General introduction on the advantages and risks of combination therapy in the clinical setting

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Conflict of Interest

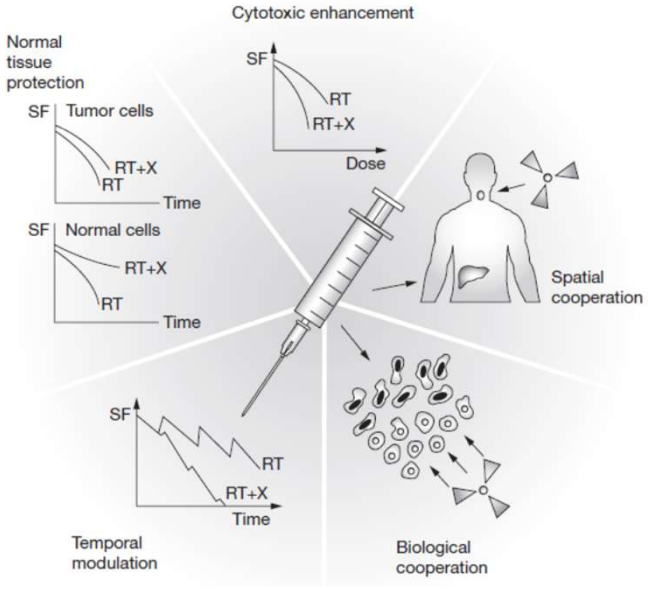
Institutional financial interests (no personal financial interests):

- Research grant/ support: Bristol-Myers Squibb, AstraZeneca, Beigene, Philips, Olink, Pfizer
- Advisory board: Bristol-Myers Squibb, AstraZeneca, Philips, Eli-Lilly

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Why combining medication with radiotherapy?

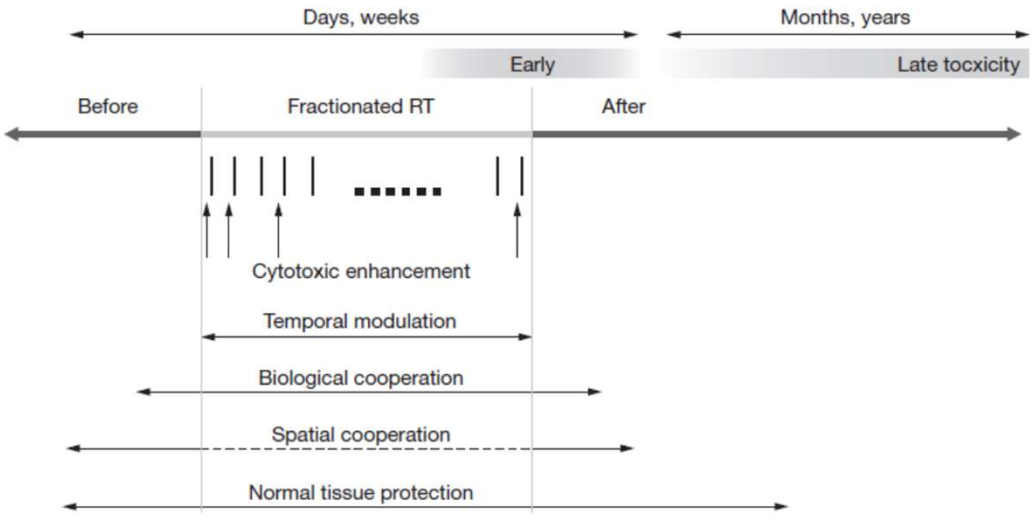


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Bentzen et al. Nature Clinical Practice Oncology 2007

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Why combining medication with radiotherapy?

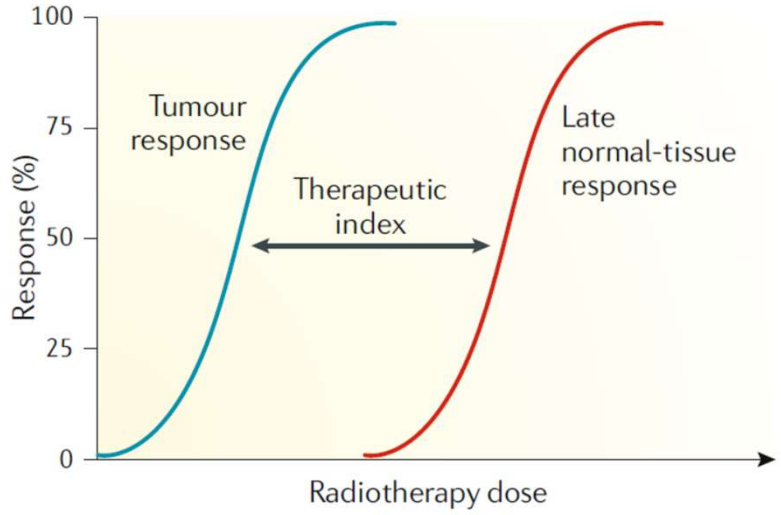


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Bentzen et al. Nature Clinical Practice Oncology 2007

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Why combining medication with radiotherapy?



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De Ruysscher et al. Nature Rev Dis Prim 2019

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Approved drugs for concurrent administration with RT

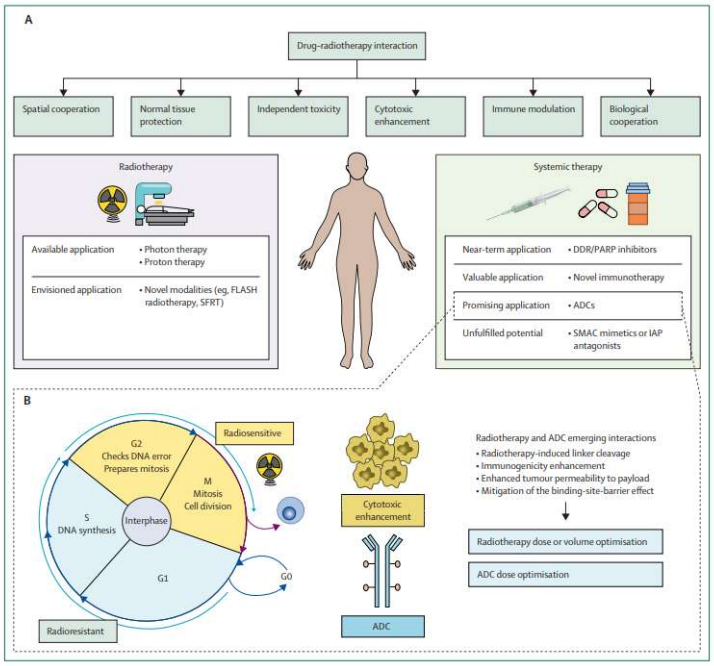
- Cisplatin (carboplatin)
- Oxaliplatin
- Etoposide
- Paclitaxel
- 5-FU (capecitabine)
- Temozolomide
- Mitomycin C

➔ Old drugs, significant, but mostly small effect (NSCLC 7 Gy/ 2 Gy), anti-proliferative (ex. small cell lung cancer), more toxicity

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De Ruysscher et al. Radiother Oncol 2009, De Ruysscher et al. J Clin Oncol 2006

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Angrisani et al. Lancet Oncol 2026

Challenge 1: Too many options

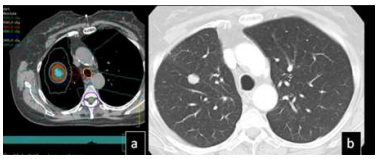
- Approximately 3000 new drugs in active development in phase I-III trials
- About *another* 5000 new drugs probably entering clinical studies withing 3 years
- Many of which are mechanistically novel, but more specific

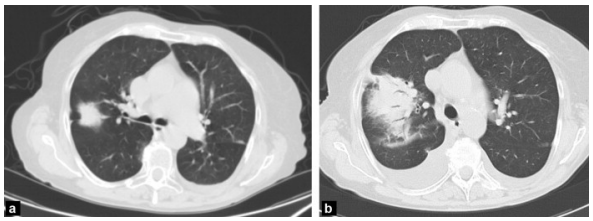
➔ Impossible to test them all with radiotherapy (dose, fractionation etc.)

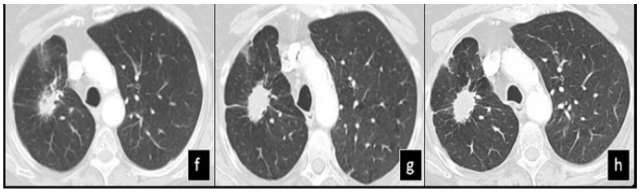
Challenge 2: Lack of surrogate endpoints for radiotherapy efficacy

RECIST 1.1	Response
CR	Disappearance of all lesions and pathologic lymph nodes
PR	≥ 30% decrease SLD no new lesions no progression of non-target lesions
SD	no PR - no PD
PD	≥ 20% increase SLD* compared to smallest SLD in study or progression of non-target lesions or new lesions

Green Criteria : disease control defined as complete disappearance of disease or stable residual abnormalities on CT at 3 months that remain unchanged at 6 & 12 months after radiotherapy







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ORR and PFS are challenging endpoints in drug-RT trials

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Challenge 3: Lack of validated surrogate endpoints for late toxicity

Comparison of Radiosensitivity Testing Methods.

Method	Principle	Advantages	Limitations	Processing Time	References
RILA (Radiation-Induced Lymphocyte Apoptosis)	Measures apoptosis levels in CD8 + T-lymphocytes after ex vivo irradiation	-Fast, reproducible, strong correlation with late toxicity -Predict radiation-induced sarcomas -Can assess tumor response -Available in most community laboratories across Europe	Limited to immune-related RS	48–72 h	(Ozsahin et al., 2005; Azria et al., 2010; Azria et al., 2015; Azria et al., 2024)
Clonogenic Survival Assay	Evaluates the ability of fibroblasts or tumor cells to form colonies after irradiation	Gold standard for cellular RS assessment	Time-consuming, requires primary cell culture	7–14 days	(Deschavanne and Fertil, 1996; Joubert et al., 2008)
γ-H2AX Foci Assay	Detects DNA double-strand breaks via phosphorylated H2AX quantification	High sensitivity, can be performed on peripheral blood lymphocytes	Inconsistent predictive value across cancer types	24–48 h	(COPERNIC project, 2016; Foray et al., 1998)
ATM Cytonuclear Translocation Assay	Measures ATM protein translocation after irradiation, reflecting DNA repair efficiency	Distinguishes radiosensitive subgroups	-Requires specialized equipment and fresh tissue samples -Limited data with the current ELISA test, without RT (only one article on acute toxicity, in head and neck cancer)	4–6 h	(Bodgi et al., 2013)
Omics-based Signatures (Genomics, Transcriptomics, Proteomics)	Identifies gene/protein expression patterns linked to RS	Potential for personalized RT strategies	Complex data integration, requires large-scale validation	Days to weeks	(Liu et al., 2020; Oike et al., 2025)

Abbreviations: RS: radiosensitivity; RILA: radiation-induced lymphocyte apoptosis; ATM: ataxia-telangiectasia mutated; RT: radiotherapy

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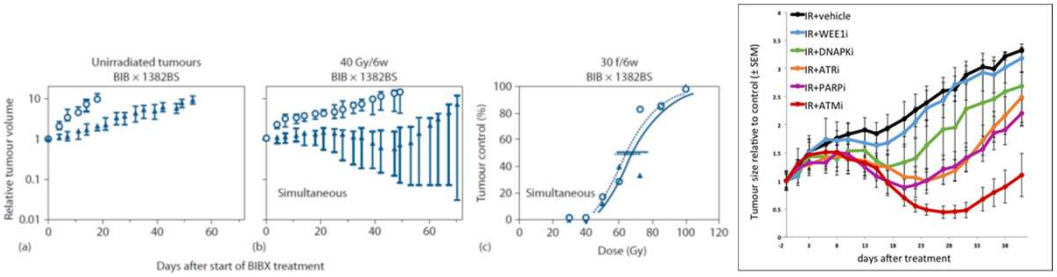
Debbi et al. Crit Rev Oncol Hematol 2025

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Challenge 4: Lack of accurate preclinical models

Growth delay is not cure

EGFR TKI on FaDu HNSCC xenografts



Calu6 lung adenocarcinoma subcutaneous xenografts

Andy Ryan, Oxford unpublished data

Open circles: controls; closed triangles: treated

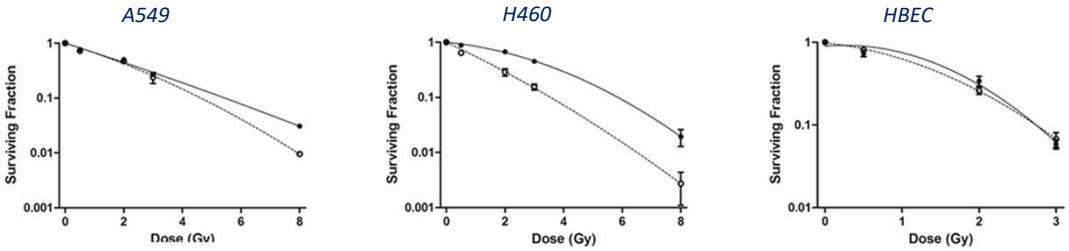
Baumann et al. Radiother Oncol 2002

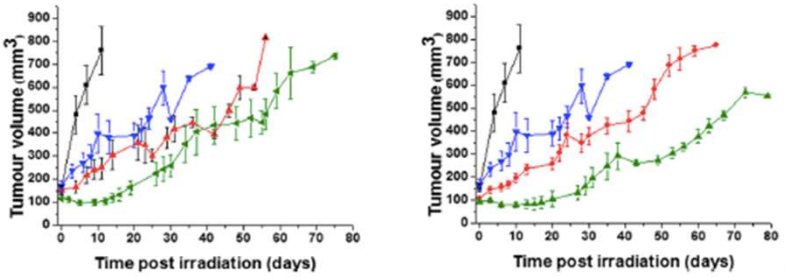
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Challenge 4: Lack of accurate preclinical models

ATR inhibitor AZD6738 variably radiosensitizes NSCLC models





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Dunne et al. Radiat Oncol 2017

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Challenge 4: Lack of accurate preclinical models

Differences between mice and humans: Examples

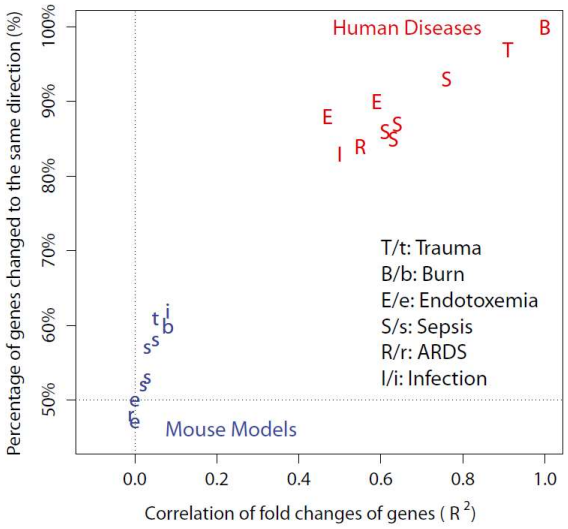
	Mouse	Human
Hemotopoiesis in spleen	Active into adulthood	Ends before birth
Presence of BALT	Significant	Largely absent in healthy tissue
Neutrophils in periph. blood	10–25%	50–70%
Lymphocytes in periph. blood	75–90%	30–50%
Hemotopoietic stem cells	c-*kit*^{high}, *flt-3*$^{-}$	c-*kit*^{low}, *flt-3*$^{+}$
TLR2 expression on PBL	Low (induced on many cells including T cells)	Constitutive (but not on T cells)
TLR3	Expressed on DC, Mac. Induced by LPS	Expressed by DC. No LPS induction
TLR9	Expressed on all myeloid cells, plasmacytoid DC and B cells	Expressed only on B cells, plasmacytoid DC and N
TLR10	Pseudogene	Widely expressed
Sialic acid Neu5GC expression	Widespread	Absent
CD4 on macrophages	Absent	Present
Predominant T cells in skin and mucosa	γ/δ TCR (dendritic epidermal T cells—DETC)	α/β TCR
γ/δ T cells respond to phospho-antigens	No	Yes

De Ruysscher et al. Radiother Oncol 1990; Eur J Cancer 1992
Mestas et al. J Immunol 2004
Fan et al. Signal Transduct Target Ther 2023

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Comparison of the genomic response to severe acute inflammation from different etiologies in human and murine models



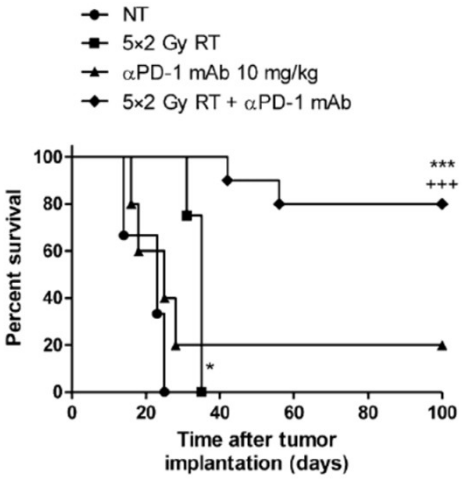
Seok J et al. PNAS 2013

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Challenge 4: Lack of accurate preclinical models

Resistance for radiation can be overcome by concurrent PD-L1 blockage

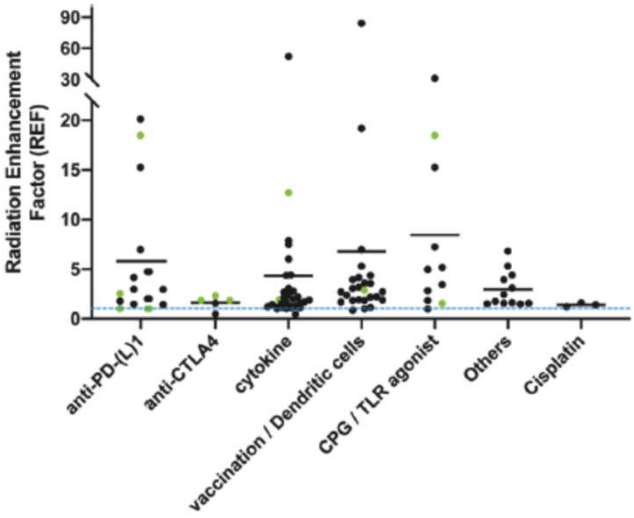


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Dovedi et al. Cancer Res 2014

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Immunotherapy as radiosensitizer? Preclinical data



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Vanneste et al. Oncoimmunol 2020

nature cancer

Article

https://doi.org/10.1038/s43018-026-01161-y

Nivolumab plus chemoradiotherapy followed by nivolumab with or without ipilimumab for untreated locally advanced stage III NSCLC: a randomized phase 3 trial

Received: 13 August 2025

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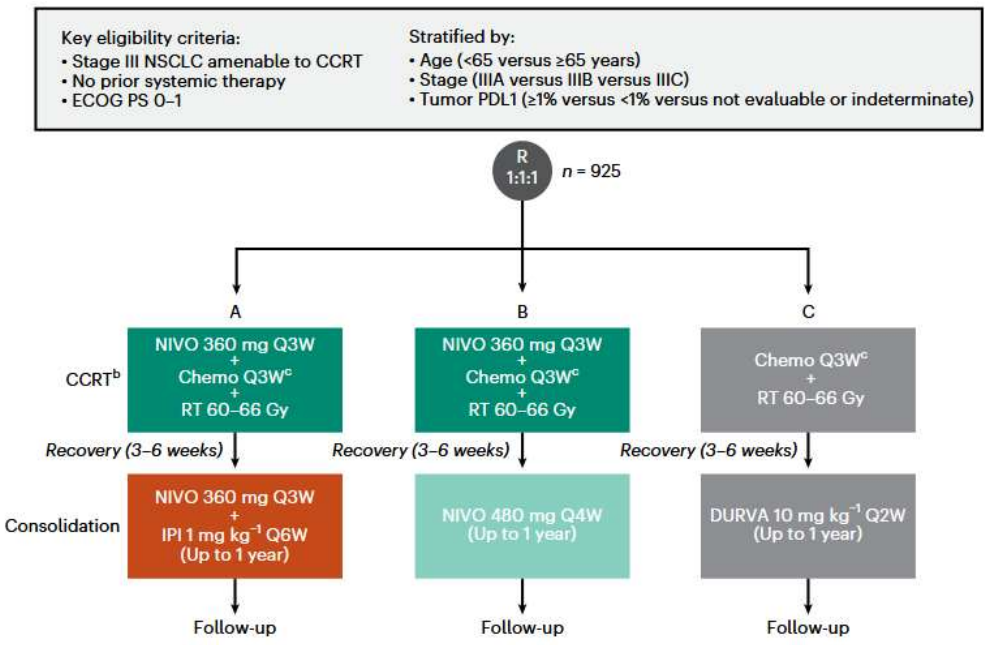
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Solange Peters[1], Daniel S. W. Tan[2,3], David E. Gerber[4], James Urbanic[5], Suresh Ramalingam[6], Jinming Yu[7], Ligang Xing[7], Achim Rittmeyer[8], Tudor-Eliade Ciuleanu[9], Juliana de Menezes[10], Hye Ryun Kim[11], Carlos Rojas[12], Konstantinos Syrigos[13], Hidetoshi Hayashi[14], Anoop Haridass[15], Diego Cortinovis[16,17], Debora Bruno[18], Martin Kimmich[19], Antonio Calles[20], Raheel Nathani[21], Geetha Pudussery[21], Luoying Yang[21] & Dirk De Ruysscher[22]

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Peters et al. Nature Cancer 2026

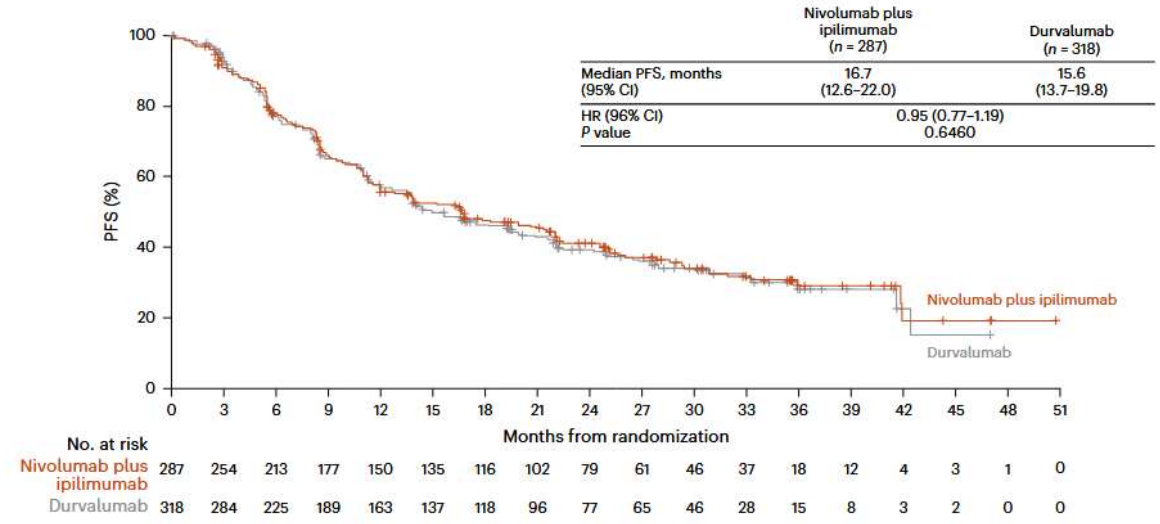
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Peters et al. Nature Cancer 2026

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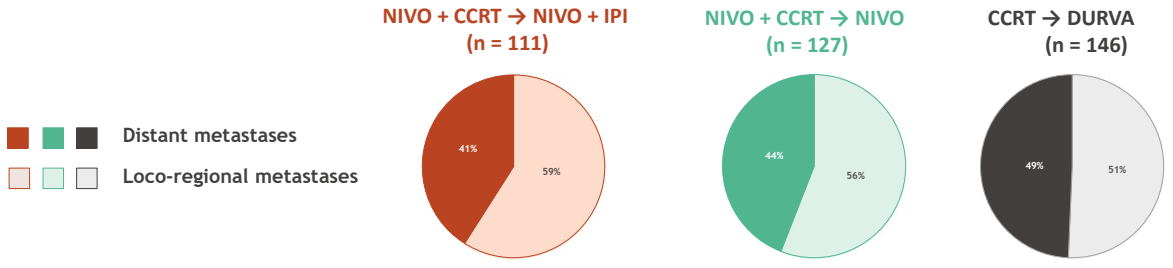
Peters et al. Nature Cancer 2026

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CheckMate 73L: NIVO + CCRT → NIVO ± IPI in unresectable stage III NSCLC

Patterns of progression and subsequent anticancer treatment

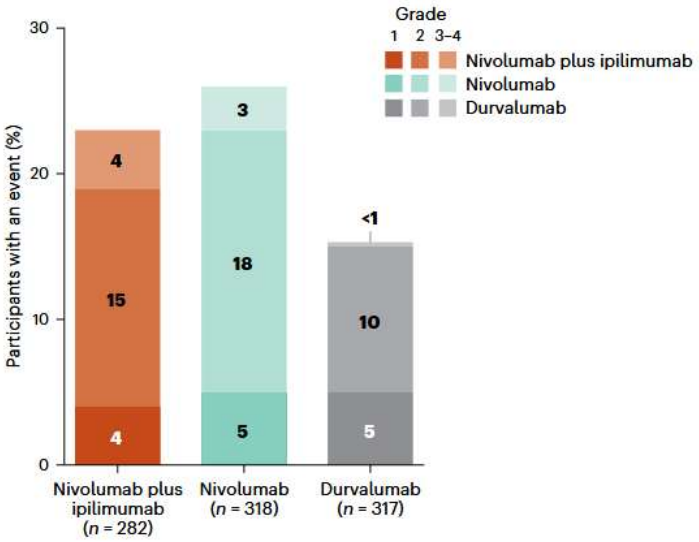
- 111/287 (39%) patients had progression in the NIVO + CCRT → NIVO + IPI arm; 127/320 (40%) and 146/318 (46%) had progression in the NIVO + CCRT → NIVO and CCRT → DURVA arms, respectively



Patients, %	NIVO + CCRT → NIVO + IPI (n = 287)	NIVO + CCRT → NIVO (n = 320)	CCRT → DURVA (n = 318)
Any subsequent therapy	25	25	39
Any subsequent radiotherapy	2	12 (4)	4
Any subsequent surgery	< 1	1 (< 1)	< 1
Any subsequent systemic therapy	24	24	31

[a]Patient may have received more than one type of subsequent therapy. Cancer-related therapy initiated after or on first dosing date (or randomization date if patient was never treated).

Pneumonitis per treatment arm



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Peters et al. Nature Cancer 2026

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For the combination of PD-(L)1 inhibitors with radiotherapy to the:				
Irradiated area	**Radiotherapy scenario**	**Recommendation**	**Agreement rate[a]**	**Level of evidence**
Skin	Low-dose palliative	Minor/no adaptation	100%	I[b]
	High-dose conventionally fractionated	Minor/no adaptation	100%	I
	High-dose stereotactic	Minor/no adaptation	100%	III
Brain	Low-dose palliative	Minor/no adaptation	100%	III[b]
	High-dose conventionally fractionated	Minor/no adaptation	100%	V
	High-dose stereotactic	Minor/no adaptation	100%	III
Head & neck	Low-dose palliative	Minor/no adaptation	100%	II[b]
	High-dose conventionally fractionated	Minor/no adaptation	95%	II
	High-dose stereotactic	Minor/no adaptation	95%	V
Thorax	Low-dose palliative	Minor/no adaptation	100%	I[b]
	High-dose conventionally fractionated	Minor/no adaptation	100%	I
	High-dose stereotactic	Minor/no adaptation	100%	II
Abdomen/pelvis	Low-dose palliative	Minor/no adaptation	100%	III[b]
	High-dose conventionally fractionated	Minor/no adaptation	100%	III
	High-dose stereotactic	Minor/no adaptation	100%	III
Musculoskeletal tissues	Low-dose palliative	Minor/no adaptation	100%	I[b]
	High-dose conventionally fractionated	Minor/no adaptation	100%	I
	High-dose stereotactic	Minor/no adaptation	100%	III

Journal Pre-proof

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van Aken et al. Ann Oncol 2025

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FDA NEWS RELEASE

FDA Announces Plan to Phase Out Animal Testing Requirement for Monoclonal Antibodies and Other Drugs

More Press Announcements

For Immediate Release: April 10, 2025

Today, the U.S. Food and Drug Administration is taking a groundbreaking step to advance public health by replacing animal testing in the development of monoclonal antibody therapies and other drugs with more effective, human-relevant methods. The new approach is designed to improve drug safety and accelerate the evaluation process, while reducing animal experimentation, lowering research and development (R&D) costs, and ultimately, drug prices.

Content current as of:
04/10/2025

Regulated Product(s)
Biologics
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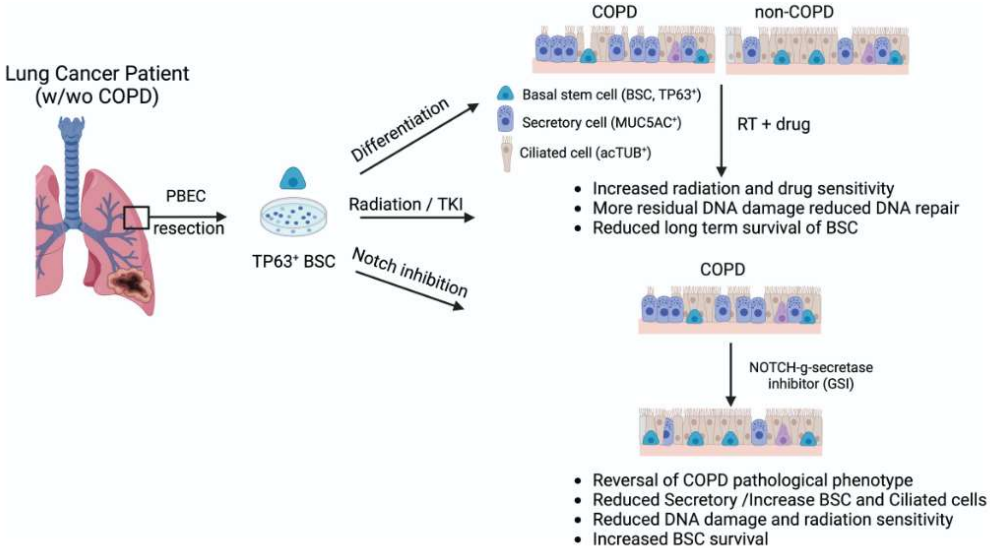
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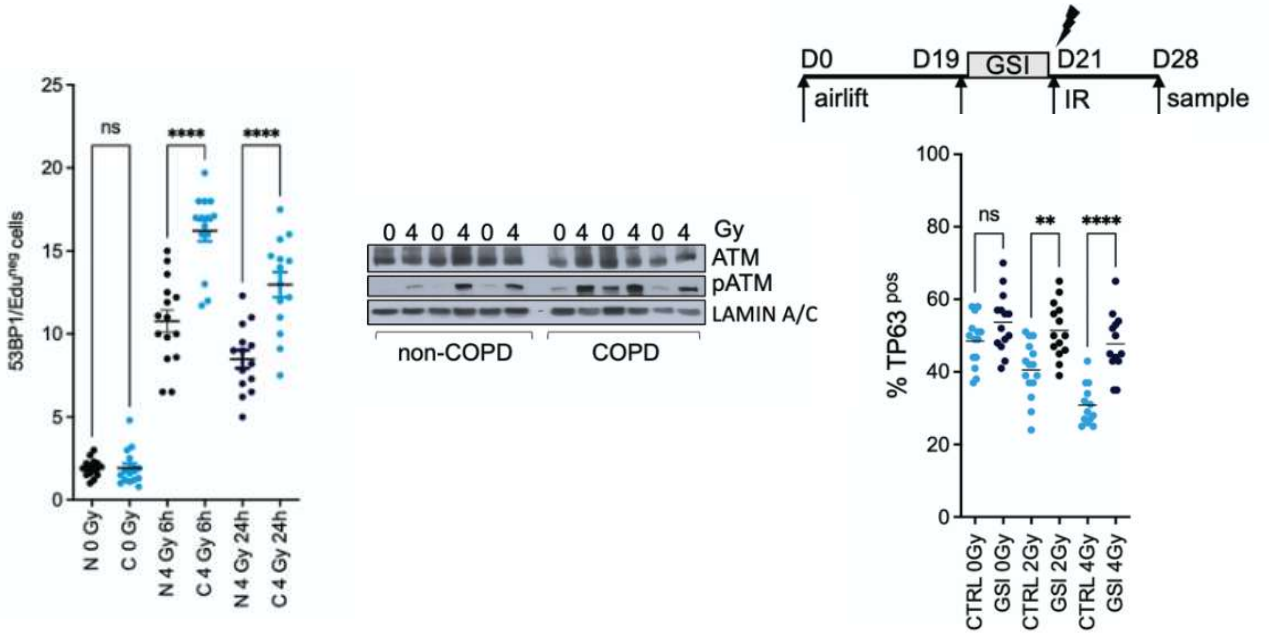
Ex-vivo predictive tests



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Giuranno L et al. Stem Cells Transl Med 2024

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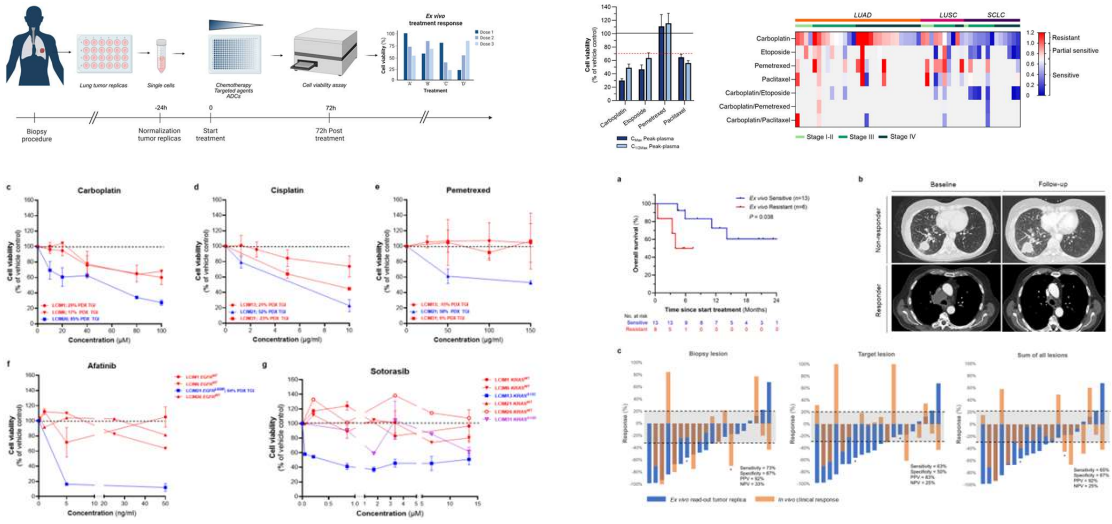


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Giuranno L et al. Stem Cells Transl Med 2024

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Ex-vivo predictive tests on tumor replica's



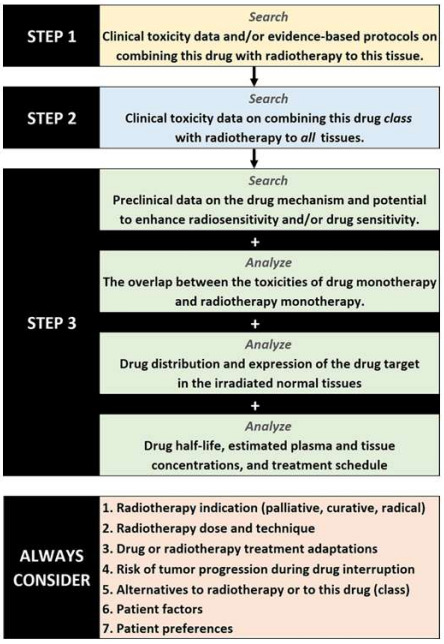
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Vaes et al. NPJ Precision Oncology 2026

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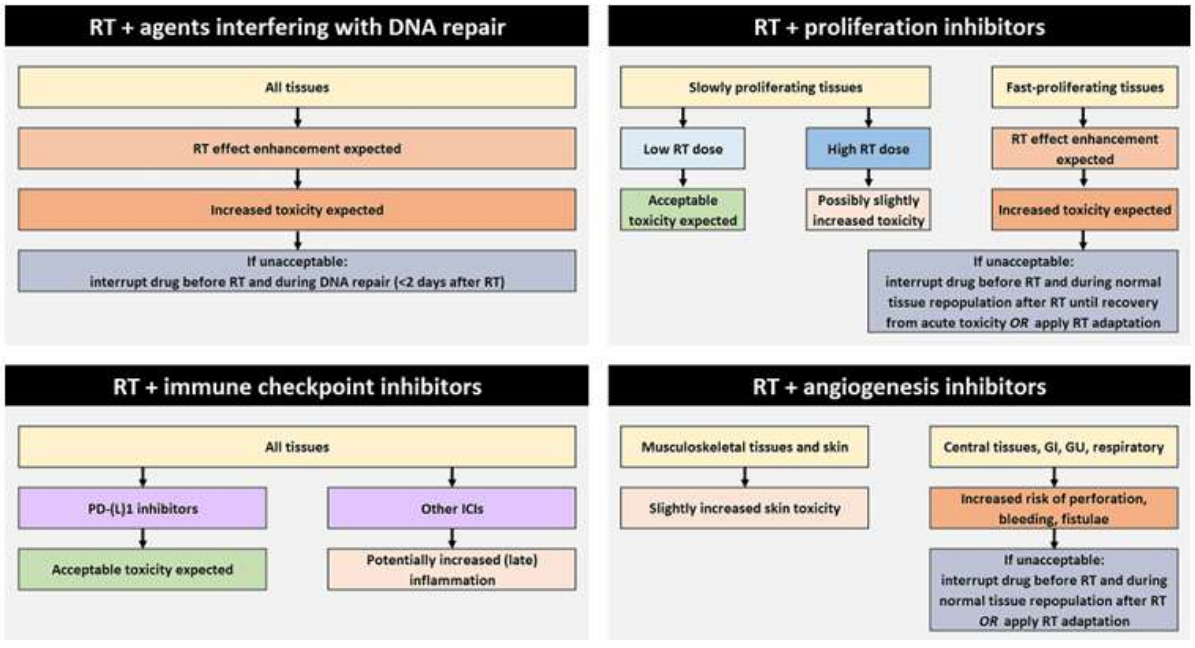
What to do in the mean time?



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van Aken et al. Radiother Oncol 2025

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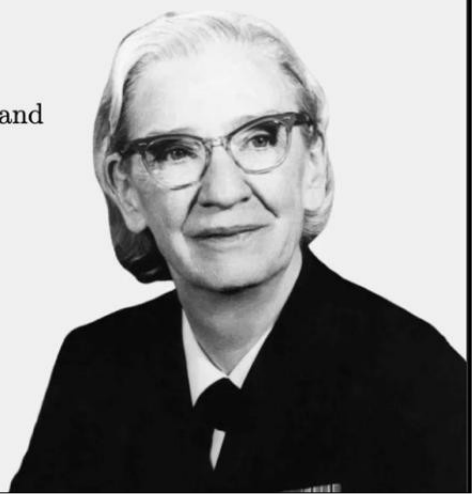
Conclusions

- Highly rational to combine radiotherapy with medication
- Lack reliable preclinical models to investigate combinations (tumor and normal tissues and organs)
- Too many combinations to test in clinical trials
- “Real world” data not reliable enough (‘phase IV”) and *not ethical* if that is all we can do: We should be more ambitious
- Need for the development of ex-vivo human systems

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One accurate measurement is worth a thousand expert opinions.

- Grace Hopper



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