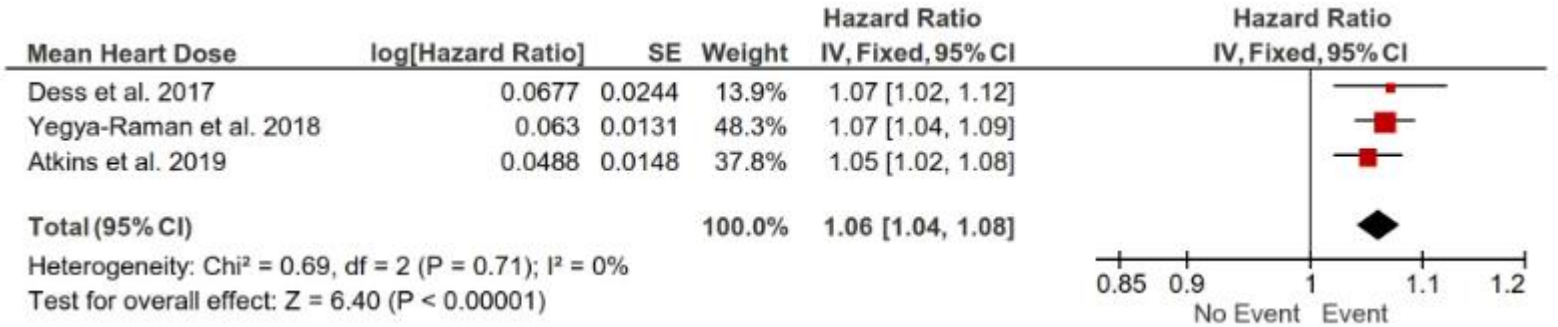
How protons can make fitter patients?

lungART data

	PORT group (n=241)	Control group (n=246)
Deaths*	99 (41%)	102 (42%)
Progression of recurrence	68 (69%)	87 (85%)
Chemotherapy toxicity	1 (1%)	..
Radiotherapy toxicity	2 (2%)	..
Cardiopulmonary disease	16 (16%)	2 (2%)
Second primary cancer	5 (5%)	1 (1%)
Pulmonary infection	1 (1%)	..
Vascular	1 (1%)	1 (1%)
Other†	..	3 (3%)
Unknown	5 (5%)	8 (8%)



Probability without grade ≥ 3 cardiac event in patients treated with IMPT versus IMRT.



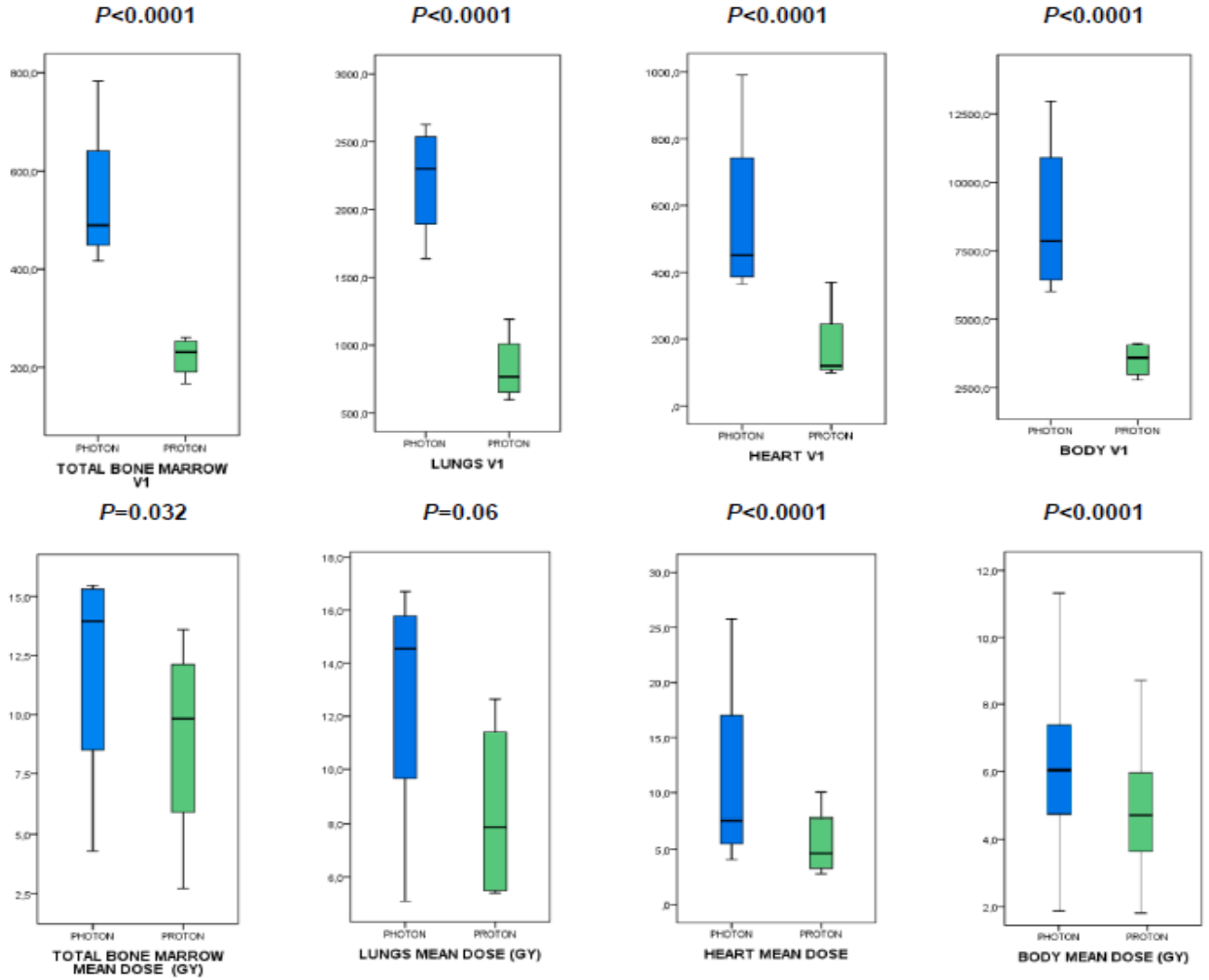
Heart dose and cardiac comorbidities increases late cardiac tox after CCRT

Maastricht UMC+

Craddock JTO 2022; Tohidinezbad CTRO 2022; Nathan Y. Yu et al, Clinical Lung Cancer 2022.

How protons can make fitter patients?

Intrapatient comparison:
IMRT vs **IMPT** plans



Maastricht UMC+

Cortiula, Radiotherapy and Oncology 2023

Take home messages

Adjuvant durvalumab is SoC after chemoradiotherapy for **fit** patients

- 1/5 is cured **WITHOUT** durva – 2/3 will relapse **DESPITE** durva

We need to **personalize treatment** in unresectable stage III NSCLC

- Ensure that patients are as fit as possible
  - Trial enrollment
  - Toxicity reduction – early start of immunotherapy
- Minimize immunosuppressive effects of radiotherapy→**better outcome**

With improving survival, (late) **toxicity prevention** is necessary

Protons can play a role in improving fitness and reducing immunosuppressive effects of Rtx ultimately leading to **better survival**

Maastro in de beste handen

Maastricht University

Thank you!