Challenges and Opportunities in the New Era of Immunotherapy and Radiotherapy Combination

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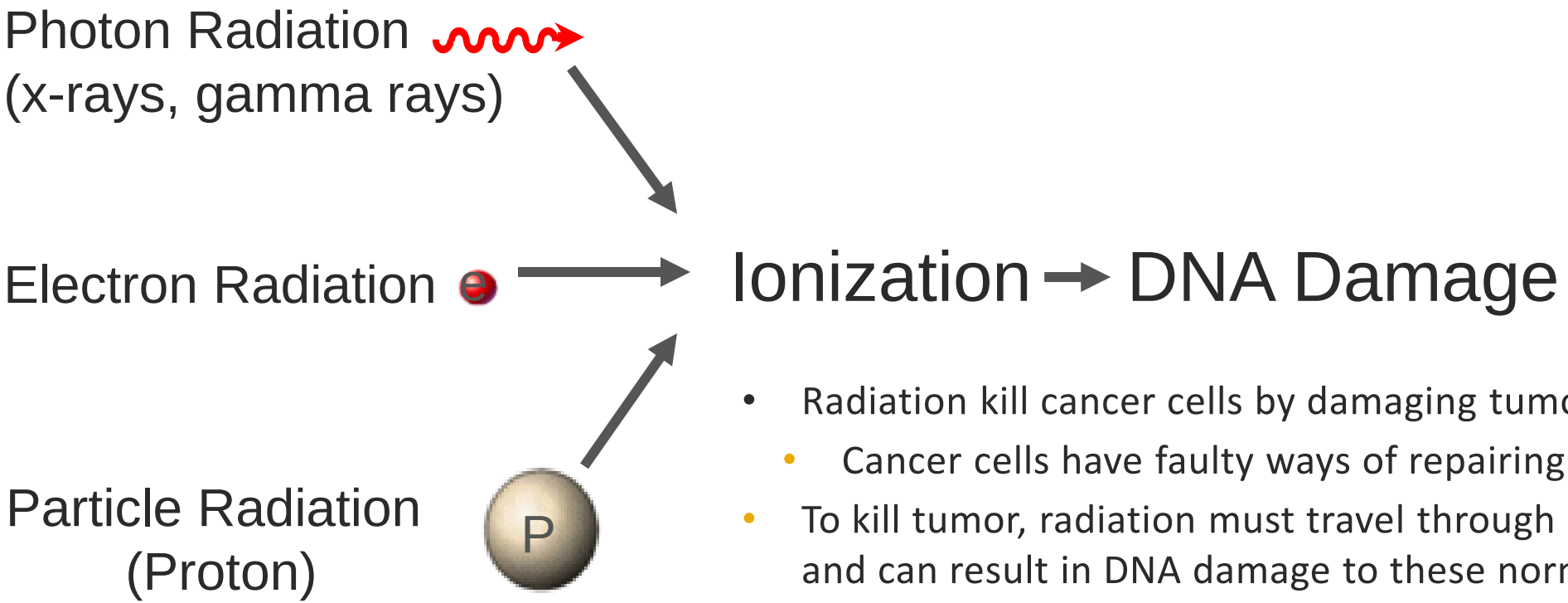
Types of Therapeutic Radiation and Mechanism of Kill

- Internal radiation therapy (ie. Brachytherapy): radioactive material is placed directly into or very close to the tumor
- External beam radiation Therapy



- Radiation kill cancer cells by damaging tumor DNA
  - Cancer cells have faulty ways of repairing DNA damage
- To kill tumor, radiation must travel through normal cells and can result in DNA damage to these normal, leading to side effects

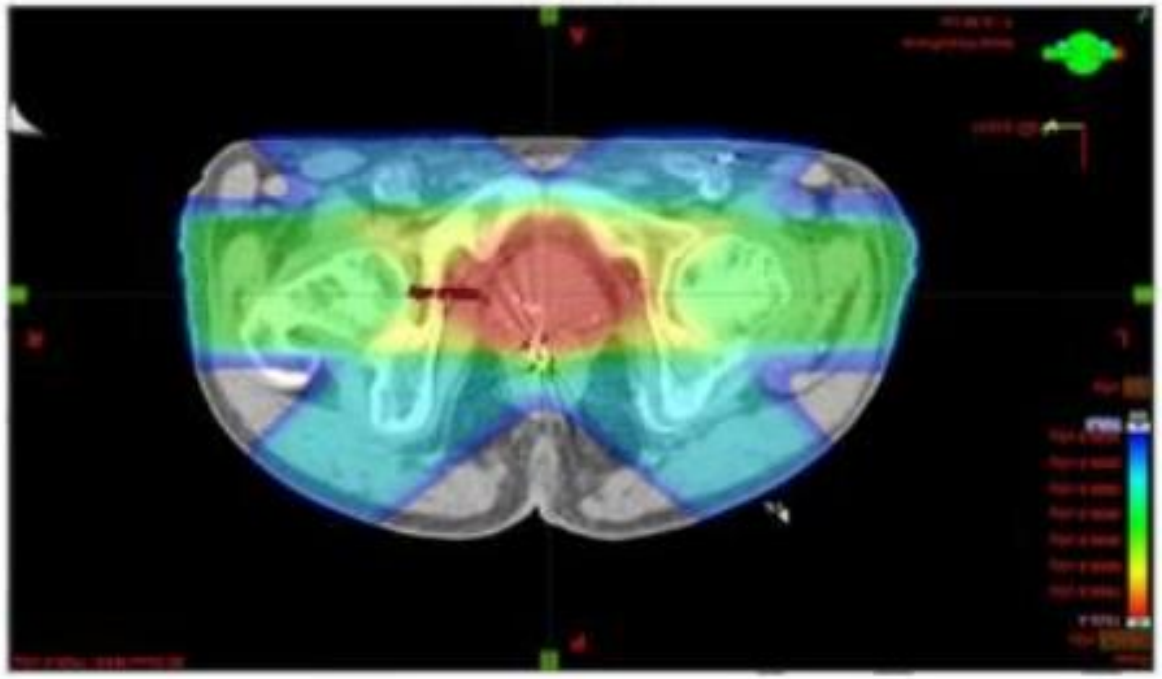
Photon Therapy: Not all X-Rays Therapies are Alike

- Conventional 2D radiation therapy (AP-PA)
- 3D conformal radiation therapy (3DCRT)
- Intensity-modulated radiation therapy (IMRT)

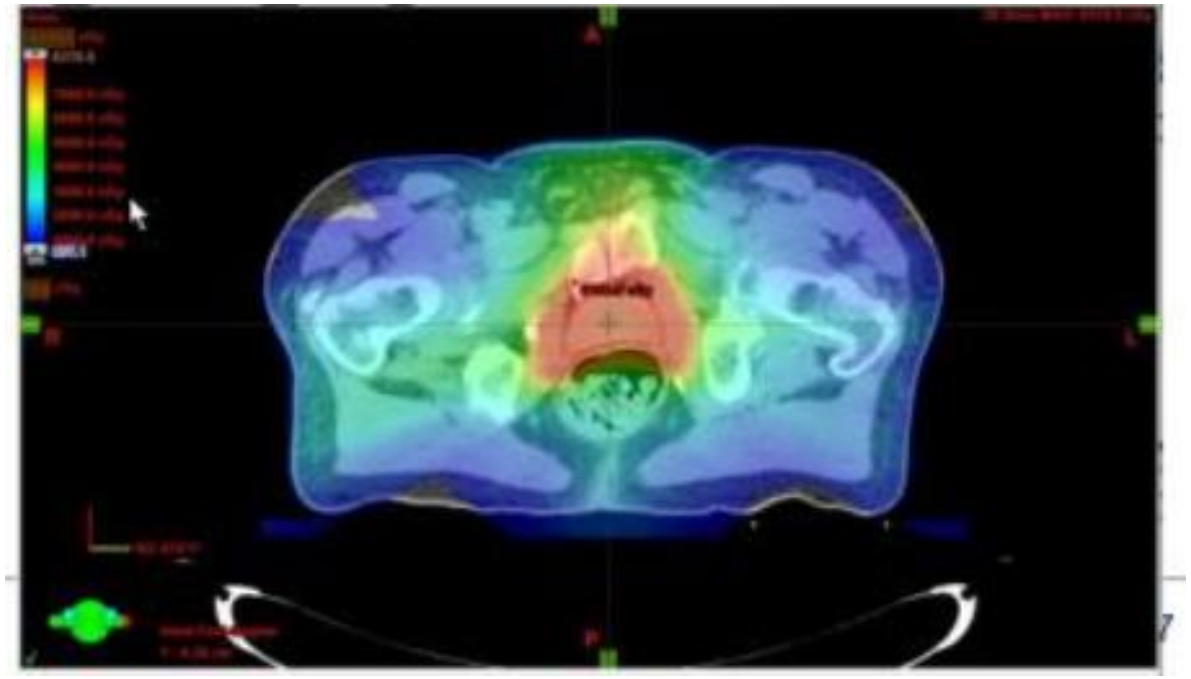
- Image-guided radiation therapy (IGRT)
  - X-ray films to align to bony landmarks or internal fiducial markers
  - CT scans to align to tumor or soft-tissue anatomy

3DCRT and IMRT/VMAT

3D-Conformal Therapy (Historical RT Treatment)

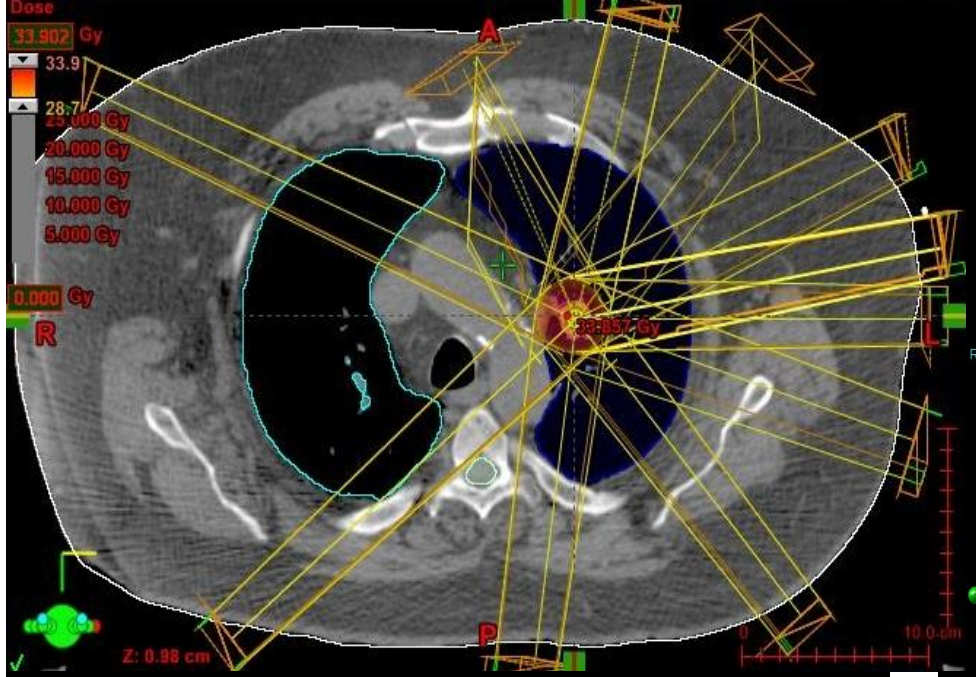


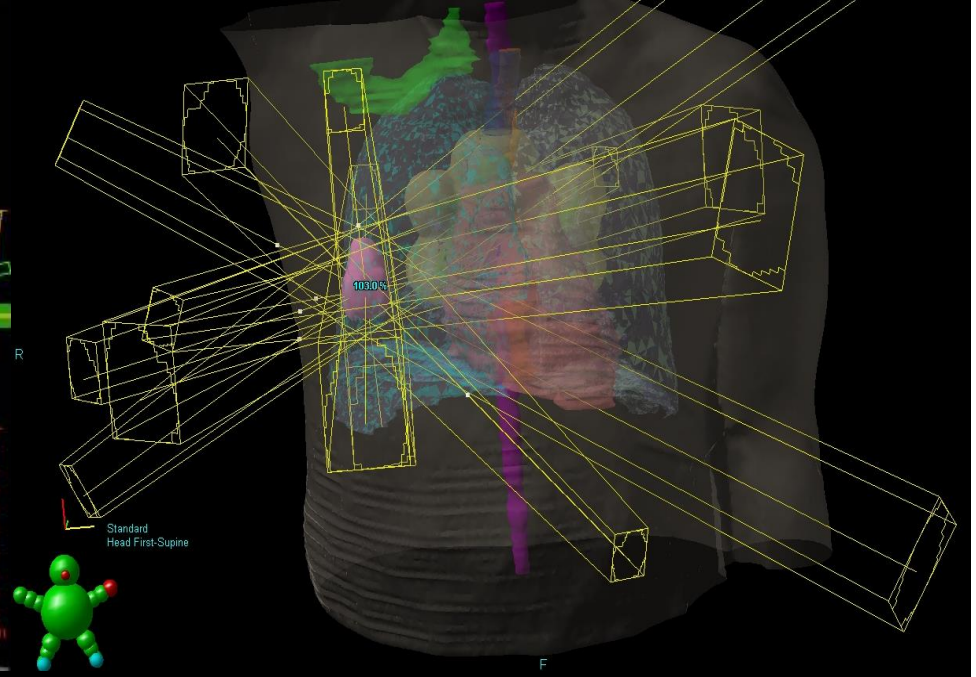
Volumetric Arc Therapy (Modern Photon Therapy)

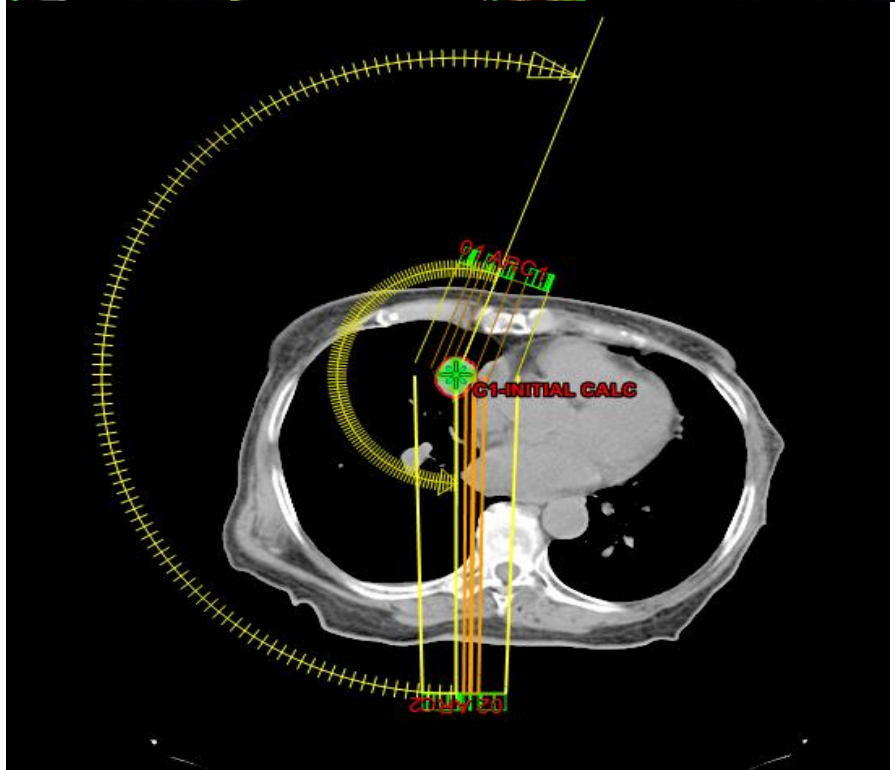


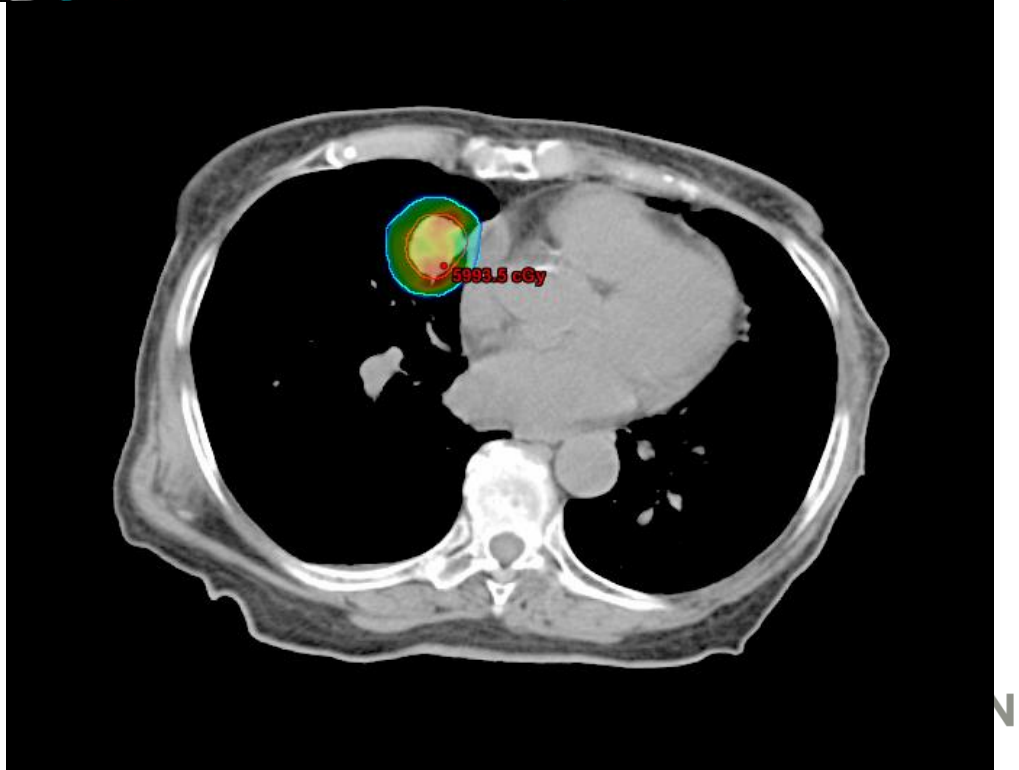
Principals of Stereotactic Body Radiotherapy

- Also called stereotactic ablative radiotherapy (SABR)
- Stereotactic: implies targeting, planning, and directing therapy using beams of irradiation along any trajectory in 3-D space toward a target of known 3-D coordinates
- Imaging guided set-up verification and external or internal markers are used to increase treatment accuracy, decrease target margin
- Typically for medically inoperable pts with tumors <5-7 cm
- Large doses per fraction (generally 1-5 treatments) to a small conformal volume with the intention of increasing the delivered effective dose of therapy
  - Conventional fractionation typically delivered over 4-8 weeks


Dose
33.902 Gy
33.9
28.7
25.000 Gy
20.000 Gy
15.000 Gy
10.000 Gy
5.000 Gy
0.000 Gy
A
R
L
P
Z: 0.98 cm
10.0 cm


103.0%
Standard
Head First-Supine
F

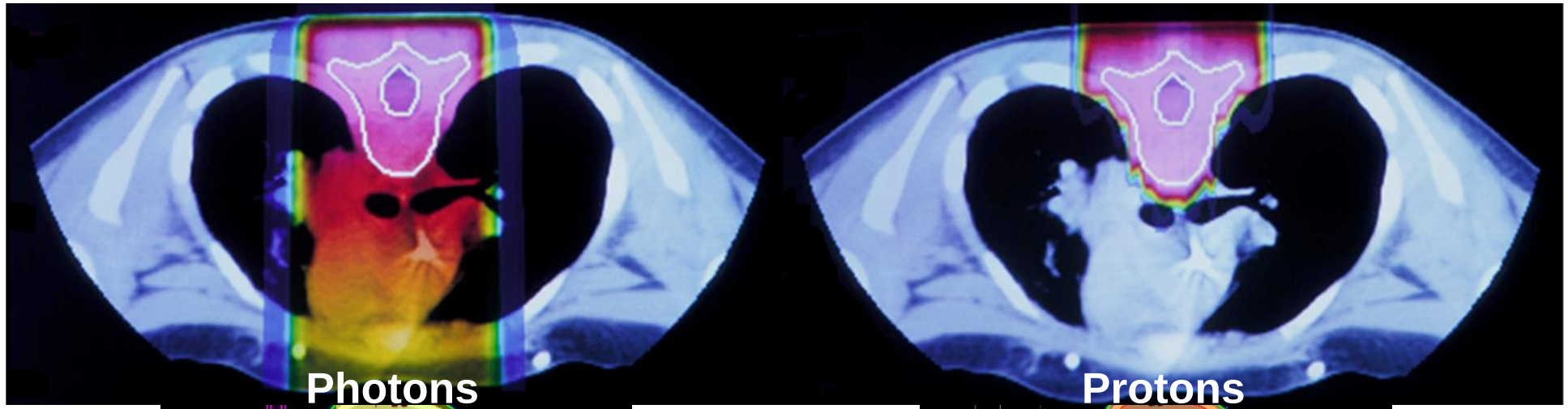

C1-INITIAL CALC


5993.5 cGy

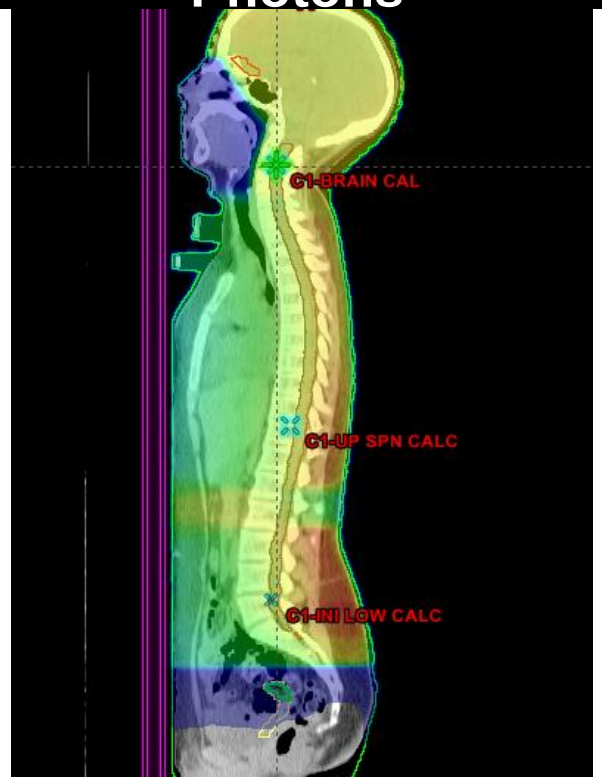
Difference Between Protons and Traditional X-Ray Radiation

- With conventional RT, photon beams travel all the way through the body
  - Healthy tissues in front of and behind the tumor are exposed to radiation
- In contrast, protons travel to a specified depth in the body (to the tumor) and then stop due to a phenomenon known as the Bragg Peak
  - This allows less radiation dose to be deposited in normal surrounding tissues

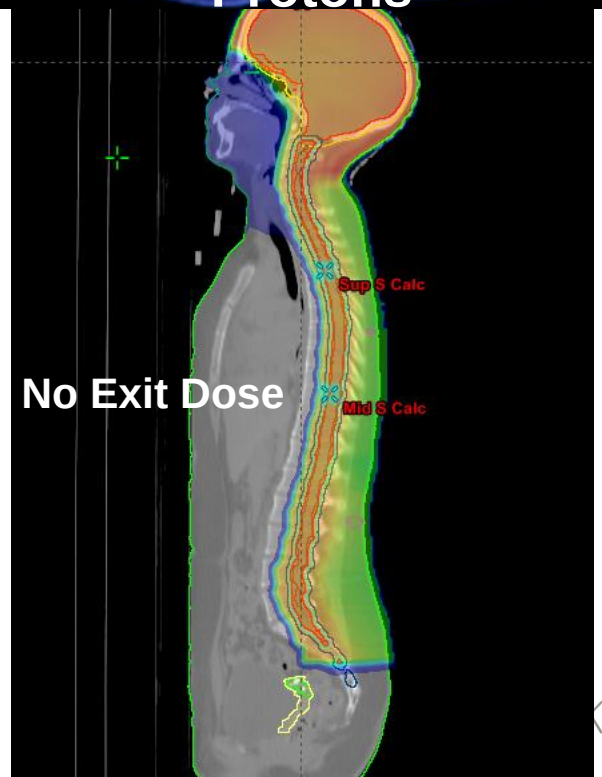
The Potentials of Proton Therapy: Craniospinal Irradiation



Photons



Protons



No Exit Dose

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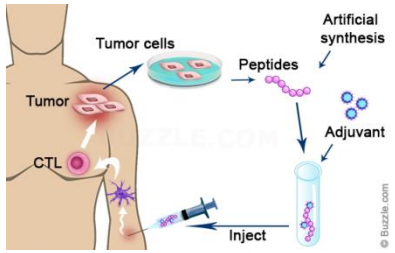
Classes of Immunotherapy

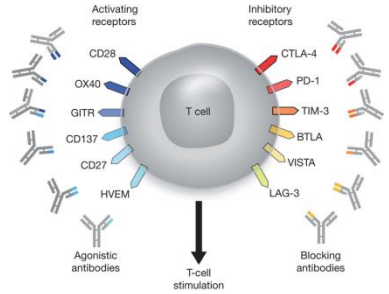
Vaccinations

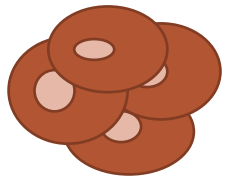
Similar to infection vaccines, retrains immune cells to recognize tumor associated antigens



Strong Immune Stimulants

General activation of the immune system in a non-specific manner

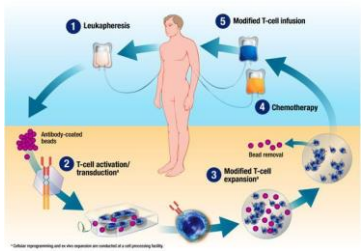




Tumor

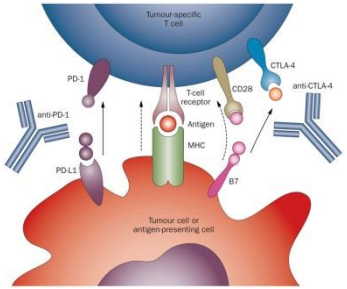
Chimeric Antigen Receptor (CAR) NK & T Cell Therapy

Genetically modified T cells manipulated *ex vivo* with engineered receptors to recognize cancer, then infuse back



Inhibitory Checkpoint Blockade

Block inhibitory signals that usually prevent immune targeting of normal tissues (release breaks/step on gas)

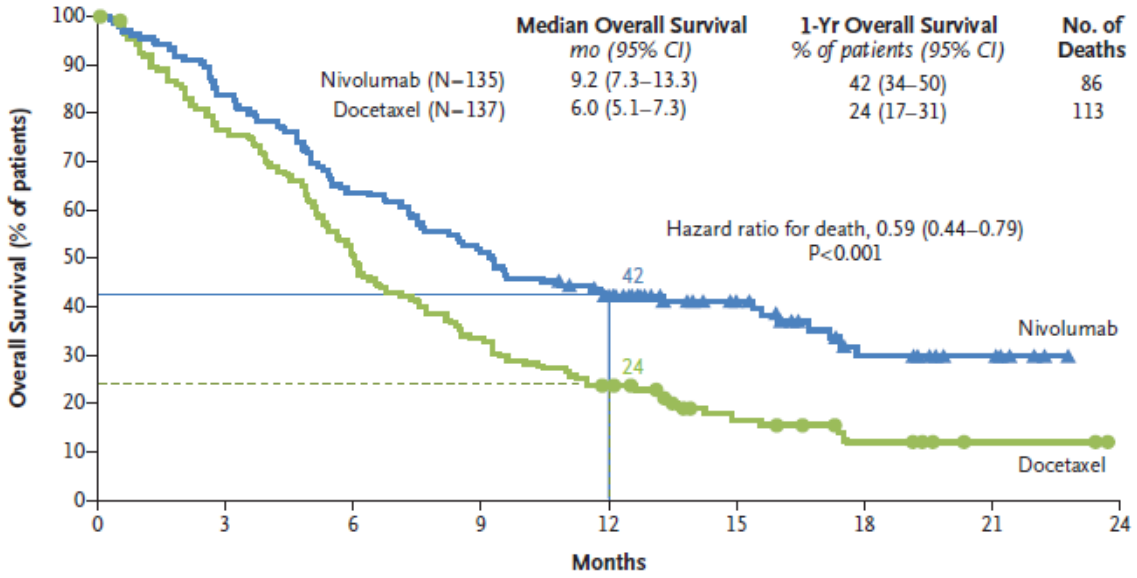


Slide Courtesy of Megan Daly

Drake CG. *Nat Rev Immunol*. 2010;10(8):580-593.

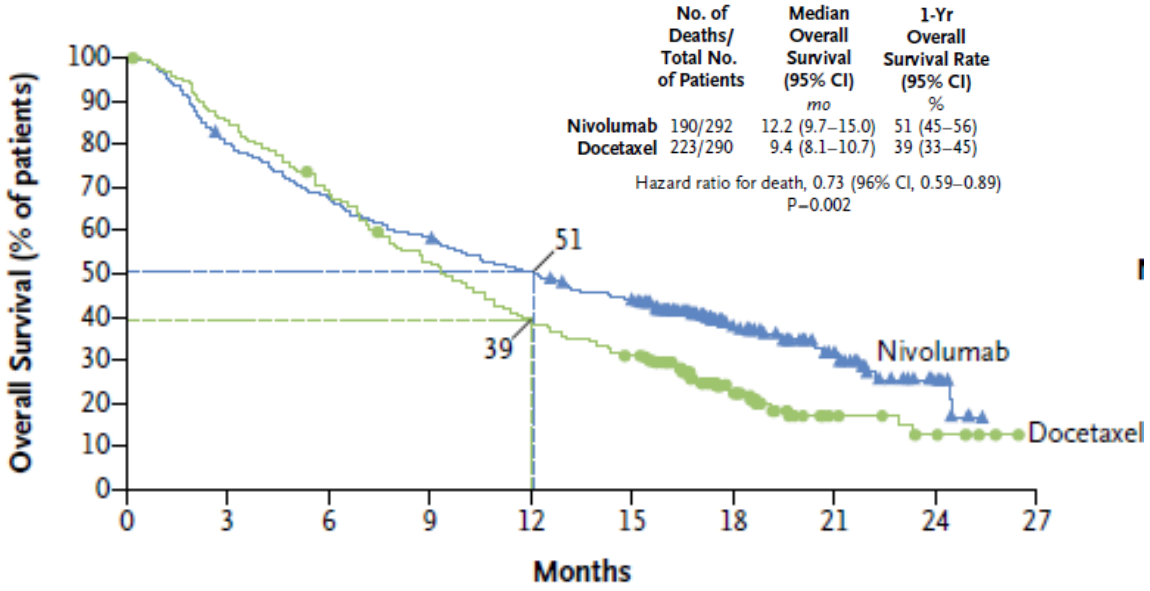
Nivolumab for Progressive NSCLC

CheckMate 017: squamous
nivolumab vs. docetaxel



Brahmer J, et al. *N Engl J Med*. 2015 Jul;373(2):123-35.

CheckMate 057: non-squamous
nivolumab vs. docetaxel



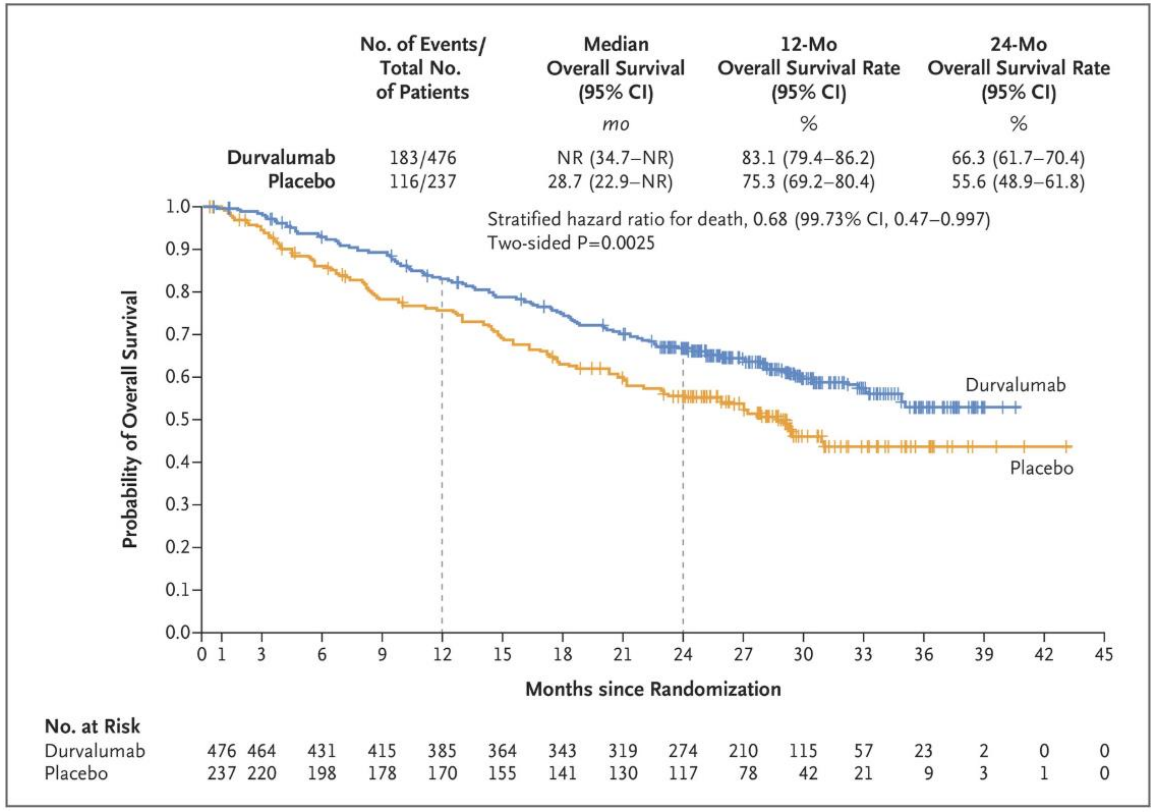
Borghaei H, et al. *N Engl J Med*. 2015 Oct;373(17):1627-39.

Maintenance Immunotherapy: PACIFIC

- 713 patients randomized 2:1 between 1-42 days after chemoradiation to durvalumab:Placebo delivered Q2 weeks for up to 12 months
- Outcomes
  - Overall survival
    - 2-yr: 66.3% vs. 55.6%, p=0.005
    - Median: NR vs. 28.7 mo, HR 0.68, p=0.0025
  - PFS median 17.2 months vs. 5.6 months
  - Median time to death or distant metastasis: 28.3 mo vs. 16.2 mo
  - Fewer new lesions, fewer brain metastases, higher response rate, longer duration of response, longer time to subsequent therapy
- Toxicities
  - Grade 3-4 AEs: 30.5% vs. 26.1%
  - Most frequent AEs leading to the discontinuation of treatment: pneumonitis (4.8% vs. 2.6%), radiation pneumonitis (1.3% vs. 1.3%), pneumonia (1.1% vs. 1.3%)
  - Grade 5 AEs: 4.4% and 6.4%

Antonia SJ, et al. *N Engl J Med. 2018;379(24):2342-2350.* Antonia SJ, et al. *N Engl J Med. 2017;377(20):1919-1929.*

PACIFIC Overall Survival



Antonia SJ, et al. *N Engl J Med. 2018;379(24):2342-2350.*

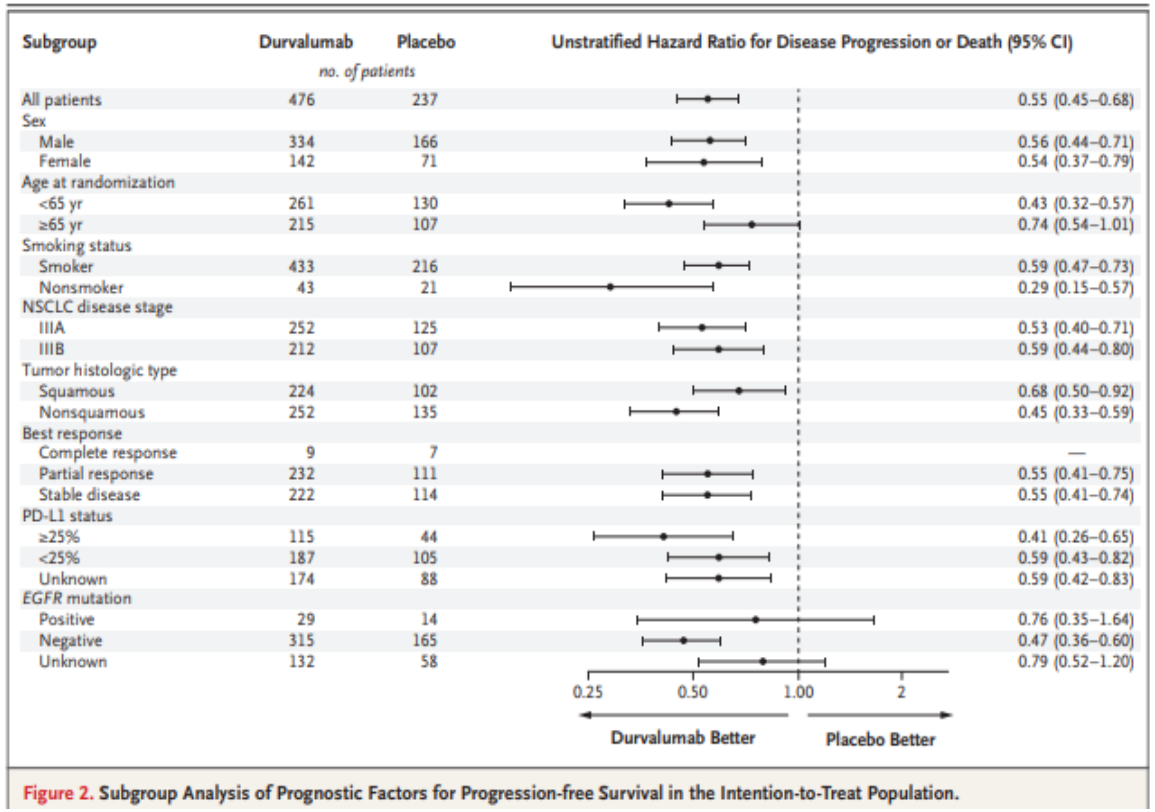


Figure 2. Subgroup Analysis of Prognostic Factors for Progression-free Survival in the Intention-to-Treat Population.

Antonia SJ, et al. *N Engl J Med. 2017;377(20):1919-1929.*

PACIFIC Patient Reported Outcome Analysis

	Durvalumab		Placebo		OR (95% CI)
	Number with improvements/ number of patients	%	Number with improvements/ number of patients	%	
Global health status or quality of life (C30)	149/418	35·6	62/208	29·8	1·30 (0·90–1·87)
Physical functioning (C30)	113/319	35·4	53/159	33·3	1·07 (0·71–1·61)
Role functioning (C30)	136/261	52·1	67/131	51·1	1·03 (0·68–1·57)
Emotional functioning (C30)	116/246	47·2	38/112	33·9	1·72 (1·08–2·76)
Cognitive functioning (C30)	106/212	50·0	53/104	51·0	0·95 (0·59–1·53)
Social functioning (C30)	153/261	58·6	65/128	50·8	1·36 (0·89–2·09)
Fatigue (C30)	208/407	51·1	93/202	46·0	1·22 (0·87–1·72)
Pain (C30)	162/272	59·6	59/118	50·0	1·32 (0·85–2·07)
Nausea or vomiting (C30)	106/140	75·7	47/63	74·6	1·08 (0·53–2·13)
Dyspnoea (C30)	113/288	39·2	48/127	37·8	1·05 (0·68–1·62)
Insomnia (C30)	111/230	48·3	45/108	41·7	1·28 (0·81–2·05)
Appetite loss (C30)	127/183	69·4	59/107	55·1	1·86 (1·13–3·10)
Constipation (C30)	104/155	67·1	56/85	65·9	1·07 (0·61–1·87)
Diarrhoea (C30)	51/75	68·0	27/44	61·4	1·51 (0·67–3·43)
Dyspnoea (LC13)	133/353	37·7	57/180	31·7	1·31 (0·89–1·92)
Cough (LC13)	116/366	31·7	68/176	38·6	0·74 (0·51–1·08)
Haemoptysis (LC13)*	26/29	89·7	14/19	73·7	3·02 (0·62–17·07)
Chest pain (LC13)	103/168	61·3	48/94	51·1	1·49 (0·89–2·51)
Arm or shoulder pain (LC13)	72/133	54·1	28/52	53·8	0·95 (0·49–1·83)
Other pain (LC13)	100/182	54·9	34/69	49·3	1·09 (0·60–1·95)

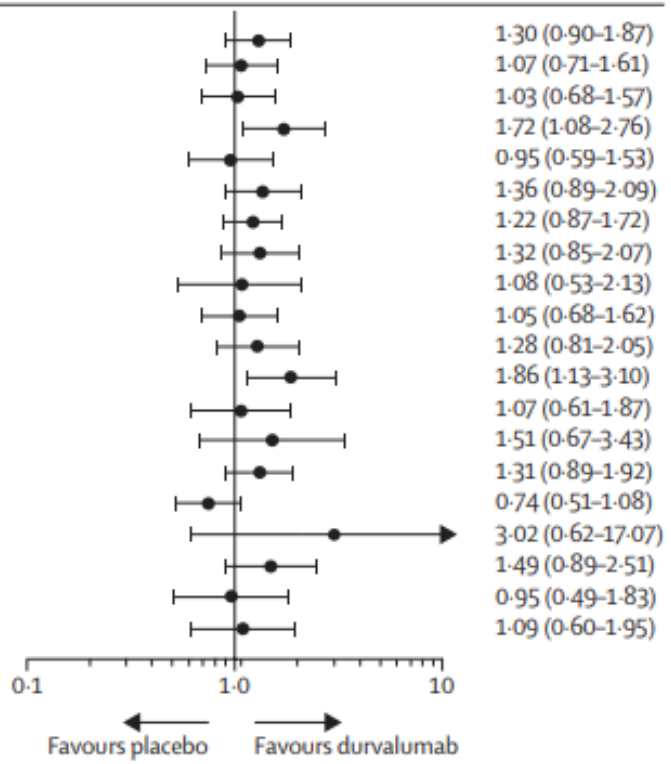


Figure 4: **Improvement in symptoms, functioning, and global health status or quality of life**

Hui R, et al. *Lancet Oncol. 2019;20(12):1670-1680.*

Current State of Immunotherapy in LA-NSCLC Trials

Table 3: Key Recruiting or Activating Trials of Combining Radiation Therapy and Immunotherapy for Locally Advanced NSCLC

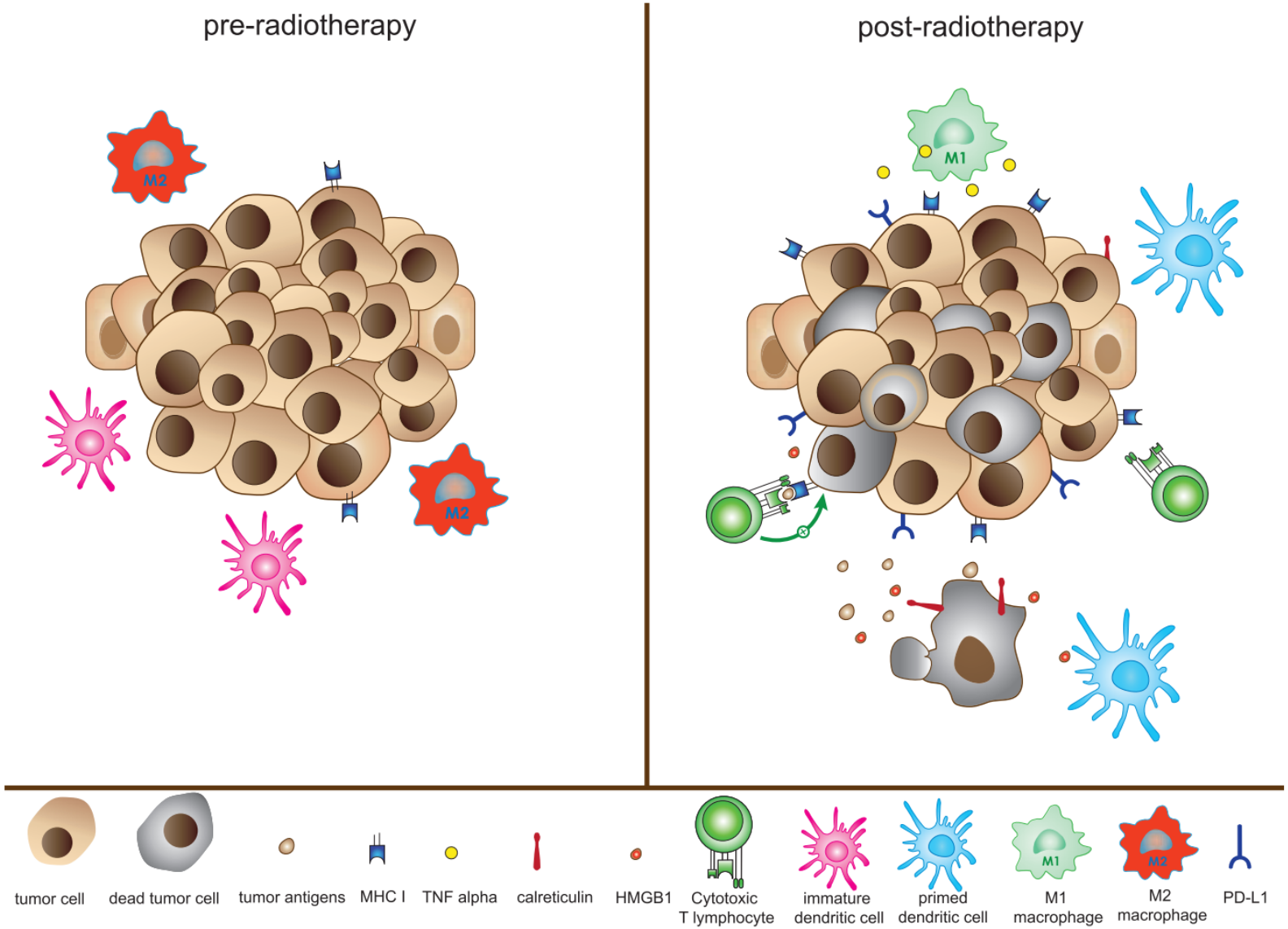
NCT number/ trial name	Study phase	*N*	Key inclusion criteria	IO agent	Trial design	RT dose	RT and IO timing	Status	Anticipated 1° completion date
Definitive Radiation									
NCT03519971 PACIFIC 2	3	328	Unresectable Stage III NSCLC	durvalumab	Concurrent IO + platinum-based chemoRT, followed by adjuvant IO	60Gy/30fx	concurrent	active, not recruiting	Aug-22
NCT03693300 PACIFIC 6	2 single arm	150	Unresectable Stage III NSCLC in pts suitable for sequential platinum-based chemo + RT	durvalumab	sequential chemotherapy and thoracic radiation, followed by IO	60Gy/30fx	IO to start within 28 days after RT completion	recruiting	Feb-23
NCT02343952 HCRN LUN14-179	2 single arm	93	Inoperable or unresectable stage IIIA/B NSCLC who have not progressed after chemoRT	pembrolizumab	platinum-based chemoRT, followed by consolidation IO up to 12 months	conventionalRT to 59.4–66.6Gy	IO to begin 28-56 days after chemoRT	active, not recruiting (enrollment complete)	Sep-20
NCT02434081 NICOLAS	2 single arm	78	Unresectable stage IIIA/B NSCLC	nivolumab	standard chemoRT + IO concurrently and adjuvantly up to 12 months	60Gy/30fx	concurrent	Ongoing not recruiting	Aug-20
NCT03102242	2 single arm	63	Unresectable stage IIIA/B NSCLC	atezolizumab	Induction IO for 4 cycles followedby carboplatin-based chemoRT, followed by adjuvant IO	60Gy/30fx	RT to start after 4 cycles IO	recruiting	Mar-20
NCT02525757 DETERRED	2 multi cohort nonrand-omized	40	Unresectable stage II-III NSCLC	atezolizumab	Carboplatin-based chemoRT +/- IO, followed by 3-4 week chemo holiday (+/- 1 dose IO), followed by 2 cycles consolidation traditional chemo + IO, followed by maintenance IO up to 12 months	conventionalRT to 60–66Gy	concurrent OR RT completed first depending on cohort	active, not recruiting (enrollment complete)	Jan-20
NCT03999710 DART	1/2 single arm	53	Unresectable stage III NSCLC patients not suitable for concurrent chemoradiation	durvalumab	IO + RT (no traditional chemo)	60Gy/30fx	RT started within 1 week of durvalumab (preferably same day)	recruiting	Jul-21
NCT03801902 ARCHON-1	1 single arm	24	Unresectable stage II-III NSCLC with high PD-L1 (>50%)	durvalumab	IO + RT (no traditional chemo)	conventional RT to 60Gy/30fx or hypofractionated RT to 60Gy/15fx	RT to start 2 weeks after 1st IO dose	recruiting	Jul-20
NCT02621398	1 multi cohort nonrand-omized	30	Unresectable stage II-III NSCLC	pembrolizumab	Platinum-based chemoRT + IO	60Gy/30fx	IO (either full-dose or reduced-dose), started concurrently, at the penultimate week of RT, or 2-6 weeks after RT completion depending on cohort	active, not recruiting (enrollment complete)	Dec-21
Neoadjuvant Radiation									
NCT03237377	2 single arm	32	Resectable stage IIIA NSCLC	durvalumab +/- tremelimumab	Neoadjuvant IO + RT, followed by surgery	45Gy/25fx	concurrent	recruiting	Sep-21
NCT03053856	2 single arm	37	Stage IIIA NSCLC with N2 disease	pembrolizumab	Neoadjuvant chemoRT, followed by surgery, followed by adjuvant IO	44Gy/22fx	RT completed before surgery, IO given in adjuvant setting	Not yet recruiting	May-21
NCT02987998 CASE4516	1	20	Resectable stage IIIA NSCLC	pembrolizumab	Neoadjuvant chemoRT + IO, followed by surgery, followed by consolidation IO	45Gy/25fx	concurrent	recruiting	Jan-24
Adjuvant Radiation									
NCT02572843	2 single arm	68	Resectable stage IIIA NSCLC with N2 disease	durvalumab	Neoadjuvant chemoRT, followed by neoadjuvant IO, then surgery. Postop R0 patients will receive adjuvant IO while R1/2 patients will receive RT followed by adjuvant IO	conventional postop RT	IO begun prior to surgery; RT may be given postop prior to additional adjuvant IO	active, not recruiting	Mar-21
Reirradiation for Local Recurrence									
NCT03087760	2 single arm	41	Pts with prior chemoRT treatment of locally advaned NSCLC, now with local recurrence in/near prior RT field	pembrolizumab	Concurrent chemo + proton RT, followed by up to 24 months IO	conventionally fractionated proton RT	RT completed first	recruiting	Dec-20

Fitzgerald K, Simone CB 2nd. *Thorac Surg Clin*. 2020;30(2):221-239.

Potential Benefits of Combining RT and Immunotherapy

- SBRT is less immunosuppressive than conventionally fractionated RT or surgery
  - SBRT specifically can even be immunostimulatory and deplete immunosuppressive cells
- RT can improve antigen presentation by antigen presenting cells
  - SBRT specifically can release high levels of tumor antigens
- SBRT upregulates immunogenic cell surface markers (ie. MHC-1)
- SBRT can induce immunogenic cell death
- RT and especially SBRT can increase homing of immune cells to tumor
- RT can shift tumor-associated macrophages polarization from M2 to M1
- RT can induce secretion of danger signals and cytokines (ie. TNFalpha)
- RT can upregulate cell-surface expression of PD-L1

Radiation-Induced Immune Activation



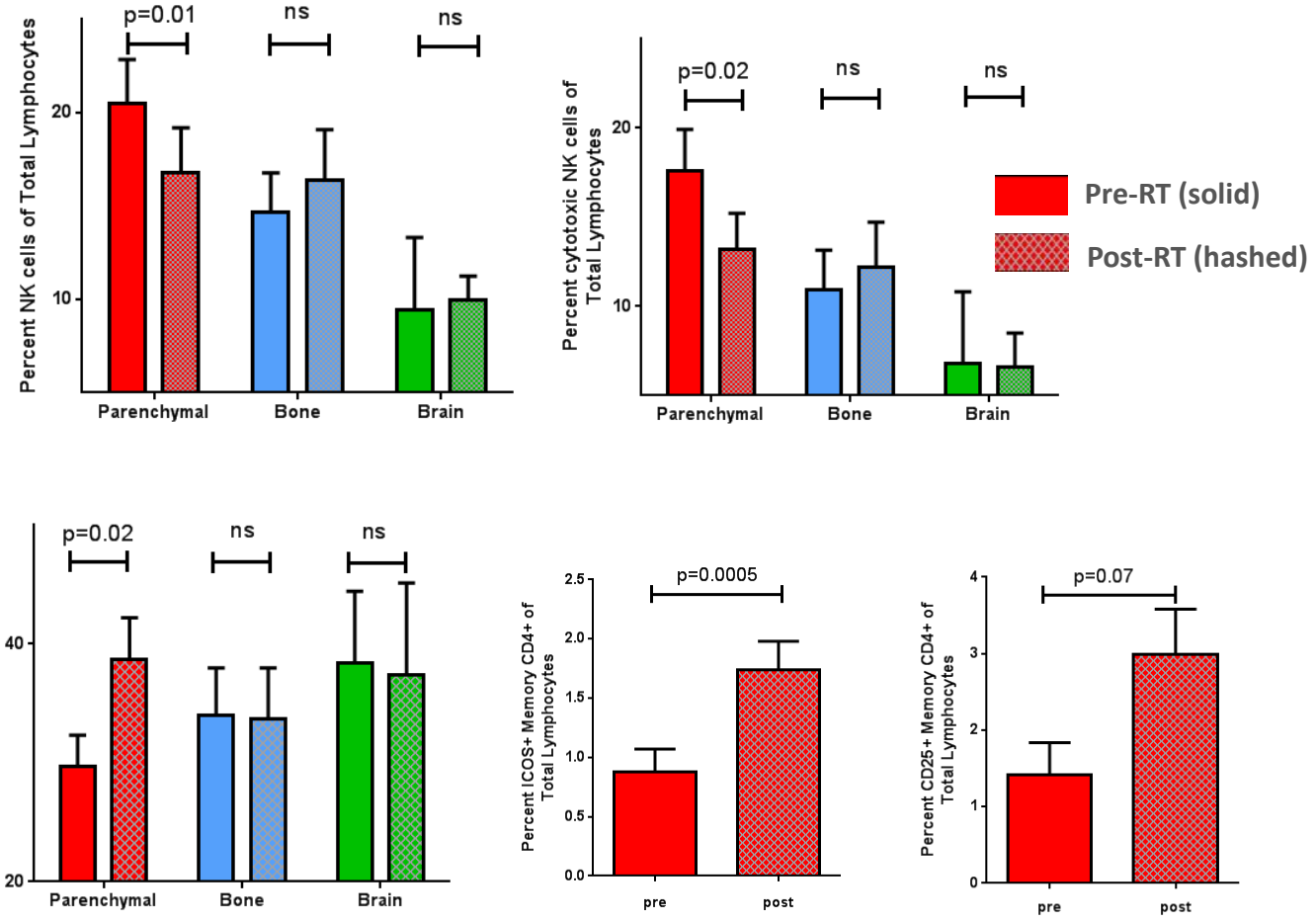
Radiotherapy-induced immunomodulation

- Homing of cytotoxic T lymphocytes to the tumor microenvironment
- Maturation of dendritic cells
- Down-regulation of immunosuppressive cells like myeloid derived suppressor cells
- Secretion of cytokines
- Shifting tumor associated macrophage polarization to M1

Daly ME, et al. *J Thorac Oncol*. 2015;10(12):1685-93.

Effects of SBRT on the Immune System

- While conventional RT is thought of as immunosuppressive due to its effects on marrow and circulating blood, focal high-dose RT can be immunostimulatory
  - 40 patient study evaluating effects of SBRT on peripheral blood immunophenotype and cytokine/chemokine profiles
  - SBRT to parenchymal organs/lung/liver decreased NK cells, decreased cytotoxic NK cells in circulating blood, and increased Memory CD4+ T cells (ie ICOS+ and CD25+ memory T cells)

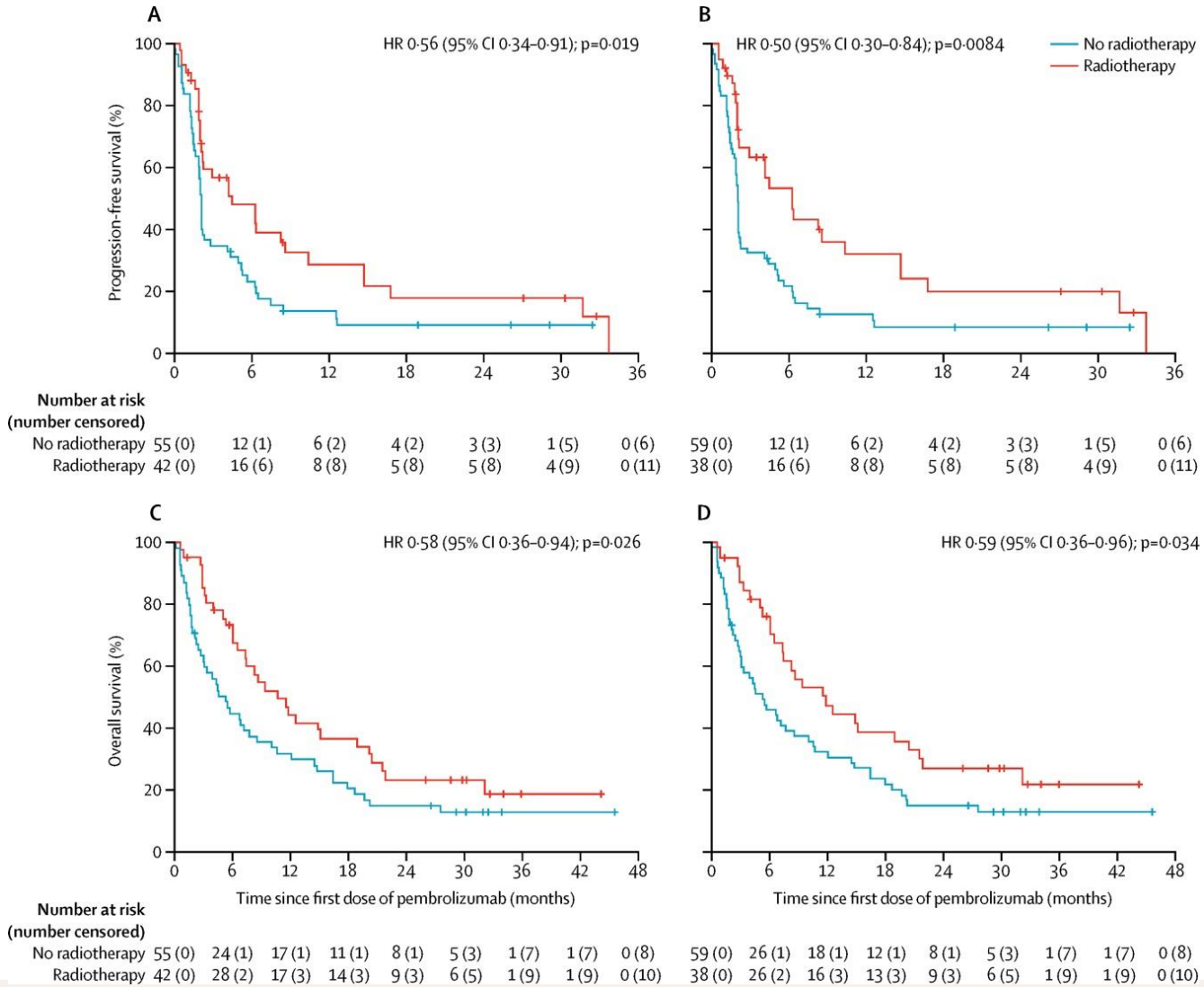


McGee HM, et al. *Int J Radiat Oncol Biol Phys*. 2018;101(5):1259-1270.

Optimizing RT Dose/Fractionation for Immune Response

First Author	Model	Dose/Treatment	Results
Lugade	Murine; heterotopic melanoma	• 15 Gy x 1 *or* • 3 Gy x 5	• Improved tumor control with 15 Gy • Increased immunogenic APCs with 15 Gy x 1 • Increased infiltration of immune cells at day 14 with 15 Gy x 1
Schaue	Murine; heterotopic melanoma	• 15 Gy in 1, 2, 3, or 5 fx • Single fx of 5, 7.5, 10, or 15 Gy	• 15 Gy in 2 fractions provided the best tumor control and tumor immunity while maintaining low Treg numbers
Dovedi	Murine lymphoma model	TLR7 agonist + • 10 Gy x 1 *or* • 2 Gy x 5	• Fractionation enhanced tumor response and mouse survival compared to single fraction
Dewan	Murine breast model, 2 sites	Anti-CTLA4 + • 20 Gy x 1 • 8 Gy x 3 • 6 Gy x 5	• Anti-CTLA4 + 8 Gy x 3 or 6 Gy x 5 generated abscopal effect in unirradiated tumor • No effect for 20 Gy x 1
Verbrugge	Murine triple negative breast model	Anti CD137/anti-PD-1 + • 4 Gy x 4 • 4 Gy x 5 • 12 Gy x 1	• 12 Gy x 1 100% response • 4 Gy x 4 40% response • 4 Gy x 5 80% response

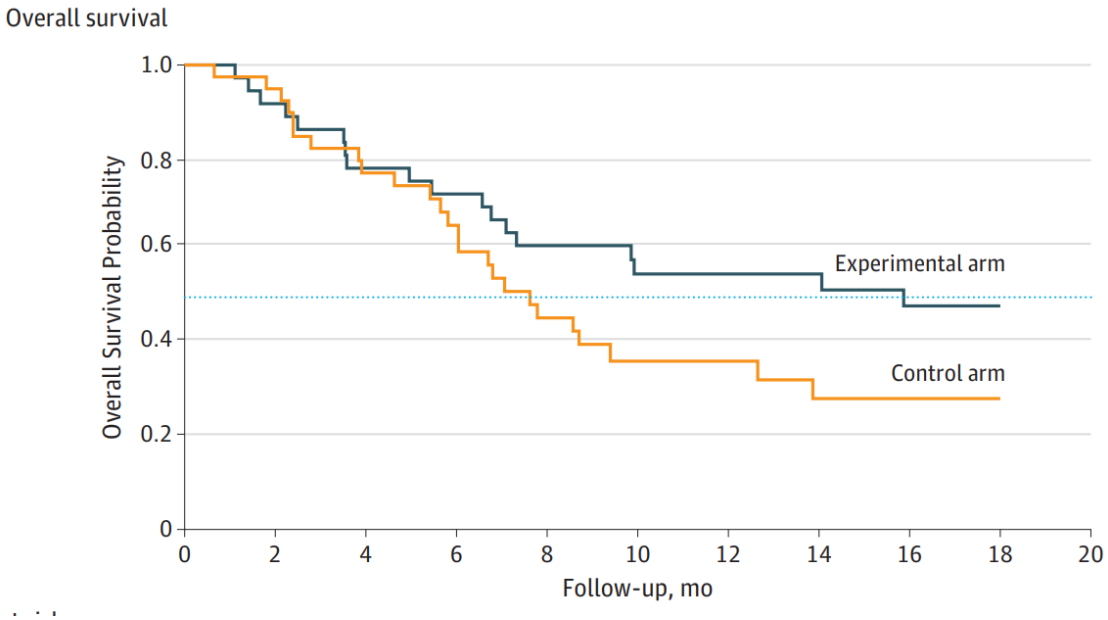
Lessons from Stage IV NSCLC: Secondary Analysis of KEYNOTE-001 (Pembro for Stage IV NSCLC) - Effect of Prior RT on Response



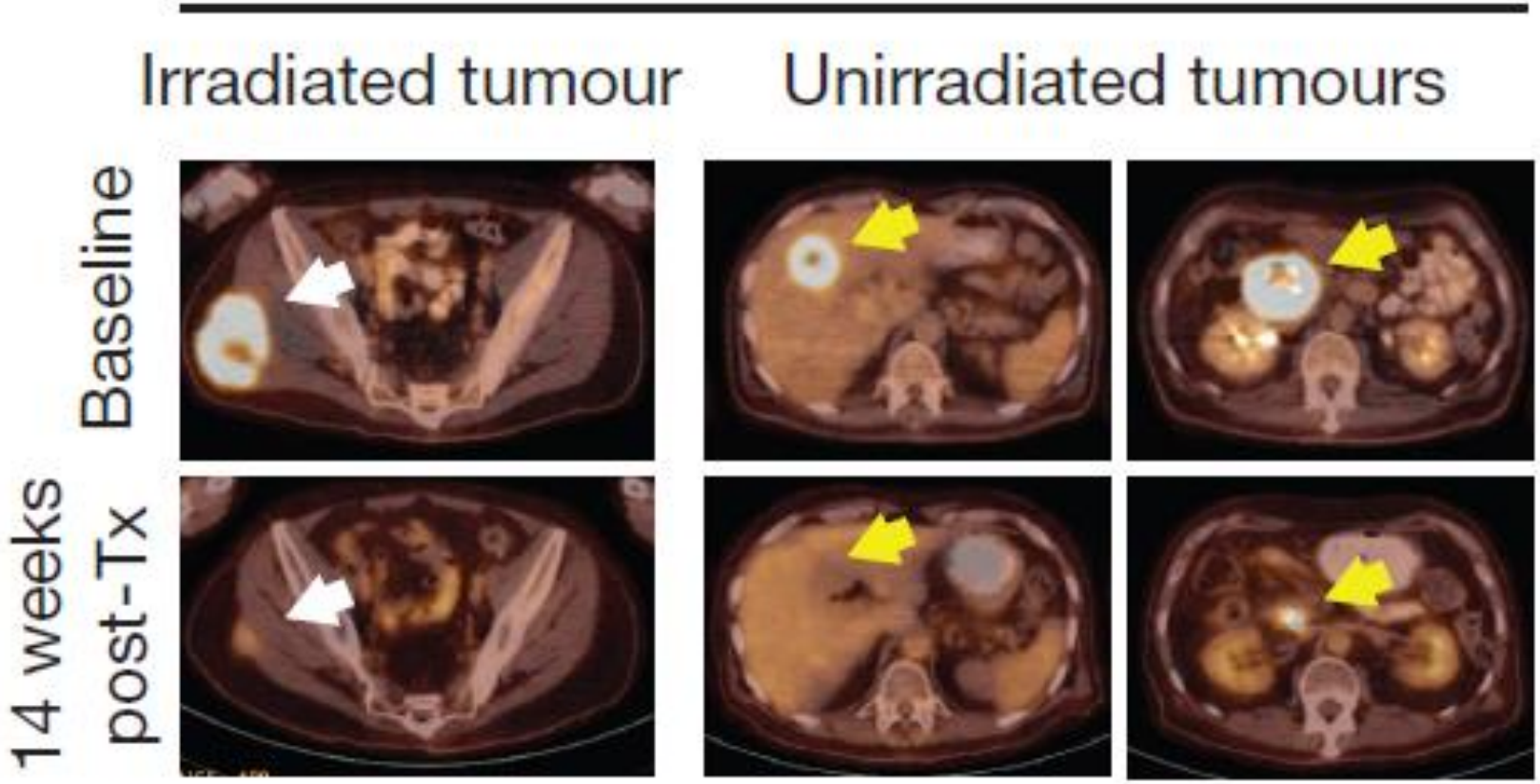
Shaverdian N, et al. *Lancet Oncol*. 2017;18(7):895-903.

Lessons Learned from Stage IV NSCLC – PEMBRO-RT Trial

- Multicenter phase 2 study (PEMBRO-RT) of 76 patients with advanced NSCLC randomized to pembrolizumab (200 mg/kg Q3 wks x 24 months) alone or after SBRT (8 Gy x 3) to a single tumor
- Overall response rate 18% vs. 36% (p=0.07)
  - Disease control rate 48% vs. 72%
- Median PFS 1.9 vs. 6.6 months (p=0.19)
- PFS and OS significantly approved among PD-L1-negative subgroup
- Median OS 7.6 vs 15.9 months (p=0.16)
- No increase in treatment-related toxicities with SBRT



SBRT + anti-CTLA-4 Antibody



Twyman-Saint Victor C, et al. *Nature*. 2015;520(7547):373-377.

LU002 Oligometastatic NSCLC

- Stage IV squamous and non-squamous histology
- No progression following 4 cycles of 1st line systemic
- ≤3 fewer discrete, extracranial sites amenable to SBRT

Randomization will be 2:1 in favor of RT (N=400)*

Arm 1	Arm 2
Maintenance systemic therapy alone**	SBRT or SBRT and Surgery to all sites of metastases plus irradiation (SBRT or hypofractionated RT) of the primary site followed by maintenance systemic therapy

*Stratification: histology (squamous vs. non-squamous), systemic therapy (immunotherapy vs. cytotoxic chemotherapy).
** Selection of regimen is at the discretion of the treating physician in agreement with the patient. Acceptable immunotherapy for NRG-LU002 is pembrolizumab either alone or in combination with pemetrexed and platinum therapy.

Prescription Dose

	Total Cumulative Dose Encompassing 95% of Planning Target Volume		
Number of Fractions	Protocol Compliant	Variation Acceptable	Deviation Unacceptable
1	21-27 Gy	<21 Gy but ≥16 Gy	<16 Gy or >27 Gy
3	26.5-33 Gy	<26.5 Gy but ≥24.5 Gy	<24.5 Gy or >33 Gy,
5	30-37.5 Gy	≥28 Gy, <30 Gy	<28 Gy or >37.5 Gy,

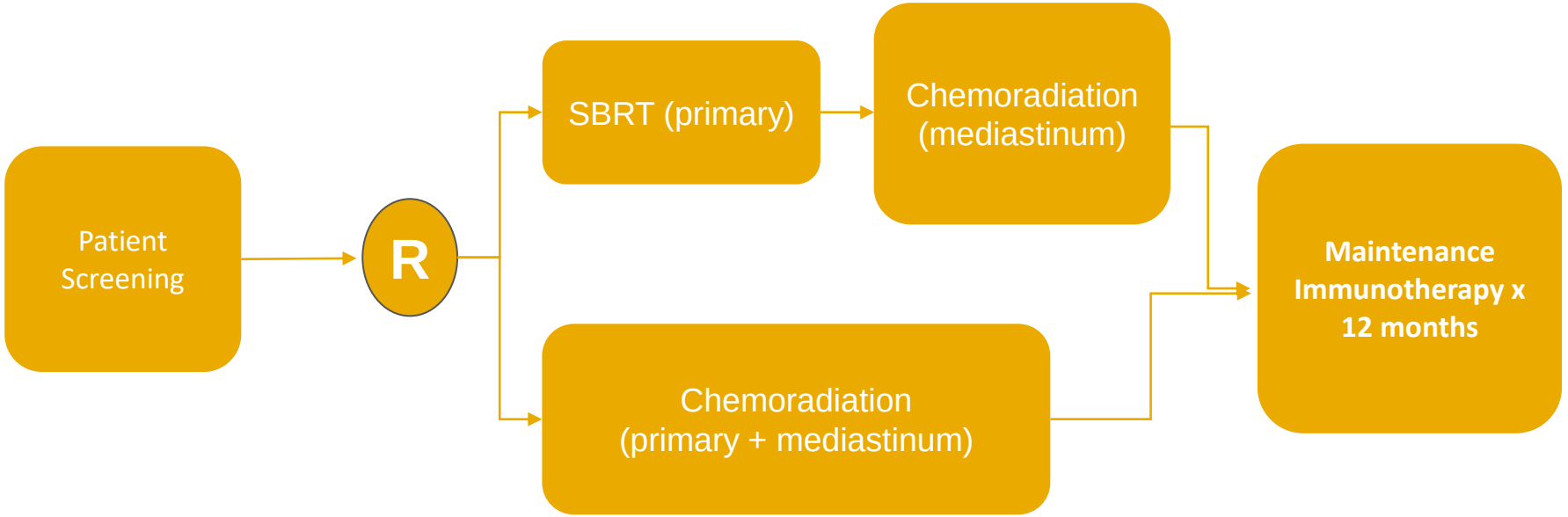
15 fraction (45 Gy) option as needed for disease not amenable to SBRT in ≤5 fractions

RTOG 1308 Locally Advanced NSCLC

STRATIFY	**Stage** 1. II/IIIA 2. IIIB **Histology** 1. Squamous 2. Non-Squamous **Concurrent Chemotherapy Doublet Type** 1. Carboplatin/paclitaxel or carboplatin/pemetrexed (non-squamous cell carcinoma only) 2. Cisplatin/etoposide **Planned use of immunotherapy** 1. Yes 2. No	RANDOMIZE	**Arm 1**: Photon dose—70 Gy*(RBE), at 2 Gy (RBE) once daily plus platinum-based doublet chemotherapy** **Arm 2**: Proton dose—70 Gy (RBE), at 2 Gy (RBE) once daily plus platinum-based doublet chemotherapy**	**Both Arms**: Standard of Care Consolidation Systemic Treatment per treating physician ***

*The total prescribed dose will be 70 Gy [Relative Biological Effectiveness (RBE)] without exceeding tolerance dose-volume limits of all critical normal structures.
**Chemotherapy delivered concurrently, cisplatin/ etoposide or carboplatin/paclitaxel, or carboplatin/pemetrexed doublets, is required. The site/investigator must declare the chemotherapy regimen that the patient will receive prior to the patient's randomization. See Section 7.0 for details.
*** Standard of Care Consolidation systemic treatment per treating physician. Consolidation immunotherapy with durvalumab may be given per treating physician after the completion of radiotherapy. If durvalumab is given, patients do not require any further consolidation chemotherapy after radiotherapy is completed. If consolidation durvalumab is NOT given, the following patients require further systemic therapy after the completion of radiotherapy:
Patients who receive concurrent weekly carboplatin/paclitaxel are required to receive 2 cycles of consolidation carboplatin/paclitaxel.
Patients who receive concurrent carboplatin/pemetrexed (non-squamous cell carcinoma only) are required to receive a total of 4 cycles of carboplatin/pemetrexed. These patients therefore will receive cycle #4 of carboplatin/pemetrexed after the completion of radiotherapy. If cycle #3 is delayed, it is possible that it will also be received after the completion of radiotherapy.

LU008 Locally Advanced NSCLC



- Control arm: chemoradiation to the primary and mediastinal disease (60 Gy/2 Gy) → immunotherapy maintenance x 12 months
- Experimental arm: SBRT to the primary (standard BED ≥100 Gy dose regimen) → chemoradiation to mediastinal disease (60 Gy/2 Gy) → immunotherapy maintenance x 12 months
  - SBRT to primary tumor:
    - 3 fractions to 54 Gy (BED_{10} of 151.2 Gy) [peripheral]
    - 4 fractions to 50 Gy (BED_{10} of 112.5 Gy) [peripheral or central]
    - 5 fractions to 50 Gy (BED_{10} of 100 Gy) [central]
  - Radiation to involved hilar/mediastinal lymph nodes: 2 Gy x 30 fx to 60 Gy, IMRT or proton therapy
  - Chemotherapy: paclitaxel + carboplatin or cisplatin + etoposide
  - Immunotherapy: durvalumab x 12 months

Rationale for Immunotherapy in Early Stage NSCLC

- Surgical lobectomy is standard-of-care for fit patients with early stage, resectable NSCLC
  - Adjuvant chemotherapy indicated for high-risk factors, improves OS
  - Adjuvant immunotherapy of interest to further improve outcomes, reduce toxicity profiles
    - ECOG-ACRIN EA5142 ANVIL phase III trial completed accrual
- SBRT is standard-of-care for medically inoperable, early stage NSCLC and can achieve excellent local control (>90%), but regional and distant failures remain significant (15-25%)
  - Adjuvant chemotherapy is typically not used following SABR (limited data, chemo is not well tolerated in this typically frail, inoperable population with multiple medical comorbidities)
- Immunotherapy may allow for fewer nodal and distant failures and be well tolerated when given before, during, or after SBRT for early stage NSCLC

ES-NSCLC: SBRT + Immunotherapy

Table 3
Key recruiting or activating trials of combining radiation therapy and immunotherapy for early-stage non–small cell lung cancer

NCT Number/ Trial Name	Study Phase	N	Key Inclusion Criteria	IO Agent	Trial Design	RT Dose	RT and IO Timing	Status	Anticipated 1° Completion Date
Definitive radiation									
NCT03833154 PACIFIC 4	3	630	Stage I–II	Durvalumab	SBRT ± IO up to 24 mo	SBRT	RT completed first	Recruiting	Oct 2023
NCT03446547 ASTEROID	2 Randomized	216	Inoperable stage I NSCLC	Durvalumab	SBRT ± IO up to 12 mo	3 or 4 fractions RT	RT completed first	Recruiting	Dec 2021
NCT03110978 I-SABR	2 Randomized	140	Inoperable stage I and IIA NSCLC	Nivolumab	SBRT ± IO up to 3 mo	SBRT to 50 Gy/4 fx, or (if constraints cannot be met) 70 Gy/10 fx	Concurrent; IO to start within 36 h before or after the first SBRT fraction	Recruiting	Jun 2022
NCT03148327	1/2 Randomized	105	Inoperable stage I/IIA NSCLC	Durvalumab	SBRT ± IO up to 5 mo	SBRT to 54 Gy/3 fx, 50 Gy/4 fx, or 65 Gy/10 fx	IO starts first, RT to start between 5 and 10 d of first dose	Recruiting	Jun 2020
NCT03050554	1/2 Single arm	56	Inoperable stage I NSCLC	Avelumab	SBRT + IO up to 2 mo	SBRT to 50 Gy/5 fx or 48 Gy/4 fx	Concurrent	Active, not recruiting	Oct 2020
NCT03383302 STILE	1/2 Single arm	31	Inoperable stage I NSCLC	Nivolumab	SBRT + IO	SBRT in 3 or 5 fractions	RT completed first; IO to start within 24 h of last fraction	Recruiting	Jun 2021
NCT02599454	1	33	Inoperable stage I NSCLC	Atezoli-zumab	SBRT + IO	SBRT to 50 Gy in 4 or 5 fractions	3 cycles of IO, then RT to start within 24–48 h of third dose	Active, not recruiting	Sep 2020
Neoadjuvant radiation									
NCT02904954	2 Randomized	60	Resectable stage I–IIIA NSCLC	Durva-lumab	Neoadjuvant IO ± SBRT, followed by surgery, followed by postoperative maintenance IO	SBRT to 24 Gy/3 fx	Concurrent	Recruiting	Jan 2020
NCT03217071 PembroX	2 Randomized	40	Resectable stage I–IIIA NSCLC	Pembro-lizumab	Neoadjuvant IO ± SBRT, followed by surgery within 6 wk	SBRT to 12 Gy/1 fx delivered to 50% of the primary lung tumor	2 cycles of IO, then RT to start within 1 wk (±3 d) of second dose	Recruiting	Sep 2019
Adjuvant radiation									
NCT02818920 TOP 1501	2	32	Resectable stage I–IIIA NSCLC	Pembro-lizumab	Neoadjuvant IO, followed by surgery, followed by adjuvant IO. Traditional adjuvant postoperative chemo-therapy ± RT will also be given based on clinical scenario	Conventional postoperative RT	IO begun before surgery; RT may be given in adjuvant setting	Active, not recruiting	Mar 2019

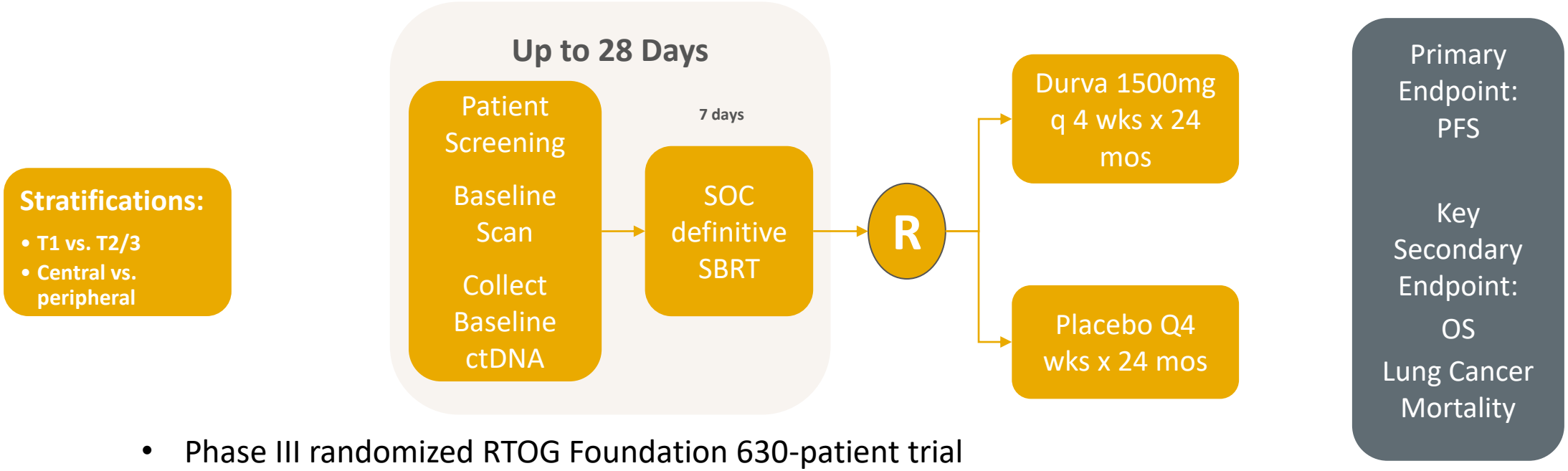
Fitzgerald K, Simone CB 2nd.
Thorac Surg Clin. 2020;30(2):221-239.

PACIFIC 4: A Phase III, Randomized, Placebo-controlled, Double-blind, Multi-center, International Study of Durvalumab Following Stereotactic Body Radiation Therapy (SBRT) for the Treatment of Patients with Stage I/II Non-small Cell Lung Cancer (PACIFIC-4/RTOG-3515)

PACIFIC 4/RTOG Foundation 3515

PI: Cliff Robinson

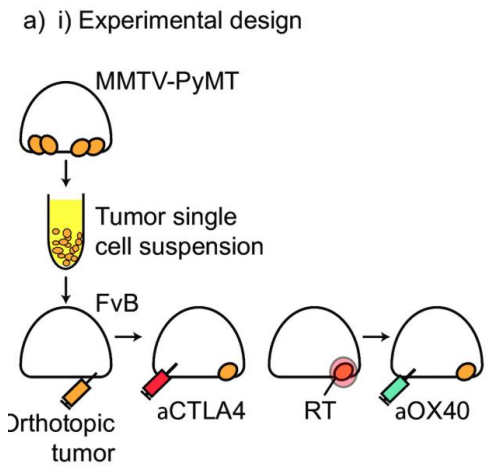
Schema and Study Specifics

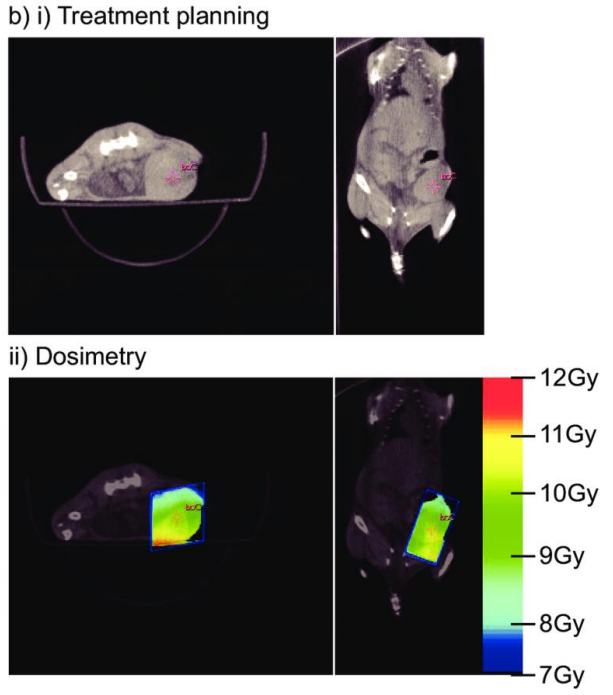


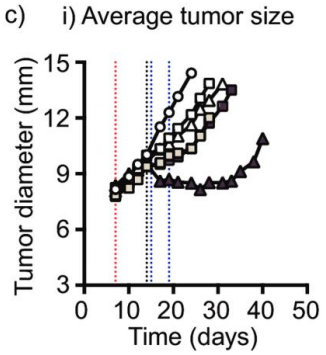
- Phase III randomized RTOG Foundation 630-patient trial
- Primary endpoint: PFS
- Key Inclusion Criteria:
  - Histologically or cytologically documented NSCLC
  - Clinical Stage I/II lymph node-negative (T1-T3 N0 M0) disease receiving SBRT
    - Enriched for T1c-T3 over T1a/b
  - Medically inoperable or refuse surgery
  - ECOG PS 0-2
  - Central or peripheral lesions eligible, “ultra-central” excluded

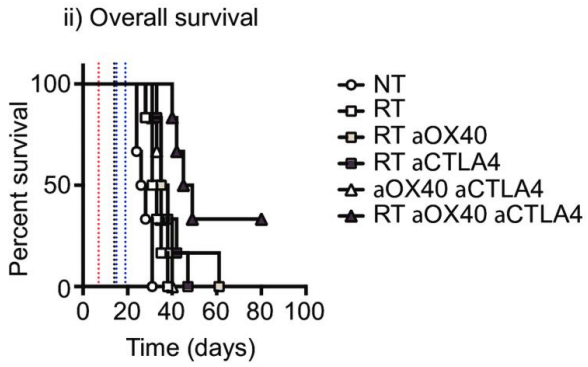
SBRT + Immunotherapy: The Importance of Timing

- Tumor bearing mice treated to 20 Gy RT with either anti-CTLA-4 or OX40 agonist antibody
- Anti-CTLA-4 was most effective when given prior to RT
  - Potentially due to regulatory T cell depletion
- OX40 agonist was most effective when delivered following RT
  - During increased antigen presentation
- Optimal timing of immunotherapy and RT depends on mechanism of immunotherapy action





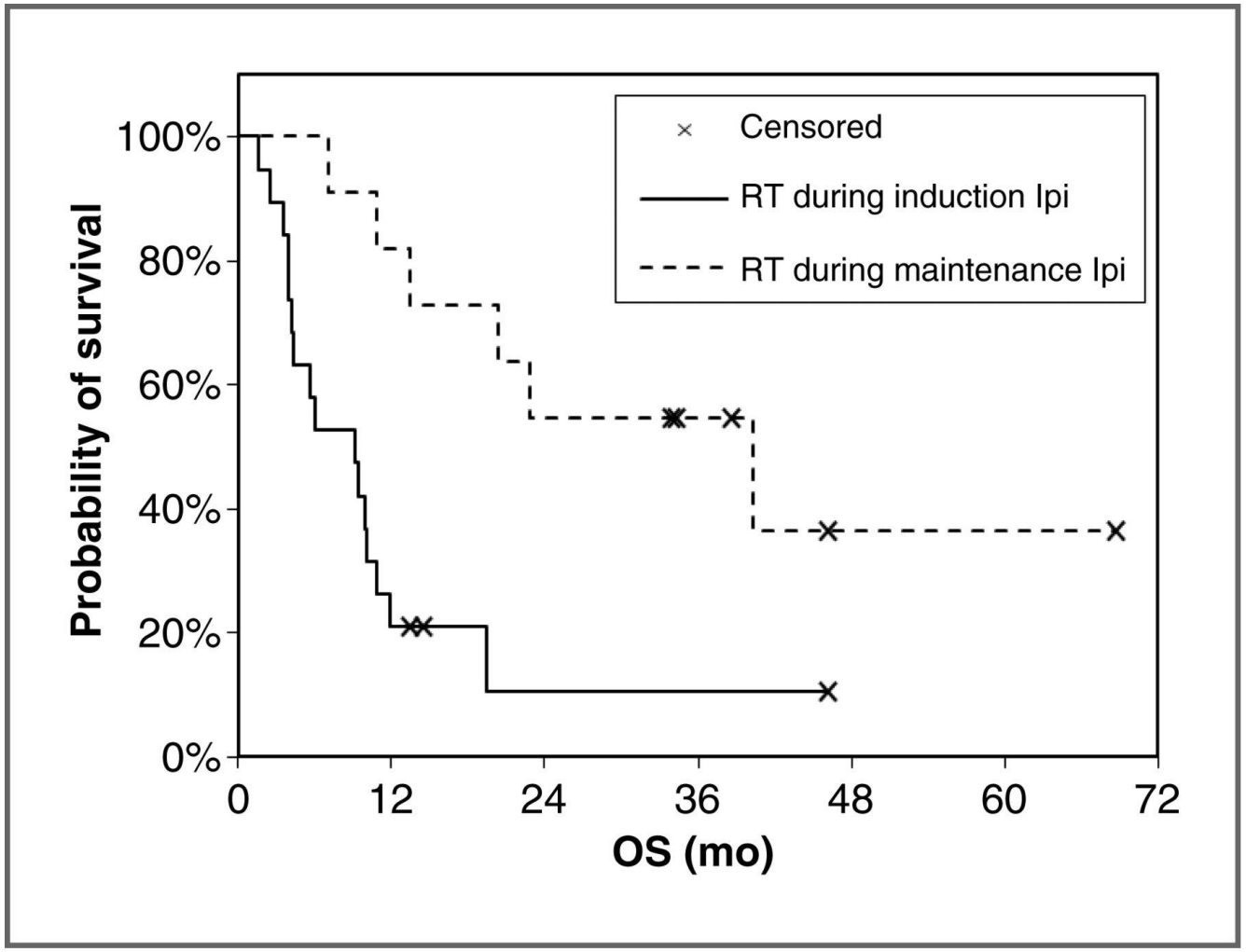




Young KH, et al. *PLoS One*. 2016;11(6):e0157164.

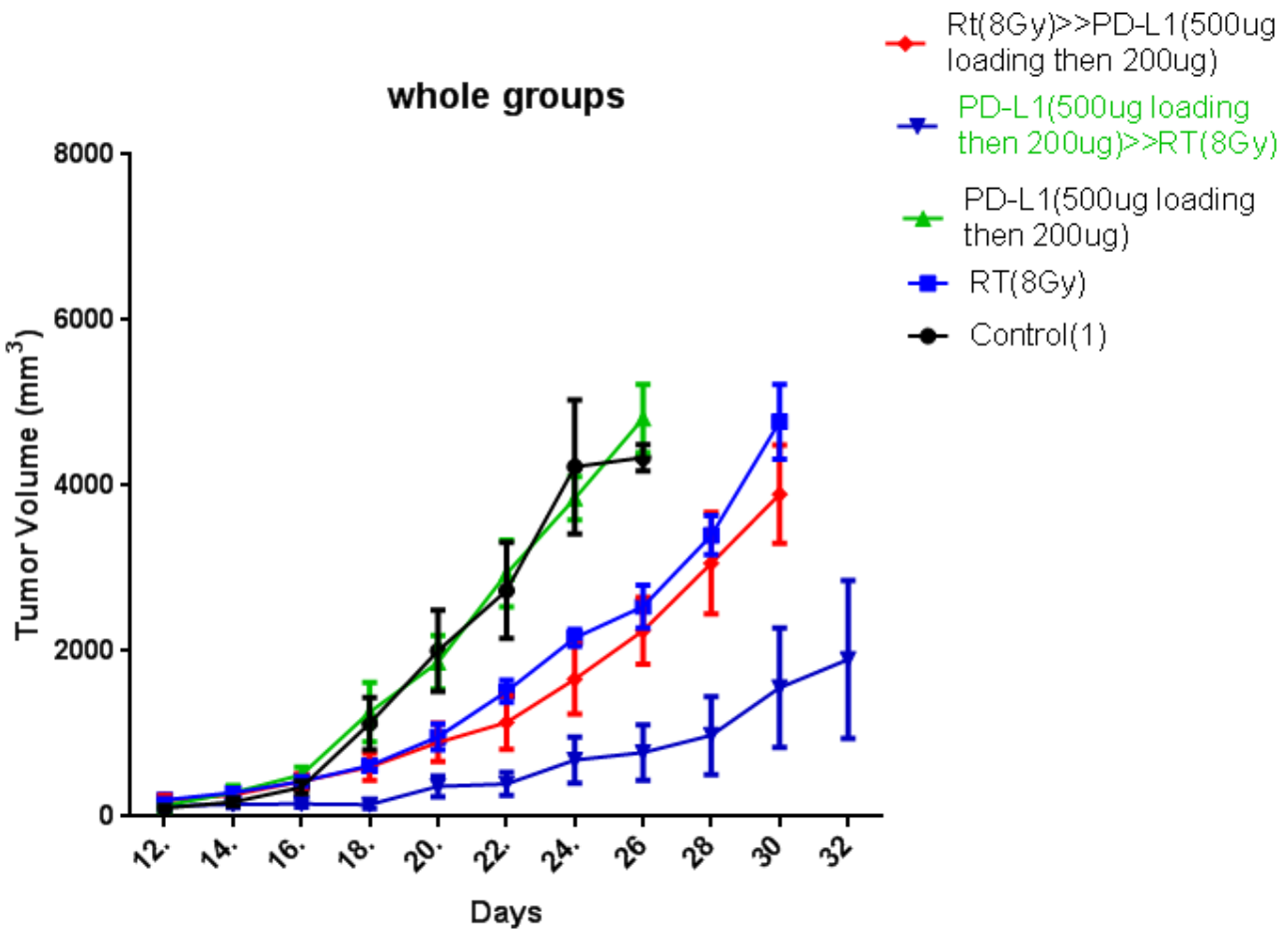
RT + Immunotherapy: The Importance of Timing

- MSKCC retrospective study of melanoma patients treated with ipilimumab and non-brain directed RT
- Median OS: 9 months when RT given during induction vs. 39 months when RT given during maintenance



Barker CA, et al. *Cancer Immunol Res*. 2013;1(2):92-98.

NSCLC Timing for SBRT + Immunotherapy



Significantly superior tumor control was achieved in Balb/c mice when the PD-L1 blockade was delivered prior to radiotherapy to 8 Gy

Kelly K, et al. 2020 ASCO Annual Meeting.

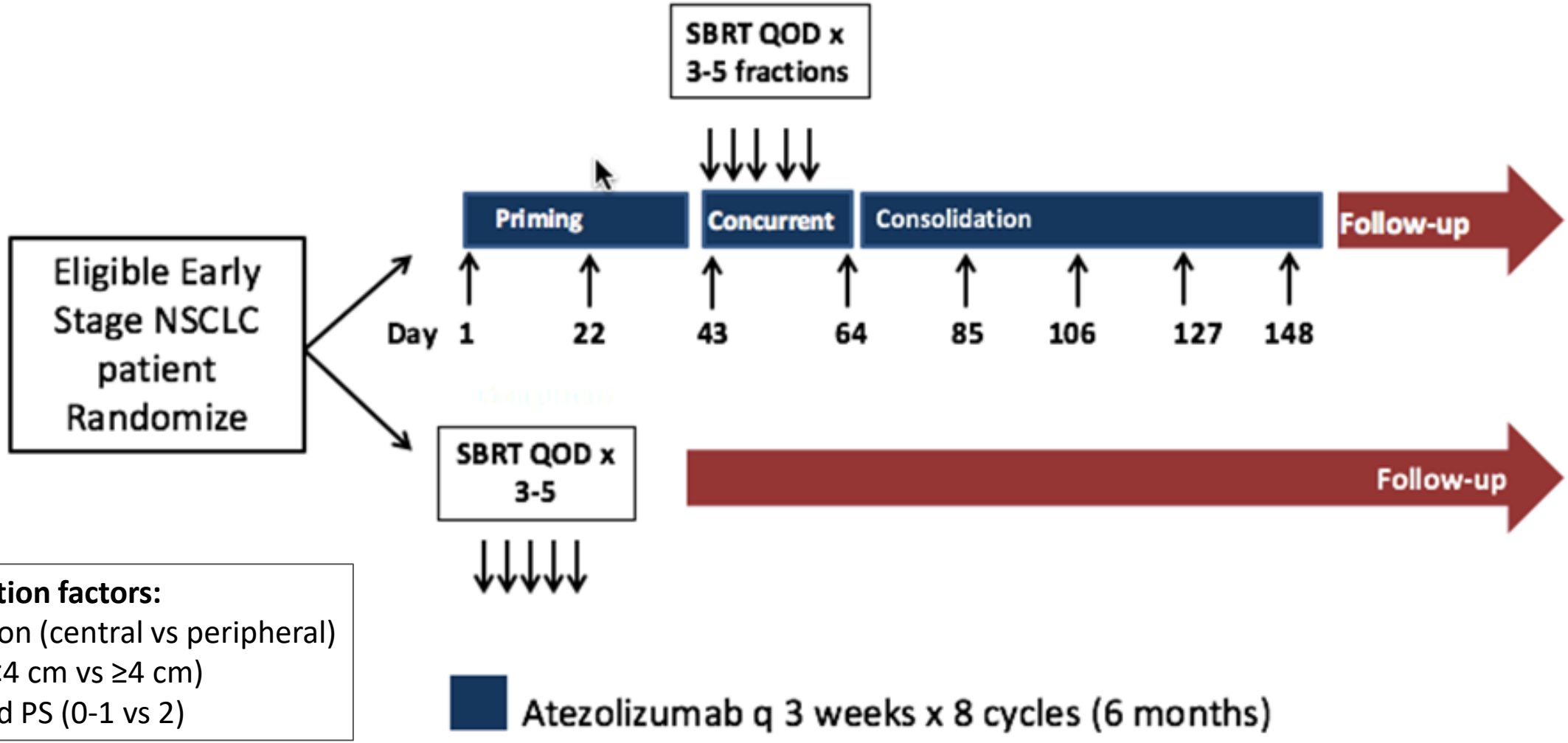
A Randomized Phase III trial of Induction/Consolidation Atezolizumab + SBRT versus SBRT Alone in High risk, Early Stage NSCLC

SWOG/NRG S1914

PI: Charles Simone (NRG)

Megan Daly (SWOG)

Schema



Stratification factors:

- Location (central vs peripheral)
- Size (<4 cm vs ≥4 cm)
- Zubrod PS (0-1 vs 2)

Study Objectives

- Hypothesis: the addition of atezolizumab to standard SBRT for early stage, medically inoperable NSCLC will improve overall survival and progression free survival as compared to SBRT alone
- Primary objective: compare overall survival in medically inoperable, early stage NSCLC patients randomized to SBRT with or without atezolizumab
- Secondary objectives:
  - Progression free survival
  - Distant, locoregional, and local failure rates
  - Frequency and severity of toxicities
  - Quality of life

Inclusion Criteria

- Adults ≥18 years of age
- Histologically proven stage I-IIA or limited T3N0M0 (stage IiB) NSCLC ≤7 cm diameter without nodal or distant involvement
  - 2022 amendment pending activation: will allow up to 2 synchronous early stage primaries to be treated (previously limited to 1 lesion)
- Medically or surgically inoperable OR unwilling to undergo surgical resection
- Zubrod performance status score of 0-2
- FEV1 ≥ 700cc and a DLCO ≥ 5.5 m/min/mmHg
- Archival tumor sample available (FNA allowed, core needle biopsy preferred)
- One or more high-risk features identified:
  - **Tumor diameter ≥ 2 cm**
  - **Tumor SUV max ≥ 6.2**
  - **Moderately or poorly differentiated or undifferentiated histology**

Treatment Specifications

- SBRT (starts with cycle 3 [week 7] in Arm A)

Dose per Fraction	Number of Fractions	Total Dose	BED_{10}	Tumor Sites
18 Gy	3	54 Gy	151.2 Gy	Peripheral
12.5 Gy	4	50 Gy	112.5 Gy	Peripheral or Central
12 Gy	4	48 Gy	105.6 Gy	Peripheral or Central
12 Gy	5	60 Gy	132 Gy	Peripheral or Central
11 Gy	5	55 Gy	115.5 Gy	Central
10 Gy	5	50 Gy	100 Gy	Central

2022 amendment pending activation: will allow 7.5 Gy x 8 for central lesions BED_{10} = 105 Gy

- Atezolizumab
  - 1200 mg IV over 60 min Q21 days for up to 8 cycles in Arm A

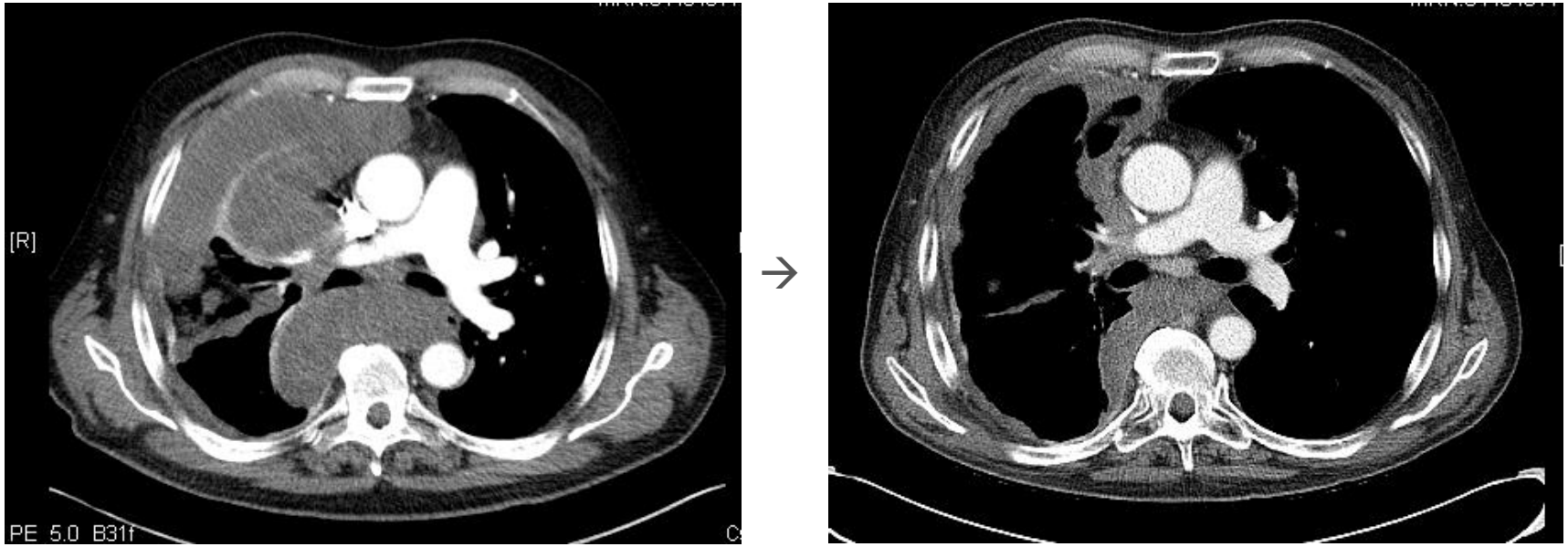
Statistical Design and Accrual

- Primary Objective: OS
  - N=432 eligible patients (480 enrolled, assuming 10% ineligible)
  - 80% power to detect HR of 0.70 (43% improvement in OS), 1-sided 0.025 level
- Secondary Objective: PFS
  - 90% power to detect HR of 0.65, 1-sided 0.025 level
- Interim Analysis
  - Four interim analyses: analyses to be done annually. All analyses will evaluate early stopping for futility (based on PFS), the 3rd and 4th will also evaluate early stopping for efficacy (based on OS)
- Planned Accrual
  - 8 patients per month
  - Accrual duration 5 years
- Study Activation: 5/28/20

Beyond Checkpoint Inhibitors: Combining RT + Immunotherapy

Ad.IFN → RT → Chemo Combination Therapy

Pre-RT **3 mo Post-RT**



Barsky AR, Simone CB 2nd, et al. *Cureus*. 2019;11(2):e4102.

Why there might be a survival advantage with protons over photons for lung cancer beyond toxicity reduction and safer dose escalation

- Immune
  - Decreased lymphopenia
  - Increase immune stimulation

International Journal of Radiation Oncology biology • physics
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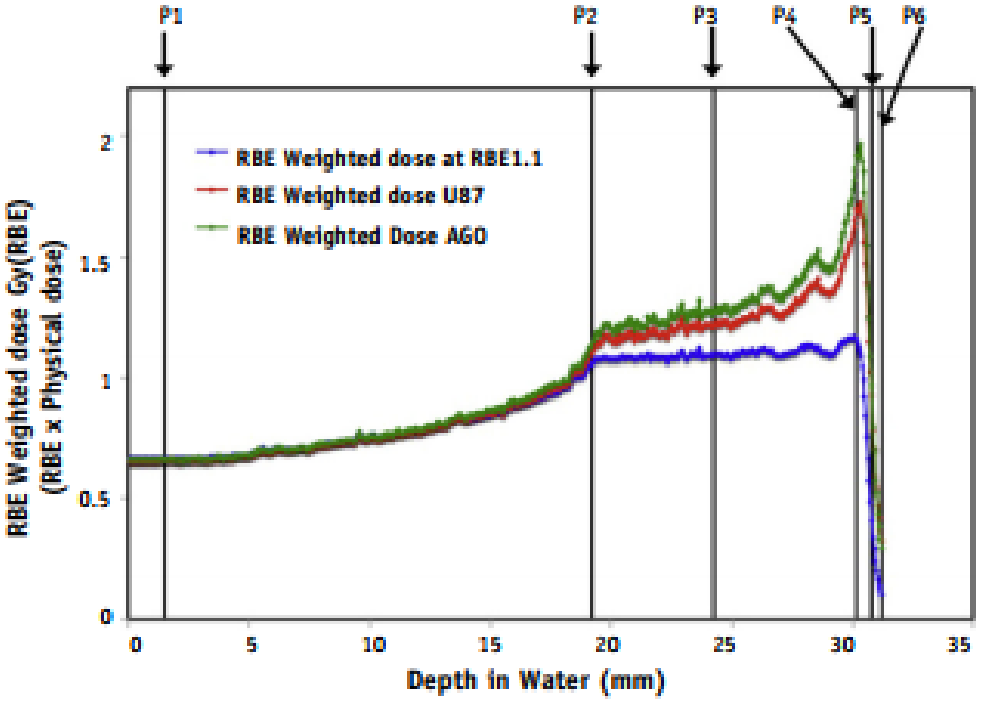
RBE and Particle Therapy Biology

Tumor Cells Surviving Exposure to Proton or Photon Radiation Share a Common Immunogenic Modulation Signature, Rendering Them More Sensitive to T Cell—Mediated Killing

Sofia R. Gameiro, PhD,* Anthony S. Malamas, PhD,* Michael B. Bernstein, MD,† Kwong Y. Tsang, PhD,* April Vassantachart, BS,† Narayan Sahoo, PhD,† Ramesh Tailor, PhD,† Rajesh Pidikiti, PhD,† Chandan P. Guha, MBBS, BS, PhD,‡ Stephen M. Hahn, MD,† Sunil Krishnan, MD,† and James W. Hodge, PhD, MBA*

**Laboratory of Tumor Immunology and Biology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland; †Division of Radiation Oncology, M. D. Anderson Cancer Center, Houston, Texas; and ‡Department of Radiation Oncology, Montefiore Medical Center, Bronx, New York*

- Increased LET/RBE
  - Overcome tumor resistance, hypoxia, enhanced effects with DNA biologics (e.g. PARP inhibitors)



Chaudhary P, et al. *Int J Radiat Oncol Biol Phys*. 2014;90(1):27-35.

Conclusions

- Immunotherapy is well entrenched as a standard of care of patients with metastatic solid tumors across a variety of cancer sites
- Immunotherapy is increasingly being shown to improve survival in non-metastatic, locally advanced cancer patients
- There is increasing interest in trialing immunotherapy with radiation therapy in early stage cancers
- Immunotherapy may improve regional and nodal failure rates in patients with early stage disease, will allowing for synergy with radiation therapy
- SBRT may induce the immune system to allow for even greater synergy with immune checkpoint inhibitors compared with conventionally fractionated radiation therapy
- Additional preclinical and clinical studies are needed to determine the optimal dose, fractionation, and timing of conventionally fractionated radiation therapy and SBRT with immunotherapy

Questions?