Combining Immunotherapy with Radiation: A Double Edged Sword

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Roadmap

- Basics about immunity and immune cells
- Cancer immunity and immune tolerance
- Effect of radiation on immunity and synergism
- Double edged swords
- Evidence from preclinical trials
- Clinical evidence
- Way forward

Immunity

Innate immune response

The first line of defense, it identifies and attacks tumor cells without antigen specificity. **Natural killer (NK) cells** are the main effector cells of innate immunity.

Adaptive immune response

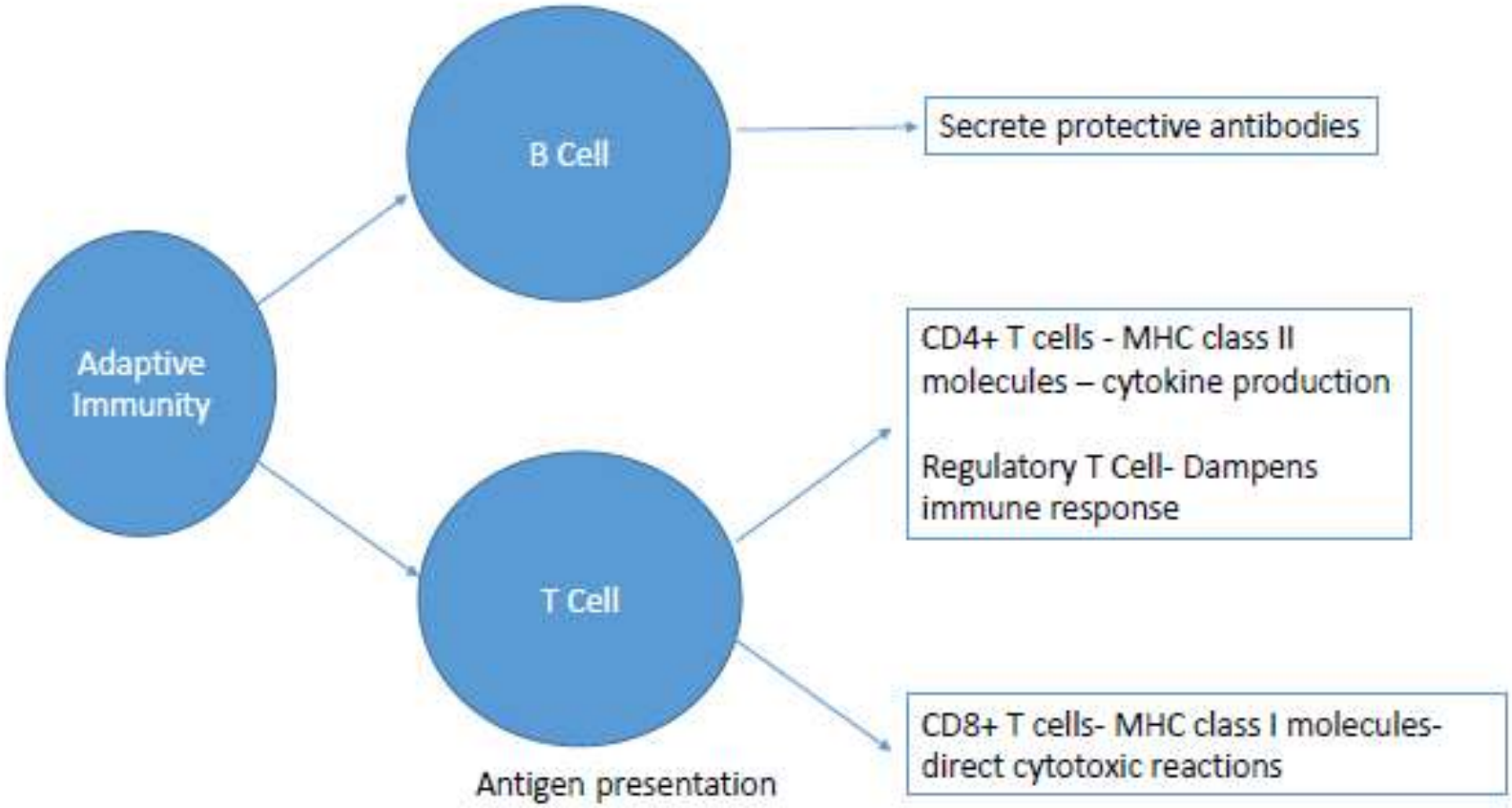
A durable response that attacks tumor antigens. Once activated, it can be sustained through a memory response. **Cytotoxic T cells** are the main effector cells of adaptive immunity.

The antitumor activity of NK cells and cytotoxic T cells is regulated through a network of activating and inhibitory signaling pathways:

⊕ **ACTIVATING**
Stimulating pathways trigger immune responses

⊖ **INHIBITORY**
Pathways that counterbalance immune activation such as checkpoints

Immune surveillance

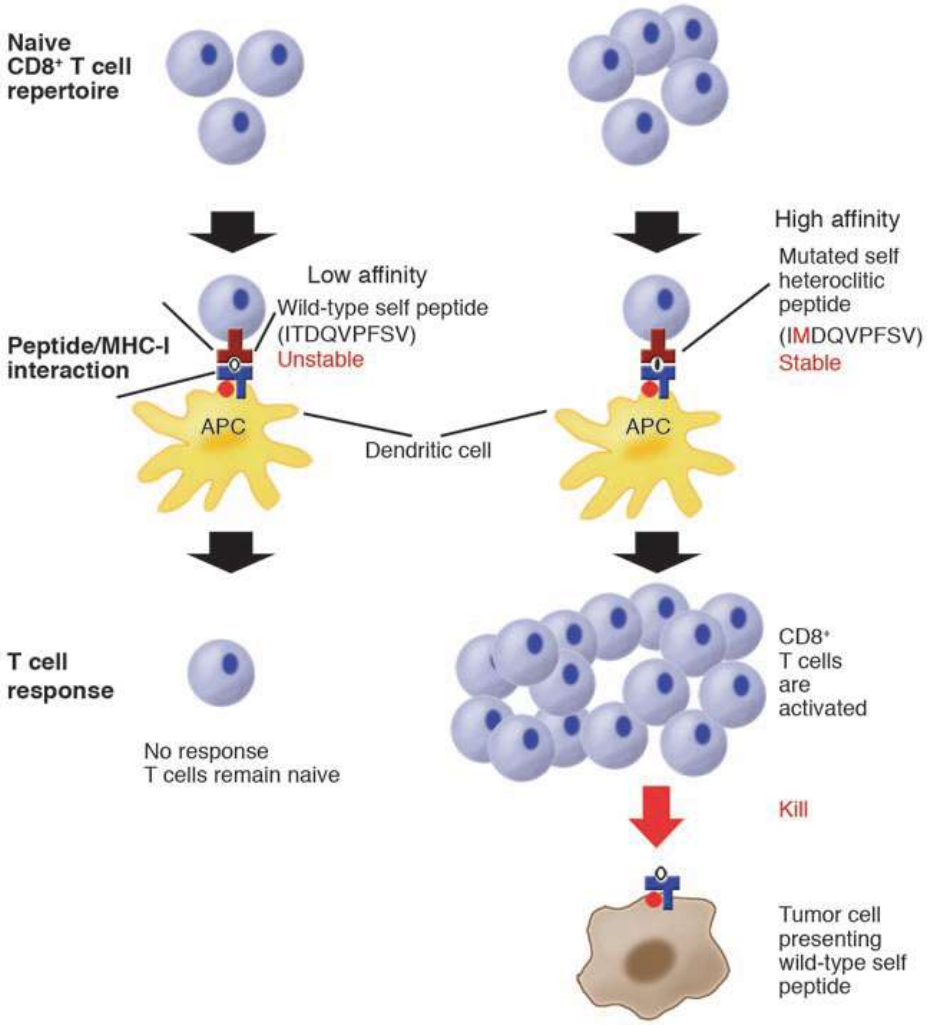


Cancer – self/ non self

- Cancers accumulate a range of genetic and molecular alterations affecting their functional properties
- Mutations in driver genes, chromosomal instability, and epigenetic alterations impact pathways related to cell signaling, metabolism, and apoptosis

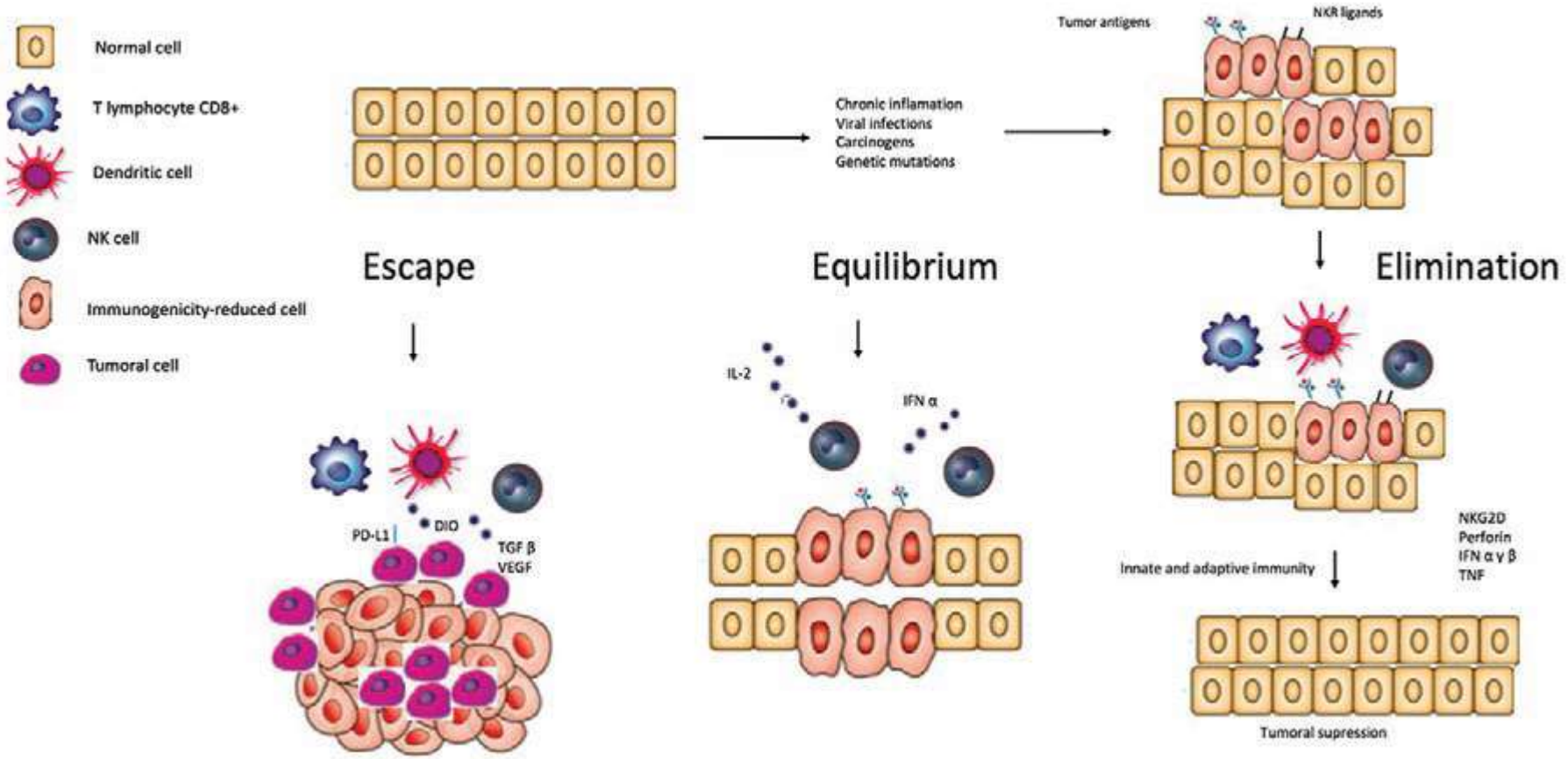
Category	TAA	Tumour
Unique tumour-specific antigens	Mutant p21/ras Immunoglobulin idiotype ß-catenin Mutant p53 CDK4 Mutant EGFR VIII CEA	Colorectal, pancreatic B cell malignancy Colorectal, breast Pancreatic Melanoma Glioblastoma, lung Colorectal
Overexpressed self-antigen peptides	Muc-1 GA733/EpCam Her-2/neu EGF Receptor	Colorectal Colorectal Breast Colorectal, lung, head, and neck
Shared tumour antigens	Melanoma antigen E (MAGE) tumour-associated antigen	Melanoma
Viral-associated antigens	Human papilloma virus (HPV) Hepatitis B virus (HBV) Epstein-Barr virus (EBV)	Cervical Hepatocellular B cell malignancy

Immunity and recognition of self

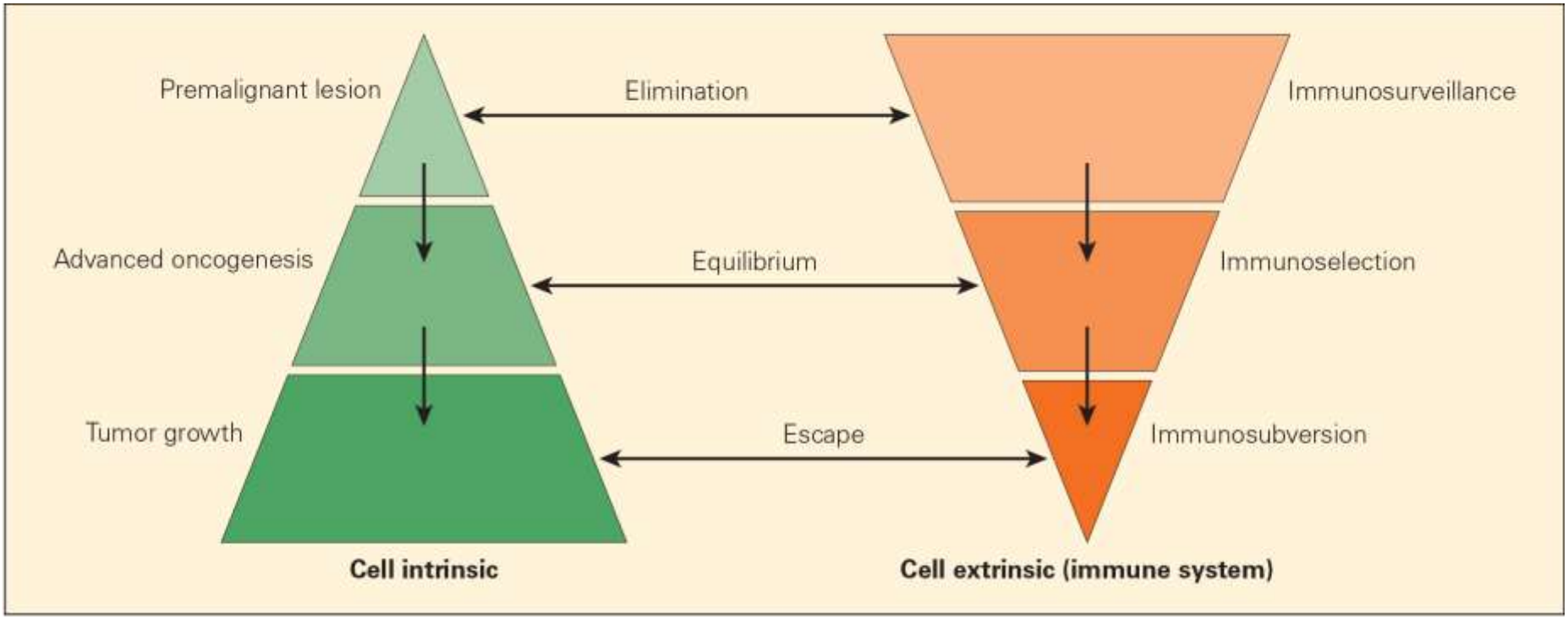


- Any immature T cell with high-affinity TCRs for a self antigen is deleted during its early development in the thymus
- Self-reactive T cells that have TCRs with relatively low affinity for self antigens
- However, these weak self antigens form unstable binding with MHC - incapable of inducing immune responses
- Mutated self peptide activates the T cells by binding strongly to MHC molecules on APC - strong immune response

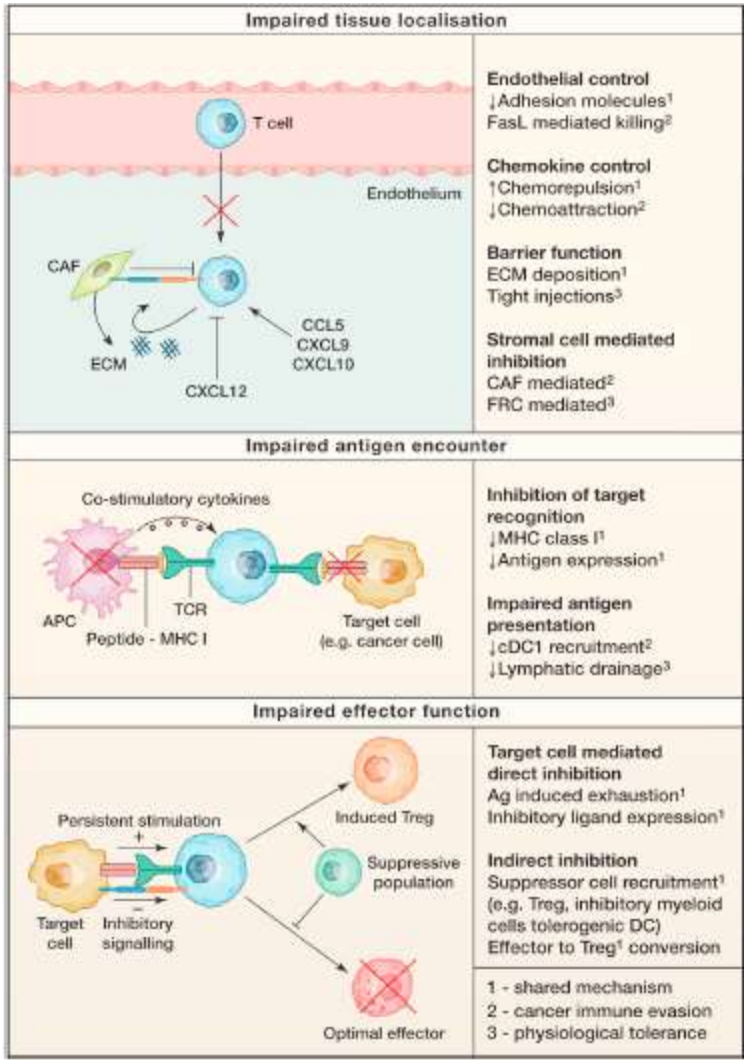
Immuno- editing



So who wins? - Cancer Immunoediting

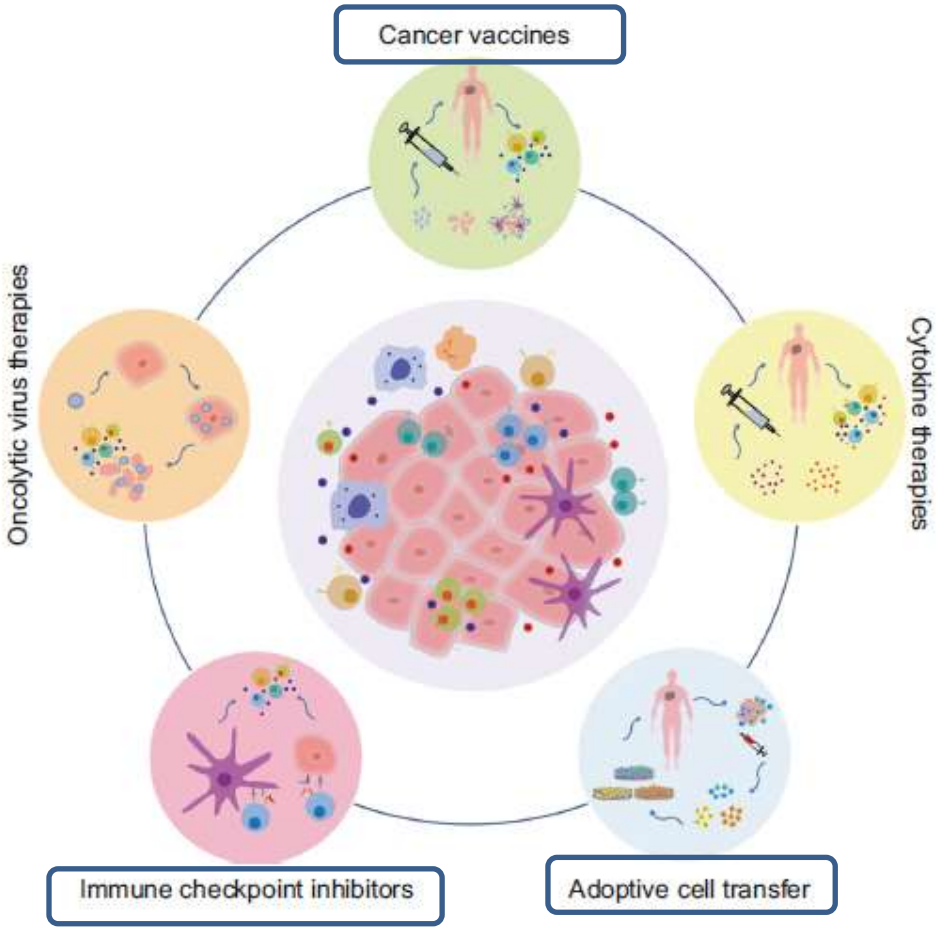


Pillars of Cancer immune tolerance



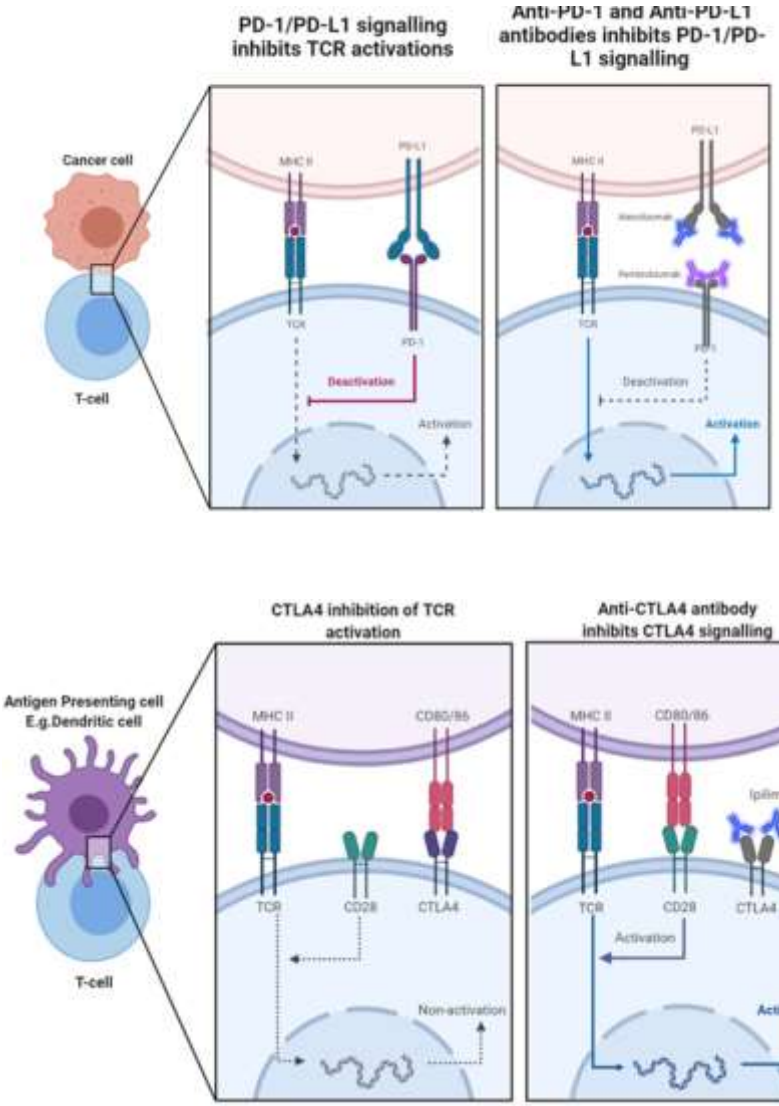
- Cancer cell control over T cell localization
  - Endothelial dysfunction
  - Stromal inhibition of T cell recruitment
  - Reduced production of chemokines involved in T cell recruitment
- Inhibition of target recognition
  - Suppression of MHC class I expression
  - Immune escape via suppression of neoantigen expression
  - Impaired target recognition through suppression of DC recruitment
- Limiting the attainment of optimal T cell effector function
  - Persistent stimulation and Ag induced exhaustion
  - Effector diversion and recruitment of suppressive populations
  - Direct induction of T cell death and co-inhibitory signaling

Immunotherapy options in modern day practice



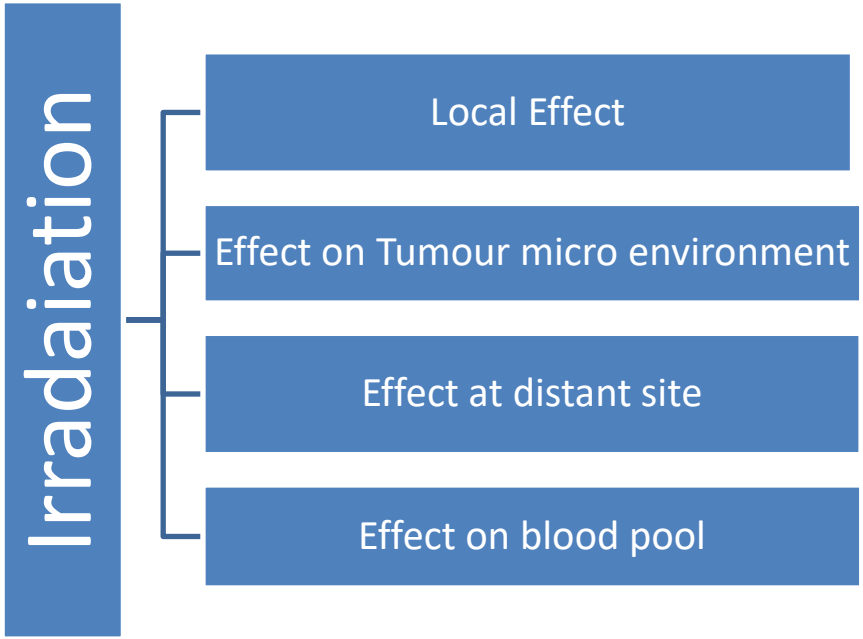
Immune check point inhibitors

- Cancer cells secrete cancer-associated antigens that are captured by APCs through the MHC-I molecule
- APCs then activate T cells, which in turn kill cancer cells
- However, immune checkpoints that are expressed on cancer cells and cancer-specific lymphocytes can inhibit T cell activation
- Activation of T cells requires the interaction between CD28 expressed on T cells and B7 on APC, CTLA-4 on T cells binds B7, competing with CD28, and suppresses T cell activation
- The interaction between PD-1 and its ligand PD-L1 induces T cell exhaustion.
- Immune checkpoint inhibitors (ICIs) are monoclonal antibodies that specifically target immune checkpoints and inhibit/blocks them



Radiation and Immunity

Effects of IR on immune response



- triggers the release and presentation of tumor-associated antigens (TAAs)
- enhance systemic responses by triggering the recruitment of antigen-presenting cells (APCs), such as macrophages, dendritic cells (DCs), and B cells
- enhance T-cell infiltration and promote anti-tumor immune responses in the host

The immune effect of RT

- COLD TME - Down regulating their immunogenic surface markers such as major histocompatibility complex-1 and Fas
- RT is able to reverse this immunosuppressive effect by acting as an *in-situ* vaccine
- the release of tumor antigens into the TME that are then engulfed by antigen-presenting cells

Radiation Activation of the the cGAS-STING Pathway

- STING is essential to protect hosts from DNA pathogens
- When the presence of cytoplasmic DNA is detected, the product of cyclic GMP-AMP synthase (cGAS), cyclic GMPAMP (cGAMP), activates STING
- Upregulate transcription of a type I interferon gene through a STING-TBK-IRF3-NFκB signaling pathway
- Activates type I interferon dependent antitumor immunity

Tumour associated neutrophils

Anti tumorigenic - N1	Pro-tumorigenic - N2
• IFN-β polarizes neutrophils to an antitumorigenic phenotype (N1) while inhibits N2 polarization • promotes tumor cell cytotoxicity/apoptosis, strengthens the (ADCC), and activates T cells	• TGF-β, polarizes neutrophils to a protumorigenic phenotype (N2) and inhibits N1 phenotypic polarization • promotes tumor growth, stemness, angiogenesis, invasion, and suppression of immunity

Action 1 ; RT has also been demonstrated as an inhibitor of the TGF-β pathway, thereby stimulating the antitumor-N1 neutrophil phenotype polarization

Action 2. : RT may promote the conversion of N1 to N2

Wisdom and his colleagues found that elevated neutrophil levels have a close relation to poor outcome of patients with cervical cancer after chemoradiation. Similarly, others have found that genetic depletion of neutrophils improves RT response in a genetically engineered mouse model of sarcoma

Tumour associated Macrophages

Tumour killing phenotype M1

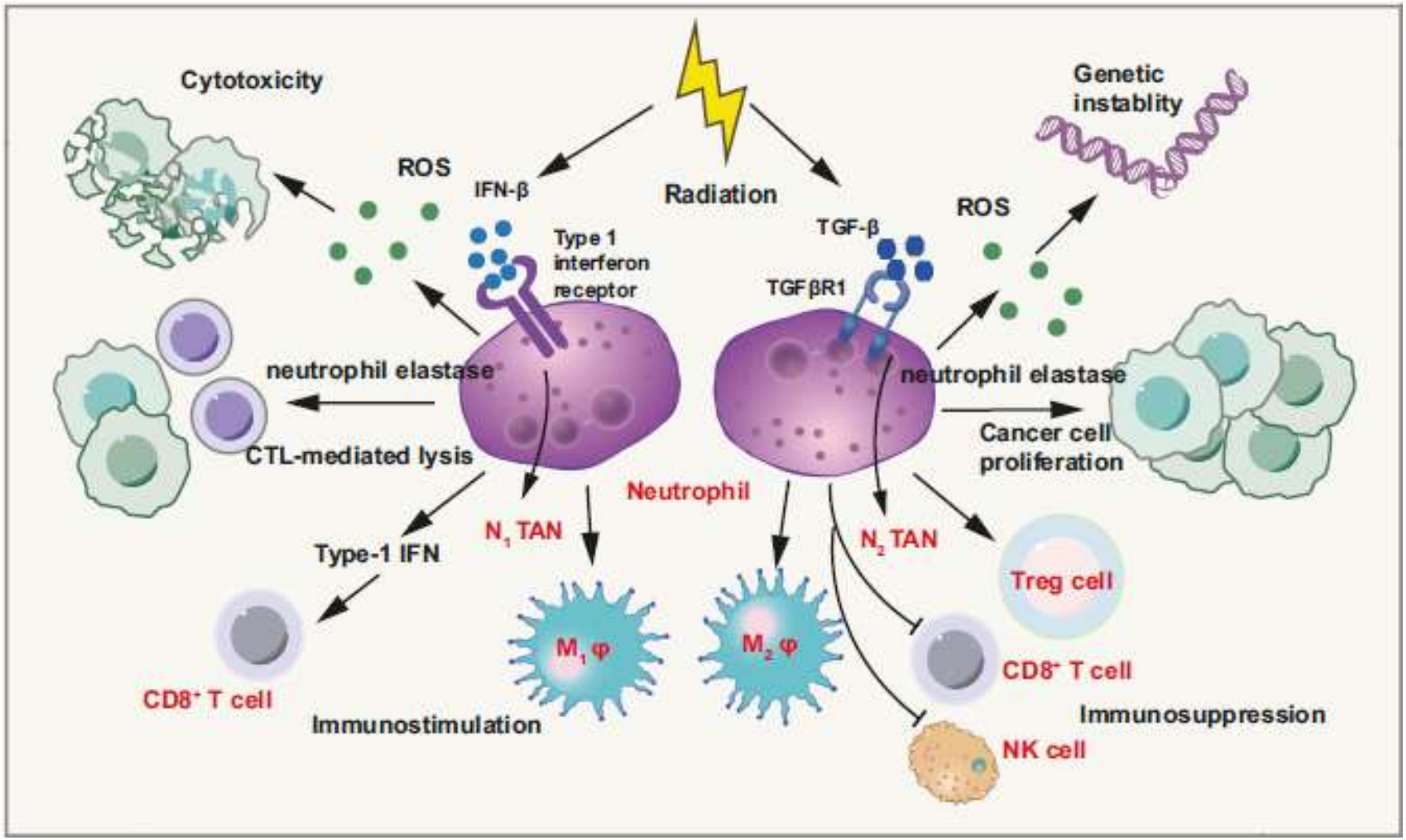
- In Vitro : high-dose IR may promote the polarization to M1

Tumour promoting phenotype M2

- low-dose IR may polarize to M2 phenotype

- There are conflicting results of Dose dependent polarisation, with polarisation to M1 occurring both with 10Gyx2# and 2Gy x10# (Meng et al)
- Conflicting results may reflect the complexity and plasticity of TAMs
- The mechanisms about the effects of radiation dose on the polarization of TAMs remain unclear : ROS, NF-.B signaling, and MAPK phosphorylation
- Critical mechanisms is the NF-.B balance-that p50–p50 NF-.B homodimer may promote the polarization towards M2 macrophages while p50–p65 NF-.B heterodimer favors the polarization towards M1 macrophages

Double edged sword



Radiation – double edged sword

- Radiation induce immunogenic tumor cell death and release of tumor-specific antigens
- local release of inflammatory cytokines
- Local release of DAMP resulting in local effects on endothelial cell expression of adhesion receptors
- production of type 1 IFN induce recruitment of effector T cells and APCs

- immune cell trafficking

- immune cell activation

- RT causes delayed increases in tumor infiltration by suppressive regulatory T cells

- RT can also drive recruitment of myeloid-derived suppressor cells

- Increased infiltration and activation of inhibitory macrophage and myeloid-derived suppressor cell lineages
- Additionally, prolonged activation of type 1 and 2 interferon can drive expression of ligands for multiple T cell inhibitory receptors

Dose fractionation of RT and immune Effects

Fractionation and Immune activation

Conventional fractionation (i.e. 1.8–2 Gy per fraction)

- stimulates pro-inflammatory factor secretion
- favors migration and maturation of immune cells
- activates cGAS-STING pathway
- induces upregulation of regulatory T cells and PDL1
- accumulation of immunosuppressive myeloid cells Death of tumor-infiltrating immune cells

Stereotactic schedules (>12–15 Gy / fraction)

- enhance the immune system by presenting many more antigens
- increases the levels of TREX1, an exonuclease that degrades dsDNA, causing ↓immune response Demaria S et al., Francolini G et al.

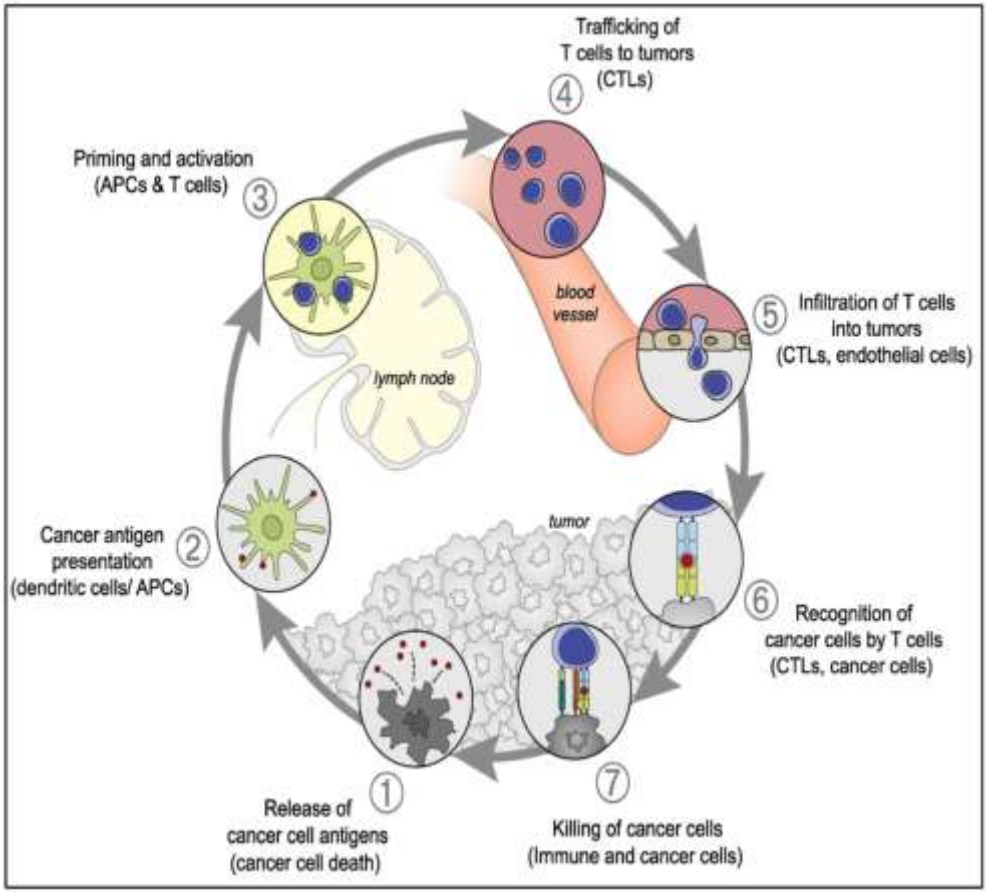
Hypo RT (6 Gy× 5# or 8 Gy × 3 #)

- superior dose in promoting anti-tumor immune response Dewan et al.

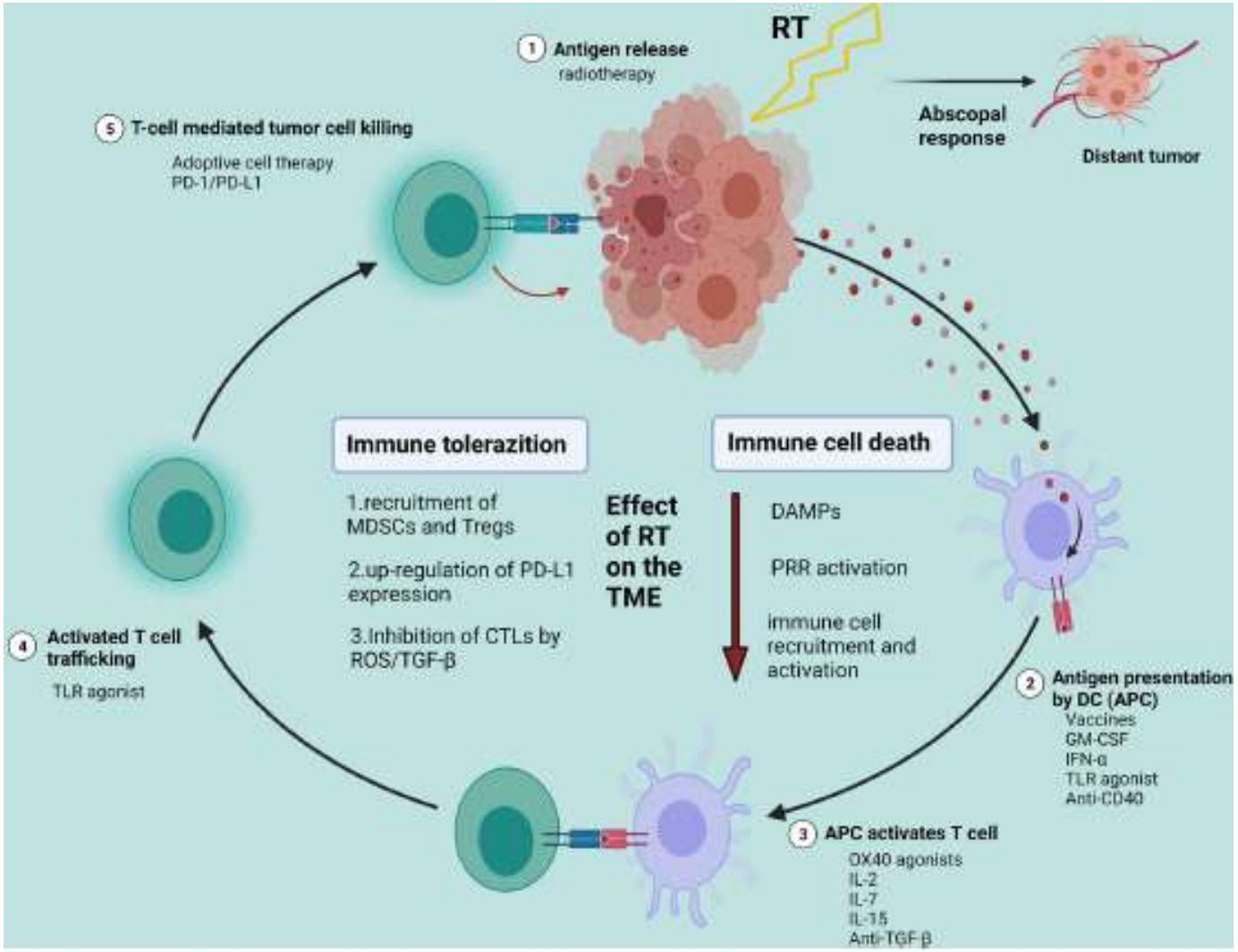
Combining RT and immunotherapy

Biological rationale for iRT

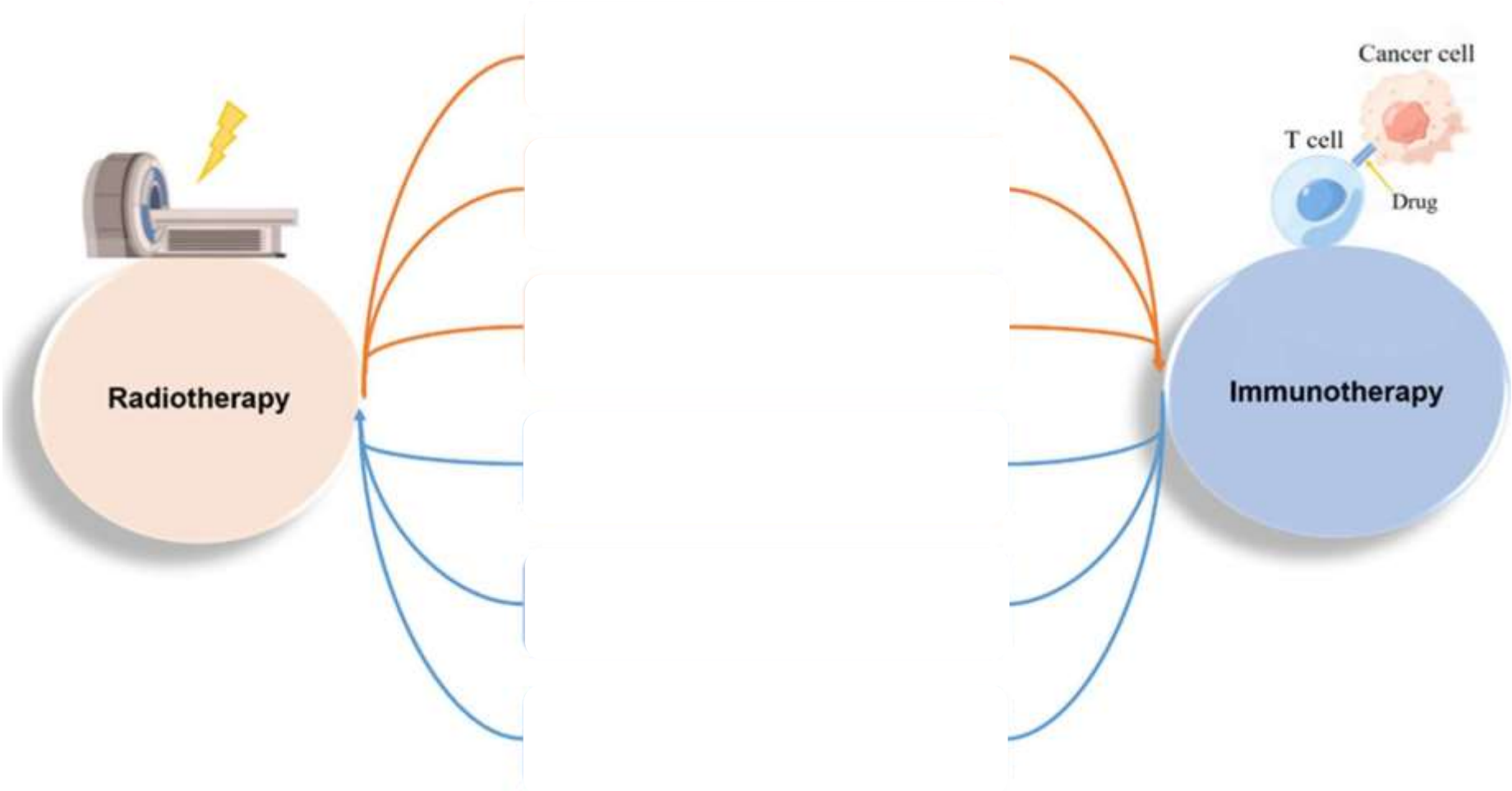
- RT exerts potent antitumor immune response : influences almost all steps in the cancer-immunity cycle.
- Stress response induced by RT – Release of DAMPs-cellular response driven by DNA damage changes the immunogenicity of the irradiated cancer cells.
- Reprogrammed tumor microenvironment(TME) induced by RT plays a role as a “game changer” to transform “cold” tumors into “hot” tumors -a pre-requisite for response to IC



Effects of radiotherapy on the TME & potential strategies for the combination



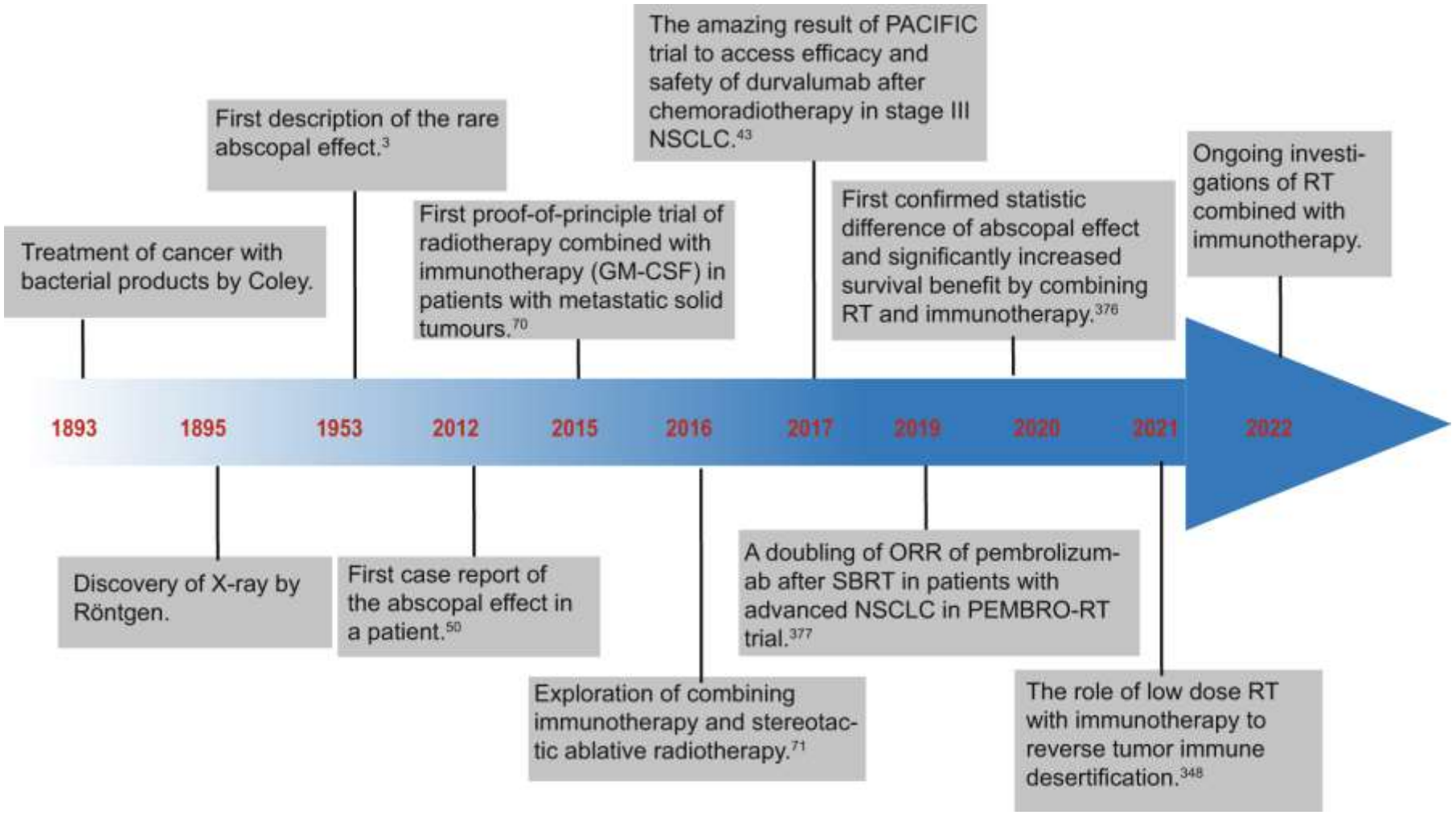
Mechanism of interaction between radiotherapy and immunotherapy



Options

- Combination of Immune Checkpoint Inhibitor Therapy and Radiotherapy
- Combination Therapy Between Cytokine Therapy and RT
- Combination Therapy Between Adoptive Cell Therapy and RT
- Combination Therapy Between Tumor Vaccine and RT

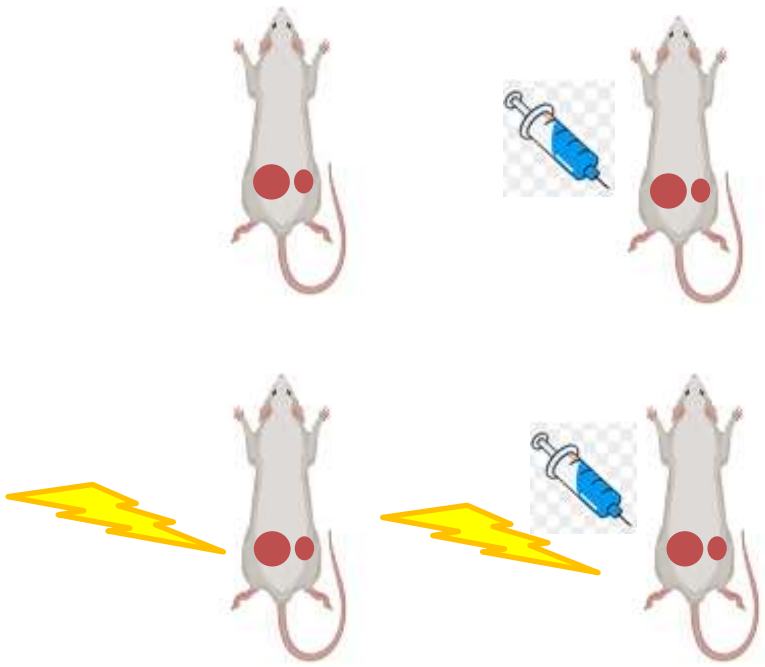
Historical timeline



Combination Therapy Between Cytokine Therapy and RT

‘Proof of principle’ trial

Mice were injected s.c. with 10^5 (“primary” tumor) and 10^4 (“secondary” tumor) 67NR cells at Day 0. Mice were either left untreated (empty diamonds), were treated with RT (filled diamonds) at Day 20 (arrow) at a single dose of 2 Gy exclusively to primaryt umors, or were given Flt3-L alone (empty circles) i.p. for 10 days **starting at Day 21 or Flt3-L in combination with RT (filled circles**)



Int. J. Radiation Oncology Biol. Phys., Vol. 58, No. 3, pp. 862–870, 2004

0360-3016/04/$–see front matter
doi:10.1016/j.ijrobp.2003.09.012

BIOLOGY CONTRIBUTION

IONIZING RADIATION INHIBITION OF DISTANT UNTREATED TUMORS (ABSCOPAL EFFECT) IS IMMUNE MEDIATED

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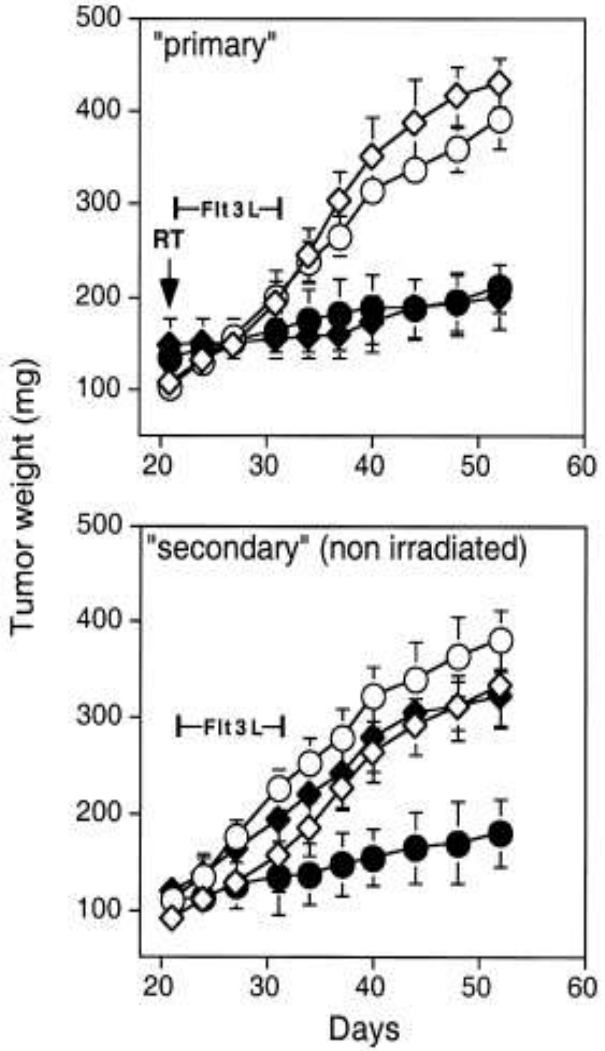


Abscopal effect

- First described in 1953, a researcher named R. H. Mole showed that radiation could shrink a tumor on one side of a mouse and lead to the regression of an untreated tumor on the other side of the animal.
- Latin for “away from the target.”
- The abscopal effect is a systemic immune response mediated by the effects of radiation on the immune system.
- the phenomenon of the abscopal effect has been observed in a variety of tumor types and settings
- The effect was rarely observed and limited to an association with radiation, the recent advent and expansion of immunotherapy have added to a new realm in the observation and benefit of the abscopal effect.

Preclinical trials- ABSCOPAL EFFECT

Tumor model	Therapy	Authors	Year
Hepatocellular	RT+aPDL1	Park et al Int J Radiation Oncol Biol Phys.	2021
Colorectal/melanoma	BO-112+ STING agonist	Alvarez et al. JITC	2021
Melanoma	aPD1+ aCD137+ BO-112	M.A. Aznar et al. Journal for Immunotherapy of cancer	2019
Lung carcinoma	Hypofractionated RT+ aPDL1	H. Wang et al. Immunotherapy	2019
Lymphoma	RT+Flt3L+TLR3 agonist	L. Hammerich et al. Nature Medicine	2019
Lung metastases from breast and colon	SD-101+ aPD1	M. Gallotta et al. Cancer Research	2018
Breast	Hypofractionated RT+aCTLA4	C. Vanpouille-Box et al. Nature Communications	2017
Head&Neck	SD-101/aTLR7+ aPD1	F.S. Kaneko et al. JCI Insight	2017
Colorectal/Melanoma/Breast	RT+aPD1+ aCD137	M.E. Rodriguez-Ruiz et al. Cancer Res	2016
Colon	SD-101+ aPD1	S. Wang et al. PNAS	2016
Lewis Lung	RT+aCD40	Y.Hao et al Physics in med &biology	2016
Mammary	Hypofractionated RT + Flt3L	Habets et al Plos One	2016
Mesothelioma	aCTLA4+ local RT	L. Wu et al Oncotarget	2015
Melanoma/Renal	RT+ aPD1	S.S. Park et al. Cancer Immunol Res	2015
Melanoma	RT+aCTLA4	V. Twyman-Saint et al Nature	2015
Mammary/Colon	RT+aPDL1	Deng et al JCI	2014
Mammary	RT+ECI301	Kanegasaki et al Cancer Res	2014
Colon	RT+ IL2	Yasuda et al Cancer Sci	2011
Breast/Colorectal	Hypofractionated RT+aCTLA4	M.Z. Dewan et al Clin Cancer Res	2009
Mammary	RT+9H10	De Maria et al Clin Cancer Res	2005
Mammary	RT+Flt3-L	Demaria et al Int j radat Oncol Biol Phys	2004
Melanoma/sarcoma MethA	RT+ DC	Teitz-Tennenbaum et al Cancer Res	2003
	RT+ DC	Nikitina et al Int J cancer	2001

RT: Radiation Therapy; aPDL1: anti-Programmed Death-Ligand 1; aPD1: anti-Programmed cell Death protein 1; aCD137: anti-CD137; Flt3L: FMS-like tyrosine kinase 3 Ligand; TLR3: Toll-Like Receptor 3; aCTLA4: Cytotoxic T-Lymphocyte Antigen 4; aTLR7: anti-Toll Like Receptor 7; aCD40: anti-CD40; DC: Dendritic Cells.

Local radiotherapy and granulocyte-macrophage colony-stimulating factor to generate abscopal responses in patients with metastatic solid tumours: a proof-of-principle trial

Encouse B Golden, Arpit Chhabra, Abraham Chachoua, Sylvia Adams, Martin Donach, Maria Fenton-Kerimian, Kent Friedman, Fabio Ponzo, James S Babb, Judith Goldberg, Sandra Demaria, Silvia C Formenti

Lancet Oncol 2015

41 patients with solid tumours

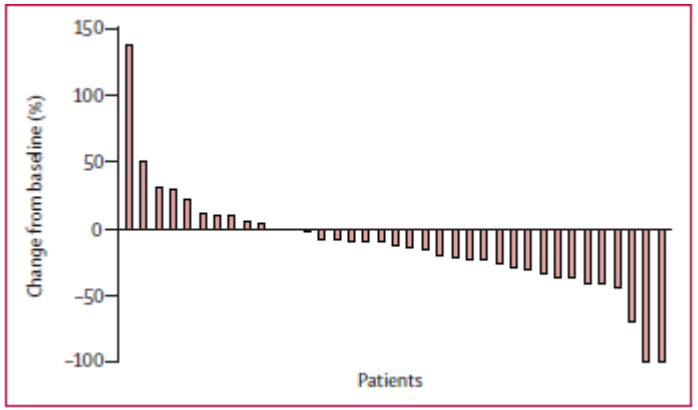
35Gy/10# to one site

GM CSF simultaneously

35 Gy to second site

Measured response at 3 sites

11 /41 patients had response



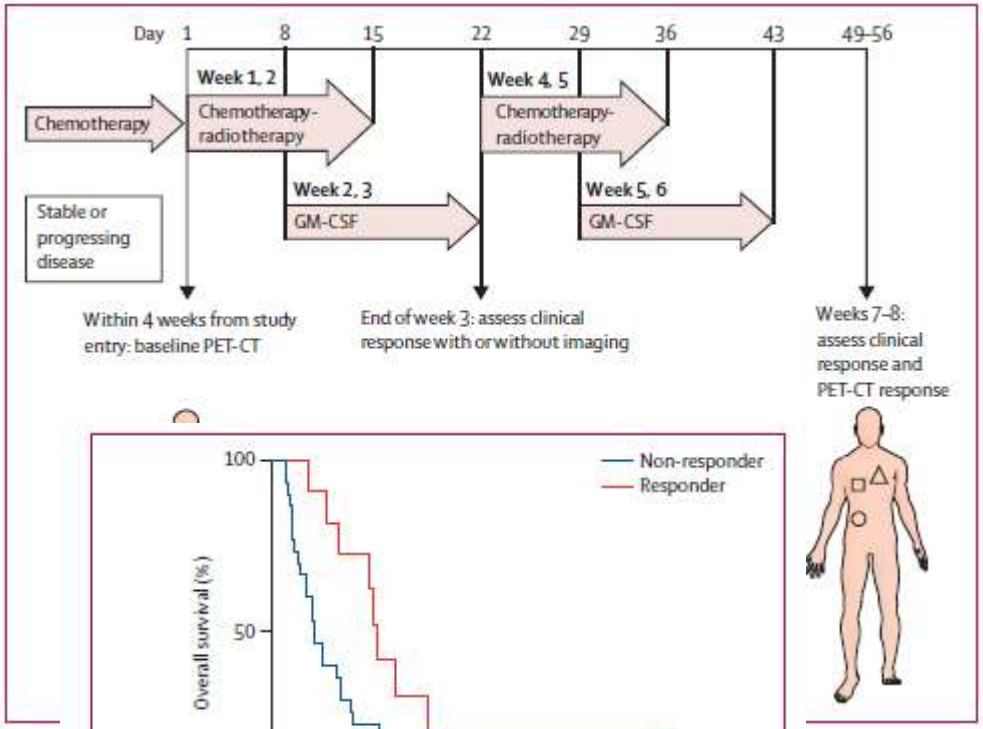
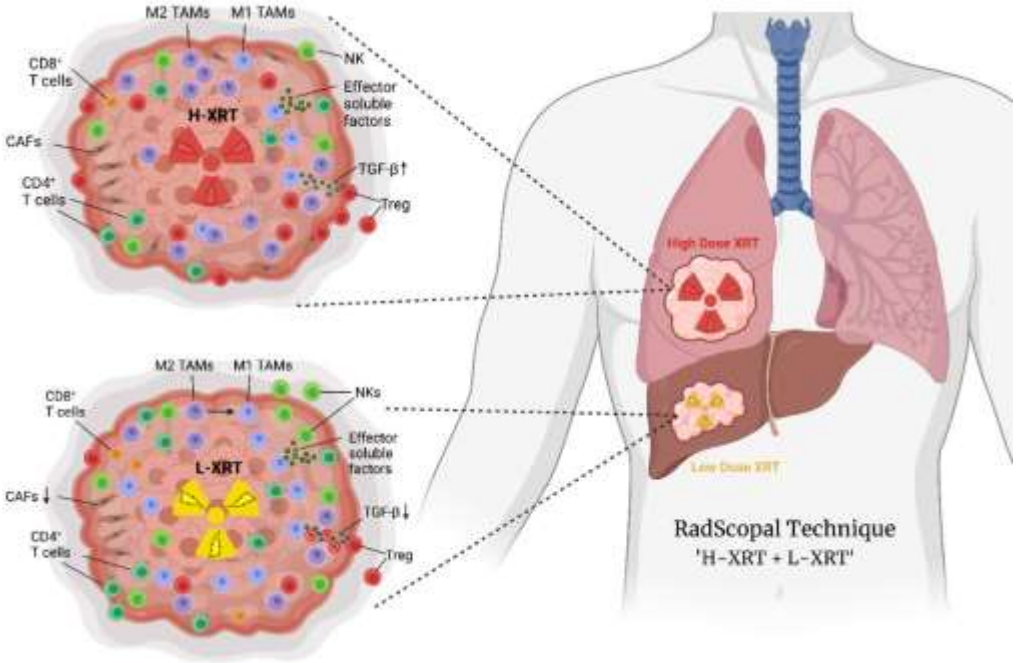


Figure 3: Overall survival for abscopal responders and non-responders in an intention-to-treat analysis

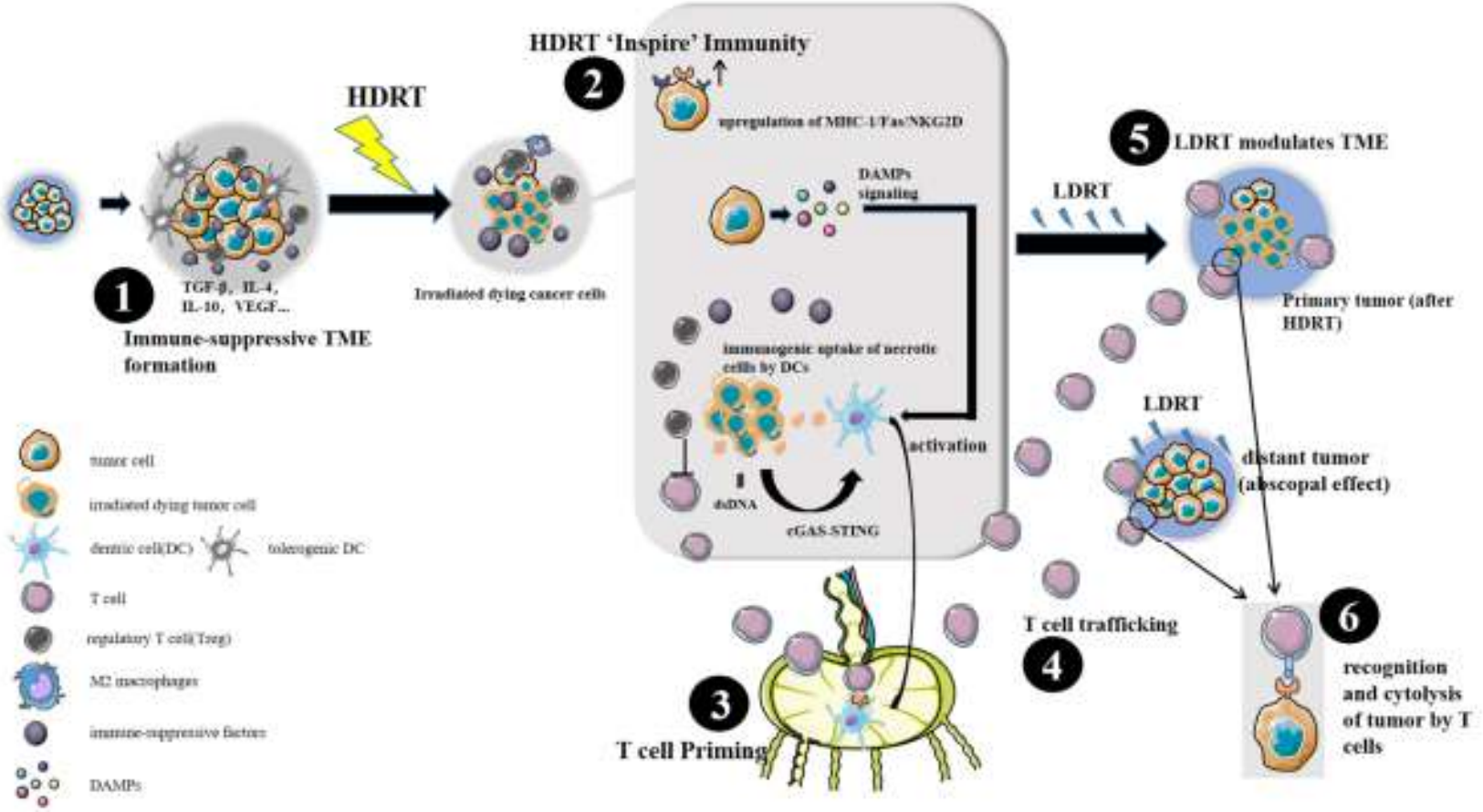
‘Pr ial

The RadScopal technique

RadScopal is a unique technique where H-XRT is applied to a primary tumor and
L-XRT is applied to secondary tumor(s) in patients undergoing or who have progressed on immunotherapy



The Hypothesis-based model explaining Radscopal effect

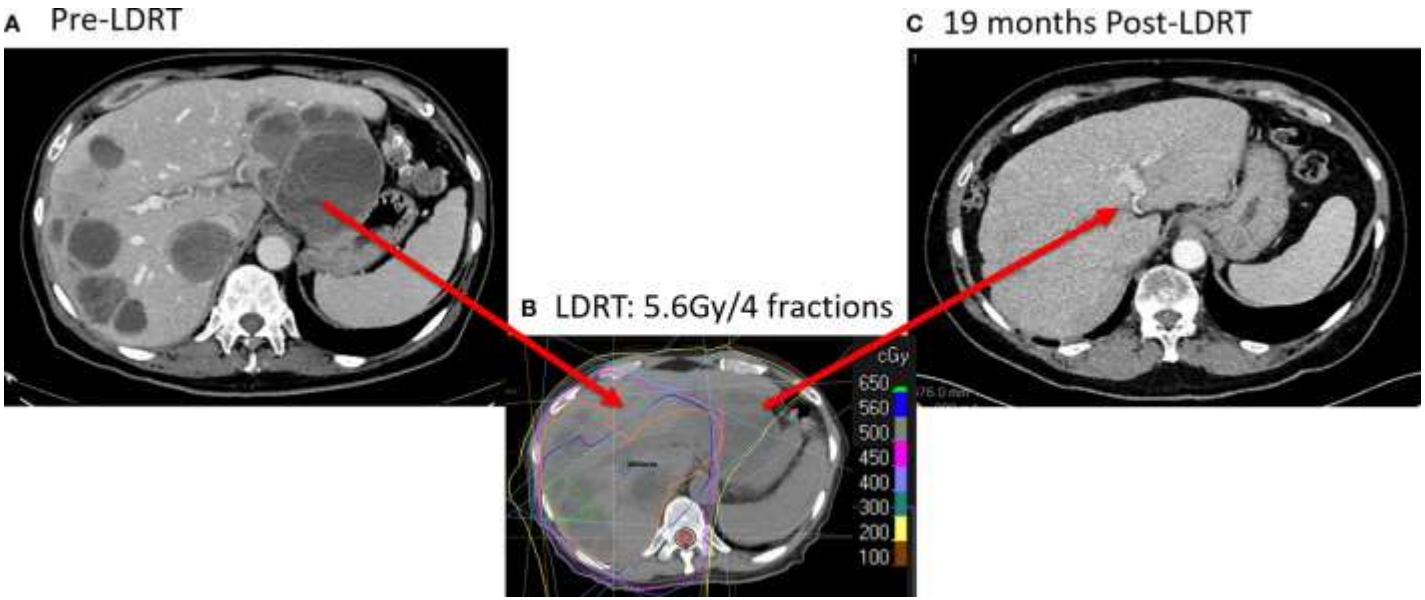


Preclinical evidence

Table 1. Key preclinical studies on evaluating the valuating immune effect of high-dose radiotherapy (HDRT) + low-dose radiotherapy (LDRT).

Authors	Mice and Cell Line	Number of Tumor Sites	RT Regimen	Immunotherapy	Results
H Barsoumian et al. [19]	129Sv/Ev mice 344SQ parental lung adenocarcinoma cell line	2	12 Gy*3 HDRT to the primary tumor + 1 Gy*2 LDRT to the secondary tumor (3 days after HDRT)	anti-CTLA-4 anti-PD1	Delayed growth in both primary and secondary tumors. Enhanced natural killer cell activation, increased M1 macrophages and CD4 + T-cells, and decreased TGF-β in secondary tumors.
H Barsoumian et al. [20]	129Sv/Ev mice 344SQ parental lung adenocarcinoma cell line	2	12 Gy*3 HDRT to the primary tumor + 1 Gy*2 LDRT to the secondary tumor (3 days after HDRT)	anti-TIGIT anti-PD1	Delayed growth in both primary and secondary tumors, reduced the exhaustion of T-cells, generated effector immune memory, and prolonged survival.
Y Hu et al. [25]	129Sv/Ev mice 344SQ parental lung adenocarcinoma cell line	2	12 Gy*3 HDRT to the primary tumor + 1 Gy*2 LDRT to the secondary tumor (3 days after HDRT)	anti-PD1 anti-CTLA4 NBTXR3 nanoparticle	Slowed the growth of both primary and secondary tumors, suppressed the appearance of lung metastases, increased survival rates, induced robust long-term immune memory, and increased the CD8/Treg ratio in the secondary tumors
T Savage et al. [26]	C57BL/6 mice Lewis Lung Carcinoma, 3LL	1	22 Gy*1 + 0.5 Gy*4(12 days after HDRT) to the tumor site	-	Delayed tumor growth, increased survival, reduced Tregs and M2 macrophages in the tumor microenvironment (TME), and increased systemic T-cell responses.
	BalB/C mice breast carcinoma cell line, 4T1	1	22 Gy*1 to the tumor site + 0.5 Gy*4(12 days after HDRT) to the whole lung (metastatic prone organ)	-	Delayed local tumor progression, suppressed pulmonary metastases, remodeled the metastatic niche with decreased Tregs and increased effector T-cell infiltration in lungs, and increased survival.

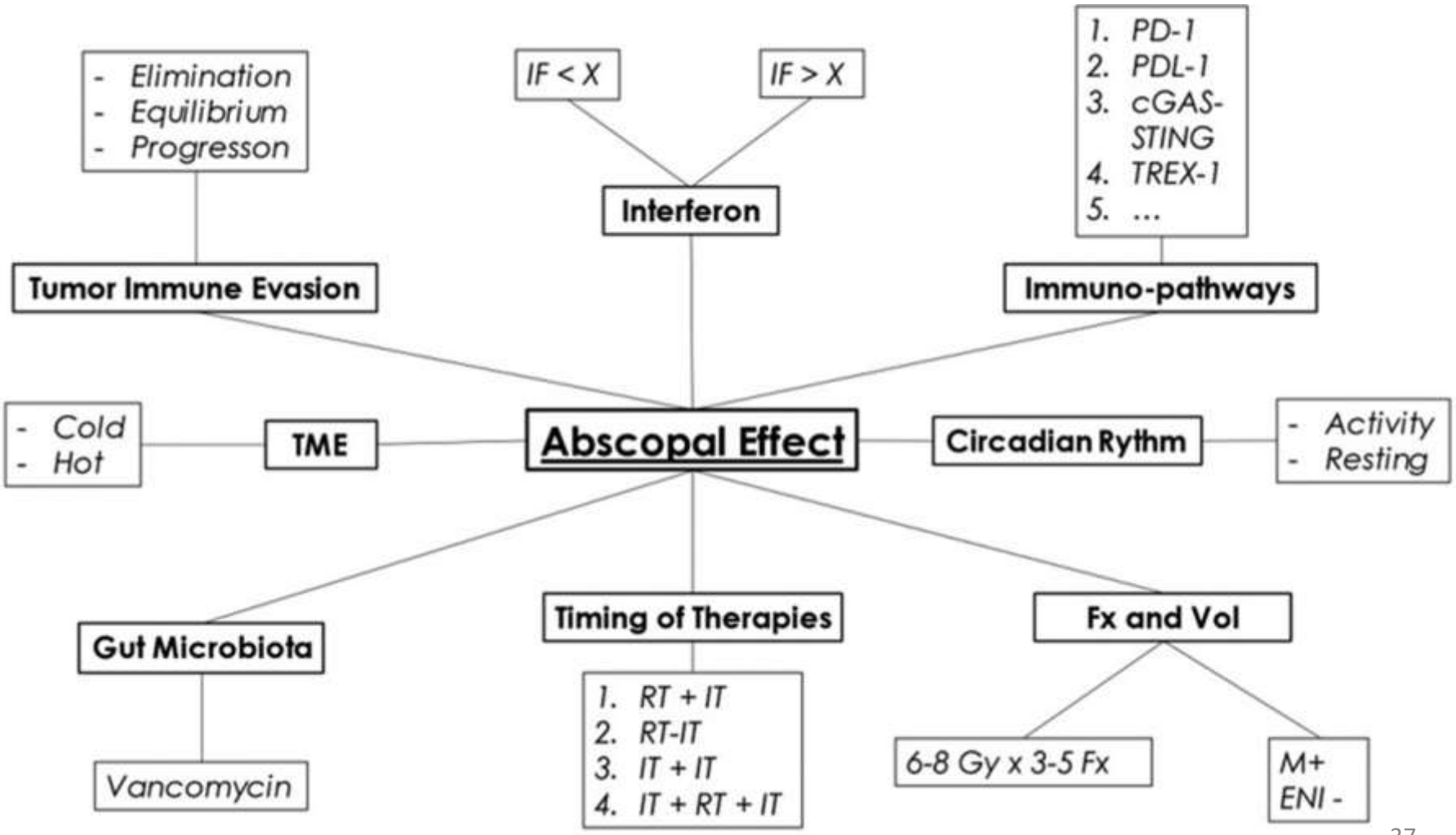
LDRT immune modulation



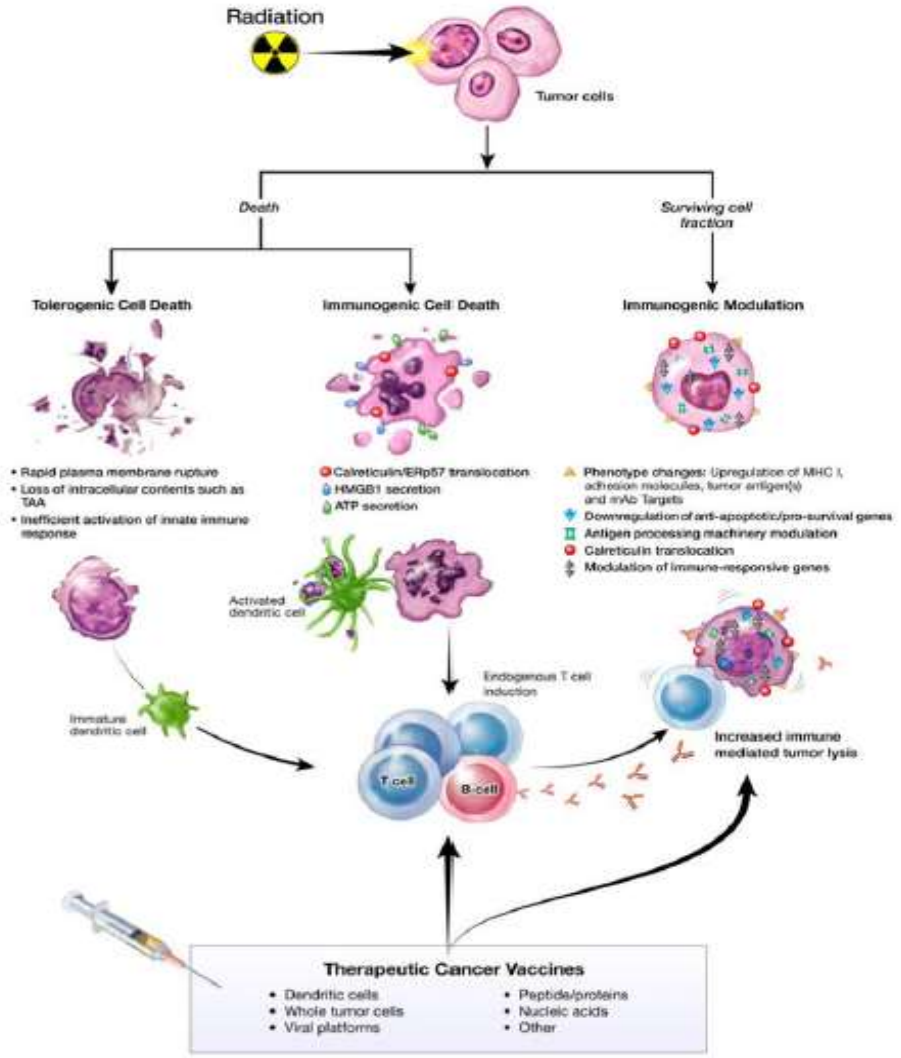
Complete Response with LDRT to Liver metastases. **(A)** CT scanning (9/4/2019) before LDRT showed multiple liver metastases. **(B)** The patient received 50 Gy/4 fractions to a lung lesion and 5.6 Gy/4 fractions to nearly the entire liver from 10/8/2019 to 10/11/2019. **(C)** 19 months after LDRT, CT scans (4/19/2020) showed a complete response in the liver.

He K, et al Novel Use of Low-Dose Radiotherapy to Modulate the Tumor Microenvironment of Liver Metastases. Front Immunol. 2021 Dec 15;12:812210.

Factors affecting Abscopal effect



Combination Therapy Between Tumor Vaccine and RT



Cancer vaccine

Type	Preclinical	Clinical
1. Dendritic-Cell Vaccines	Murine model of MCA-102 fibrosarcoma, intratumoral injection of DCs following 15 Gy of external-beam radiation therapy (EBRT)	• Sipuleucel-T (Provenge®; Dendreon) plus RT –mcrpc • combination of RT plus injection of autologous immature DCs in advanced-stage/metastatic hepatoma • DC-based vaccine in combination with conformal RT for metastatic and recurrent solid tumours
2. Whole Tumor-Cell Vaccines	Whole-brain RT enhanced the effectiveness of immunotherapy with irradiated GL261 cells secreting GM-CSF as a WTCV (GVAX)	• Ongoing phase I study : in patients with resected adenocarcinoma of the pancreas46 is comparing GVAX vaccine, fractionated SBRT (6.6 Gy), and FOLFIRINOX chemotherapy

Vaccine and Radiation – Randomised Trial

CANDEL THERAPEUTICS

Candel Therapeutics Announces CAN-2409 Achieved Primary Endpoint in Phase 3 Prostate Cancer Trial, Showing Significantly Improved Disease-Free Survival

Intermediate Risk prostate cancer
- Planned for prostate-only RT
- ECOG PS: 0-2

R 2:1

CAN 2409 +RT + valacyclovir ± SCADT

Placebo + RT + valacyclovir ± SCADT

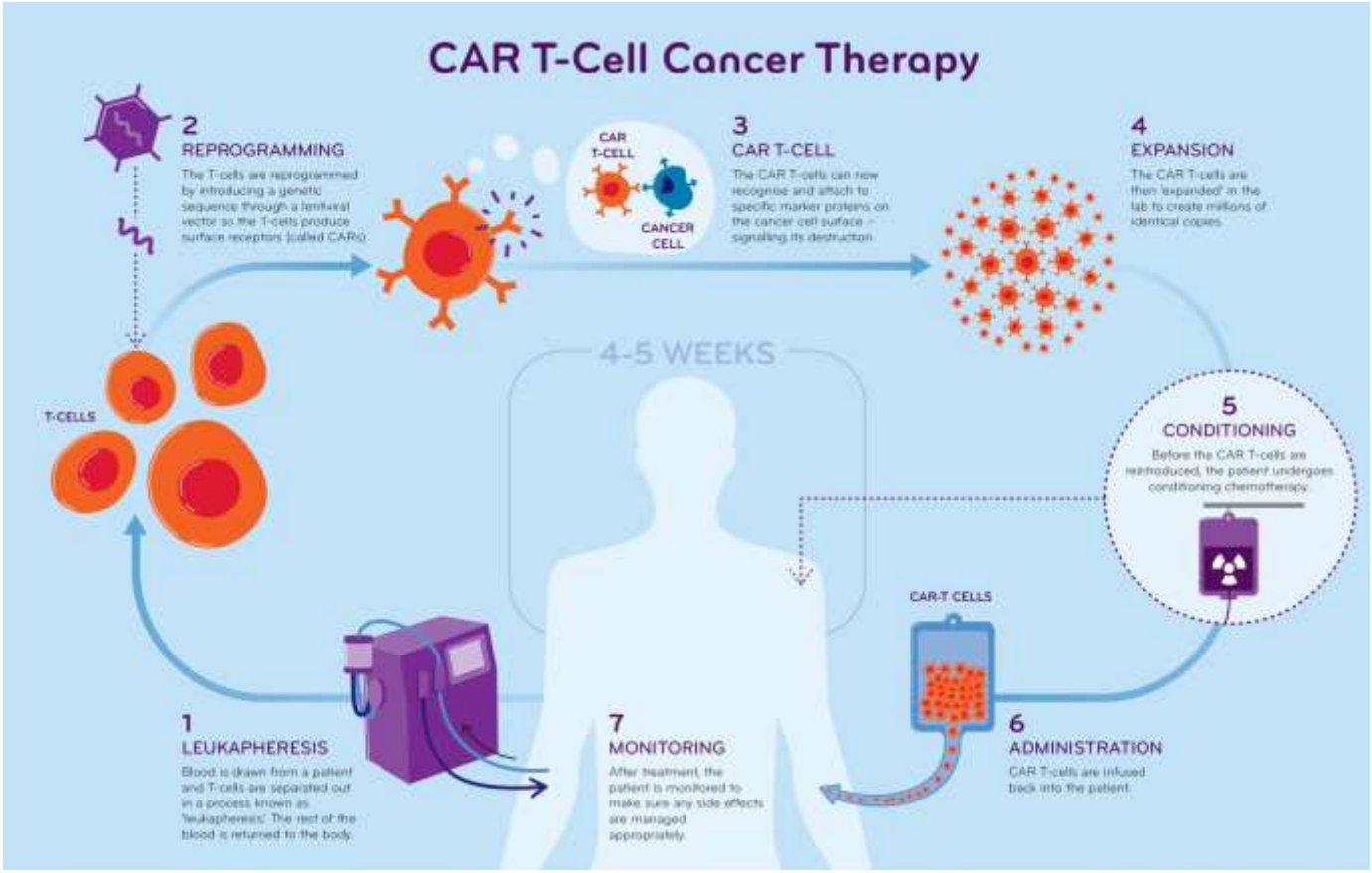
With a median follow up of 50.3 months The study met its primary endpoint

- Significant improvement in DFS for CAN-2409 plus radiation therapy (n=496) vs. radiation therapy alone (n=249) (p=0.0155; HR 0.7) in the ITT population
- 14.5% relative improvement in DFS observed at 54 months
- DFS improvement was observed both in patients receiving short term ADT and not receiving ADT
- CAN-2409 showed a highly significant effect (p=0.0046; HR 0.6) on prostate cancer-free survival
- It induced 80.4% pathological complete responses (pCRs) in the 2-year post-treatment biopsies compared to 63.6% in the control arm (p=0.0015)

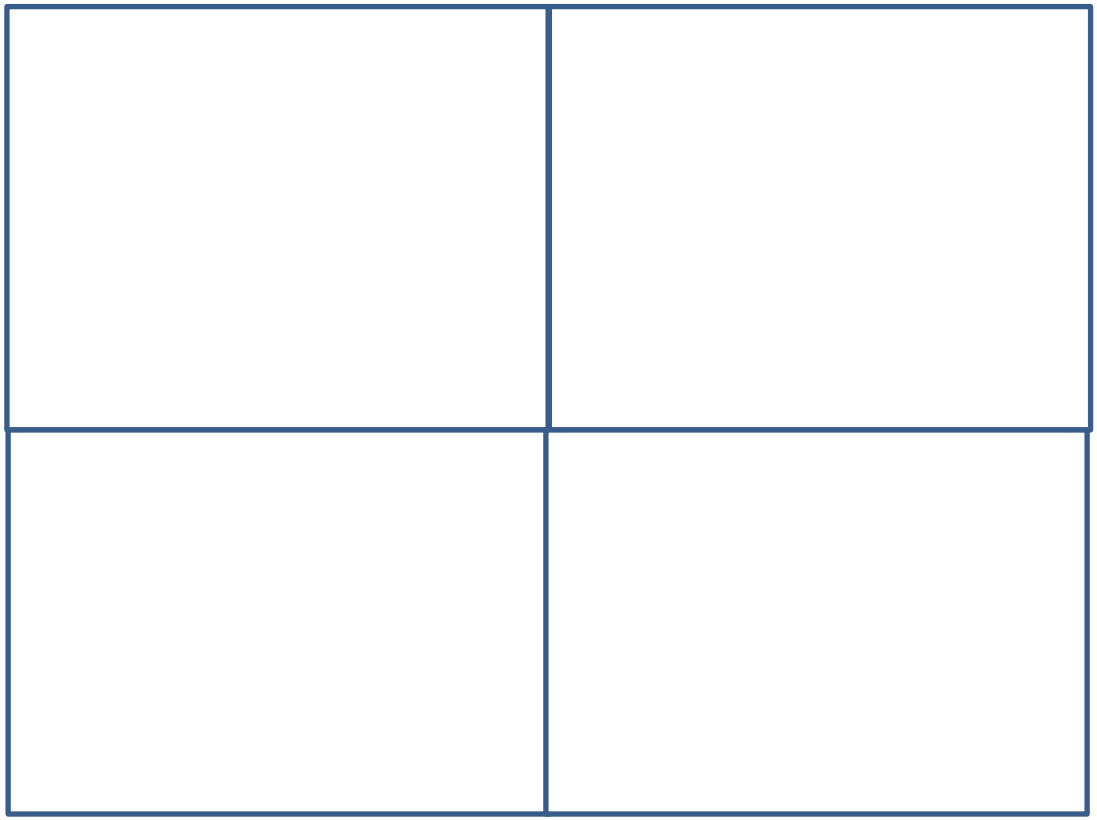
Combination Therapy Between Adoptive Cell Therapy and RT

Adoptive cell therapy (ACT)

ACT can target antigen-specific tumor cells by isolating immunoreactive cells from patients, inducing differentiation, modification, and amplification in vitro, and then transfusing them back into patients



Adoptive Immunity and Radiation Synergry



(A) RT promotes the expansion of CAR-T cells and ↑their killing effect on tumor cells.

(B) RT modulates the inflammatory TME and ↑the secretion of chemokines and proinflammatory cytokines, leading to the homing of CAR-T cells.

(C) RT induces an ↑in the expression of the integrins ICAM-1 and VCAM-1 in vascular endothelial cells, which facilitates the migration of CAR-T cells across the vascular endothelium into the tumor tissue and normalizes tumor blood vessel

(D) RT potentially improves the efficacy of CAR-T cell therapy by activating and enhancing endogenous target antigen-specific immune responses.

Preclinical and clinical studies

A, Preclinical studies

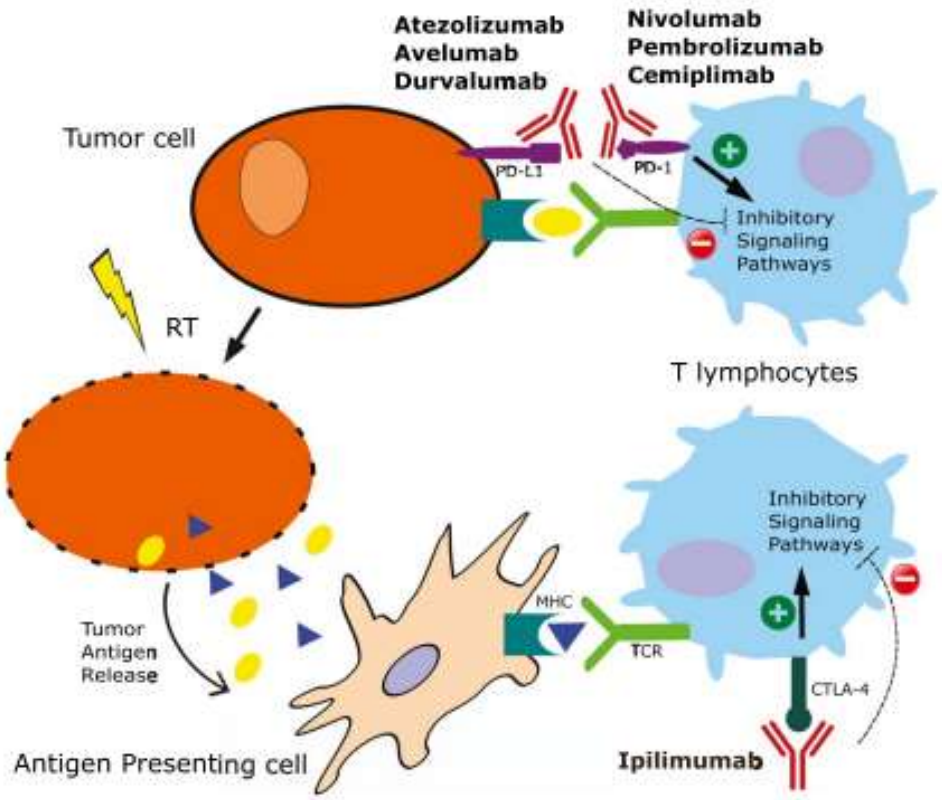
First author, year	Tumor model	Target	Scheme	(Refs.)
Weiss *et al*, 2018	Glioblastoma	NKG2D	4 Gy x1	(31)
DeSelm *et al*, 2018	Pancreatic cancer	sLeA	2 Gy x1	(80)
Murty *et al*, 2020	Glioblastoma	GD2	5 Gy x1	(99)

B, Clinical studies

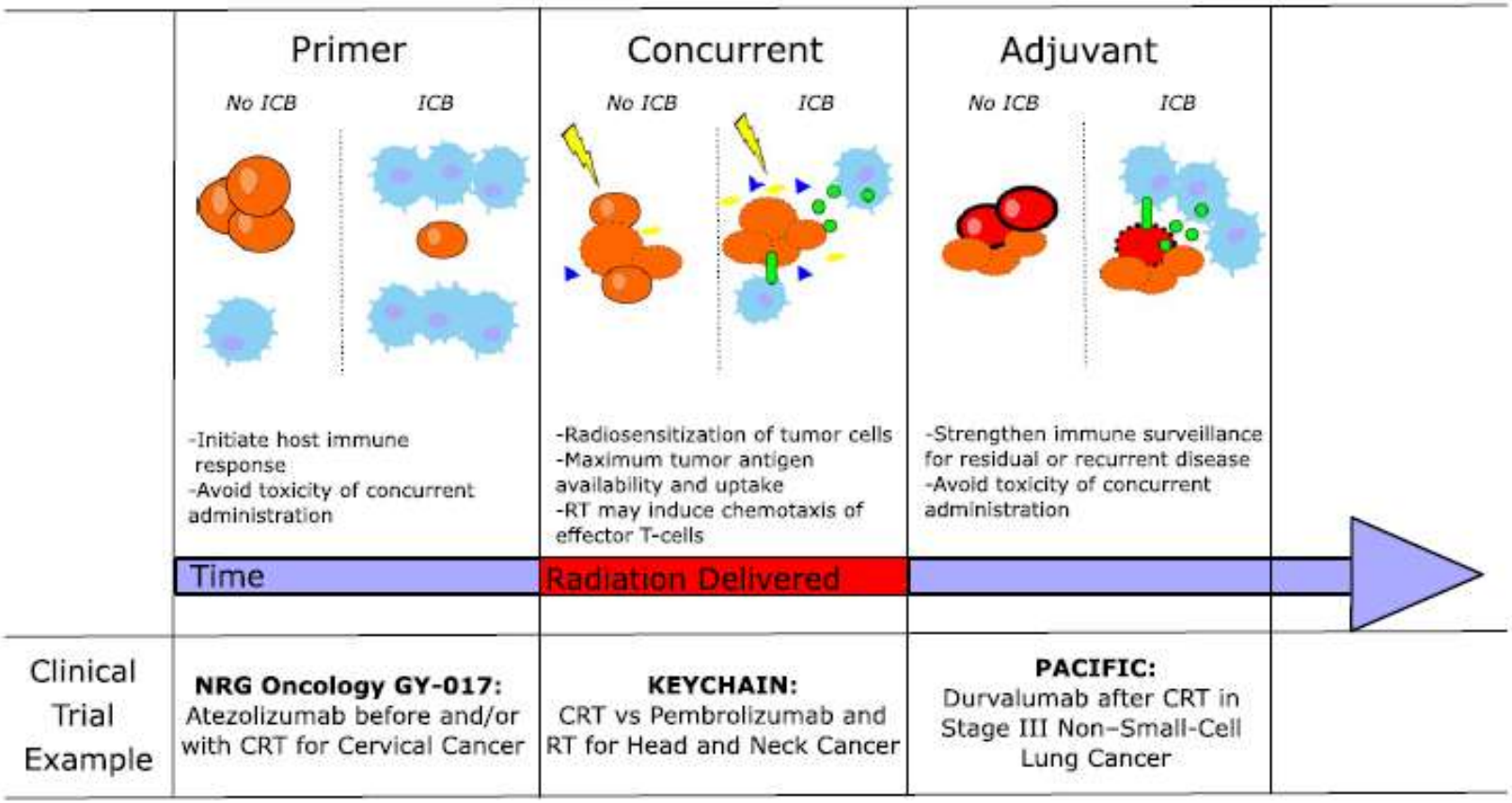
First author, year	Tumor model	Target	Scheme	(Refs.)
Sim *et al*, 2019	Diffuse large B-cell lymphoma	CD19	2-4 Gy/fraction (range, 6.0-36.5 Gy)	(61)
Smith *et al*, 2019	Multiple myeloma	BCMA	4 Gy x5	(103)
Qu *et al*, 2020	Diffuse large B-cell lymphoma	CD19/CD20/ CD22	2 Gy x20	(89)
Saifi *et al*, 2022	Relapsed and/or refractory NHL	CD19	Median 20 Gy in 5 fractions	(105)

Immune check point inhibitors and Radiation

Rationale of synergy between immune check point inhibitors and RT



Schema of different sequencing with immunecheck point inhibitors



Evidence from clinical trials

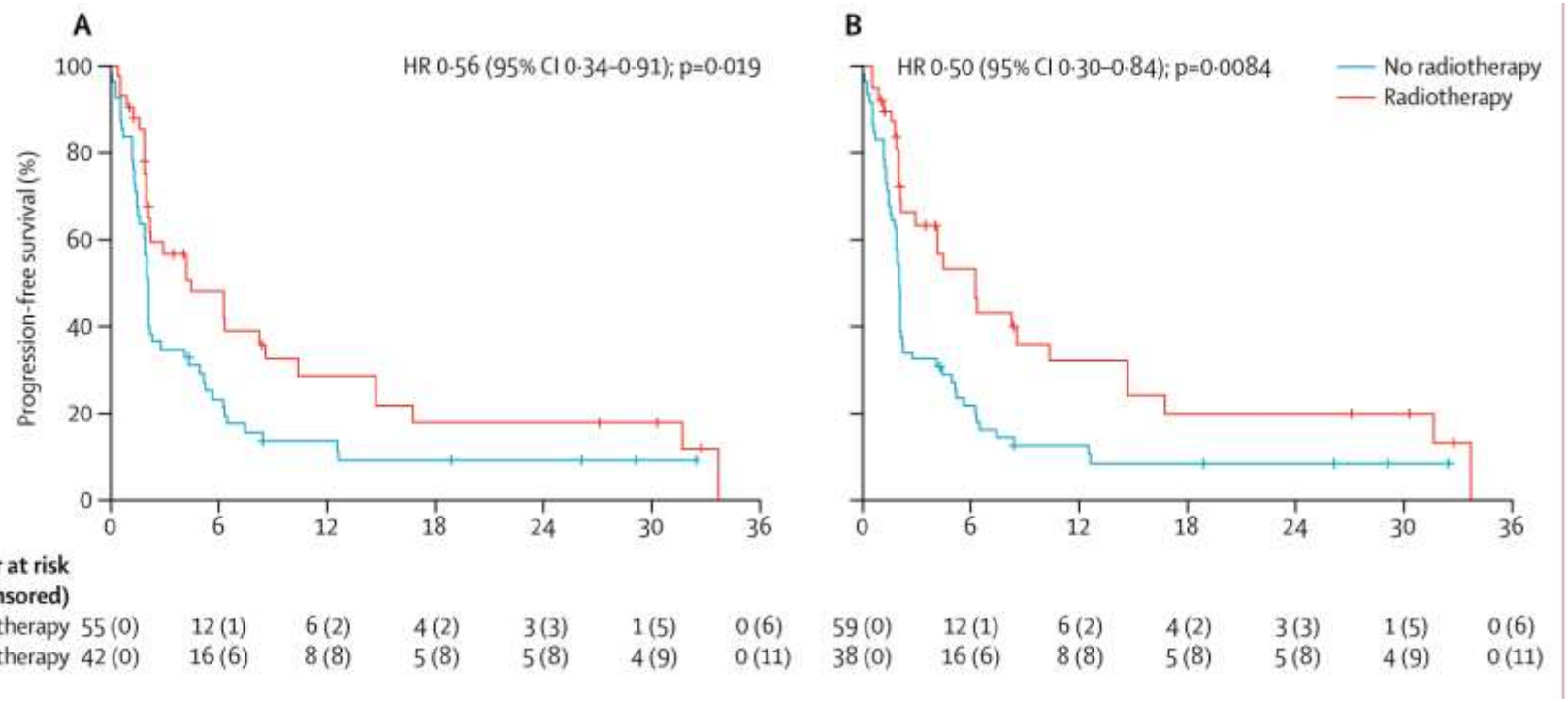
Metastatic Disease

KEYNOTE 001

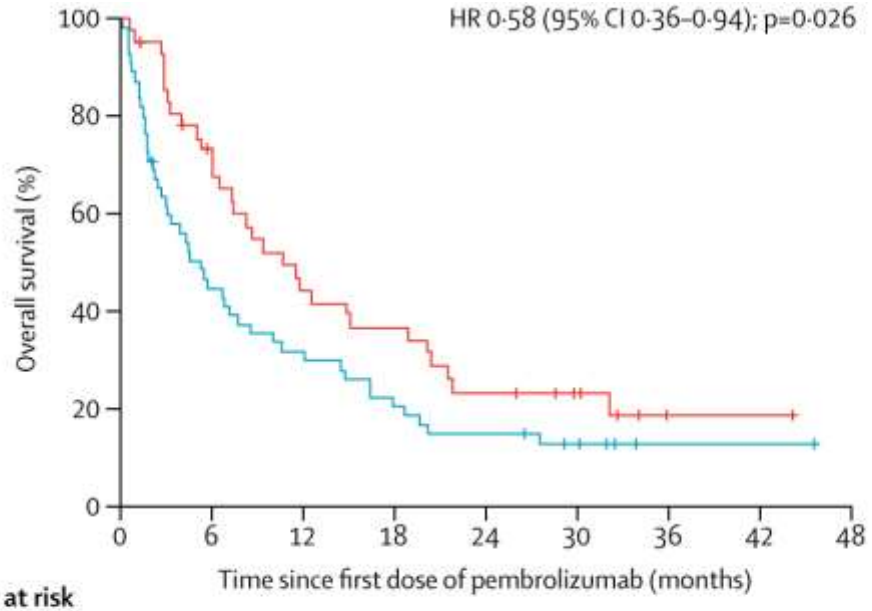
THE LANCET
Oncology

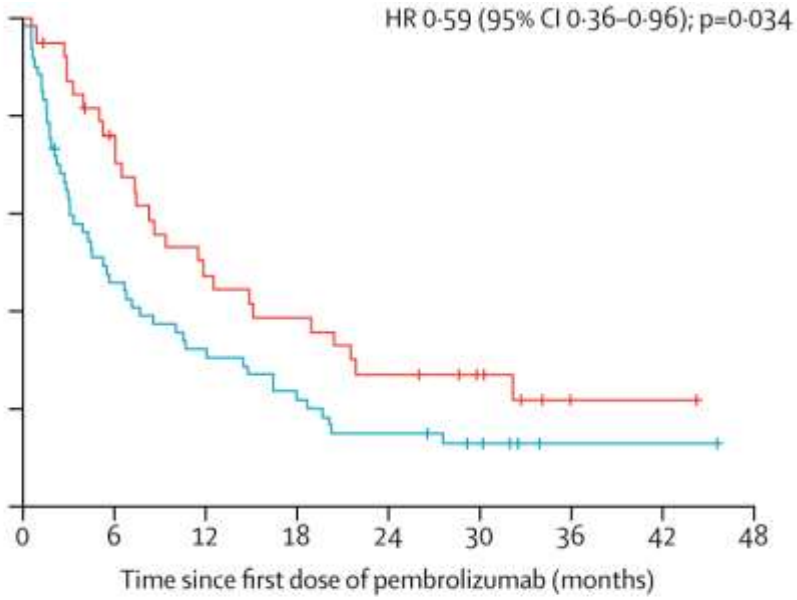
Previous radiotherapy and the clinical activity and toxicity of pembrolizumab in the treatment of non-small-cell lung cancer: a secondary analysis of the KEYNOTE-001 phase 1 trial

Narek Shaverdian, MD [a,*] · Aaron E Lisberg, MD [b,*] · Krikor Bornazyan, MD [b] · Darlene Veruttipong, MPH [a] · Jonathan W Goldman, MD [b] · Silvia C Formenti, MD [c] · et al. Show more



KEYNOTE 001





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)	59 (0)	26 (1)	18 (1)	12 (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)	38 (0)	26 (2)	16 (3)	13 (3)	9 (3)	6 (5)	1 (9)	1 (9)	0 (10)

- patients who had previously received RT for the treatment of NSCLC before receiving pembrolizumab had significantly longer PFS and OS
- higher number of patients with treatment related pulmonary toxicity after pembrolizumab treatment and thoracic radiotherapy, but not more grade 3 or greater
- combination of RT with pembrolizumab has a clinically acceptable safety profile and shows promising activity among patients with advanced NSCLC

KEYNOTE-867

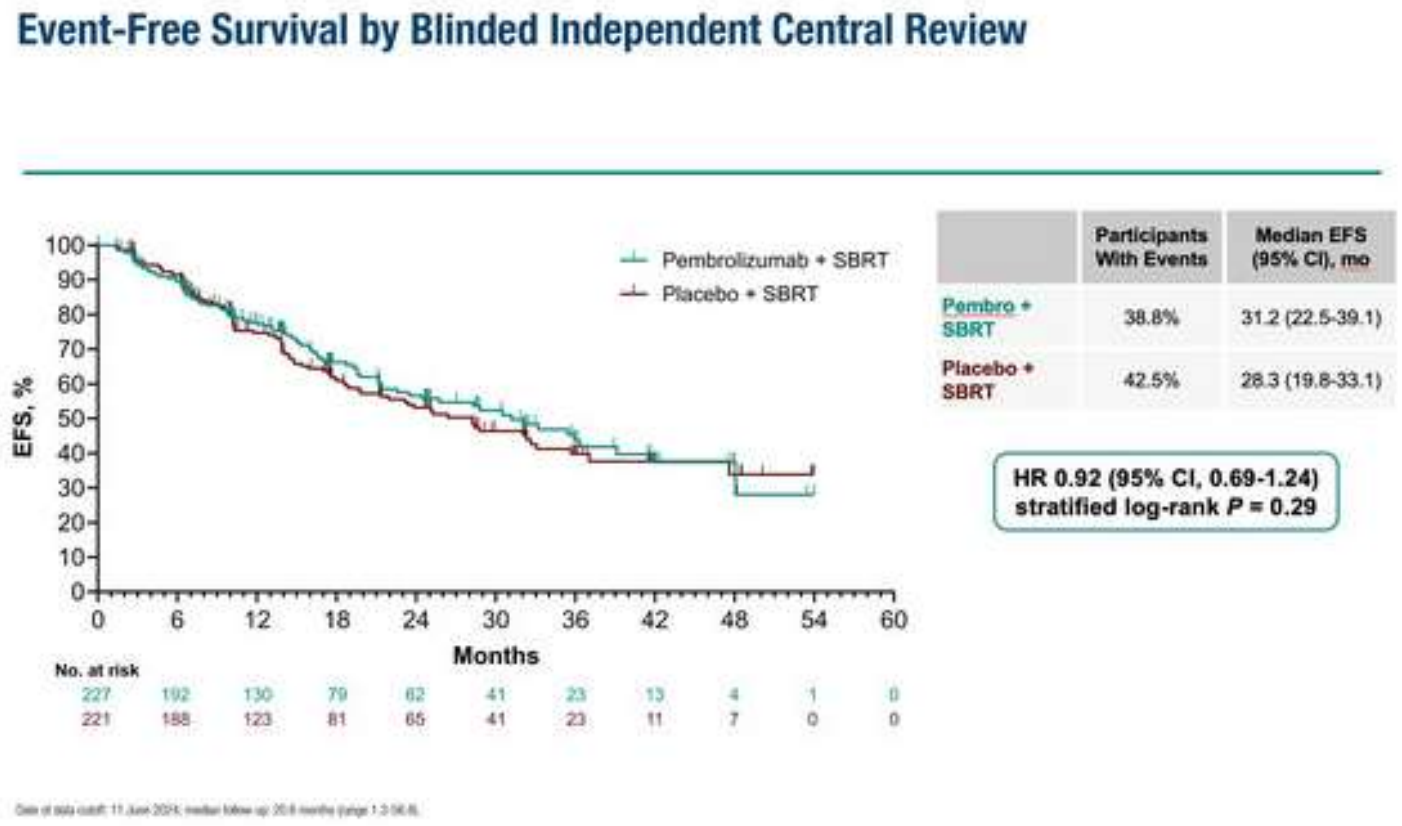


Figure. Event-free survival was not improved with pembrolizumab versus placebo administered with radiotherapy in patients with unresected stage I/II NSCLC in the KEYNOTE-867 trial (ESMO Immuno-Oncology Congress 2024, Abstract 1170).

THE LANCET
Oncology

ARTICLES · Volume 15, Issue 7, P700-712, June 2014 Download Full Issue

Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184-043): a multicentre, randomised, double-blind, phase 3 trial

Prof Eugene D Kwon, MD [a] · Charles G Drake, MD [b] · Prof Howard I Scher, MD [c] · Prof Karim Fizazi, MD [d] ·

- Adenocarcinoma prostate,
- at least one bone metastasis
- Received at least 1 docetaxel-containing regimen
- Progressed

R (1:1)

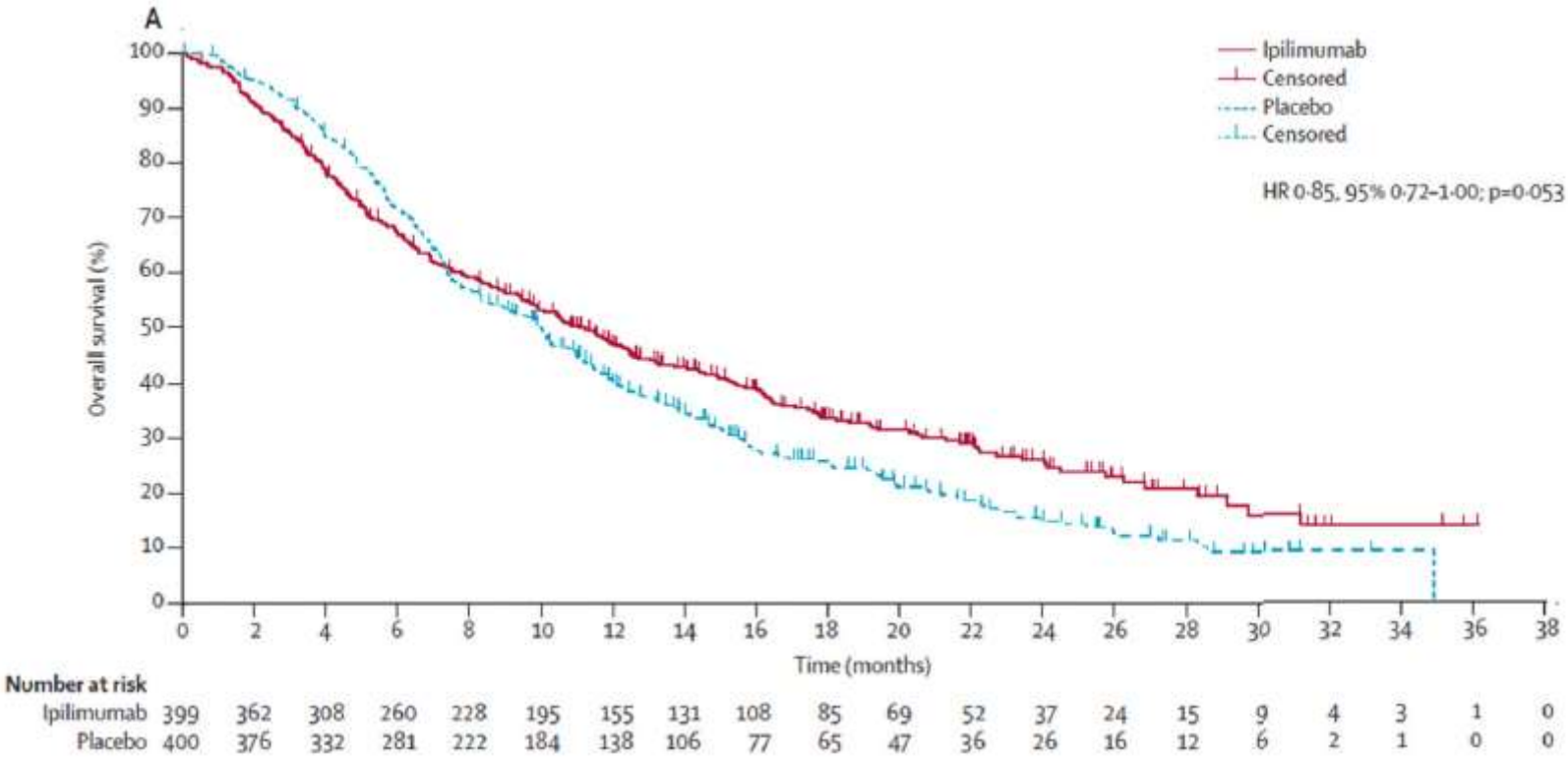
RT to bone mets 8Gy /1#

Ipilumumab 10mg/kg q3weeks x 4 doses

RT to bone mets 8Gy /1#

Placebo

OS



- no difference in overall survival between patients who received ipilimumab vs placebo after bone-directed radiotherapy
- an exploratory piecewise hazard model suggested that the HR decreased over time: ipilimumab seeming to be associated with better survival than placebo at later time points.
- Ipilimumab was associated with reductions in PSA concentration and an improvement in progression-free survival

original reports

Randomized Phase II Trial of Nivolumab With Stereotactic Body Radiotherapy Versus Nivolumab Alone in Metastatic Head and Neck Squamous Cell Carcinoma

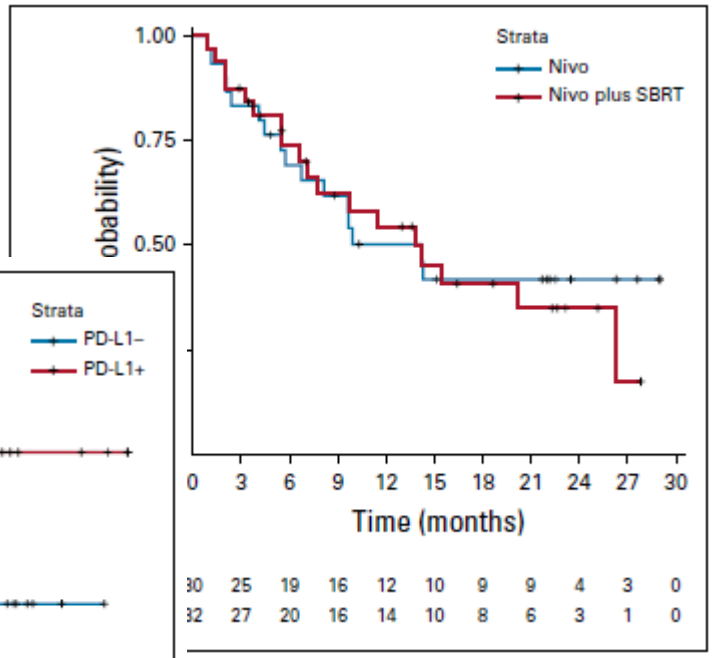
Sean McBride, MD, MPH[1]; Eric Sherman, MD[2,3]; C. Jillian Tsai, MD, PhD[1]; Shrujal Baxi, MD, MPH[2]; Jahan Aghalar, MD[1]; Juliana Eng, MD[1]; Wanqing Iris Zhi, MD, PhD[1]; Daniel McFarland, DO[1]; Loren Scott Michel, MD[1]; Robert Young, MD[4]; Robert Lefkowitz, MD[4]; Daniel Spielsinger, BS[1]; Zhigang Zhang, PhD[5]; Jessica Flynn, BS[5]; Lara Dunn, MD[2,3]; Alan Ho, MD, PhD[2,3]; Nadeem Riaz, MD, MSc[1]; David Pfister, MD[2,3]; and Nancy Lee, MD[1]

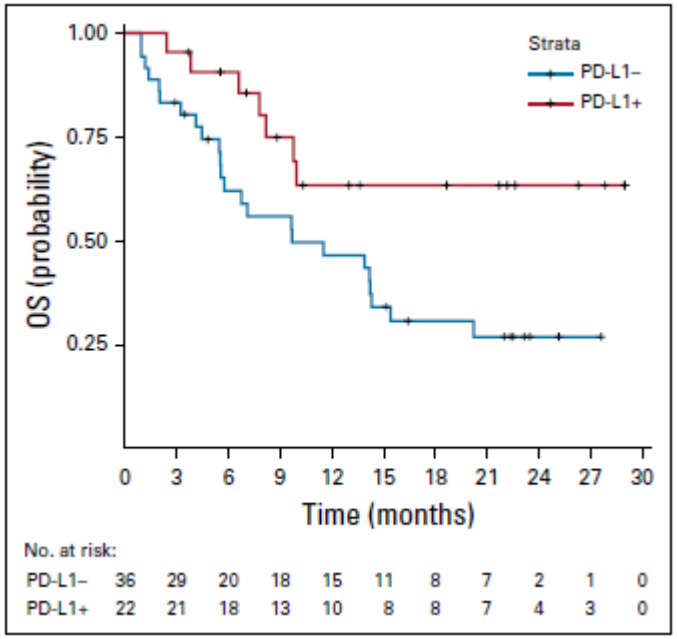
SBRT to one lesion

Met HNSCC

Nivo q2wks . 96 wks

Nivo c





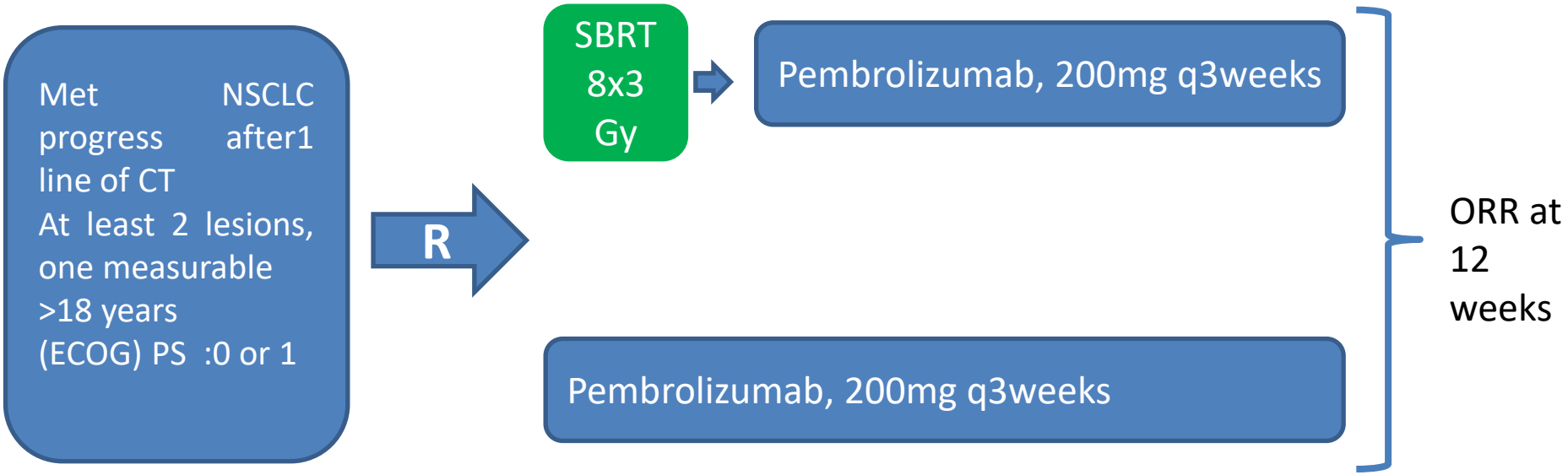
- Combination of nivolu ivolumab alone
- Combined therapy did t in ORR, PFS, or OS

JAMA Oncology | Original Investigation

Effect of Pembrolizumab After Stereotactic Body Radiotherapy vs Pembrolizumab Alone on Tumor Response in Patients With Advanced Non–Small Cell Lung Cancer
Results of the PEMBRO-RT Phase 2 Randomized Clinical Trial

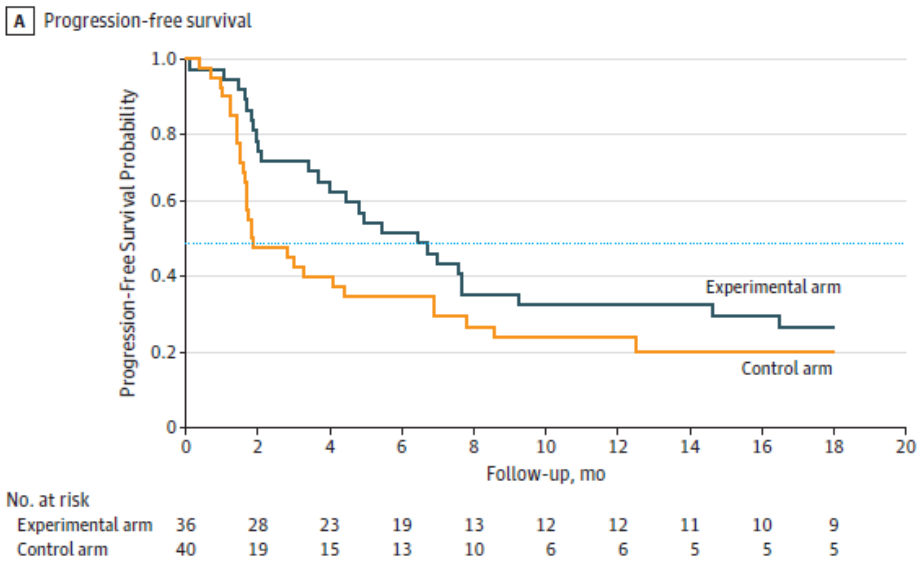
Willemijn S. M. E. Theelen, MD; Heike M. U. Peulen, MD, PhD; Ferry Lalezari, MD; Vincent van der Noort, PhD; Jeltje F. de Vries, PhD; Joachim G. J. V. Aerts, MD, PhD; Daphne W. Dumoulin, MD; Idris Bahce, MD, PhD; Anna-Larissa N. Niemeijer, MD; Adrianus J. de Langen, MD, PhD; Kim Monkhorst, MD, PhD; Paul Baas, MD, PhD

PEMBRO RT



Results

Response	Experimental Arm, No./Total No. (%) (n = 36)[a]	Control Arm, No./Total No. (%) (n = 40)[b]
Best overall response, No.		
Complete response	3	1
Partial response	14	8
Stable disease	9	10
Progressive disease	10	21
Objective response rate at 12 wk		
Overall[c]	13/36 (36)	7/40 (18)
PD-L1 TPS, %		
0	4/18 (22)	1/25 (4)
1-49	3/8 (38)	3/8 (38)
≥50	6/10 (60)	3/5 (60)
Disease control rate at 12 wk[d]	23/36 (64)	16/40 (40)



ISABR

Study	Design	Inventions	Fractionation	Target volume	Sequence	Outcomes	Toxicity
Theelen et al. (70)	RCT, phase 2	Pembro after vs. without radiotherapy (n=92, failed first-line chemotherapy)	24Gy/3F	Partial (1 lesion)	SBRT before immunotherapy	mPFS:1.9 vs. 6.6 months (P=0.19) mOS: 7.6 vs. 15.9 months (p=0.16)	Pneumonia (8% vs. 26%, P=0.06); G3+ immune-related pneumonitis (0% vs. 5%)
Ni et al. (71)	Single-arm, phase 2	SBRT followed by Sintilimab and GM-CSF (n=20, failed first-line chemotherapy)	24Gy/3F	Partial (1 lesion)	SBRT before immunotherapy	The triple regimen is safe and well tolerated	No patients had DLTs and 18 patients experienced treatment-related AE.
Schoenfeld et al. (72)	RCT, phase 2	Durvalumab/ Tremelimumab alone vs. with LDRT vs. with HFRT(n=90)	LDRT: 0.5 Gy bid x 8 days; HFRT: 8Gy×3F	Partial (1-2 lesions)	Concurrent	ORR: 11.5% vs. 7.7% vs. 11.5%; DCR: 30.8% vs. 23.1% vs. 34.6%	G3+ AE possibly related to study therapy (15% vs. 31% vs. 12%, P=0.27); median follow-up time was 12.4 months
Bestvina et al. (73)	RCT, phase 1	Concurrent vs. sequential SBRT with Nivolumab and Ipilimumab (n=37)	30Gy/3F; 45Gy/3F; 50Gy/5F	Partial (2-4 lesions)	Concurrent or sequential	mPFS: 7.9 vs. 4.7 months (P = 0.43)	G3+ irAEs in 13 patients in the concurrent group vs. 14 patients in the sequential group; median follow-up time was 17 months
Welsh et al. (74)	RCT, phase 1/2	Pembro vs. Pembro +SBRT vs. Pembro +CFRT (n=100, with 1-4 lung or liver lesions)	SBRT: 50Gy/4F; CFRT: 45Gy/15F	Partial	Concurrent	Out-of-field ORR: 25% vs. 38% vs. 10%; PFS: 5.1 vs. 20.8 vs. 6.8 months	Two G4 AE and two G3 AE in the Pembro+SBRT group; Five G3 AE in Pembro+ CFRT group; median follow-up time was 20.4 months
Mattes et al. (91)	Single-arm	ICI with vs. without SBRT (n=35, CPI-naïve)	48Gy (IQR:43 – 60 Gy)/3–5 F	Partial	Concurrent	mOS: 15.0 months ; mPFS: 6.9 months; mTTP: 11.2 months	Radiation-induced toxcity (56% vs. 32%, P<0.01), no G3+ radiation-induced toxicities; median follow-up time was 14.0 months

Ongoing trials

ClinicalTrials.gov identifier	Trial Phase	Condition or disease	Sequence	RT	IO	Results	Sponsors	Estimated/actual study completion date
NCT02474186	Phase 1 Phase 2	Various	Concurrent	35 Gy in 10 fractions	GM-CSF	Abscopal responses in 27.6% of patients	NYU Langone Health	July 2015
NCT02125461	Phase 3	NSCLC	RT, IO	54 to 66 Gy	Durvalumab	Durable PFS and sustained OS benefit with durvalumab after chemoradiotherapy	AstraZeneca	December 30, 2022
NCT02608385	Phase 1	Solid tumors	SBRT, IO	SBRT dosing varied by site and ranged from 30 to 50 Gy in three to five fractions	Pembrolizumab	Well tolerated with acceptable toxicity	University of Chicago	July 2022
NCT02221739	Phase 1 Phase 2	NSCLC	Concurrent	6 Gy x5, later changed to 9.5 Gy x3	Ipilimumab	Objective responses were observed in 18%, and 31% had disease control	NYU Langone Health	October 27, 2015
NCT02434081	Phase 2	NSCLC	Concurrent	66 Gy in 33 fractions	Nivolumab	The addition of nivolumab to concurrent CRT is safe and tolerable	European Thoracic Oncology Platform	March 31, 2020
NCT02492568	Phase 2	NSCLC	RT, IO	SBRT 3 doses of 8 Gy	Pembrolizumab	Well tolerated and a doubling of ORR	The Netherlands Cancer Institute	June 2018
NCT02444741	Phase 1 Phase 2	NSCLC	Concurrent	Various	Pembrolizumab	Safe and more beneficial for patients with low PD-L1 expression	M.D. Anderson Cancer Center	September 17, 2022
NCT02343952	Phase 2	Carcinoma, NSCLC	RT, IO	59.4 to 66.6 Gy	Pembrolizumab	PFS and OS improvement with consolidation pembrolizumab	Nasser Hanna, M.D.	September 2022
NCT03631784	Phase 2	NSCLC	Concurrent	60 Gy in 30 daily fractions	Pembrolizumab	Promising antitumor activity and manageable safety	Merck Sharp & Dohme Corp.	May 15, 2023

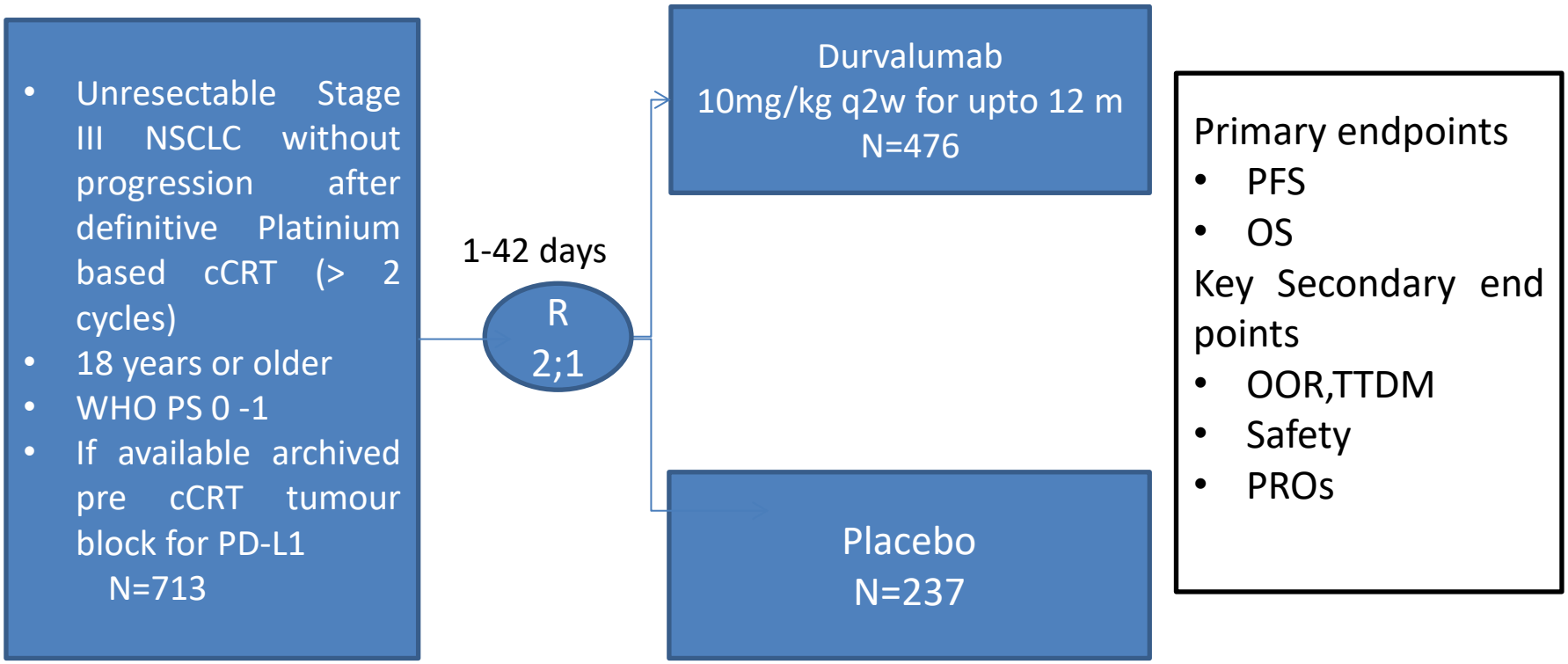
Localised disease

Localised disease

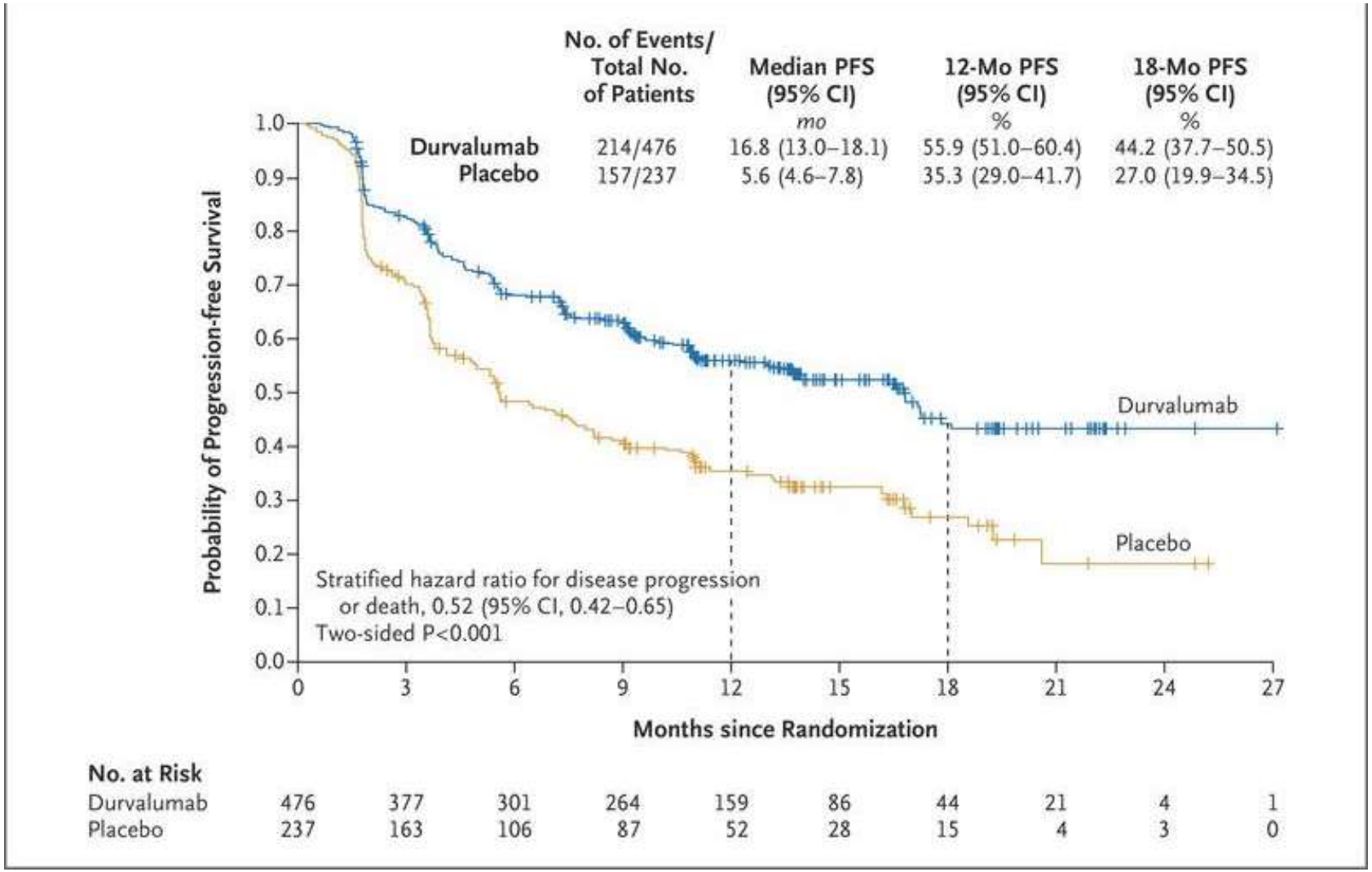
Randomized trials combining radiotherapy with ICI in non-metastatic disease.

Study	Cancer Type (n)	Disease Stage	Treatment Setting	ICI Agent	Radiation Details (Gy / fractions)	Trial Design	Selected Results
Spigel et al. (PACIFIC)	NSCLC ($n = 709$)	III	Adjuvant	Durvalumab	60-66 Gy in 30-33 fractions to primary tumor and involved nodes	Durvalumab following no PD[1] after definitive CRT[2]	mOS[3] 47.5 ICI vs. 29.1 mo placebo mPFS 16.9 mo vs. 5.6 mo placebo 5OS[4] 42.9% vs. 33.4% placebo 5PFS[4] 33% vs. 19% placebo
Kelly et al. (Checkmate-577)	Esophageal/GEJ ($n = 794$)	II/III	Adjuvant	Nivolumab	Definitive RT dose (not specified) to primary tumor and nodes (involved and elective)	Neoadjuvant CRT with PR followed by R0 resection of stage II/III cancer	mPFS 22.4 mo ICI vs. 11.0 mo placebo
Lee et al. (JAVELIN)	HNSCC ($n = 697$)	HPV-/Non-Opx[8] HPV+: III/IVA/IVB OPx HPV+: T4/N2c/N3	Definitive	Avelumab	70 Gy in 35 fractions to primary tumor and nodes (involved and elective)	Locally advanced SCC[5] treated with CRT with concurrent ICI vs placebo	mPFS not reached (95% CI 16.9 mo – not reached for ICI vs. 23.0 mo – not reached for placebo)
Bourhis et al. (PembroRad)	HNSCC ($n = 131$)	III/IVA/IVB	Definitive	Pembrolizumab	69.96 Gy in 33 fractions to primary tumor and nodes (involved and elective)	Non-operable SCC receiving CRT (cetuximab) vs. ICI + RT	15mo LRC 59% CRT vs. 60% ICI-RT (NS) 2PFS[7] 40% CRT vs. 42% ICI-RT (NS) 2OS[7] 55% CRT vs. 62% ICI-RT (NS)
Lim et al. (Checkmate-548)	MGMT methylated GBM ($n = 320$)	-	Definitive	Nivolumab	60 Gy in 30 fractions to primary tumor	RT + TMZ + placebo vs. RT + TMZ + ICI	mPFS 10.6 mo ICI vs. 10.3 mo placebo mOS 28.9 mo ICI vs. 32.1 mo placebo

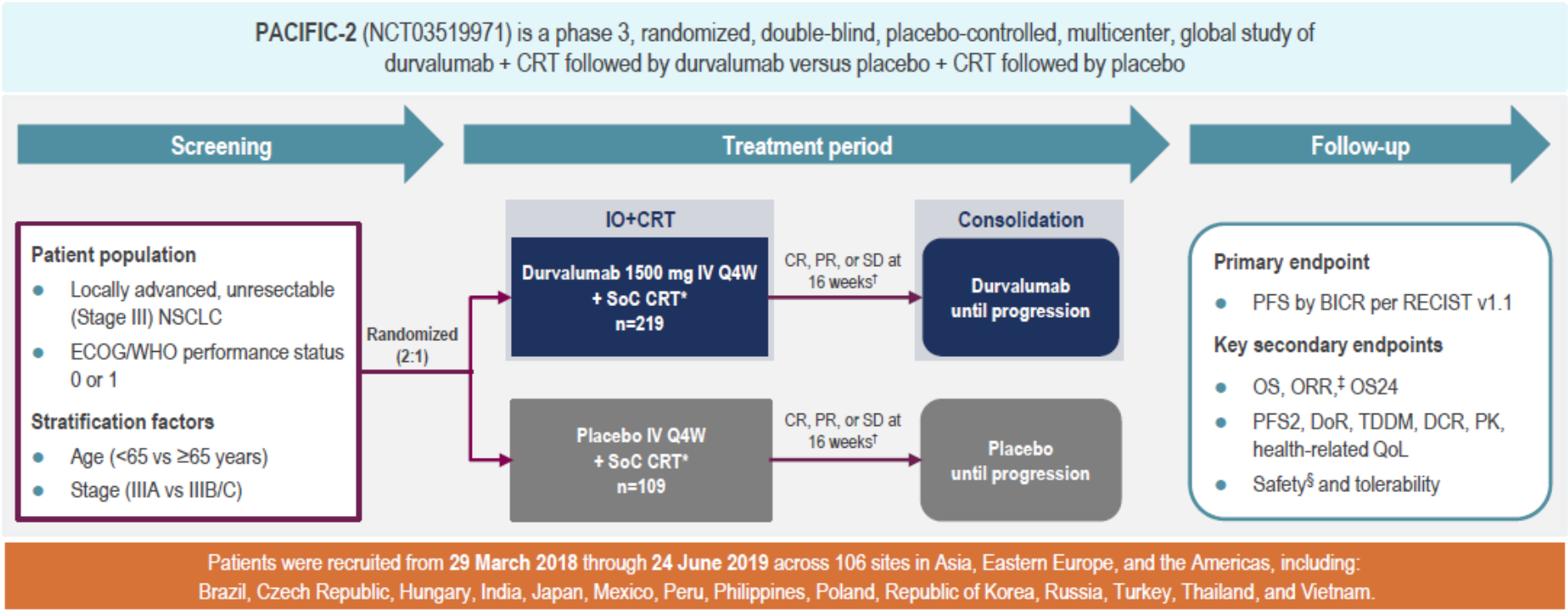
PACIFIC Trial



PACIFIC trial

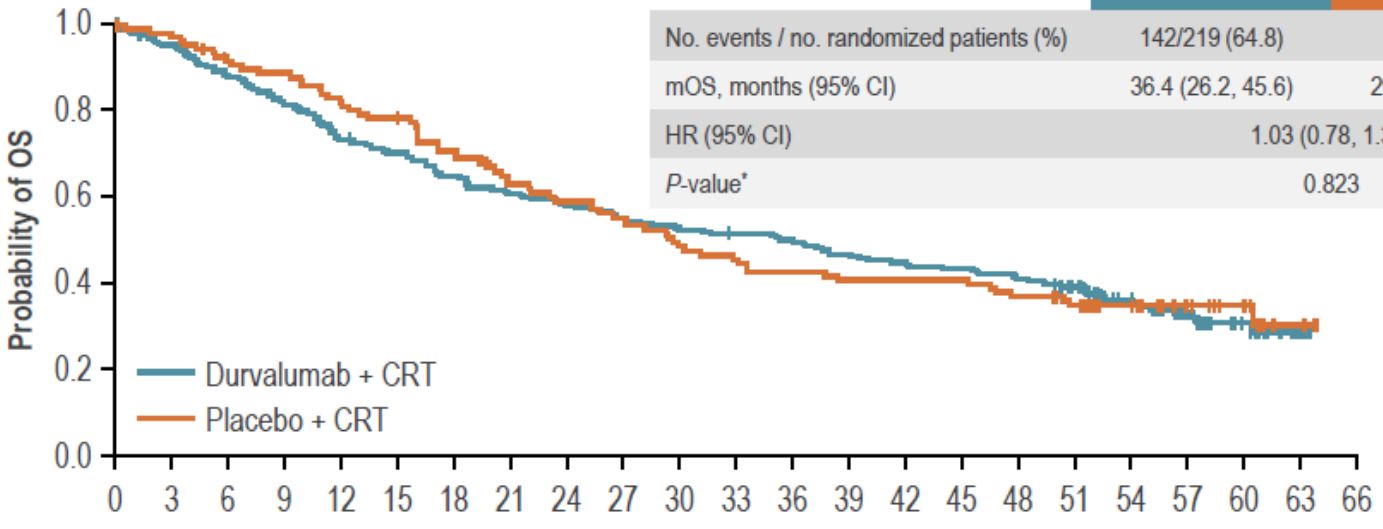


PACIFIC II


PACIFIC-2 (NCT03519971) is a phase 3, randomized, double-blind, placebo-controlled, multicenter, global study of durvalumab + CRT followed by durvalumab versus placebo + CRT followed by placebo
Screening
Treatment period
Follow-up
Patient population
Locally advanced, unresectable (Stage III) NSCLC
ECOG/WHO performance status 0 or 1
Stratification factors
Age (<65 vs ≥65 years)
Stage (IIIA vs IIIB/C)
Randomized (2:1)
IO+CRT
Durvalumab 1500 mg IV Q4W + SoC CRT* n=219
Placebo IV Q4W + SoC CRT* n=109
CR, PR, or SD at 16 weeks†
Consolidation
Durvalumab until progression
Placebo until progression
Primary endpoint
PFS by BICR per RECIST v1.1
Key secondary endpoints
OS, ORR,‡ OS24
PFS2, DoR, TDDM, DCR, PK, health-related QoL
Safety§ and tolerability
Patients were recruited from 29 March 2018 through 24 June 2019 across 106 sites in Asia, Eastern Europe, and the Americas, including: Brazil, Czech Republic, Hungary, India, Japan, Mexico, Peru, Philippines, Poland, Republic of Korea, Russia, Turkey, Thailand, and Vietnam.

OS and ORR (ITT population)

	Durvalumab + CRT	Placebo + CRT
No. events / no. randomized patients (%)	142/219 (64.8)	69/109 (63.3)
mOS, months (95% CI)	36.4 (26.2, 45.6)	29.5 (23.2, 45.1)
HR (95% CI)	1.03 (0.78, 1.39)	
P-value*	0.823	



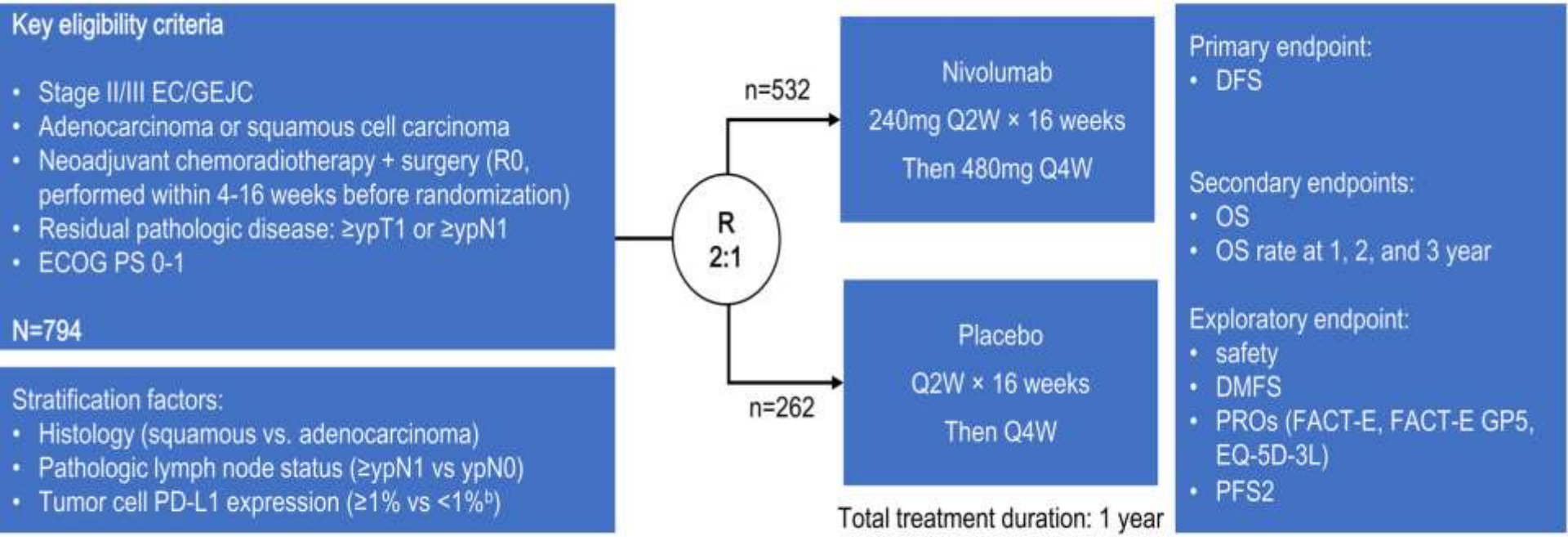
No. at risk:																							
Durvalumab + CRT	219	207	191	177	160	152	141	132	126	120	114	111	107	100	95	94	89	75	49	31	15	1	0
Placebo + CRT	109	106	98	95	87	83	75	66	62	57	51	47	45	43	43	43	39	35	27	17	9	2	0

There was no difference in ORR between the durvalumab (60.7%; 95% CI: 53.9, 67.2) and placebo (60.6%; 95% CI: 50.7, 69.8) arms (p=0.976).

Time to onset	Any AE*		AEs of maximum grade 3/4*†		AEs leading to death	
	Durvalumab + CRT (n=219)	Placebo + CRT (n=108)	Durvalumab + CRT (n=219)	Placebo + CRT (n=108)	Durvalumab + CRT (n=219)	Placebo + CRT (n=108)
Any time	216 (98.6)	108 (100)	117 (53.4)	64 (59.3)	30 (13.7)	11 (10.2)
0 to ≤4 months‡	216 (98.6)	107 (99.1)	125 (57.1)	57 (52.8)	15 (6.8)	5 (4.6)
>4 to ≤16 months§	142 (64.8)	74 (68.5)	34 (15.5)	16 (14.8)	5 (2.3)	5 (4.6)
>16 months¶	67 (30.6)	32 (29.6)	16 (7.3)	13 (12.0)	10 (4.6)	1 (0.9)

CheckMate 577

- CheckMate 577: a global, phase III, randomized, double-blind, placebo-controlled trial

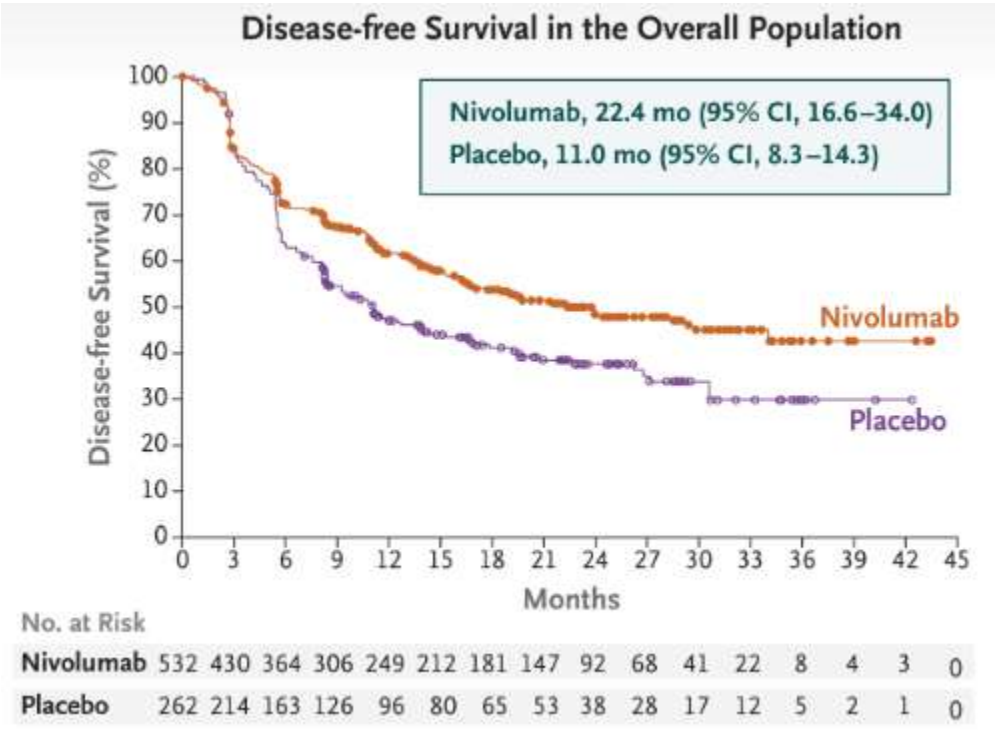


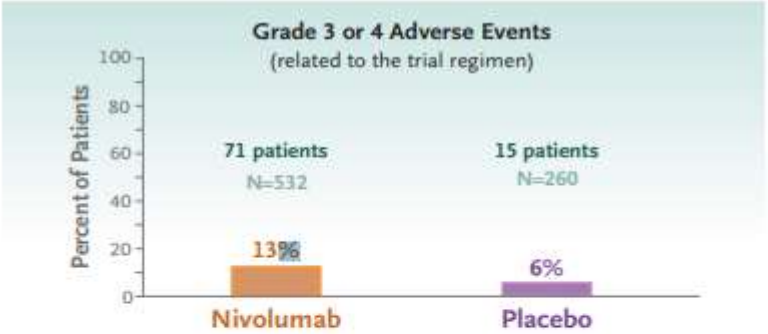
- Median follow-up was 24.4 months (range, 6.2 to 44.9)
- Geographical areas: Europe (38%), Canada and USA (32%), Asia (13%), others (16%)

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Nivolumab (N = 532)	Placebo (N = 262)
Median age (range) — yr	62 (26–82)	61 (26–86)
Male sex — no. (%)	449 (84)	222 (85)
Race — no. (%)†		
White	432 (81)	216 (82)
Asian	83 (16)	34 (13)
Black	7 (1)	2 (<1)
Other	10 (2)	9 (3)
Not reported	0	1 (<1)
Geographic region — no. (%)		
Europe	202 (38)	101 (39)
United States or Canada	167 (31)	88 (34)
Asia	77 (14)	29 (11)
Rest of the world‡	86 (16)	44 (17)
ECOG performance-status score — no. (%)§		
0	308 (58)	156 (60)
1	224 (42)	106 (40)
Disease stage at initial diagnosis — no. (%)		
II	179 (34)	99 (38)
III	351 (66)	163 (62)
Not reported	2 (<1)	0
Tumor location at trial entry — no. (%)		
Esophagus	311 (58)	151 (58)
Gastroesophageal junction	221 (42)	111 (42)
Histologic type — no. (%)¶		
Adenocarcinoma	376 (71)	187 (71)
Squamous-cell carcinoma	155 (29)	75 (29)
Other	1 (<1)	0
Tumor-cell PD-L1 expression at trial entry — no. (%)‖		
<1%	374 (70)	196 (75)
≥1%	89 (17)	40 (15)
Indeterminate or could not be evaluated	69 (13)	26 (10)
Pathological lymph-node status at trial entry — no. (%)**		
≥ypN1	305 (57)	152 (58)
ypN0	227 (43)	109 (42)
Not known	0	1 (<1)
Pathological tumor status at trial entry — no. (%)**		
ypT0	31 (6)	16 (6)
ypT1 or ypT2	202 (38)	106 (40)
ypT3 or ypT4	296 (56)	140 (53)
Not known	3 (<1)	0

* Percentages may not total 100 because of rounding. ECOG denotes Eastern Cooperative Oncology Group, and PD-L1 programmed death ligand 1.
† Race was reported by the patients.
‡ The "rest of the world" category comprised Argentina, Australia, Brazil, Israel, Mexico, and Turkey.
§ ECOG performance-status scores range from 0 to 5, with higher scores indicating greater disability.
¶ One patient in the nivolumab group had a histologic type of "other" (protocol deviation).
‖ In most patients, tumor-cell PD-L1 expression was determined with the use of the PD-L1 IHC 28-8 pharmDX assay





CONCLUSIONS

Adjuvant nivolumab significantly prolonged disease-free survival among patients with an incomplete pathological response after standard therapy for esophageal or gastroesophageal junction cancer.

Avelumab plus standard-of-care chemoradiotherapy versus chemoradiotherapy alone in patients with locally advanced squamous cell carcinoma of the head and neck: a randomised, double-blind, placebo-controlled, multicentre, phase 3 trial

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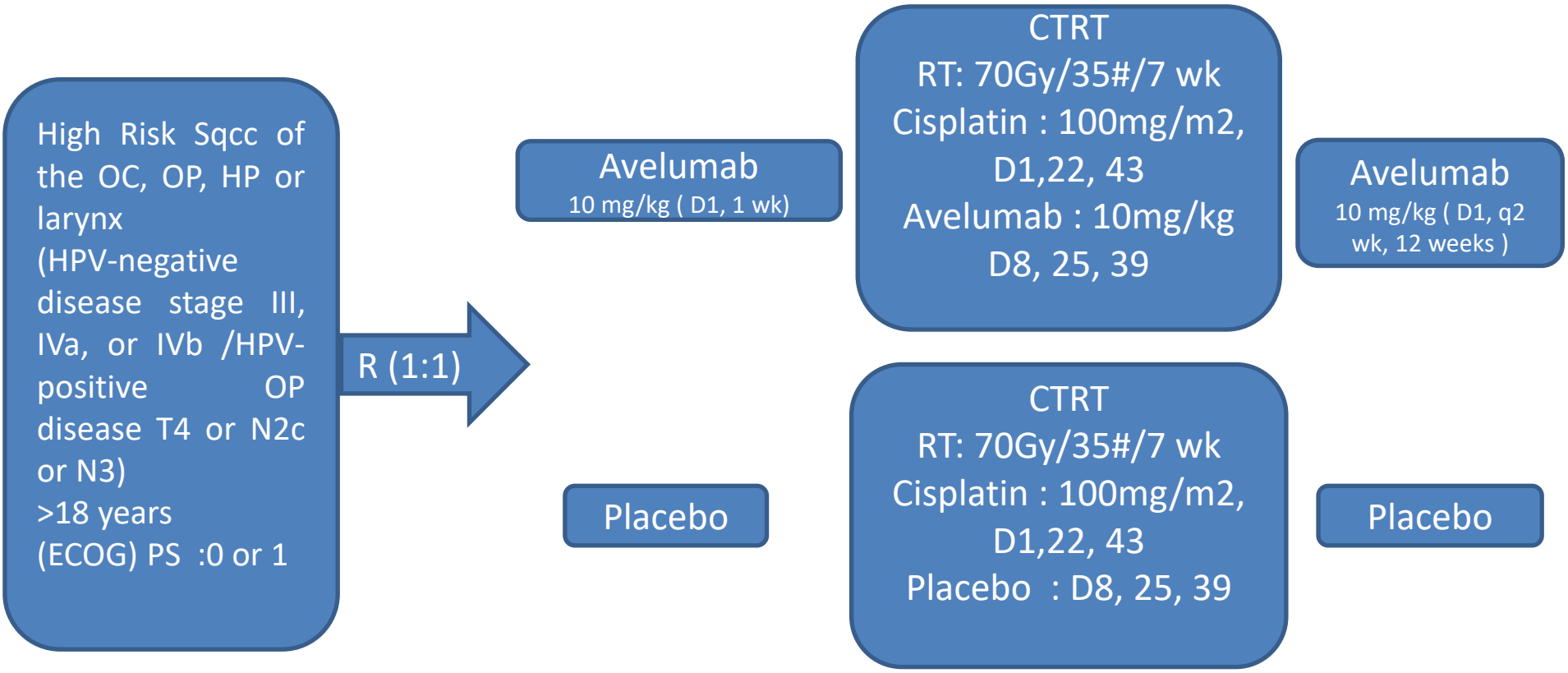
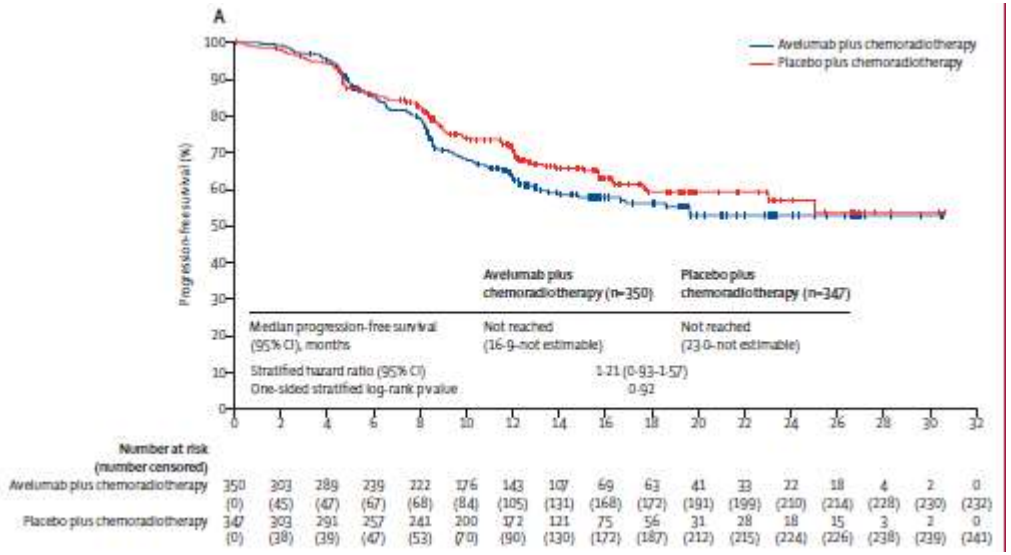
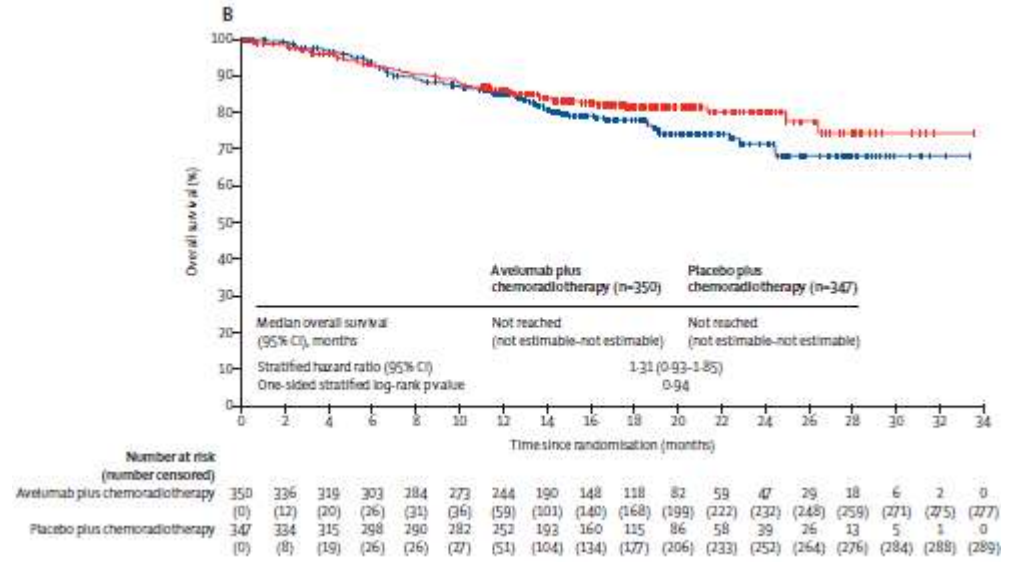
JAVELIN Head and Neck 100



The primary endpoint was progression-free survival, Secondary endpoints were overall survival

	Avelumab plus chemoradiotherapy group (n=350)	Placebo plus chemoradiotherapy group (n=347)
Age		
Median (IQR), years	60 (54-65)	59 (54-65)
<65 years	248 (71%)	247 (71%)
≥65 years	102 (29%)	100 (29%)
Sex		
Male	290 (83%)	285 (82%)
Female	60 (17%)	62 (18%)
Eastern Cooperative Oncology Group performance status score		
0	193 (55%)	214 (62%)
1	157 (45%)	133 (38%)
Geographical region		
North America	82 (23%)	92 (27%)
Western Europe	106 (30%)	113 (33%)
Eastern Europe	52 (15%)	45 (13%)
Asia	100 (29%)	84 (24%)
Rest of the world	10 (3%)	13 (4%)
Human papillomavirus status		
Positive	121 (35%)	117 (34%)
Negative	229 (65%)	230 (66%)
Tumour stage at baseline†		
<T4	198 (57%)	193 (56%)
T4	152 (43%)	154 (44%)
Nodal stage at baseline†		
N0-N1-N2a-N2b	184 (53%)	181 (52%)
N2c-N3	166 (47%)	166 (48%)
Site of primary tumour		
Oral cavity	47 (13%)	49 (14%)
Oropharynx	157 (45%)	169 (49%)
Larynx	59 (17%)	65 (19%)
Hypopharynx	87 (25%)	64 (18%)





Barriers to effective translation of preclinical findings to clinical trials

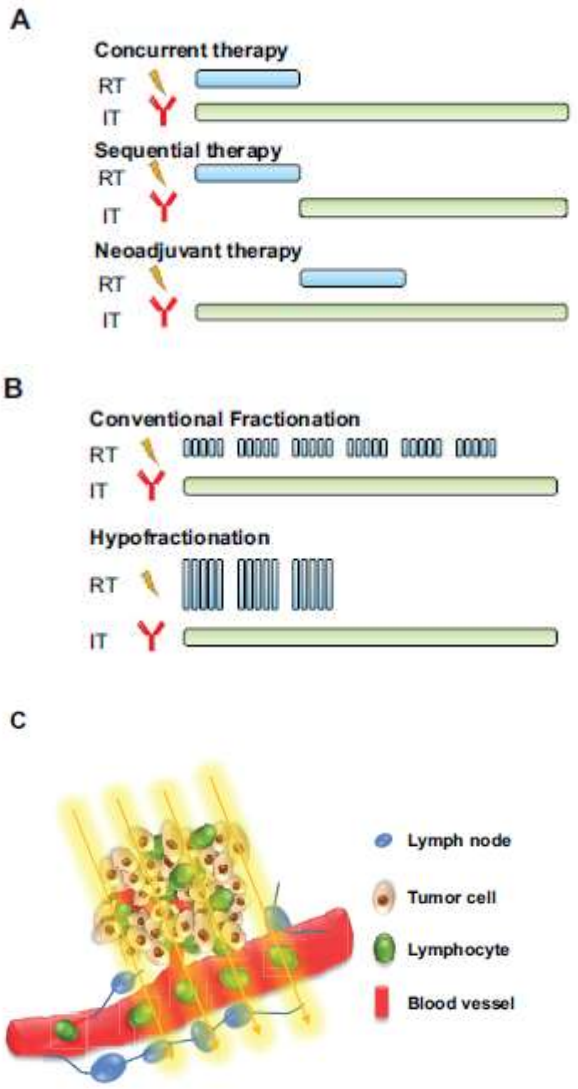
1. Preclinical model limitations
   i. murine cancer cell lines are generally more immunogenic than human tumors
   ii. studies in mice lacking a functional immune system cannot be used to study the capacity of immunotherapy to act on these tumors via endogenous immune elements
2. Limited number of phase I & phase II clinical trials
3. Uncertainty in understanding the effect of Scheduling and sequencing , optimal dose and other cofactors

Current challenges of IRT

A. Optimization of treatment timing: using immunotherapy concurrently, sequentially, or as neoadjuvant therapy with radiotherapy

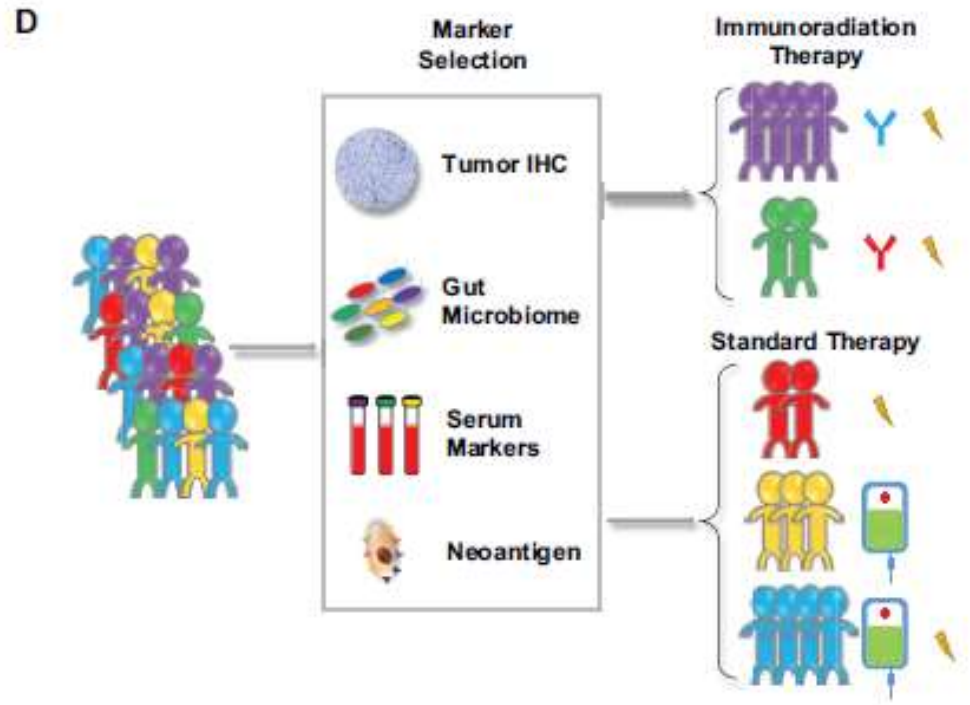
B. Optimization of radiation dosing: conventional fractionation or hypofractionation

C. Reduction of the radiation-induced toxicity of circulating and tumor-infiltrated lymphocytes.s

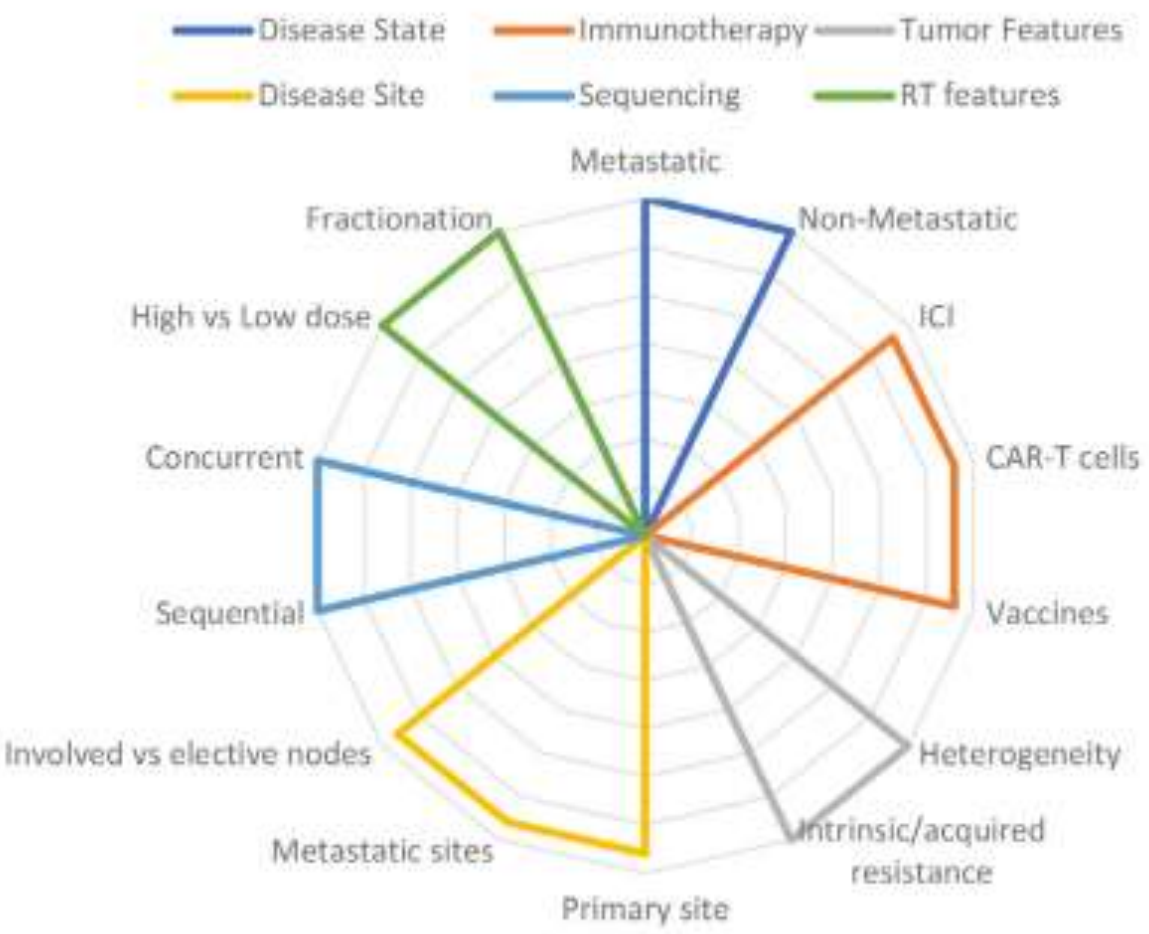


Current challenges of IRT

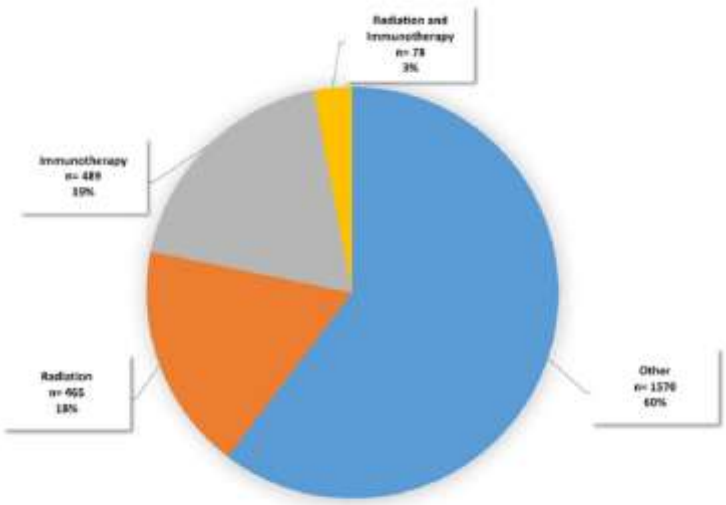
D. Selection of immunoradiation therapy or standard therapy for patients based on predictive biomarkers



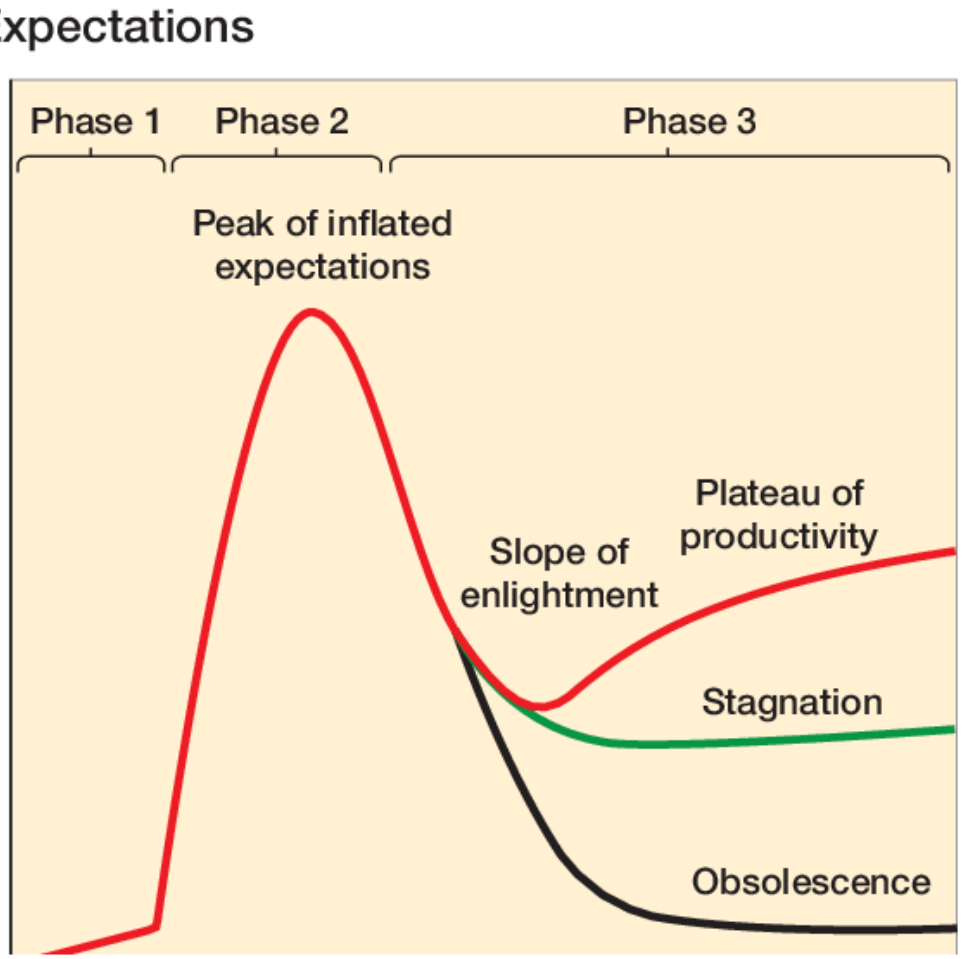
Factors associated with efficacy of radio-immunotherapy



The way forward



Phase 3 Interventional Clinical Trials



Take home points

- Strong biological rationale of combination use – potential for synergistic effects
- Abundance of encouraging preclinical data supporting this synergism
- Initial Clinical Evidence of efficacy in NSCLC, bladder cancer and melanoma have stemmed up the enthusiasm
- However there are challenges in translation, warranting further well formulated clinical research
- Need for personalized approaches – owing to variability in tumour biology and patient responses

We still don’t have the complete picture