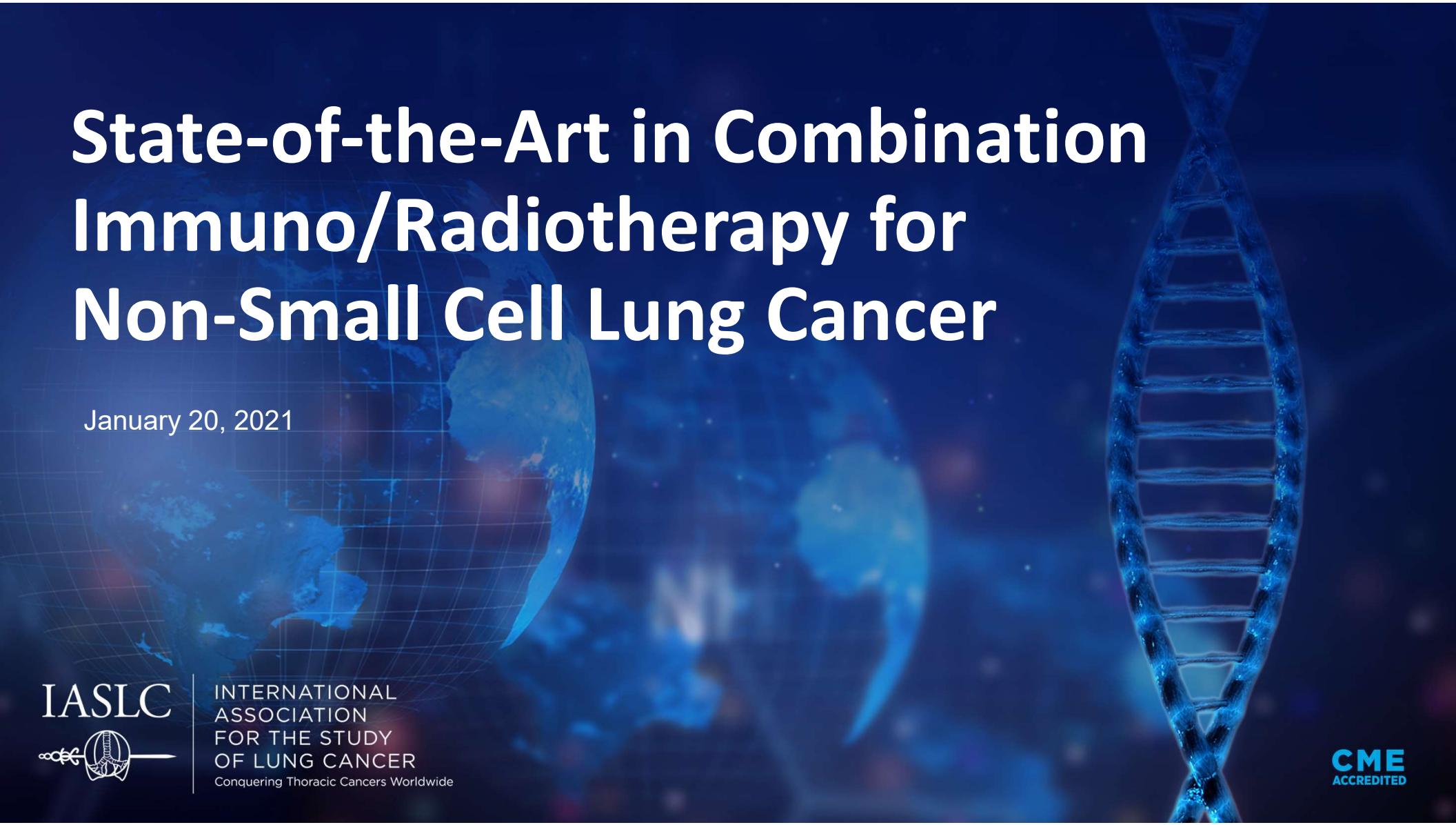
State-of-the-Art in Combination Immuno/Radiotherapy for Non-Small Cell Lung Cancer

January 20, 2021



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Conquering Thoracic Cancers Worldwide

CME ACCREDITED

Disclosures

Siva Shankar, MBBS, FRANZCR, PhD

- Astra Zeneca (speaker honoraria, travel)
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All relevant financial relationships have been mitigated.

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The current Era of Immuno-Oncology

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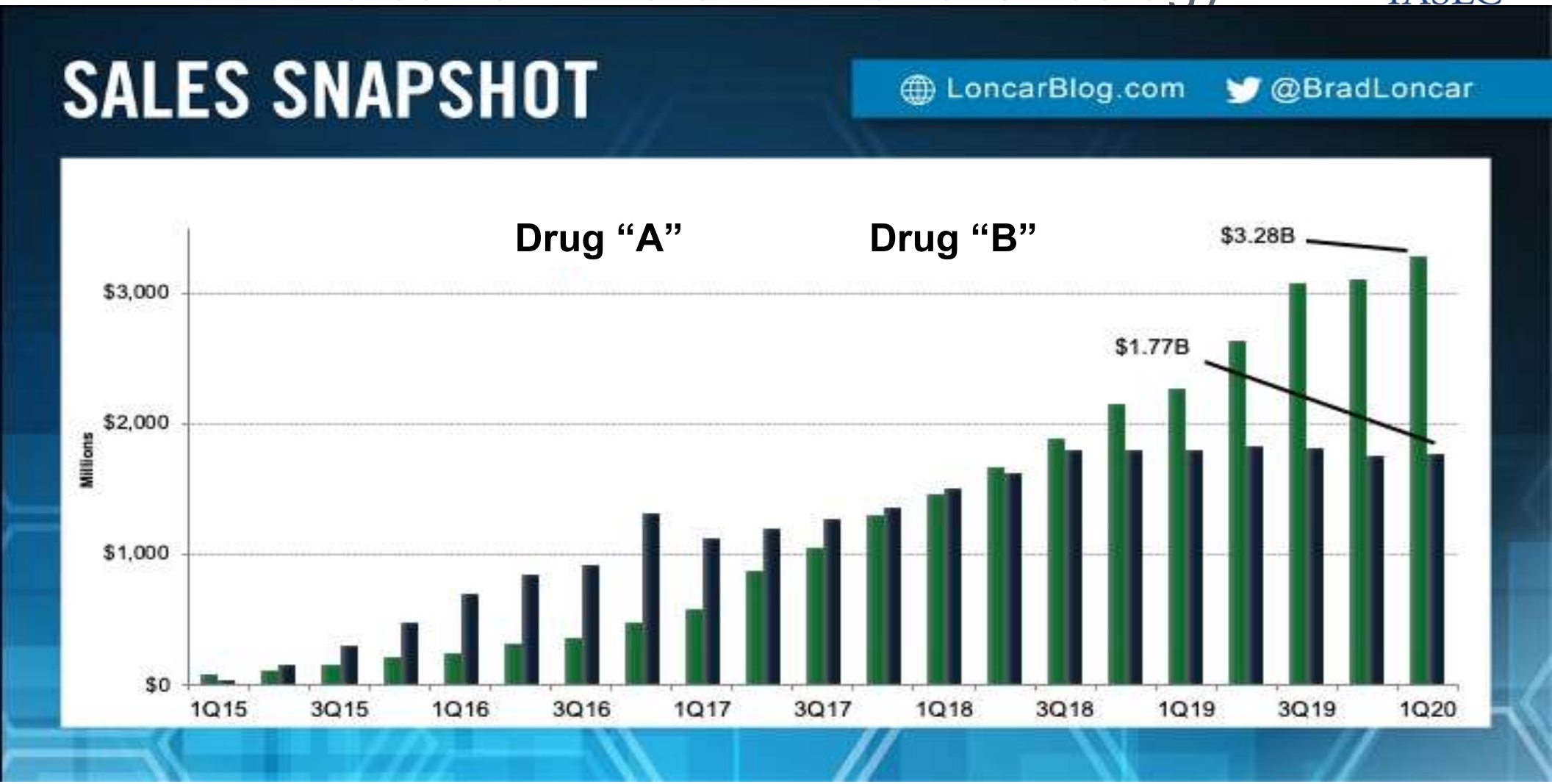
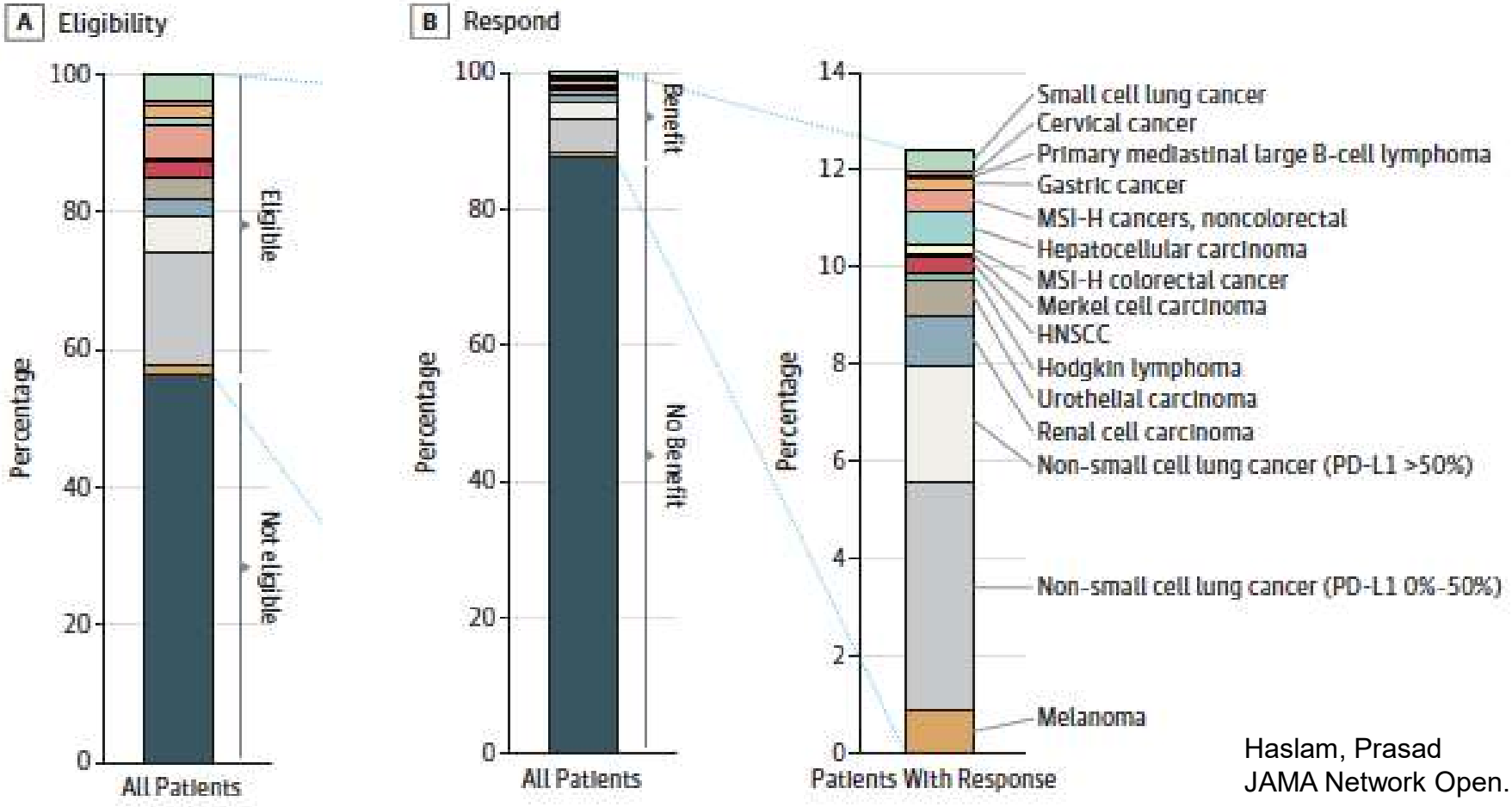


Need to improve outcomes from checkpoint blockade inhibitors

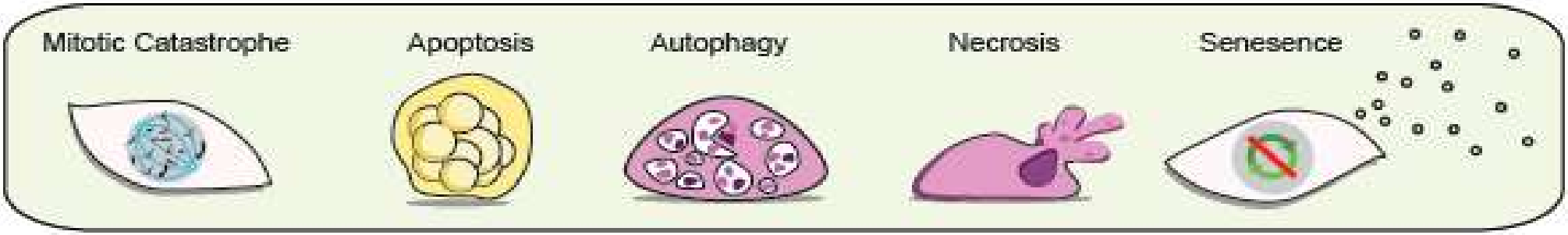


Haslam, Prasad
JAMA Network Open. 2019;2(5):e192535.

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



Anti-inflammatory

Pro-inflammatory

RADIATION DOSE

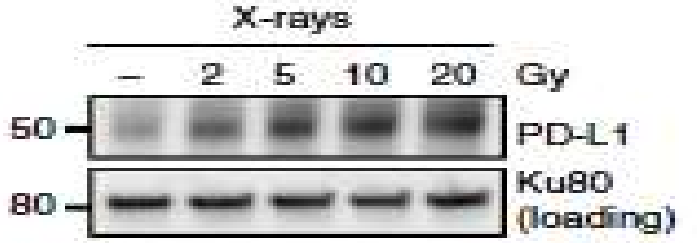
Conventional fractionated

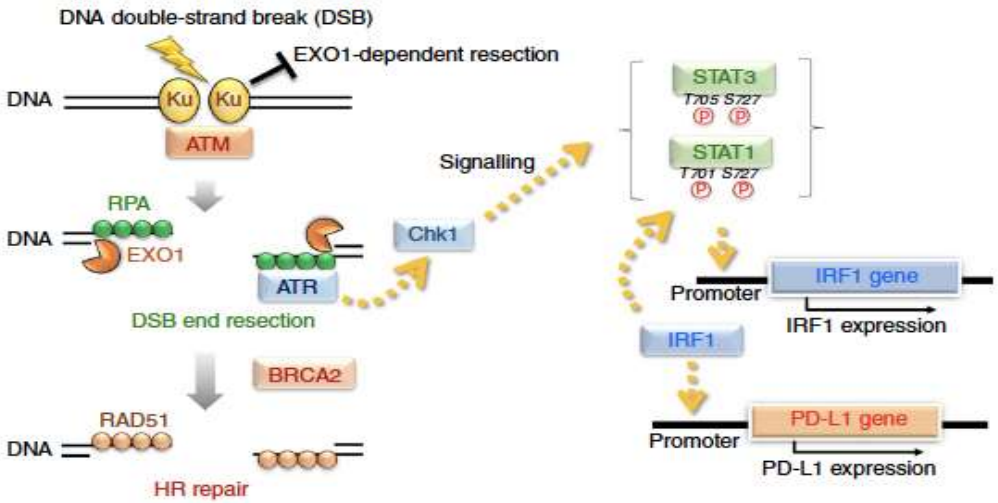
Hypofractionated

Adapted Haikerwal et al. Cancer Letters 2015

Radiation upregulates tumor cell checkpoints

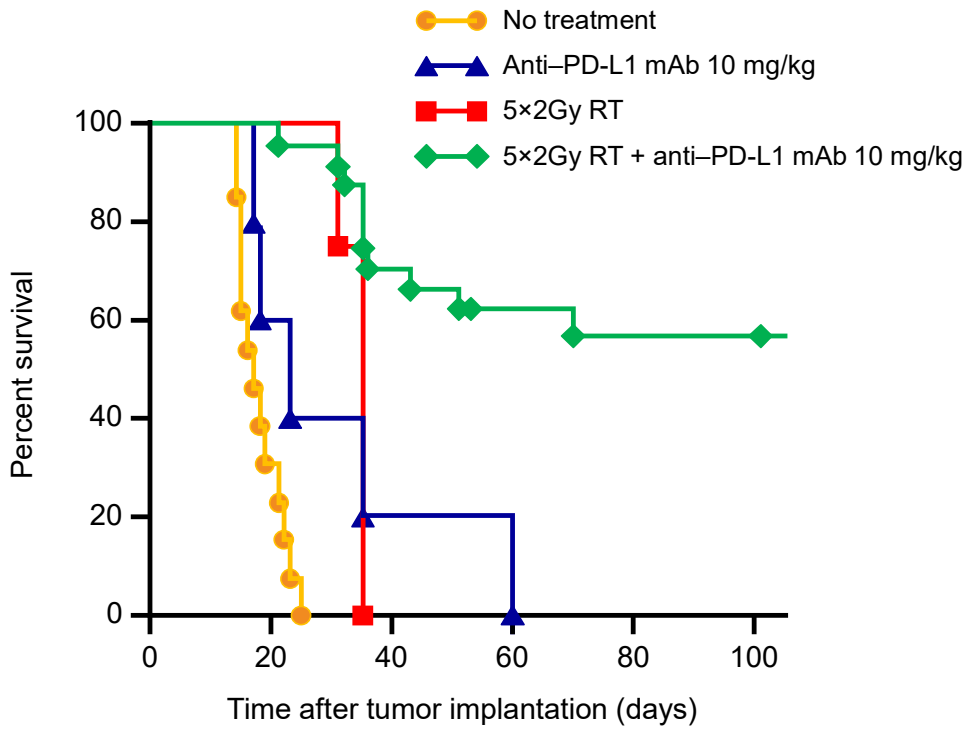
PD-L1 upregulation appears RT dose dependent





Sato et al. Nature communications 2017.

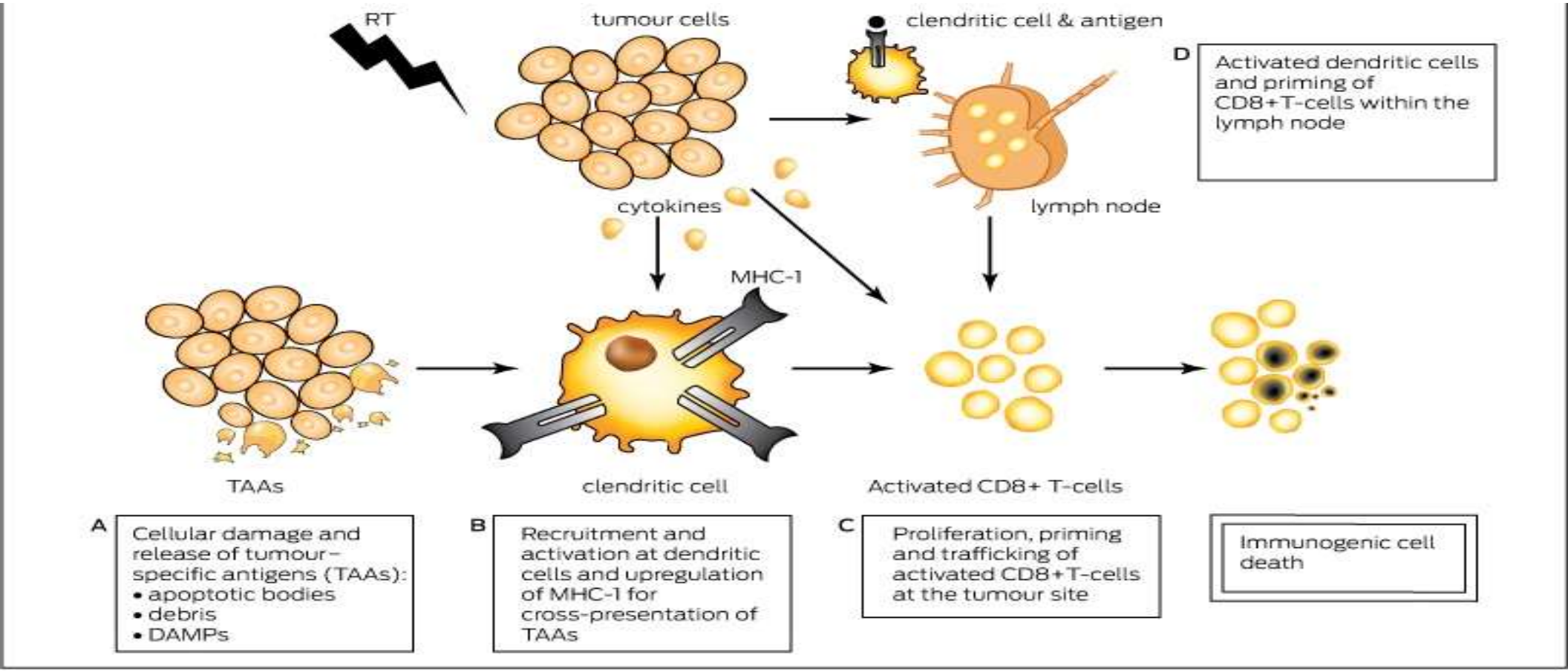
Synergy b/w anti–PD-L1 and RT in murine model



Ctr, control; mAb, monoclonal antibody; PD-L1, programmed cell death ligand-1; RT, radiotherapy.

Dovedi SJ, et al. AACR 2014. Poster A5034.

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



*Turgeon & Siva, *Medical Journal of Australia* 2018 *S. Siva et al. et al. *Cancer letters* 2015;356:82-90.

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Overview

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

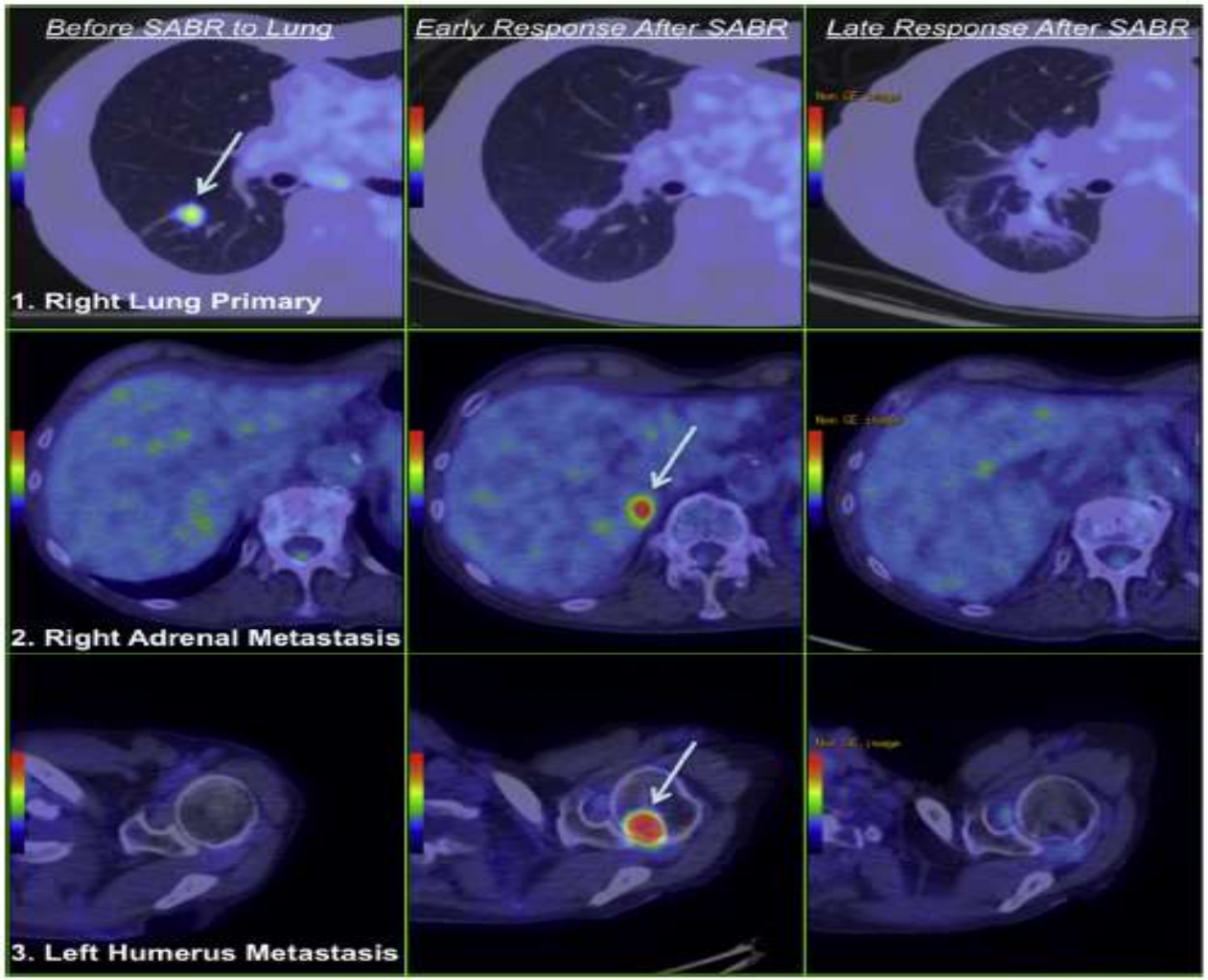
D. Xing *, S. Siva *†, G.G. Hanna *†

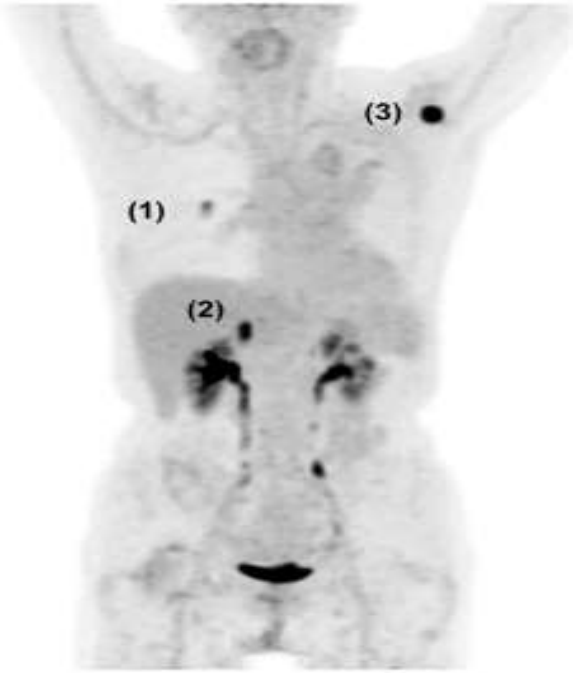
* Division of Radiation Oncology, Peter MacCallum Cancer Centre, Melbourne, Australia
† Sir Peter MacCallum Department of Oncology, University of Melbourne, Parkville, Australia

*2019;31:432-443.

- Latin: "ab" - away "scopus" – target*
- Defined 1953 – R. J. Mole

ABSCOPAL EFFECTS OF RADIATION





*Siva S, Callahan J, MacManus MP, et al, Journal of Thoracic Oncology 2013;8:e71-72.

Cannot Rely on Abscopal Effects?

VOLUME 36 · NUMBER 25 · SEPTEMBER 1, 2018

JOURNAL OF CLINICAL ONCOLOGY

CORRESPONDENCE

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,[4] 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,[4] (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

J Clin Oncol. 2018 Jun 1;36(16):1611-1618.

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?

DOI: 10.1158/2326-6066.CIR-14-0138

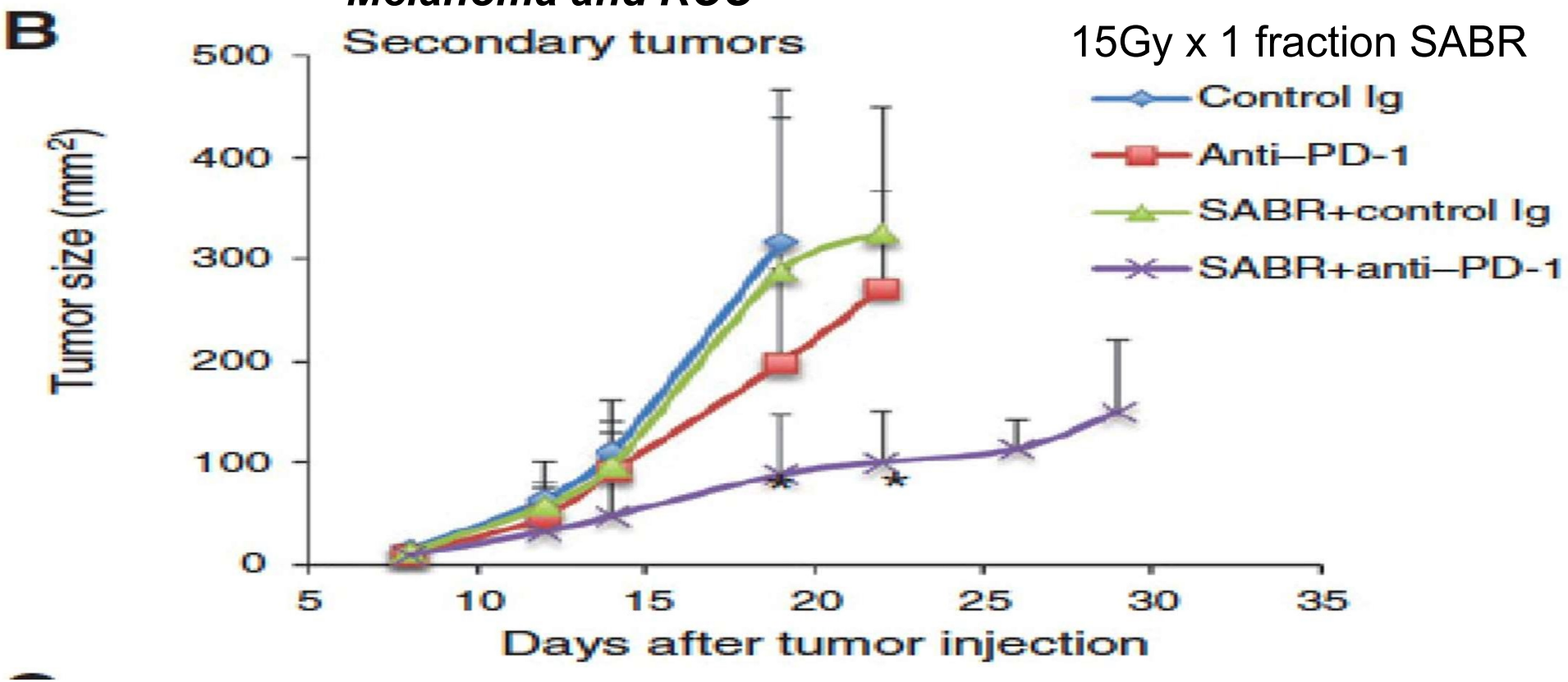
Research Article

Cancer Immunology Research

PD-1 Restrains Radiotherapy-Induced Abscopal Effect

Sean S. Park[1], Haidong Dong[2,3], Xin Liu[3], Susan M. Harrington[3], Christopher J. Krco[3], Michael P. Grams[1], Aaron S. Mansfield[4], Keith M. Furutani[1], Kenneth R. Olivier[1], and Eugene D. Kwon[2,3]

Melanoma and RCC



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)

*Deng L et al. (2014), The Journal of clinical investigation 124: 0-0.

- Single fraction 30 Gy, not 10 x 3Gy increases CD8+ TILs, cross-presentation, reduced Tregs (colon cancer model)
  - *Filatenkov et al. Clinical Cancer Research 2015

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Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

Anti-Tumour Treatment

Cancer Treatment Reviews 41 (2015) 503–510

The abscopal effect of local radiotherapy: using immunotherapy to make a rare event clinically relevant

Kobe Reynders [a,*], Tim Illidge [b], Shankar Siva [c,d], Joe Y. Chang [e], Dirk De Ruysscher [a]

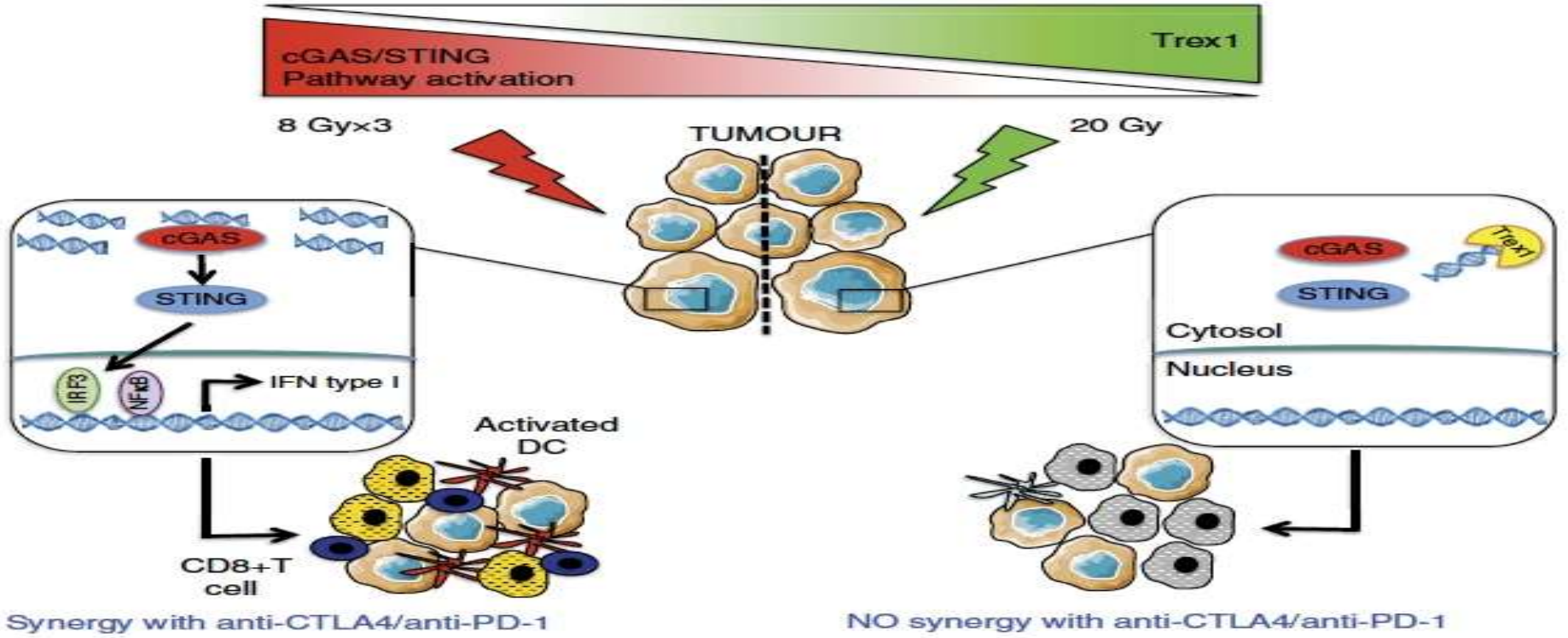
Table 1
Overview of preclinical studies according to the search criteria.

Pub. year	Refs.	Tumor type	Irradiated site/dose	Immune therapy	Observed abscopal effect	Suggested mediator
2014	[26]	TUBO mammary/MCA38 colon	Flank/12 Gy	Anti-PD-L1	Distant tumor growth inhibition	CD8-lymphocytes
2014	[48]	FM3A mammary	Flank/6 Gy	ECI301	Distant tumor growth inhibition	HMGB1
2014	[38]	HCT116 colon	Flank/10–20 Gy	None	Distant tumor growth inhibition	p53
2011	[22]	Colon26	Flank/20 Gy	IL-2	Decreased n° of hepatic M+	CD4-lymphocytes
2009	[49]	TSA mammary/MCA38 colon	Flank/20–24–30 Gy	9H10	Distant tumor growth inhibition	unknown
2008	[23]	Colon26/MethA sarcoma/LLC	Flank/6 Gy	ECI301	Distant tumor growth inhibition	CD4+/CD8+/NK-cells
2007	[50]	SCC VII	Femur/4–10 Gy	DC	Distant tumor growth inhibition	DC/gp96
2005	[24]	4T1 mammary	Flank/12–24 Gy	9H10	Distant tumor growth inhibition	CD8-lymphocytes
2004	[21]	67NR mammary	Flank/2–6 Gy	Flt3-L	Distant tumor growth inhibition	DC/T cells
2003	[39]	LCC/T241 fibrosarcoma	Hind leg/24–50 Gy	None	Distant tumor growth inhibition	p53
2003	[51]	D5 melanoma/MCA 205 sarcoma	Flank/42.5 Gy	DC	Distant tumor growth inhibition	DC
2001	[52]	C3 cervical/MethA sarcoma	Hind leg/30–50 Gy	DC	Distant tumor growth inhibition	DC
1999	[19]	LCC	Foot/60 Gy	Flt3-L	Lung M+ regression	DC

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

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

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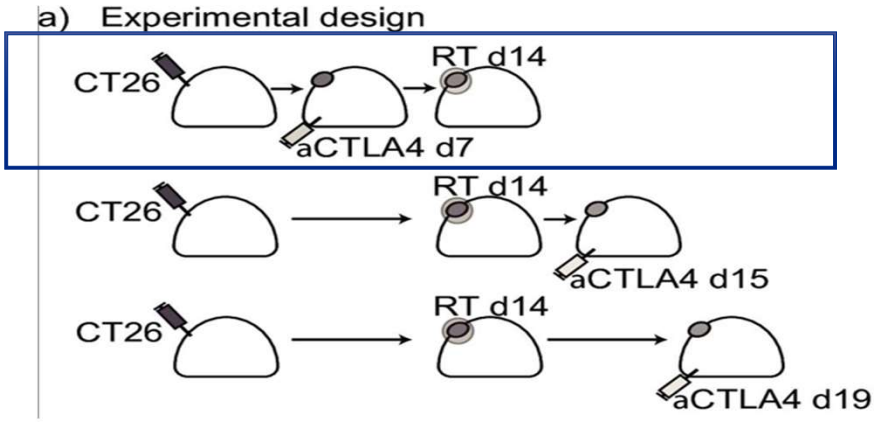
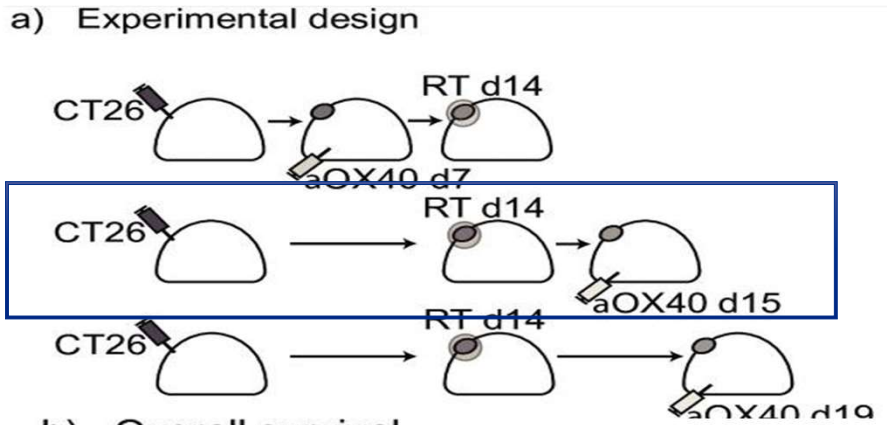
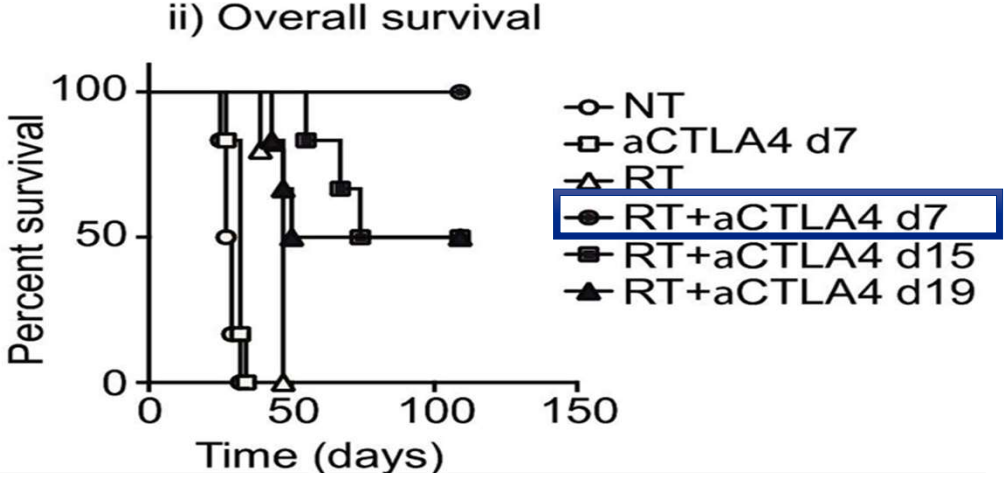
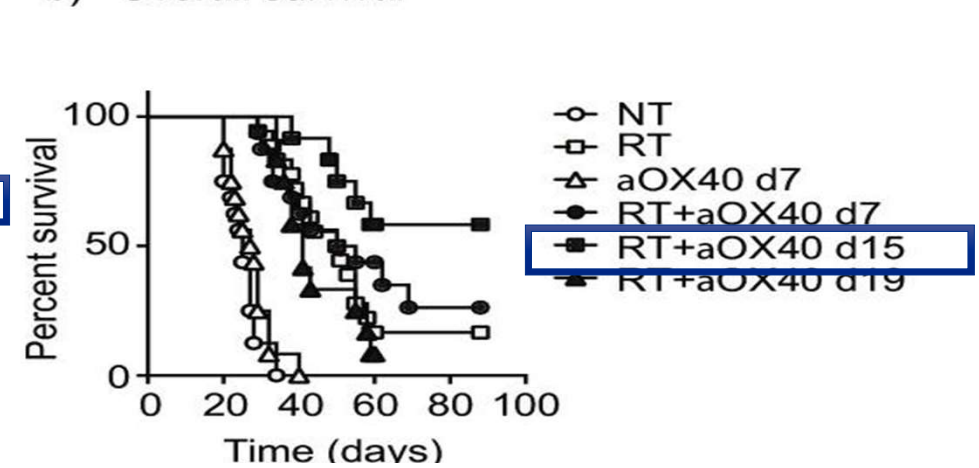
SINGLE FRACTION 20Gy, CT26 murine colorectal carcinoma









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

Golden et al. Lancet Oncol 2015; 16: 795–803.

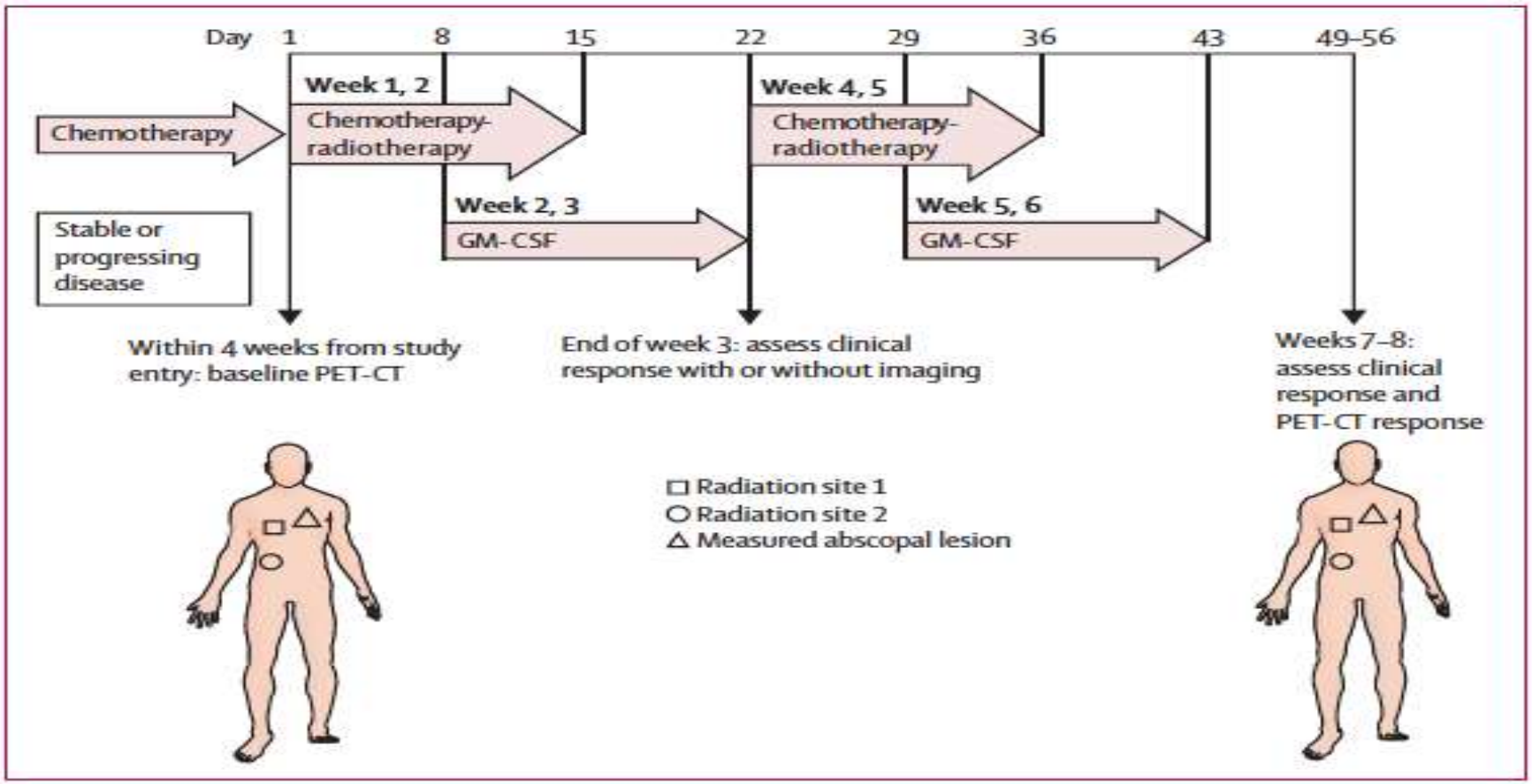


Figure 1: **Treatment and assessment schema for induction and determination of abscopal responses**

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

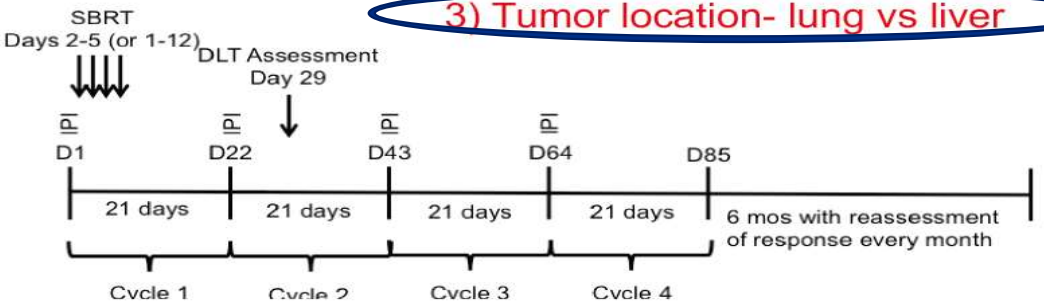
Aung Naing MD, David Hong MD

Erminia Massarelli MD

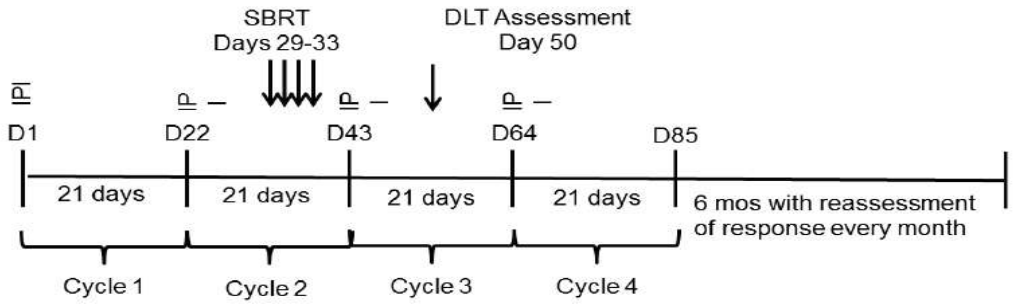
Chad Tang, MD

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

Rodabe Amaria MD



Adi Diab, MD



THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Tang et al. CCR 2017
DOI: 10.1158/1078-0432.CCR-16-1432

Translational Cancer Mechanisms and Therapy

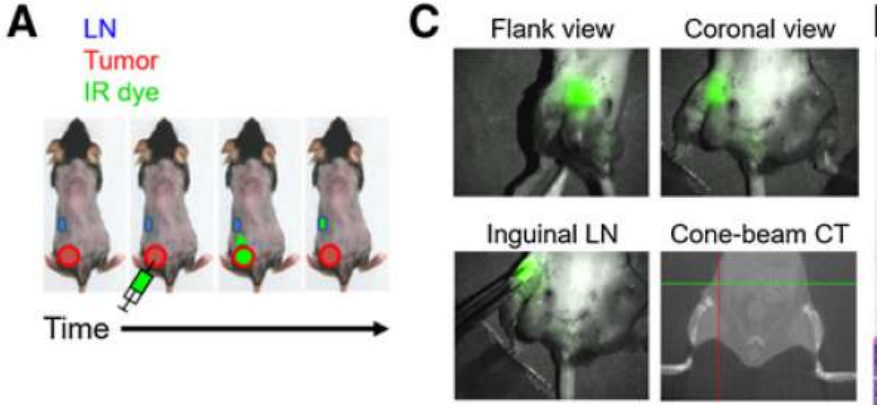
Clinical Cancer Research

IASLC

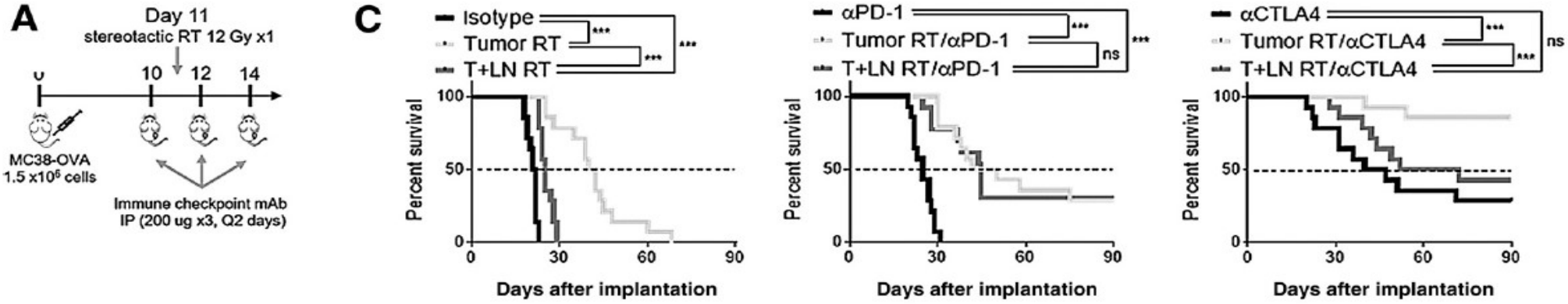
› doi: 10.1158/1078-0432.CCR-17-3427

Elective Nodal Irradiation Attenuates the Combinatorial Efficacy of Stereotactic Radiation Therapy and Immunotherapy

Ariel E. Marciscano[1], Ali Ghasemzadeh[2], Thomas R. Nirschl[2], Debebe Theodros[2], Christina M. Kochel[2], Brian J. Francica[2], Yuki Muroyama[2], Robert A. Anders[2,3], Andrew B. Sharabi[4], Esteban Velarde[1], Wendy Mao[2], Kunal R. Chaudhary[5], Matthew G. Chaimowitz[6], John Wong[1], Mark J. Selby[7], Kent B. Thudium[7], Alan J. Korman[7], David Ulmert[8], Daniel L.J. Thorek[2,9], Theodore L. DeWeese[1,2], and Charles G. Drake[2,6]



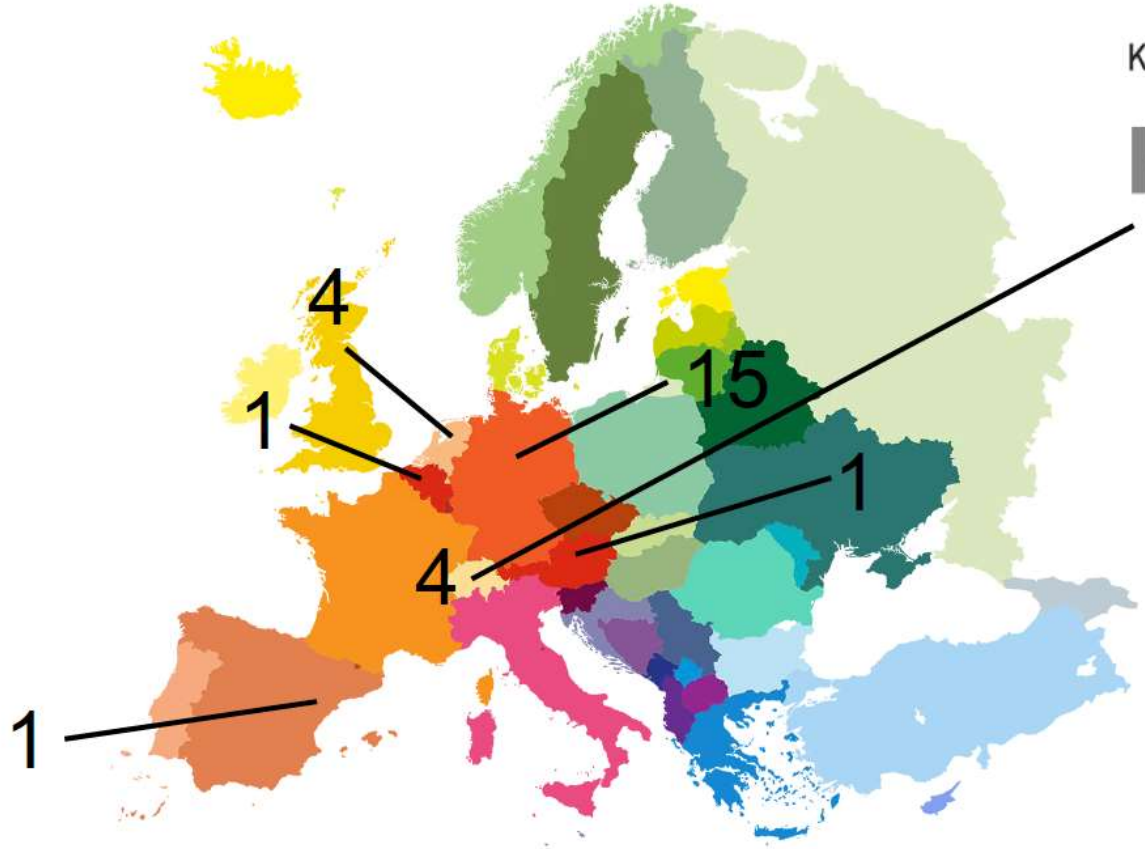
"The addition of ENI attenuated chemokine expression, restrained immune infiltration, and adversely affected survival when combined with ICB, especially with anti-CLTA4 therapy."



What is the toxicity of combining SABR + Immunotherapy?

TOaSTT

Retrospective and prospective international database collection



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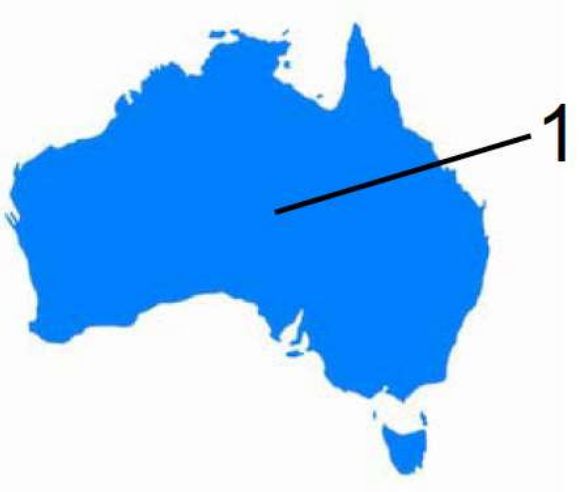


UniversitätsSpital Zürich

Universität Zürich[UZH]

Combination SABR and TT or IO

SBRT	Acute toxicity (n)			Late toxicity (n)		
	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5
Fatigue	14			1		
Weight Loss/Anorexia	1	1				
Dyspnea	1	1				
Pneumonitis	3	2				
Upper gastrointestinal hemorrhage		1				
Gastritis	1					
Nausea/Vomiting	7					
Abdominal pain	2	1				
Diarrhea	4	3				
Colitis	6	3				
Ascites		2				
Hepatitis	1					
Bone pain		2				
Spinal fracture	3					

** Slide courtesy of S Kroeze*

N=483 patients prospectively collected

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

No added benefit with pausing systemic therapy

- Stereotactic **R**adiotherapy and **A**nti-**P**D1 antibody (**P**embroluzimab) for **O**ligometastatic **R**enal **T**umours (RAPPORT)

Clinicaltrials.gov ID (NCT02855203)

Radiotherapy

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

Immunotherapy

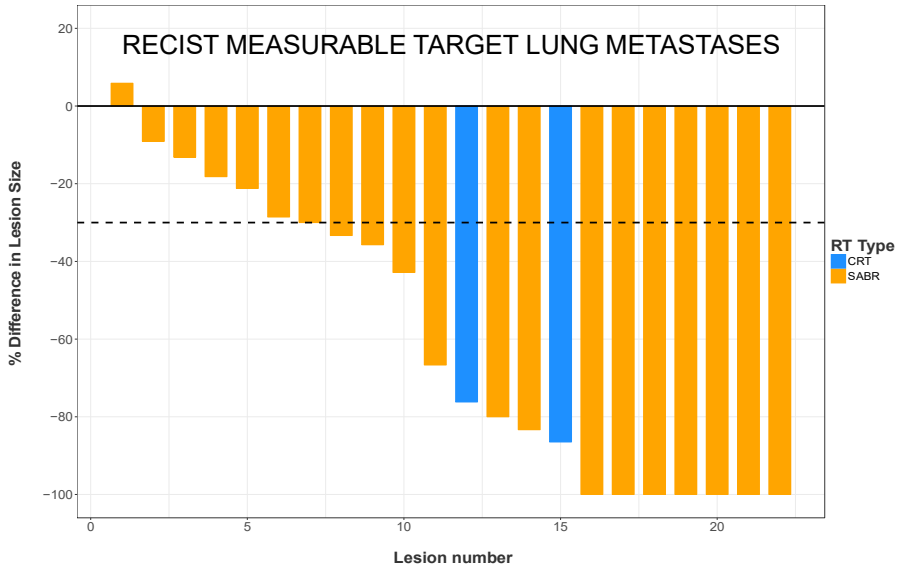
- 6 months (8 cycles) of 'adjuvant' pembrolizumab
- 3-weekly, 200mg i.v. infusions
- Begins 5-7 days after SABR (+/- 3d)

n = 21 patients, total of 43 lung oligometastases

Treatment Characteristic	Result
RT modality per lesion, n (%)	
SABR (20Gy/1fx)	41 (95%)
Conventional (30Gy/10fx)	2 (5%)
No. of lung metastases, n (%)	
1	9 (43%)
2	4 (19%)
3	6 (29%)
4	2 (10%)

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.



Disease control (CR, PR or SD for >6m)	
No	5 (31%)
Yes	11 (69%)

RECIST 1.1 response at 6 months	
CR	1 (6%)
PR	6 (38%)
SD	4 (25%)
PD	5 (31%)
CR/PR	7 (44%)

SUMMARY

- 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?

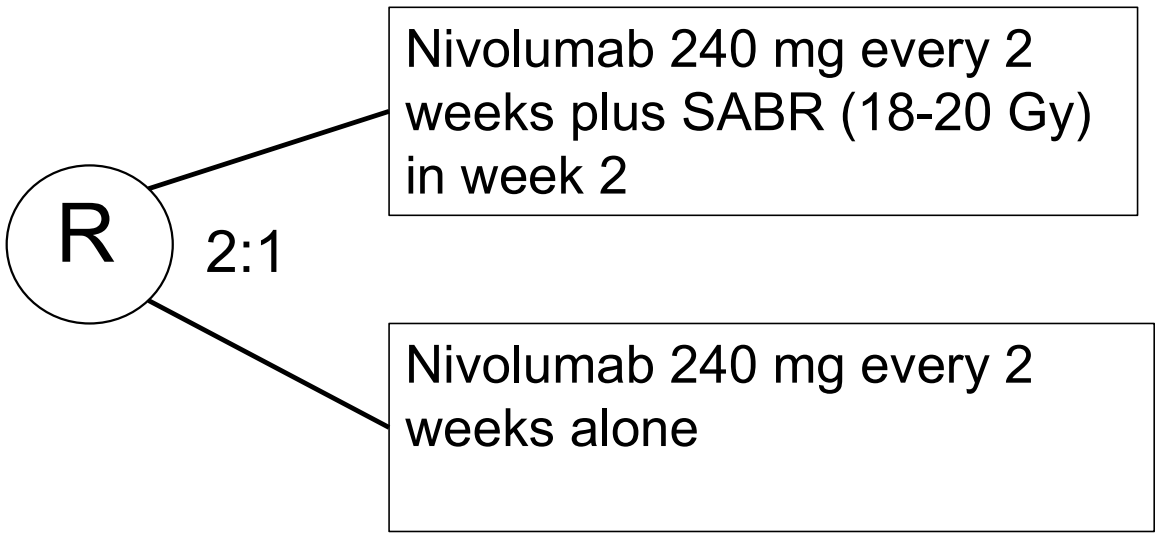
- Unanswered Questions
  - Timing of SABR around systemic therapy (Pause? Before? After?)
  - Ideal dose/fractionation
  - Optimal agent for combination
  - Optimal target site for irradiation
  - Single site irradiation or maximal cytoreduction

- Clinical data is still emerging….

TROG 16.01 / ALTG 14.002 RANDOMIZED PH II STUDY

Eligibility

Advanced NSCLC, Progression after 1 or 2 lines of chemotherapy, extrathoracic metastasis suitable for SABR



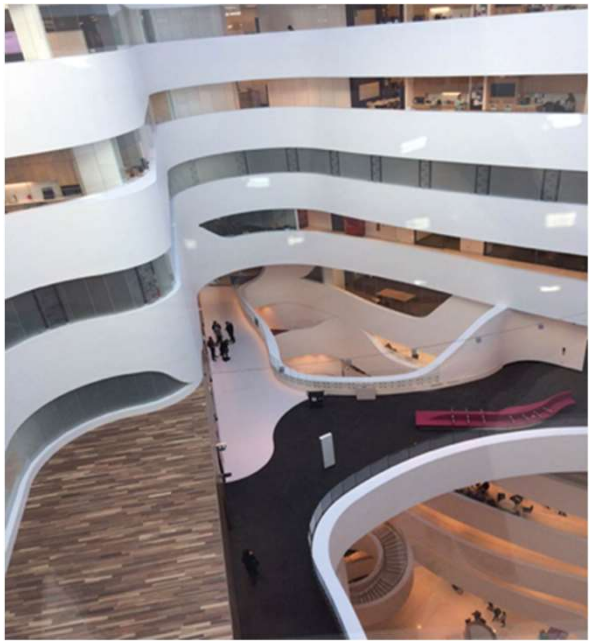
Stratification

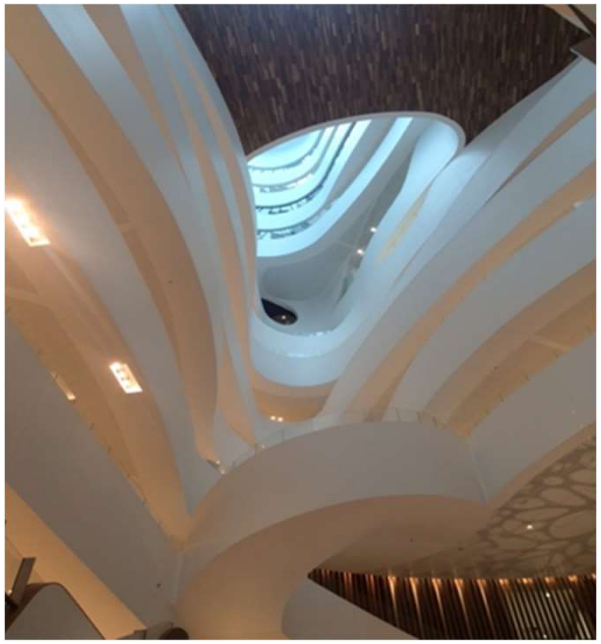
Age (18-70 versus > 70)
Lines of chemotherapy (1 versus 2)
Histology (squamous versus non-squamous)
Treating institution

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





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

Pulmonologist at the Netherlands Cancer Institute
Amsterdam, Netherlands

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Facts and current clinical situation in advanced NSCLC

- 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 irrispective of PD-L1 expression without the addition of significant toxicity[6-8]

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

1. Gettinger, JCO 2015; 2. Garon, JCO 2019; 3. Borghaei, NEJM 2015; 4. Brahmer, NEJM 2015; 5. Reck, NEJM 2016; 6. Gandhi, NEJM 2018; 7. Paz-Ares, NEJM 2018, 8. Socinski, NEJM 2018

Facts and current clinical situation in advanced NSCLC

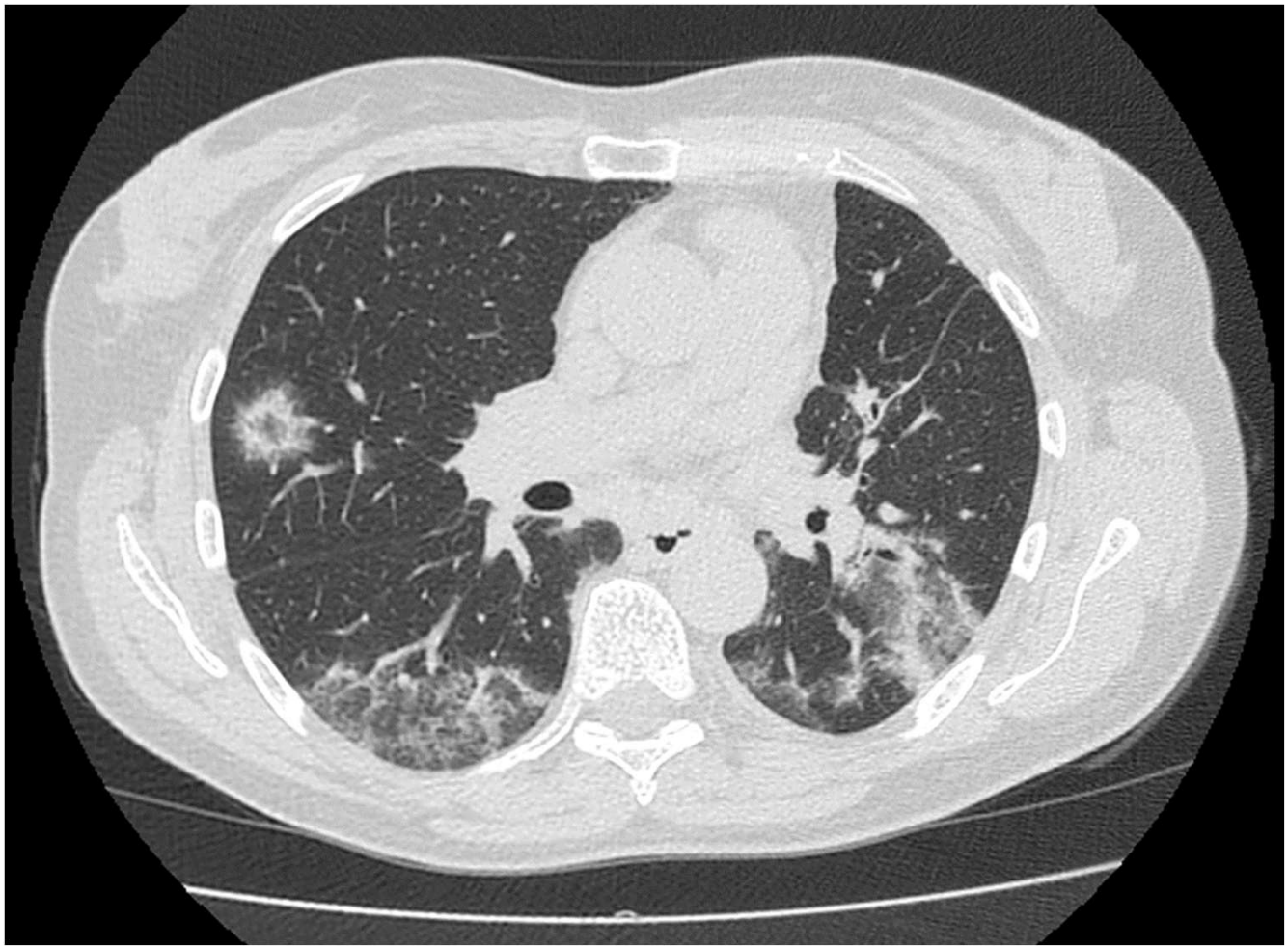
- Addition of aCTLA-4 has led to significantly more toxicity, but might be a immunotherapy solution for PD-L1 negative tumors or patients that do not want or tolerate chemotherapy[9-11]

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?

9. Rizvi, JAMA Oncol 2020; 10. Ramalingam, ASCO 2020; 11. Paz-Ares, ASCO 2020

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]

1. Shaverdian, Lancet Oncol 2017; 2. Luke, J Clin Oncol 2018; 3. Formenti, Nat Med 2018

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 >5Gy[1]

⇒ This may support to reduce MLD far below current guidelines in these patients

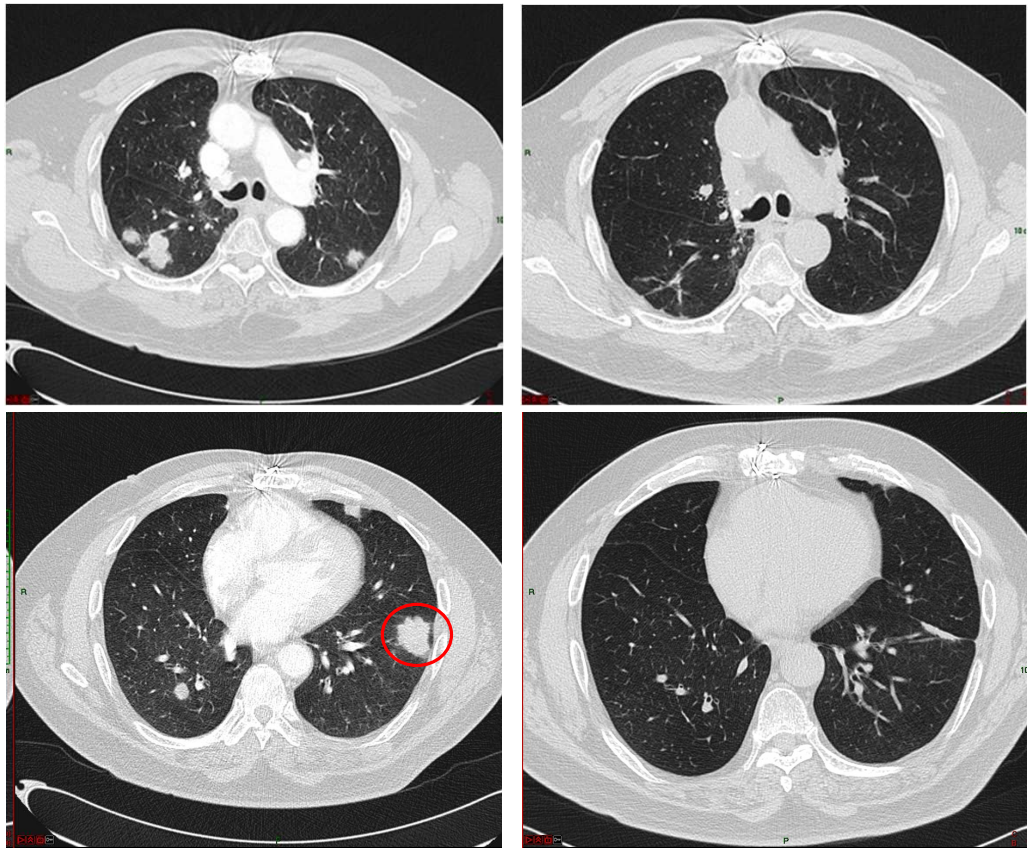
- Increased development -doubling of the incidence- of radiation necrosis in patients that had received radiotherapy for brain metastases, especially in melanoma, but also for NSCLC patients[2-3]

⇒Upfront RT for brain mets needs to be carefully evaluated, especially when asymptomatic and a high chance of response to ICI is anticipated.

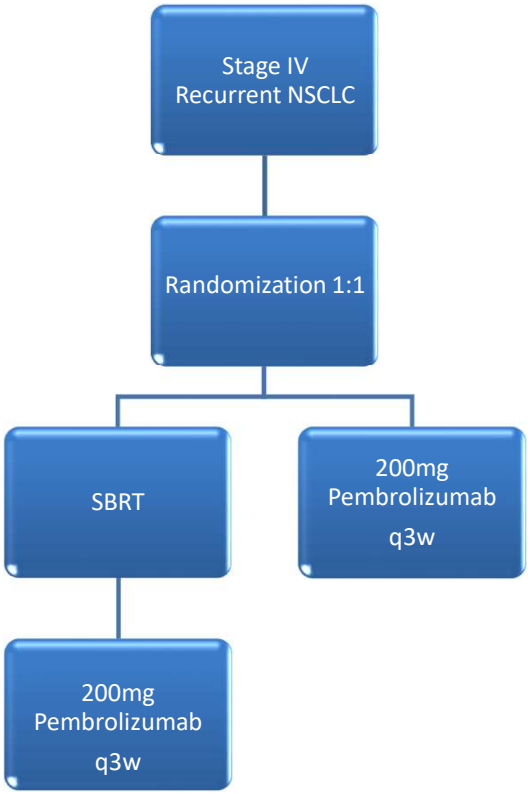
1. Shaverdian, Ann Oncol 2020; 2. Colaco, J Neurosurg 2016; 3. Martin, JAMA Oncol 2018

Efficacy

June 2016 June 2020



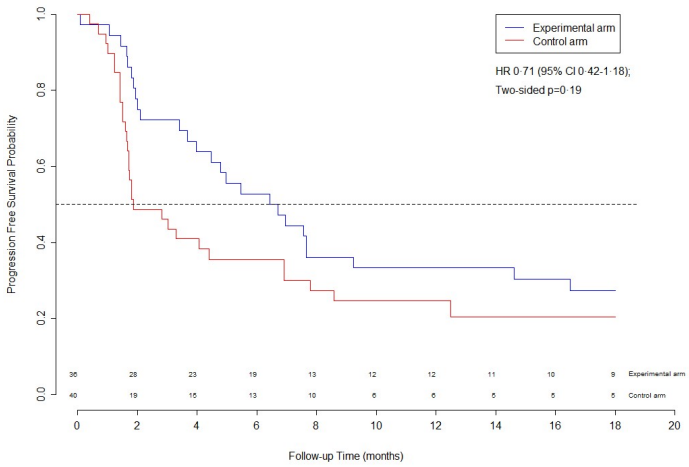
The PEMBRO-RT study



- 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

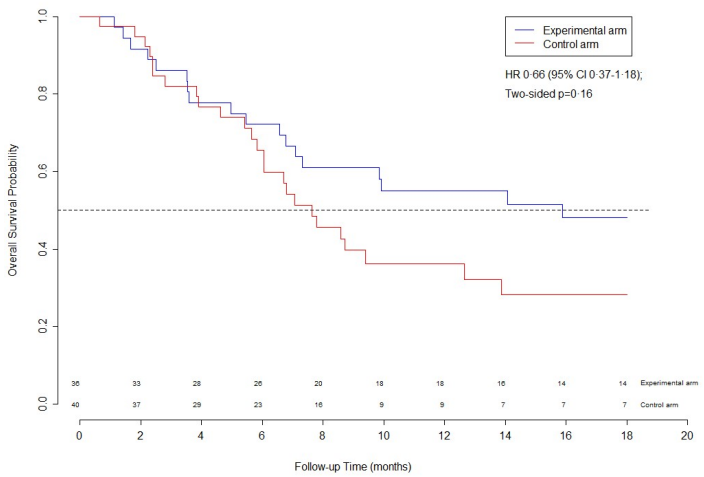
Results PEMBRO-RT study

› PFS



- 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).

› OS



- 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

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

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:

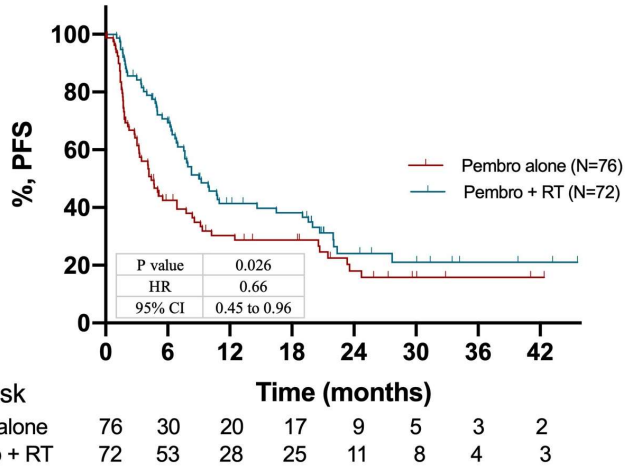
Pembrolizumab (n=76) vs Pembrolizumab + RT (n=72)

Baseline characteristics well ballanced between control vs experimental group especially in respect to PD-L1 status.

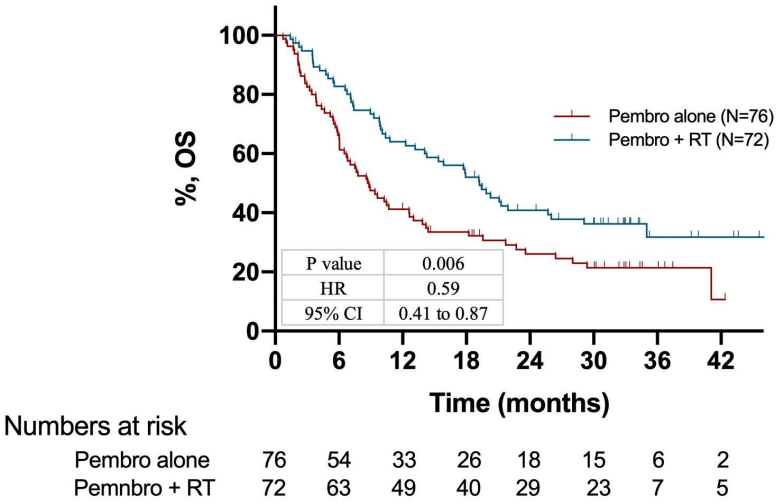
Welsh, JCO 2019 (abstract)

Results pooled analysis

› PFS

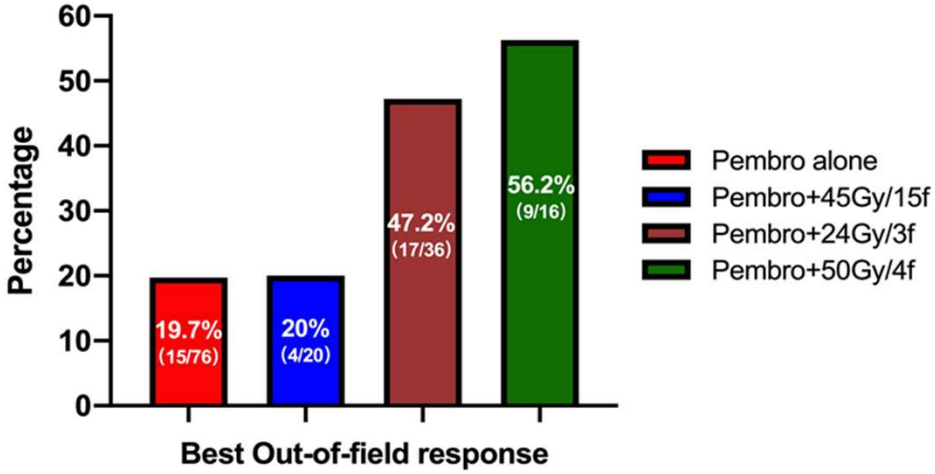


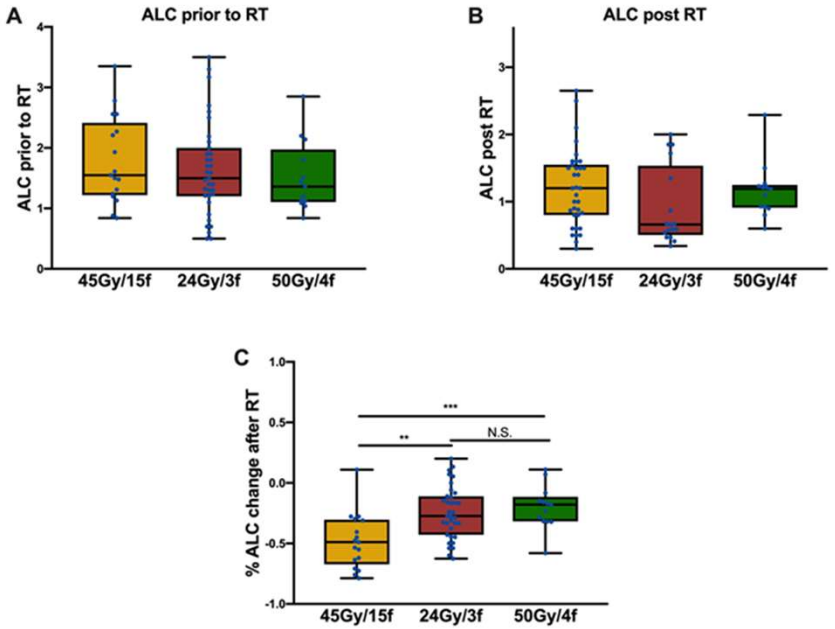
› OS



Theelen, Lancet Respir Med 2020

Comparison of RT regimens





Theelen, Lancet Respir Med 2020

ICI in oligometastatic NSCLC

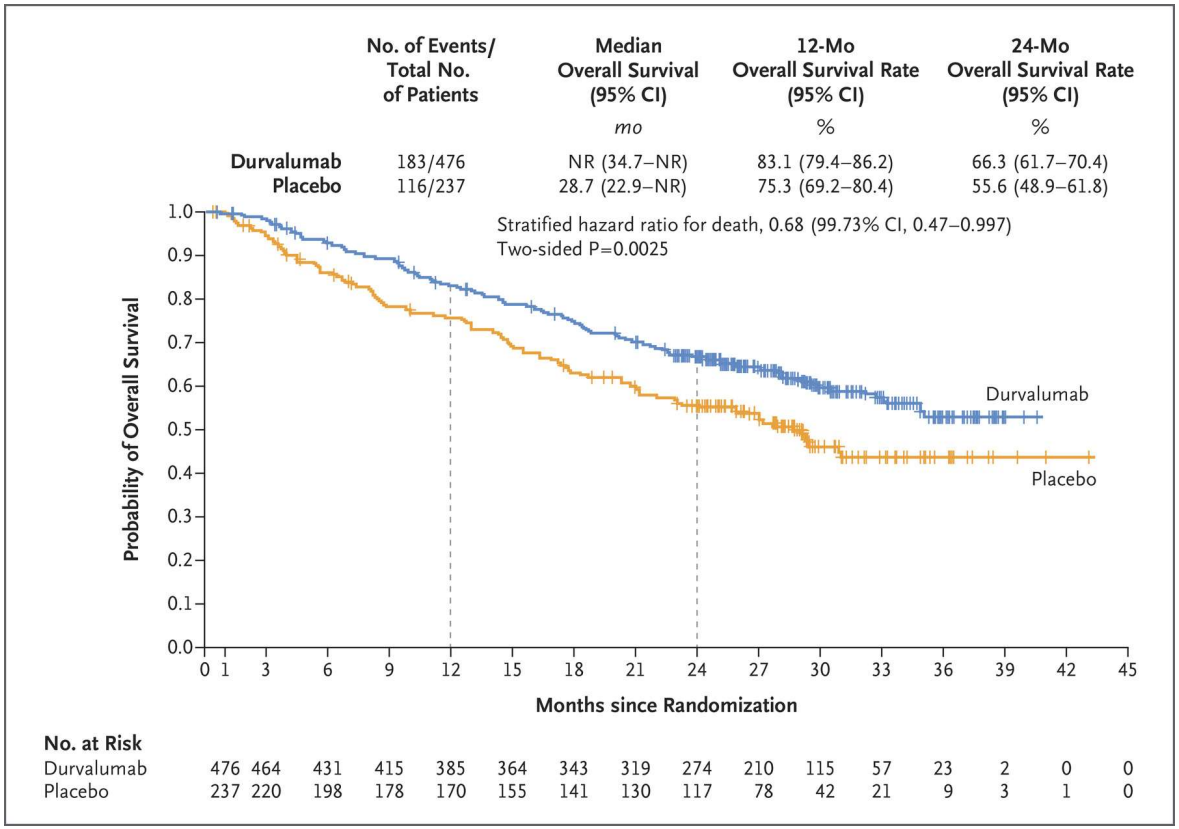
- Locally ablative therapy (LAT) to all tumor sites adjuvant to non-progression on platinum-doubley chemotherapy was already associated with improved PFS and OS[1,2]

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

1. Gomez, JCO 2019; 2. Iyengar, JAMA Oncol 2018; 3. Bauml, JAMA Oncol 2019

ICI and chemoradiation in NSCLC –PACIFIC[1]

- 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%

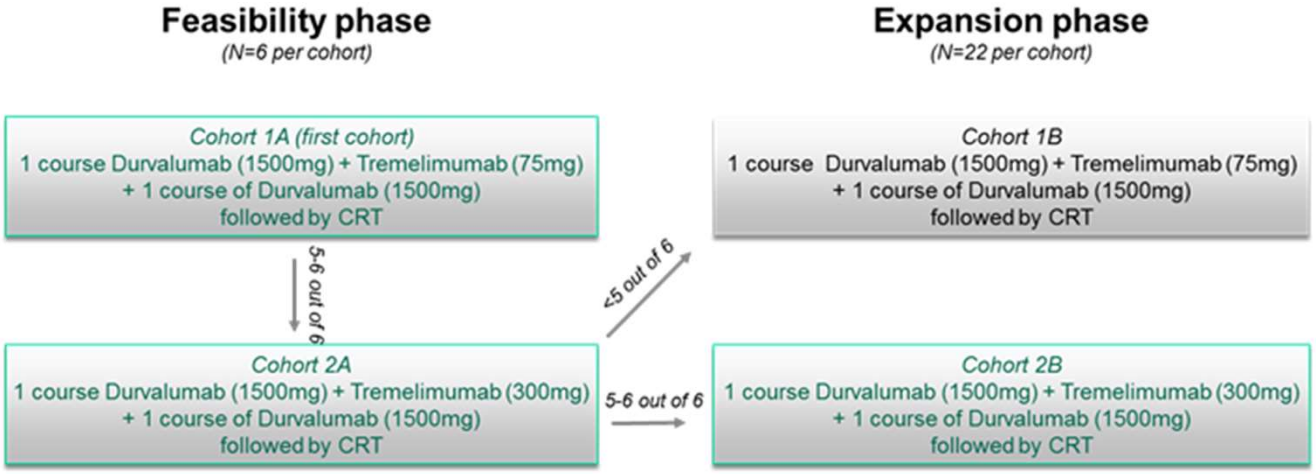


Also, NICOLAS study: nivolumab concurrently with CCRT is deemed safe[2]

1. Antonia, NEJM 2018; 2. Peters, Lung Cancer 2019

ICI and chemoradiation in NSCLC

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



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

1. Garelli, Immunotherapy 2019; 2. Trommer, Front Pharmacol 2019

Thank you!


Q & A
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