Controversies in Cancer Care: Evidence, Interpretation, & Clinical Decision Making

Radiation Plus Immunotherapy: Synergy or Added Toxicity?

A multidisciplinary review of mechanisms, clinical trial evidence, and toxicity management

Karan Shah, MD, MBA

Assistant Clinical Professor
Department of Radiation Oncology
City of Hope Chicago

Disclosures

I do not have any relevant financial relationships.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:
The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:
Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

This presentation is dedicated solely to research or other issues that do not contain a direct patient care component.

Learning Objectives

- **Mechanistic Rationale:** Understand how radiation reshapes tumor immunogenicity-immunogenic cell death, antigen release and abscopal effect
- **Clinical Evidence:** Review trial data across lung cancer, cervical cancer, oligometastatic disease, and melanoma brain metastases
- **Timing and Sequencing:** Concurrent vs Sequential vs Consolidative
- **Toxicity:** Recognize overlapping and compounded toxicity

Clinical Question

Patient with unresectable stage III NSCLC completes concurrent platinum-based chemoradiation and is eligible for adjuvant durvalumab.

Is this an example of radiosensitizing synergy, sequential treatment, or compounded toxicity?

Pacific Trial: Sequenced RT and immunotherapy can improve outcomes: 5yr OS 42.9% with durvalumab vs 33.4% with placebo and 5yr PFS was 33.1% vs 19.0%

Spiegl et al., J Clin Oncol 2022

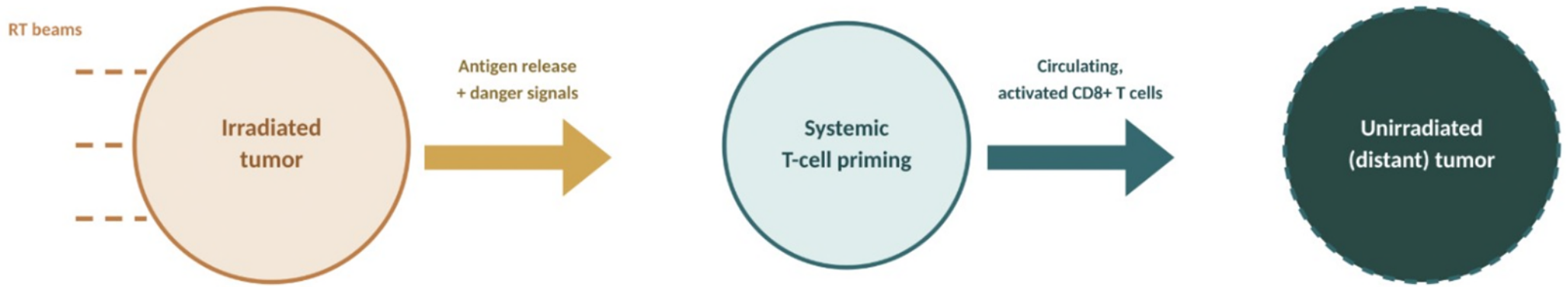
Biologic Rationale: *Radiation is more than local therapy*

Mechanism	Description
Immunogenic Cell Death[1]	Release of calreticulin, HMGB1, and ATP signals dying tumor cells to dendritic cells
Antigen Release	Tumor debris supplies neoantigen for cross-presentation and T-cell priming
MCH-I Upregulation[3]	Irradiation tumor cells become more visible and recognizable to CD8+ T Cells
Vascular and Cytokine Release[4]	Chemokine release and vascular normalization aid T-Cell trafficking into tumor; cGAS-STING pathway

[1]Golden et al. Oncoimmunology 2014.
[2]Formenti et al. J Natl Cancer Inst 2013.
[3]Retis et al. J Exp Med 2006.
[4]Matsumura et al. J Immunol 2008

Abscopal Effect

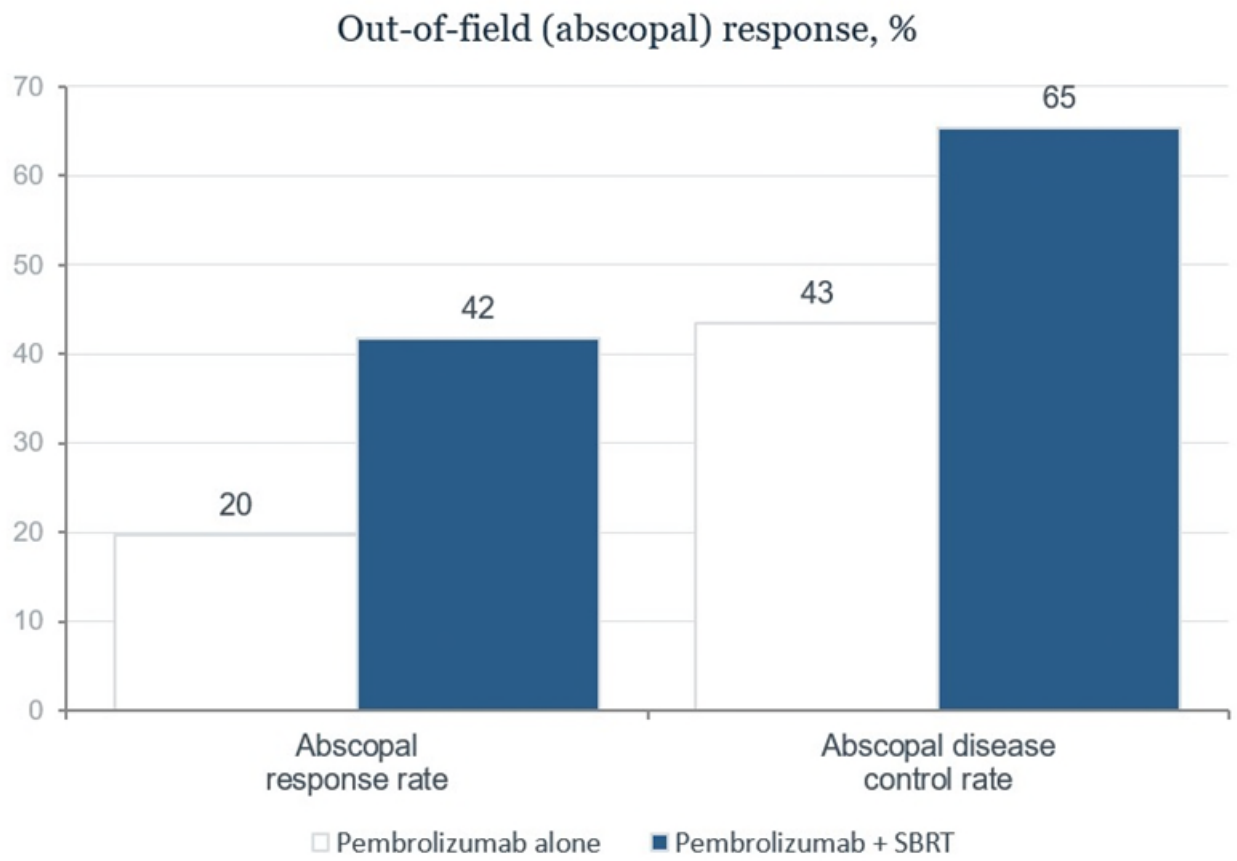
Regression of tumor outside the irradiated field-an immune-mediated, systemic response due to local radiation



Checkpoint inhibition removes the brakes on this newly primed T-cell response — the core rationale for combining radiation therapy with immune checkpoint inhibitors.

Abscopal Effect

PEMBRO-RT (sequential SBRT→pembrolizumab) and MDACC (concurrent) randomized trials for Metastatic NSCLC



Survival signal

	Pembro alone	Pembro + RT
Median PFS	4.4 months	**9.0 months**
Median OS	8.7 months	**19.2 months**

Thelen et al. Lancet Respir Med 2021.

Radiation suppressing immunity

- Larger fields and protracted treatment leading to lymphocyte depletion
- Adaptive PD-L1 upregulation
- Irradiation of circulating blood and lymphoid structures
- TGF-B signaling, hypoxia, and adverse vascular effects
- Treg and suppressive myeloid-cell recruitment
- Inflammation and tissue injury

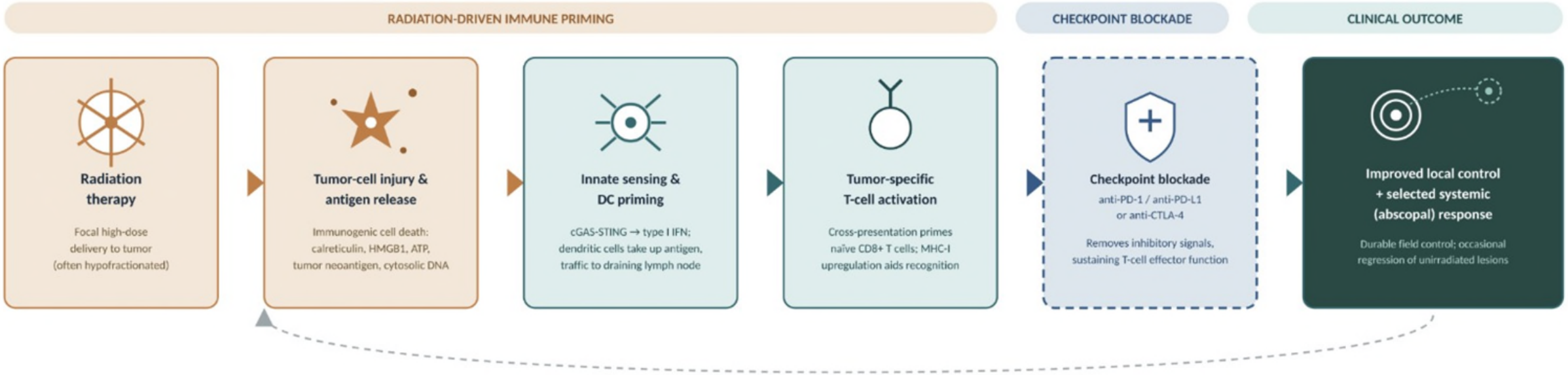
Dose and Fractionation

Net immune effect is dose, volume, site, timing, tumor, and host dependent

Conventional Fractionation (1.8-2 Gy/fx)	Hypofractionated/SBRT/SRS (3-10 Gy x 3-15 fx)	Single Fraction (>15Gy/fx)
Lower per fraction immunogenic cell death Larger fields may deplete circulating lymphocytes Standard for definitive chemoRT	Favors immunogenic cell death & antigen release Smaller, conformal fields	May Trigger TREX1 exonuclease, degrading cGAS-STING signal Potential ceiling effect on immune activation Rationale for 3-5 fraction SBRT over single mega-fraction in some protocols

RT + Immunotherapy Synergy

From local tissue injury to systemic anti-tumor immune response



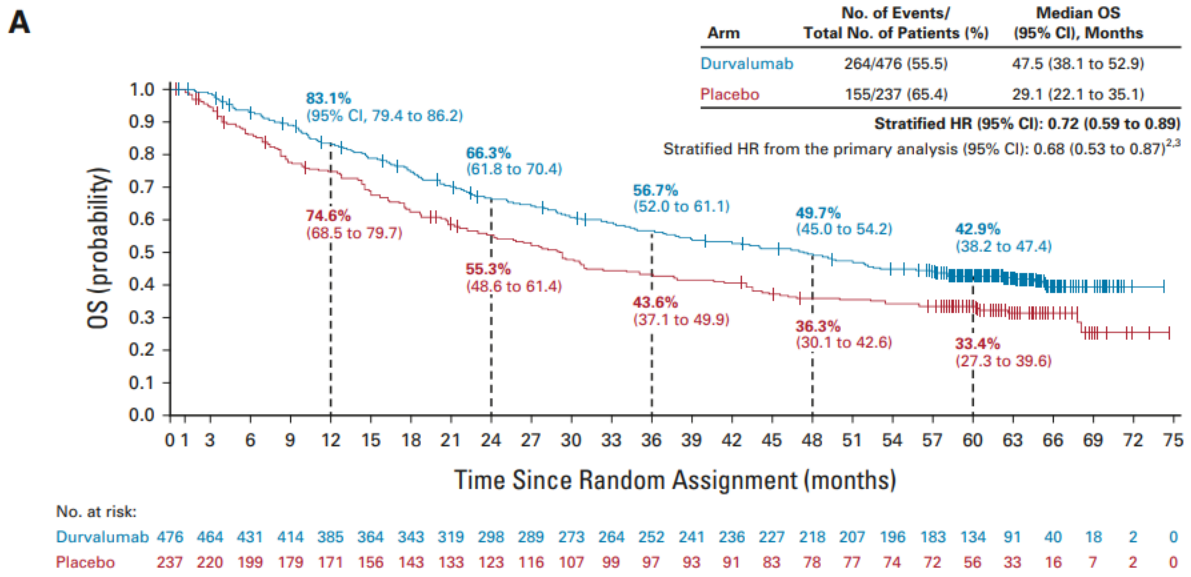
Twyman-Saint Victor et al. Nature 2015.

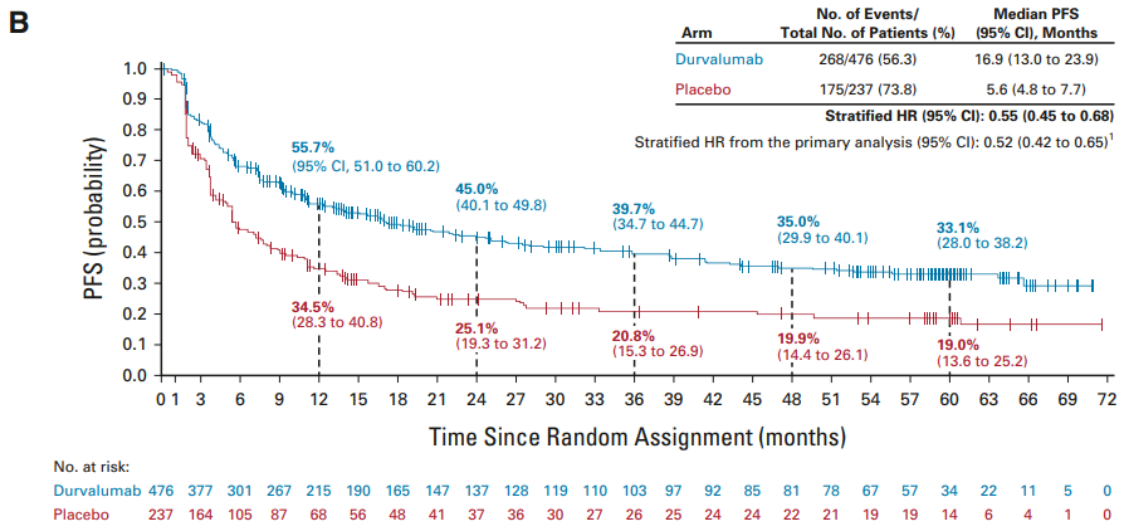
Sequencing Strategies

Strategy	Detail	Evidence
Consolidative	IO initiated after definite ChemoRT is completed	PACIFIC
Concurrent	RT and IO overlap	PACIFIC 2, Keynote A-18, Concurrent SRS + IO in Melanoma brain mets
Sequential (IO→RT)	IO first, then RT layered	H&N Trial
Sequential (RT→IO)	RT initiated before IO	PEMBRO-RT

Consolidative: PACIFIC Trial

PACIFIC-Unresectable Stage III NSCLC-Darvlumab started 1-42 days post CRT

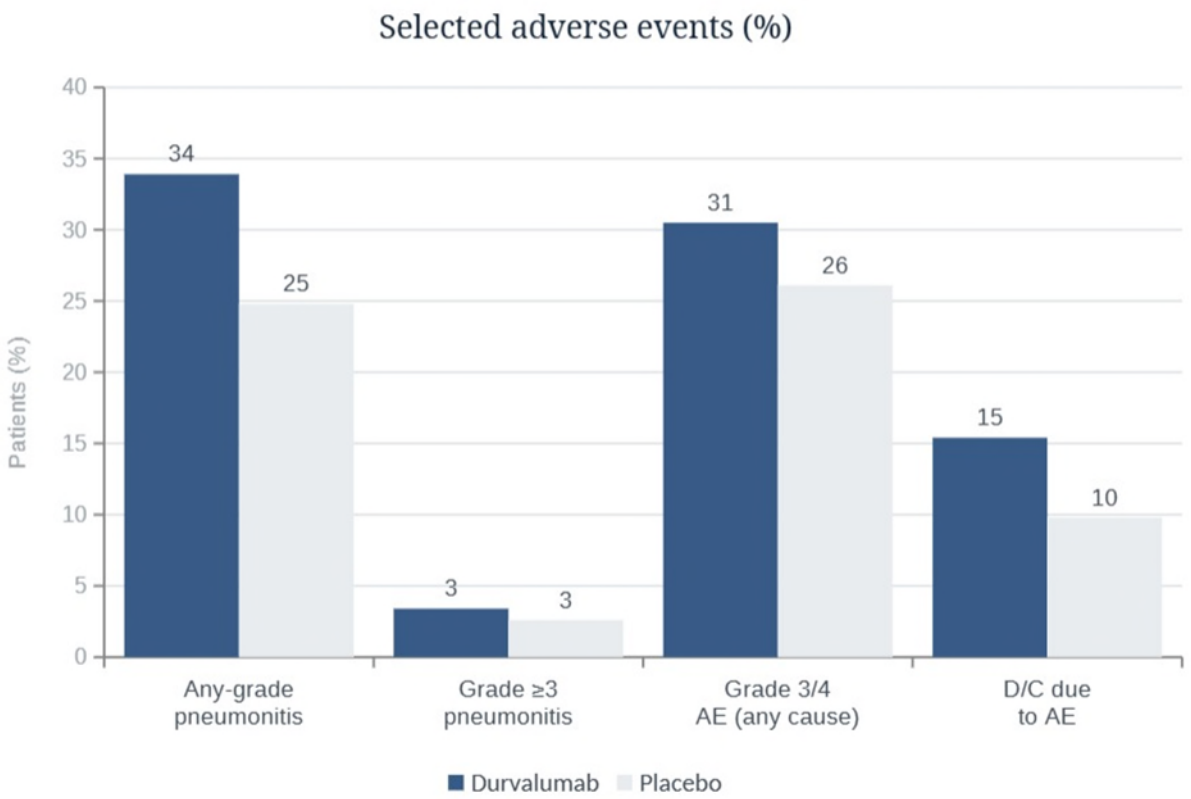




Spigel DR et al, JCO 2022

PACIFIC Trial

Toxicity



Any grade pneumonitis: 33.9% (durvalumab) vs 24.8% (placebo)

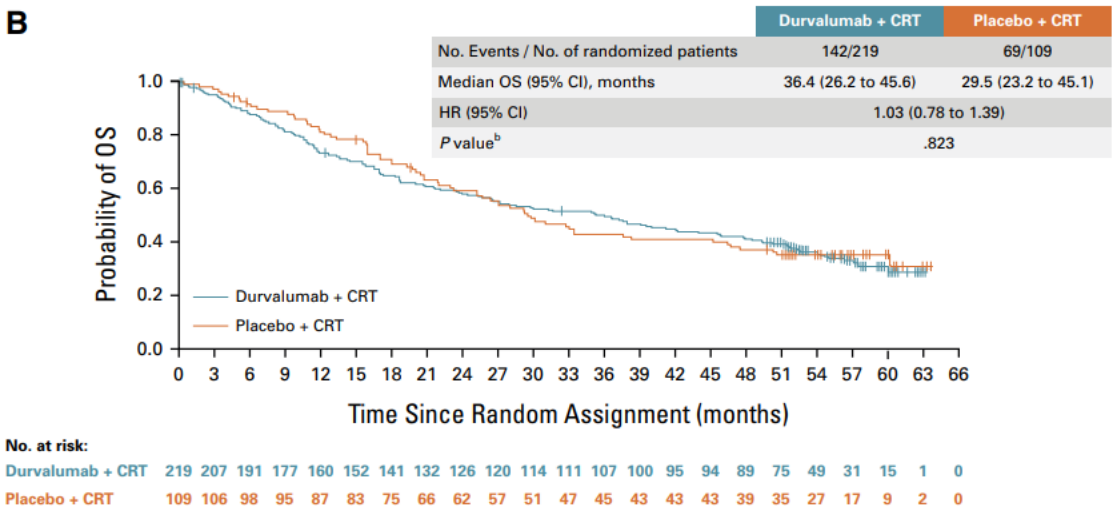
Pneumonitis was concentrated in medium/low-dose lung regions-no high dose fields- suggesting a distinct immune-mediated pattern layered on radiation injury

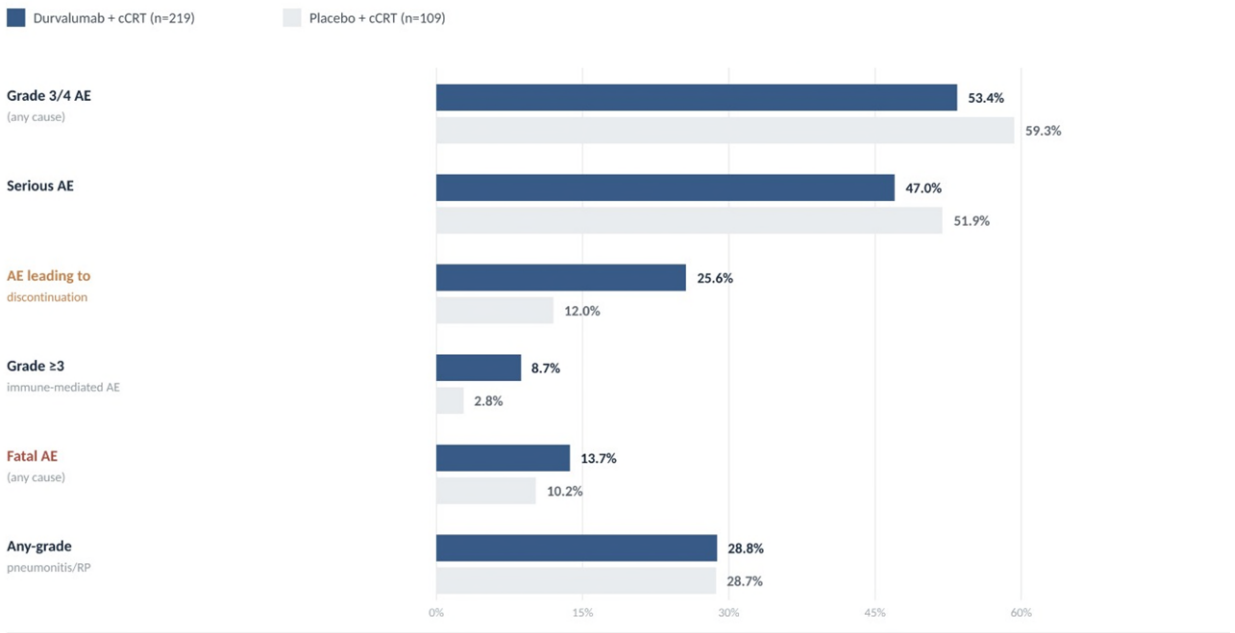
Despite higher rates, most pneumonitis events were low-grade

Pneumonitis was the leading cause of treatment discontinuation in the durvalumab arm

Concurrent: PACIFIC-2 Trial

Concurrent durvalumab from start of CRT for unresectable Stage III NSCLC





Bradley et al., JCO 2025

Concurrent: Keynote A18

ENGOT-cx11/GOG-3047/Keynote A18

82.6%

36-month OS (2nd interim)

vs. 74.8% placebo · HR 0.67 (0.50–0.90)

0.73

OS hazard ratio (final analysis)

95% CI 0.57–0.94 · median follow-up 41.9 mo

64.3%

36-month PFS (final analysis)

vs. 55.6% placebo · HR 0.72 (0.59–0.87)

Toxicity (final analysis)

	Pembro + CRT	Placebo + CRT
TRAE, grade ≥3	69.5%	61.5%
Serious TRAE	19.7%	13.6%
TRAE → discontinuation	18.9%	13.0%
Immune-mediated AE (any grade)	39.8%	17.5%
Immune-mediated AE, grade ≥3	5.1%	1.3%
Fatal TRAE	2 pts	2 pts

- Most common immune-mediated AEs: hypothyroidism (22.5% vs. 6.8%) and hyperthyroidism (12.1% vs. 2.8%)

Lorusso et al., Lancet 2024.

Concurrent: Melanoma Brain Metastases

Single institution retrospective review

101 patients, 435 melanoma brain metastases

Concurrent: IO within 4 weeks after SRS vs Non-Concurrent: SRS alone or IO> 4 weeks

63.8% of patients received systemic immunotherapy within 4 weeks of SRS (Concurrent)-significantly lower risk of local progression in multivariate analyses

6-month local control: 91%	**6-month local control: 74%**	**12-month local control:**
Concurrent SRS + IT within 4 weeks	**Non-concurrent SRS +/- IO**	**86% (concurrent) vs 68% (non-concurrent)**

Shanker et al., J Med Imaging Radiat Oncol 2022

Sequential: IO→RT

Phase 2 trial of refractory recurrent or metastatic head and neck squamous cell carcinoma

Patients already on pembrolizumab and progressed

SBRT added to single lesion (Cohort A) vs SBRT to all sites of oligomets/oligoprogression (Cohort B)

Endpoint	Cohort A	Cohort B
PFS	17%	67%
Median OS	7.6 mo	10.1 mo

So J et al., Int J Radiat Oncol Biol Phys 2026

Sequential: PEMBRO-RT

Randomized Phase 2 Trial, 92 patients, 1:1 randomization

Experimental Arm: SBR to single tumor site- 24 Gy in three fractions delivered every other day followed by first pembrolizumab dose within 7 days of SBRT completion

Conventional arm: Pembrolizumab 200mg IV every 3 weeks alone

Endpoint	Control	Experimental
ORR at 12 weeks	18%	36%
Median PFS	1.9 mo	6.6 mo
Median OS	7.6 mo	15.9 mo

Theelen WSME et al., JAMA Oncol 2019

Oligometastatic Disease

Pooled three Phase 2 clinical trials comparing IO alone vs IO + RT in advanced lung cancer:

PEMBRO-RT

Durvalumab + Tremelimumab +/- low dose or hypofractionated RT

Durvalumab + Tremelimumab +/- SBRT

Enpoint	IO+ RT	IO
Median PFS	3.8 mo	2.4 mo
Median OS	9.5 mo	6.1 mo

Wang BC et al., J Oncol 2022

Organ Specific Toxicity

Site	Toxicity	Symptoms
Skin	Dermatitis	Erythema, desquamation, recall reaction
CNS	Radionecrosis	Headache, nausea, seizure, focal neurologic deficit
Lung	Pneumonitis	Cough, dyspnea, hypoxia
GI	Enteritis/Colitis/Proctitis	Diarrhea, Nausea, Pain
Liver	Hepatitis	Transaminiits, liver dysfunction

Radiation vs Immunotherapy AE

More likely Radiation injury	More likely Immunotherapy AE
Changes confined to treatment field/dose distribution Time course fits known RT injury latency (weeks-months) Imaging matches isodose distribution No systemic/multi-organ features	Changes extend beyond treatment field Onset can be more viable, delayed after therapy stops Associated with other concurrent AE's (dermatitis, thyroiditis, colitis, pneumonitis) May respond rapidly to corticosteroids and treatment break/discontinuation

Pneumonitis

Clinical symptoms: dry cough, dyspnea on exertion, low grade fever, chest tightness

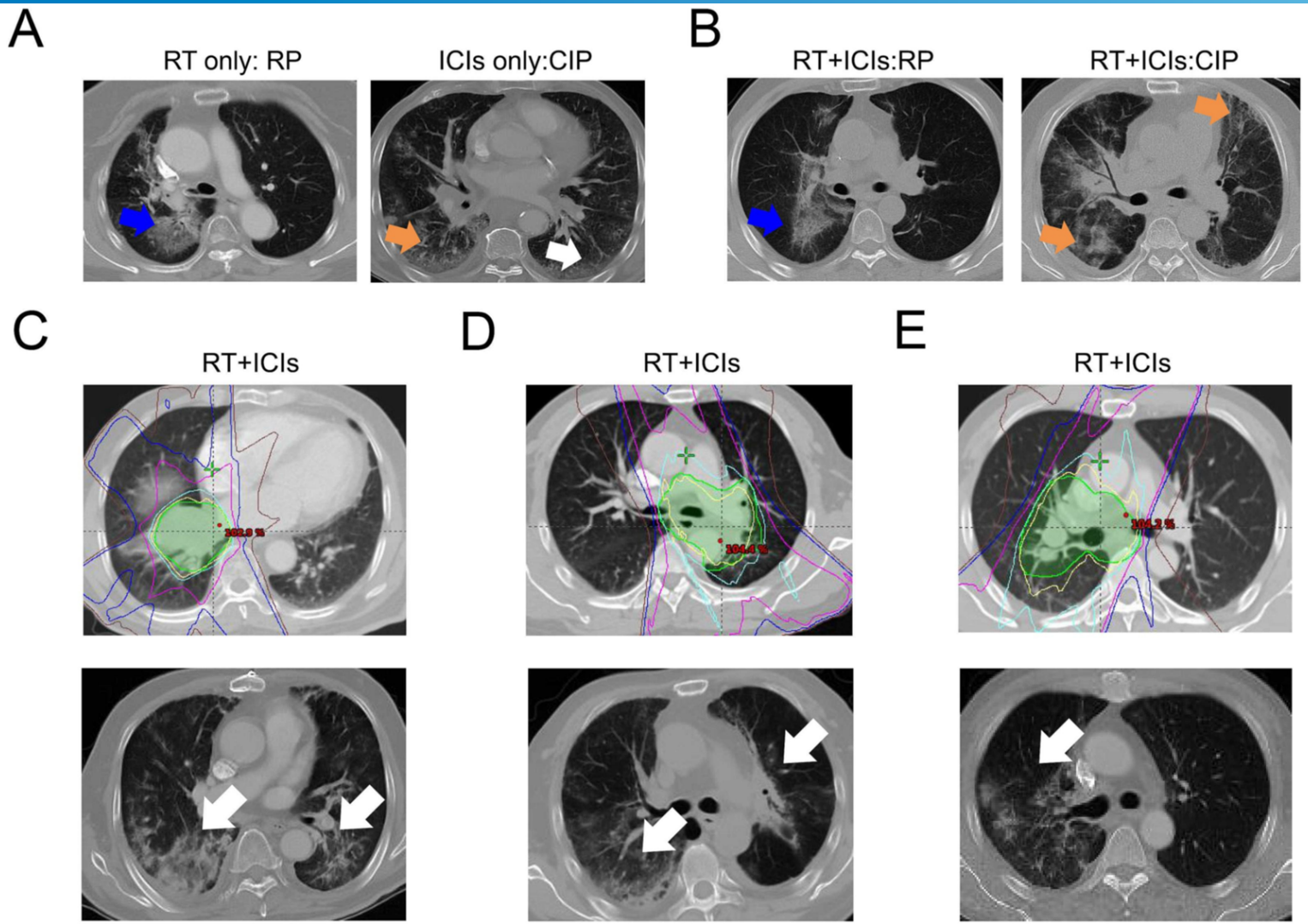
Physical exam signs: hypoxia, bibasilar or field confined crackles

Modality	Any Grade	Grade>3
Immunotherapy alone	3-5%	1-2%
Radiation alone	25-30%	2-3%
Combined RT + IO	34-36%	3-4%

- Conventional RT > SBRT for any grade pneumonitis (37% vs 26%)
- Anti-PD1 agents trended higher than anti-PD-L1 (40% vs 20%)
- IO-first followed by RT higher rates of pneumonitis than RT-first followed by IO and concurrent RT + IO

Li J et., Front Oncol 2025
Mi S et al., Clin Lung Cancer 2023

Pneumonitis: Radiographic features



Wang MP et al., Int Immunopharm 2024

Pneumonitis: Treatment

CTCAE Grading	Management
G1: asymptomatic, radiographic only	Hold therapy, monitor closely
G2: symptomatic, limits instrumental ADL's	Hold ICI/RT, prednisone 1mg/kg/day
G3: severe, limits self-care, O2 indicated	Hospitalize, IV methylprednisolone 1-2 mg/kg/day, taper 4-5 wks; consider infliximab/MMF if refractory
G4-5: life threatening/death	

Schneider et al., J Clin Oncol 2021

Radionecrosis

Radiation Necrosis: delayed injury to normal brain tissue caused by prior radiation therapy-not a recurrence or persistence of tumor

Category	Incidence
SRS alone	5-10%
SRS + IO	5.3%
Concurrent vs Sequential	6.6% vs 5.5%

Risk Factors (dose/volume) rather than IO timing:

- Tumor/PTV volume-strongest predictor
- Total dose, dose inhomogeneity, and V12/V20/V23 brain volume
- Reirradiation or prior whole-brain RT

Lehrer EJ et al., Radiother Oncol 2019
Kim PH et al., Korean J Radiol 2021

Radionecrosis: diagnosis and treatment

Diagnostic Challenge:

Radionecrosis	Pseudoprogression
Delayed onset (months-years)	Early onset, then regresses on serial MRI
Low perfusion on MRI	More frequent with concurrent IO (14% vs 4%)
Confined to high-dose area	RANO-BM Criteria
May need additional tests or tissue sampling	Continued therapy +/- short interval rescan

Imaging Tools

Perfusion MRI

Amino-acid PET

MR Spectroscopy

Contrast Clearance Analysis

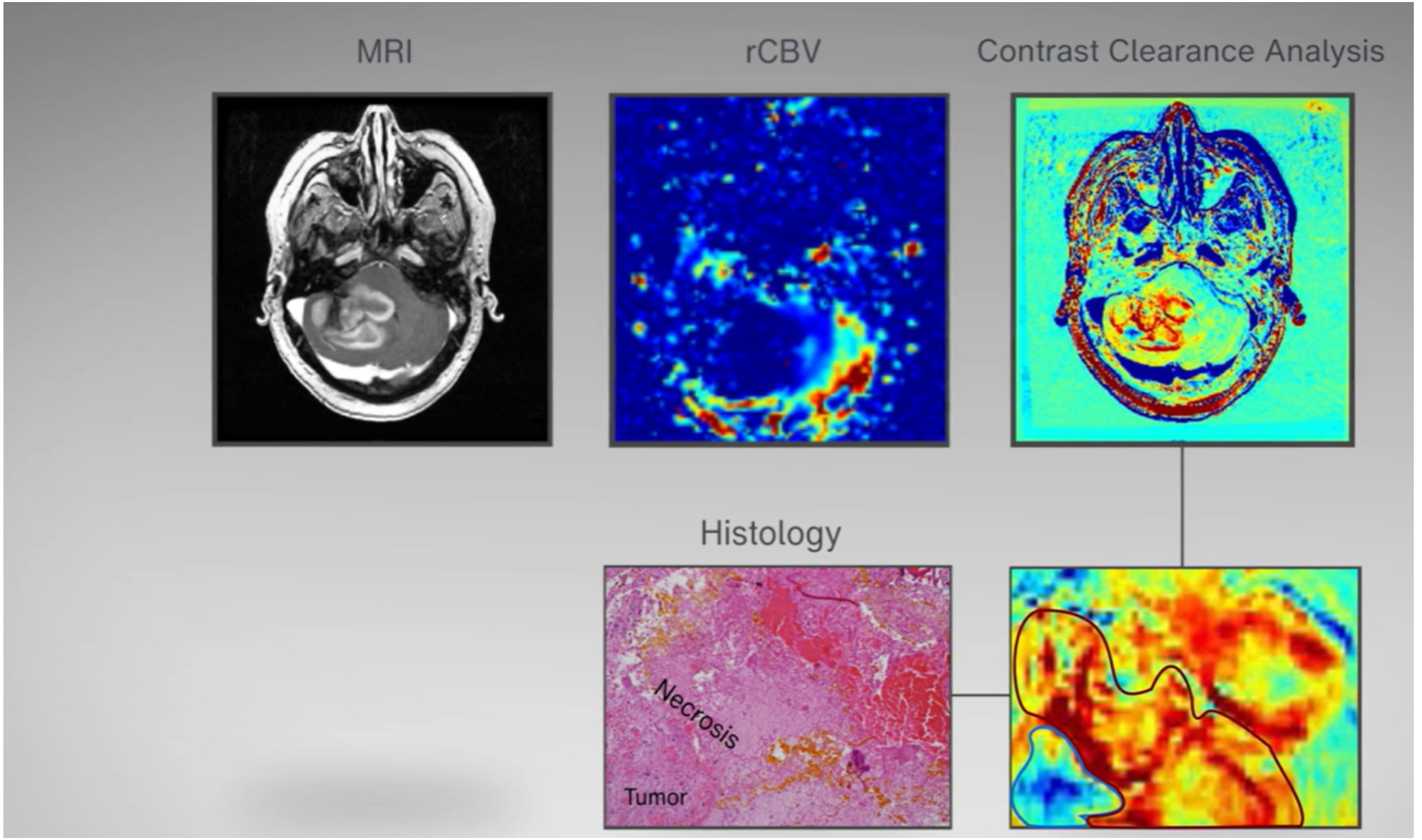
Treatment:

Asymptomatic or small-serial MRI q2-3 months

Corticosteroids

Bevacizumab for steroid-refractory

Surgical resection or Laser Interstitial Thermal Therapy



https://www.brainlab.com/radiosurgery-products/elements/contrast-clearance-analysis/

Conclusion

- Radiation can prime anti-tumor immunity- mechanistic rationale for RT + IO is well documented and abscopal responses are reproducible in randomized data
- Benefit is sequence-depending, not automatic: PACIFIC vs PACIFIC 2
- Toxicity is evident but manageable: pneumonitis risk rises with thoracic combinations
- Distinguishing between radiation AE vs immune-related AE requires multidisciplinary approach and recognition of pattern/timing

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