From immune-sparing to immune-adapted radiotherapy

Tumour, host and immune geography

Eric Deutsch

LySAIRI, ATRA, ILDR and lymph-node sparing

This project has received funding from the French ANR under grant agreement ANR-21-RHUS-0005.

Programme

From the clinical evidence to testable interventions

01 **Clinical evidence**
The treatment backbone and trial design determine attribution.

02 **The host response**
LySAIRI, myeloid biology and the thymic reserve.

03 **Intestinal low-dose radiation**
Initial data, independent replication and ILDR-01.

04 **Immune preservation**
Lymph nodes, circulating blood and delivery technology.

05 **Clinical translation**
Residual burden, trial architecture and recovery.

02

Living update, search through 3 September 2026

The randomized component changes the clinical question

51 randomized trials, 16,678 patients

Overall survival

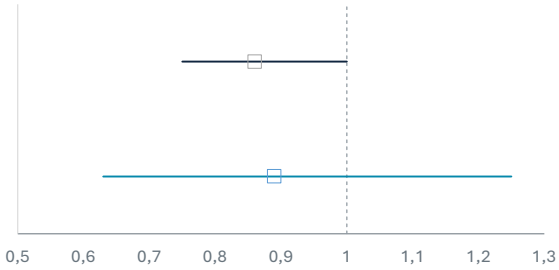
HR (95% CI)

ICI added to RT
42 trials

0.86
(0.75 to 1.00)

RT added to ICI
9 trials

0.89
(0.63 to 1.25)



PFS HR 0.78 and EFS HR 0.71 when ICI is added to RT

Adding RT to ICI: no significant pooled OS or PFS benefit

Preliminary living update. OS benefit depends on tumour type and sequence.

Tomassen et al. Eur J Cancer 2026. PMID 42208279. Published analysis: 41 trials. Living update shown: preliminary.

03

Clinical context

I-SABR and TREASURE test different treatment strategies

	I-SABR	TREASURE
Population	Early-stage or isolated lung recurrence Node-negative NSCLC	Extensive-stage SCLC After induction chemoimmunotherapy
Randomized addition	Nivolumab to ablative SABR	Thoracic RT to atezolizumab 30 Gy in 10 fractions
Efficacy	4-year EFS: 77% vs 53% ITT HR 0.42	No OS benefit Median OS: 6.7 vs 13.4 months
Safety	15% grade 3 immune adverse events No grade 4 or higher toxicity	Stopped early for safety Fatal outcomes: 19.4% vs 3.0%

Cross-trial contrast: different diseases, treatment backbones and radiation intentions.

Chang et al. Lancet 2023. PMID 37478883. Bozorgmehr et al. JAMA Oncol 2026. PMID 42424047.

04

Lessons from direct RT-addition trials

Local control and systemic benefit are separate endpoints

Trial	What was tested	Implication for the next trial
PEMBRO-RT	Single-site SBRT before pembrolizumab Primary endpoint not met	Prespecify the biological subgroup and the systemic endpoint
CHEERS	SBRT to up to 3 lesions during ICI No PFS or OS improvement	Measure untreated viable burden and how much disease RT controls
TREASURE	Thoracic consolidation during atezolizumab No OS benefit, excess serious toxicity	Measure lymphocyte trajectories and prespecify infection/respiratory harm

A negative or unsafe trial narrows the question for a subsequent randomized test.

PEMBRO-RT: PMID 31294749. CHEERS: PMID 37410476. TREASURE: PMID 42424047.

05

Levels of evidence

From biological perturbation to clinical attribution

01 **Local perturbation**
DNA release, interferon signalling or PD-L1 induction

02 **Tumour-specific immunity**
Clonotype tracking and functional tumour reactivity

03 **Clinical attribution**
Randomized benefit with the radiation variable isolated

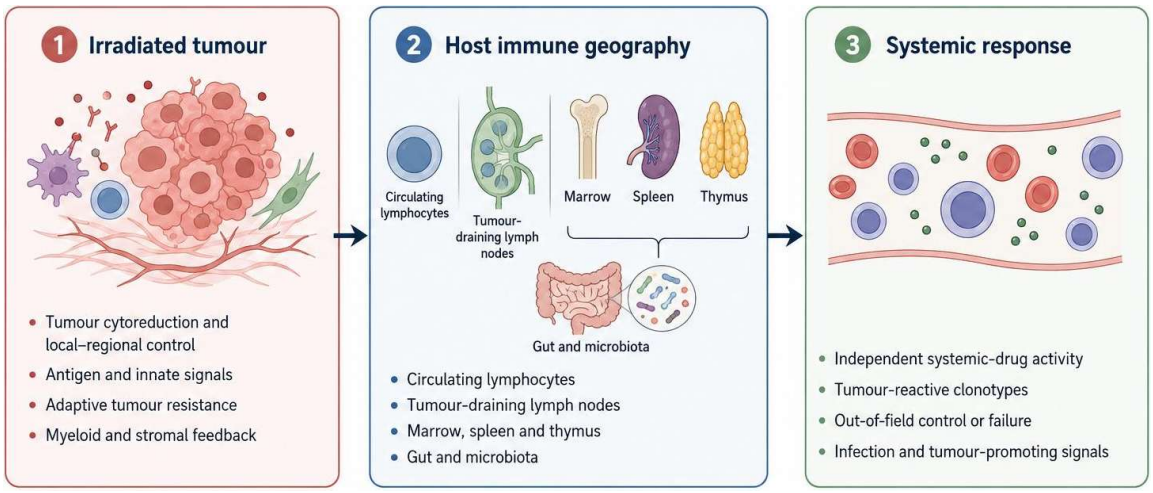
04 **Causal mediation**
Immune change precedes benefit and explains part of the effect

Radiation can activate immunity and cause immune injury within the same course.

06

NRCO framework

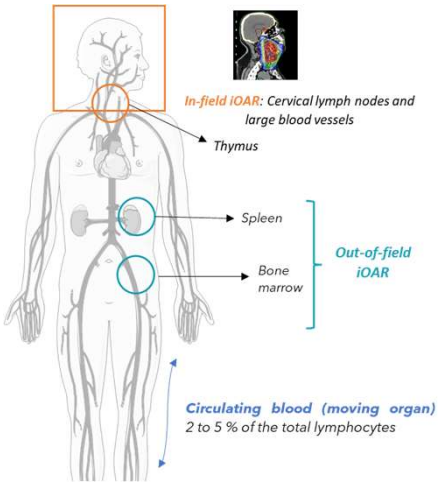
The tumour, immune geography and systemic response



07

Immune geography

The immune footprint has to be measured anatomically



Beyond tumour dose

Circulating blood and lymphocytes
Tumour-draining lymph nodes
Marrow and lymphoid reservoirs
Gut and microbiota

Dose, volume and delivery time are distinct exposures. Their value as a combined clinical score remains unvalidated.

LySAIRI meeting deck. de Kermenguy et al. Phys Med Biol 2024. PMID 38593817.

08

NRCO framework

Potential immune gain and immune cost of irradiation

Potential immune gain

Antigen release
Tumour cell death and neoantigen liberation

Dendritic-cell priming
Antigen presentation and co-stimulation

Inflamed tumour microenvironment
Innate activation and increased chemokines and cytokines

Tumour-reactive clonotypes
Expansion and diversification of effector T cells

Possible out-of-field benefit
Systemic trafficking and tumour control at distant sites

Potential immune cost

Circulating-lymphocyte depletion
Lymphopenia and clonal attrition

Tumour-draining-node injury
Disruption of antigen presentation and T-cell priming

Marrow, thymus and spleen exposure
Impaired lymphopoiesis, T-cell output and immune reserve

Myeloid and stromal reprogramming
Immunosuppressive phenotypes, fibrosis and barrier formation

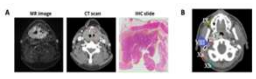
Tumour-promoting or suppressive signalling
Release of factors that support tumour growth and metastasis

09

LySAIRI programme

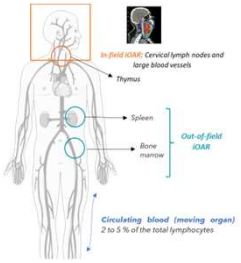
Four linked components of immune-adapted radiotherapy

Characterize



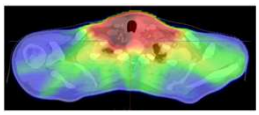
Tumour and immune infiltration

Model



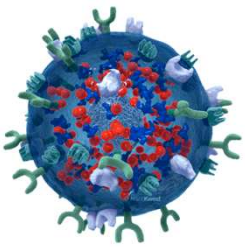
Dose to immune compartments

Plan



Adapt target volumes and treatment delivery

Intervene



RT + ATRA clinical translation

LySAIRI programme, ANR-21-RHUS-0005. Supplied source deck, September 2026. Programme overview.

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LySAIRI-RETRO

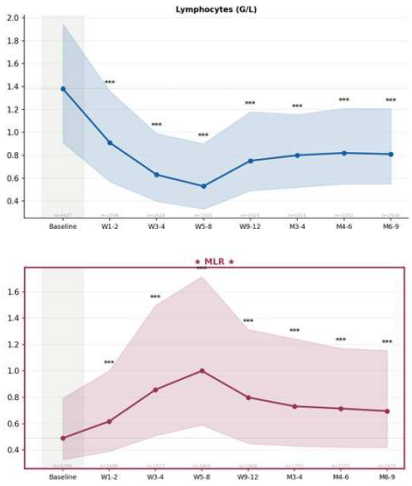
Blood trajectories quantify the immune cost of radiotherapy

3,404 patients
57,858 measurements

Across tumour types

MLR change: +104.1%
Lymphocytes: −61.6%

Most affected window:
5 to 8 weeks after RT starts



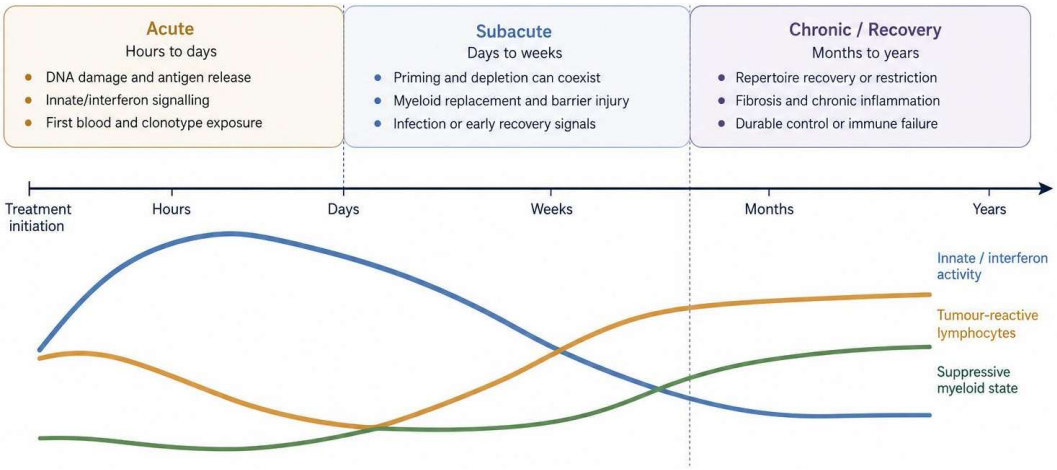
Original panels: median and interquartile range

LySAIRI-RETRO. Internal analysis, 11 September 2026..

11

NRCO framework

Immune injury and recovery follow different time courses

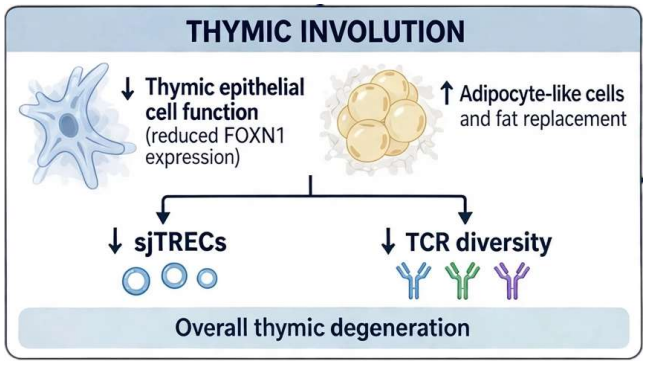


Conceptual trajectories: qualitative curves, without a common quantitative scale.

12

Thymus 1/4

Thymic reserve and renewal of the T-cell repertoire



A measurable host compartment

CT-derived thymic health is an imaging surrogate of residual thymic structure.

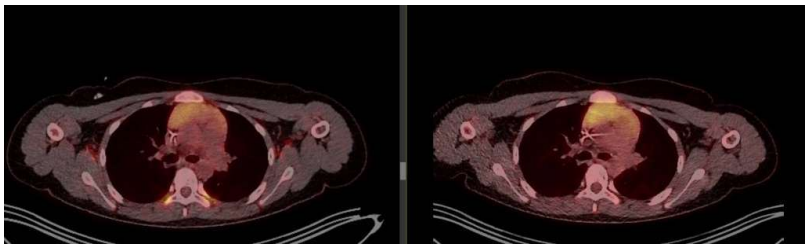
In 1,218 patients with NSCLC receiving ICI, higher thymic health was associated with better outcomes.

Prognostic association. ICI-specific predictive value and clinical utility remain unproven.

13

Thymus 2/4

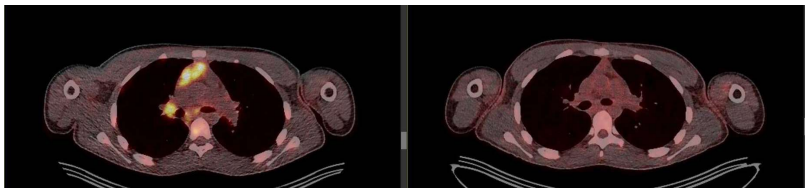
Tumour response can occur without thymic rebound



Patient 1: two views during nivolumab

Patient 2: before PEMBRO + GVD

After PEMBRO + GVD



Thymic rebound

During nivolumab
Hodgkin lymphoma

Homogeneous thymic FDG uptake

Response without rebound

After pembrolizumab + GVD

Both PETs preceded mediastinal RT

PET_rebound Immunorad.pdf, pp. 2, 6-7. Illustrative cases, unpublished. FDG uptake alone does not establish thymic function.

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Thymus 3/4

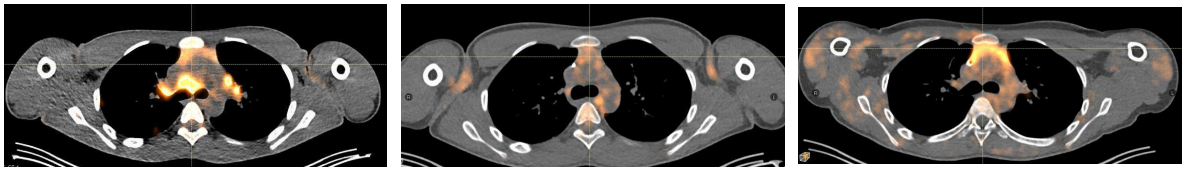
Persistent thymic uptake after PD-1-based treatment

Metastatic EBV-positive nasopharyngeal carcinoma (UCNT)

24 Oct 2023
Baseline

19 Feb 2024
After induction chemo + nivolumab

10 Aug 2026
Capecitabine

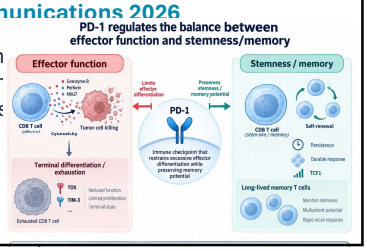


Clinical observation

Persistent thymic uptake with a reported inverse relationship to tumour burden.
SUV and metabolic-volume data remain to be analysed.

Mao et al., Nature Communications 2026

Pdcd1 deletion primes thym
Short-course anti-PD-1 did r
this phenotype in their mous



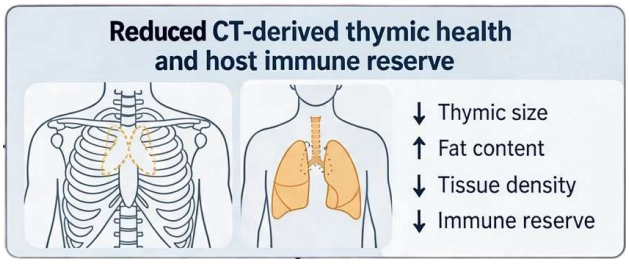
Chemotherapy confounds attribution. Anti-PD-1 specificity remains unproven.

Institutional case, unpublished: PET_rebound.pdf, pp. 8-9. Mao et al. Nat Commun 2026;17:6769. PMID 42177167.

Thymus 4/4

Imaging, thymic output and repertoire need joint validation

Biological correlates in treatment-naive TRACERx patients



Thymic output | n = 45

Higher sjTREC levels with higher thymic health.

Blood TCR diversity | n = 50

Greater peripheral blood α- and β-chain diversity.

Biological validation in surgical patients, not prediction of ICI benefit.

Radio-immunotherapy test

NCT02904954: 60 patients, durvalumab with or without primary-tumour SBRT (8 Gy × 3).

Prospective measurements

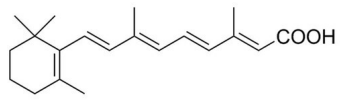
Serial CT, sjTRECs and TCR diversity, linked to continuous thymic and blood-pool dose.

Bernatz, PMID 41851467. Altorki, PMID 34015311. Ito, PMID 28319462. JITC revised working manuscript, Figure 1 excerpt.

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LySAIRI translational strategy

ATRA targets myeloid suppression after radiotherapy



All-trans retinoic acid

The biological rationale

Radiation changes both the lymphoid and myeloid compartments.

ATRA can promote inflammatory macrophage differentiation and reduce suppressive myeloid states.

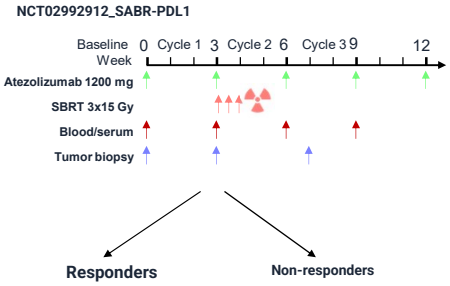
A rationale for testing RT + ATRA, not evidence of clinical benefit.

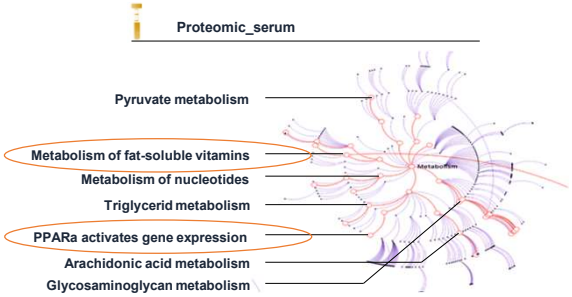
Related published mechanism: Rao et al. Sci Immunol 2021. PMID 34723044.

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Human exploratory biology

Serum proteomics points towards retinoic-acid biology





Evidence of ATRA-related dysregulation also in the blood
>> ATRA

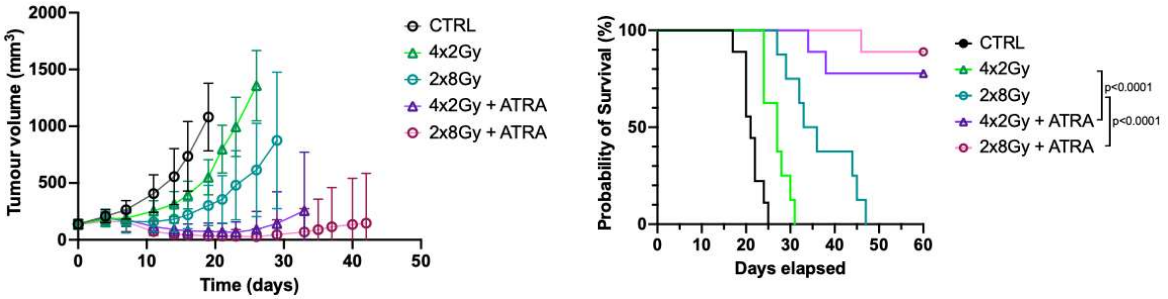
NCT02992912. LySAIRI serum proteomics and tumour RNA-seq, internal exploratory analyses. No PMID.

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LySAIRI preclinical data

RT + ATRA: tumour growth and survival in the MC38 model

Original source curves



Two radiation schedules: 4 × 2 Gy or 2 × 8 Gy, with or without ATRA

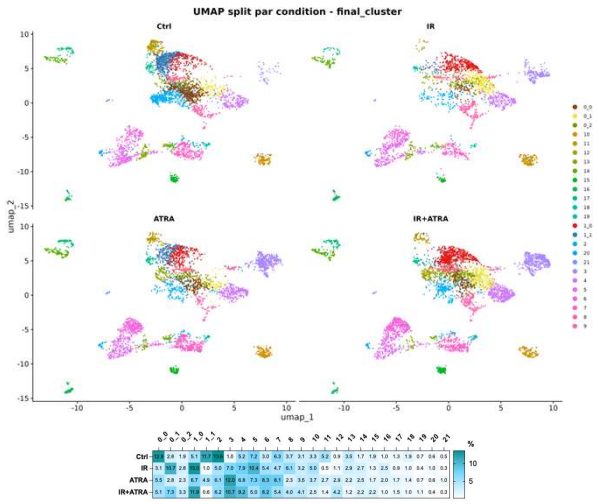
Internal preclinical evidence. These curves are not figures from Rao et al.

Rao et al. Sci Immunol 2021. PMID 34723044.

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MC38 tumour CD45+ single-cell RNA-seq

RT + ATRA changes the myeloid compartment



Control / RT / ATRA / RT + ATRA

Fewer suppressive myeloid states
(TREM2+, RETNLA+, C1Q+)

More NOS2+ and
IFN-responsive myeloid cells

Rao et al. 2021. PMID 34723044.

20

Spatial transcriptomics and metabolomics

RT + ATRA changes metabolism and immune-cell geography

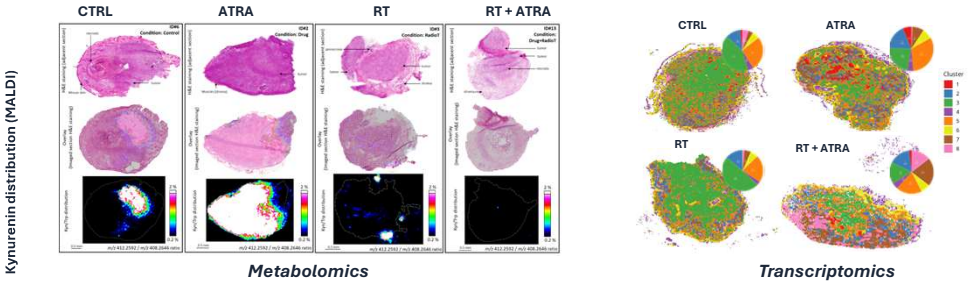


MC38

- CONTROL
- ATRA
- RT (4x2 Gy)
- RT + ATRA

Mechanistic dissection

→ **Spatial transcriptomics/metabolomics**



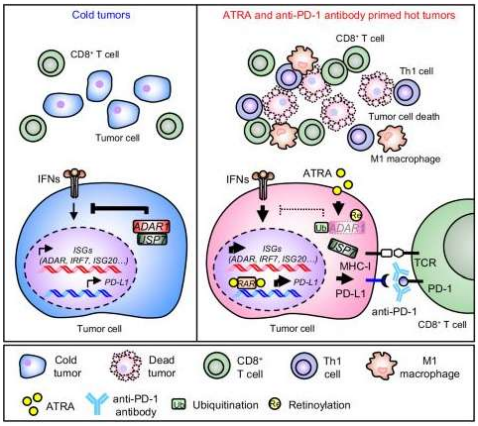
Metabolomics *Transcriptomics*

RT + ATRA reduced the kynurenine/tryptophan ratio and redistributed inflammatory macrophages within the tumour.

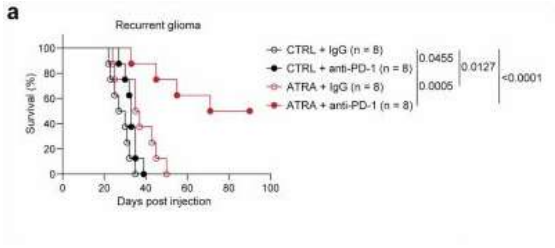
Two independent 2026 publications

ATRA acts on tumour sensing and T-cell state

Tumour-intrinsic sensing



Response to anti-PD-1 in recurrent glioma



ATRA restrains terminal CD8 exhaustion through WNT/β-catenin and TCF-1βBD.

Neither study tested a radiotherapy combination.

Li et al. Nat Commun 2026. PMID 42115161, Fig. 7f. Kang et al. STTT 2026. PMID 42642387, Fig. 6a.

LySATRA clinical translation

From preclinical mechanism to a randomized test

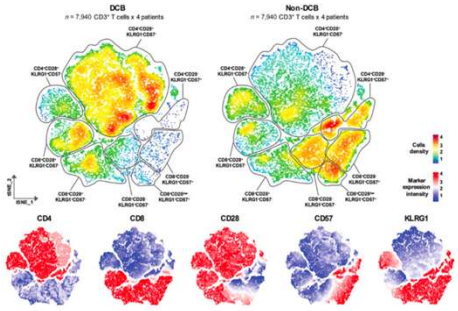
Oligometastatic solid tumours
1 to 5 active lesions

RT to all active lesions

versus

RT to all active lesions + ATRA

Primary endpoint: lymphopenia
6 weeks after RT



Translational readout: viSNE maps of CD3+ T cells (~7,940 cells, n = 4 per group)
Durable clinical benefit vs non-DCB; density shifts toward CD28- KLRG1+ CD57+ senescent clusters

Recruitment: 9 / 52

Update, September 2026
No efficacy conclusion at this stage

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LySARI phase III protocol

Separating the radiation strategy from the ATRA effect

Locally advanced head and neck squamous-cell carcinoma

Standard volumes and doses	Tailored volumes and doses
Without ATRA	Without ATRA
With ATRA	**With ATRA**

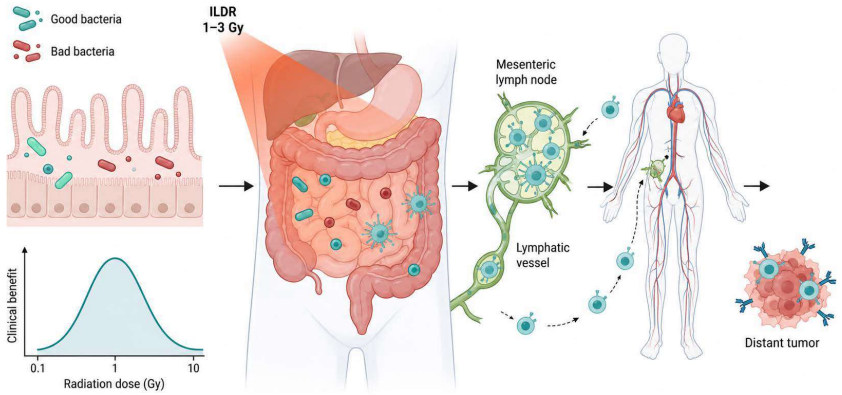
Four-arm randomization: 1:1:1:1

Regional control remains central when modifying elective nodal treatment.

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Intestinal low-dose radiation

The gut as a potential immune target

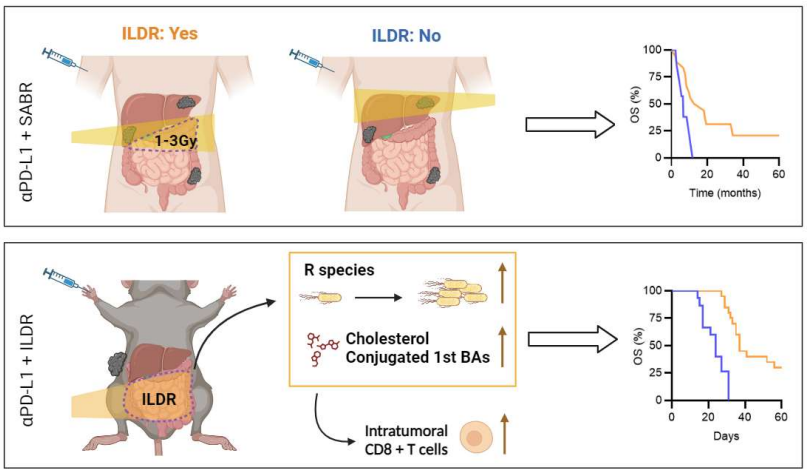


Chen et al. Cancer Cell 2025. PMID 40068595.

25

From incidental dose to mechanism

A reproducible intestinal dose window, with a biological hypothesis



87

discovery patients

388

patients across eight cohorts

Association in patients; mechanism tested in mice.

Chen et al. Cancer Cell 2025;43:361-379.e10. PMID 40068595. doi:10.1016/j.ccell.2025.02.010.

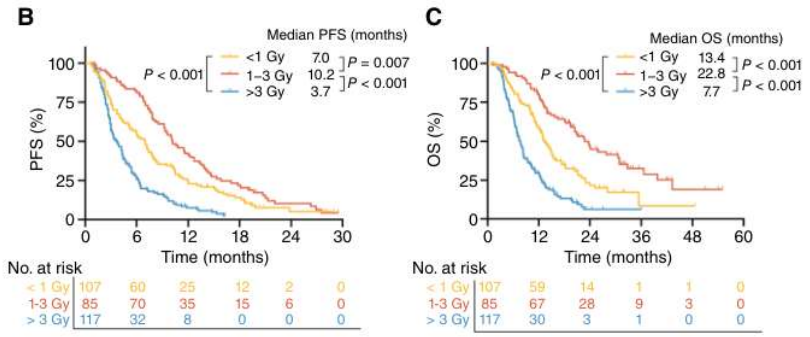
26

ILDR 1/2

Our ILDR dose window is reproduced in an independent cohort

Our initial signal: 388 patients across 8 cohorts, with a favourable low-dose window.

Huang et al., CCR 2026: independent multicentre study in metastatic NSCLC



309 patients

PD-1-based therapy
+ abdominopelvic RT

1 to 3 Gy

Mean small-bowel dose associated with the best PFS and OS

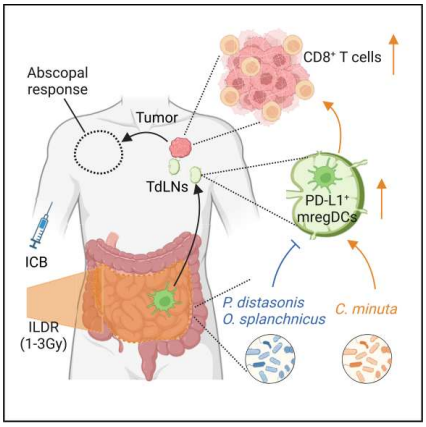
Independent replication of the association. Intestinal dose was not randomized.

Chen, Levy et al. Cancer Cell 2025;43:361-379.e10. PMID 40068595. Huang et al. Clin Cancer Res 2026;32:3586-3598. PMID 41849236.

ILDR 2/2

Prospective data and biology reinforce the initial ILDR signal

Our mechanistic model



Independent prospective cohort, n = 30



Best disease control and PFS again at 1 to 3 Gy mean small-bowel dose.

DCR: P = 0.041 PFS: P = 0.046

Concordant microbiota and immune correlates

Responders: enrichment in Bacillota / Clostridia and indole derivatives.

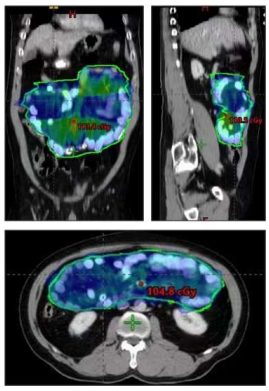
1 to 3 Gy: higher circulating MIP-3α and fewer α4β7+ regulatory T cells.

Correlative biology. Planned 1-Gy ILDR still requires randomized validation.

Chen, Levy et al. Cancer Cell 2025;43:361-379.e10. PMID 40068595. Huang et al. Clin Cancer Res 2026;32:3586-3598. PMID 41849236.

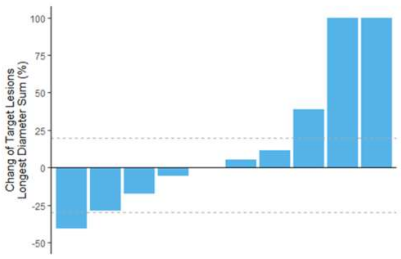
ILDR-01, NCT06076135

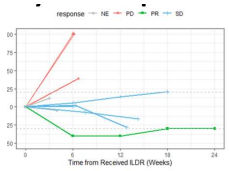
A deliberate intestinal exposure before ICI rechallenge



1 Gy ILDR

First published cohort





Investigator update

24 treated
20 evaluable

ORR 25%
DCR 55%

Not peer reviewed.
Small, heterogeneous cohort; no control arm.

Published panels: Chen et al. Cancer Cell 2025. PMID 40068595..

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ILDR: interpretation of the dose window

The intestinal dose window needs prospective validation

What the cohorts show

Mean small-bowel dose of 1 to 3 Gy was associated with better outcomes than <1 Gy or >3 Gy.

What the comparison cannot establish

A causal dose optimum
A universal 3-Gy toxicity threshold
Equivalence to a planned 1-Gy exposure

Prospective test

Randomized intestinal exposure with fixed systemic therapy, explicit bowel volume and longitudinal microbiome/immune readouts.

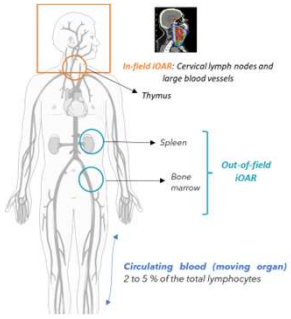
Tumour coverage and established bowel constraints remain essential.

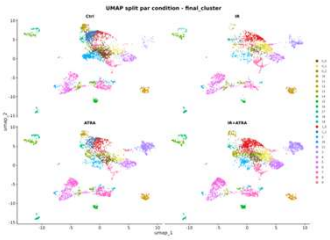
Chen et al. Cancer Cell 2025. PMID 40068595. Huang et al. Clin Cancer Res 2026. PMID 41849236.

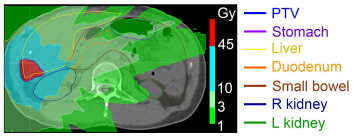
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Three distinct interventions

Immune-adapted does not always mean immune-sparing







Preserve

Blood, lymphoid reservoirs
and selected uninvolved nodes

Reprogram

Myeloid suppression
and tumour immune state

Irradiate deliberately

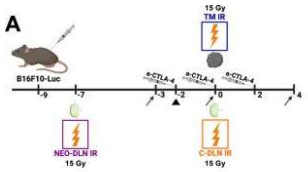
A tested intestinal dose window,
not general dose escalation

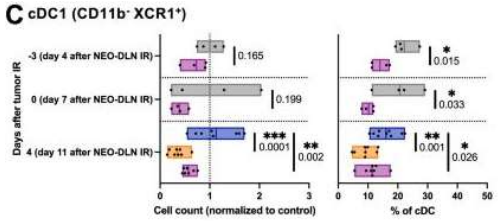
PMID 38593817, 34723044, 40068595.

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Tumour-draining lymph nodes

Preserve immune priming without compromising regional control







Mouse experiment

Nodal irradiation
alters the cDC1
compartment.

mRCAT-III

Phase III abstract, ASCO 2026
pMMR/MSS rectal cancer, n=154

pCR
61.4% vs 28.6%

Both nodal volume and PD-1 blockade changed. The benefit cannot be attributed to node sparing alone.

Telarovic et al. Nat Commun 2024. PMID 38951172, Fig. 10A,C.. Shen et al. 2025. PMID 40229241. Song et al. ASCO 2026, LBA3515

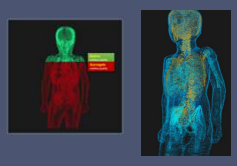
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LYMPHODOSE

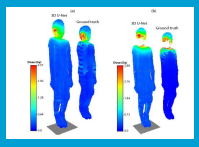
Blood is a moving organ at risk

Whole-body dose, circulation and lymphocyte recirculation

Step 1: Extend the patient's anatomy

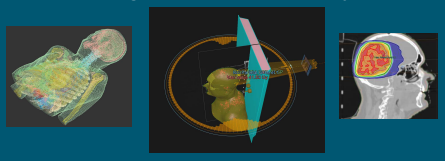


Step 2: Computation of whole-body doses

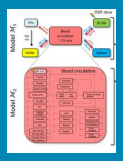


LymphoDOSE: Integrated tool for calculating doses to the lymphocyte pool

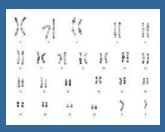
Starting point: DICOM objects summarizing the radiotherapy treatment



Step 3: Lymphocyte dynamics modelling



Step 4: Biological validation



Lymphocyte modelling: de Kermenguy et al. 2024, PMID 38593817. Dose maps: Benzazon et al. IJROBP 2024, PMID 38554830.

Radiation technology and immune preservation

Radiation delivery chang



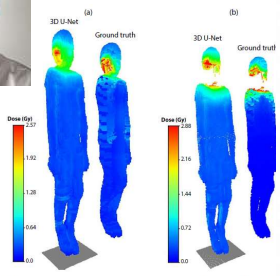


Fig. 3. Comparison of out-of-field dose maps predicted by the 3D U ground truth (b), for 3 patients of varying performance (test set only). Pa percentile of the distribution) corresponds to a 15-year-old girl diagnose and treated with a Neptune 6 MV device. Patient b (test set 3: RMSD = 0 also a 15-year-old girl who was treated in 1982 for an intracranial neopl set 5: RMSD = 1.00 cGy/Gy, below 95% percentile of the distribution) is year with a 1.25 MV betatron device for an astrocytoma.
Abbreviation: RMSD = root mean square deviation.

Illustration: reconstruction of out-of-field dose

Landscape of immune dosimetry models: what are we actually estimating?

From simple dosimetric surrogates to mechanistic immune system modelling

Model	What is estimated?	Strength	Main limitation
EDIC (Effective Dose to Immune Cells)	**Effective dose to circulating immune cells (blood surrogate)** *Based on irradiation of highly perfused organs (lungs, heart, ± liver)*	✓ Simple and fast ✓ **Clinically implementable** ✓ Multiple prognostic associations reported	⚠ Simplified circulation assumptions ⚠ Mainly validated in thoracic anatomies
HEDOS (Hematopoietic and Endothelial Dose Optimization System)	**Dynamic stochastic dose to circulating blood cells** *Explicit modelling of blood flow through multiple physiological compartments*	✓ Physiologically richer than EDIC ✓ Captures circulation dynamics ✓ **Allows personalization** (via patient-specific blood flow models, e.g. FLIP)	⚠ Higher computational complexity ⚠ Dependent on physiological assumptions and input data (validation ongoing)
LymphoDOSE	**Dose to recirculating lymphocyte populations across compartments** *Stochastic continuous-time semi-Markov model including trafficking and homing*	✓ Includes trafficking, homing and recirculation ✓ Accounts for lymphoid organs and tissues ✓ Captures out-of-field contributions	⚠ Strong biological assumptions ⚠ Early translational stage, limited clinical standardization
BLOOD /newer frameworks	**Whole-system immune exposure + survival / replenishment** *Includes secondary lymphoid organs, survival, proliferation and replenishment dynamics*	✓ Most biologically comprehensive ✓ Integrates survival, replenishment and whole-body absorbed dose	⚠ Very high complexity ⚠ Limited clinical use so far; standardization needed

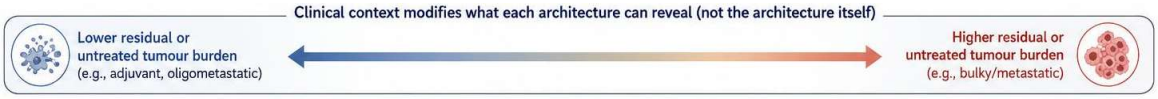
KEY MESSAGE: These models are complementary—not competing—because they do not model the same biological question.

Pair physical exposure with lymphocyte kinetics and a clinical endpoint.

: Benzazon et al. IJROBP 2024, Fig. 3. PMID 38554830. FLASH: PMID 38081067; PMID 40291670.

NRCO clinical context

Residual tumour burden changes the biological question



After treatment of gross disease

ctDNA can distinguish molecular residual disease from an apparently complete response.

Moding et al.: 65 patients after CRT, 218 plasma samples, 28 receiving consolidation ICI.

When substantial disease remains

Focal RT leaves a different balance of tumour burden, resistance and immune suppression.

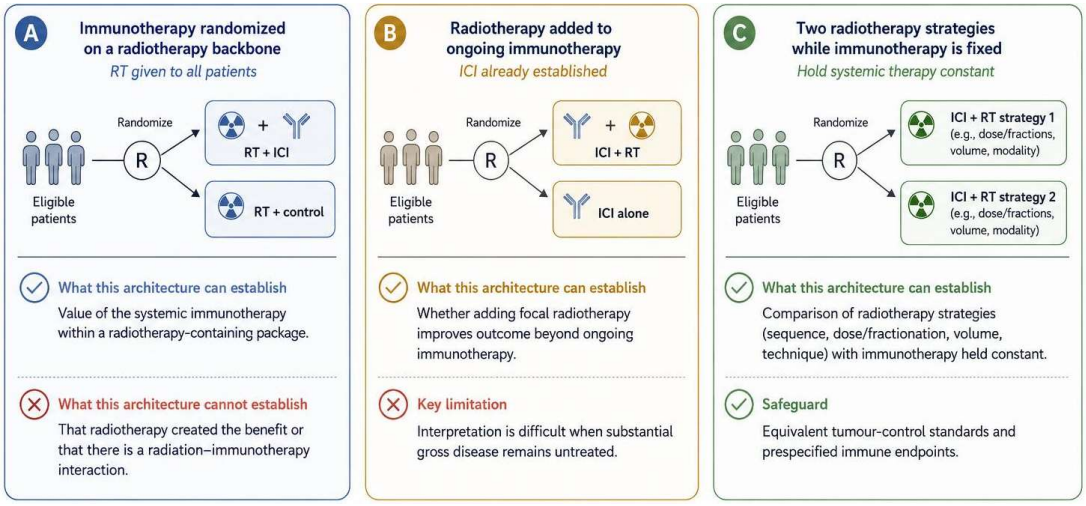
Complete ablation as an immune-enrichment strategy remains a prospective hypothesis.

. Moding et al. Nat Cancer 2020. PMID 34505064.

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NRCO trial interpretation

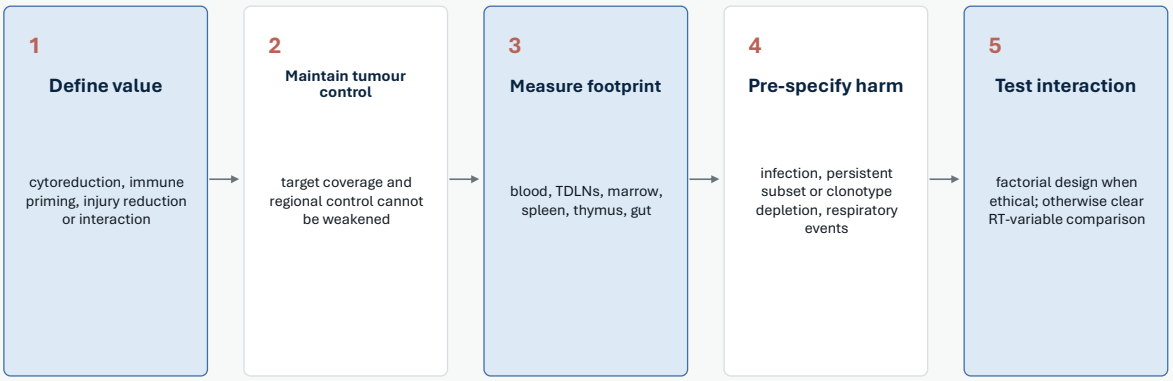
Trial architecture determines attribution



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Designing the next generation of trials

Protocols should prospectively vary the radiation variable that matters.



The protocol should specify dose, volume, time, sequence and the systemic partner.

Trial-design synthesis. Tomassen et al. Eur J Cancer 2026. PMID 42208279. Preserve tumour control and isolate the radiation variable.

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Minimum reporting dataset

A trial needs both physical exposure and immune trajectories

Domain	Minimum information
Radiotherapy	Targets and nodal strategy, dose/fractionation, integral dose, low-dose bath, treatment duration and beam-on time
Immune geography	Estimated blood dose, draining nodes, marrow, spleen, thymus and gut Steroids, infection and other treatment-related exposures
Tumour and host	Viable/metabolic burden, ctDNA, tumour immune phenotype Baseline lymphocyte subsets, myeloid profile and inflammatory state
Longitudinal biology	Blood/stool timing, TCR repertoire, sjTREC or recent thymic emigrants Clinical harm, regional control and recovery

. Lymphocyte modelling: PMID 38593817.

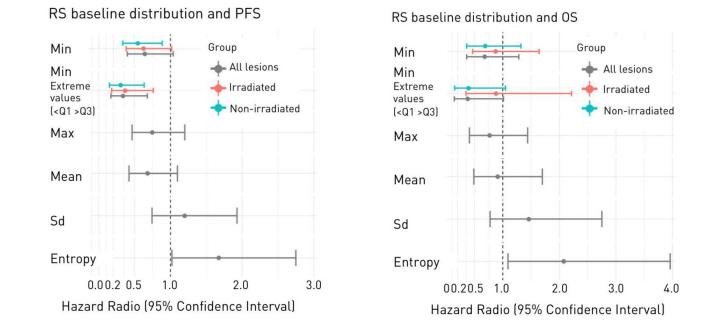
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Radiomics 1/2

Radiomics maps immune heterogeneity across lesions

94 patients receiving RT + ICI

100 irradiated and 189 non-irradiated lesions



Biological anchor

Contrast-enhanced CT signature linked to CD8 gene expression.

Lesion-level information

Minimum lesion score associated with survival in melanoma:
136 patients, 1,120 baseline lesions.

Lesion-level biology complements total tumour burden.

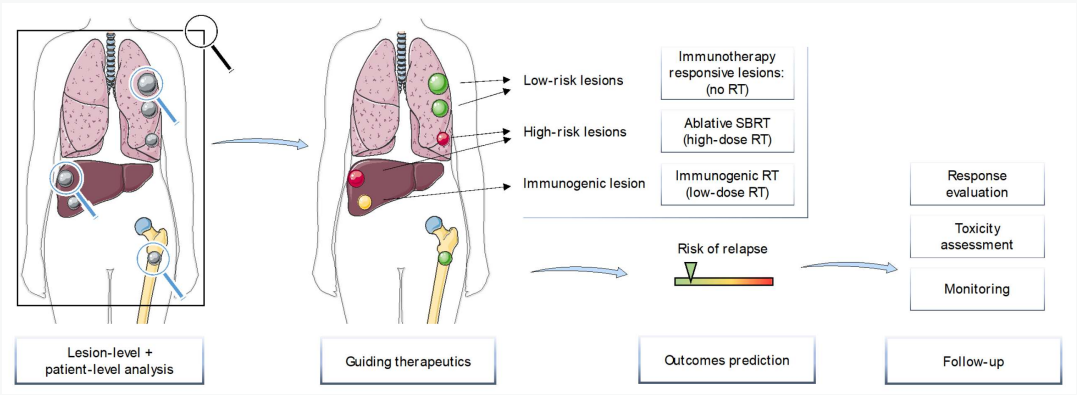
Imaging surrogate. Prognostic association does not establish an RT target-selection rule.

Sun et al. Lancet Oncol 2018. PMID 30120041. Sun et al. JITC 2020. PMID 33188037. Sun et al. JITC 2022. PMID 36307149.

Radiomics 2/2

Radiomics could guide immune-adapted target selection

Conceptual framework, not a validated treatment rule



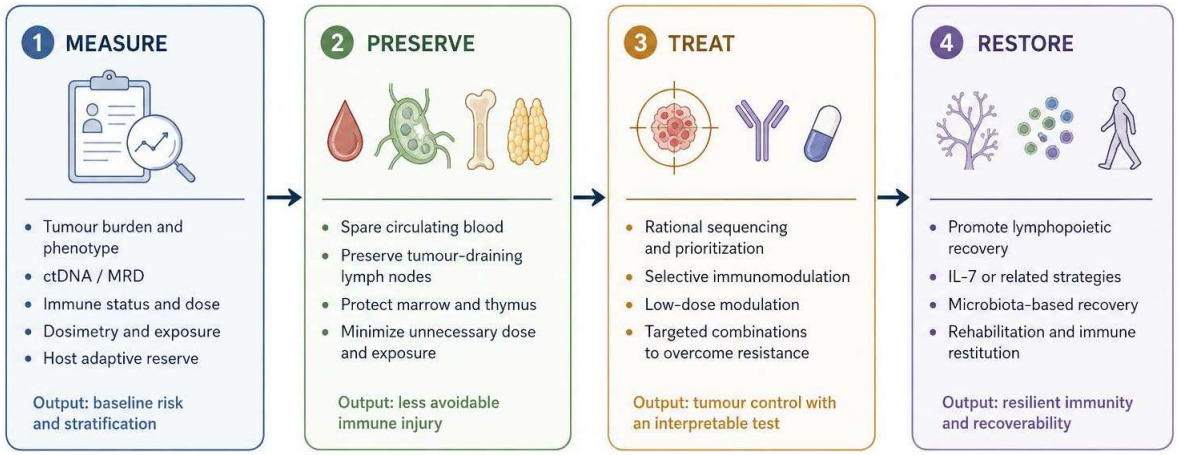
Lesion selection must also account for blood, nodal and thymic exposure.

Prospective test: radiomics-guided versus conventional targeting, with the same ICI backbone.

Sun et al. JITC 2022, PMID 35793875.

NRCO synthesis

Measure, preserve, treat, restore

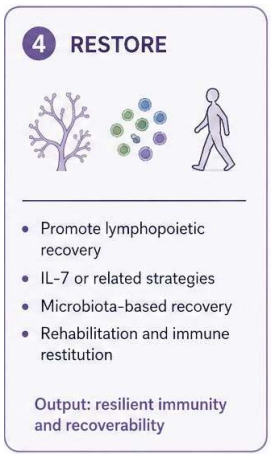


Restoration remains experimental, after adequate tumour control and a documented deficit.

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Experimental restoration

Host-directed recovery starts with a measured deficit



Entry condition

Adequate tumour control and a documented host deficit

Research intervention

A recovery strategy matched to the measured compartment

Benefit and safety

Immune function, infection, autoimmunity and tumour control

See Bernatz et al. Nature 2026, PMID 41851467.

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From framework to protocol

Three questions define three trial concepts

Clinical question	Comparative design	Key readouts
Can gross disease be controlled?	Complete ablation ± ICI Where omission of ICI is ethical	Residual ctDNA Recurrence and clonal response
Can immune exposure be reduced safely?	Two oncologically adequate RT plans Systemic treatment held constant	Exposure and lymphocyte kinetics Regional control and infection
Does a host deficit persist after treatment?	Deficit-defined recovery intervention Randomized against usual care	Functional immune recovery Autoimmunity and tumour control

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LySAIRI programme

The programme links cohort biology to randomized intervention

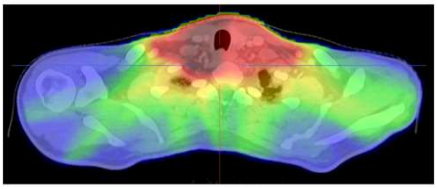
September 2026	**LySAIRI-RETRO** Extension of longitudinal host-response analyses
September 2026	**LySATRA** 9 / 52 patients recruited
October 2026	**LySATRA review** Planned IDMC review
Development	**ATRA formulation** Formulation development, patent EP24306081.1
Next studies	**LySARI and FLASH** Randomized volume/ATRA strategy and physical-modality studies

LySAIRI programme update, September 2026. Internal milestones, not published outcomes.

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Conclusions

Adapt radiotherapy to the tumour and the host



Measure

Baseline immune state and radiation exposure

Choose the intervention

Preserve, reprogram or irradiate a defined compartment

Demonstrate clinical benefit

Maintain tumour control and isolate the radiation variable

The next trial should isolate an explicit radiation strategy and its clinical benefit.

Tomassen 2026, PMID 42208279; de Kermenguy 2024, PMID 38593817; Chen 2025, PMID 40068595.

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ImmunoRad 2026

Acknowledgements

Patients and their families

Clinical teams and translational platforms
Gustave Roussy, Inserm U1355 and Université Paris-Saclay
LySAIRI consortium and collaborators



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