Disclosures

Siva Shankar, MBBS, FRANZCR, PhD
› Astra Zeneca (speaker honoraria, travel)
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Willimejn Theelen, MD, PhD
› Astra Zeneca (research grant)

Corinne Faivre-Finn, FRCR, MD, PhD
› Astra Zeneca (research grant, advisory board, scientific committee)
› MSD Pharmaceuticals, Elekta (research grant)

All other planners, reviewers and staff reported no relevant financial relationships.
All relevant financial relationships have been mitigated.
Shankar Siva, MBBS, FRANZCR, PhD
Associate Professor, Radiation Oncology
University of Melbourne
Peter MaCallum Cancer Centre
Melbourne, Australia
The current Era of Immuno-Oncology

SALES SNAPSHOT

Drug “A”          Drug “B”

Millions

$0     $1,000     $2,000     $3,000

1Q15  3Q15  1Q16  3Q16  1Q17  3Q17  1Q18  3Q18  1Q19  3Q19  1Q20

$3.28B $1.77B
Need to improve outcomes from checkpoint blockade inhibitors

Haslam, Prasad
How do we make these drugs work better?

Standard approach: give another drug that is delivered through the blood stream?
Alternative: give a local modality delivered through another mechanism?
Types of RT Induced Cell Death

- Mitotic Catastrophe
- Apoptosis
- Autophagy
- Necrosis
- Senescence

Anti-inflammatory vs. Pro-inflammatory

Conventional fractionated vs. Hypofractionated

Adapted Haikerwal et al. Cancer Letters 2015
Radiation upregulates tumor cell checkpoints

**PD-L1 upregulation appears RT dose dependent**

<table>
<thead>
<tr>
<th>X-rays</th>
<th>2</th>
<th>5</th>
<th>10</th>
<th>20 Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>80</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Synergy b/w anti–PD-L1 and RT in murine model**

- No treatment
- Anti–PD-L1 mAb 10 mg/kg
- 5×2Gy RT
- 5×2Gy RT + anti–PD-L1 mAb 10 mg/kg


Might ablative RT be a good fit with I/O?

*Turgeon & Siva, Medical Journal of Australia 2018  
Overview

The Abscopal Effect of Stereotactic Radiotherapy and Immunotherapy: Fool’s Gold or El Dorado?

D. Xing *, S. Siva *,†, G.G. Hanna †‡

* Division of Radiation Oncology, Peter MacCallum Cancer Centre, Melbourne, Australia
† Sir Peter MacCallum Department of Oncology, University of Melbourne, Parkville, Australia

Latin: “ab” - away  
“scopus” – target

Defined 1953 – R. J. Mole

*2019;31:432-443.
ABSCOPAL EFFECTS OF RADIATION

Cannot Rely on Abscopal Effects?

Given the current lack of clear clinical evidence for the abscopal response from radiation, as well as heterogeneity in the immune contexture within multiple metastases from an individual patient, we postulate that priority should be given to the following: (1) reduction of tumor volume, which would increase the ratio of proliferating (Ki-67–positive) T cells to tumor cells, (2) palliative care of the patient by decreasing the likelihood of metastases causing harm, and (3) affording immunotherapy agents sufficient time to generate an effect. We look forward to similar trials conducted by others. We hope that more groups obtain biopsies to better characterize the impact of radiation and immunotherapy on the tumor microenvironment.

Jason J. Luke and Steven J. Chmura
University of Chicago, Chicago, IL

In reply to correspondence from Formenti and Demaria


An alternative point of view:
1. Treat to achieve local control, rather underdose for immune stimulation
2. Debulk most/all sites of disease, rather than just one for ‘abscopal effects’
What is the optimal dose/fractionation of radiotherapy, sequence with IO, and target volume?
PD-1 Restrains Radiotherapy-Induced Abscopal Effect

Sean S. Park¹, Haidong Dong²,³, Xin Liu³, Susan M. Harrington³, Christopher J. Kroc³, Michael P. Grams¹, Aaron S. Mansfield⁴, Keith M. Furutani¹, Kenneth R. Olivier¹, and Eugene D. Kwon²,³

Melanoma and RCC

15Gy x 1 fraction SABR
Controversy regarding dose / fractionation

- Cross-priming of anti-tumour T-cells by a single fraction 15Gy in the draining lymph nodes
  - The Journal of Immunology. 2005;174(12):7516-23

- Fractionated, not single fraction enhances immune response, breast murine model (TSA) (3 x 8 Gy)
  - Dewan et al. (NYU) Clin Cancer Res 2009
  - Vanpouille-Box, (NYU), J immunotherapy Cancer 2014

- Single fraction SABR synergizes efficacy of anti-PD-1 in breast murine model (TUBO) (20Gy)

- Single fraction 30 Gy, not 10 x 3Gy increases CD8+ TILs, cross-presentation, reduced Tregs (colon cancer model)
### Table 1
Overview of preclinical studies according to the search criteria.

<table>
<thead>
<tr>
<th>Pub. year</th>
<th>Refs.</th>
<th>Tumor type</th>
<th>Irradiated site/dose</th>
<th>Immune therapy</th>
<th>Observed abscopal effect</th>
<th>Suggested mediator</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014</td>
<td>[26]</td>
<td>TUBO mammary/MCA38 colon</td>
<td>Flank/12 Gy</td>
<td>Anti-PD-L1</td>
<td>Distant tumor growth inhibition</td>
<td>CD8-lymphocytes</td>
</tr>
<tr>
<td>2014</td>
<td>[48]</td>
<td>FM3A mammary</td>
<td>Flank/6 Gy</td>
<td>ECI301</td>
<td>Distant tumor growth inhibition</td>
<td>HMGB1</td>
</tr>
<tr>
<td>2014</td>
<td>[38]</td>
<td>HCT116 colon</td>
<td>Flank/10–20 Gy</td>
<td>None</td>
<td>Distant tumor growth inhibition</td>
<td>p53</td>
</tr>
<tr>
<td>2011</td>
<td>[22]</td>
<td>Colon26</td>
<td>Flank/20 Gy</td>
<td>IL-2</td>
<td>Decreased n° of hepatic M+</td>
<td>CD4-lymphocytes</td>
</tr>
<tr>
<td>2003</td>
<td>[51]</td>
<td>D5 melanoma/MCA 205 sarcoma</td>
<td>Flank/42.5 Gy</td>
<td>DC</td>
<td>Distant tumor growth inhibition</td>
<td>DC</td>
</tr>
<tr>
<td>2001</td>
<td>[52]</td>
<td>C3 cervical/MethA sarcoma</td>
<td>Hind leg/30–50 Gy</td>
<td>DC</td>
<td>Distant tumor growth inhibition</td>
<td>DC</td>
</tr>
<tr>
<td>1999</td>
<td>[19]</td>
<td>LCC</td>
<td>Foot/60 Gy</td>
<td>Flt3-L</td>
<td>Lung M+ regression</td>
<td>DC</td>
</tr>
</tbody>
</table>

M+ = metastasis. LCC = Lewis lung carcinoma, DC = dendritic cells, SCC = squamous cell carcinoma.
Trex1 story

- Single fraction doses 12Gy-18Gy induce Trex, DNA exonuclease that degrades cytosolic DNA
- Reduced activation of cGAS / STING pathway, INF-beta, and DC-mediated CD8+ T-cell priming
c.f. 8Gy x 3fx… TSA mammary model / NSCLC model

Vanpouille-Box et al. 2017, DOI: 10.1038/ncomms15618
Optimal timing of RT


SINGLE FRACTION 20Gy, CT26 murine colorectal carcinoma

Anti-CTLA4 most effective given prior to RT

Anti OX40 most effective given after RT
Optimal RT courses - more than once?

41 patients, 3+ mets, mixed cohort


Figure 1: Treatment and assessment schema for induction and determination of abscopal responses.
Does the Target Site for Irradiation Matter?

Phase I/II Trial of Ipilimumab (Immunotherapy) and Hypofractionated Stereotactic Radiation Therapy in Patients with Advanced Solid Malignancies

Aung Naing MD, David Hong MD

Chad Tang, MD

5 arms 3 Questions:
1) Dose- 50Gy/4 vs 70Gy/10
2) Sequencing- concurrent vs sequential
3) Tumor location- lung vs liver

SBRT Days 2-5 (or 1-12)
DLT Assessment Day 29

Cycle 1
Cycle 2
Cycle 3
Cycle 4

D1 D22
D22 D43
D43 D64
D64 D85

21 days 21 days 21 days 21 days

6 mos with reassessment of response every month

D85

Cycle 1
Cycle 2
Cycle 3
Cycle 4

D1 D22
D22 D43
D43 D64
D64 D85

21 days 21 days 21 days 21 days

6 mos with reassessment of response every month

Erminia Massarelli MD
Rodabe Amaria MI
Adi Diab, MD

Tang et al. CCR 2017
DOI: 10.1158/1078-0432.CCR-16-1432
"The addition of ENI attenuated chemokine expression, restrained immune infiltration, and adversely affected survival when combined with ICB, especially with anti-CLTA4 therapy."
What is the toxicity of combining SABR + Immunotherapy?
Retrospective and prospective international database collection
## Combination SABR and TT or IO

<table>
<thead>
<tr>
<th>SBRT</th>
<th>Acute toxicity (n)</th>
<th>Late toxicity (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td>Fatigue</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Weight Loss/Anorexia</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Upper gastrointestinal hemorrhage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastritis</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Colitis</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Ascites</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Bone pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spinal fracture</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

N=483 patients prospectively collected

Acute G3+ AEs of SBRT+TT/ICI is 12%

No added benefit with pausing systemic therapy

* Slide courtesy of S Kroeze
Stereotactic Radiotherapy and Anti-PD1 antibody (Pembroluzimab) for Oligometastatic Renal Tumours (RAPPORT)

Clinicaltrials.gov ID (NCT02855203)

Radiotherapy

- Single fraction SABR 20Gy to each oligometastasis, If dose constraints not met, 30 in 3Gy fractions

Immunotherapy

- 6 months (8 cycles) of ‘adjuvant’ pembrolizumab
- 3-weekly, 200mg i.v. infusions
- Begins 5-7 days after SABR (+/- 3d)

n = 21 patients, total of 43 lung oligometastases

<table>
<thead>
<tr>
<th>Treatment Characteristic</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RT modality per lesion, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>SABR (20Gy/1fx)</td>
<td>41 (95%)</td>
</tr>
<tr>
<td>Conventional (30Gy/10fx)</td>
<td>2 (5%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No. of lung metastases, n (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9 (43%)</td>
</tr>
<tr>
<td>2</td>
<td>4 (19%)</td>
</tr>
<tr>
<td>3</td>
<td>6 (29%)</td>
</tr>
<tr>
<td>4</td>
<td>2 (10%)</td>
</tr>
</tbody>
</table>
TOXICITY (Particularly Pneumonitis) was acceptable

• Worst grade of treatment related AEs was grade 3 in 4 pts (20%),

• n=3 stopped with G3 pneumonitis (15%) after 3, 6 and 7 cycles of pembrolizumab.

• These patients had 1, 2 and 1 lung oligometastases, respectively.

• There were no grade 4 or 5 AEs, and 5 patients (25%) had no treatment related AEs.

<table>
<thead>
<tr>
<th>Disease control (CR, PR or SD for &gt;6m)</th>
<th>RECIST 1.1 response at 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>CR</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>PR</td>
<td>6 (38%)</td>
</tr>
<tr>
<td>SD</td>
<td>4 (25%)</td>
</tr>
<tr>
<td>PD</td>
<td>5 (31%)</td>
</tr>
<tr>
<td>CR/PR</td>
<td>7 (44%)</td>
</tr>
</tbody>
</table>
Combination of Radiotherapy and Immunotherapy has strong preclinical rationale

Abscopal effects are rare with radiotherapy alone

Synergy with RT + I/O to enhance abscopal responses – toxicities; additive rather than synergistic?

Unanswered Questions
  - Timing of SABR around systemic therapy (Pause? Before? After?)
  - Ideal dose/fractionation
  - Optimal agent for combination
  - Optimal target site for irradiation
  - Single site irradiation or maximal cytoreduction

Clinical data is still emerging....
Eligibility
Advanced NSCLC, Progression after 1 or 2 lines of chemotherapy, extrathoracic metastasis suitable for SABR

Nivolumab 240 mg every 2 weeks plus SABR (18-20 Gy) in week 2

Nivolumab 240 mg every 2 weeks alone

Stratification
Age (18-70 versus > 70)
Lines of chemotherapy (1 versus 2)
Histology (squamous versus non-squamous)
Treating institution

N = 120 (80 allocated nivolumab plus SABR and 40 allocated nivolumab alone)
Nivolumab continued until disease progression or prohibitive toxicity
Thank you very much for your attention!

Peter MacCallum Cancer Centre  

@_ShankarSiva
Willemijn S.M.E. Theelen, MD, PhD

Pulmonologist at the Netherlands Cancer Institute
Amsterdam, Netherlands
ORR of aPD-(L)1 monotherapy are around 20% and long, durable responses have been observed, improving 5-year OS in the early phase I trials\(^1,2\).

Response rates depend on PD-L1 expression on tumor cells: from 9% in PD-L1 negative towards 45% in PD-L1 high (≥50%) tumors\(^3-5\).

For patients whose tumors express PD-L1 ≥50% pembrolizumab beat platinum-based chemotherapy as first-line treatment choice\(^5\).

Also, the combination of aPD-(L)1 with platinum-based chemotherapy in first-line improved patient outcomes over chemotherapy alone irrespective of PD-L1 expression without the addition of significant toxicity\(^6-8\).

⇒ aPD-(L)1 treatment is now SoC in first-line advanced NSCLC

Facts and current clinical situation in advanced NSCLC

Addition of aCTLA-4 has led to significantly more toxicity, but might be a immunotherapy solution for PD-L1 negative tumors or patients that do not want or tolerate chemotherapy\textsuperscript{9-11}

Still, primary and secondary resistance to immunotherapy develops and further interventions are needed to optimize NSCLC patient outcomes:

May abscopal responses induced by radiotherapy be the way forward?

Safety
Safety of RT-induced inflammation and immunotherapy (advanced NSCLC)

- Many retrospective small series have been evaluated, but no real concerns in regard to safety have been established.

- A subgroup analysis from the Keynote-001 study for patients that had received previous extracranial RT vs no RT (n=97):
  - Treatment-related pulmonary toxicity after chest RT: 13% (3/24) vs 1% (1/73); grade 3 one per group
  - Improved PFS (6.3m vs 2.0m, HR 0.50) and OS (11.6m vs 5.3m, HR 0.59)\(^1\)

- A prospective safety study (n=73) for pembrolizumab after SBRT on 2-4 lesions:
  - 6x grade 3 toxicities: 3x pneumonitis (lung SBRT), 2x colitis and 1x hepatitis\(^2\)

- Formenti et al. combined 2 different fractionated RT regimes to 1 metastatic lesion concurrently with ipilimumab:
  - Adverse events were comparable to ipi monotherapy
  - Increased T cell activation in all patients, but in responders upregulation of RT-related genes were seen, suggesting a significant role for RT\(^3\)

Concerns

› Patients with a history of an irAE on ICI had a higher risk on developing radiation pneumonitis after thoracic RT (61%, 25/41)
  › Associated with height of MLD, but also already at MLD >5Gy¹
  => This may support to reduce MLD far below current guidelines in these patients

› Increased development -doubling of the incidence- of radiation necrosis in patients that had received radiotherapy for brain metastases, especially in melanoma, but also for NSCLC patients²-³
  => Upfront RT for brain mets needs to be carefully evaluated, especially when asymptomatic and a high chance of response to ICI is anticipated.

Efficacy

June 2016

June 2020
The PEMBRO-RT study

- Number of patients: 74
- Stage IV NSCLC; at least 1 regimen of chemotherapy
- SBRT: 3 x 8Gy to a single tumor lesion
- At least 2 separate lesions:
  - for SBRT
  - for repeat biopsies
- No RT < 6 months
- Stratification: smoking status
Results PEMBRO-RT study

- **mPFS 1.9 months (95% CI 1.7-6.9) in the control arm** vs **6.6 months (95% CI 4.0-14.6) in the experimental arm.**

- A significant benefit of SBRT with respect to PFS was seen in the PD-L1 negative subgroup (HR 0.49; 95% CI 0.26-0.94; p = 0.032).

- **mOS 7.6 months (95% CI 6.0-13.9) in the control arm** vs **15.9 months (95% CI 7.1-NA) in the experimental arm.**

- A significant benefit of SBRT with respect to OS was seen in the PD-L1 negative subgroup (HR 0.48; 95% CI 0.24-0.99, p = 0.046).

Theelen, JAMA Oncol 2019
### Toxicities related to pembrolizumab

<table>
<thead>
<tr>
<th></th>
<th>All grades</th>
<th></th>
<th>Grades 3-5</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Experimental arm n = 35</td>
<td>Control arm n = 37</td>
<td>Experimental arm n = 35</td>
<td>Control arm n = 37</td>
</tr>
<tr>
<td>All adverse events</td>
<td>283</td>
<td>235</td>
<td>28</td>
<td>27</td>
</tr>
<tr>
<td>All immune toxicities</td>
<td>85</td>
<td>68</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>4 (11%)</td>
<td>2 (5%)</td>
<td>0</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Colitis</td>
<td>1 (3%)</td>
<td>2 (5%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Duodenitis</td>
<td>1 (3%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>0</td>
<td>1 (3%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>2 (6%)</td>
<td>2 (5%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>1 (3%)</td>
<td>2 (5%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nephritis</td>
<td>1 (3%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>6 (16%)</td>
<td>0</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>2 (6%)</td>
<td>1 (3%)</td>
<td>2 (6%)</td>
<td>1 (3%)</td>
</tr>
</tbody>
</table>

Toxicity of SBRT and immunotherapy: one patient developed a nephritis after the third course of pembrolizumab after receiving SBRT on a retroperitoneal lesion in close relation to the kidney.

Theelen, JAMA Oncol 2019
Pooled analysis with MD Anderson Cancer Center

A similar study with 2 RT cohorts\(^1\):

› Pembrolizumab (n=18) vs combined with 45Gy/15 fractions (n=20)
› Pembrolizumab (n=18) vs combined with 50Gy/4 fractions (n=16)

Pooled:

Pembrolizumab (n=76) vs Pembrolizumab + RT (n=72)
Baseline characteristics well ballanced between control vs experimental group especially in respect to PD-L1 status.

Welsh, JCO 2019 (abstract)
Results pooled analysis

- **PFS**

- **OS**

Numbers at risk

**Pembro alone (N=76)**
- Pembro alone
- Pembro + RT (N=72)

P value: 0.026
HR: 0.66
95% CI: 0.45 to 0.96

P value: 0.006
HR: 0.59
95% CI: 0.41 to 0.87

Theelen, Lancet Respir Med 2020
Comparison of RT regimens

The graph shows the percentage of best out-of-field responses for different RT regimens:
- Pembro alone: 19.7% (15/76)
- Pembro+45Gy/15f: 47.2% (17/36)
- Pembro+24Gy/3f: 20% (4/20)
- Pembro+50Gy/4f: 56.2% (9/16)

The box plots illustrate the changes in ALC (absolute lymphocyte count) before and after RT for different radiation doses:

A. ALC prior to RT
B. ALC post RT

each RT regimen at 45Gy/15f, 24Gy/3f, and 50Gy/4f.

Theen, Lancet Respir Med 2020
ICI in oligometastatic NSCLC

› Locally ablative therapy (LAT) to all tumor sites adjuvant to non-progression on platinum-doubley chemotherapy was already associated with improved PFS and OS\textsuperscript{1,2}

› Single-arm phase II (n=45) received adjuvant pembrolizumab after LAT:
  › PFS 19.1m (vs historical control 6.6m); 11% pneumonitis\textsuperscript{3}

ICI and chemoradiation in NSCLC – PACIFIC

- Locally advanced, unresectable NSCLC treated with CCRT that showed no disease progression afterwards
- Q2w durvalumab (anti-PD-L1) 10mg/kg vs placebo for 12 months
- Pneumonitis any grade 33.9% vs. 24.8%; grade 3/4 3.4% vs. 2.6%

Also, NICOLAS study: nivolumab concurrently with CCRT is deemed safe

ICI and chemoradiation in NSCLC

Induction-1 trial (NKI): Neo-adjuvant ICI (durva/treme) before CCRT for locally advanced NSCLC, phase 1.

Feasibility phase
(N=6 per cohort)

- Cohort 1A (first cohort)
  - 1 course Durvalumab (1500mg) + Tremelimumab (75mg)
  - + 1 course of Durvalumab (1500mg) followed by CRT

Expansion phase
(N=22 per cohort)

- Cohort 1B
  - 1 course Durvalumab (1500mg) + Tremelimumab (75mg)
  - + 1 course of Durvalumab (1500mg) followed by CRT

- Cohort 2A
  - 1 course Durvalumab (1500mg) + Tremelimumab (300mg)
  - + 1 course of Durvalumab (1500mg) followed by CRT

- Cohort 2B
  - 1 course Durvalumab (1500mg) + Tremelimumab (300mg)
  - + 1 course of Durvalumab (1500mg) followed by CRT

Decision rules feasibility phase:
- Treatment is deemed feasible if 5-6 out of 6 patients complete planned definitive treatment consisting of chemoradiotherapy (CRT).
- If ≤2 out of 6 patients do NOT complete planned CRT, then that feasibility cohort is closed; a delay of 4 weeks due to toxicity management is deemed acceptable.

Decision rules expansion phase:
- If > 30% do NOT complete planned treatment, then the immuno-induction is not feasible.
Future perspectives

**Advanced stage**
Studying underlying mechanisms of abscopal responses:
› Translational research PEMBRO-RT trial
› Diagnostic trials comparing timing and/or different RT regimes
Treating secondary ICI resistance with the addition of RT$^{1,2}$

**Earlier stage:**
Trials exploring the safety and efficacy of:
› adjuvant ICI treatment after SBRT and CRT
› concurrent application of ICI with CCRT
› NKI: neo-adjuvant pembro vs. SBRT vs. pembro + SBRT before surgery

Thank you!

Q & A