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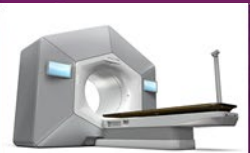
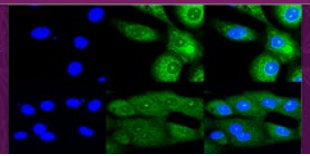
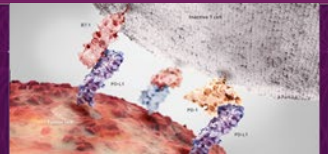

New Horizons for Radiation in the Management of Smoking – Related Cancer

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Disclosures

- **None**

Topics for discussion

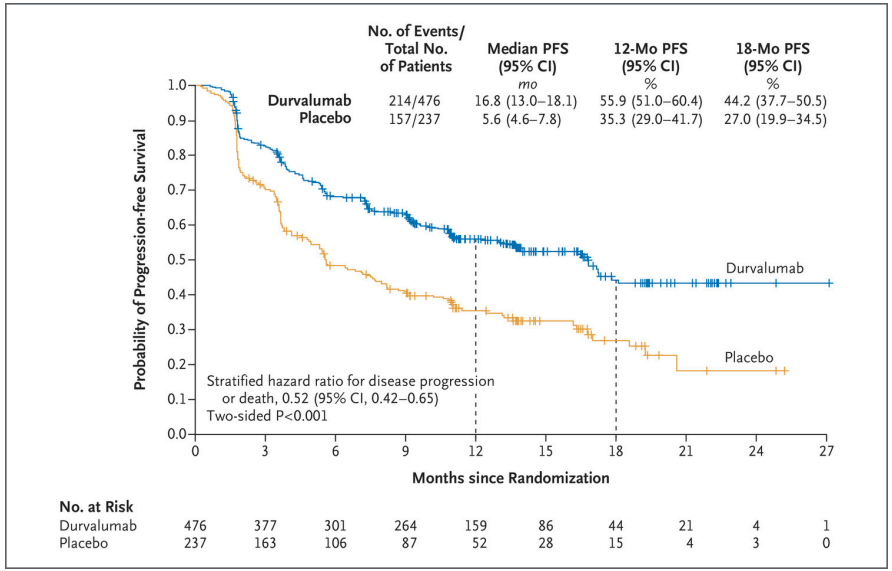
- Current standard of care for locally advanced:
  - Non-Small Cell Lung Cancer
  - Head and Neck Cancer
- Is there a role for radiation in the metastatic setting other than palliation?
- Where do novel forms of radiation fit in (if anywhere)?

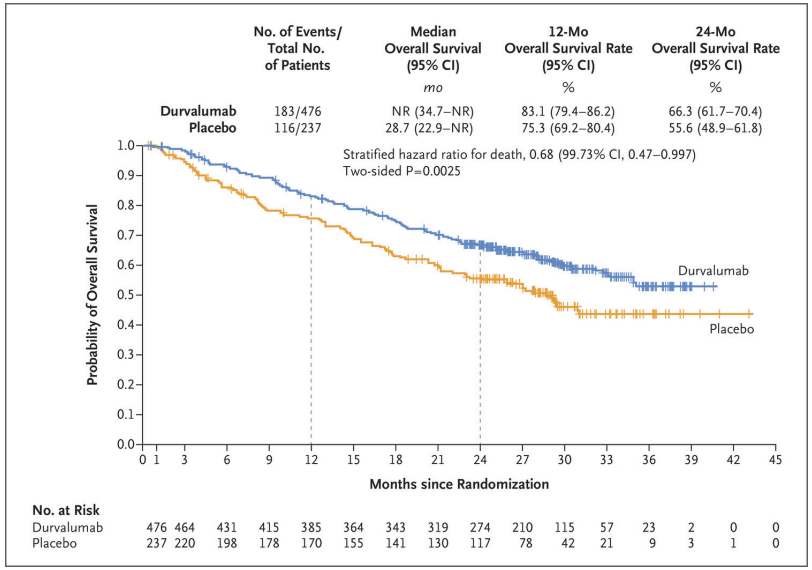
SOC in locally advanced NSCLC and HNSCC and new clinical horizons

Locally advanced Non-small cell lung cancer (NSCLC)

- Standard of care for inoperable locally advanced NSCLC is concurrent chemoradiation to 60 Gy in 2 Gy daily fractions.
- Relatively recent data have led to the integration of immunotherapy (Durvalumab) into this paradigm.

PACIFIC





Antonia SJ et al. N Engl J Med 2017, SJ Antonia et al. N Engl J Med 2018

NRG LU001

STRATIFY

Zubrod Performance Score
1. 0
2. 1

Histology
1. Squamous
2. Non-Squamous

Clinical Stage
1. IIIA
2. IIIB

RANDOMIZE

Arm 1: Concurrent Chemoradiotherapy

RT: 60 Gy/30 fx with chemotherapy for 6 weeks

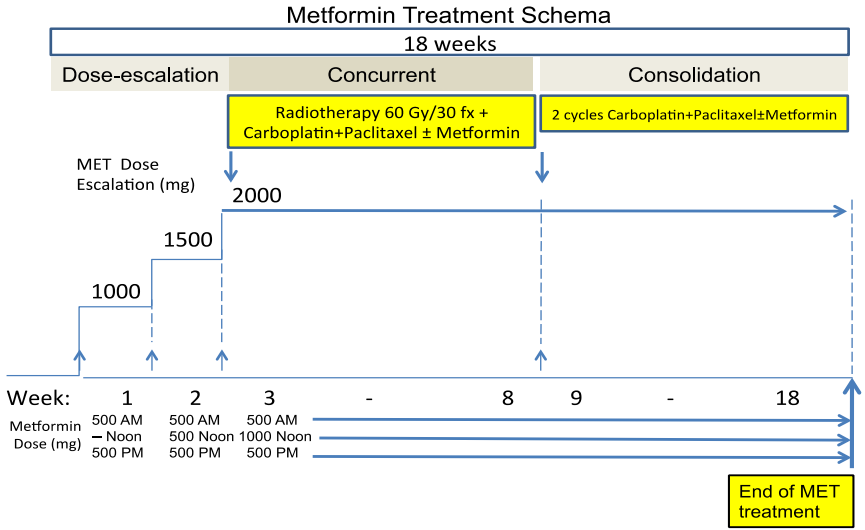
Followed by Consolidation Chemotherapy for 6 weeks

Arm 2:

MET Dose Escalation: 1000 mg to 2000 mg daily for 2 weeks

Concurrent Chemoradiotherapy + MET: RT: 60 Gy/30 fx with Chemotherapy and MET (2000 mg, p.o. daily) for 6 weeks

Consolidation Chemotherapy + MET: Consolidation chemotherapy for 6 weeks and MET (2000 mg p.o. daily) for 10 weeks.



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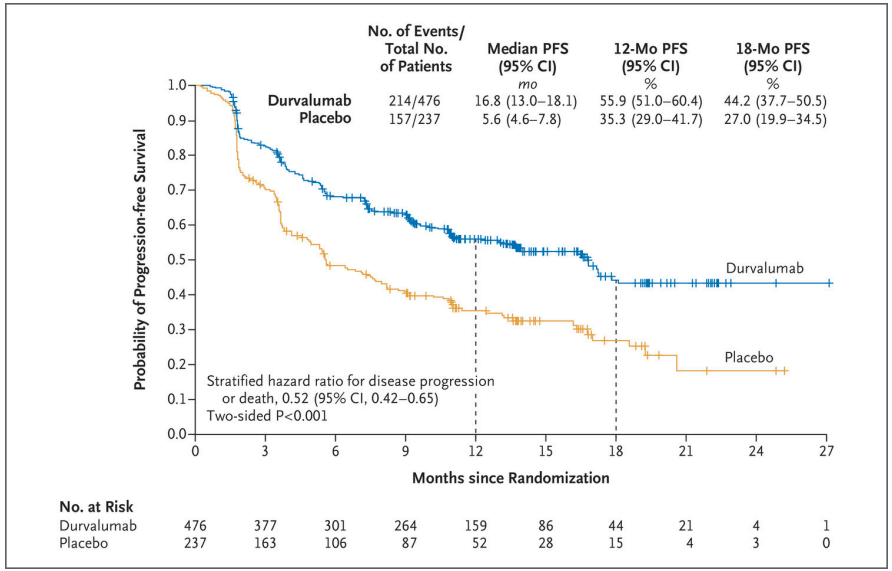
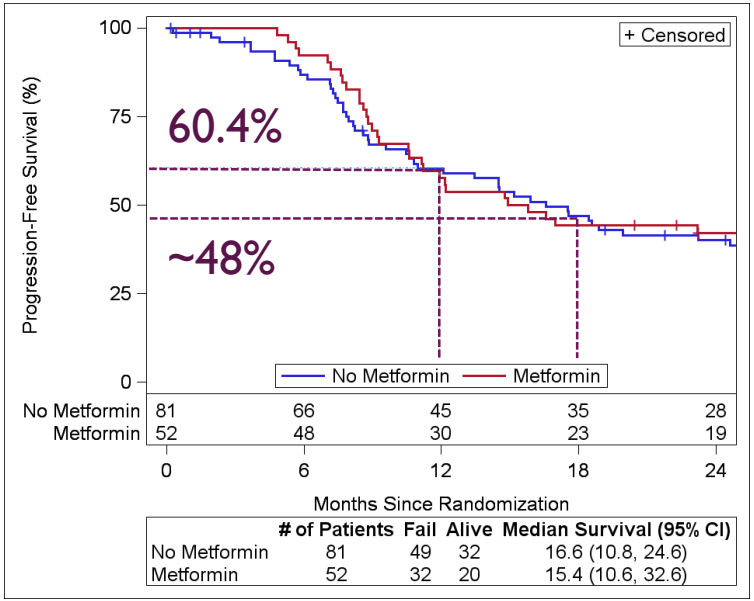
PACIFIC vs. NRG LU001



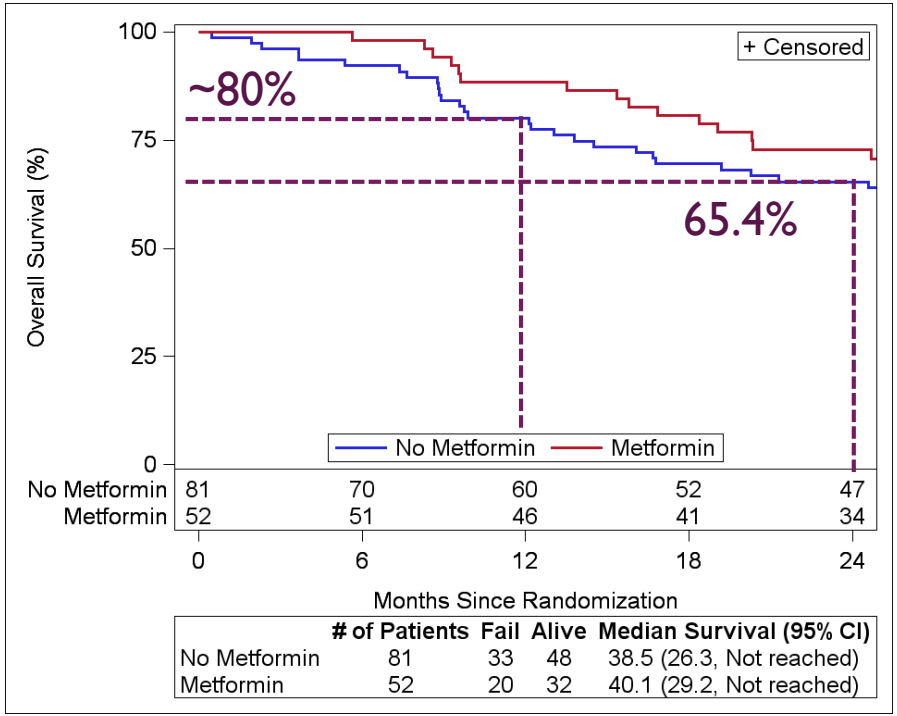
Metformin Per Protocol



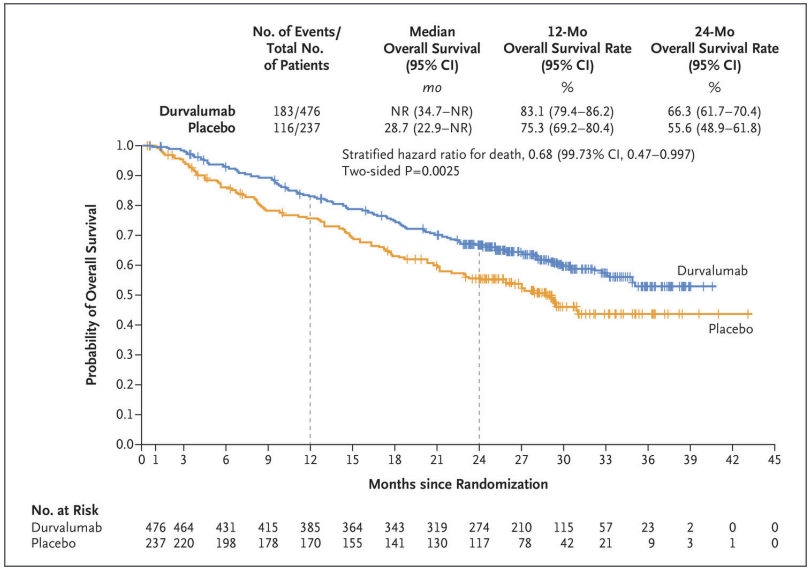
Antonia SJ et al. N Engl J Med 2017;Tsakiridis T, Chen H, Skinner H et al. ASCO Annual meeting 2019

PACIFIC

Metformin Per Protocol



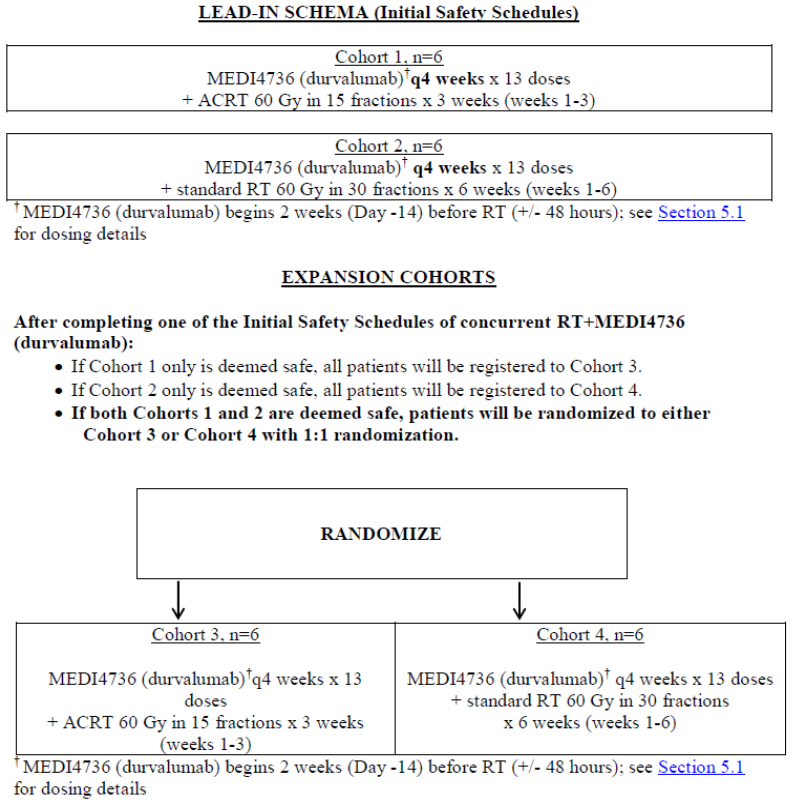
	# of Patients	Fail	Alive	Median Survival (95% CI)
No Metformin	81	33	48	38.5 (26.3, Not reached)
Metformin	52	20	32	40.1 (29.2, Not reached)



Tsakiridis T, Chen H, Skinner H et al. ASCO Annual meeting 2019, SJ Antonia et al. N Engl J Med 2018

What is on the horizon for LA-NSCLC?

- Not a lot from the cooperative groups unfortunately…
  - NRG-LU004
    - Unresectable LA-NSCLC, PD-L1 ≥ 50%
    - Phase 1 lead in w 2 cohorts
    - If both are safe, expand to randomized study



LEAD-IN SCHEMA (Initial Safety Schedules)

Cohort 1, n=6
MEDI4736 (durvalumab)† **q4 weeks** x 13 doses
+ ACRT 60 Gy in 15 fractions x 3 weeks (weeks 1-3)

Cohort 2, n=6
MEDI4736 (durvalumab)† **q4 weeks** x 13 doses
+ standard RT 60 Gy in 30 fractions x 6 weeks (weeks 1-6)

† MEDI4736 (durvalumab) begins 2 weeks (Day -14) before RT (+/- 48 hours); see Section 5.1 for dosing details

EXPANSION COHORTS

After completing one of the Initial Safety Schedules of concurrent RT+MEDI4736 (durvalumab):

- If Cohort 1 only is deemed safe, all patients will be registered to Cohort 3.
- If Cohort 2 only is deemed safe, all patients will be registered to Cohort 4.
- **If both Cohorts 1 and 2 are deemed safe, patients will be randomized to either Cohort 3 or Cohort 4 with 1:1 randomization.**

RANDOMIZE

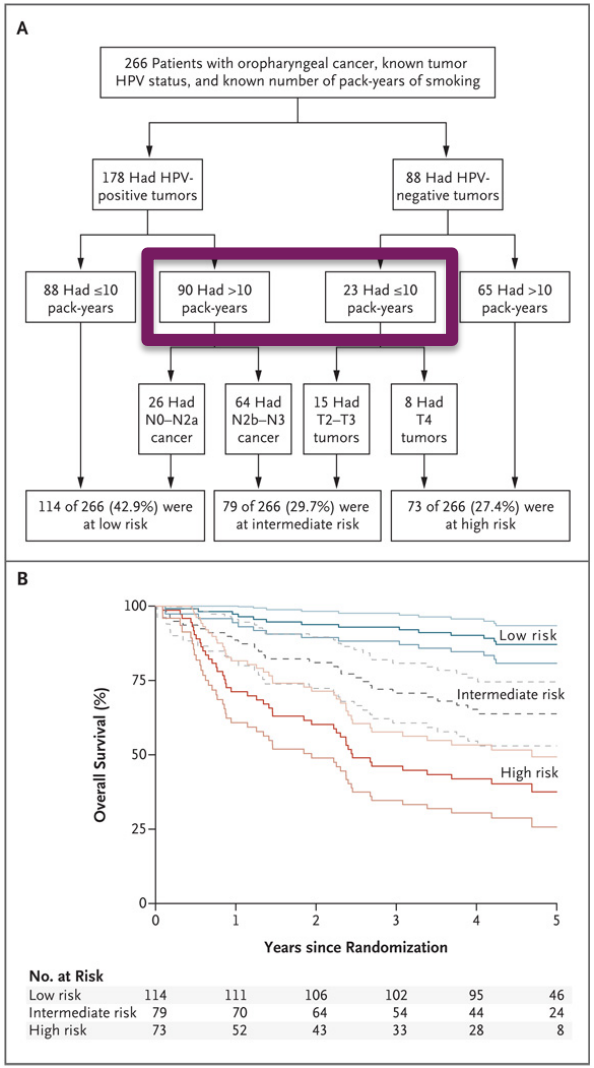
Cohort 3, n=6
MEDI4736 (durvalumab)†q4 weeks x 13 doses
+ ACRT 60 Gy in 15 fractions x 3 weeks (weeks 1-3)

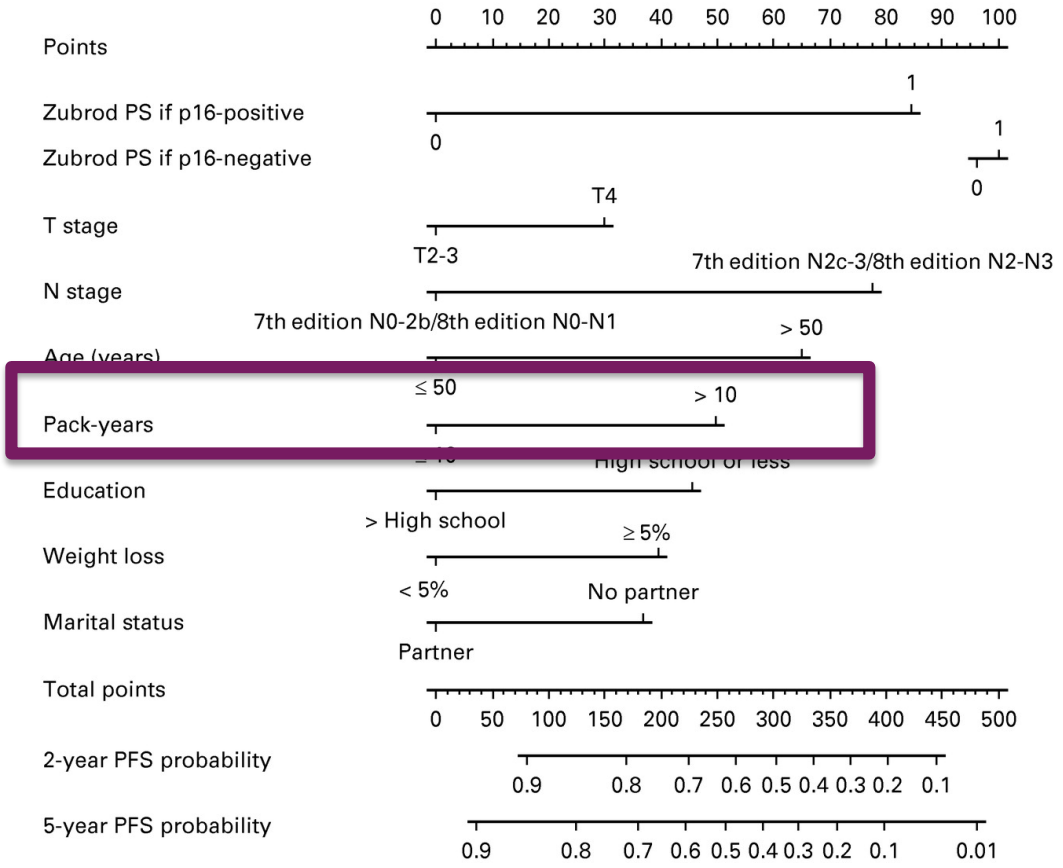
Cohort 4, n=6
MEDI4736 (durvalumab)† q4 weeks x 13 doses
+ standard RT 60 Gy in 30 fractions x 6 weeks (weeks 1-6)

† MEDI4736 (durvalumab) begins 2 weeks (Day -14) before RT (+/- 48 hours); see Section 5.1 for dosing details

Unresectable locally advanced Head and Neck squamous cell carcinoma (HNSCC)

- Two different diseases:
  - HPV positive: comparatively better outcomes, more sensitive to chemotherapy and radiation
  - HPV negative: comparatively worse outcomes, more resistant to chemotherapy and radiation
- Although smoking is tied to the development of HPV negative, smoking affects HPV positive disease as well.





Ang et al. NEJM, 2011; Fakhry et al. JCO, 2017

Locally advanced Head and Neck squamous cell carcinoma (HNSCC)

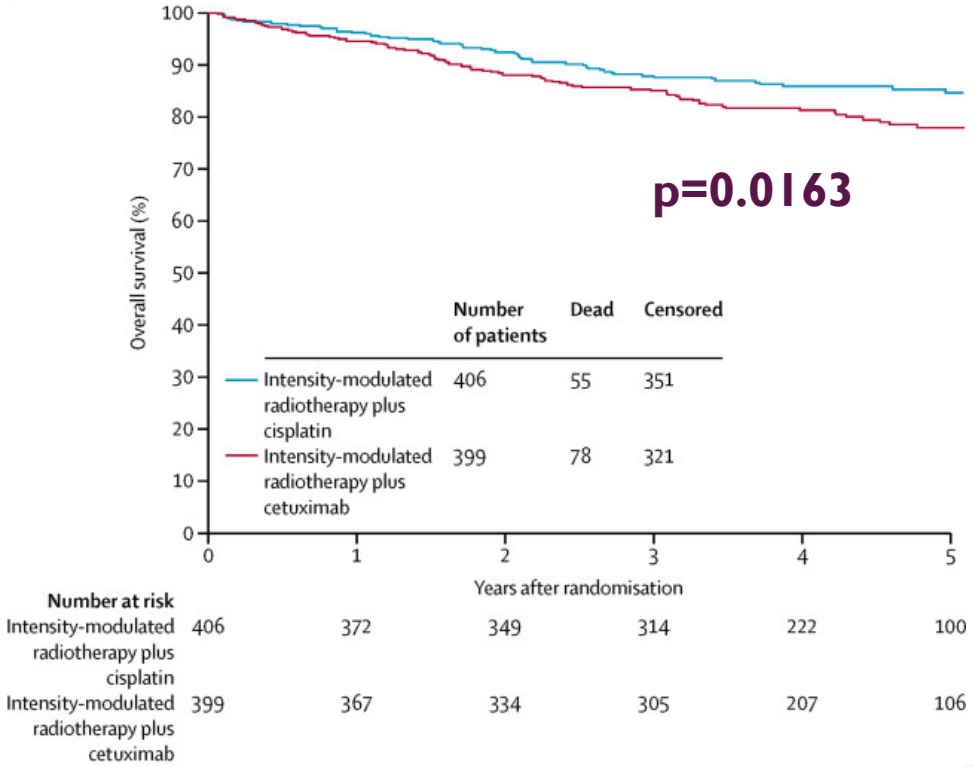
- Regardless of HPV status though, the standard for unresectable locally advanced HNSCC is radiation and platinum-based chemotherapy…NOT cetuximab
- Why?

Cetuximab inferior to cisplatin

RTOG 1016

- HPV-positive OPSCC;
- T1–T2, N2a–N3 M0 or T3–T4, N0–N3 M0
- Stratified by ≤10 vs >10 pack year smoking
- Cetuximab WORSE than CDDP with IMRT

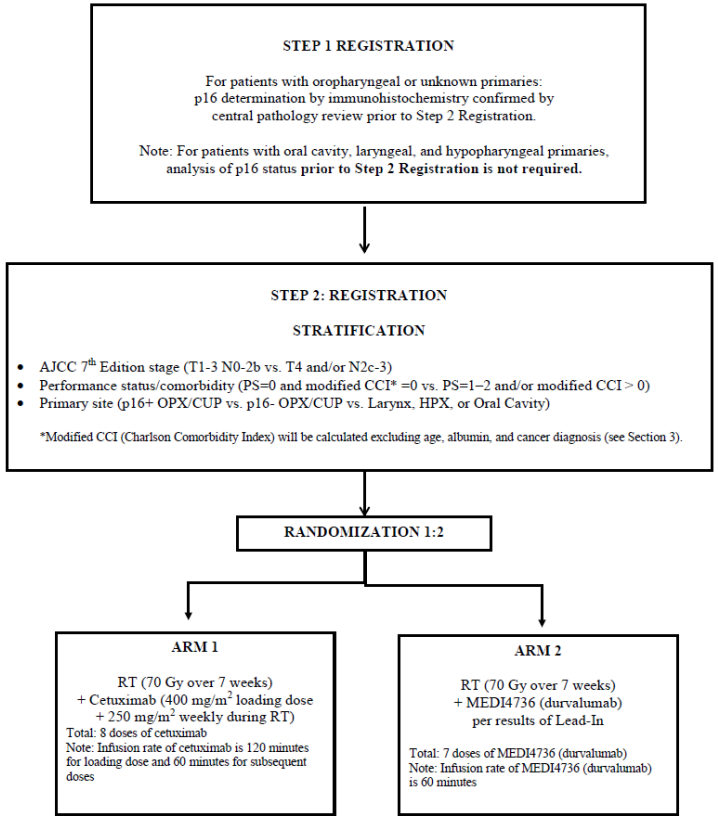
Similar results in De-ESCALaTE trial



Gillison et al., Lancet, 2019

What is on the horizon for cisplatin ineligible?

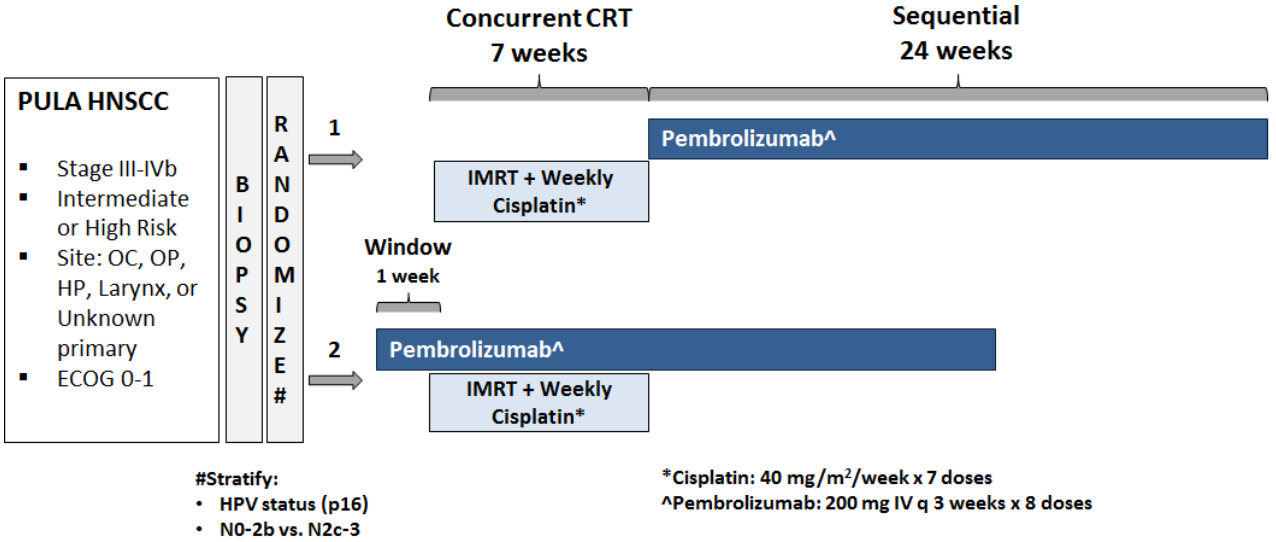
- NRG HN004
  - Phase I lead in with 10 patients showed NO DLTs
  - Phase II/III currently accruing with goal of ~444 patients
  - Primary endpoint
    - Phase II – PFS
    - Phase III – OS



What is on the horizon for cisplatin eligible?

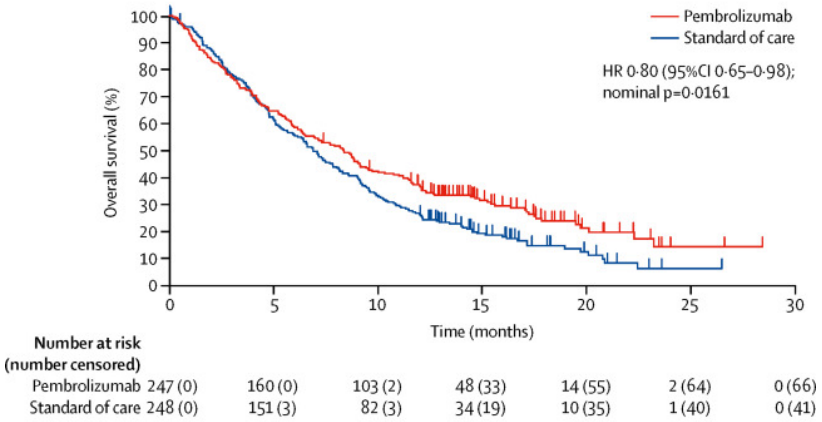
- Completed:
  - RTOG 3504
    - Complex schema, but tested nivo + cisplatin or cetixumab in Phase 1 with reasonable toxicity
    - Follow-up study pending
- Ongoing:
  - UPCI 15-123
    - High or intermediate risk unresectable HNSCC (includes LA HPV positive with smoking history)
    - Comparing concurrent versus adjuvant pembrolizumab

What is on the horizon for cisplatin eligible?



Why PD-1/PD-L1 driven therapy?

Keynote 040 (Ph III R/M HNSCC)



Keynote 048 (Ph III first line R/M HNSCC)

	CPS ≥1		CPS ≥20		Total Population	
	Pembro	EXTREME	Pembro	EXTREME	C + P*	EXTREME
OS						
Median (mo)	12.3	10.3	14.9	10.7	13	10.7
1 year	51%	43.6%	56.9%	44.9%	53%	43.9%
2 year	30.2%	18.6%	38.3%	22.1%	29%	18.7%
PFS						
Median (mo)	3.2	5.0	3.4	5.0	4.9	5.1
1 year	19.6%	11.9%	22.9%	12.4%	16.7%	12.1%
2 year	11.2%	5.4%	14.9%	4.8%	9.8%	4.6%
ORR	19.1%	34.9%	23.1%	36.1%	35.6%	36.3%
Duration of Response (mo)	20.9	4.5	20.9	4.5	6.7	4.3

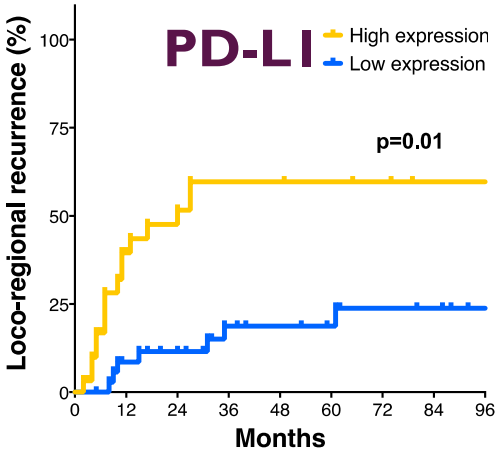
Cohen et al., Lancet, 2019; Burtness et al. ESMO Annual Congress 2018 (Table from Zandberg, Skinner & Ferris, ASCO Post 2019)

Why PD-1/PD-L1 driven therapy with radiation?

RPPA

PD-L1

mRNA

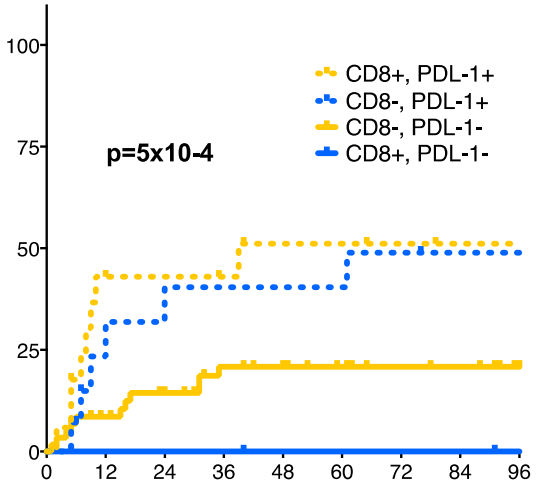


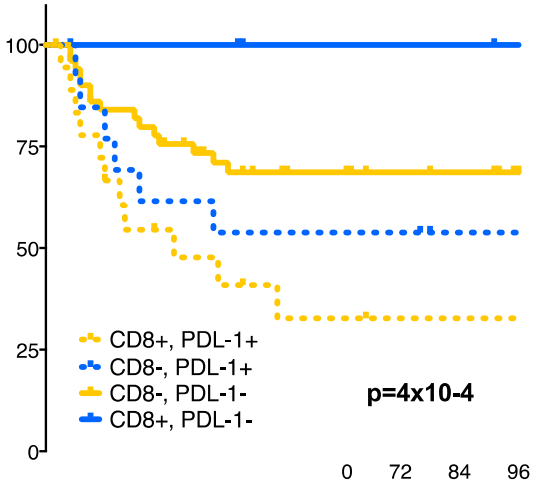
TMA

PD-L1

Skinner et al., CCR, 2016

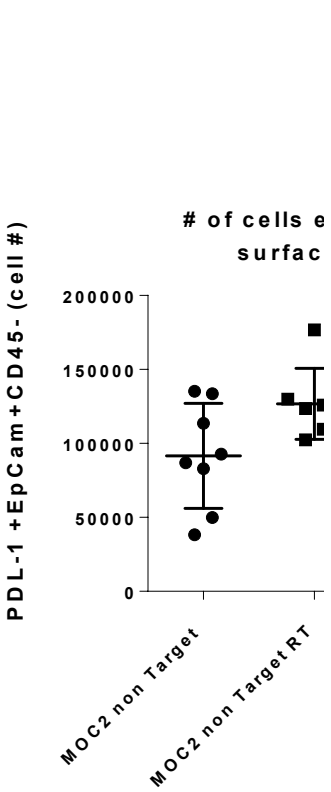
Why PD-1/PD-L1 driven therapy with radiation?

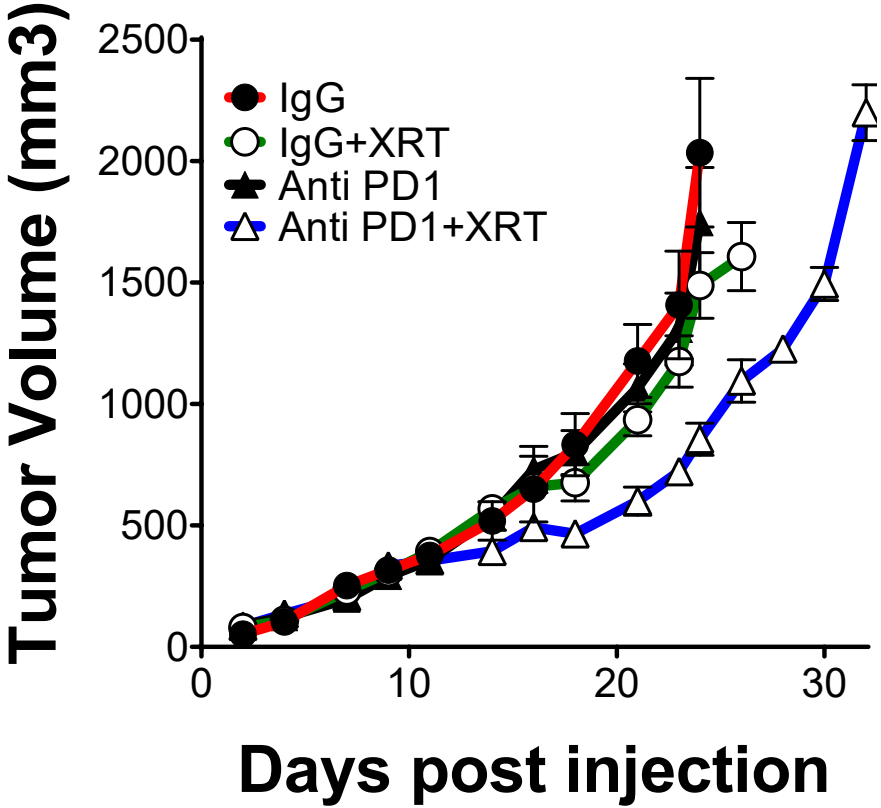


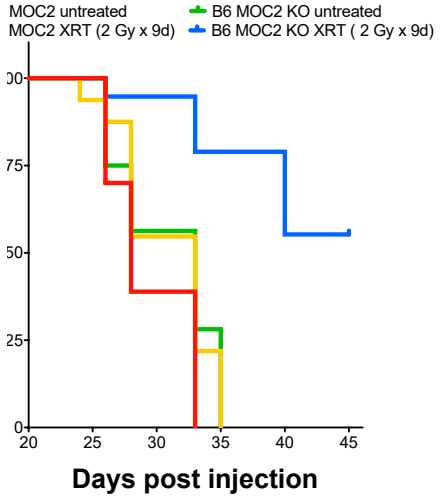


Skinner et al., CCR, 2016

Why PD-1/PD-L1 driven therapy



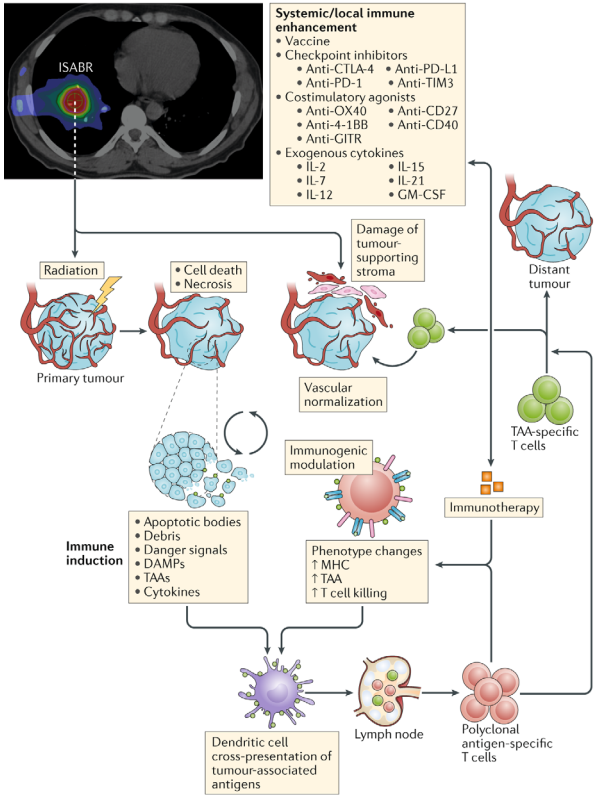




Skinner et al., In preparation

Is there a role for radiation in the metastatic setting in NSCLC and/or HNSCC other than palliation?

Abscopal effects – What do we hope may happen?



- High dose radiation (may):
  - Promote immunogenic cell death (necrosis)
  - Increase major histocompatibility complex class I (MHC I)
  - Promote activation through the stimulator of interferon genes protein (STING)
  - Activate antigen-presenting cells (APCs) and primes TAA-specific cytotoxic T cells

Brooks et al., Nat Rev Clin Onc, 2018

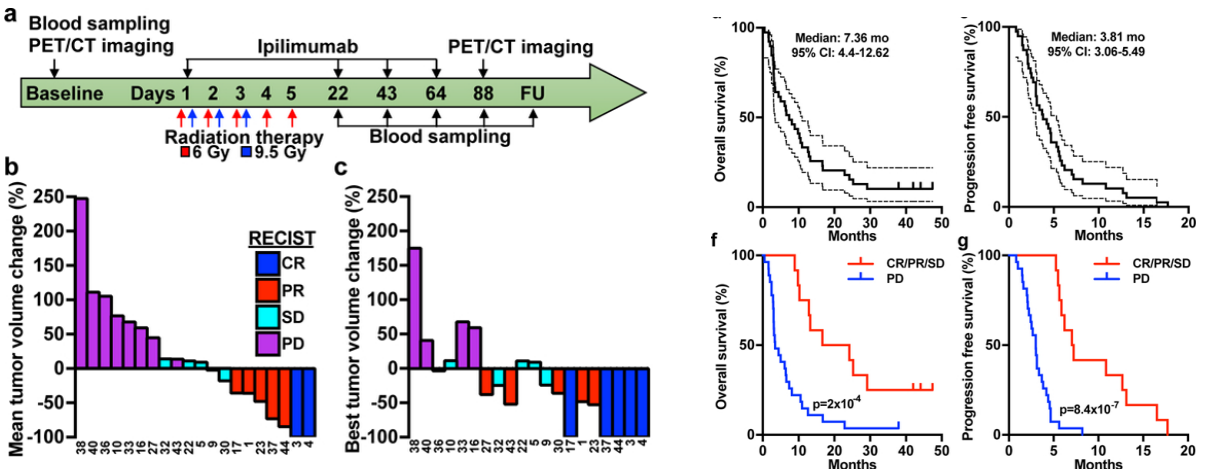
Abscopal effects – What is going on right now?

Title (study drug if not in title)	Recruitment	Study endpoint	Phase	Enrollment
Ipilimumab and Stereotactic Body Radiation Therapy (SBRT) in Advanced Solid Tumors	MD Anderson, Houston, TX; recruiting 120	Safety, irRC response rate	1–2	Active, closed to enrollment
Pembrolizumab and Stereotactic Body Radiation Therapy (SBRT) in Patients With Non-Small Cell Lung Cancer (NSCLC)	MD Anderson, Houston, TX; recruiting 104	Safety, irRC response rate, PFS	1–2	Open
FLT3 Ligand Immunotherapy and Stereotactic Radiotherapy for Advanced Non-small Cell Lung Cancer (FLT3)	Albert Einstein, NYC, NY; recruiting 29	4-month PFS	2	Open
Radiation and Immune Checkpoints Blockade in Metastatic NSCLC (nivolumab/ipilimumab)	Cornell, NYC, NY; recruiting 45	Response rate, PFS, OS	1–2	
Phase Ib Study of Stereotactic Body Radiotherapy (SBRT) in Oligometastatic Non-small Lung Cancer (NSCLC) With Dual Immune Checkpoint Inhibition (durvalumab/tremelimumab)	University of Wisconsin, Madison; recruiting 21	Safety, PFS, OS	1	Open
Evaluate Concurrent Or Sequential Ipilimumab, Nivolumab, and Stereotactic Body Radiotherapy in Patients With Stage IV Non-Small Cell Lung Cancer	University of Chicago, IL; recruiting 80	Safety, response rate	1	Open
Priming Immunotherapy in Advanced Disease With Radiation (any checkpoint inhibitor)	University of Kentucky, Lexington; recruiting 57	6-month PFS	2	Open
Hypofractionated Radiation Therapy to Improve Immunotherapy Response in Non-Small Cell Lung Cancer (nivolumab, pembrolizumab, or atezolizumab)	West Virginia University; recruiting 33	Response rate, OS, PFS, QoL	1	
Trial of Stereotactic Body Radiation and Gene Therapy Before Nivolumab for Metastatic Non-Small Cell Lung Carcinoma (ENSIGN)	Methodist Hospital, Houston, TX; recruiting 29	Response rate, PFS, OS	2	Open
A Pilot Study of Interlesional IL-2 and RT in Patients With NSCLC (nivolumab/pembrolizumab)	University of California, Davis; recruiting 30	Safety, DFS	1	Open
Avelumab and Stereotactic Ablative Radiotherapy in Non-responding and Progressing NSCLC Patients	University of California, Davis; recruiting 26	Response rate, PFS, OS, irRC	1	Open
Radical-Dose Image Guided Radiation Therapy in Treating Patients With Metastatic Non-small Cell Lung Cancer Undergoing Immunotherapy (nivolumab, pembrolizumab, or atezolizumab)	Stanford University, CA; recruiting 85	PFS, OS, ctDNA changes	2	Open
Image Guided Hypofractionated Radiation Therapy, Nelfinavir Mesylate, Pembrolizumab, Nivolumab and Atezolizumab in Treating Patients With Advanced Melanoma, Lung, or Kidney Cancer	University of Washington, Seattle; recruiting 120	Response rate, PFS, OS	2	Open
A Study of SBRT in Combination With rhGM-CSF for Stage IV NSCLC Patients Who Failed in Second-line Chemotherapy	Wuhan University, China; recruiting 60	Abscopal effect rate, OS, PFS	2	Open
Phase I Multicenter Trial Combining Nivolumab, Ipilimumab and Hypo-fractionated Radiotherapy for Pretreated Advanced Stage Non-small Cell Lung Cancer Patients				

Lin et al., TLCR, 2019

Abscopal effects – What has actually happened to date?

- Largely small case series showing modest out of field effects in lung
- 6 Gy x 5 or 9 Gy x 3 + **CTLA-4 blockade**



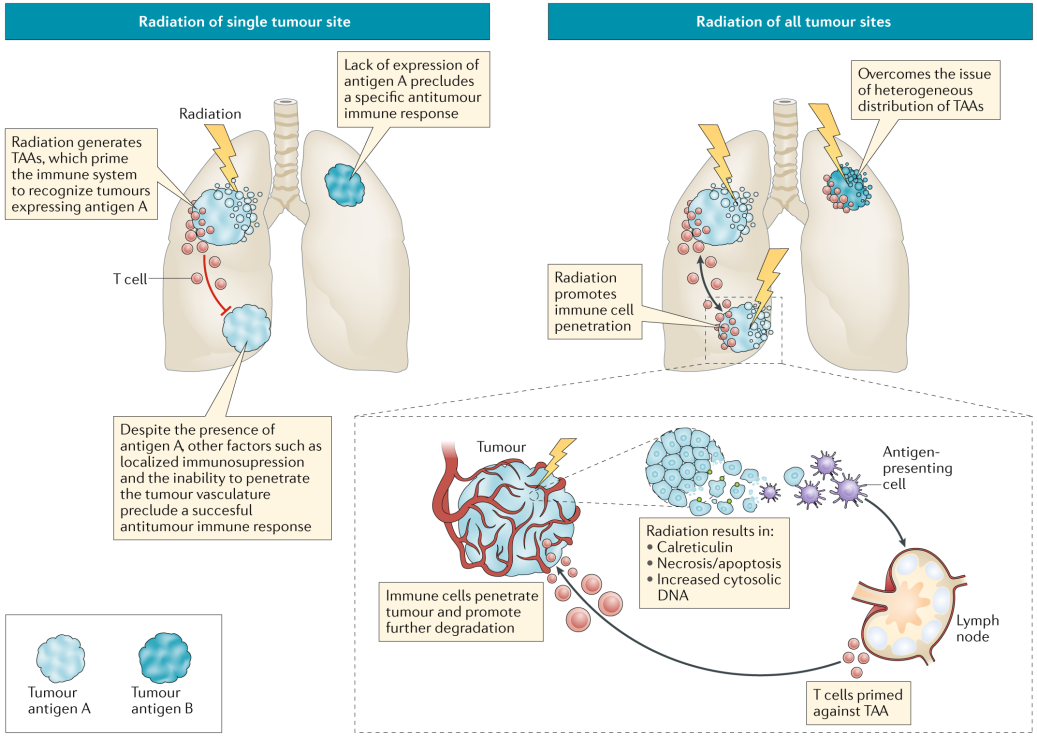
Formenti et al., Nat Med, 2018

Abscopal effects – What has actually happened to date?

- Randomized trial of nivolumab +/- SBRT (9 Gy x 3) to one metastatic site
- 53 patients (Nivo vs. Nivo + SBRT)
  - ORR: 26.9% (95% CI: 13.7, 46.1%) vs 22.2% (95% CI: 10.6%, 40.8%)(p=0.94)
  - 1 yr OS 64% (95% CI: 47%, 88%) vs 53% (95% CI: 36%, 79%) (p = 0.79)

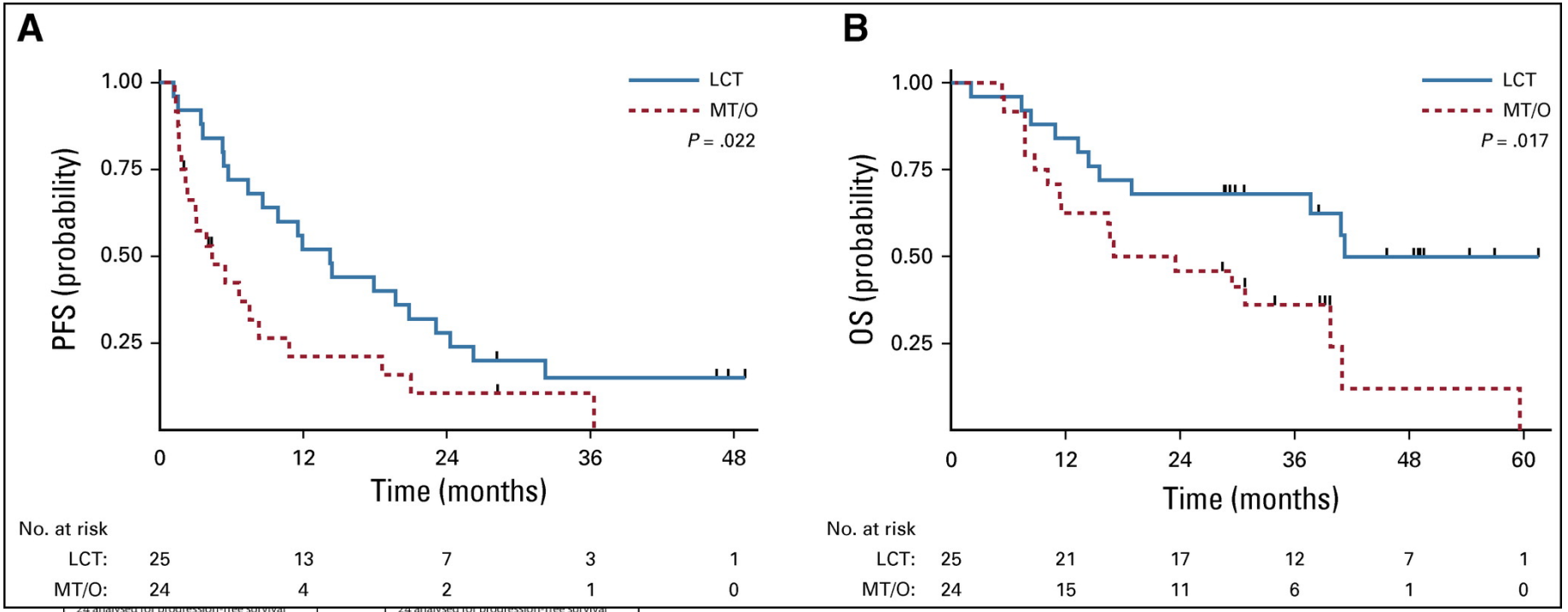
McBride et al., ASCO Annual meeting, 2018

Abscopal effects – What might be missing?



Brooks et al., Nat Rev Clin Onc, 2018

What might be missing? Consolidative XRT?



and time to new lesion

and time to new lesion

Gomez et al., Lancet Onc, 2016; Gomez et al. JCO 2019

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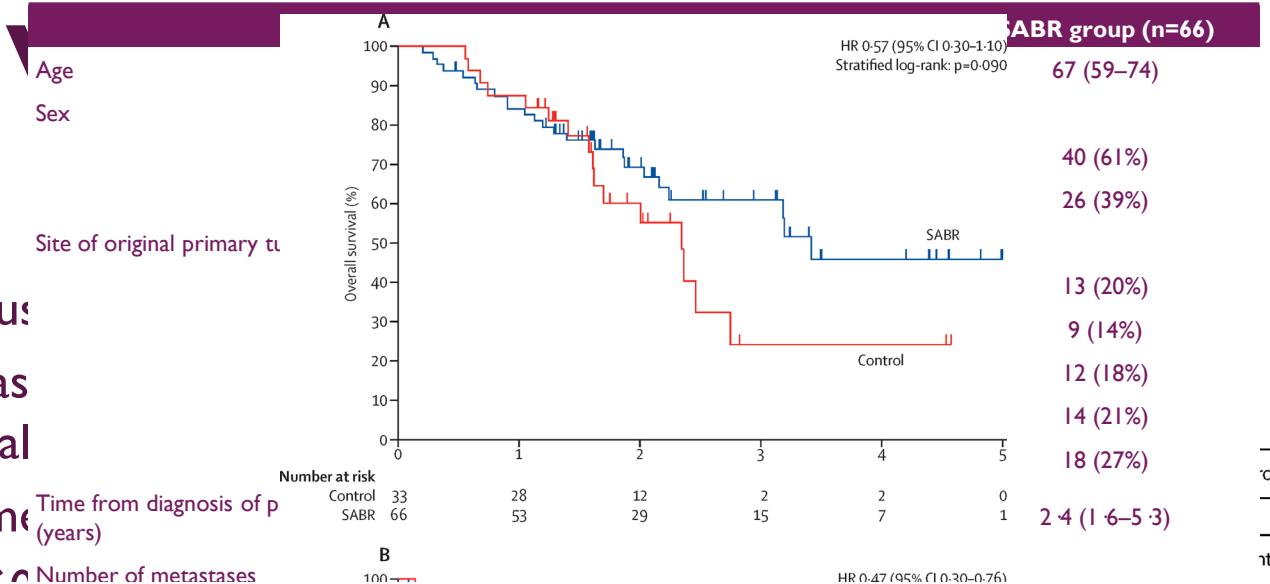


- Primary mus
- ≤3 metastas
  and≤ 5 total
- No brain me
- SABR: 30–60
- [illegible]
- [illegible]
- [illegible]

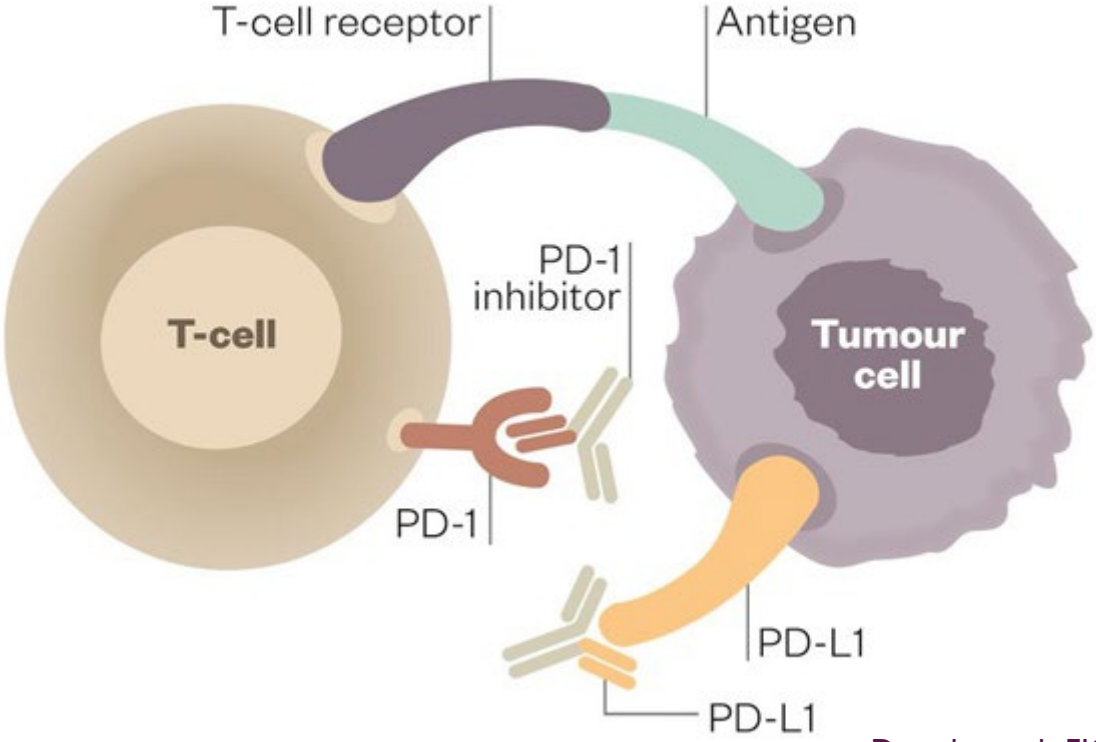
"We used a randomised phase 2 screening design,[14] with a two-sided α of 0·20 and a power of 80% as recommended for such studies.[14] In a phase 2 screening design, the α level is set higher than the 0·05 level that is used for a phase 3 design, recognising that even if the phase 2 trial is positive (ie, if the ultimate p value is less than 0·20), such a positive result is not usually considered definitive without a subsequent phase 3 trial. The choice of a two-sided α of 0·20, rather than the usual one-sided testing for phase 2 randomised trials[15] allowed for the possibility of finding inferior overall survival with SABR due to toxicity."

What might be missing? Consolidative XRT +I/O?

- NRG LU002
- **Randomized**
- Goal: 200 patients
- Ongoing
- High flexibility in XRT dosing

Patients with metastatic NSCLC having completed 4 cycles or courses 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 +/- Surgery	**S T R A T I F Y**	**Histology:** Squamous vs. Non-squamous **Systemic Therapy:** Immunotherapy* vs Cytotoxic Chemotherapy	**R A N D O M I Z E**	**Arm 1**: Maintenance systemic therapy alone** **Arm 2:** SBRT or SBRT and Surgery to all sites of metastases (≤ 3 discrete sites) plus irradiation (SBRT or hypofractionated RT) of the primary site followed by maintenance systemic therapy. All Arm 2 patients, even if treated with Surgery, must have one site of disease (metastasis or primary) treated with radiation.** **** As noted in Section 5**

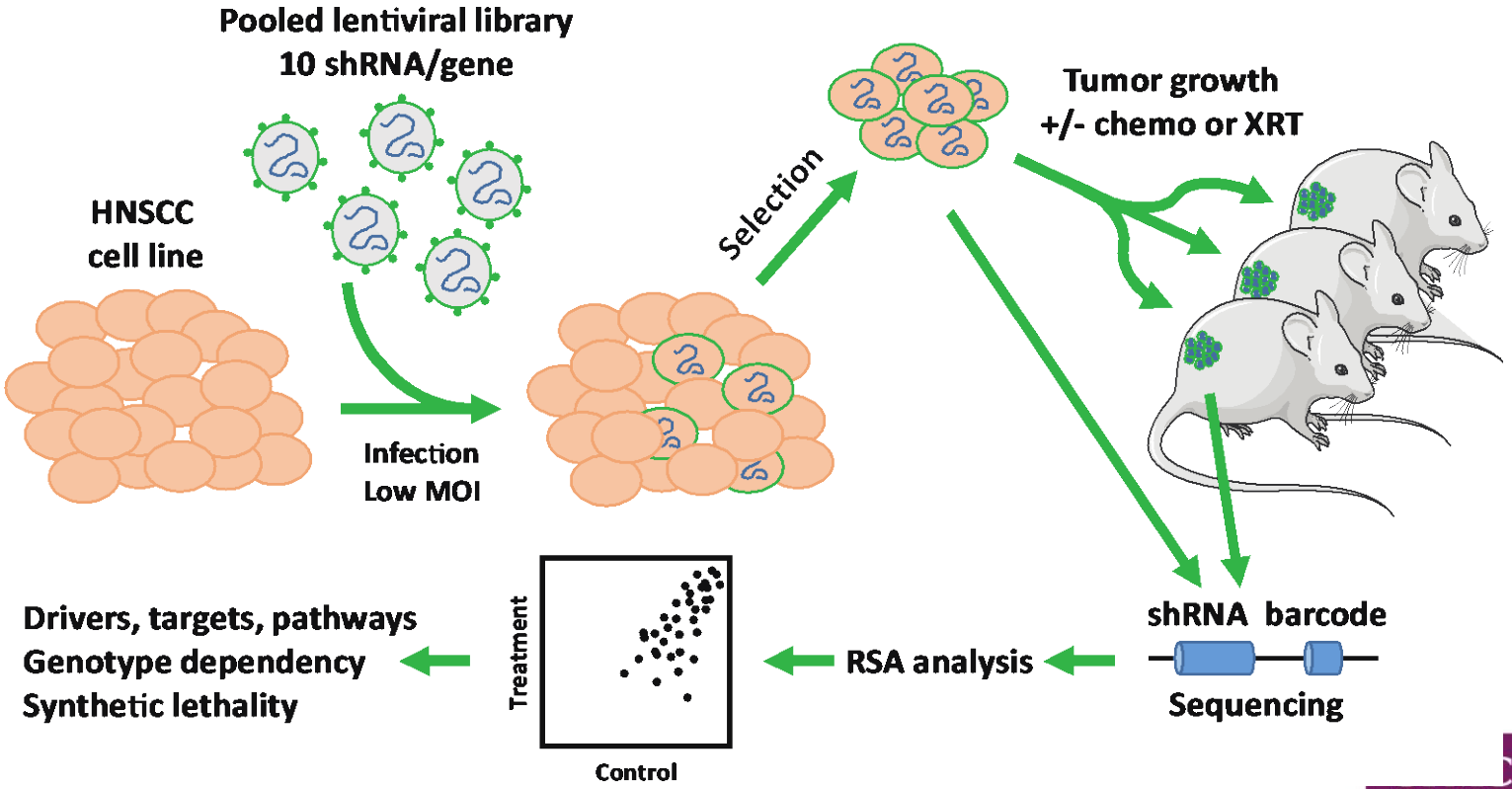
Abscopal effects – What might be missing?



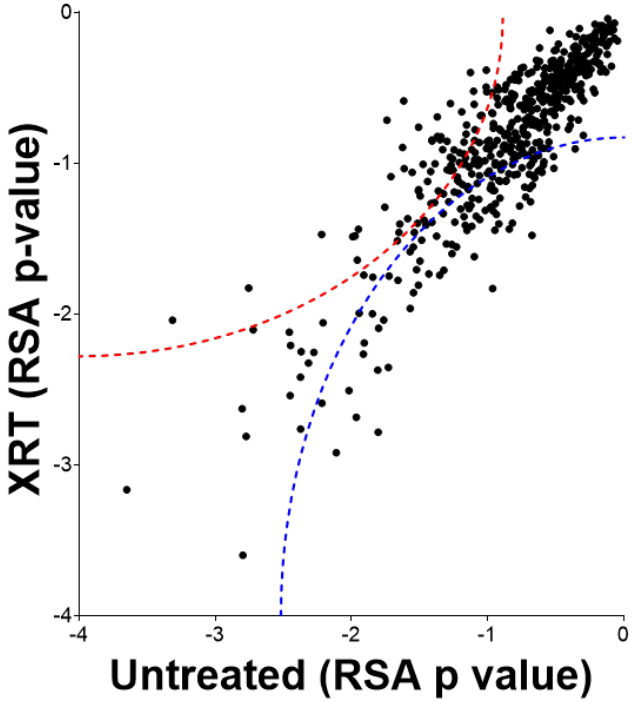
- Most studies in HN and lung have focused on CTLA-4 or **PD-1/PD-L1**
- Do better targets exist?

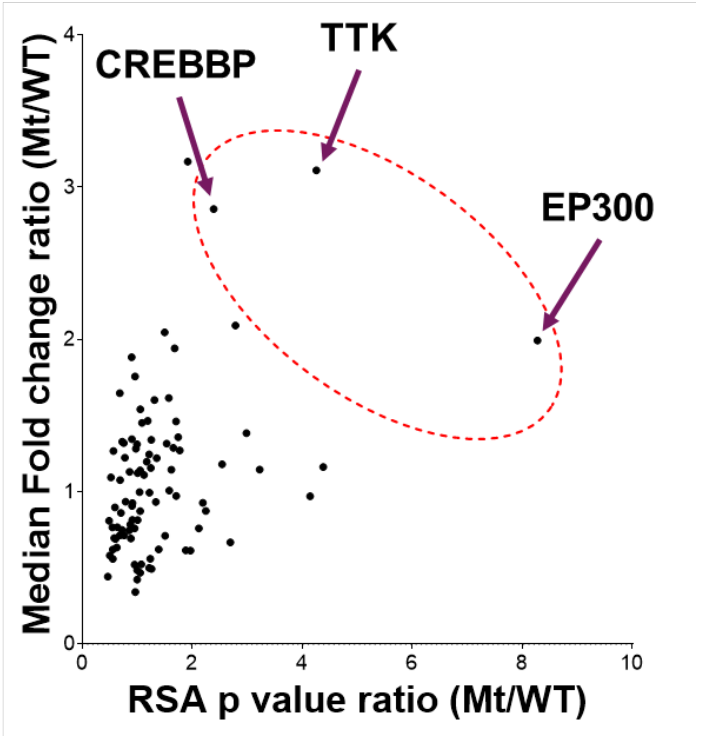
Dempke et al., EJC, 2017; M. Guha, Pharm Jour, 2014

In vivo screening of radiosensitizing targets using shRNA libraries



In vivo screening of radiosensitizing targets using shRNA libraries





Kumar et al., AACR annual meeting, 2018

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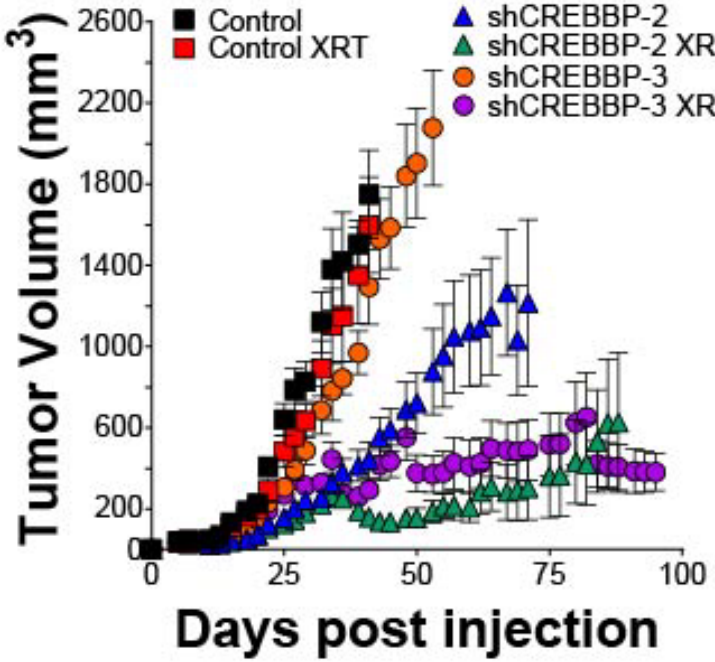

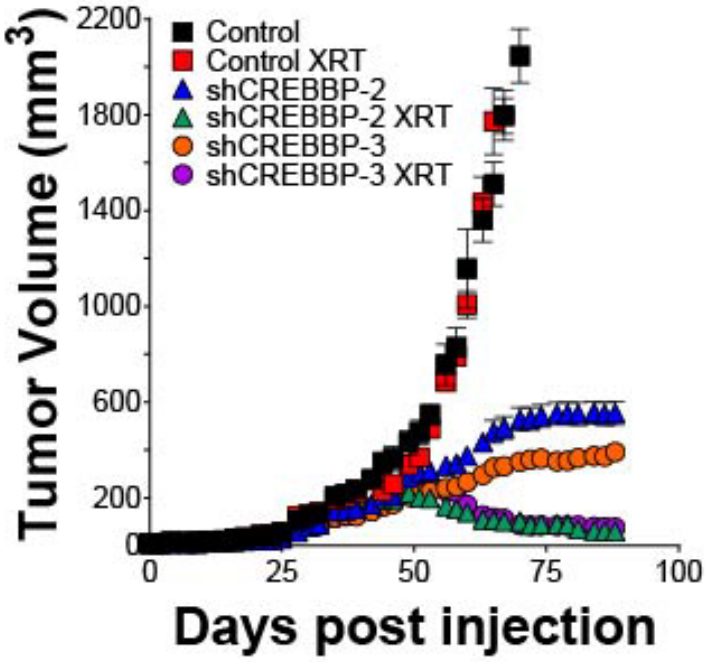

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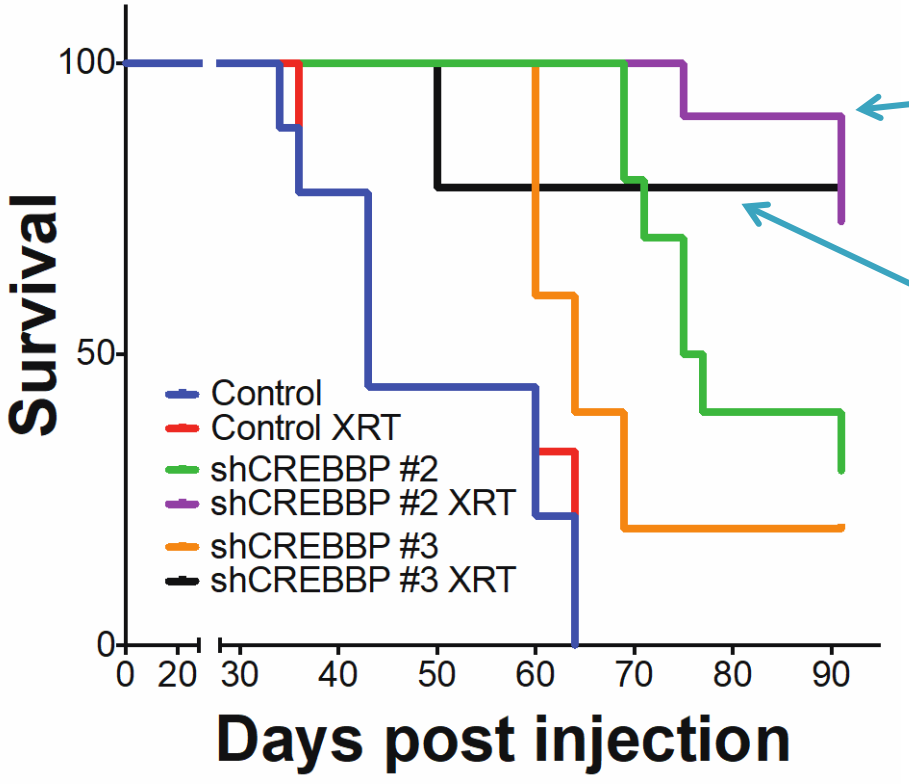
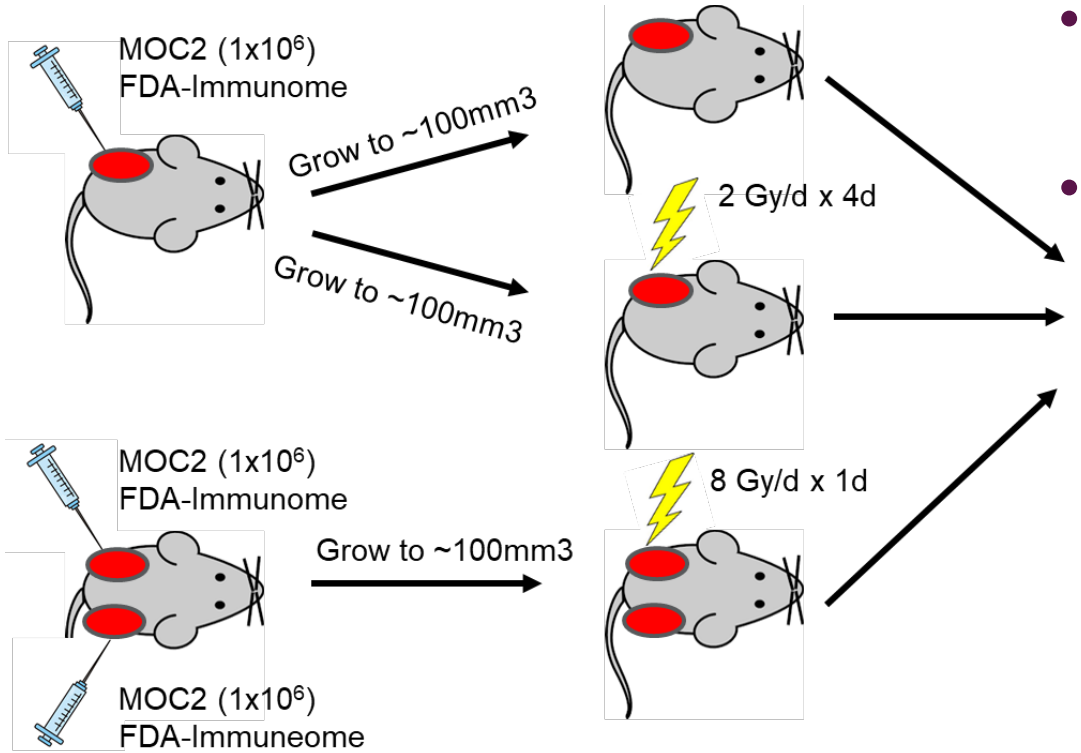


10/11 with no tumor

7/11 with no tumor

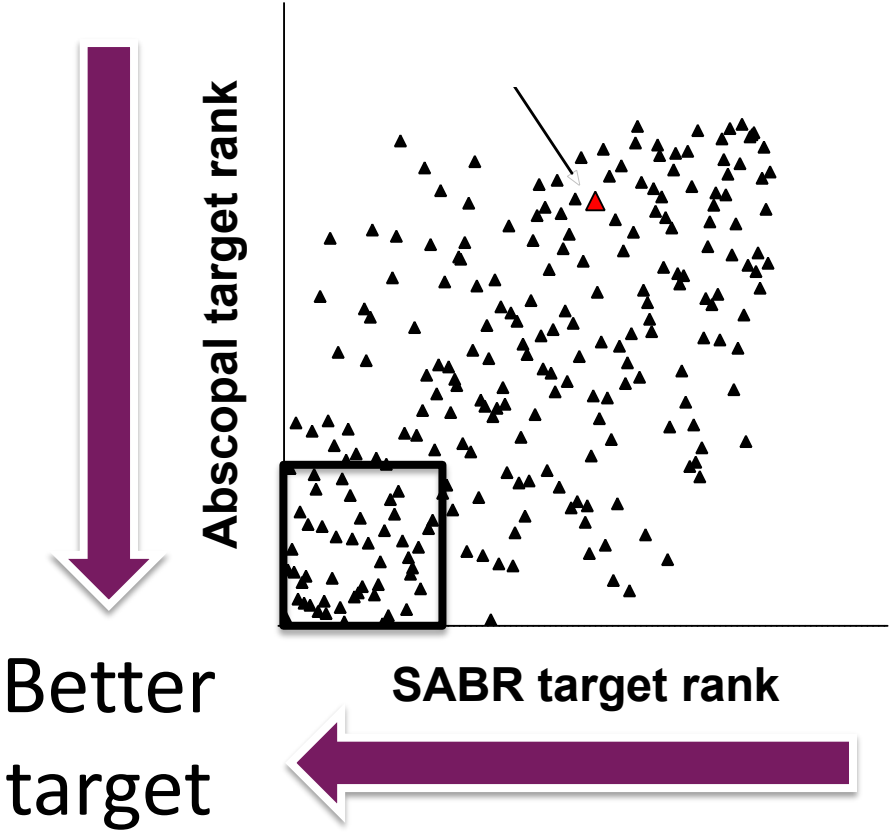
Kumar et al., AACR annual meeting, 2018

In vivo screening of radiosensitizing targets using shRNA libraries



- "FDA-immunome" (199 genes)
- MOC2 cell line

In vivo screening of radiosensitizing targets using shRNA libraries

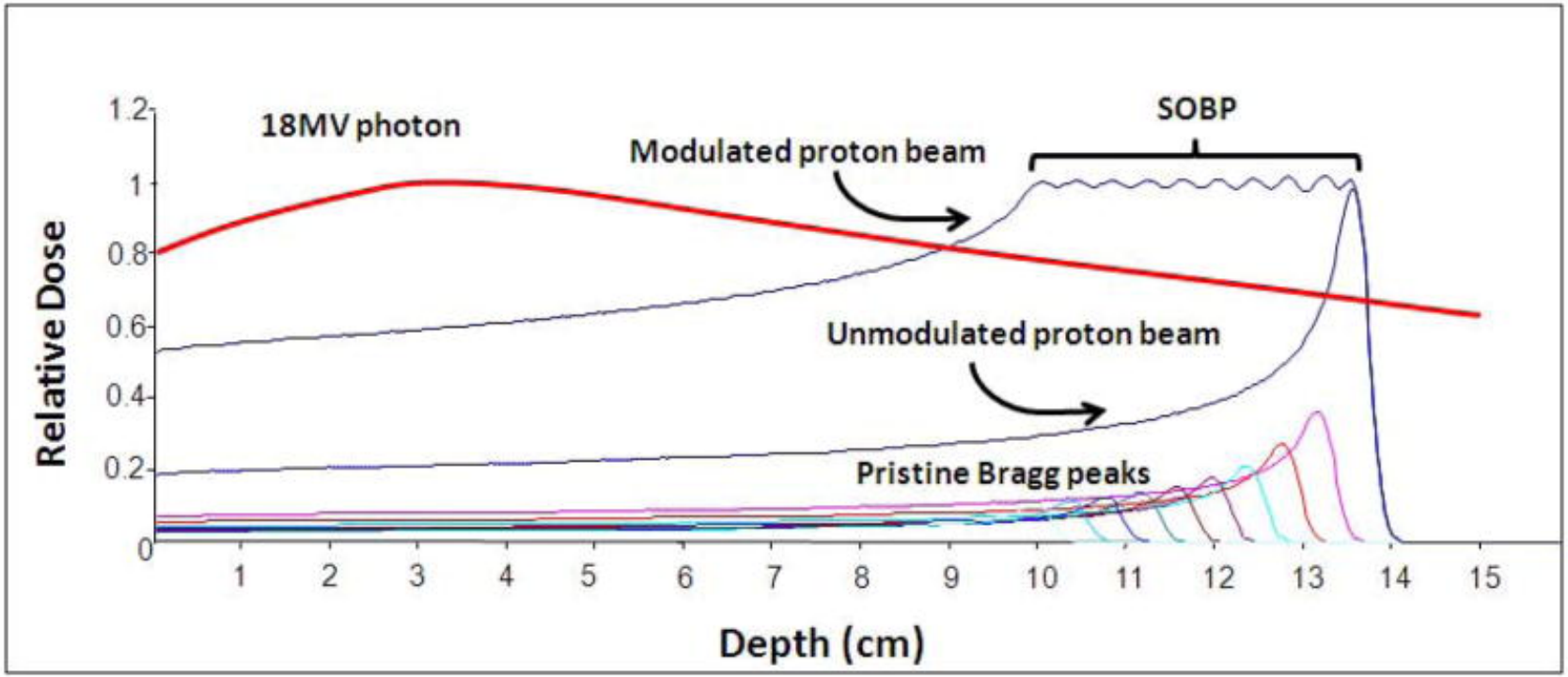


Where do novel forms of radiation fit in (if anywhere)?

Novel technology?

- Heavy particle therapy
  - –Protons
  - –Carbon ion
  - –More exotic particles

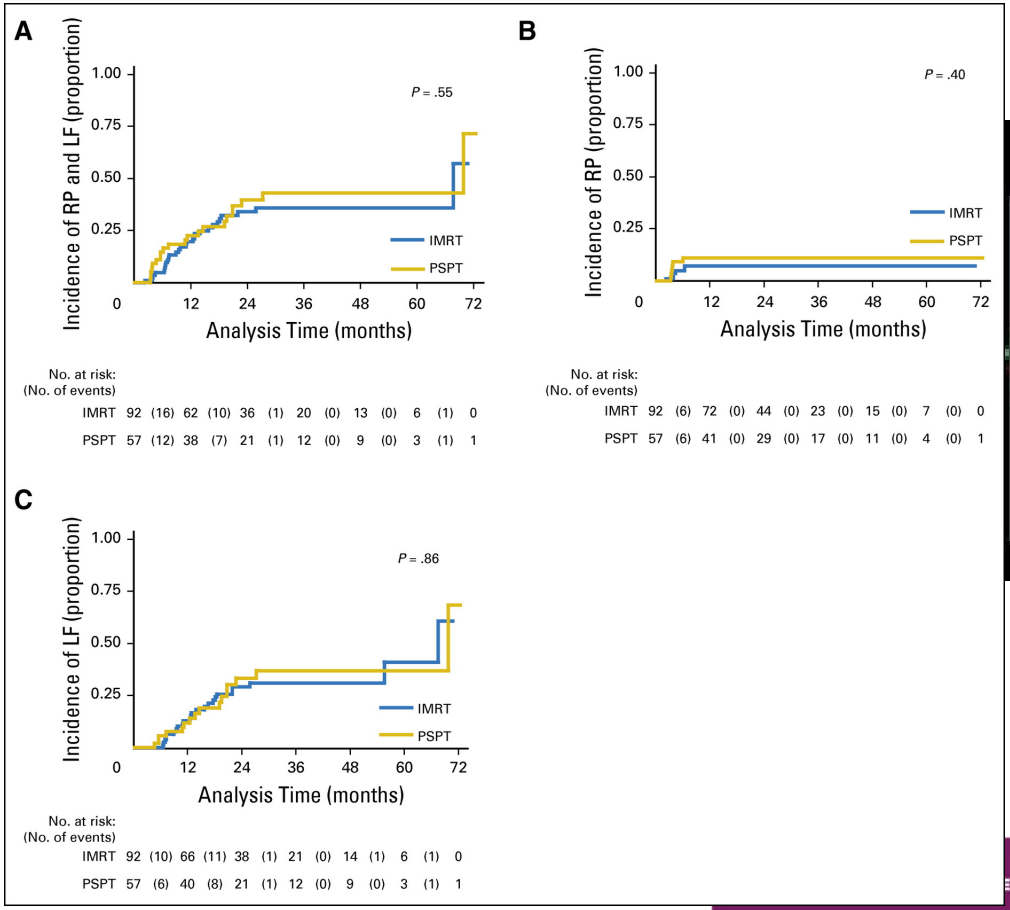
Novel technology?



Skinner et al., Sem Rad Onc , 2011

Novel technology?

- Locally advanced unresectable NSCLC
- Chemoradiation up to 74 Gy
- Randomized to IMRT vs protons
- Many patients not treated per arm



Sio et al. IJROBP, 2016; Liao et al. JCO, 2018

Novel technology?

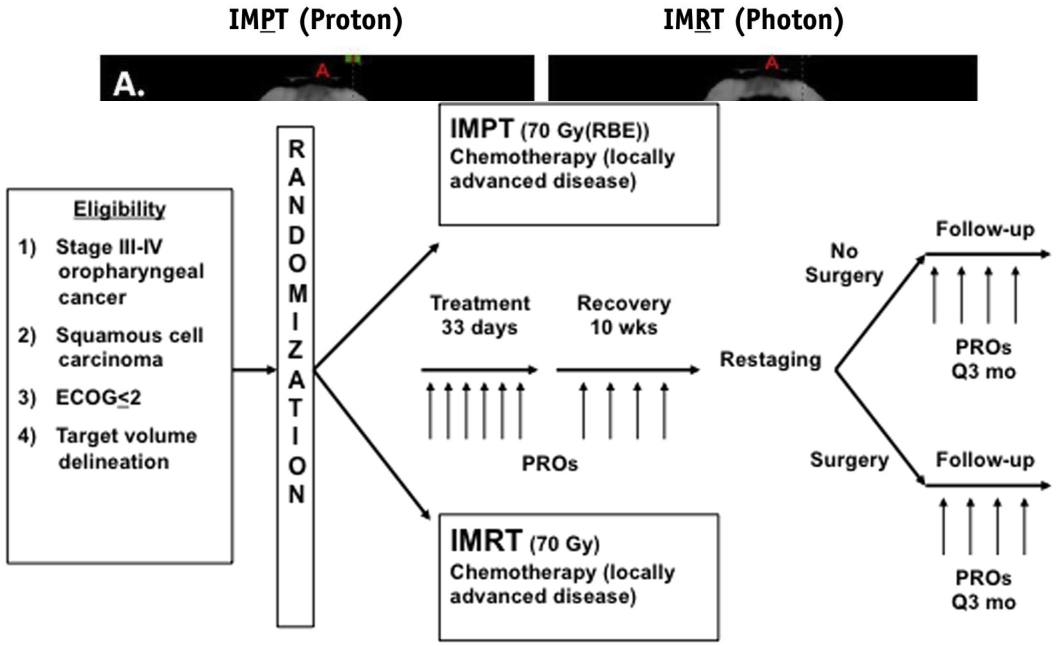
- RTOG 1308: Phase III Randomized Trial Comparing Overall Survival After Photon Versus Proton Chemoradiotherapy for Inoperable Stage II-IIIB NSCLC
- 70 Gy (if constraints met)
- Adjuvant I/O allowed

SCHEMA (15-MAR-2018)

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 ***

Novel technology?

- Intensity modulated PROTON therapy
- Phase III (now)
- Non-inferiority trial for 3 yr PFS with multiple secondary endpoints



Sio et al. IJROBP, 2016; Liao et al. JCO, 2018

Conclusions

- Much room to improve
- Unclear the best setting (or best agent) to use with I/O + radiation in the definitive setting
- Irradiation of a single site may not be sufficient to support I/O response
- The role of protons is unclear in these tumors

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Thank you!!!!!

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