Immunotherapy Killed the IGRT Star: Integrating Radiotherapy Into Systemic Therapy for Metastatic Disease

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AAPM 2019

Disclaimer

- **Spouse**: Medical Oncologist & Medical Director for Oncology Products at Astellas Pharmaceutical
- ReflexXion Medical Systems

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40 Minute Outline

- Expanding the role of radiotherapy for:
  - Local therapy for ***Limited*** (Oligometastatic) Disease
- What is immunotherapy? A Primer
- Can Radiotherapy Enhance Immunotherapy?
  - Local Therapy for ***Widespread*** Disease (polymetastatic) with Immunotherapy be a new paradigm?

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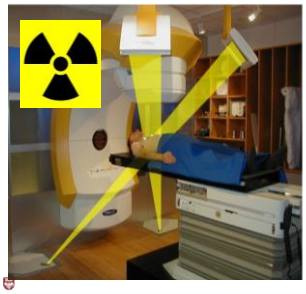
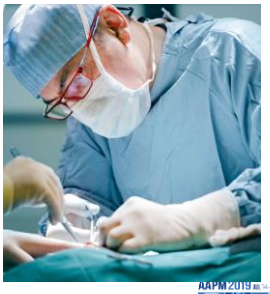
Radiotherapy for metastatic Disease

The Clinical Problem of Metastasis

- Metastasis accounts for 85-90% of cancer mortality
- Regarded as *widely disseminated* and *incurable* in adult solid tumors
- Treated with systemic therapies: *usually not curative*





Overarching Clinical Question:

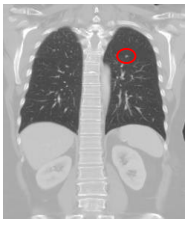
How can we cure more patients with metastatic disease?

Oligometastasis Hypotheses and Characteristics

- Metastasis represents a *spectrum* of disease:
  number of metastases/organs involved/pace of progression
- Subsets of patients with limited (oligometastatic)disease are *potentially curable* with *metastasis-directed therapies (SBRT)*
- *Cytoreduction* with could synergize with systemic agents to improve outcomes

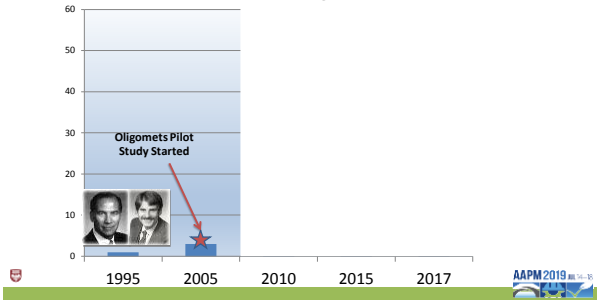
Spectrum of Metastatic Disease

Limited Spread (Oligometastasis)
1-5 Metastases



Widely Disseminated
(Polymetastases)

Pubmed Results: Interest in Oligometastasis over time



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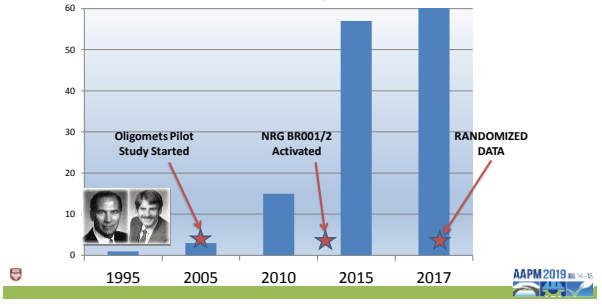
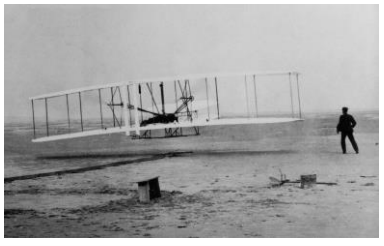


What have we learned?



Oligometastases exist and are common

Many claim to see them….

Oligometastatic Patients *Exist*…
Breast Cancer

Table 1. Frequency of Patients Enrolled on First-Line Metastatic Breast Cancer Trials With a Limited Number of Metastatic Sites Who Appear Potentially Eligible for Ablative Therapy

First Author	Phase	n	ER/PR + (%)	HER2+	≤ 2 Met sites (%)	≤ 4 Met Sites (%)	Arms	PFS (mo)
Albain 2008[54]	II	599	32	—	57	91	1. Gem + Paclitaxel	9.89
							2. Paclitaxel	8.4
Bergh 2012[55]	III	593	72	Pos	52	—	1 Sunitinib+ Docetaxel	8.6
							2. Docetaxel	8.3
Tawfik 2013[56]	II	30	77	Neg	50	—	1. Vinorelbine, capecitabine	8.6*
Hurvitz 2013[57]	IIR	137	54	Pos	49.3	—	1. Trastuz + Docetaxel	9.2
							2. T-DM1	14.2
Gianni 2013[58]	III AVEREL	424	51	Pos	50	—	1. Docetaxel+ Trastuz	13.7*
							2. Docet + Tras + BEV	16.5
Sledge 2003[59]	III E1193	739	45	—	49	—	1. Doxorubicin	6*
							2. Paclitaxel	6.3*
							3. Doxorubicin + Paclitaxel	8.2*

*Time to failure.
Abbreviations: ER/PR, estrogen receptor/progesterone receptor; met sites, metastatic sites; PFS, progression-free survival; Pos, positive; Neg, negative; Gem, gemcitabine; T-DM1, trastuzumab emtansine; Docet, docetaxel; Tras, trastuzumab; BEV, bevacizumab.

50% have <4 sites of metastases at diagnosis

Salama, et al. Seminars Oncology 2014

Patients with oligometastases have *indolent disease*:
Metastatic Breast Cancer Patients

Multivariate Analysis of Prognostic Factors in Metastatic Breast Cancer

By G. N. Hortobagyi, T. L. Smith, S. S. Legha, K. D. Swenerton,* E. A. Gehan, H.-Y. Yap, A. U. Buzdar, and G. R. Blumenschein

- 1.7% of 1,581 patients remained alive/ complete remission >10 year
- 619 patients treated with anthracycline chemo
- Minimum f/u 4 years

Table 7. Regression Model Relating Survival to Pretreatment Characteristics

Characteristics	Regression Coefficient	Significance Level of Entry	Relative Risk		
			Favorable	Unfavorable	Ratio U/F
LDH	0.362	<0.01	0.83	1.70	2.0
Performance status	0.281	<0.01	0.81	1.41	1.7
Lung	0.470	<0.01	0.88	1.42	1.6
Prior radiotherapy	0.302	<0.01	0.76	1.40	1.8
Alkaline phosphatase	0.188	<0.01	0.83	1.43	1.7
Extent of disease	0.154	<0.01	0.80	1.26	1.6

NOTE. Favorable risk was LDH ≤ 225, performance status 0–1; lung not involved; no prior radiotherapy; alkaline phosphatase ≤ 85; and extent of disease ≤ 5. Unfavorable risk was LDH > 450; performance status 3–4; lung involved; prior radiotherapy > 3; alkaline phosphatase > 350; and extent of disease > 20.

Hortobagyi, et al. JCO 1985 Vol 3a (12):1776

Patients with oligometastases have ***indolent disease***:
Metastatic Breast Cancer Patients

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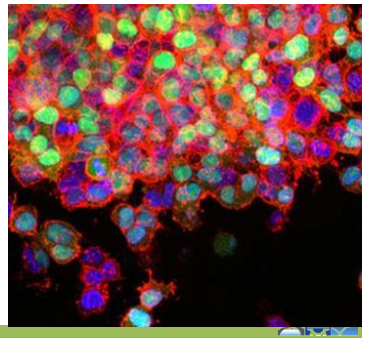
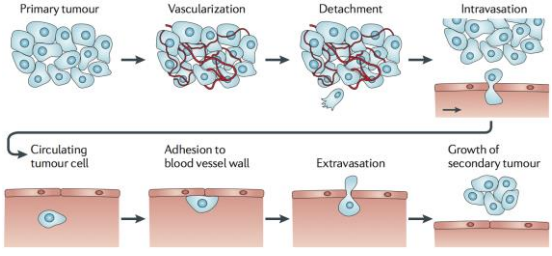
Hortobagyi, et al. JCO 1988; Vol. 6 (3): 776

A Biologic Basis exists:

Metastatic disease evolves



Intravasation, Survival, Extravasation

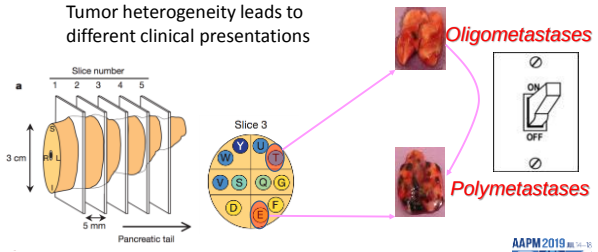


Caveat: known to be an inefficient process; not **"everywhere, always"**

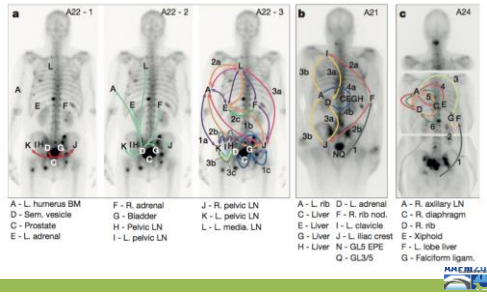
Wirtz D. et al. Nat Rev Cancer. 2011; 11: 387-395

Clonal heterogeneity of primary tumors and selection of secondary tumors -> types of metastases

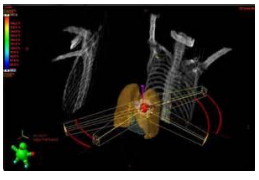
Tumor heterogeneity leads to different clinical presentations



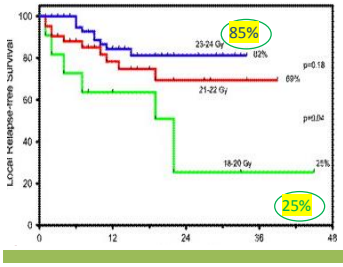
Darwinian Evolution: (Human) Metastasis-to-Metastasis



Intensified Treatments and ***integration*** with systemic therapy leads to ***Improved outcomes***



SPINE SBRT: Dose Matters (Single Fraction)

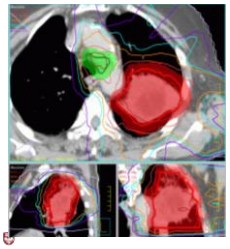


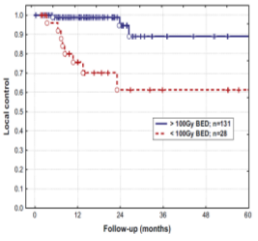
23-24Gy (Ablative)

18-20Gy (Homeopathic)

McCammon, IJROBP 2009; Greco, IJROBP 2009

SBRT: Dose Matters (Lung mets)





>100 BED

<100 BED

Onishi, J of Thorac Onc 2007; Guckenberger, IJROBP 2010

NRG ONCOLOGY

Advancing Research. Improving Lives.™

NRG-BR001: A Phase 1 Study of Stereotactic Body Radiotherapy (SBRT) for the Treatment of Multiple Metastases

Steven J Chmura, MD, PhD[1], Kathryn A Winter, MS[2], Joseph K Salama, MD[3], Clifford Robinson, MD[4], Thomas M. Pisansky, MD[5], Virginia Borges, MD[6], Hania Al-Hallaq, PhD[1], Martha Matuszak, PhD[7], Sean S Park, MD[5], Victor Gonzalez, MD[8], Yasmin Hasan, MD[1], Jose Bazan, MD[9], Philip Wong, MD[10], Harold A Yoon, MD[11], Janet K Horton, MD[3], Gregory N Gan, MD PhD[12], Michael T Milano, MD, PhD[13], Elin Ruth Sigurdson, MD[14], Jennifer Moughan, MS[2], Julia White, MD[9]

[1] University of Chicago Comprehensive Cancer Center; [2] NRG Oncology Statistics and Data Management Center/ACR; [3] Duke University Medical Center; [4] Washington University in St. Louis; [5] Mayo Clinic; [6] University of Colorado – Anschutz Medical Center; [7] University of Michigan; [8] University of Arizona Medical Center – University Campus; [9] Ohio State University Comprehensive Cancer Center; [10] Centre Hospitalier de l'Université de Montréal; [11] Heartland Cancer Research NCORP; [12] University of New Mexico Comprehensive Cancer Center; [13] University of Rochester; [14] Fox Chase Cancer Center

ASTRO Annual Meeting: 10/24/2018

NRG BR001: Treat Multiple Sites in the Lung

NRG-BR001
ClinicalTrials.gov NCT02206334

A Phase 1 Study of Stereotactic Body Radiotherapy (SBRT) for the Treatment of Multiple Metastases

- Hypothesis: 3-4 or 2 anatomically close metastases can be safely treated with established SBRT doses
- Primary Objective: To determine the recommended SBRT dose for each of the metastatic locations
- Inclusion: Metastatic NSCLC, Breast and Prostate patients
- Sample size: 42-84 patients

COMPLETED ACCRUAL 1/2018!!!

Table 6-1 — BED >100

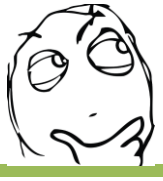
Metastatic Locations	Prescription Doses Initial Starting Dose
Lung--Peripheral	45 Gy (3 fractions)
Lung—Central	50 Gy (5 fractions)
Mediastinal/Cervical Lymph Node	50 Gy (5 fractions)
Liver	45 Gy (3 fractions)
Spinal/Paraspinal	30 Gy (3 fractions)
Osseous	30 Gy (3 fractions)
Abdominal-pelvic metastases (lymph node/adrenal gland)	45 Gy (3 fractions)

Protocol Specified DLTs - None

Metastatic Location	#Enrolled for DLT Assessment	#Evaluable for DLT Assessment	#DLTs
Bone/Osseous Starting Dose	8	6	0
Spinal/Paraspinal Starting Dose	7	6	0
Peripheral Lung Starting Dose	7	6	0
Abdominal-pelvic Starting Dose	9	7†	0
Central lung Starting Dose	8	7†	0
Liver Starting Dose	9	5	0
Mediastinal/Cervical Starting Dose	7	6	0

†The DLT analysis was based on the first 6 of these 7 patients.

…But Do These Treatments Help?



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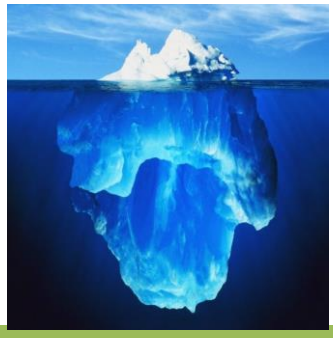
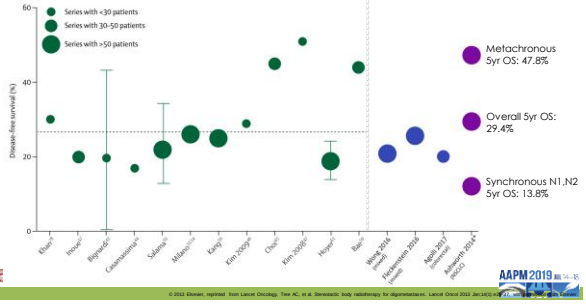
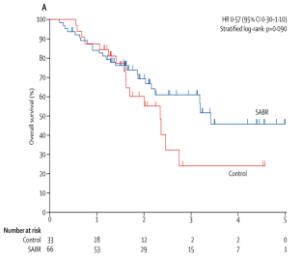


Metastasis-directed treatment and Survival



COMET:
SBRT *Improves Survival* (Phase II)



Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial

David A Palma, Robert Olson, Stephen Harrow, Stewart Gaede, Alexander M Louie, Cornelis Haasbeek, Liam Mulroy, Michael Lock,

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Radiation for (limited) metastatic disease

- Clinical presentation of Oligometastases is common, Biologic evidence exists that drives the clinical phenotype
- **SBRT Dose Matters: BED >100 for control of oligometastases**
- Randomized data ->***with ablative techniques improves PFS and OS***
- Ongoing trials will answer whether local ablative therapy with surgery or (real) SBRT improves OS in specific disease types

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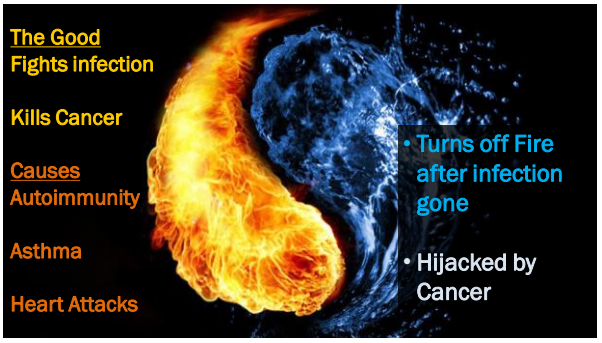
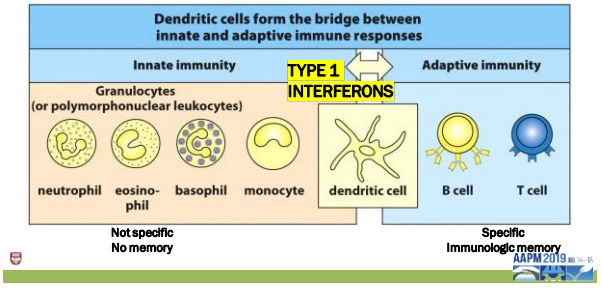
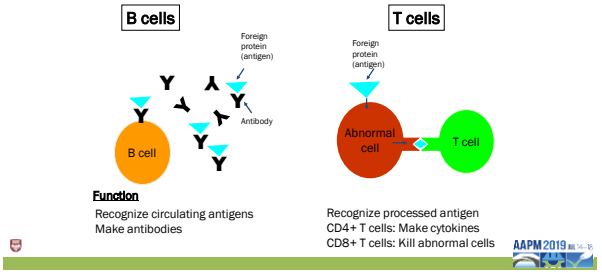


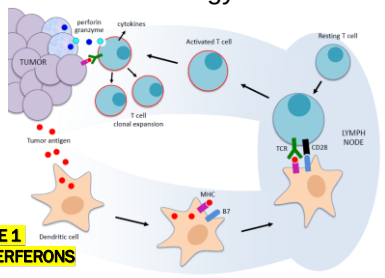
Innate and Adaptive Immunity



Function of Adaptive Immunity

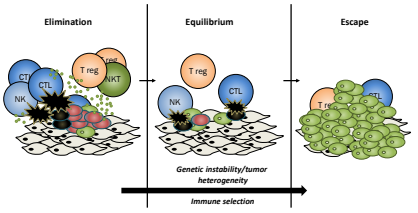


Tumor Immunology: Overview



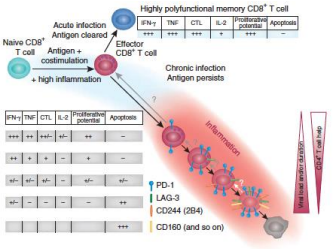
Courtesy of Scott Gettinger, MD, Yale.

The Immunoediting Hypothesis: Shaping Tumor Development



Dunn, et al. Nat Immuno. 2002
Schreiber, et al. Science. 2011
Mittal, et al. Curr Opin Immunol. 2014

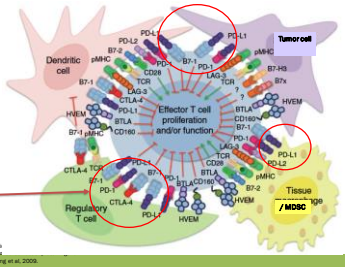
T-Cell Exhaustion During Chronic Antigen Exposure



Wherry, 2011.

***Science* names "Cancer Immunotherapy" the "Breakthrough of the Year" for 2013.**

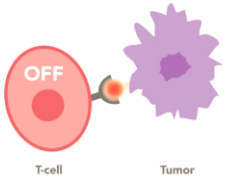
Targeting The ICE: Immune Checkpoints in the Tumor Microenvironment



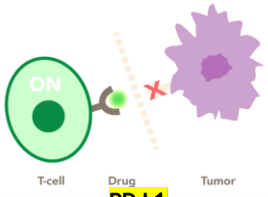
CTLA-4, cytotoxic T-lymphocyte antigen-4; PD-L1, programmed death ligand-1.
Pentcheva-Hoang, et al. 2009.

How Does Immunotherapy Work?

Tumor cells bind to T-cells to deactivate them

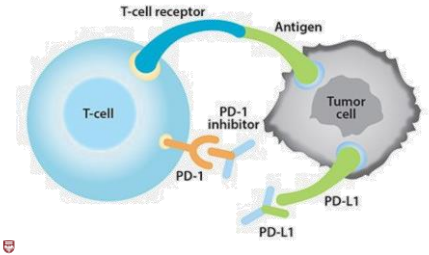


Immunotherapy drugs can block tumor cells from deactivating T-cells



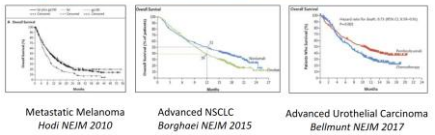
PD-L1

Targeting PD-L1: Our best target so far



Opdivo
pembrolizumab
Keytruda
nivo
Durvelamab

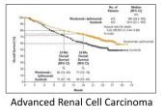
Immunotherapy (PD-L1) works



Metastatic Melanoma
Hodi NEJM 2010

Advanced NSCLC
Borghaei NEJM 2015

Advanced Urothelial Carcinoma
Bellmunt NEJM 2017



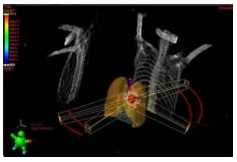
Advanced Renal Cell Carcinoma
Motzer NEJM 2018

15%-20% responders

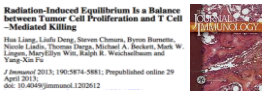
Immune System Background Summary

- Immune system balancing attack **(Fire/Hot)** with Suppression **(Cold)**
- Immune system has innate (nonspecific) and adaptive (specific) elements
- The persistence of cancer leads to immune dysfunction and **Exhausting T-Cells that mount the response!**
- Immune checkpoints and features of tumor microenviroment ***are targets for drug development***

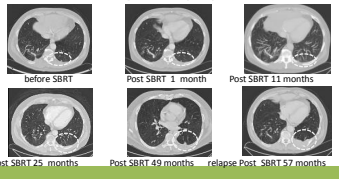
Does the Immune System Augment Stereotactic Body RadioTherapy (SBRT)?



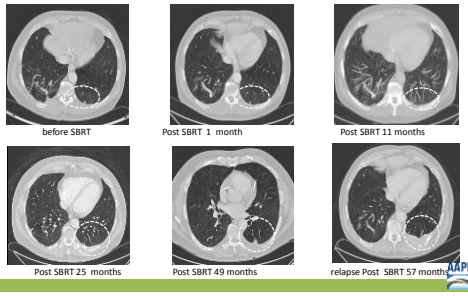
Radiation-Induced Equilibrium Is a Balance between Tumor Cell Proliferation and T Cell–Mediated Killing



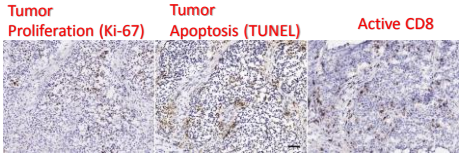
RT-induced dormancy can relapse years later

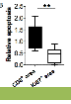


Radiation-Induced Equilibrium Is a Balance between Tumor Cell Proliferation and T Cell–Mediated Killing



Radiation-induced tumor equilibrium (RITE) is a balance between cell birth (Ki67 positive), and cell death (TUNEL positive), mediated principally by CD8⁺ T cells.

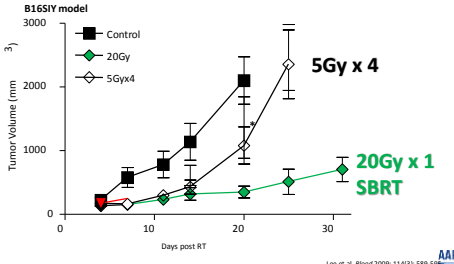




Apoptosis co-localized with CD8⁺ cells in Stable Tumors

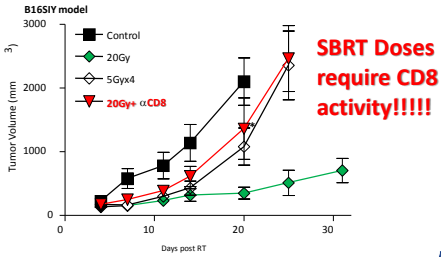
Liang H, Deng L et al. *J Immunol*. 2013; 190(11):5874-5881.

Depleting CD8 cells reduces SBRT Tumor Killing



Lee et al. *Blood* 2009; 114(3): 589-595

Depleting CD8 cells reduces SBRT Tumor Killing



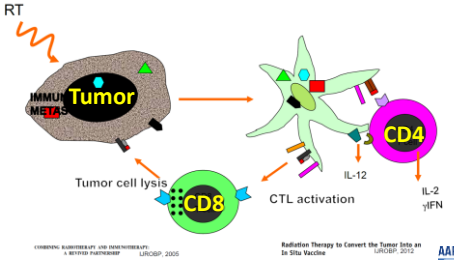
Lee et al. *Blood* 2009; 114(3): 589-595

Immune System augments SBRT

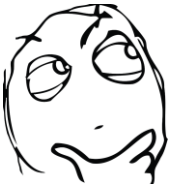
- Tumor cells and immune system evolve and escape
- CD8+ T cells Cells Contribute to SBRT tumor cell killing and can ***lead to lasting immunity***
- **Opportunity: Immunotherapy to Improve Radiotherapy and local control**

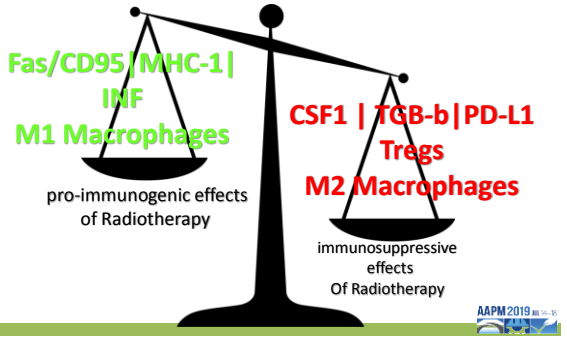
Can Radiotherapy Augment the immune response?

ABSCOPAL: IN SITU VACCINATION HYPOTHESIS



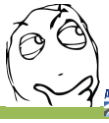
Why is **AB**scopal so rare?



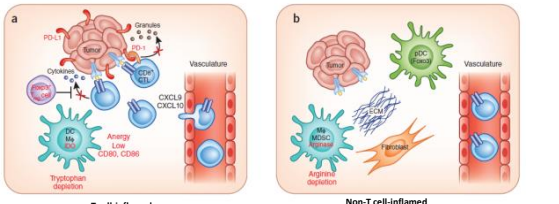


Given so many potential options, is there a way to rationally guide immunotherapy

And radiation development?



Working model: immunobiology of T cell-inflamed and non-inflamed tumor microenvironment



T cell-inflamed

- $CD8^+$ T cells, Type I IFN signature, High mutational burden, PDL-1 positive, Chemokines,
- Immune escape: Inhibitory pathways
- ***Most immunotherapy responders have this phenotype***

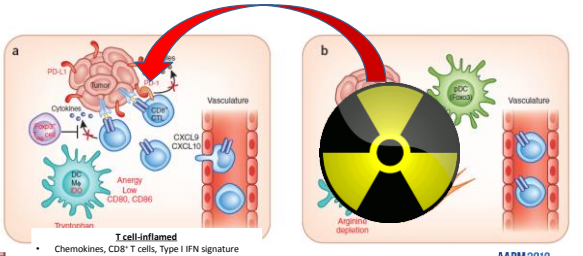
Non-T cell-inflamed

- Low inflammatory signature, absent intratumoral $CD8^+$ T cells
- Immune escape: T cell exclusion

Most patients are this type

Gajewski *et al.* Nature Immunol. 2013

Radiation Converts tumors to Inflamed Phenotype: Therapeutic Potential?



T cell-inflamed

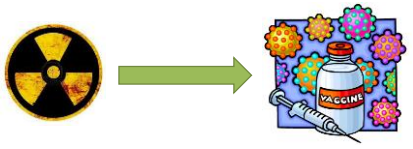
- Chemokines, $CD8^+$ T cells, Type I IFN signature
- Immune escape: Inhibitory pathways

Gajewski *et al.* Nature Immunol. 2013

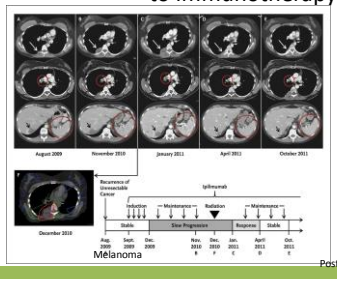
If we can see it, we can Study it…

Abscopal Clinical Data and Design

Treat **One** site hope for Vaccine effect



Abscopal: SBRT overcomes resistance to Immunotherapy



Melanoma

Melanoma ***progressing*** on IPI

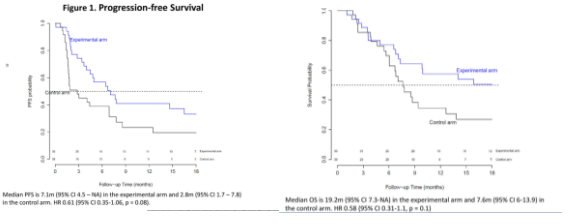
Single Site Progress

SBRT

Systemic Clearing

Postow et al. 2012. NEJM

Randomized phase II study of anti-PD-1 alone vs. anti-PD-1+SBRT in patients with **advanced NSCLC** (n=64)

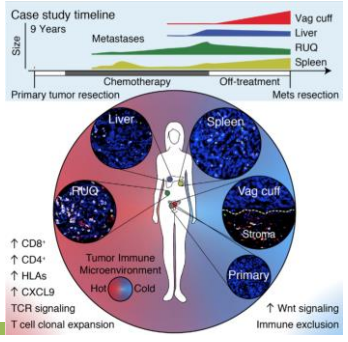


- Median PFS was **1.8** months in the PD-1 alone arm vs 6.4 months in the PD-1+SBRT arm

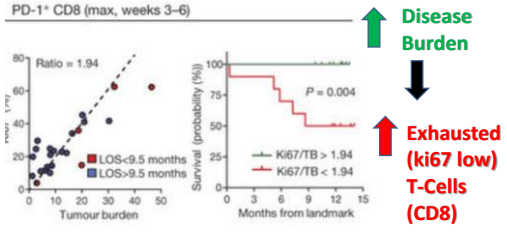
ASCO 2018 abstract: Theelan W, et al. (Netherlands

Barriers to a Better Response? … Opportunities

Heterogenous Tumor-Immune Microenvironments among *Differentially growing* metastases



Large Tumor Burden -> Poor αPD1 response



Disease Burden

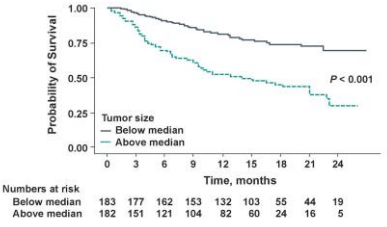
Exhausted (ki67 low) T-Cells (CD8)

Objective response rate for Ki67 versus tumor burden by LOS (left) (n = 18). Kaplan-Meier OS for high vs. low post-treatment Ki67 expression to tumor burden (right).

Huang et al. 2017. nature

Disease Burden Impacts Response

Figure 2. Kaplan-Meier estimates of OS by tumor size at baseline.



Melanoma cohort of Keynote-001 Joseph et al. Presented at ASCO 2014

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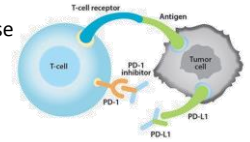
Who responds *BEST* to immunotherapy?

Immunologically **"Hot"** or **"Inflamed"** tumors

- Patients with small volume disease
- Tumors that are PDL-1 positive
- Tumor with high mutational burden



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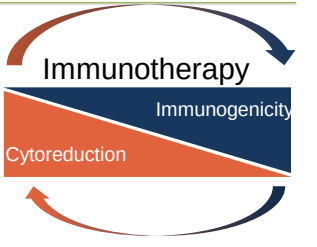
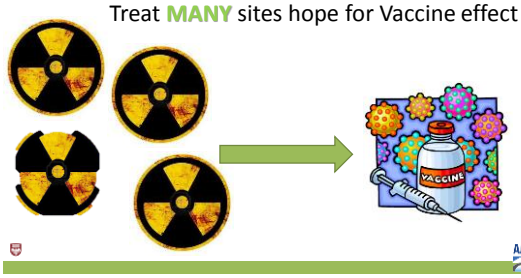
Hypothesis: **Potentiation** of Immunotherapy and combination w/RT

- **Potentiation** of immunotherapy and combination with XRT ***produce T-cell inflamed phenotype "HOT"***
- **Cytoreduction → relieve** immune suppression and overcome heterogeneity



MOSART Clinical Data and Design

Treat **MANY** sites hope for Vaccine effect



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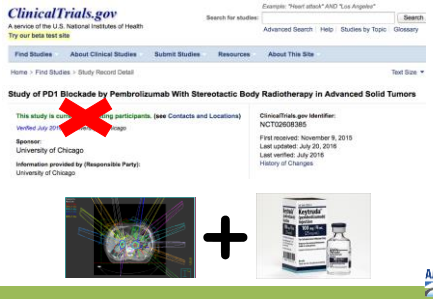
iMOSART (SBRT+PEMBRO)



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Treatment Related Severe Dose-Limiting Toxicity (DLTs) by Anatomic Cohort

	Anatomic Cohort							
	Lung-Peripheral	Lung-Central	Med/Thoracic	Liver	Spinal	Osseous	Abd/Pelvic	Total
Dose limiting toxicity events (ratio)	1/12	2/11						
Toxicity for cohort patients evaluable at 3 months (ratio, percent)	1/12 (8.3%)	2/10 (20.0%)						6/62 (9.7%)

6/73

- Median follow-up for trea … 3.1)
- 62 patients with at least 3 …
- All pts who experienced D …
- 3/6 had both lesions in the same anatomic locations and 3/6 pts had lesions treated in separate anatomic locations

–No SBRT dose reductions

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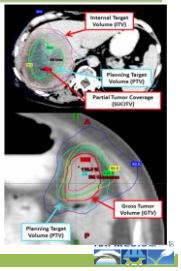
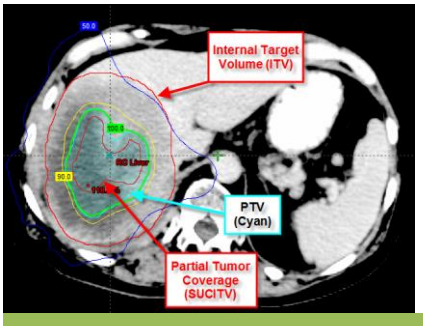
Systemic
Therapy
Augments
Radiotherapy?

IGRT not needed: Partial Tumor Radiation

- 17/68 patients (21 lesions) had at least one lesion larger than 65cc and least one imaging follow-up
- Median initial gross tumor volume (GTV)
  - Partially irradiated: **116.6cc** (IQR 90.7-219.7cc)
  - Completely irradiated: **7.2cc** (IQR 2.6-14.8cc)





Median coverage:
20% isodose line
IQR 7%-51%

Results

Characteristic	Complete-Rx (118 Mets)	Partial-Rx (21 Mets)
Treated Metastasis Location		
Abdomen/Pelvis	17 (14.4%)	9 (42.9%)
Liver	12 (10.2%)	8 (38.1%)
Lung-Central	21 (17.8%)	2 (9.5%)
Lung-Peripheral	30 (25.4%)	0 (0.0%)
Mediastinum/Cervical	14 (11.9%)	1 (4.8%)
Osseous	12 (10.2%)	0 (0.0%)
Spinal	12 (10.2%)	1 (4.8%)
★ **Largest Treated Tumor Volume (cubic ccs), Mean (SD)**	12.8 (14.8)	157.6 (95.7)
★ **Dose to OARs (Minimum BED_3), Mean (SD)**	222.8 (93)	42.4 (59.3)
★ **Dose to Tumor (Minimum BED_{10}), Mean (SD)**	95.0 (35.3)	23.8 (25.8)

Results

Characteristic	Complete-Rx (118 Mets)	Partial-Rx (21 Mets)
Largest Treated Tumor Volume (cubic ccs), Mean (SD)	12.8 (14.8)	157.6 (95.7)
Dose to OARs (Minimum BED_3), Mean (SD)	222.8 (93)	42.4 (59.3)
Dose to Tumor (Minimum BED_{10}), Mean (SD)	95.0 (35.3)	23.8 (25.8)

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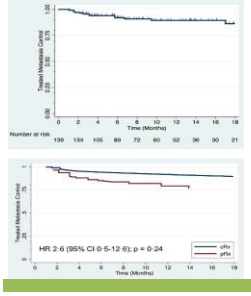
Results: Treated Metastasis Control (TMC)



- 1-yr TMC – 89.5%
- No difference between Complete-Rx vs Partial-Rx Despite:
  - V95% of 67.2% (Partial-Rx) vs 100% (Complete-Rx)
  - Minimum BED_{10} of 23.8 Gy (Partial-Rx) vs 95.0 Gy (Complete-Rx)

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Systemic

Therapy

Augmented by

Radiotherapy?

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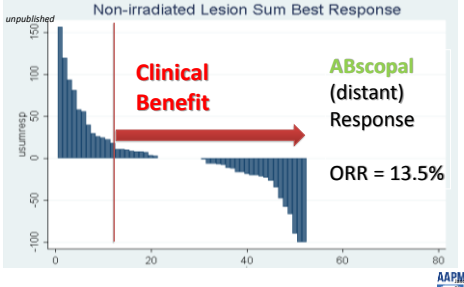
ABscopal (non-irradiated) RECIST response



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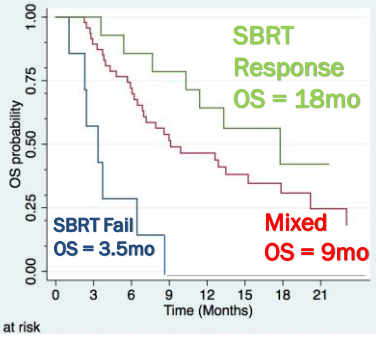
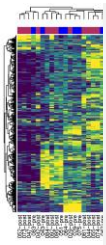
No difference for Partial vs Complete Tumors

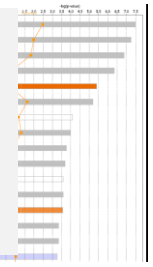


Number at risk

post-SBRT biopsies: Unsupervised 2-way hierarchical clustering -> Innate + Adaptive Immunity, *ACROSS* histologies



- Type-1 Interferon
- Immunе function
- DNA repair

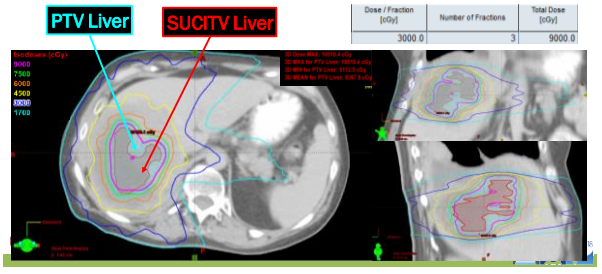


Radio-immunotherapy Platform to test for *specific* Hypotheses

The RIT™ Pipeline

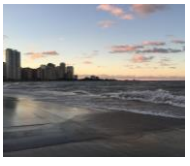
			8 Disease Sites				
	Breast Cancer (M1)		NSCLC (M1)	Small cell (M1)		Pancreases (M1)	
	Pre-op Rectal		Pre-op Esophogus	GBM recurrent		Merkel (M1)	
CodeName	Phase I	R/NI	Type	LOI Submitted	Accepted	Activated	Accrual Start
iMOSART	X, n=82		SBRT+αPD1 any solid tumor				Completed
POSTER	X, n=110	X	SBRT+αPD1 any solid tumor				June 2017
BAD4BAT	X, n=42		SBRT+αPD1 >5cm tumors				Dec 2017
COSINR	X, n=81	X	Randomized SBRT+αPD1+αCTLA4 1st line NSCLC				Nov 2017
Alliance 09156	X, n=100	X	Randomized SBRT+αPD1 1st line Merkel				Jan 2018
NRG BR001/2	X, n=423	x	Randomized SBRT for Breast Cancer Oligomets				Dec 2014
C4-MOSART	X, n=82		SBRT+αPD1+ (41bb or CSF1r) any solid tumor				Mar 2018
ADVISE	X, n=123		Personalized IO: αPD1+ 7 novel agents (SBRT 7th agent) after Pd1 progression				Mar 2018
SBRT IDOx2	X, n=80		SBRT + dual IDO blockade				
HCC SBRT	X n=50		SBRT+αPD1+αCTLA4 HCC				Oct 2017

Project ICARUS



Courtesy of Sam Mazin PhD, Julien Partouche PhD, and Angela Del Savio PhD

Conclusions



- SBRT may improve survival in Oligometastases with **High Doses** (BED >100)
- Best responders to immunotherapy (minority) have ***low disease low tumor burden, Type 1 INF PDL-1 positive (checkpoints),*** and high ***Tumor Mutational Burden***
- SBRT modulates immune pathways through Type-1 Interferon, Innate and Adaptive immune function, and DNA repair
- SBRT may turn patients from **"cold"** to **"hot"** and respond to immunotherapy -> Immunotherapy may improve local control **assuming some portion receives high BED** (NRG BR001/BR002/Lu002)

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Acknowledgments





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Dr. Salama
Dr. Al-Hallaq
Dr. Luke
Dr. Patel

University of Chicago Radiation Oncology Residents