Radiotherapy in NSCLC: State-of-the-art

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Maastricht
The Netherlands

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Disclosure

Advisory board of:

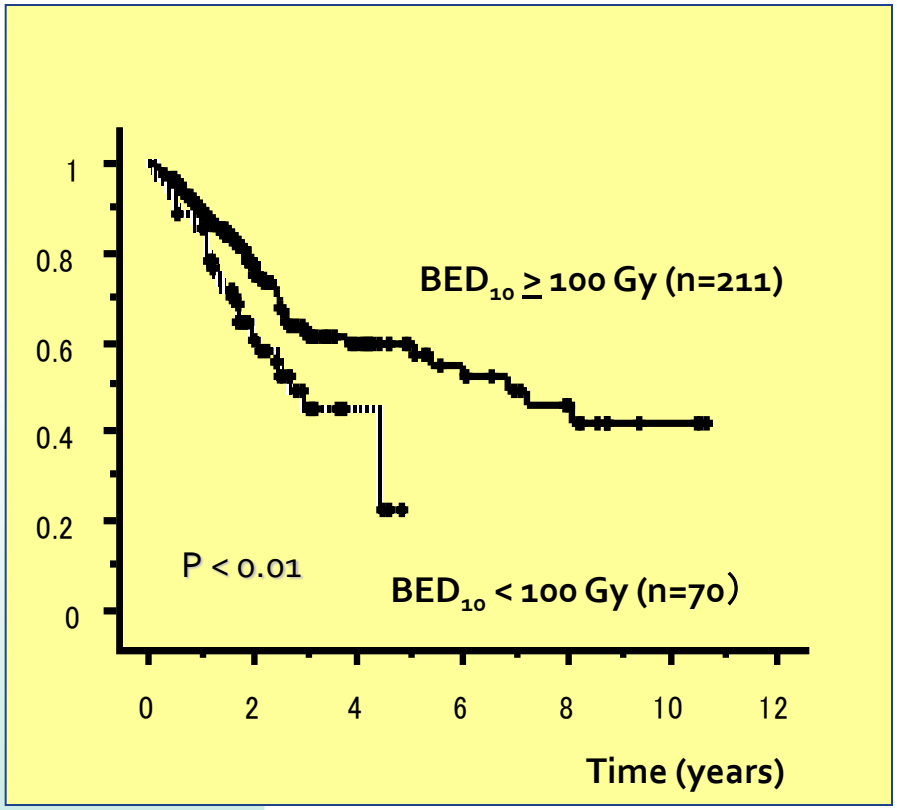
- Merck/ Pfizer
- BMS
- Roche/ Genentech
- Celgene
- AstraZeneca

Unrestricted research funding of:

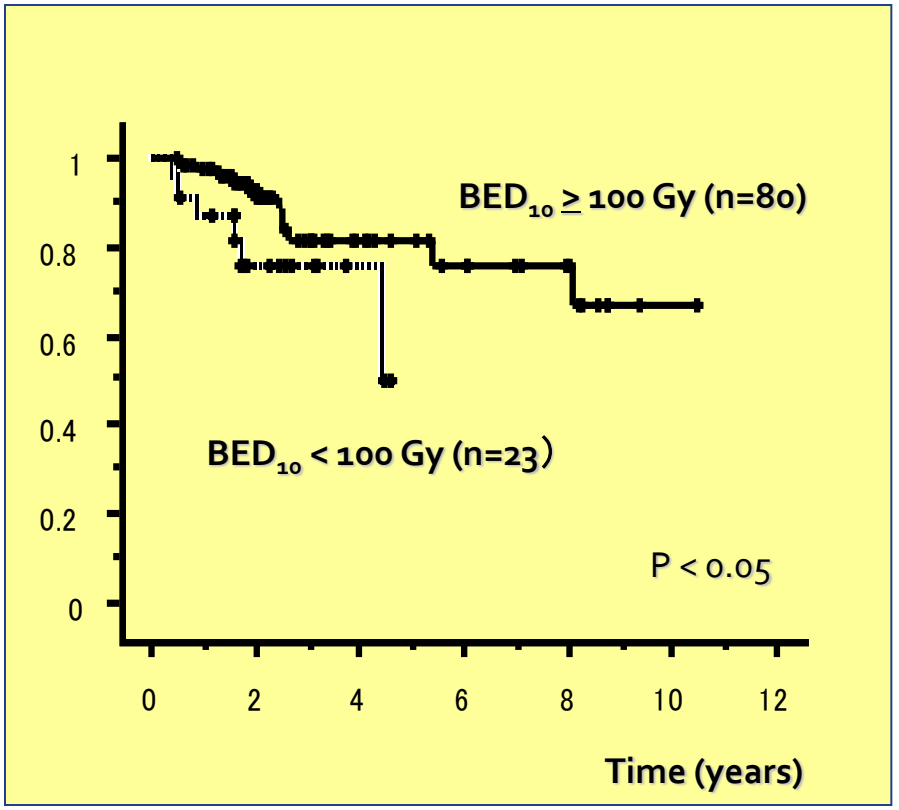
- BMS
- Boehringer Ingelheim

Stage I

Overall survival $BED_{10} < 100$ vs. $BED_{10} \geq 100$



Overall survival in all patients



Overall survival in operable patients

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Onishi H et al. Cancer 2004

SPACE study

3x15 Gy on the PTV edge
= 103 Gy EQD2,T (a/b=8 Gy)

Randomized phase II trial

NSCLC
$T_{1-2}N0M0$
< 6 cm
PS 0-2

A: SBRT 22 Gy x 3 to 66 Gy in one week

B: 3DCRT 2 Gy x 35 to 70 Gy in 7 weeks

= 58 Gy EQD2,T (a/b=8 Gy)

Primair eindpunt:
PFS

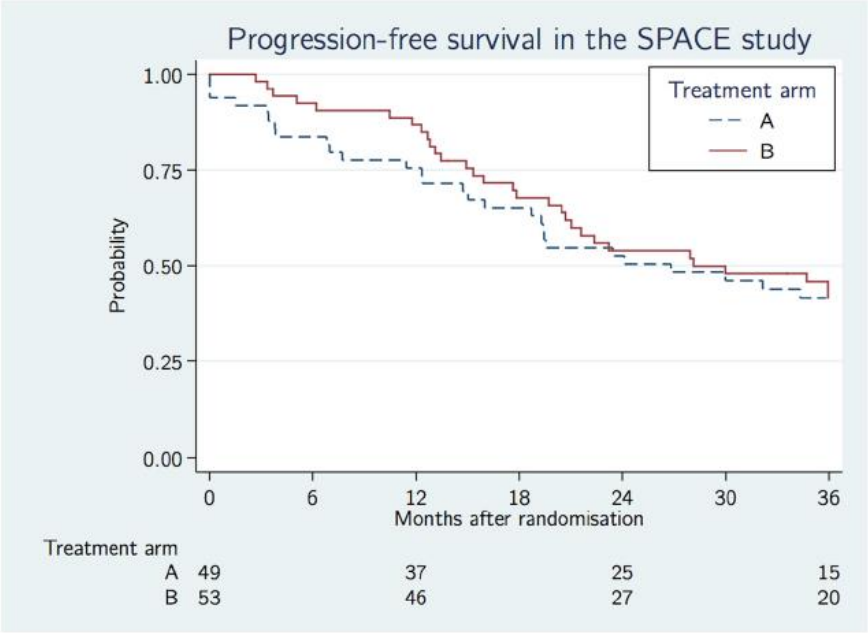


Fig. 1. Progression free survival by treatment arm (A = SBRT, B = 3DCRT), ITT analysis. HR = 0.85, 95% CI: 0.52–1.36.

Nyman et al. Radiother Oncol 2016

CHISEL: A randomized phase III trial of SABR vs conventional radiotherapy for inoperable stage I non-small cell lung cancer
TROG 09.02, ALTG 09.05

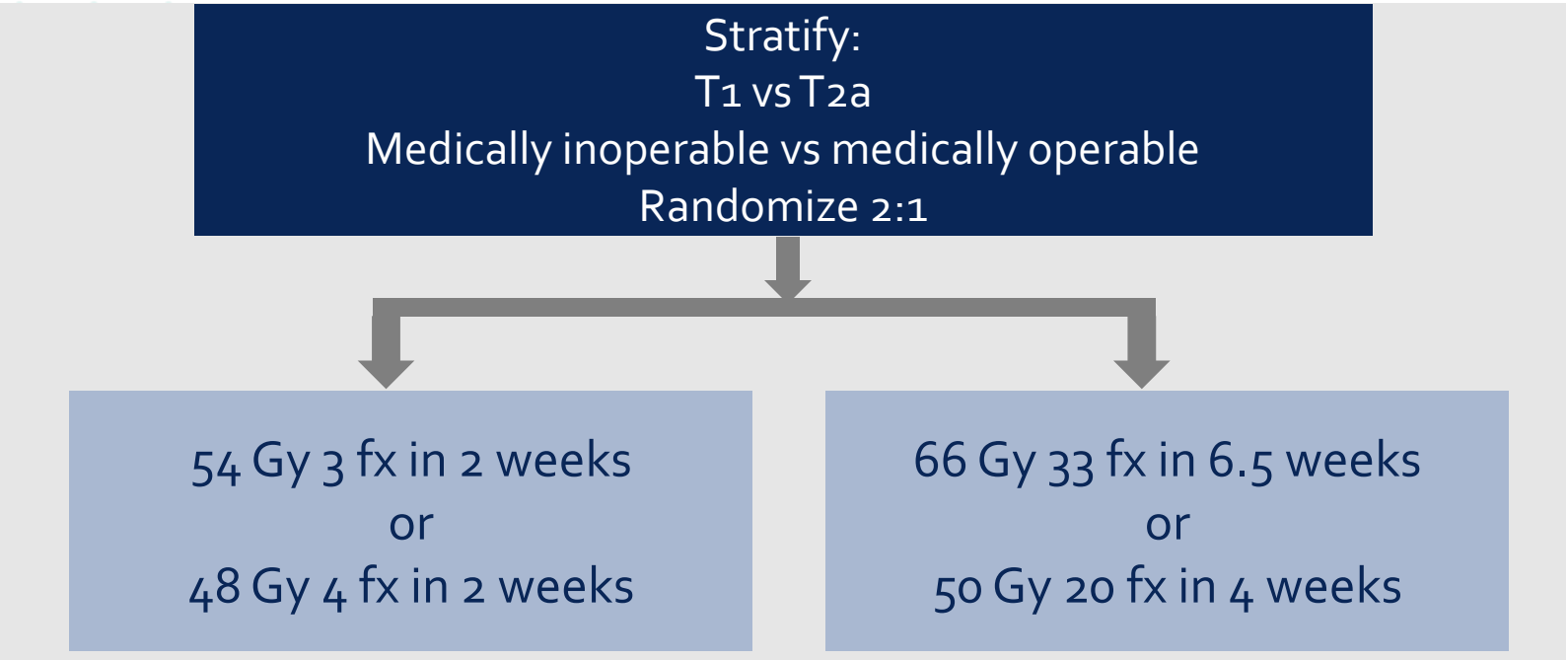
Trial Registration NCT01014130

David Ball, Tao Mai, Shalini Vinod, Scott Babington, Jeremy Ruben, Tomas Kron, Brent Chesson, Alan Herschtal, Marijana Vanevski, Angela Rezo, Christine Elder, Marketa Skala, Andrew Wirth, Greg Wheeler, Adeline Lim, Mark Shaw

On behalf of the CHISEL investigators

IASLC 2017

Study design



140 Gy EQD2T

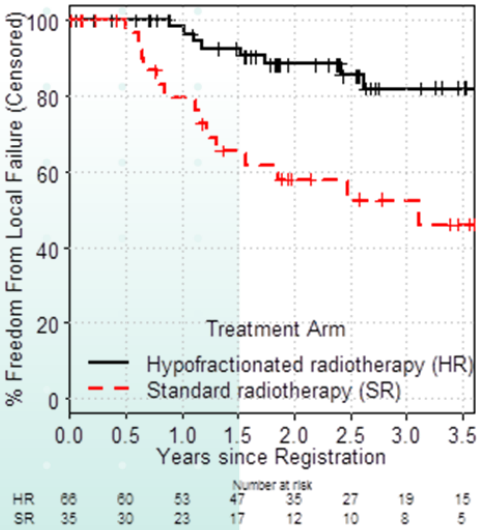
96 Gy EQD2T

56 Gy EQD2T

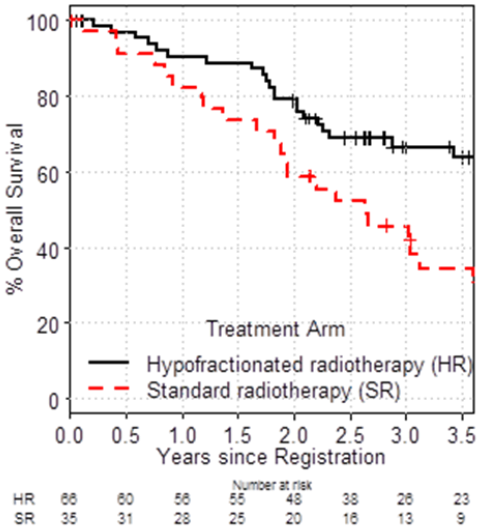
53 Gy EQD2T

66 Gy/ 24 fractions = 67 Gy EQD2T

Freedom from local failure and overall survival



HR 0.29,
95% CI 0.13, 0.66
P = 0.002



HR 0.51
95% CI 0.29, 0.91
P = 0.020

IASLC 2017

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Grade 3+ toxicities by arm

	SABR	Conventional
Dyspnoea	2 (1 grade 4)	0
Cough	2	0
Fatigue	1	0
Chest wall pain/pain	1	2
Lung infection	1	0
Hypoxia	1	0
Weight loss	1	0

Toxicity and second primary lung cancers in late survivors following lung SBRT. Giuliani et al.

Second primaries:

2-4 %/year up to 18 years following treatment

Janssen-Heijnen et al. J Thorac Oncol 2012

- 1192 patients
- 5 y OS: 14 % (182 patients)
- *Toxicity*
  - G2 fatigue: 5/182 (2.7 %)
  - G2 rib fracture: 1/182
  - G2 chronic myositis: 8/182 (4.4 %)
- *Failures*
  - LR: 3/182; regional failure: 2/182; DM: 5/182
- *Second primary lung cancers*
  - 22 (12 %)

Conclusions

- SBRT is superior to conventional radiotherapy ➔ No change of current practice in The Netherlands
- The incidence of second cancers after SBRT and other treatment is ± 4%/year: equals highest risk groups in screening study ➔ life-long yearly low-dose chest-CT?

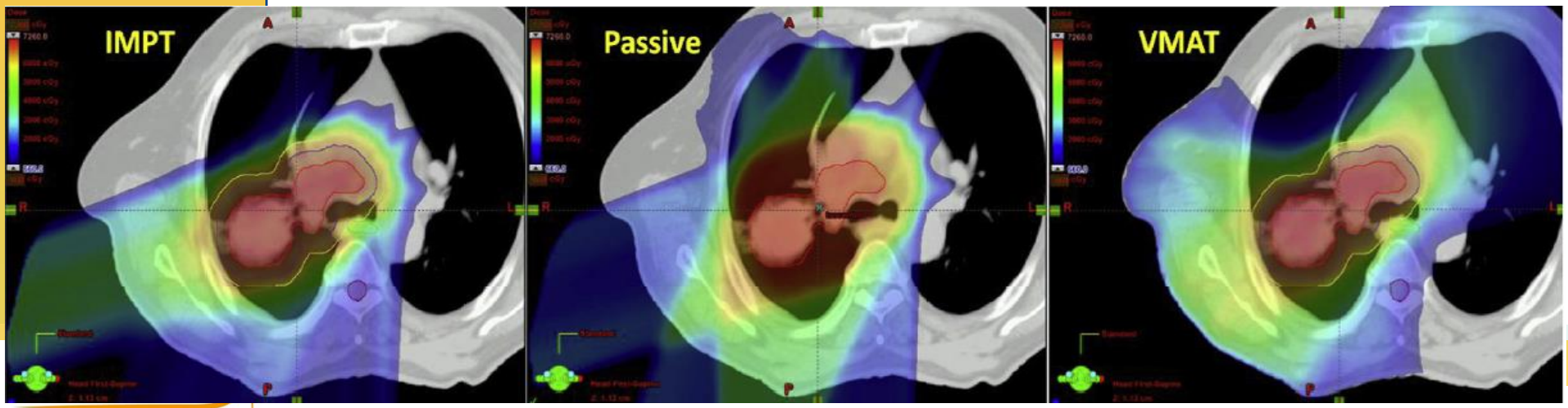
Stage III

Proton Therapy

Critical Review

Consensus Statement on Proton Therapy in Early-Stage and Locally Advanced Non–Small Cell Lung Cancer

Joe Y. Chang, MD, PhD,* Salma K. Jabbour, MD,† Dirk De Ruysscher, MD,‡ Steven E. Schild, MD,§ Charles B. Simone, II, MD,‖ Ramesh Rengan, MD,¶ Steven Feigenberg, MD,# Atif J. Khan, MD,† Noah C. Choi, MD,** Jeffrey D. Bradley, MD,†† Xiaorong R. Zhu, PhD,‡‡ Antony J. Lomax, PhD,§§ and Bradford S. Hoppe, MD‖‖, on behalf of the International Particle Therapy Co-operative Group (PTCOG) Thoracic Subcommittee



I am still sober …

Critical Review

Proton Therapy in Children: A Systematic Review of Clinical Effectiveness in 15 Pediatric Cancers

Roos Leroy, PhD,* Nadia Benahmed, MSc,* Frank Hulstaert, MD,* Nancy Van Damme, PhD,† and Dirk De Ruysscher, PhD‡

Leroy et al. Int J Radiat Oncol Biol Phys 2016

Radiotherapy and Oncology 83 (2007) 110–122
www.thegreenjournal.com

Systematic review

A systematic literature review of the clinical and cost-effectiveness of hadron therapy in cancer

Mark Lodge[a,*], Madelon Pijls-Johannesma[b], Lisa Stirk[c], Alastair J. Munro[d], Dirk De Ruysscher[b,e], Tom Jefferson[a]

VOLUME 25 · NUMBER 8 · MARCH 10 2007

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Proton Therapy in Clinical Practice: Current Clinical Evidence

Michael Brada, Madelon Pijls-Johannesma, and Dirk De Ruysscher

Radiotherapy and Oncology 103 (2012) 5–7

Contents lists available at SciVerse ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

ELSEVIER

Systematic review

Charged particles in radiotherapy: A 5-year update of a systematic review

Dirk De Ruysscher[a,*], M. Mark Lodge[b], Bleddyn Jones[c], Michael Brada[d], Alastair Munro[e], Thomas Jefferson[f], Madelon Pijls-Johannesma[a]

CLINIC

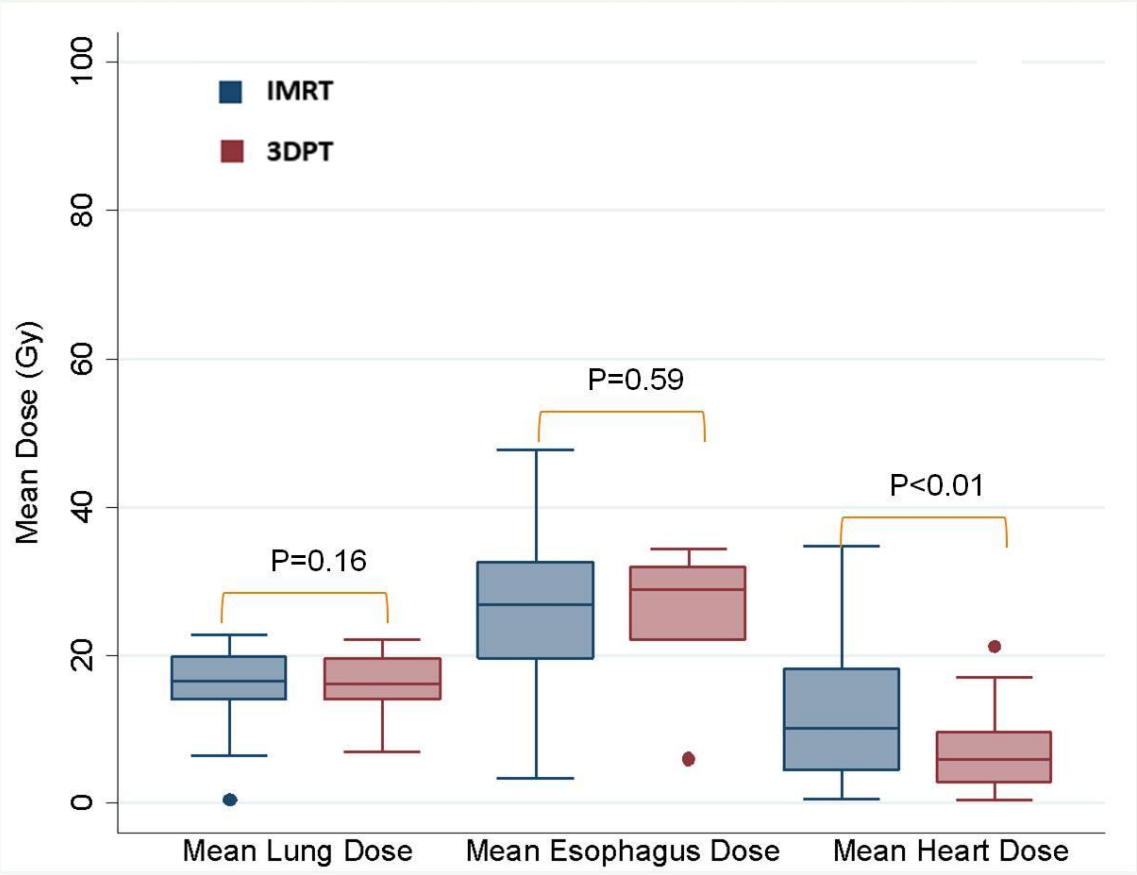
A Bayesian Randomization Trial of Intensity Modulated Radiation Therapy (IMRT) vs. 3-Dimensional Passively Scattered Proton Therapy (3DPT) for Locally Advanced Non-Small Cell Lung Carcinoma

(clinicaltrials.gov identifier NCT00915005)

Zhongxing Liao, J. Jack Lee, Ritsuko Komaki, Daniel R. Gomez, Michael O'Reilly, Pamela K. Allen, Frank Fossella, John V. Haymach, George R. Blumenschein, Noah Chan Choi, Thomas F. Delaney, Stephen M. Hahn, Charles Lu, James D. Cox, and Radhe Mohan

Supported in part by NCI grants P01 CA021230 and U19 CA021239.

Lung, Esophagus and Heart Mean Dose



Note: Analysis carried out using the Wilcoxon rank-sum test (also known as Mann-Whitney Two Sample Statistic)

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Making Cancer History®

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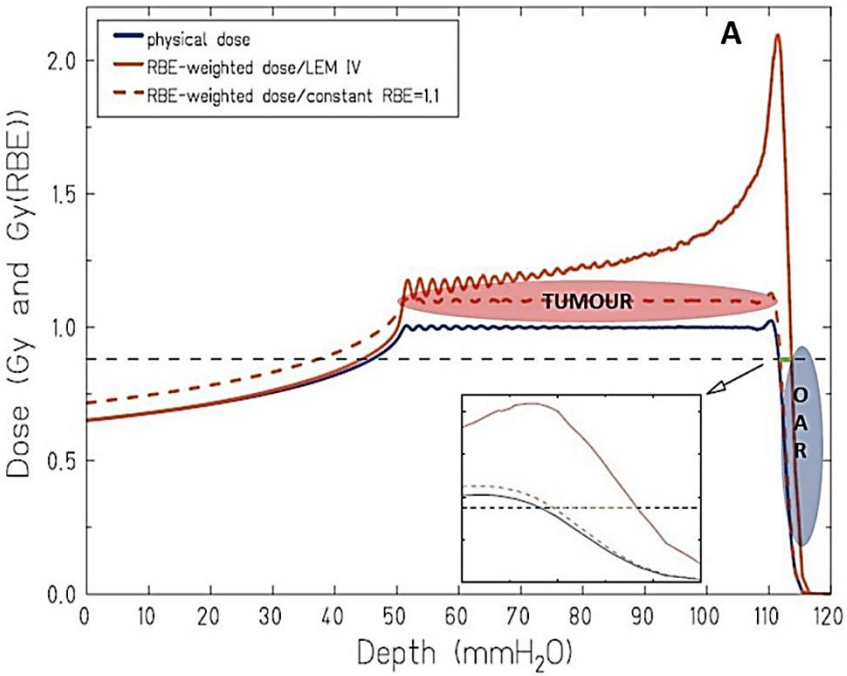
Systematic introduction of new technology

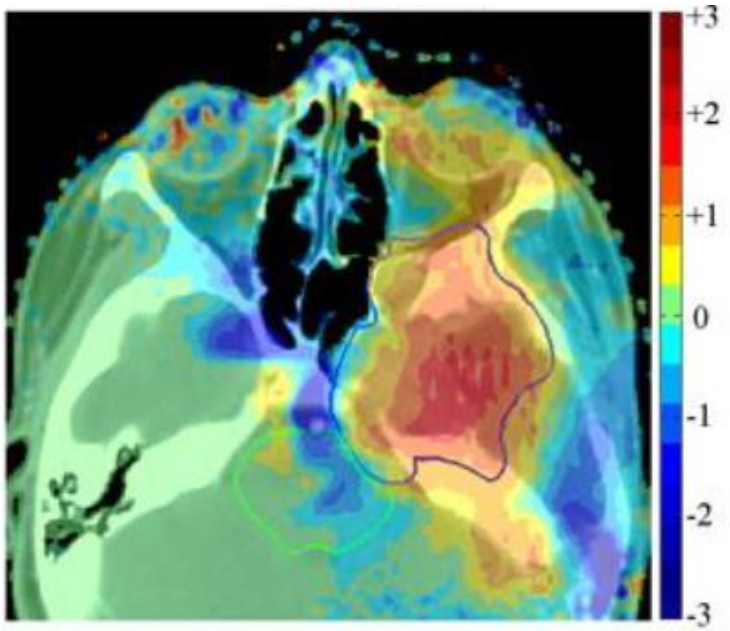
- Phase 0: "In silico" **quantitative** modelling: Is a **measurable clinical benefit** probable?
- Phase I: Can the technology be applied safely?
- Phase II: Prospective clinical study
- Phase III: Randomised trial if possible/ needed (**evident** gain is necessary)
- Phase IV: Outcome of wide-scale implementation

Fiona Hegi, Dirk De Ruysscher, Paul Keall: et al. Submitted 2016

Potentials and limitations of proton therapy

- IMPT with robust plans? Passive Scattering PT?
- Uncertainties
  - Anatomical changes
  - Range uncertainties
  - Set-up/Movement
  - RBE


physical dose
RBE-weighted dose/LEM IV
RBE-weighted dose/constant RBE=1.1
A
TUMOUR
OAR
Dose (Gy and Gy(RBE))
Depth (mmH2O)
0.0
0.5
1.0
1.5
2.0
0
10
20
30
40
50
60
70
80
90
100
110
120


+3
+2
+1
0
-1
-2
-3

Model-based indications

Radiotherapy and Oncology 107 (2013) 267–273

Contents lists available at SciVerse ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

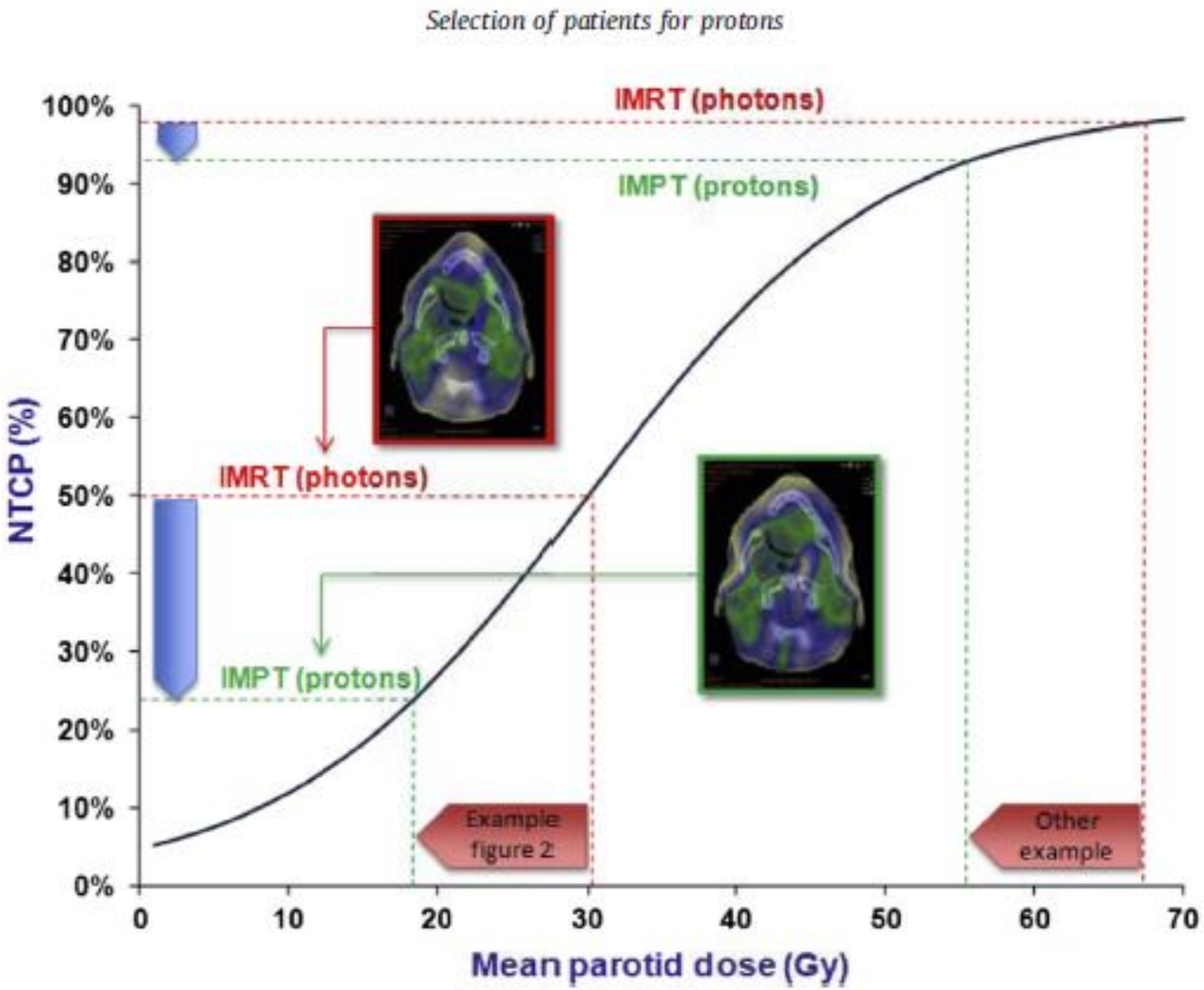
Proton radiotherapy

Selection of patients for radiotherapy with protons aiming at reduction of side effects: The model-based approach

Johannes A. Langendijk [a,*], Philippe Lambin [b], Dirk De Ruysscher [c], Joachim Widder [a], Mike Bos [d], Marcel Verheij [e]

[a] Department of Radiation Oncology, University Medical Center Groningen, University of Groningen, The Netherlands; [b] Department of Radiation Oncology (MAASTRO Clinic) & Research Institute GROW, University Hospital Maastricht, The Netherlands; [c] Department of Radiation Oncology, University Hospitals Leuven/KU Leuven, Belgium; [d] Health Council of the Netherlands; [e] Department of Radiotherapy, The Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, The Netherlands

Model-based indications



ΔNTCP

- Grade 1: are not taken into account
- Grade ≥ 2: minimal **10%**
- Grade ≥ 3: minimal **5%**
- Grade ≥ 4: minimal **2%**

When several side effects are occurring simultaneously:

- Grade ≥ 2: Σ ΔNTCP minimal 15%
- Grade ≥ 3: Σ ΔNTCP minimal 7.5%
- Grade ≥ 4: Σ ΔNTCP minimal 3%

Choice of the NTCP model

Annals of Internal Medicine

RESEARCH AND REPORTING METHODS

Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD): The TRIPOD Statement

Gary S. Collins, PhD; Johannes B. Reitsma, MD, PhD; Douglas G. Altman, DSc; and Karel G.M. Moons, PhD

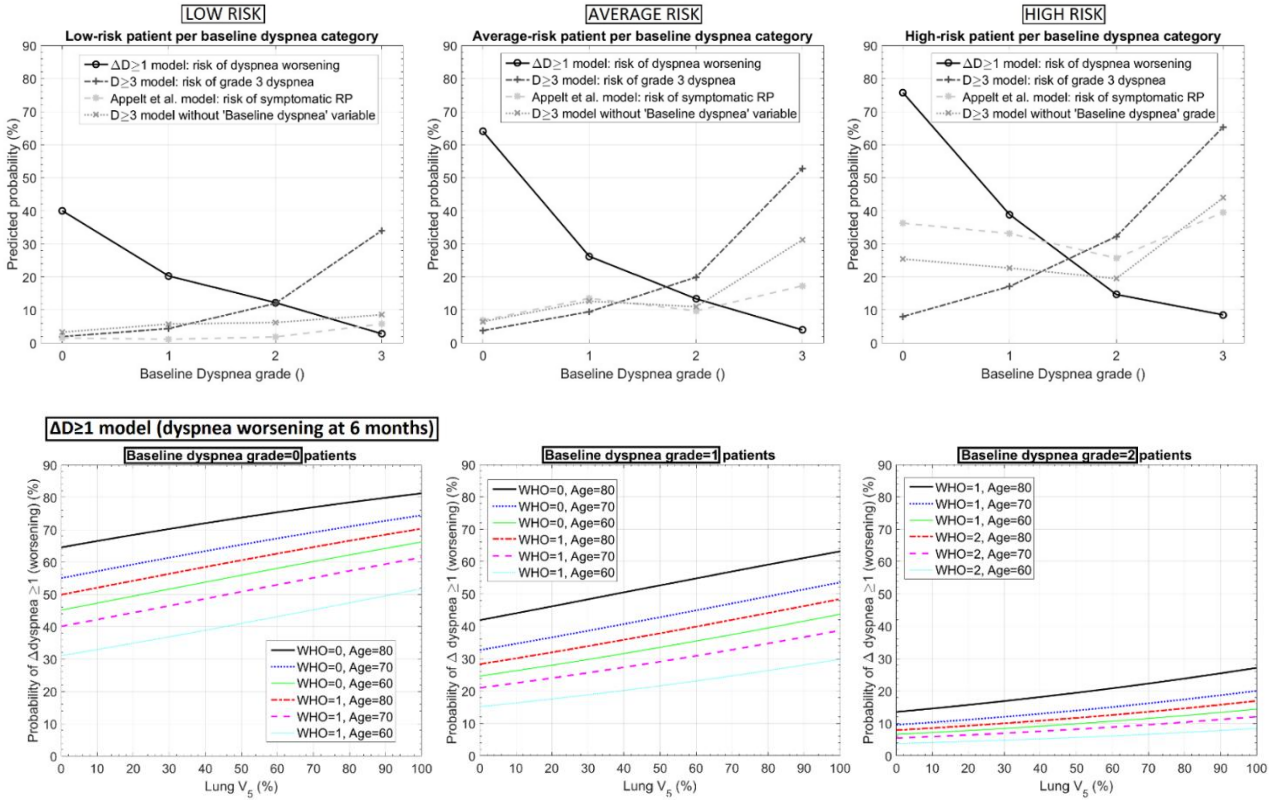
Prediction models are developed to aid health care providers in estimating the probability or risk that a specific disease or condition is present (diagnostic models) or that a specific event will occur in the future (prognostic models), to inform their decision making. However, the overwhelming evidence shows that the quality of reporting of prediction model studies is poor. Only with full and clear reporting of information on all aspects of a prediction model can risk of bias and potential usefulness of prediction models be adequately assessed. The Transparent Re-

2011 with methodologists, health care professionals, and journal editors. The list was refined during several meetings of the steering group and in e-mail discussions with the wider group of TRIPOD contributors. The resulting TRIPOD Statement is a checklist of 22 items, deemed essential for transparent reporting of a prediction model study. The TRIPOD Statement aims to improve the transparency of the reporting of a prediction model study regardless of the study methods used. The TRIPOD Statement is best used in conjunction with the TRIPOD explanation

www.tripod-statement.org

Improvement of prediction models

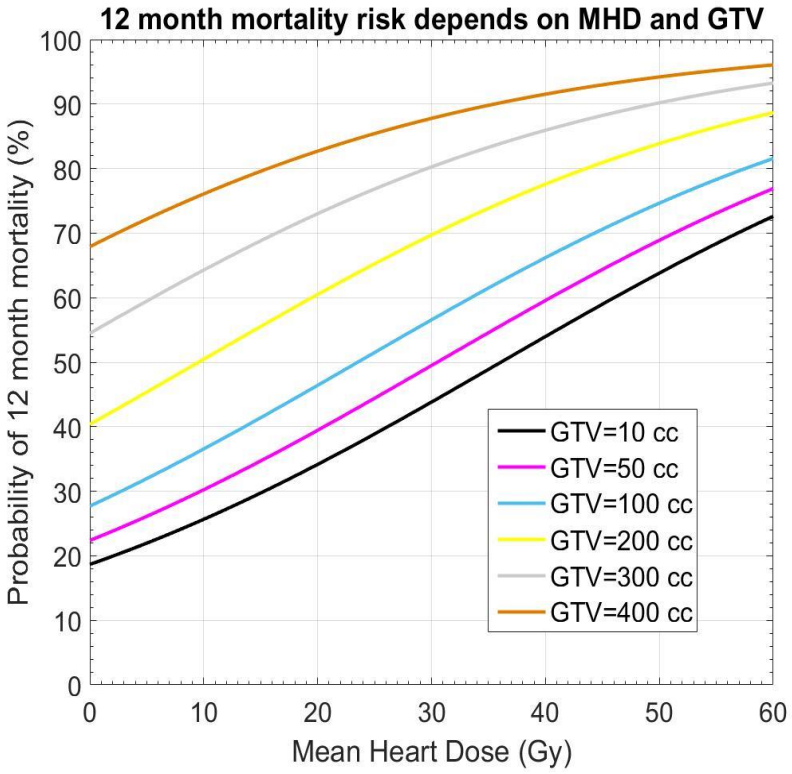
Lung cancer



Defraene et al. Submitted 2018

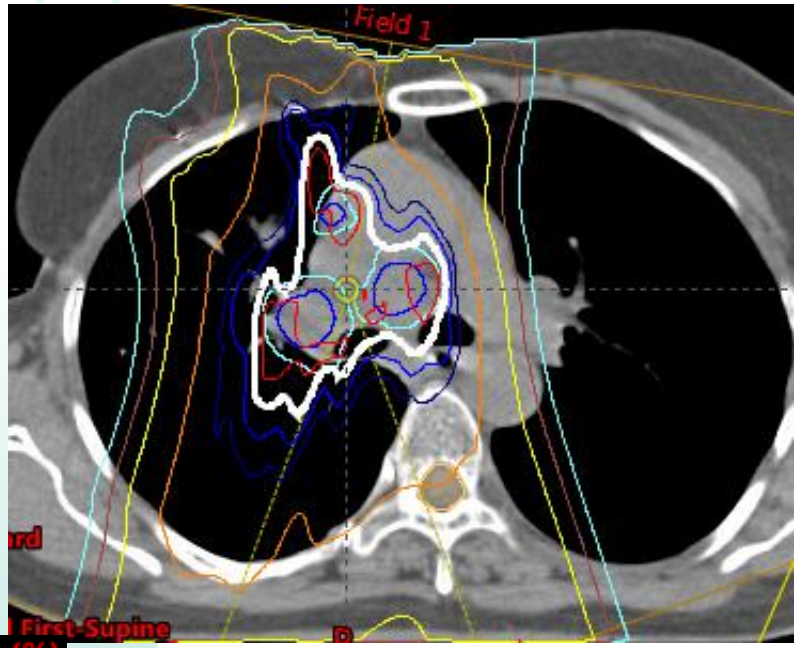
Improvement of prediction models

Lung cancer

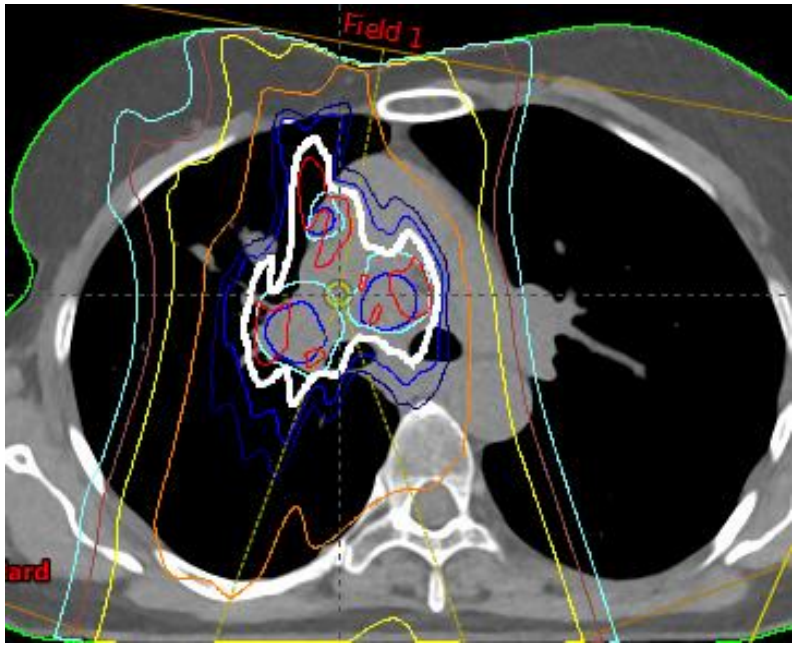


De Ruysscher et al. WCLC 2017

Proton Plan Dose Calculation on DECT vs SECT

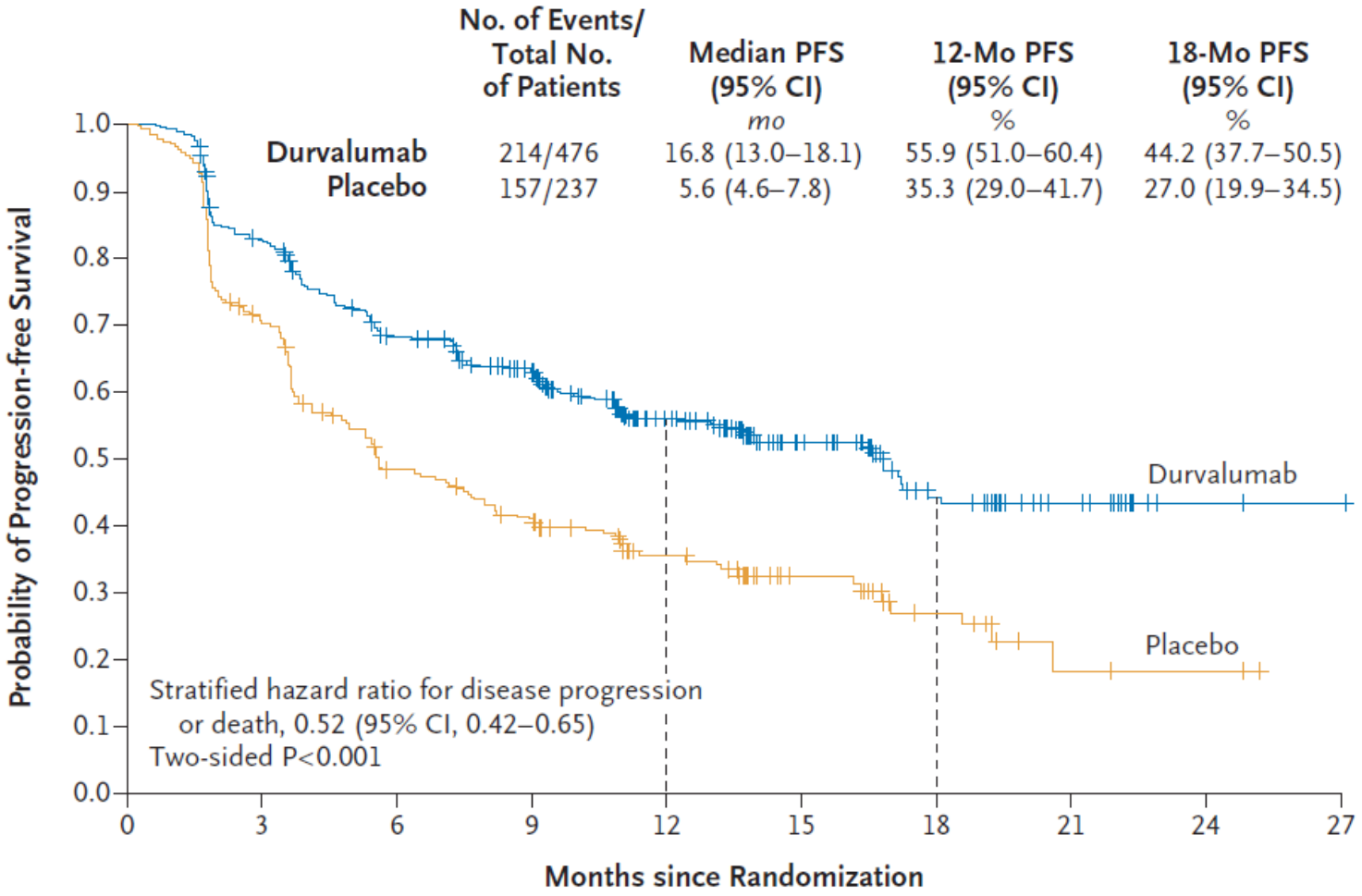


DECT



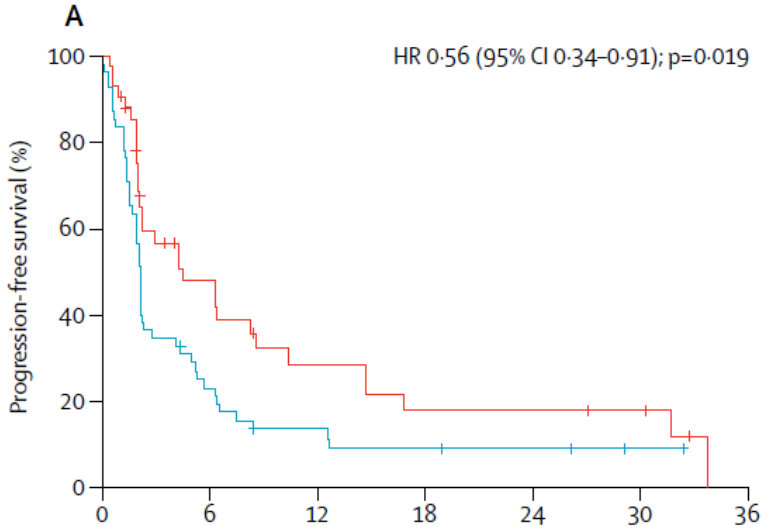
SECT

PACIFIC

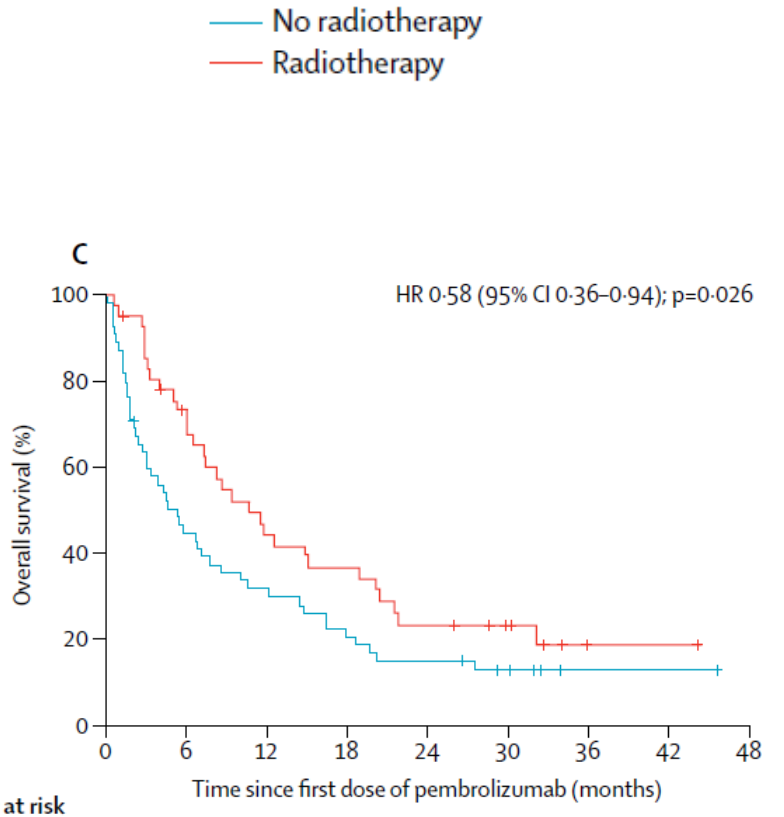


Antonia et al. New Engl J Med 2017

Subgroup analysis of KEYNOTE-001



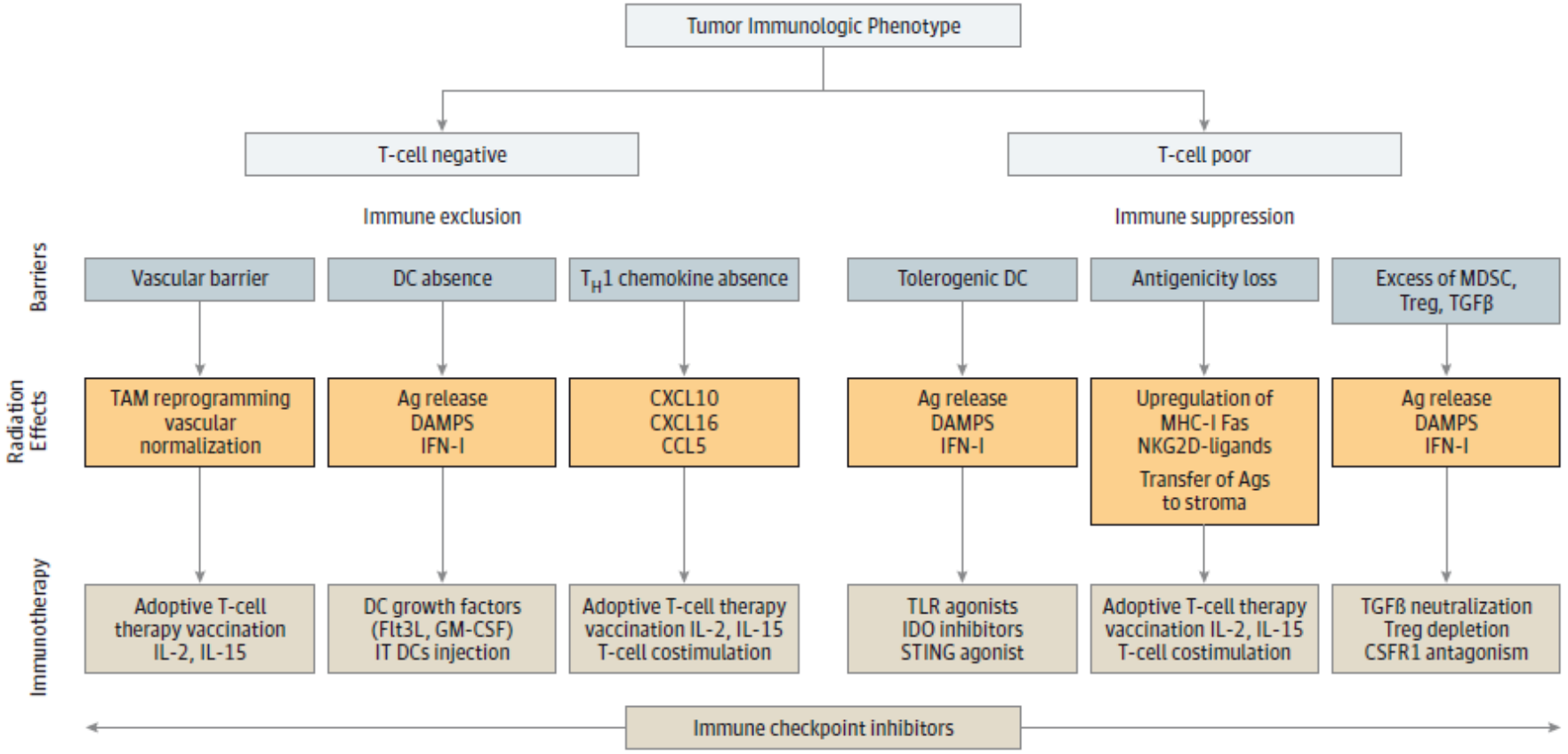
Number at risk (number censored)							
No radiotherapy	55 (0)	12 (1)	6 (2)	4 (2)	3 (3)	1 (5)	0 (6)
Radiotherapy	42 (0)	16 (6)	8 (8)	5 (8)	5 (8)	4 (9)	0 (11)



Number at risk (number censored)									
No radiotherapy	55 (0)	24 (1)	17 (1)	11 (1)	8 (1)	5 (3)	1 (7)	1 (7)	0 (8)
Radiotherapy	42 (0)	28 (2)	17 (3)	14 (3)	9 (3)	6 (5)	1 (9)	1 (9)	0 (10)

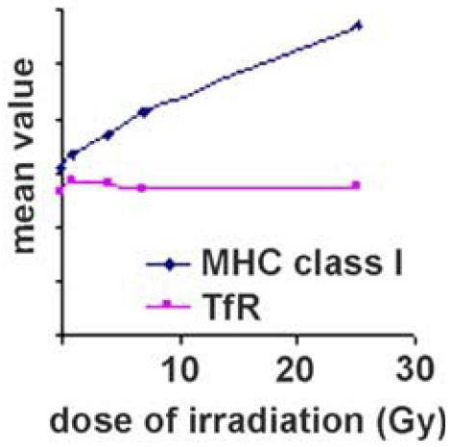
Shaverdian et al. Lancet Oncol 2017

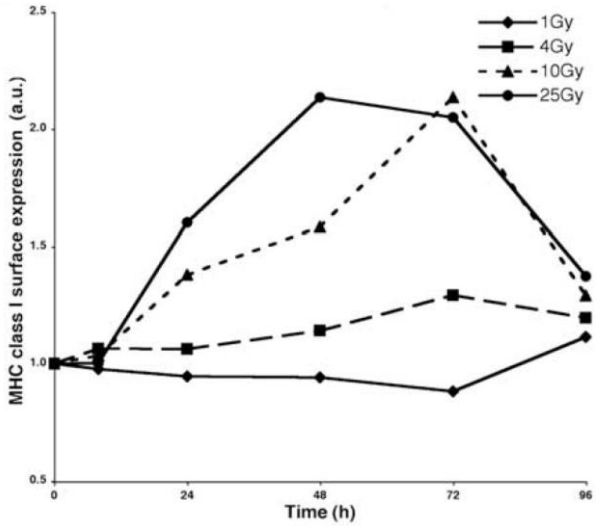
Barriers for successful immune treatment



Demaria et al. JAMA Oncology 2015

Upregulation of MHC class I by radiation





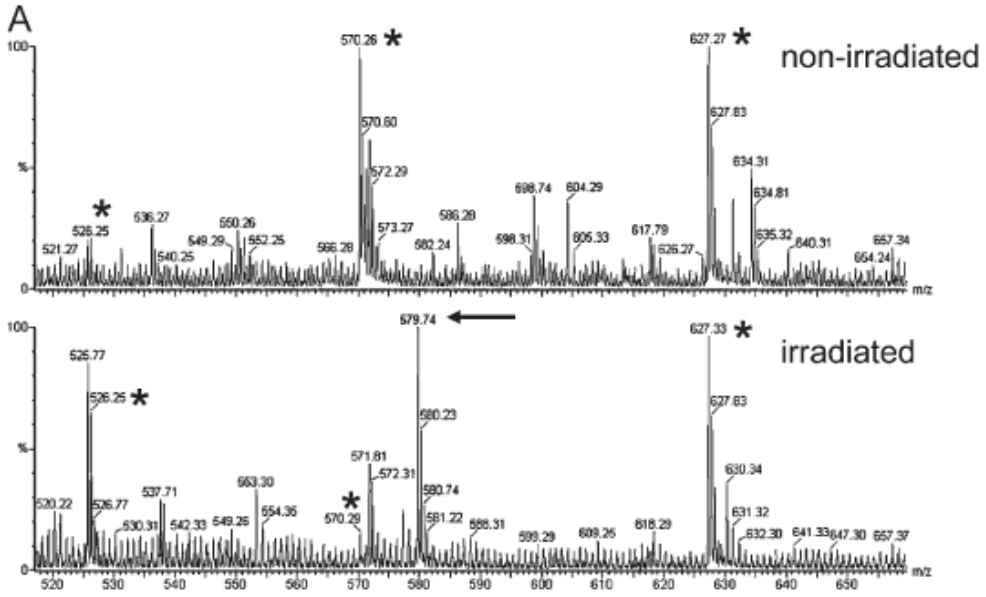
Reits et al. J Exp Med 2006

Upregulation of TAAs by radiation

- Caco-2, HCT116, WiDr, HT-29, LS 174T, SW1463, SW403, SW480, SW620, T84, LoVo, and COLO 205
- A549, SK-LU-1, SW900, HLF-a, NCI-H23, NCI-H647, Calu-1, H460, Calu1 and Calu3
- 22Rv1, DU 145, PC-3, PC3, DU145 and LNCaP
- MelJuSo, SK-MEL-37, CaSki and SiHa
- MDA-MB-469, MDA-MB-231 and MCF 7
- Saos, LM5, 143B, HOS, HU09, and M132

Dudek et al. Cyt Growth Fact Rev 2013

Radiation alters the MHC class I–associated peptide profile



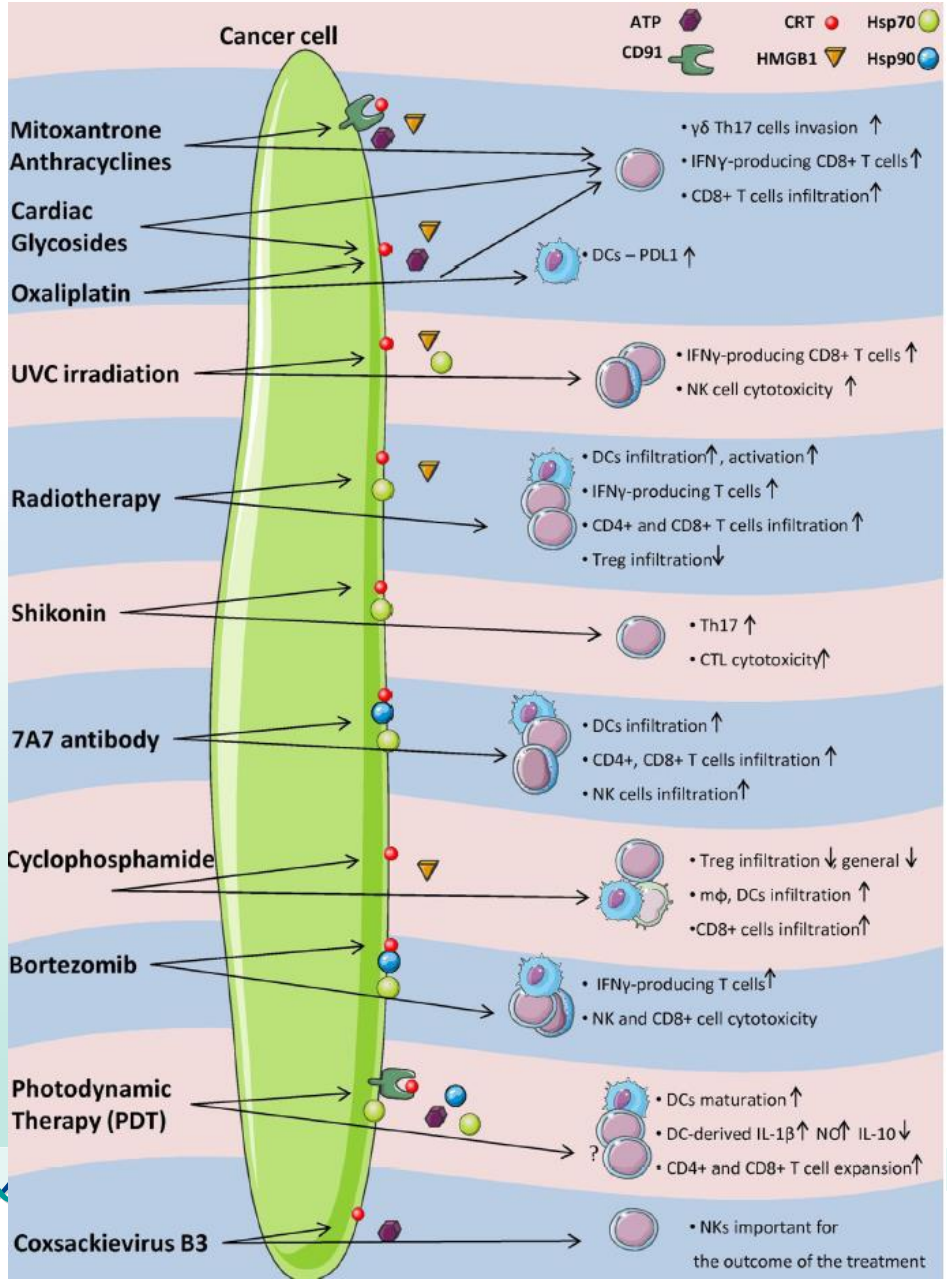
B

Peptides specific for irradiated cells

ETDRGMSAEY	Mitochondrial protein CGI-51$_{206-215}$
YSDSLVQKGY	DNA repair protein MSH6$_{469-478}$
VTDVGIRY	F-box protein Fbl7$_{355-362}$
IADMGHLKY	PCNA$_{242-249}$

Reits et al. J Exp Med 2006

Main mechanisms of ICD-inducers

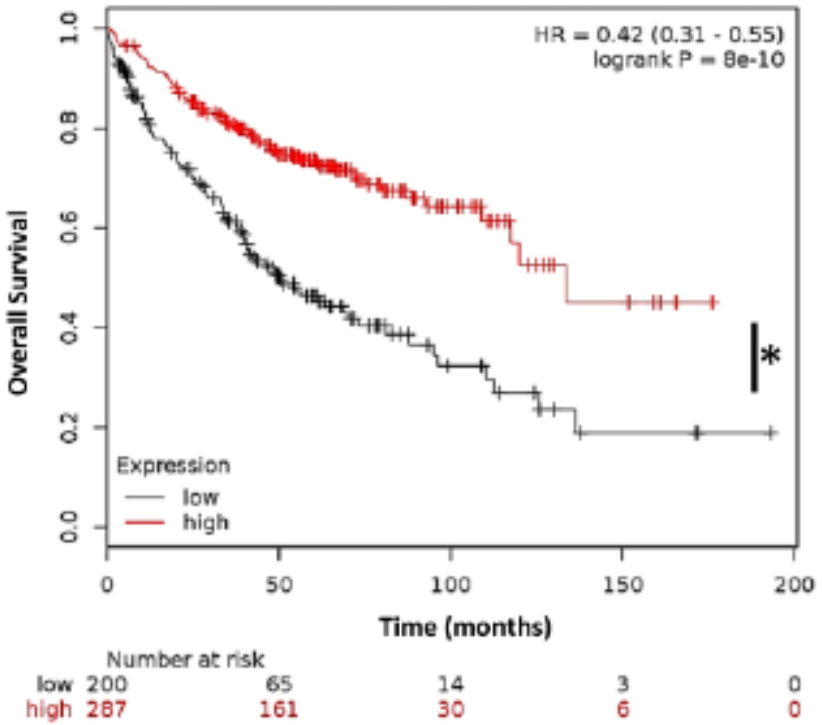


Dudek et al. Cytokine & Growth Factors Rev 2013

Prognostic value of ICD-genes

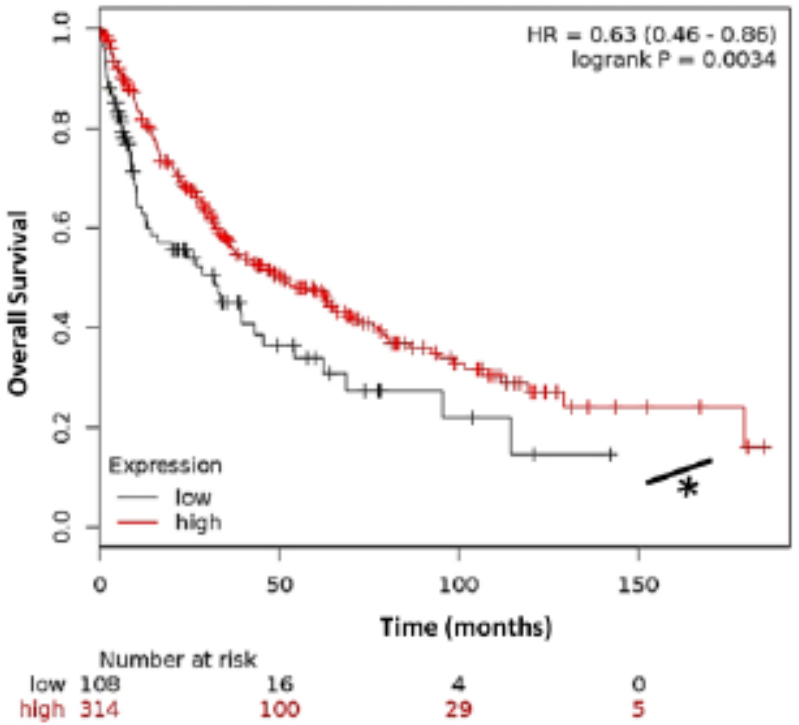
C

Prognostic impact of Lung Cancer-specific ICD-derived metagene signature in Lung Adenocarcinoma



D

Prognostic impact of Lung Cancer-specific ICD-derived metagene signature in Lung Squamous Cell Carcinoma



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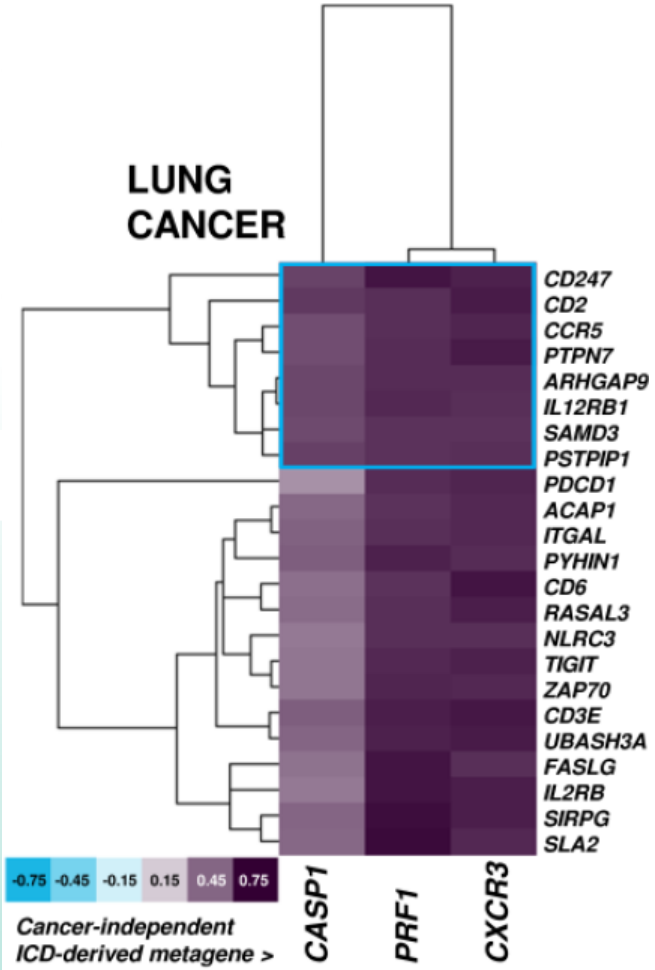
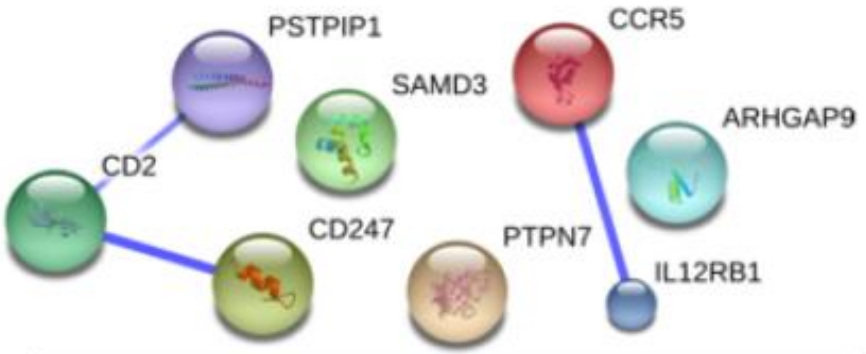
Garg A. et al. OncoImmunology 2016

Prognostic value of ICD-genes: Biological meaning

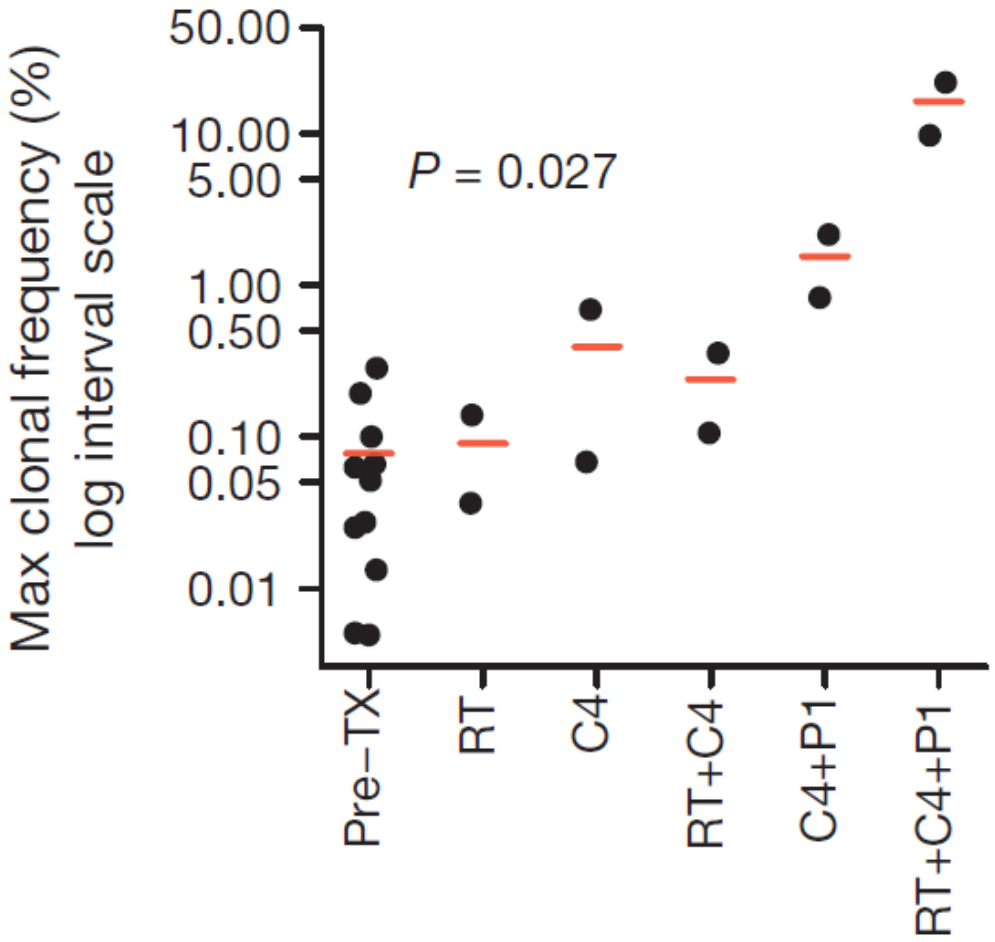




GO Biological Process	P-value
Regulation of T cell activation	0.00008
Regulation of Leukocyte cell-cell adhesion	0.00008
Regulation of homotypic cell-cell adhesion	0.00009

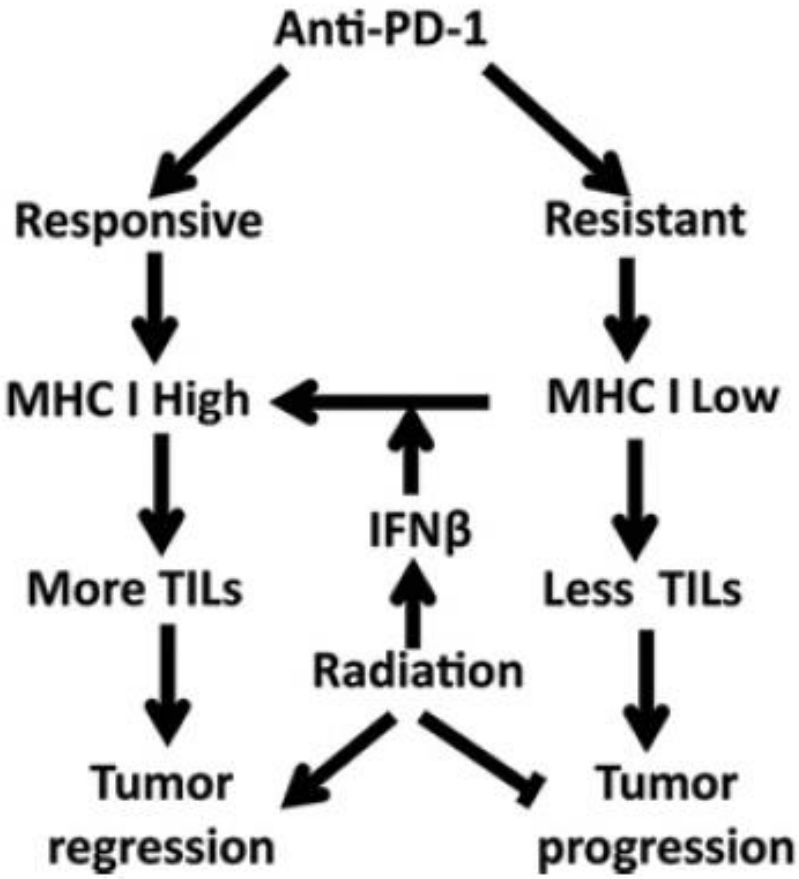
Garg A. et al. OncoImmunology 2016

Maximum clonal frequency in post-treatment blood of the most frequent TCR clonotypes found in TILs.

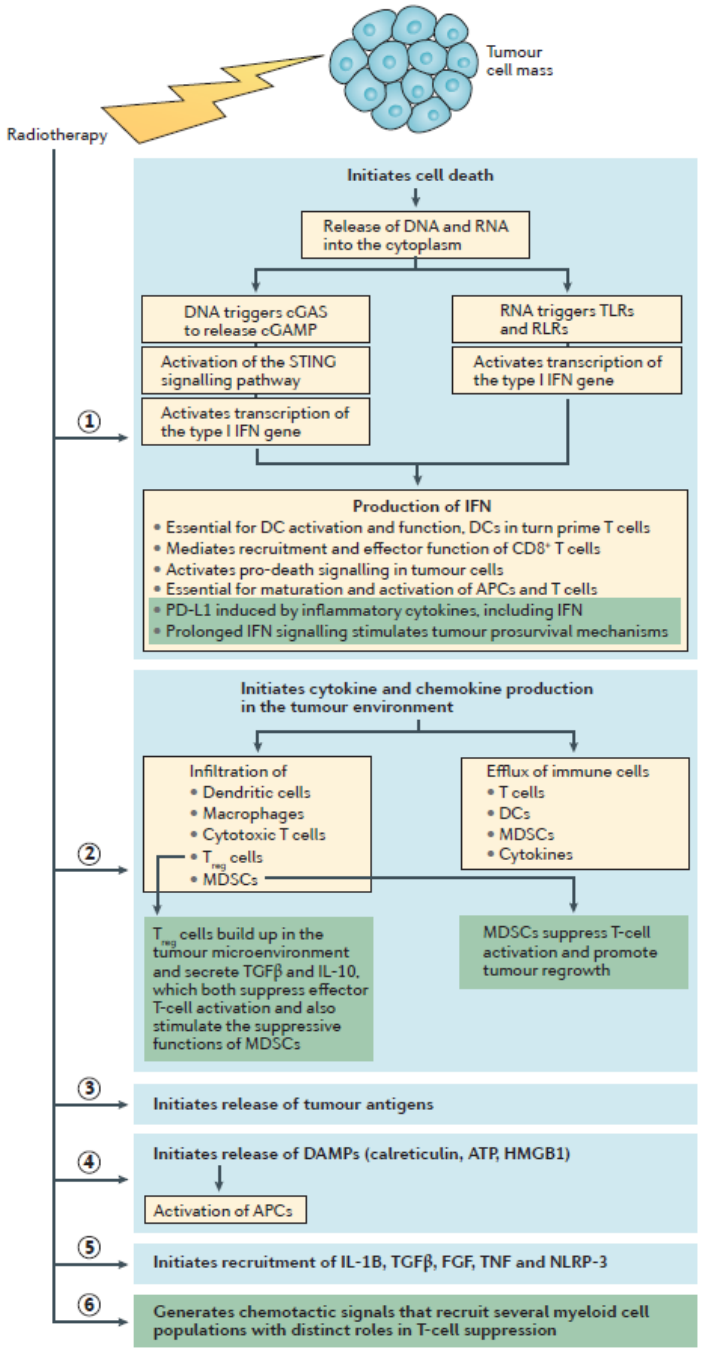


Twyman-Saint Victor et al. Nature 2015

Resistance for anti-PD1 can be overcome by radiation



Wang et al. Cancer Res 2016



Weichselbaum et al.
Nature Rev Clin Oncol 2017

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Which toxicity may be increased?

	Durvalumab (N=475)	Placebo (N=234)
Any-grade all-causality AEs, n (%)	460 (96.8)	222 (94.9)
Grade 3/4	142 (29.9)	61 (26.1)
Grade 5	21 (4.4)	13 (5.6)
Leading to discontinuation	73 (15.4)	23 (9.8)
Any-grade treatment-related AEs, n (%)	322 (67.8)	125 (53.4)
Any-grade all-causality AESIs, n (%)	311 (65.5)	114 (48.7)
Grade 3/4	39 (8.2)	9 (3.8)
Grade 5	4 (0.8)	4 (1.7)
Requiring concomitant treatment	200 (42.1)	40 (17.1)
Any-grade immune-mediated AEs, n (%)	115 (24.2)	19 (8.1)
Grade 3/4	16 (3.4)	6 (2.6)
Grade 5	4 (0.8)	3 (1.3)

Antonia et al, New Engl J Med 2017

Paz-Ares et al, LBA1, ESMO 2017

Which toxicity may be increased?

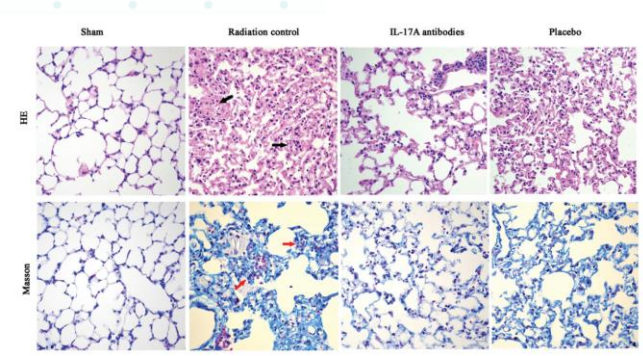
Event	Durvalumab (N=475)		Placebo (N=234)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Any event, n (%)	460 (96.8)	142 (29.9)	222 (94.9)	61 (26.1)
Cough	168 (35.4)	2 (0.4)	59 (25.2)	1 (0.4)
Pneumonitis/radiation pneumonitis†	161 (33.9)	16 (3.4)	58 (24.8)	6 (2.6)
Fatigue	113 (23.8)	1 (0.2)	48 (20.5)	3 (1.3)
Dyspnea	106 (22.3)	7 (1.5)	56 (23.9)	6 (2.6)
Diarrhea	87 (18.3)	3 (0.6)	44 (18.8)	3 (1.3)
Pyrexia	70 (14.7)	1 (0.2)	21 (9.0)	0
Decreased appetite	68 (14.3)	1 (0.2)	30 (12.8)	2 (0.9)
Nausea	66 (13.9)	0	31 (13.2)	0
Pneumonia	62 (13.1)	21 (4.4)	18 (7.7)	9 (3.8)
Arthralgia	59 (12.4)	0	26 (11.1)	0
Pruritus	58 (12.2)	0	11 (4.7)	0
Rash	58 (12.2)	1 (0.2)	17 (7.3)	0
Upper respiratory tract infection	58 (12.2)	1 (0.2)	23 (9.8)	0
Constipation	56 (11.8)	1 (0.2)	20 (8.5)	0
Hypothyroidism	55 (11.6)	1 (0.2)	4 (1.7)	0
Asthenia	51 (10.7)	3 (0.6)	31 (13.2)	1 (0.4)
Back pain	50 (10.5)	1 (0.2)	27 (11.5)	1 (0.4)

Antonia et al, New Engl J Med 2017

Paz-Ares et al, LBA1, ESMO 2017

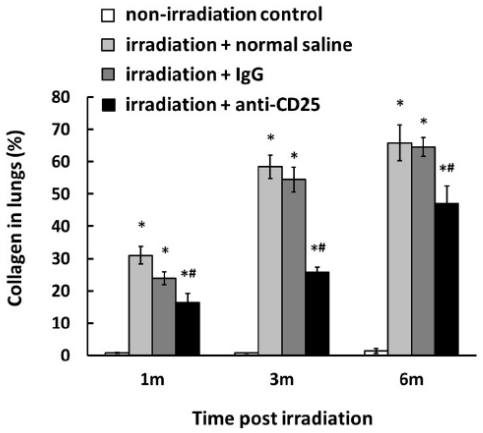
Examples of *experimental* mitigators of radiation-induced lung damage

IL-17 antibodies



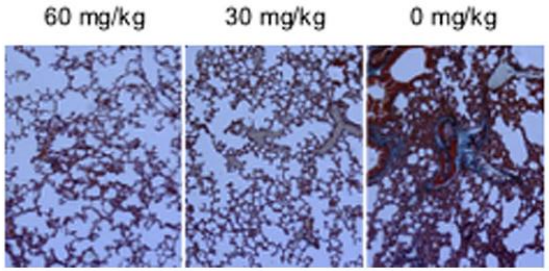
Wang et al. Exp Lung Res 2014

Anti-CD25 (Treg depletion)



Xiong et al. Immunobiology 2015

nintedanib



De Ruysscher et al. Radiother Oncol 2017

ETOP 6-14 NICOLAS

EudraCT 2014-005097-11
BMS grant

PI :

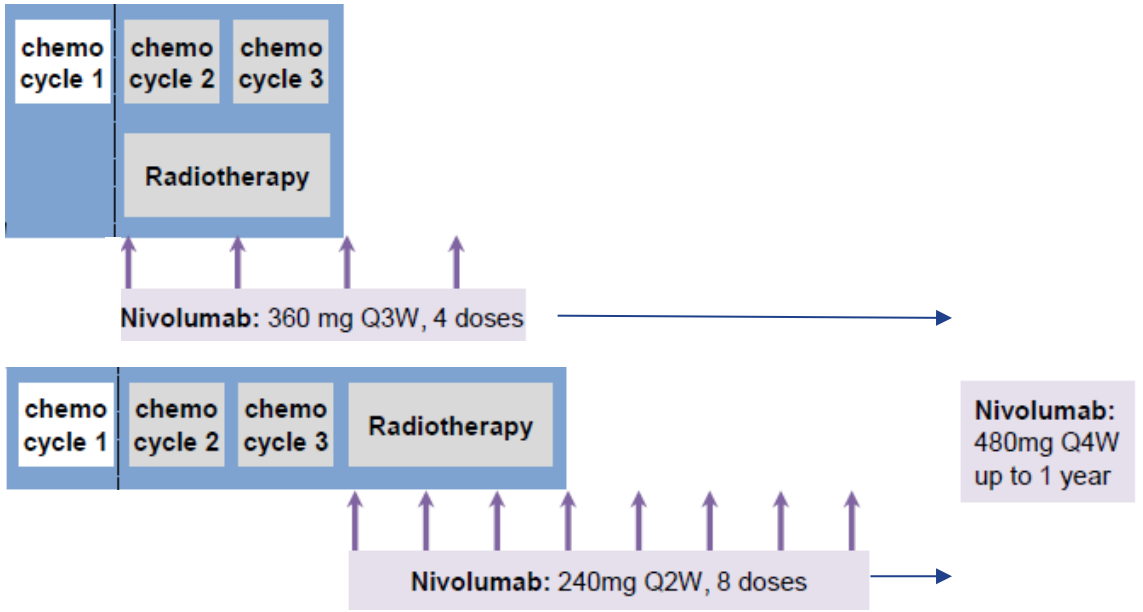
S. Peters and D. De Ruysscher

Primary endpoint

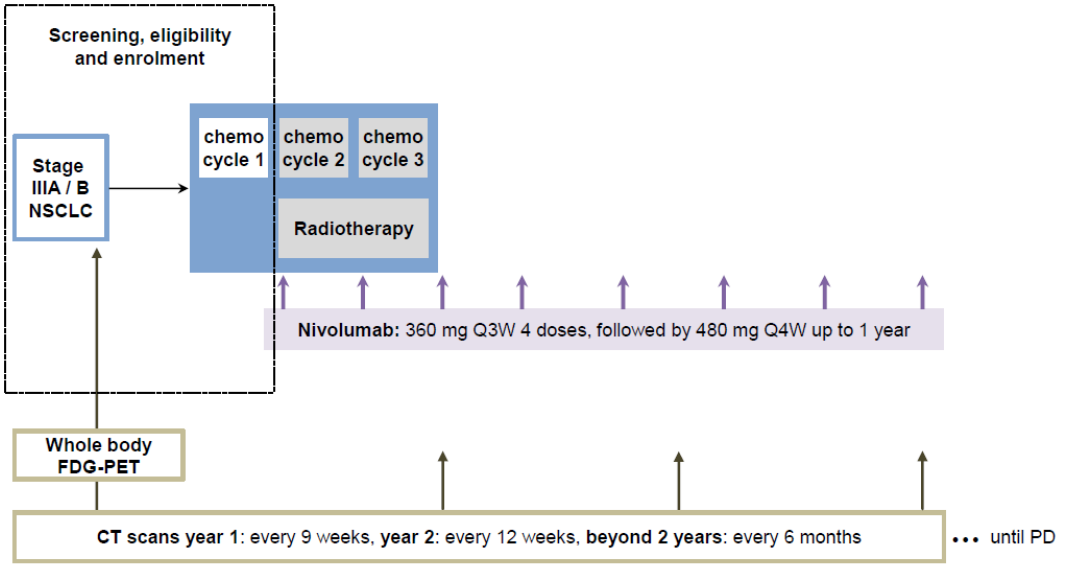
Grade >3 pneumonitis any time during 6 m from end of RT

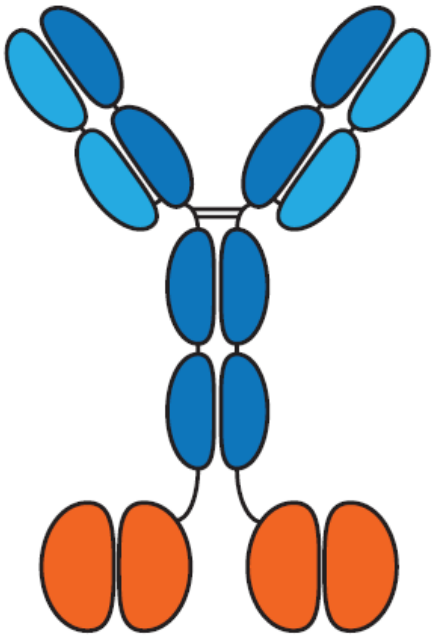
Key secondary endpoint:

1-year PFS



Amended protocol





van den Heuvel *et al. Journal of Translational Medicine* (2015) 13:32
DOI 10.1186/s12967-015-0397-0

JOURNAL OF TRANSLATIONAL MEDICINE

RESEARCH Open Access

NHS-IL2 combined with radiotherapy: preclinical rationale and phase Ib trial results in metastatic non-small cell lung cancer following first-line chemotherapy

Michel M van den Heuvel[1*], Marcel Verheij[2], Rogier Boshuizen[1], José Belderbos[2], Anne-Marie C Dingemans[3], Dirk De Ruysscher[4], Julien Laurent[5], Robert Tighe[6], John Haanen[1] and Sonia Quaratino[5,7]

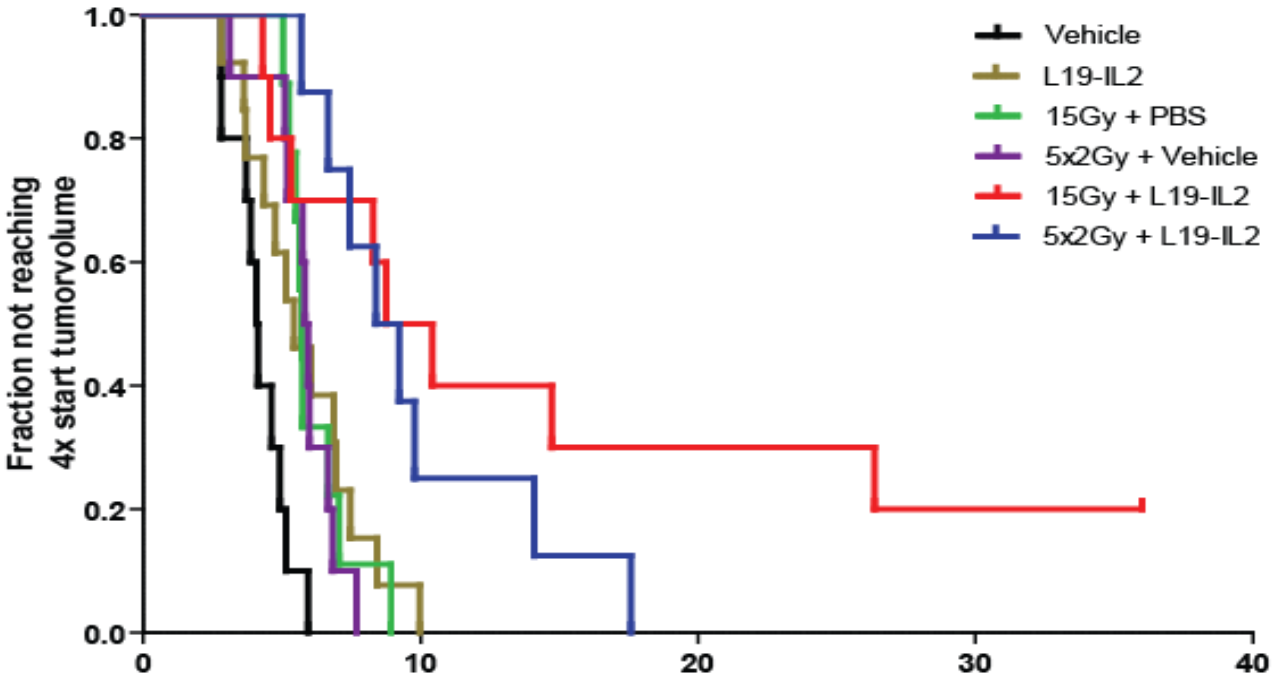
Radiotherapy primary tumour 5x4 Gy, followed by selectikine

Clinical outcome

No objective responses were observed during the trial, based on RECIST v1.0 criteria for tumor response, PFS, and OS. Median PFS was 2.9 months (95% confidence interval [CI] 1.5; 3.1) and median OS was 8.6 months (95% CI 4.9; not evaluable). As of the day of reporting there are 2 long-term survivors (both in good performance status 4 years after start of first-line chemotherapy). One patient discontinued treatment with NHS-IL2 in November 2013 and there were still no signs of disease activity in August 2014. Of note, both long-term survivors developed thyroiditis during treatment.

2/13 (15 %) patients no progression after 4 years!

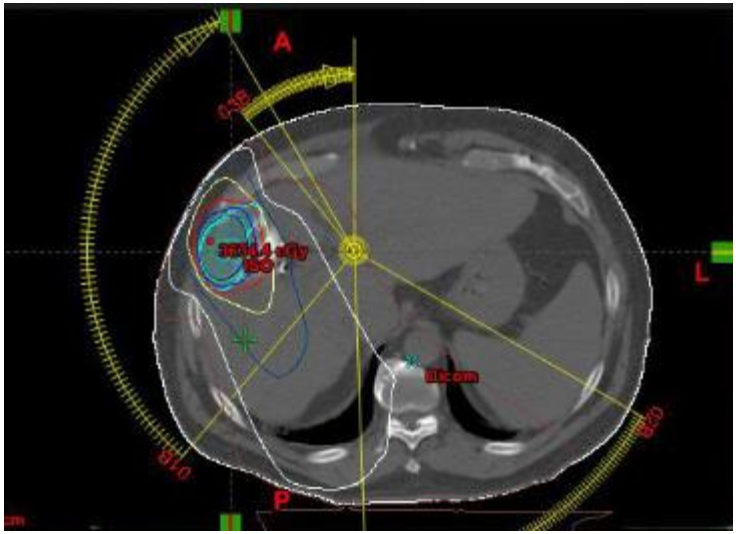
Abscopal effect of L19-IL2 and radiation



Rekers N et al. Nature Comm 2015

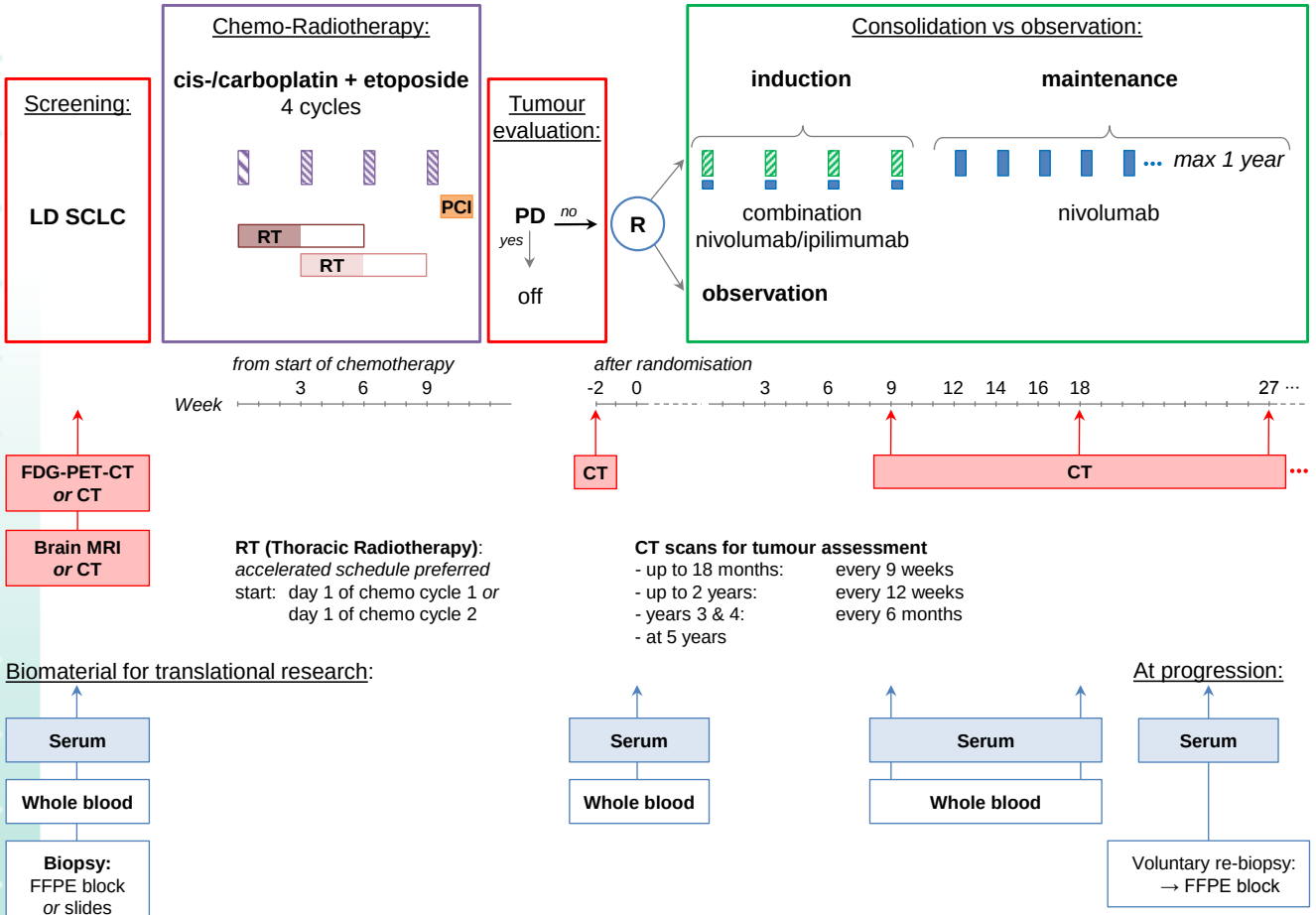
Phase I trial SBRT + L19-IL2 NCT02086721

- Synchronous or metachronous **oligometastatic** solid tumor (NSCLC, RCC, HNSCC, CRC, melanoma)
- Or poly-metastatic NSCLC
- SBRT to all (up to 5) oligometastatic sites ➔ L19-IL2 (6 cycles: day 1,3,5; Q 21 days)



➔ Randomised phase II trial in stage IV NSCLC: HORIZON 2020

Phase II trial stage I-III small cell lung cancer "ETOP- STIMULI"



Randomized phase III NVALT-11/ DLCRG02 study of prophylactic cranial irradiation vs. observation in stage III NSCLC

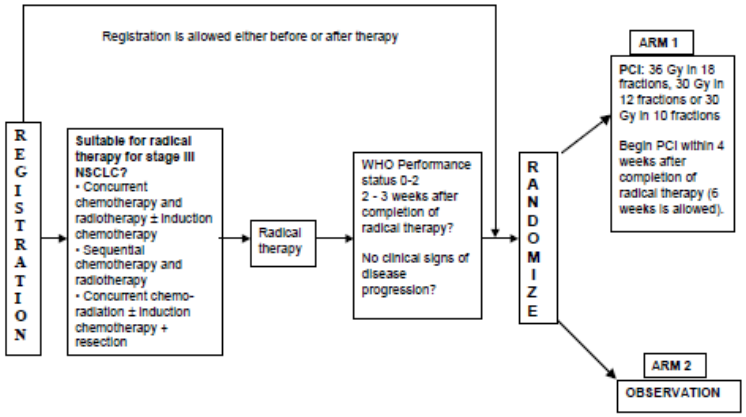
De Ruysscher DKM (1), Dingemans A (1), Praag J (2), Belderbos J (3), C. Tissing-Tan C (4), Herder G (5), Haitjema T (6); Ubbels F (7); Lagerwaard J (8); Stigt J (9); Smit E (10); van Tinteren H (10), van der Noort V (10), Groen HJM (7)

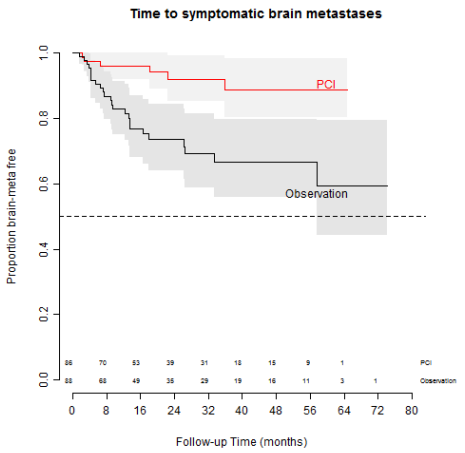
1 University Medical Center Maastricht and Maastro Clinic, Maastricht; 2 Erasmus Medical Center, Rotterdam; 3 Anthonie van Leeuwenhoek hospital, Amsterdam; 4 Radiotherapeutic Institute Arnhem; 5 Antonius hospital Nieuwegein; 6 Medical Center Alkmaar; 7 University Medical Center Groningen; 8 Free University Medical Center, Amsterdam;
9 Isala hospital, Zwolle; 10 Netherlands Cancer Institute, Amsterdam; All in The Netherlands

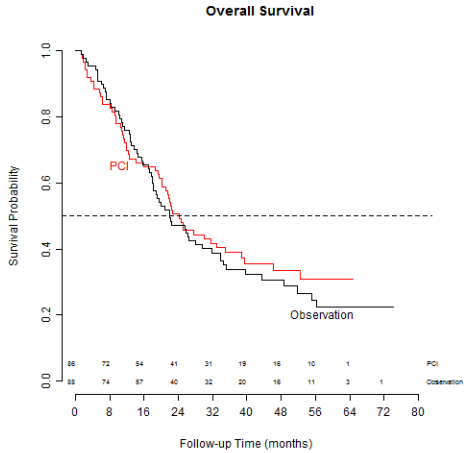
IASLC 2017

Primary endpoint: Incidence of symptomatic brain metastases

	PCI (n=86)	Observation (n=88)	p
BM + neuro symptoms	6 (7.0 %)	24 (27.2 %)	< 0.001







All neurological adverse events: Physician rated

	All grades		Grade 3, 4, 5	
	PCI	Observation	PCI	Obs
	86	88	86	88
Memory impairment	26	7	0	0
Cognitive disturbance	18	3	2	0

After Holms-Bonferoni correction: significant differences between arms considering all grades: **Memory impairment and cognitive disturbance.**

Grade 3-5: number of AE too small to see significant differences.

Patient reported adverse events

	All grades		Grade 3, 4	
	PCI	Observation	PCI	Obs
	86	88	86	88
Dizziness	50	36	1	0
Headache	55	36	4	2
Fatigue	69	70	3	5
Memory impairment	50	47	2	1
Vomiting	16	6	0	0

After Holms-Bonferoni correction: significant differences between arms considering all grades: **headache**

Grade 3-5: number of AE too small to see significant differences.

MAASTRO CLINIC

Conclusions

- PCI reduces *symptomatic* brain metastases (7 % vs. 27 %), but at the expense of increased side effects
- When rated by physicians, *G1-2* cognitive disturbance (3.4 % vs. 20.9 %) and *G1-2* memory impairment (7.9 % vs. 30.2 %) are significantly increased
- Rated by patients, only headache *G1-2* (40.9 % vs. 63.2 %) is significantly increased

➔ Detailed analysis of QoL is ongoing

➔ Strategies to reduces the toxicity of PCI (an efficient treatment) is needed (hippocampus sparing?)