Society for Immunotherapy of Cancer

Advances in Cancer Immunotherapy™

Immunotherapy and Radiation: Considerations on Outcomes and Toxicity in Lung Cancer

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Disclosures

- AstraZeneca (consulting fees, speaker's bureau)
- Bristol Myers Squibb (speaking fees)
- Galera Medical (advisory board)
- Grand Rounds Health (consulting fees)
- Guidepoint (consulting fees)
- Healthcasts (consulting fees)
- Healthline (honoraria)
- LaGrippe Research, Inc. (honoraria)
- Med Learning Group (honoraria)
- RefleXion Medical (research funding)
- I will be discussing non-FDA approved indications during my presentation.

Outline

- Radiotherapy in lung cancer
- Mechanisms of synergy and toxicities between radiotherapy (RT) and immune checkpoint inhibitors (ICI)
- Outcomes, toxicities, and ongoing trials of combined RT-ICI

Radiotherapy in lung cancer

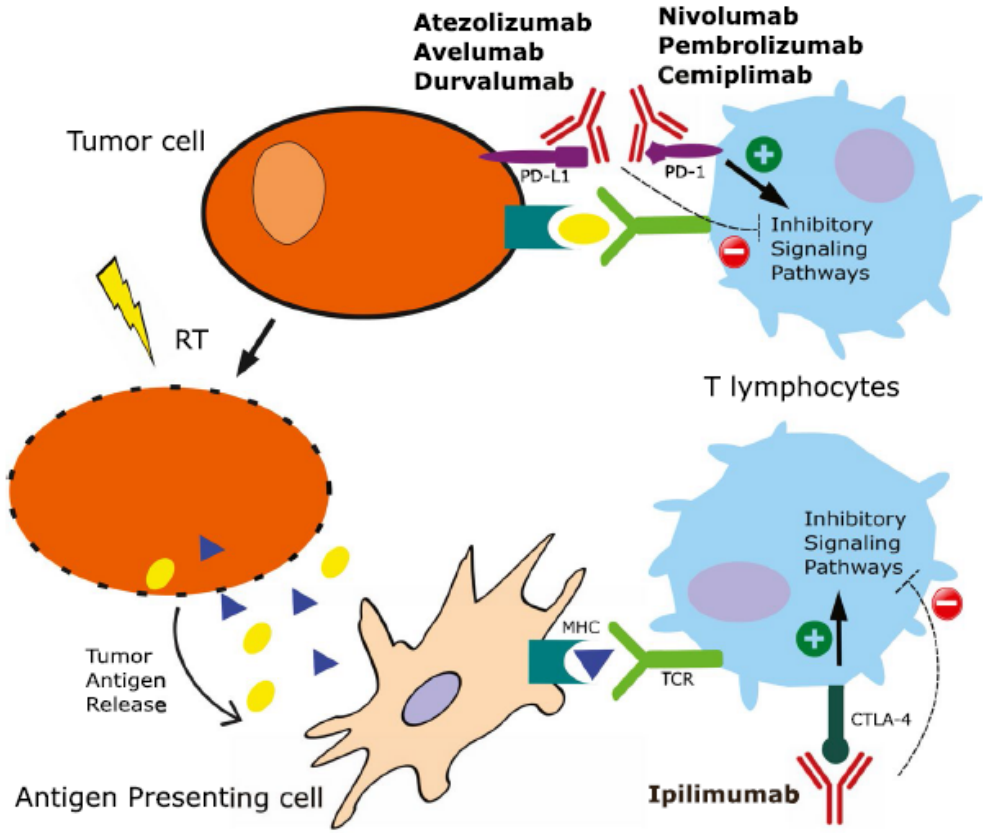
- Stage I:
  - Definitive SBRT in 3-5 fractions if inoperable
- Stage II-III NSCLC:
  - Definitive chemo-RT in 30-35 fractions if inoperable or extensive nodal disease
- Stage IV NSCLC:
  - Palliative RT in 1-10 fractions for symptom control or impending functional compromise
  - Definitive or palliative SBRT in 3-5 fractions for consolidation in oligometastatic disease or tumor control in oligoprogressive disease
- Limited-stage SCLC:
  - Definitive chemo-RT in 30-35 fractions
- Extensive-stage SCLC:
  - Palliative RT in 1-15 fractions for symptom control or consolidation

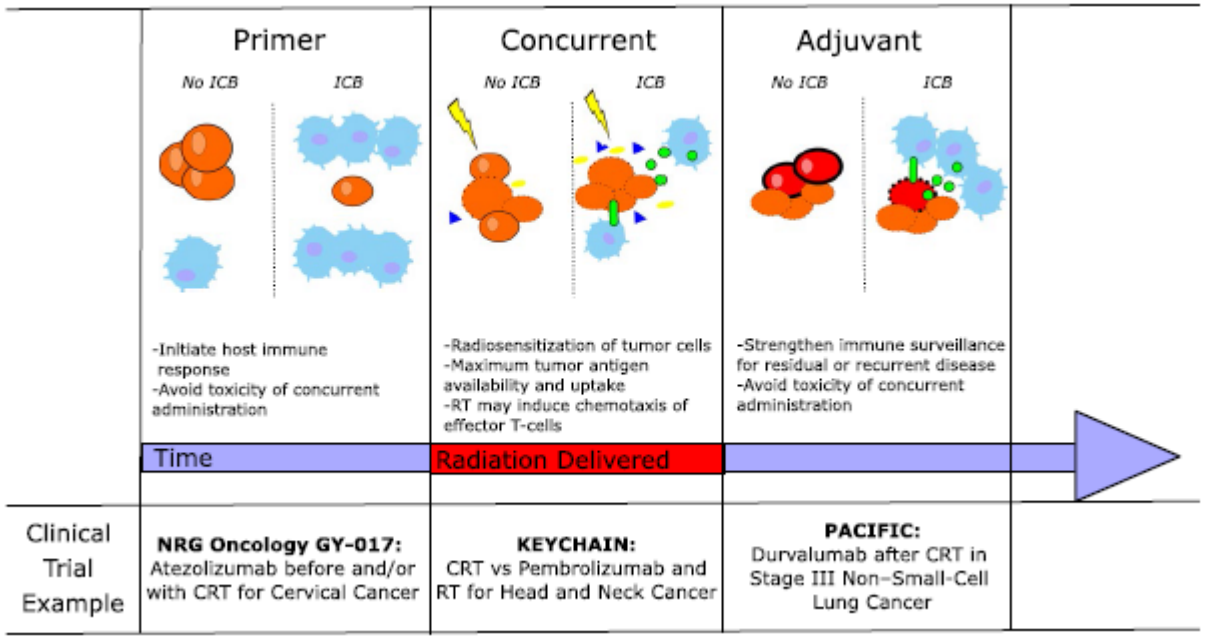
Mechanisms of RT-ICI Synergy

- Potential benefits of RT (especially SBRT) when combined with ICI
  - Induce immunogenic cell death
  - Improve tumor antigen presentation by maturation of antigen-presenting cells
  - Bolster cytotoxic T-lymphocyte activity
  - Induce secretion of cytokines/chemokines to improve homing to primary irradiated site and possible distant non-irradiated sites (abscopal effect?)
  - SBRT (higher dose per fraction in fewer number of fractions) less immunosuppressive than conventional RT, and possibly immunostimulatory by depleting immunosuppressive cells

Heinzerling JH et al, Transl Cancer Res 2021

Mechanisms of RT-ICI Synergy





SWOG S1914 KEYNOTE-867 PACIFIC-4

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Williamson CW et al, Cancer 2021

Mechanisms of RT-ICI Toxicities: Pneumonitis/Fibrosis

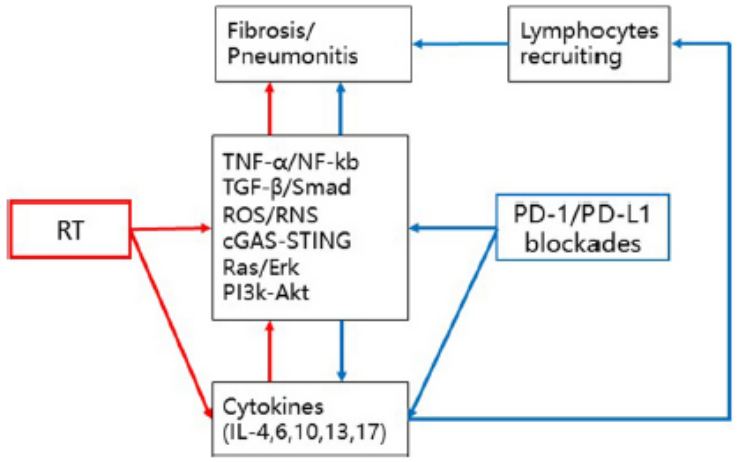

Fig. 1 Cytokines and relative signaling pathways potentially involved in RRP. Tumor necrosis factor-α (TNF-α); transforming growth factor β (TGF-β); interleukins 4, 6, 10, 13, 17, and 18 (IL-4, 6, 10, 13, 17, 18); myeloid differentiation primary response 88 (MyD88); cGMP–AMP synthase (cGAS)–stimulator of interferon genes (STING); nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB); reactive oxygen species/reactive nitrogen species (ROS/RNS); extracellular regulated protein kinases (Erk); and phosphatidylinositol 3-kinase (PI3K)

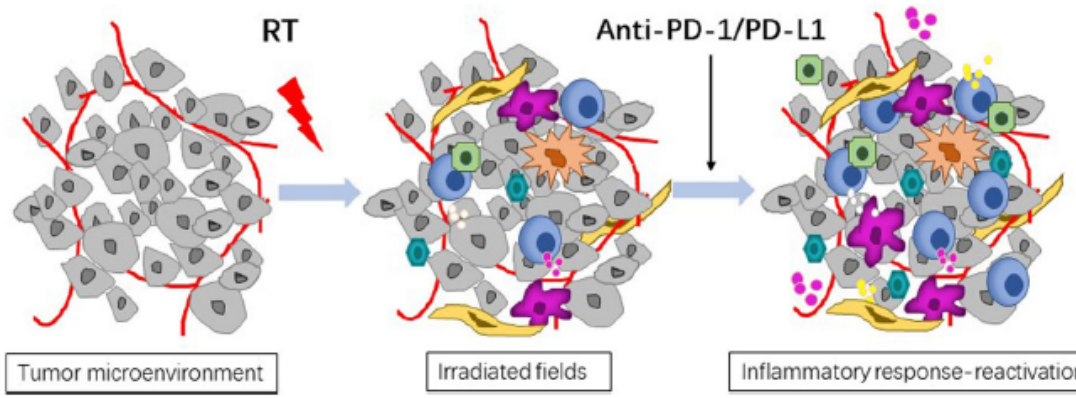

Fig. 2 Immune mechanisms of RRP triggered by anti-PD-1/PD-L1. The immune checkpoint inhibitors evoke an inflammatory reaction in previously irradiated fields

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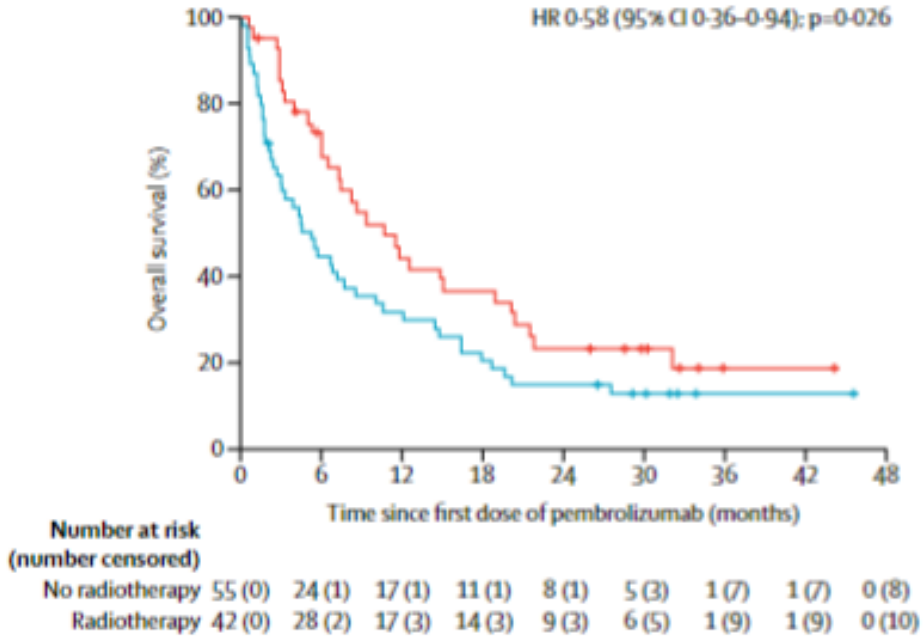
Teng F et al, BMC Med 2021

RT-ICI Combinations: Metastatic NSCLC

- **KEYNOTE-001** secondary analysis
  - Phase 1: 97 stage IV patients treated with pembro
  - Those with **previous** RT (43%) had improved:
    - PFS (HR 0.50, p=0.0084, median 6.3 vs. 2.0 months)
    - OS (HR 0.58, p=0.026, median 10.7 vs. 5.3 months)
    - Pulmonary toxicities 13% vs. 1%, but 1% vs. 1% were grade 3+



Shaverdian N, et al. Lancet Oncol 2017

RT-ICI Combinations: Metastatic NSCLC

- **PEMBRO-RT**
  - Phase 2: 76 stage IV patients treated with pembro with **previous** RT to 1 metastatic site prior to ICI
  - Primary endpoint was ORR at 12 weeks EXCLUDING irradiated lesion
  - ORR doubled from 18% to 36% (p=0.07), driven by PD-L1 negative
    - Did not meet prespecified endpoint of 50% ORR
  - Toxicities similar (overall 17% grade 3+)

Table. Response to Treatment

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)

Abbreviations: PD-L1, programmed death–ligand 1; TPS, tumor proportion score.

[a] Patients who received pembrolizumab therapy after stereotactic body radiotherapy.

[b] Patients who received pembrolizumab therapy alone.

[c] $P = .07$.

[d] $P = .04$.

Theelen WS et al, JAMA Oncol 2019

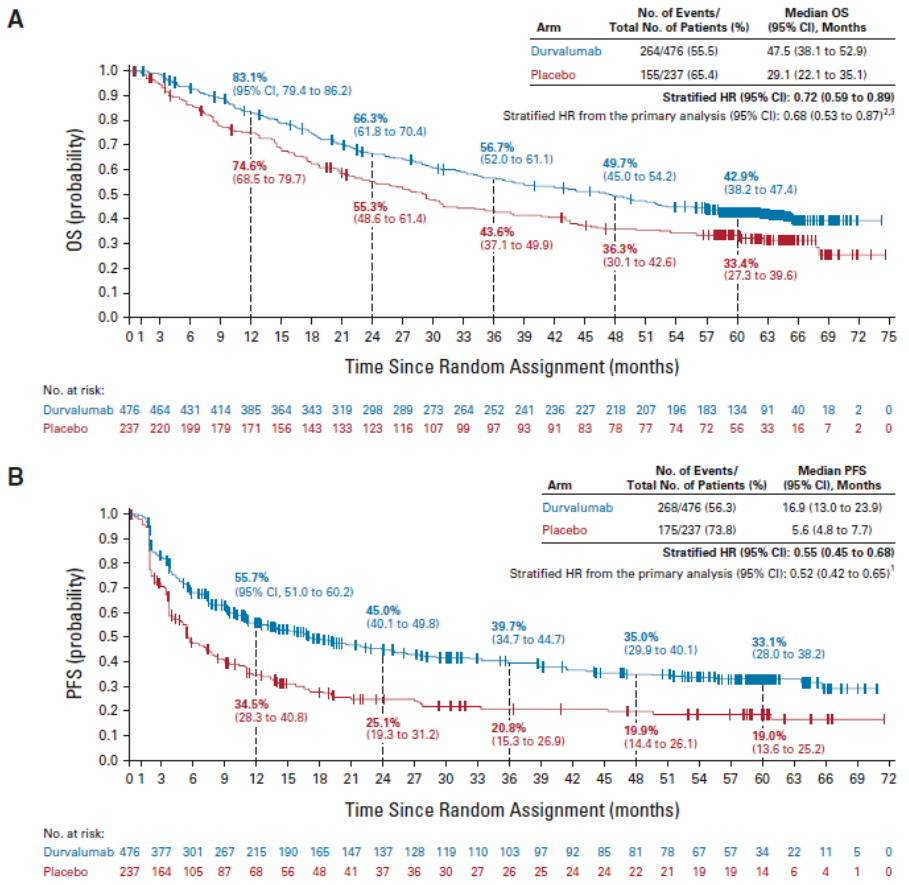
RT-ICI Combinations: Metastatic NSCLC

- Ongoing phase 3 trial:
  - NRG **LU002** (limited metastatic disease with maintenance systemic therapy +/- **consolidative** SBRT, now allows for immunotherapy)

Patients with metastatic NSCLC having completed 4 cycles of first-line/induction systemic therapy Restaging studies reveal no evidence of progression and limited (≤ 3 discrete sites) metastatic disease, all of which must be amenable to SBRT	**STRATIFY**	**Histology:** Squamous vs. Non-squamous	**RANDOMIZE**	**Arm 1**: Maintenance systemic therapy alone* **Arm 2:** SBRT to all sites of metastases (≤ 3 discrete sites) plus irradiation of the primary site (SBRT or hypofractionated RT) followed by maintenance systemic therapy* *** As noted in Section 5**

RT-ICI Combinations: Locally Advanced NSCLC

- PACIFIC
  - 709 stage III patients treated with chemo-RT +/- **consolidative** durvalumab
  - Survival:
    - 5-year PFS 33% vs. 19%
    - 5-year OS 43% vs. 33%
  - Toxicities:
    - G3-4 any-cause AEs in 30.5% of durvalumab and 26.1% of placebo group
    - Discontinued durva due to AEs in 15.4% of durvalumab and 9.8% (mostly pneumonitis and pneumonia)



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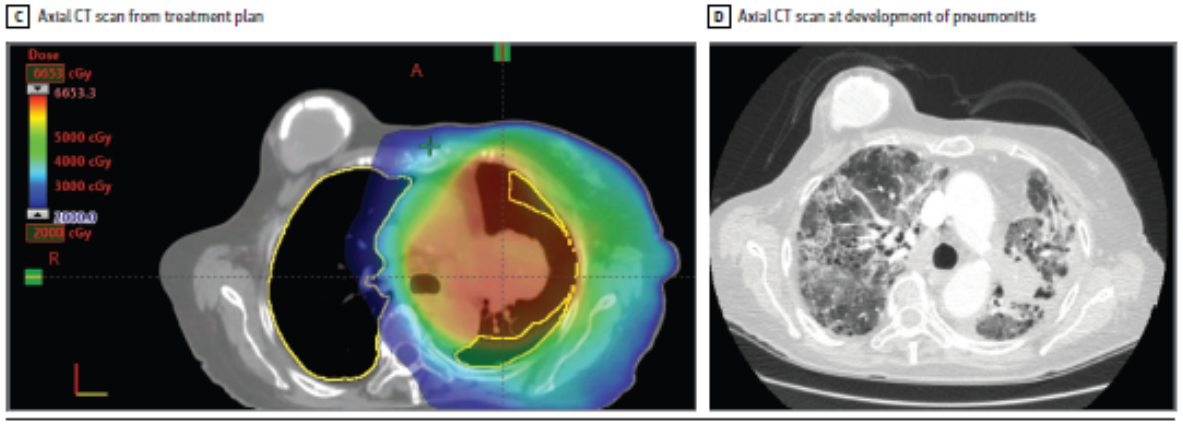
Antonia SJ et al, NEJM 2018
Spigel DR et al, JCO 2022

RT-ICI Combinations: Locally Advanced NSCLC

- Chemo-RT with **concurrent** pembro:
  - Phase 1: Rutgers-based
    - 21 patients
    - 1-year PFS 70%
    - Grade 3-5 AEs 18% with 1 death
  - Phase 2: **KEYNOTE-799**
    - 214 patients
    - ORR 71%
    - Grade 3-5 pneumonitis 7%
    - Grade 3-5 AEs overall 57%
  - Phase 3: KEYLYNK-12 (ongoing)



A, Time to immune-related adverse events (IRAEs) including pneumonitis in 14 patients who developed IRAEs of at least grade 2. B and C, Axial and coronal computed tomographic (CT) images from the radiotherapy plan demonstrating radiation distribution targeting non-small cell lung cancer in the left lung. D, Axial (1D) CT image at time of diagnosis of pneumonitis showing bilateral lung involvement in a patient with grade 5 pneumonitis outside the high-dose radiation field and involving bilateral lungs.

[a] Ongoing treatment at time of last follow-up.

[b] Death during treatment due to grade 5 IRAE (pneumonitis).

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Jabbour et al, JAMA Oncol 2020
Jabbour et al, JAMA Oncol 2021

RT-ICI Combinations: Locally Advanced NSCLC

- Ongoing phase 3 trials of **concurrent** ICI:
  - **KEYLYNK-12** (chemo-RT + consolidative durva vs. chemo-RT + concurrent/consolidative pembro ± consolidative olaparib)
  - ECOG-ACRIN **EA5181** (chemo-RT + consolidative durva ± concurrent durva)
  - **PACIFIC 2** (chemo-RT ± concurrent durva)
- Ongoing phase 1-2 trials in special populations (**no chemo**):
  - ECOG PS 2: SWOG **S1933** (RT ± consolidative atezo)
  - PD-L1 ≥50%: NRG **LU004**/ARCHON-1 (concurrent durva-RT)

RT-ICI Combinations: Early-Stage NSCLC

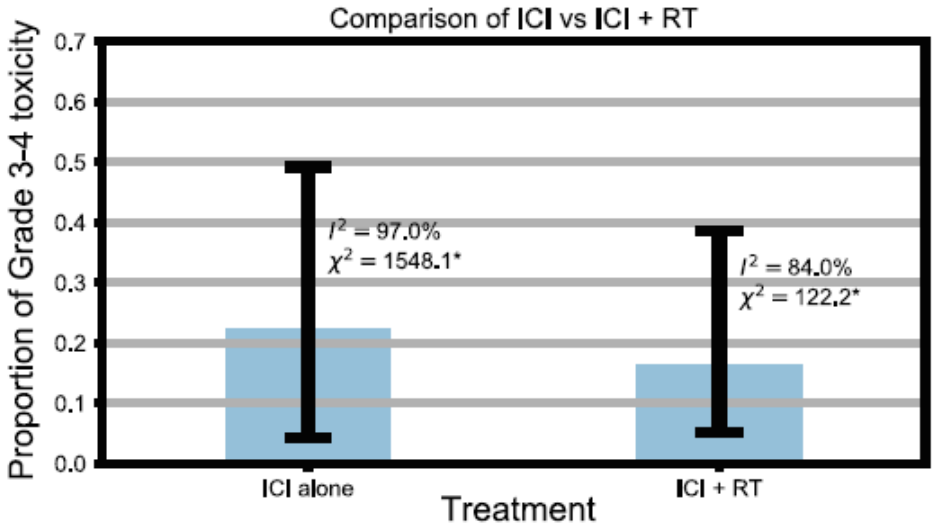
- Regional/distant recurrences common despite excellent local control with SBRT
- Chemotherapy not often well-tolerated in medically frail population, so immunotherapy more appealing
- Ongoing phase 3 trials:
  - **PACIFIC 4** (SBRT ± consolidative durva)
  - SWOG **S1914** (SBRT ± priming/concurrent/consolidative atezo)
  - **KEYNOTE-867** (SBRT ± concurrent/consolidative pembro

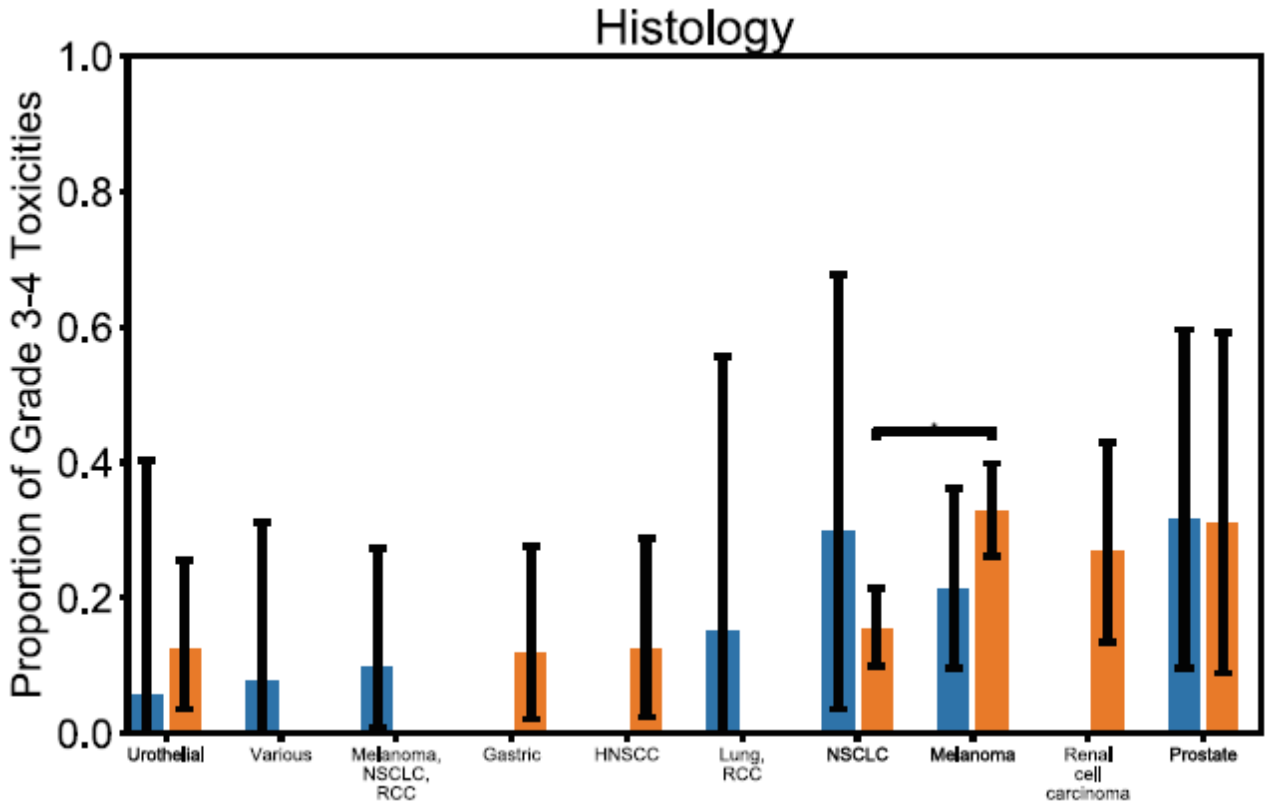
RT-ICI Combinations: SCLC

- IMpower133 and CASPIAN in extensive-stage with smaller benefit to addition of ICI to chemotherapy compared to NSCLC (no extracranial RT was allowed in either trial)
- Ongoing phase 3 trial in **extensive-stage**:
  - NRG **LU007**/RAPTOR (chemo-atezo then maintenance atezo ± consolidative RT with
- Ongoing/closed phase 3 trials in **limited-stage**:
  - NRG **LU005** (concurrent chemo-RT +/- concurrent atezo)
  - **ADRIATIC** (concurrent chemo-RT +/- consolidative durva +/- treme)

Horn L, et al, NEJM 2018
Paz-Ares L, et al, Lancet 2019

Toxicities of RT-ICI Combinations: Meta-Analysis





Blue bars indicate ICI + RT while orange bars indicate ICI alone.

Sha CM et al, Radiother Oncol 2020

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Conclusions and future directions

- RT and ICI combinations are generally safe (acceptably low G3+ toxicities) and appear to have synergistic effectiveness in lung cancer
- However, patients should be monitored closely for additive toxicities (especially pneumonitis)
- Questions remain regarding optimizing balance between synergistic effectiveness and additive toxicities with thoracic RT
  - Sequencing: priming vs. concurrent vs. consolidative
  - Dose-fractionation: ablative high doses (SBRT) vs. immunostimulatory intermediate doses vs. tumor microenvironment-modifying low doses
  - Ideal RT targets: 1 versus multiple
  - ICI agent: PD-1 vs. PD-L1

Thank You!

Questions?

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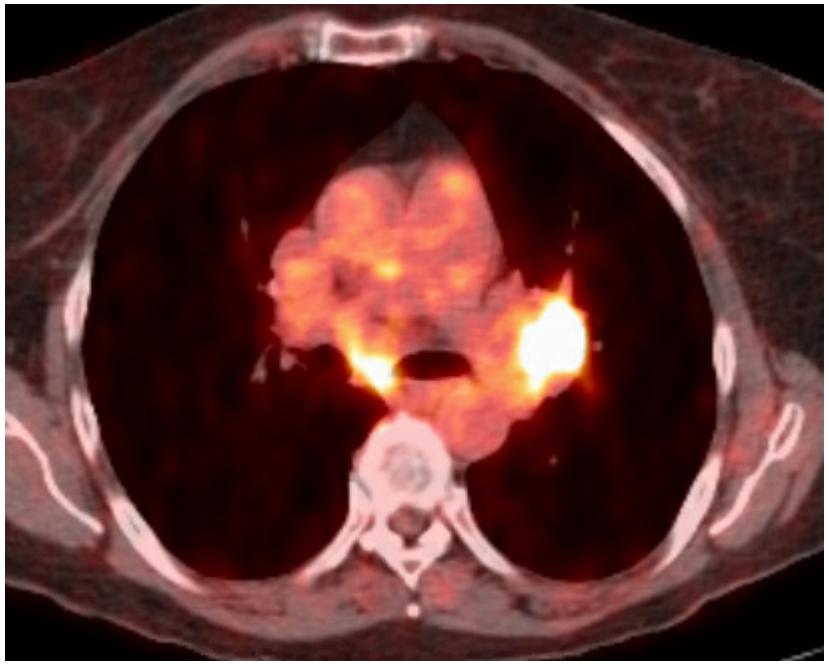
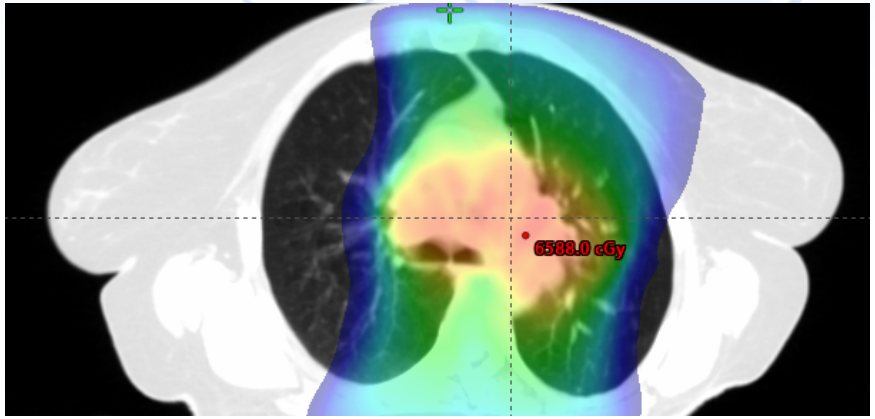
Case discussion

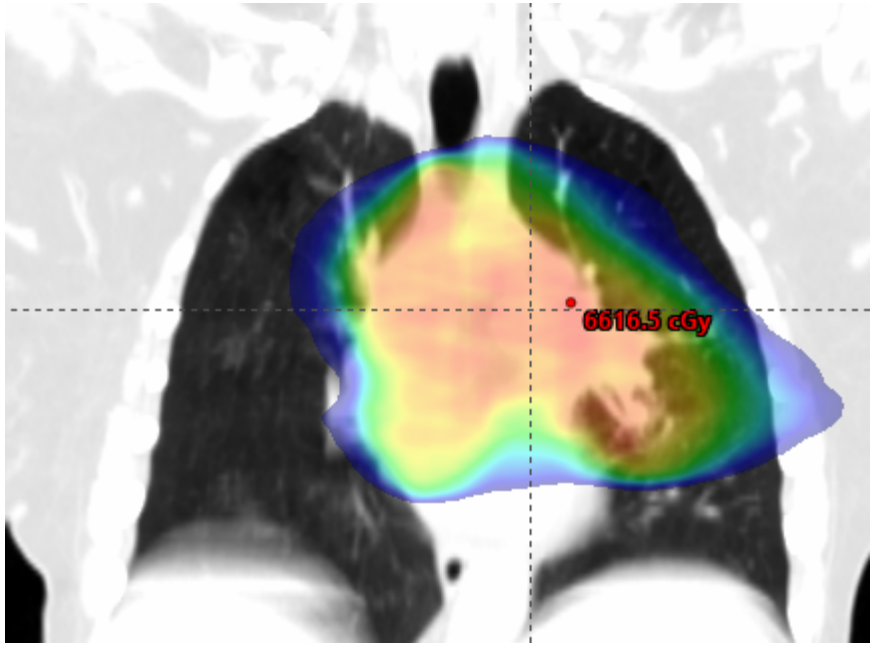
- 72F with L lingular NSCLC (adeno), at least stage IIIB (cT2aN3M0).
- After presenting with wheezing and hemoptysis:
  - CT chest: 3.5 cm L lingular mass severely narrowing LUL bronchus and lingular bronchi to near-complete obliteration, multistation mediastinal LN
  - PET-CT: hypermetabolism in L hilar, AP window, R paratracheal, subcarinal
  - EBUS: extrinsic compression of LUL bronchus, endobronchial involvement. Path positive for adenocarcinoma in endobronchial LUL bronchus, L hilar mass, and stations 4R/4L/7, negative in 11R.
  - Tumor profiling PD-L1 >50%, Oncomine KRAS G12D
  - MRI brain: negative

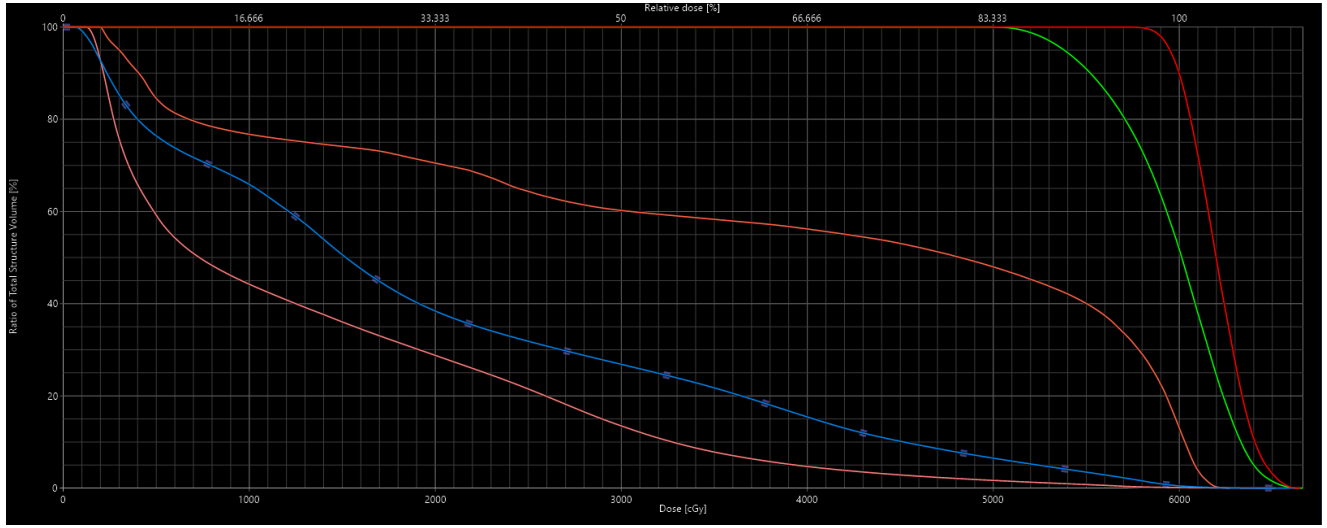


Case discussion

- Definitive chemo-RT to 60 Gy in 30 fractions with concurrent carbo/taxol (completed 12/2019).
- Lung mean 19.9 Gy, lung V20 38.4%, lung V5 76.4%
- Compromised target coverage (similar to 54 Gy)







Case discussion

- Struggled with pneumonitis/pneumonias for several months afterwards (treated with long prednisone taper and antibiotics)
- Never received consolidative durvalumab
- Developed widely metastatic recurrence in 10/2020
- Pembrolizumab 11/2020 to 8/2021 until POD
- Cisplatin/pemetrexed 9/2021 to 1/2022 until POD
- On supportive care since 2/2022

Case discussion

- How long would you wait for post-chemo-RT pneumonitis to resolve before starting consolidative ICI? How severe must the pneumonitis be before holding ICI?
- What would be your preferred approach for a patient with such a large RT field and high PD-L1?
  - Proceed with standard PACIFIC regimen (concurrent chemo-RT then ICI)
  - Proceed with standard PACIFIC regimen modified to decrease RT margins?
  - Induction ICI alone then concurrent chemo-RT if no progression?
  - Induction ICI+chemo then concurrent chemo-RT if no progression?
  - Definitive RT+ICI without concurrent chemo?
  - Palliative ICI+chemo without plans for definitive RT?