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Clinical Development of Drug-Radiotherapy Combinations

February 22-23, 2018 | Bethesda, MD

@FDAOncology @AACR @ASTRO_org @CR_UK

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Introduction

Phuoc T. Tran, MD, PhD
David G. Kirsch, MD, PhD

Targeting Molecular Pathways to Optimize Radiation and Drug Combinations

David Kirsch MD, PhD

Barbara Levine University Professor

Duke Cancer Institute
A National Cancer Institute-designated Comprehensive Cancer Center

DUKE UNIVERSITY SCHOOL OF MEDICINE
Department of Radiation Oncology
radonc.duke.edu

PHARMACOLOGY & CANCER BIOLOGY

Disclosures

- Scientific Advisory Board: Lumicell Inc.
- Stockholder in: Lumicell Inc., X-RAD Therapeutics
- Research Support from: Eli Lilly, X-RAD Therapeutics, and Merck
- Patent: co-inventor (US patent 8,983,581) of an imaging device

64TH ANNUAL RRS MEETING (2018)

OPEN

Clinical development of new drug–radiotherapy combinations

Ricky A. Sharma[1], Ruth Plummer[2], Julie K. Stock[3], Tessa A. Greenhalgh[4], Ozlem Ataman[5], Stephen Kelly[6], Robert Clay[7], Richard A. Adams[8], Richard D. Baird[9], Lucinda Billingham[10], Sarah R. Brown[11], Sean Buckland[6], Helen Bulbeck[12], Anthony J. Chalmers[13], Glen Clack[14], Aaron N. Cranston[15], Lars Damstrup[16], Roberta Ferraldeschi[17], Martin D. Forster[1], Julian Golec[18], Russell M. Hagan[19], Emma Hall[20], Axel-R. Hanauske[21], Kevin J. Harrington[20], Tom Haswell[12], Maria A. Hawkins[4], Tim Illidge[22], Hazel Jones[3], Andrew S. Kennedy[23], Fiona McDonald[20], Thorsten Melcher[24], James P. B. O'Connor[22], John R. Pollard[18], Mark P. Saunders[22], David Sebag-Montefiore[11], Melanie Smitt[25], John Staffurth[8], Ian J. Stratford[22] and Stephen R. Wedge[2] on behalf of the NCRI CTRad Academia-Pharma Joint Working Group

CONSENSUS STATEMENT

- Approximately 60% of cancer patients receive radiation therapy as part of their treatment
- 40% of cancer cures include the use of radiotherapy
- Can be one of the most cost-effective cancer therapies

Sharma RA et al, Nature Reviews Clinical Oncology 2016

VOLUME 32 · NUMBER 26 · SEPTEMBER 10 2014

JOURNAL OF CLINICAL ONCOLOGY

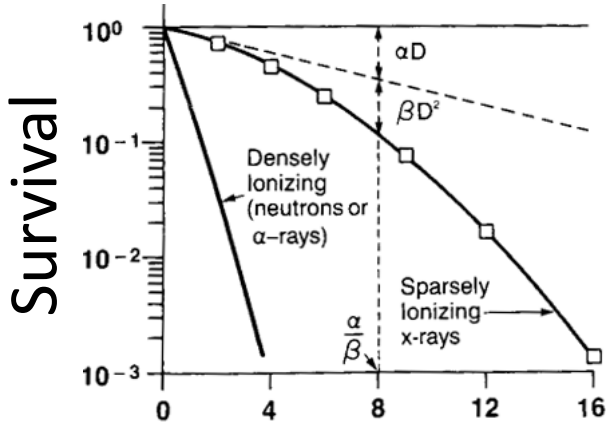
E D I T O R I A L

Enhancing the Efficacy of Radiation Therapy: Premises, Promises, and Practicality

C. Norman Coleman, *National Cancer Institute, Bethesda, MD*
Theodore S. Lawrence, *University of Michigan School of Medicine, Ann Arbor, MI*
David G. Kirsch, *Duke University School of Medicine, Durham, NC*

Premises

- Radiation therapy is a spatially focused therapy
- Accurate radiation dosimetry to tumor and normal tissues
- Radiation is very potent in killing cancer cells
- Success is measured by increasing local control or survival



In Vitro

Coleman CN et al, Journal of Clinical Oncology 2014

Curing Cancer Requires Killing Many Logs of Cells

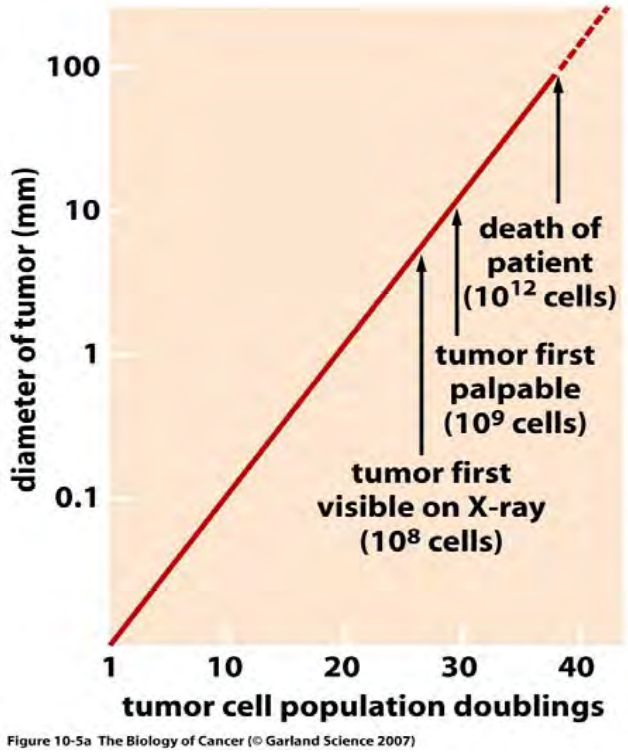
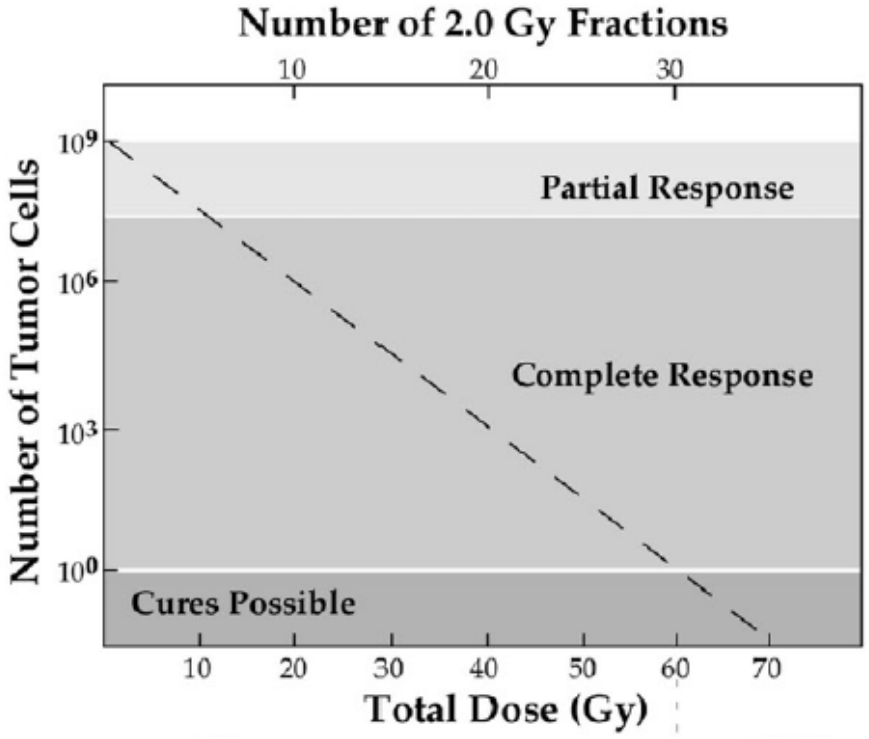


Figure 10-5a The Biology of Cancer (© Garland Science 2007)



Courtesy of Elaine Zeman, PhD

OXFORD

REVIEW

The Future of Radiobiology

David G. Kirsch, Max Diehn, Aparna H. Kesarwala, Amit Maity, Meredith A. Morgan, Julie K. Schwarz, Robert Bristow, Sandra Demaria, Iris Eke, Robert J. Griffin, Daphne Haas-Kogan, Geoff S. Higgins, Alec C. Kimmelman, Randall J. Kimple, Isabelle M. Lombaert, Li Ma, Brian Marples, Frank Pajonk, Catherine C. Park, Dörthe Schaue, Eric J. Bernhard

Areas of Current and Future Focus for Radiation Research

- Modulating DNA Damage Response to Increase Radiosensitivity of Tumors
- Minimizing Radiation Toxicity to Normal Tissues/Stem Cells
- Metabolism
- Cancer Stem Cells
- Tumor Microenvironment
  - Combining Radiotherapy with Immunotherapy
  - Hypoxia, Tumor Vasculature
  - Extracellular Matrix and Physical-Mechanical Properties of Tumors
- Predictive Biomarkers

JNCI J Natl Cancer Inst (2018) 110(4): djx231

doi: 10.1093/jnci/djx231
First published online November 3, 2017
Review

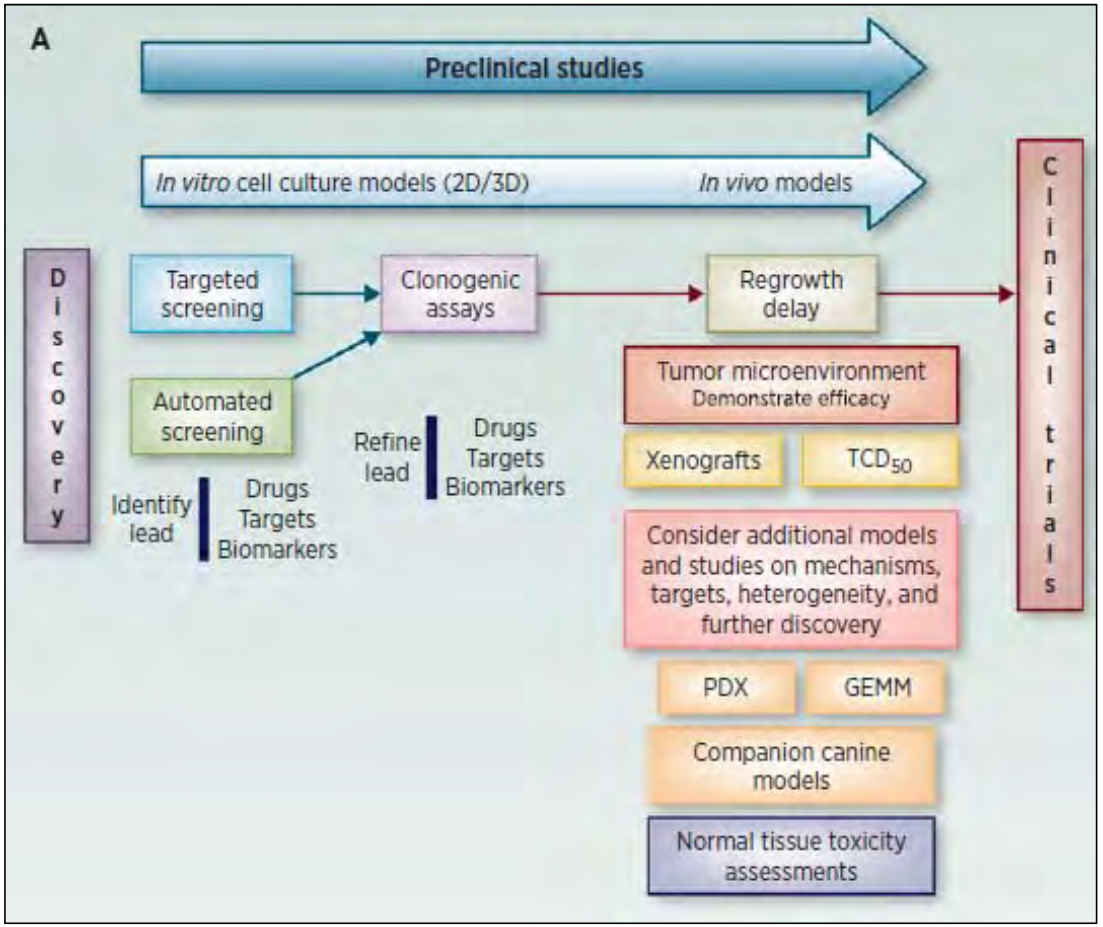
Kirsch DG et al, Journal of the National Cancer Institute 2018

Review

Clinical Cancer Research

Improving the Predictive Value of Preclinical Studies in Support of Radiotherapy Clinical Trials

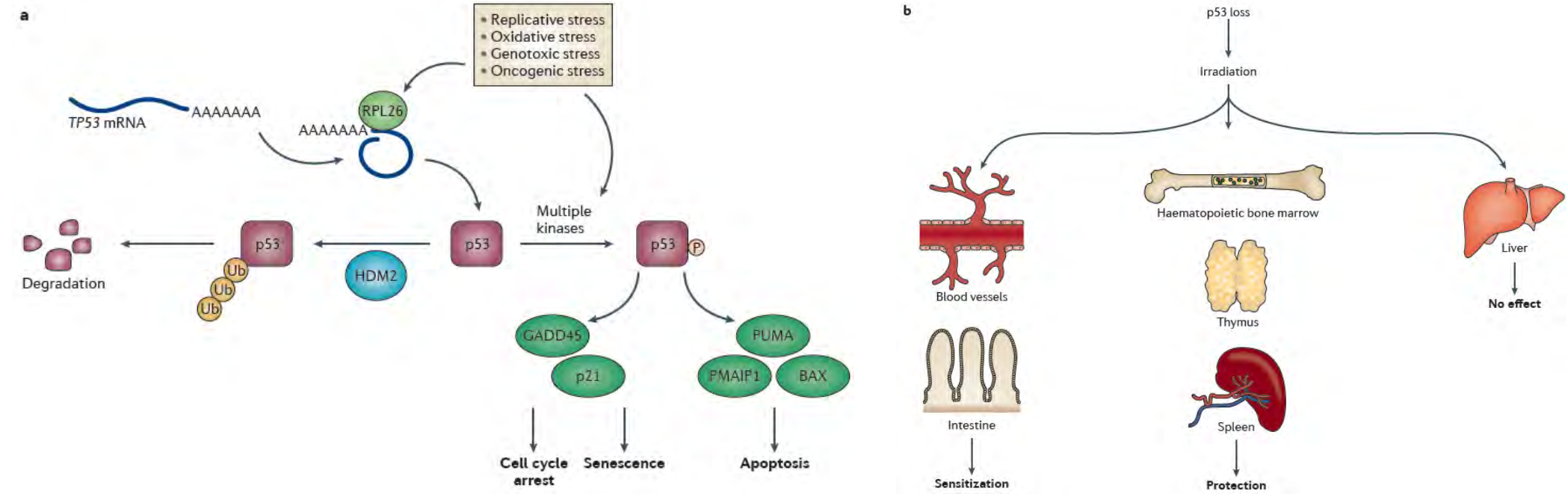
C. Norman Coleman[1], Geoff S. Higgins[2], J. Martin Brown[3], Michael Baumann[4], David G. Kirsch[5], Henning Willers[6], Pataje G.S. Prasanna[1], Mark W. Dewhirst[7], Eric J. Bernhard[1], and Mansoor M. Ahmed[1]



Coleman CN et al, Clinical Cancer Research 2016

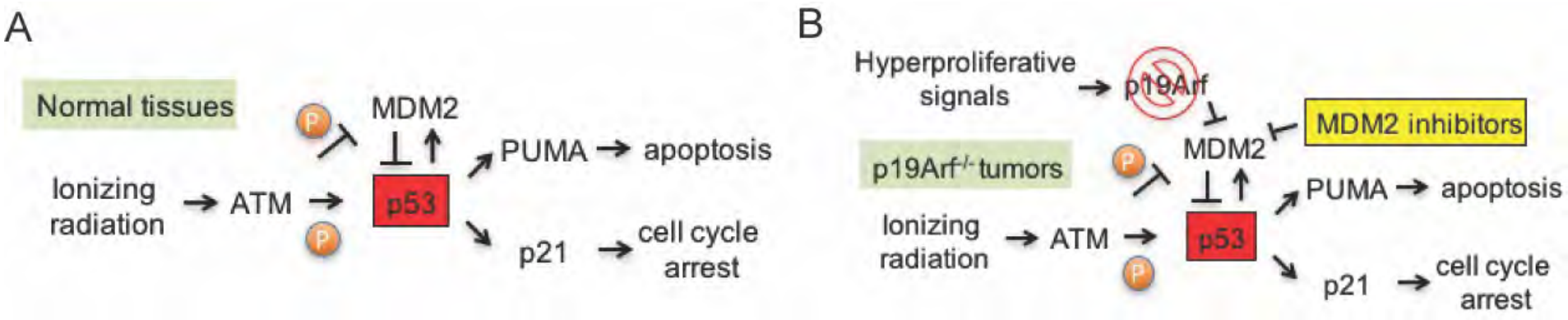
Strategies for optimizing the response of cancer and normal tissues to radiation

Everett J. Moding[1], Michael B. Kastan[1] and David G. Kirsch[1,2]

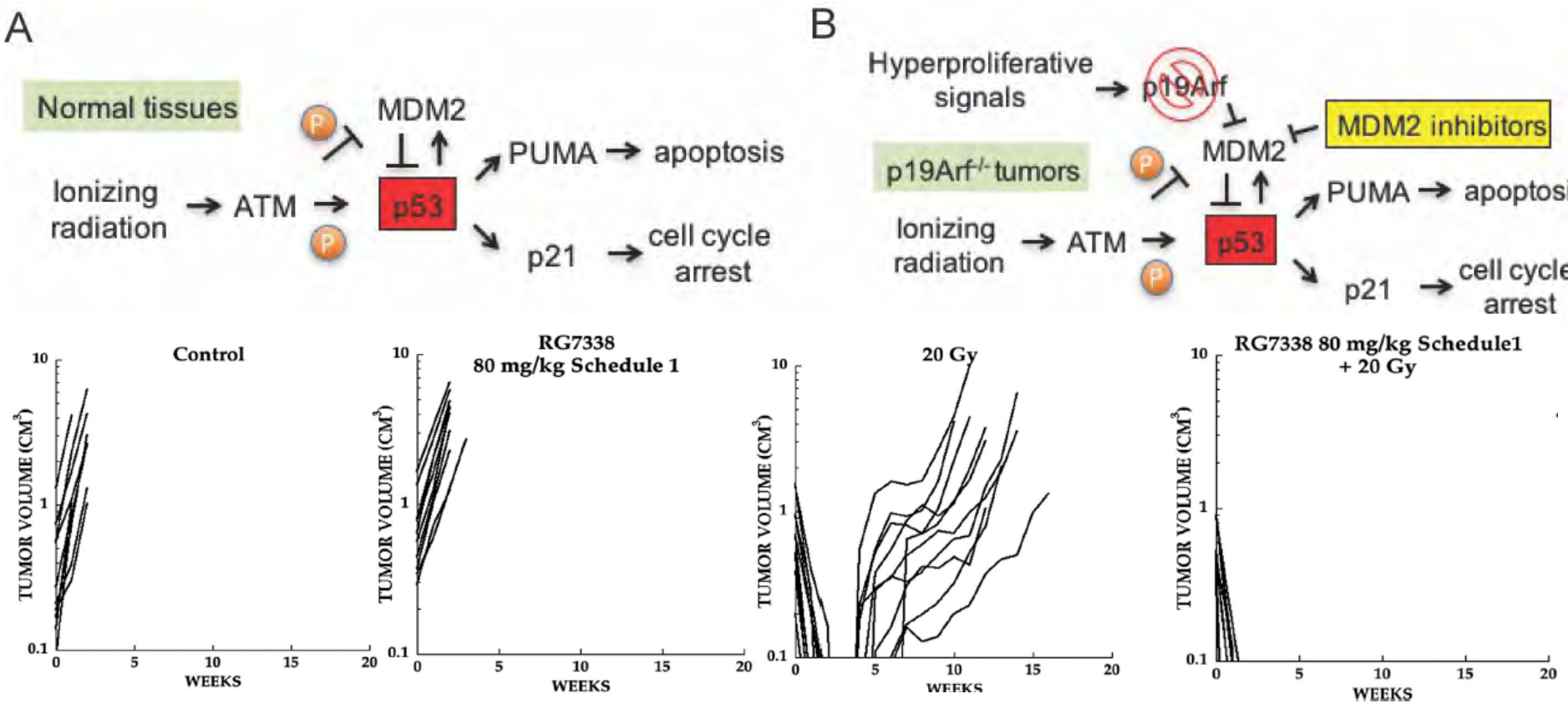


Moding EJ et al, Nature Reviews Drug Discovery 2013

Rationale for Radiation Therapy + MDM2 Inhibitor



Rationale for Radiation Therapy + MDM2 Inhibitor



Phelps D et al, Pediatrics Blood & Cancer 2015

NRG-DT01 (NCT03217266)

A Phase IB Trial of Neoadjuvant AMG 232 Concurent with Preoperative Radiotherapy in Wild Type p53 Soft Tissue Sarcomas

SCHEMA (16NOV2017)

Cohort A: Extremity/body wall
Cohort B: Abdomen/pelvis/retroperitoneum

STEP 1

Biopsy submission for TP53 NGS sequencing

AMG 232 administration (on week -1 only*) (see escalated dose level)

NOTE: Tumor tissue must be received and NGS sequencing results must be completed before STEP 2 registration can occur.

*Patients can continue on AMG-232 week 1 dose if there is a delay in NGS sequencing results.

↓

STEP 2

p53 wild-type (data collection for MTD/RP2D)	**p53 deleted/mutant**
Continue AMG 232 week 1 to 5 at assigned dose level, and RT (Week 1-5), followed by surgery (5-8 weeks after RT completion)	Change to standard of care (RT alone) (Week 1-5) followed by surgery (5-8 weeks after RT completion)

AMG 232 Dose Escalation/De-escalation Table for MTD/RP2D Determination*

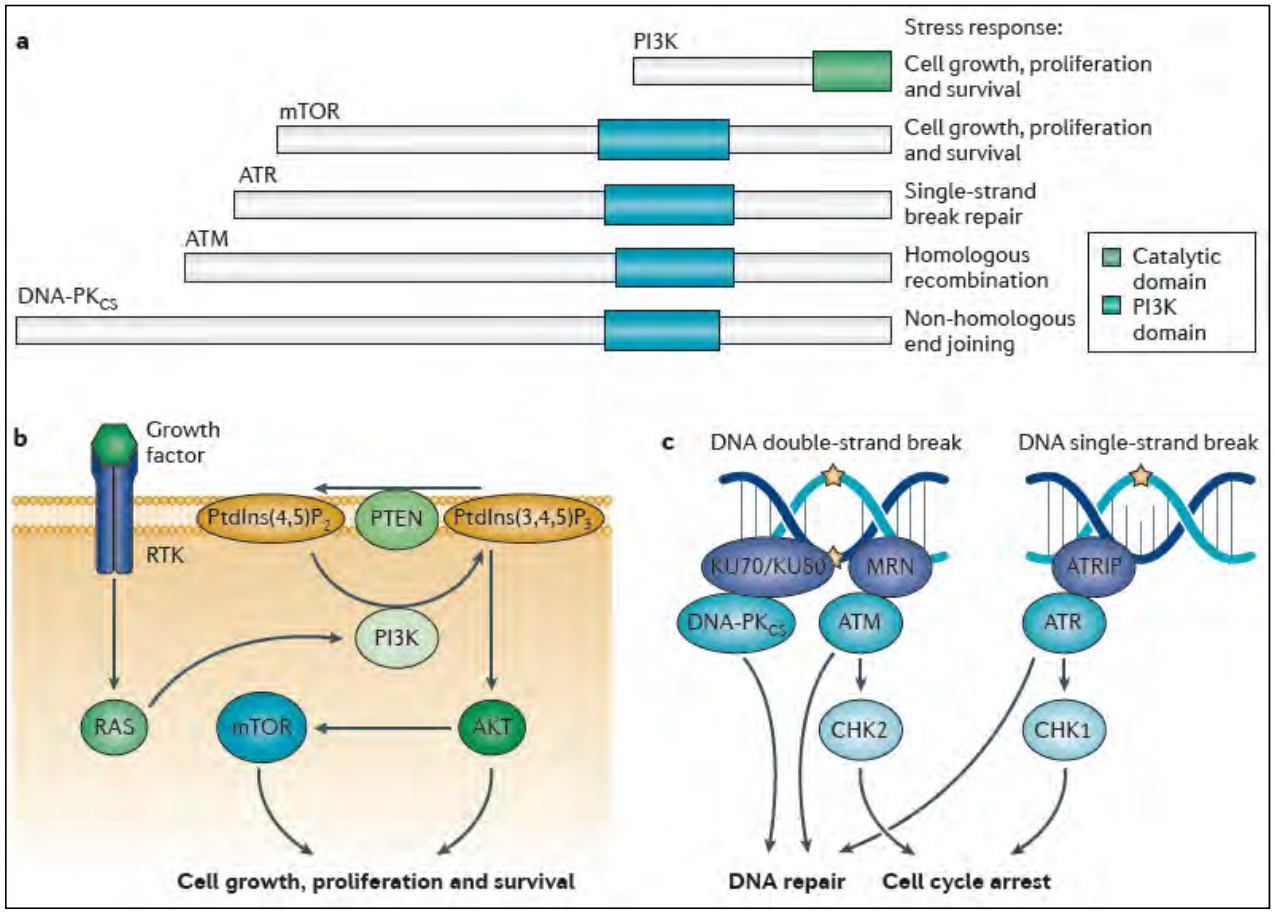
Dose Level	Dose Frequency	Dose (mg)
-1	2x/week	120 mg
1**	3x/week	120 mg
2	4x/week	120 mg
3	5x/week	120 mg

* For detailed information on the process of dose escalation/de-escalation to determine MTD/RP2D as well as the DLT definition, please refer to section 14.
** Dose level 1 is the starting dose level.

NCI Experimental Therapeutics Clinical Trials Network (ETCTN)

PI: Meng Welliver MD, PhD

Targeting Kinases that Regulate the Response to DNA Damage



Moding EJ et al, Nature Reviews Drug Discovery 2013

SARC028 Results

- Multicenter phase II study of **pembrolizumab** for advanced soft tissue sarcoma
  - n = 40 patients (10/subtype)

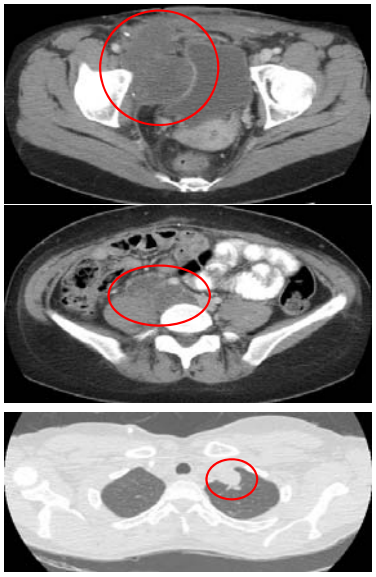
	Complete response	Partial response	Stable disease	Progressive disease
Soft-tissue sarcomas (n=40)	1 (3%)	6 (15%)	15 (38%)	18 (45%)
Leiomyosarcoma (n=10)	0 (0%)	0 (0%)	6 (60%)	4 (40%)
Undifferentiated pleomorphic sarcoma (n=10)	1 (10%)	3 (30%)	3 (30%)	3 (30%)
Liposarcoma (n=10)	0 (0%)	2 (20%)	4 (40%)	4 (40%)
Synovial sarcoma (n=10)	0 (0%)	1 (10%)	2 (20%)	7 (70%)

UPS: 40% response
LPS: 20% response

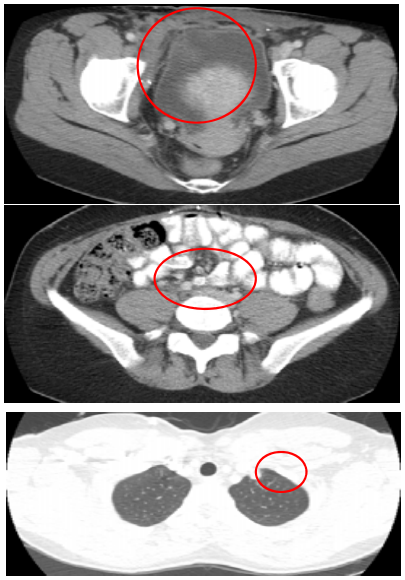
Tawbi et al, Lancet Oncology 2017

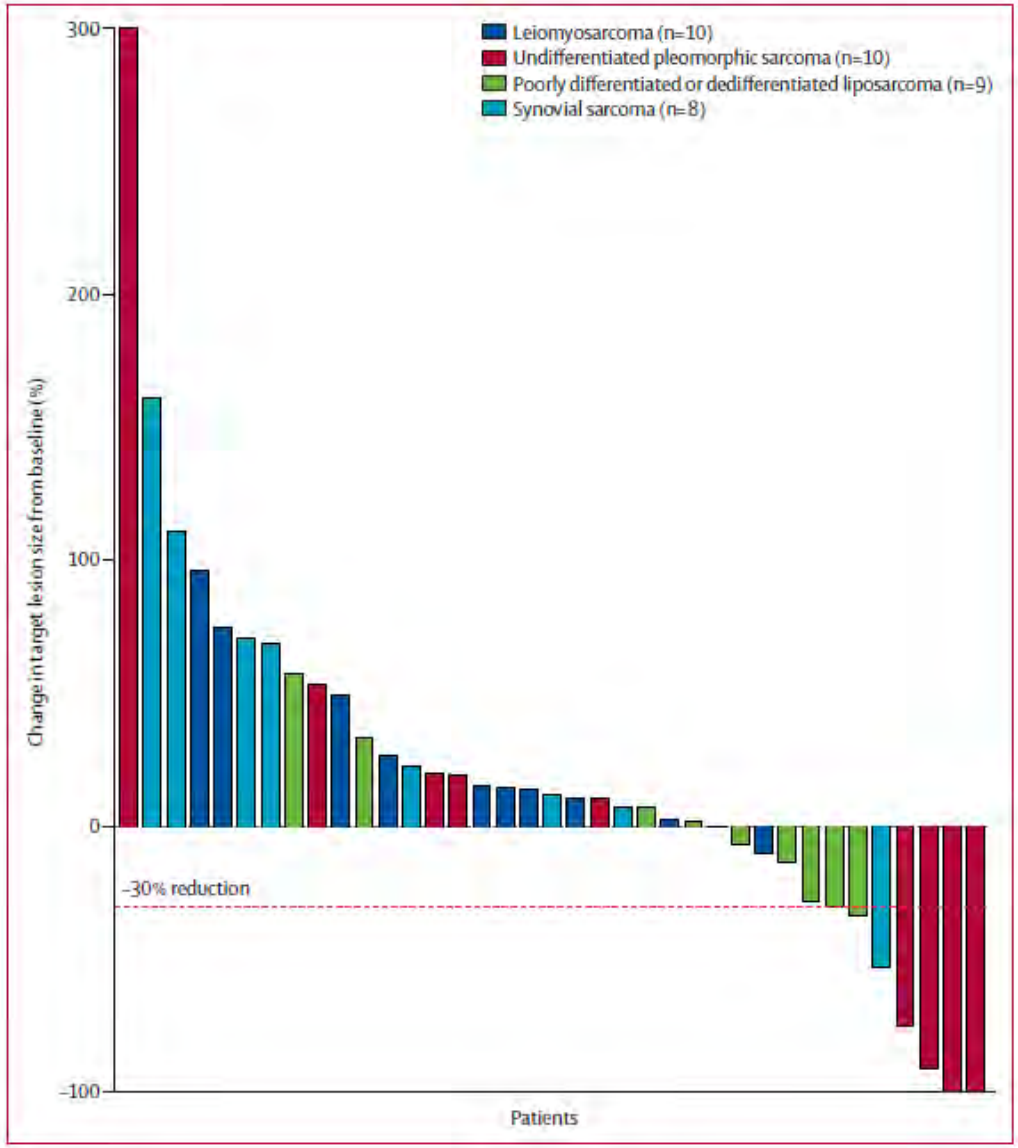
SARC028 Results

Pre-Treatment



Post-Treatment





Tawbi et al, Lancet Oncology 2017

SU2C-SARC032 (NCT03092323)

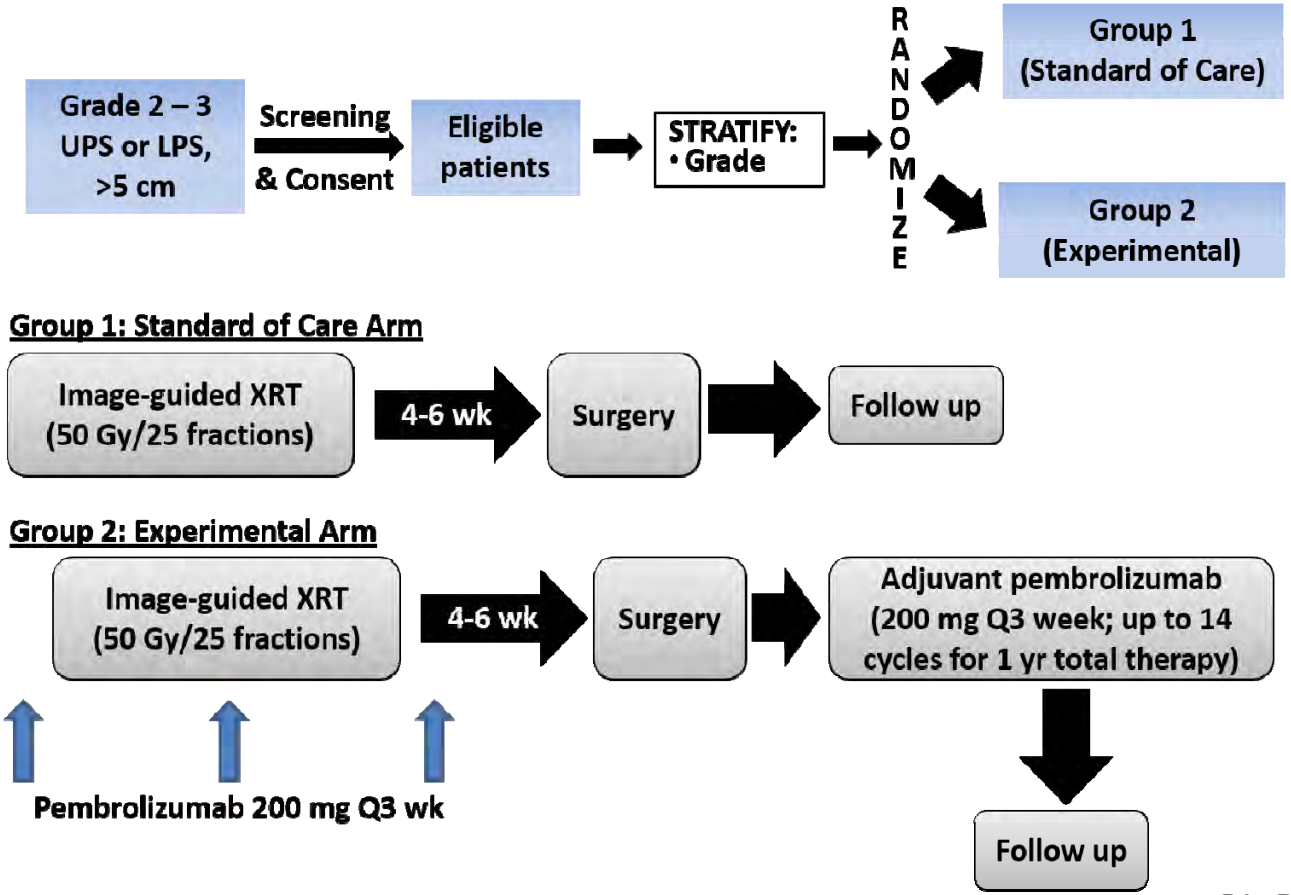
Aim 1: Multi-institutional clinical trial to test the safety and efficacy of pembrolizumab and pre-operative radiotherapy to reduce the development of metastatic disease in sarcoma patients

- 1° endpoint: 2-year disease-free survival

Aim 2: Characterize immune response to radiotherapy with or without pembrolizumab and identify predictors of pembrolizumab response in patients with soft tissue sarcoma

PI: David Kirsch MD, PhD

SU2C-SARC032 Trial Schema



PI: David Kirsch MD, PhD

Summary

- Tremendous Opportunity for Translation of Cancer and Radiation Research by Combining Molecularly Targeted Drugs with Radiotherapy
- To maximize success of clinical trials:
  - Rationale should be based on solid understanding of basic radiation biology
  - Pre-clinical models should be carefully selected
  - Pre-clinical data should provide compelling data for translation into clinical trials
- MDM2 inhibitor (AMG232 + RT) for p53 wild type sarcomas
- ATM inhibitor (AZD1390 + RT) for glioblastomas
- PD-1 inhibitor (Pembrolizumab + RT) for UPS and LPS

Acknowledgments

The Kirsch Lab
Katherine Castle
Amy Wisdom
Yvonne Mowery

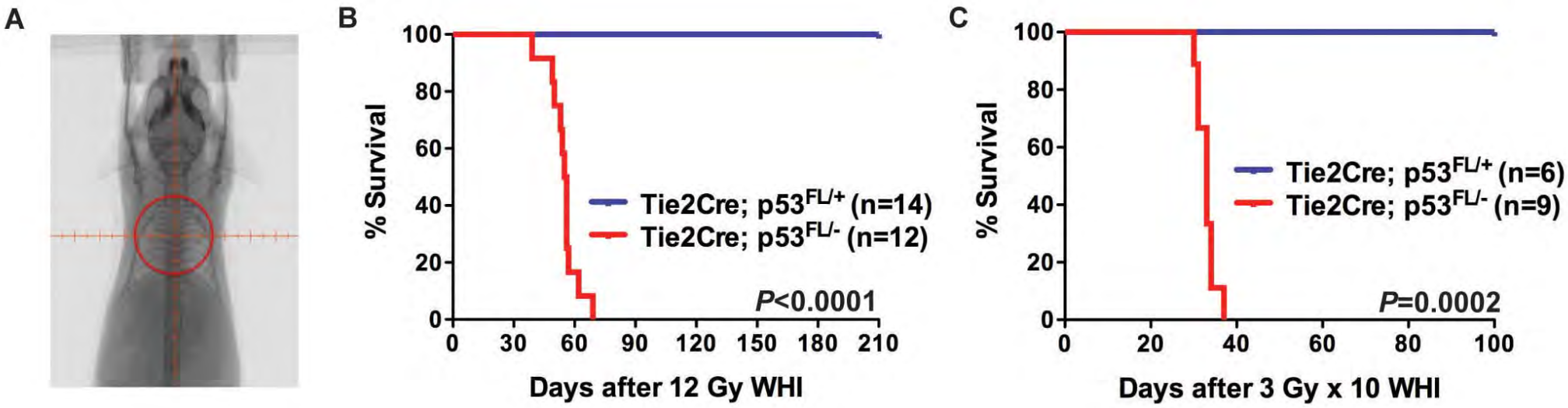
Collaborators
Oren Becher
Meng Welliver
Dian Wang

SARC
collaborating to cure sarcoma

STAND UP TO CANCER™

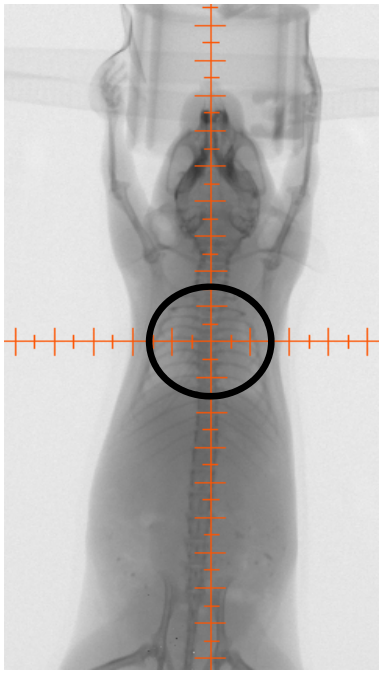
MERCK

Deletion of p53 in Endothelial Cells Sensitizes Mice to Whole Heart Irradiation

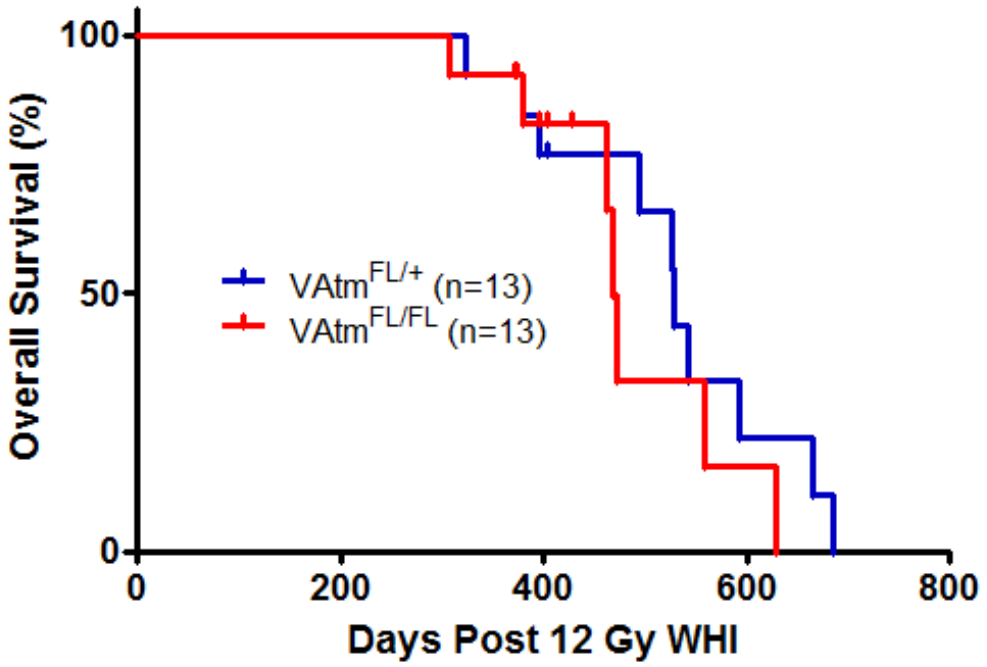


Lee et al, Science Signaling 2012

Loss of *Atm* in Endothelial Cells Does Not Sensitize Mice to Whole Heart Irradiation

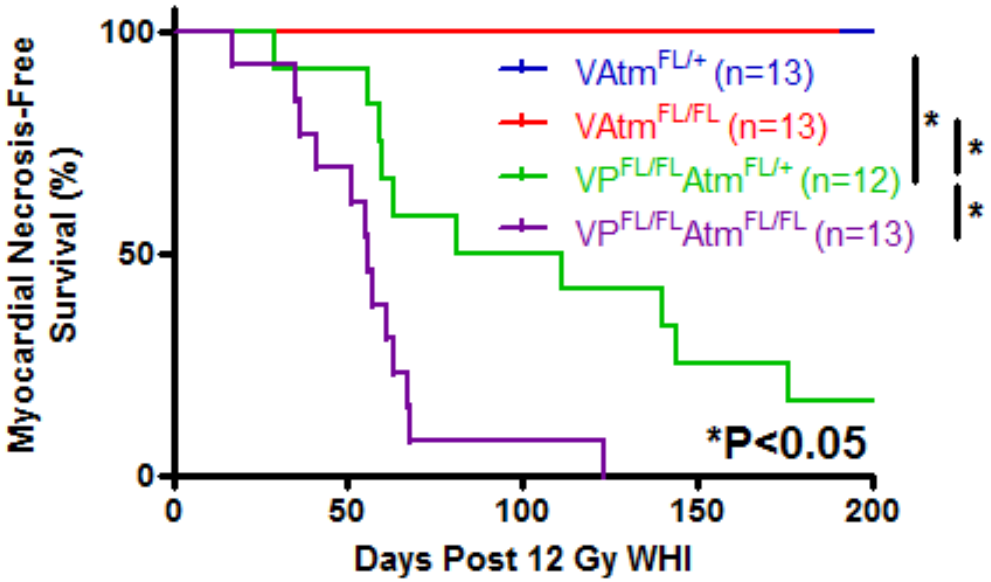


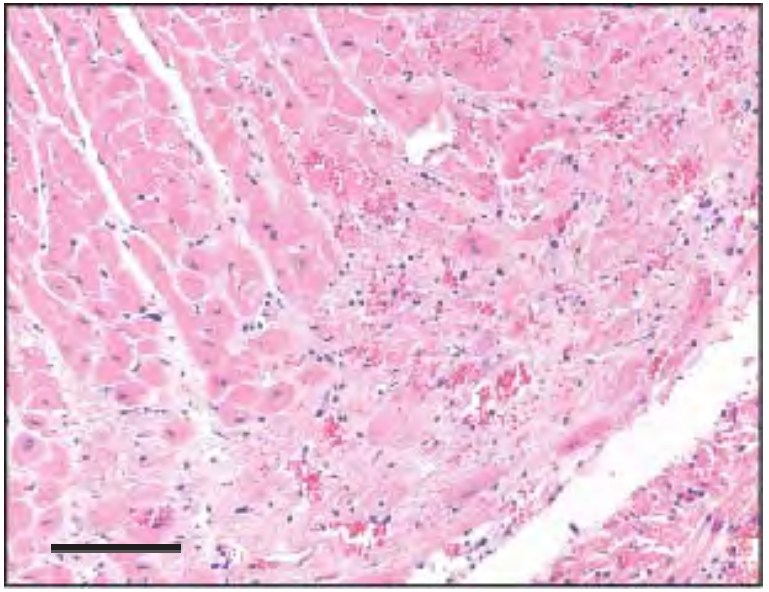
12 Gy WHI



Moding et al, Journal of Clinical Investigation 2014

Loss of *Atm* Sensitizes *p53* Null Endothelial Cells to Radiation





Moding et al, Journal of Clinical Investigation 2014

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SESSION III:

Immunotherapy

Session Cochairs: Marka Crittenden, MD, PhD, and Andrew B. Sharabi, MD, PhD

Speakers:

Marka Crittenden, MD, PhD

Andy J. Minn, MD

Steven J. Chmura, MD, PhD

Jonathan D. Schoenfeld, MD, MPhil, MPH

Robert W. Franz Cancer Research Center
Earle A. Chiles Research Institute

PROVIDENCE Cancer Center

Demystifying the abscopal effect

Marka Crittenden MD, PhD
EACRI, Providence Cancer Center
Portland Oregon

PROVIDENCE Cancer Center

Disclosures

- Institutional support from BMS, Medimmune.
- Laboratory support from BMS, Jounce, Nanobiotix, NCI, NIAID

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Outline

- Mechanisms of immune radiation interactions
- Dose, timing and fractionation
- Prospective clinical trials of radiation and IO in metastatic setting-searching for abscopal responses
- Optimizing RT as a vaccine to enhance abscopal responses

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Mechanisms of interactions for radiation and immune response

- Interaction 1:Radiation can function as an *in situ* vaccine and enhance immune control of distant disease (Abscopal response)

- Interaction 2: The immune system can function to enhance control of irradiated tumors because of changes in the cancer cell and microenvironment induced by radiation (Immunogenic modulation)

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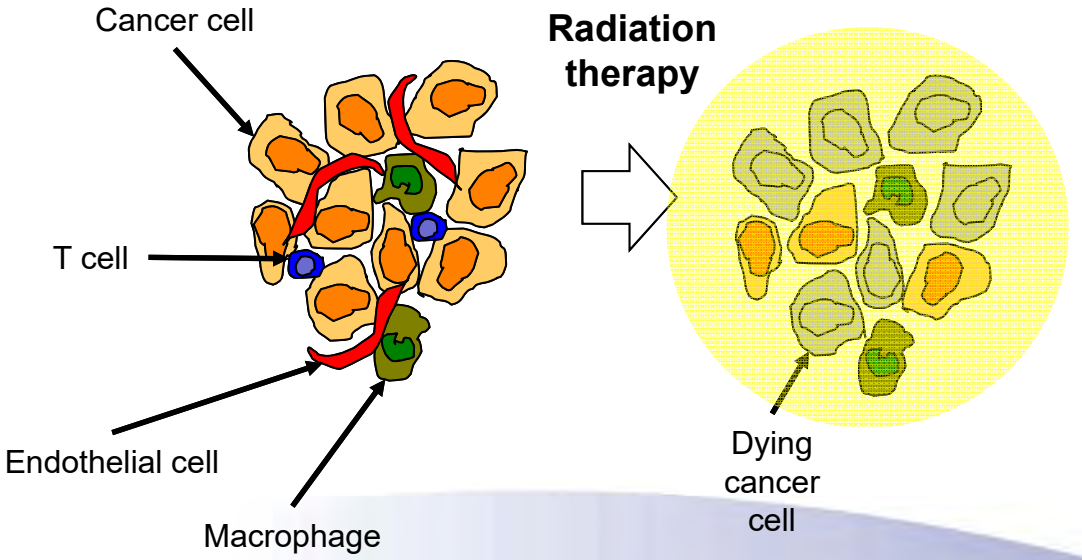
Radiation therapy as an endogenous vaccine



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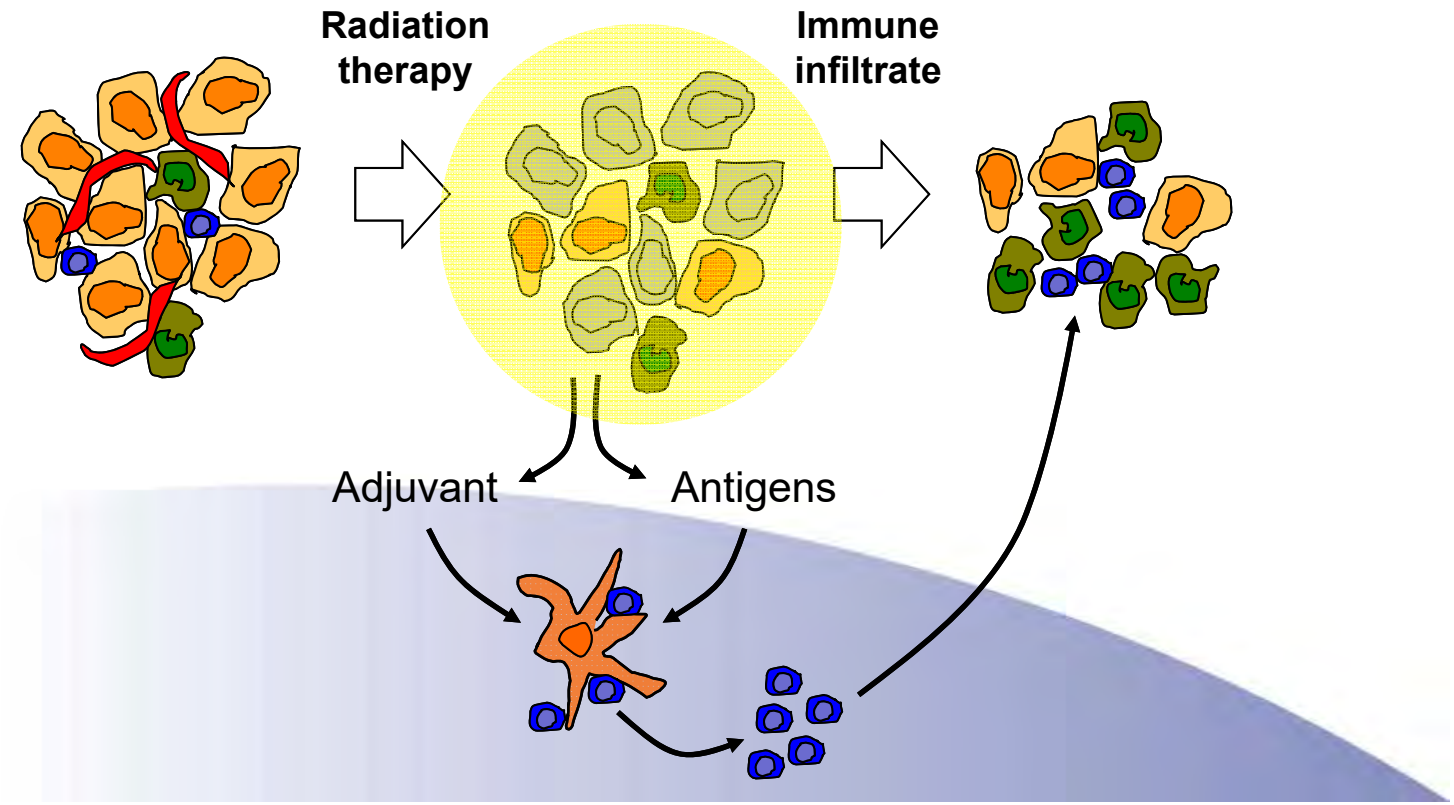
Radiation therapy as an endogenous vaccine



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Mechanisms of interactions between radiation and immune response

- Tumor antigen release and increased priming
- Tumor adjuvant release (DAMPS)
- Deletion of anergic and regulatory T cells and activation of T cells
- Antigen processing machinery and death receptor upregulation
- Cytokine and chemokine induction
- Enhanced immune cell trafficking

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Radiation as an *in situ* vaccine

Two fundamental components for vaccination.

- Antigen-without adjuvant can lead to tolerance.
  - Has to get into Dendritic cells for priming of T cells. Low level chronic antigen release tends to lead to tolerance or anergy
- Adjuvent-without antigen can lead to an immune refractory period
  - DAMPS(uric acid, HMGB1, Calreticulin, dsDNA) and PAMPS (CpG, pIC, LPS)

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Radiation as an *in situ* vaccine

- Priming versus Boosting
  - Priming requires higher threshold and is dendritic cell dependent. Also requires secondary lymphoid tissue. (7-10 days)
  - Boosting does not require dendritic cells, starts sooner but may require overcoming anergy and can occur in the tumor. (3-5 days)

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Outline

- Mechanisms of immune radiation interactions
- Dose, timing and fractionation
- Prospective clinical trials of radiation and IO in metastatic setting-searching for abscopal responses
- Optimizing RT as a vaccine to enhance abscopal responses

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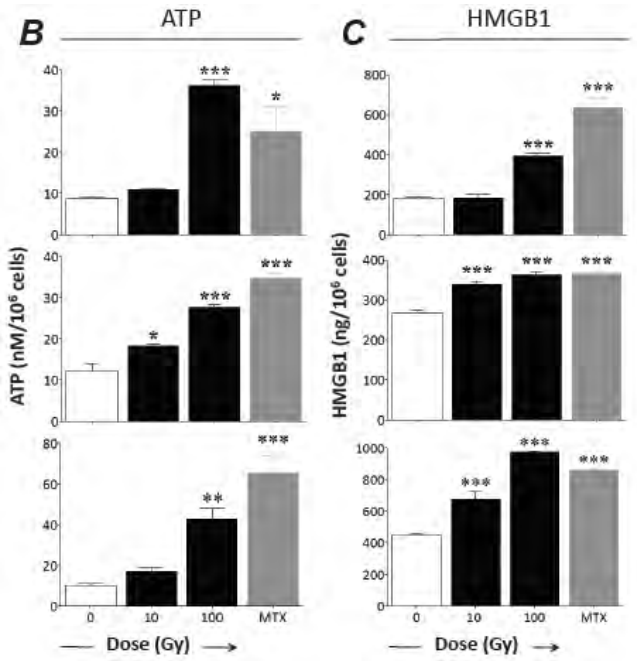
Release of DAMPS following radiation-Dose



Radiation-induced immunogenic modulation of tumor enhances antigen processing and calreticulin exposure, resulting in enhanced T-cell killing

Sofia R. Gameiro[1], Momodou L. Jammeh[1], Max M. Wattenberg[1], Kwong Y. Tsang[1], Soldano Ferrone[2], and James W. Hodge[1]

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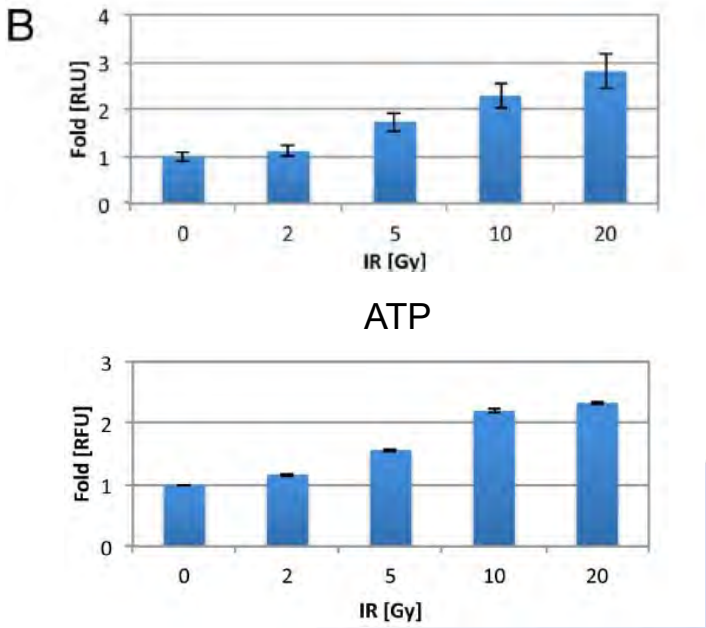
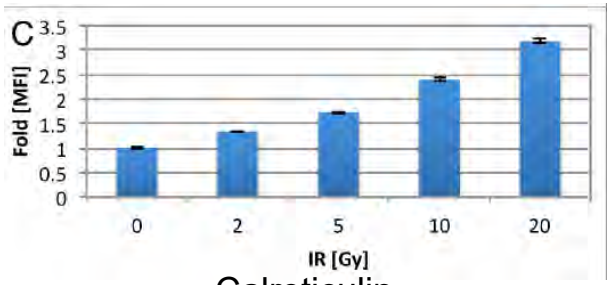
Release of DAMPS Following Radiation-Dose



ATP

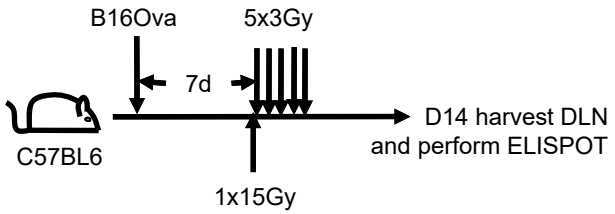


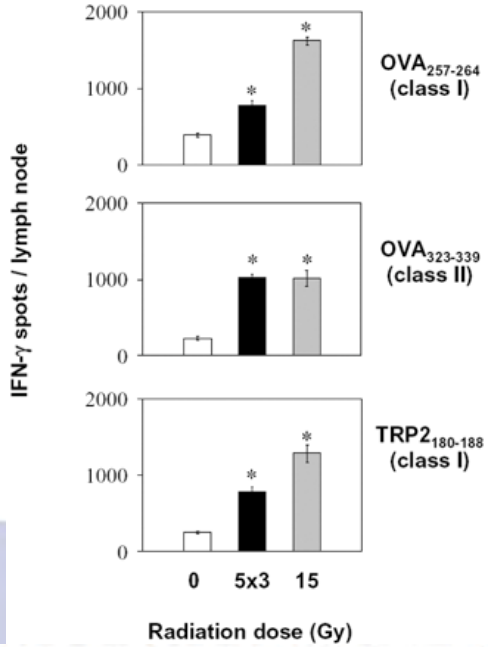
Calreticulin

HMGB1

Radiation fosters dose-dependent and chemotherapy-induced immunogenic cell death.
Golden EB1, Frances D1, Pellicciotta I1, Demaria S2, Helen Barcellos-Hoff M1, Formenti SC1.

Tumor antigen release and enhanced priming in preclinical mouse models-Dose





Local Radiation Therapy of B16 Melanoma Tumors Increases the Generation of Tumor Antigen-Specific Effector Cells That Traffic to the Tumor[1]

Amit A. Lugade,[2] James P. Moran,[2] Scott A. Gerber, Robert C. Rose, John G. Frelinger, and Edith M. Lord[3]

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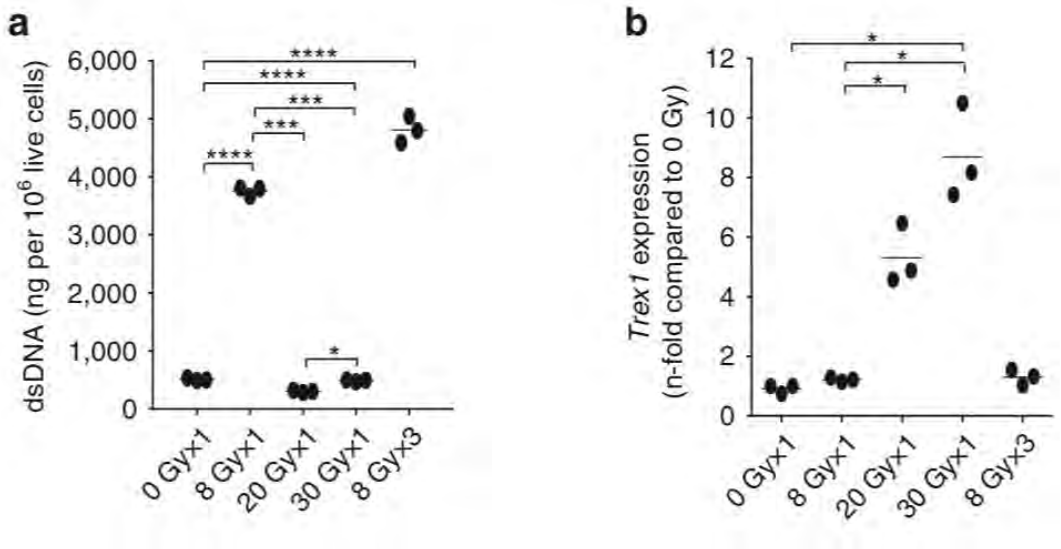
dsDNA degradation at high radiation doses



Vanpouille-Box Nat Comm 2017

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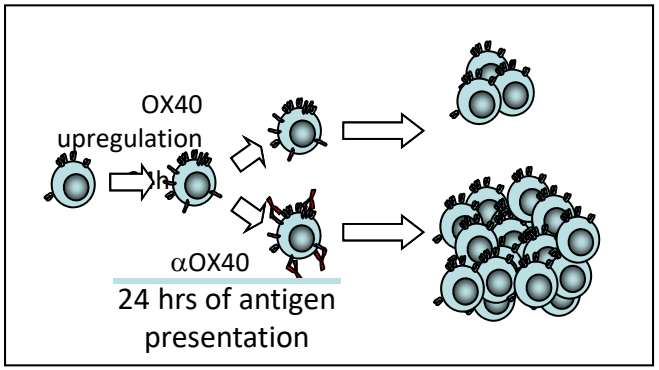
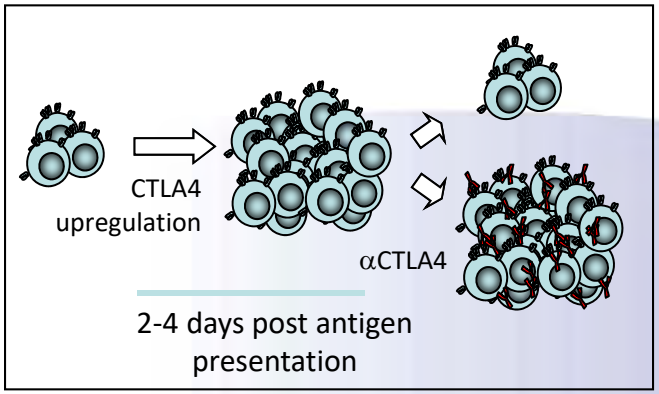
Co-stimulation and Checkpoint Regulation



Best concurrent or immediate post radiation since expression is tightly regulated with antigen presentation



Best post radiation since that is when it is upregulated of T cells

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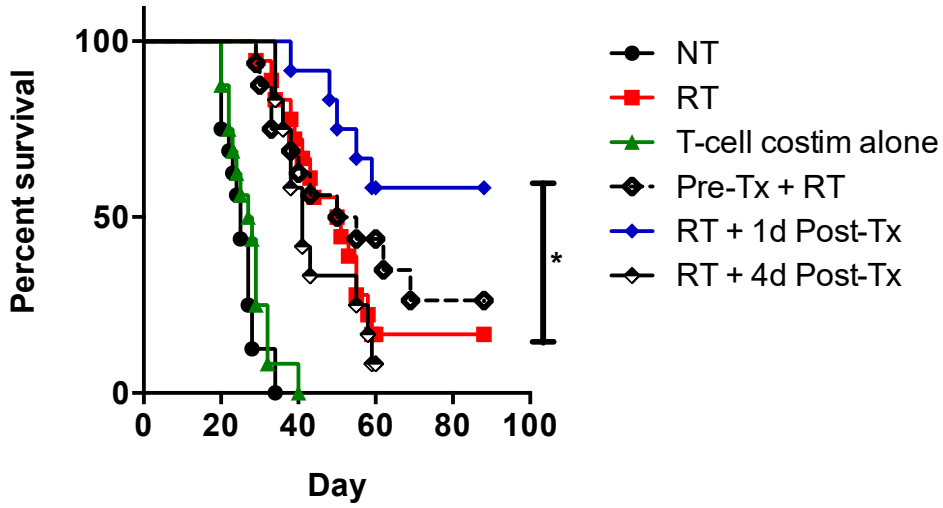
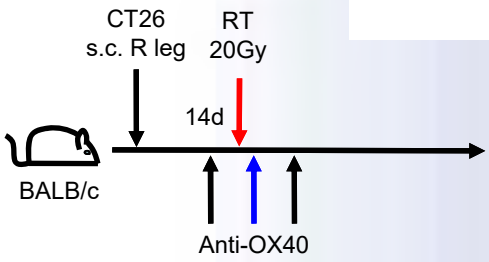
Timing matters when treating with anti-OX40





Young et al PLOSone 2016

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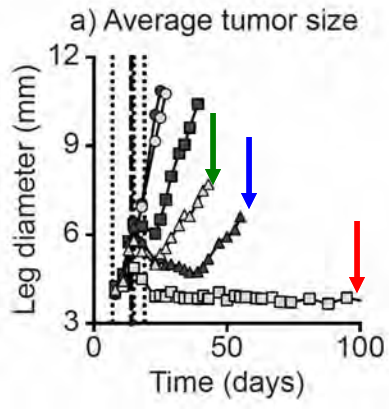
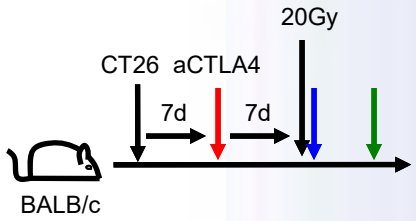
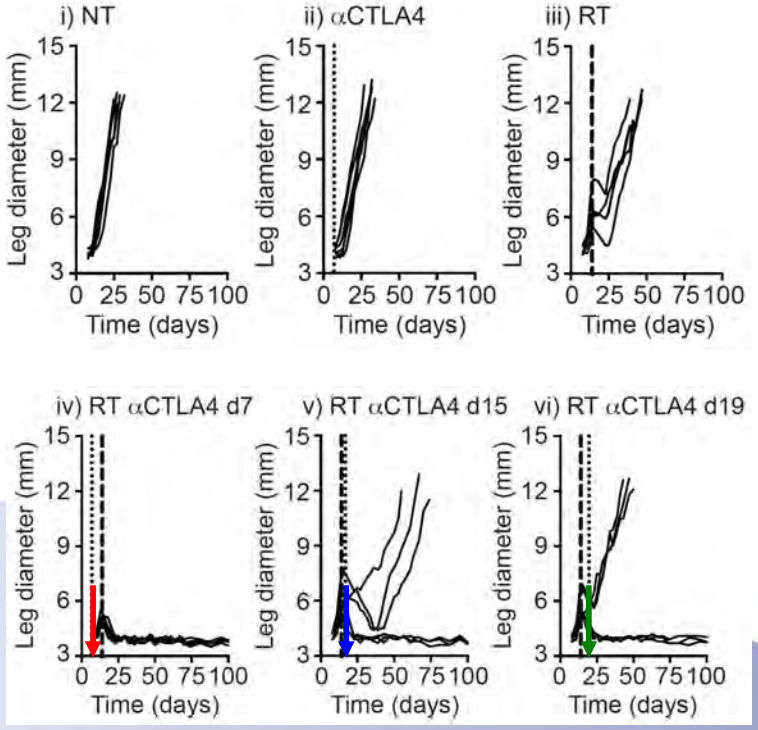
Timing dependent improvement in control of residual disease by anti-CTLA4

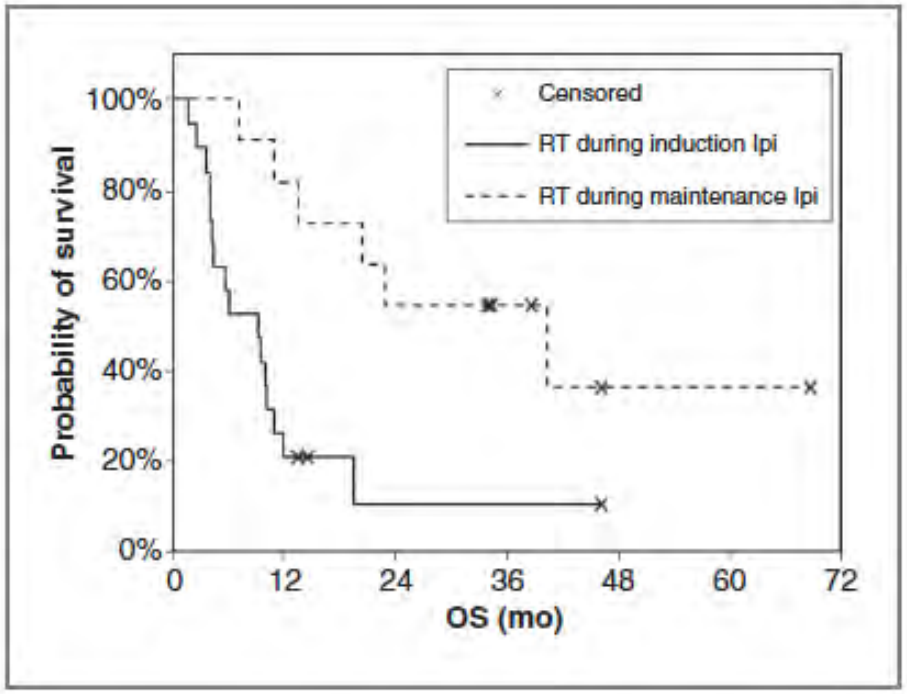






Young et al PLOSone 2016

T cell co-inhibition molecules and timing



- Patients with metastatic melanoma
- Treated with RT during maintenance Ipilimumab increased survival compared to during induction
- Non-randomized

Barker et al CIR, 2013

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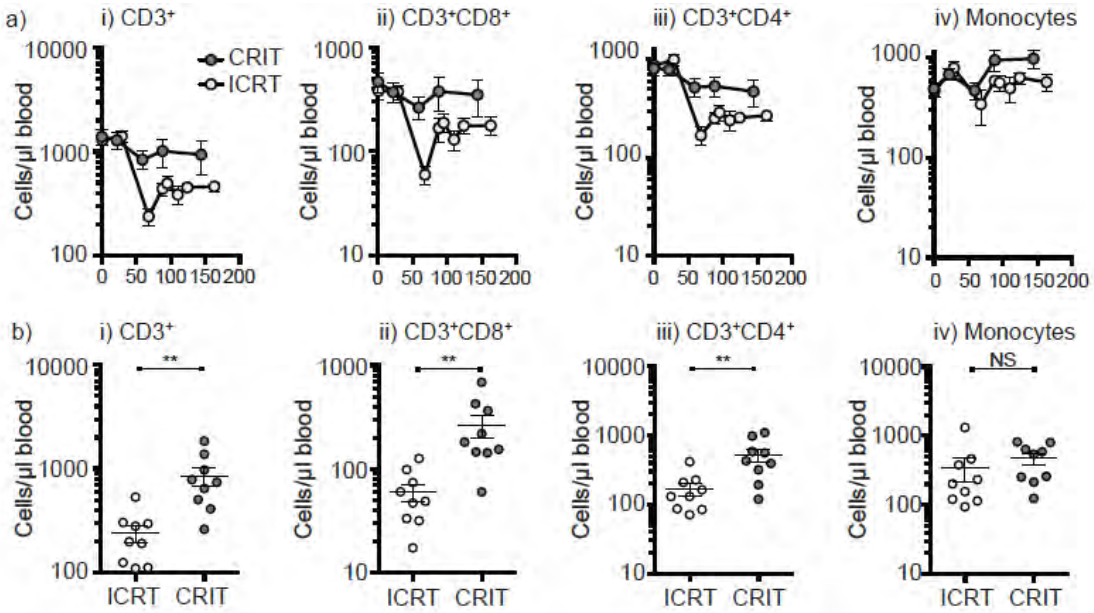
Radiation Therapy and Immunotherapy in Patients With Pancreatic Cancer

Hypofractionation preserves immune cells



STUDY	ICRT	CRIT
Percent of patients with normal ALC for 2 consecutive measurements post RT	40% (4/10)	70% (7/10)
Mean time to normal ALC for patients that normalize	272 days (108-523 days)	50 days (all patients)

Crocenzi et al JITC 2016

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Dose, timing and fractionation

- Dose-for endogenous vaccine effect higher is better but in some tumors the may be an inflexion point
- Timing of radiation and immunotherapy combinations will depend on agent used and preclinical may help guide testing
- Fractionation is good but too much may be bad

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Outline

- Mechanisms of immune radiation interactions
- Dose, timing and fractionation
- Prospective clinical trials of radiation and IO in metastatic setting-searching for abscopal responses
- Optimizing RT as a vaccine to enhance abscopal responses

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Prospective Clinical Trials

IO Agent	Tumor	Patient number	RT dose	RT site	ORR	Publication
High dose IL-2	Melanoma, RCC, bladder, sarcoma	28	5Gy x 2-4	Multiple	7%	Lange et al Journal of Immunotherapy 1992
High dose IL-2	RCC	16	8Gy x 1	Multiple	12.50%	Redman et al CCR 1998
High dose IL-2	Melanoma, RCC	12	20Gy x 1-3	Lung and Liver met	66.60%	Seung et al Sci Tr Med
Anti-CTLA4	Melanoma	22	6-8Gy x 2-3	Multiple	18%	Tyman-Saint Victor Nature 2015
Anti-CTLA4	Melanoma	22	2.5-25Gy x1-15	Multiple	27%	Hiniker et al IJORBP 2016
Anti-CTLA-4	Solid tumors	35	6-12.5 Gy	Lung and Liver met	10%	Tang et al CCR 2016
GM-CSF	Solid tumors	41	3.5Gy x10	Multiple	Not reported	Golden et al Lancet Oncology 2015
Anti-PD1	Solid tumors	73	10-15Gy x3-5	Multiple	13.20%	Luke et al JCO 2018
Anti-CTLA4	Melanoma	315	None	None	19%	Wolchok et al NEJM 2017
Anti-PD1	Melanoma	316	None	None	44%	Wolchok et al NEJM 2017

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Clinical Trials

- Most trials have been single arm phase I-II studies of IO agents with immunotherapy.
- Suggestion of higher response rates when combined with high-dose IL-2 if RT is given in ablative doses.
- Response rates with checkpoint inhibitors have not shown the degree of combined benefit as preclinical studies have suggested.

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Outline

- Mechanisms of immune radiation interactions
- Dose, timing and fractionation
- Prospective clinical trials of radiation and IO in metastatic setting-searching for abscopal responses
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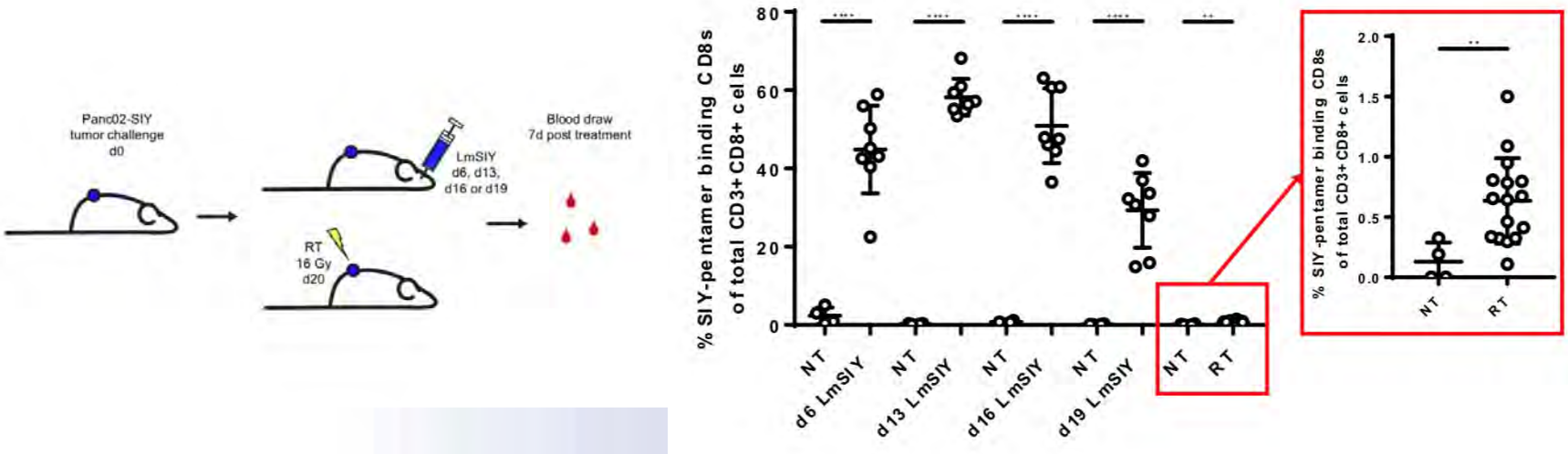
Radiation alone is a second rate vaccine



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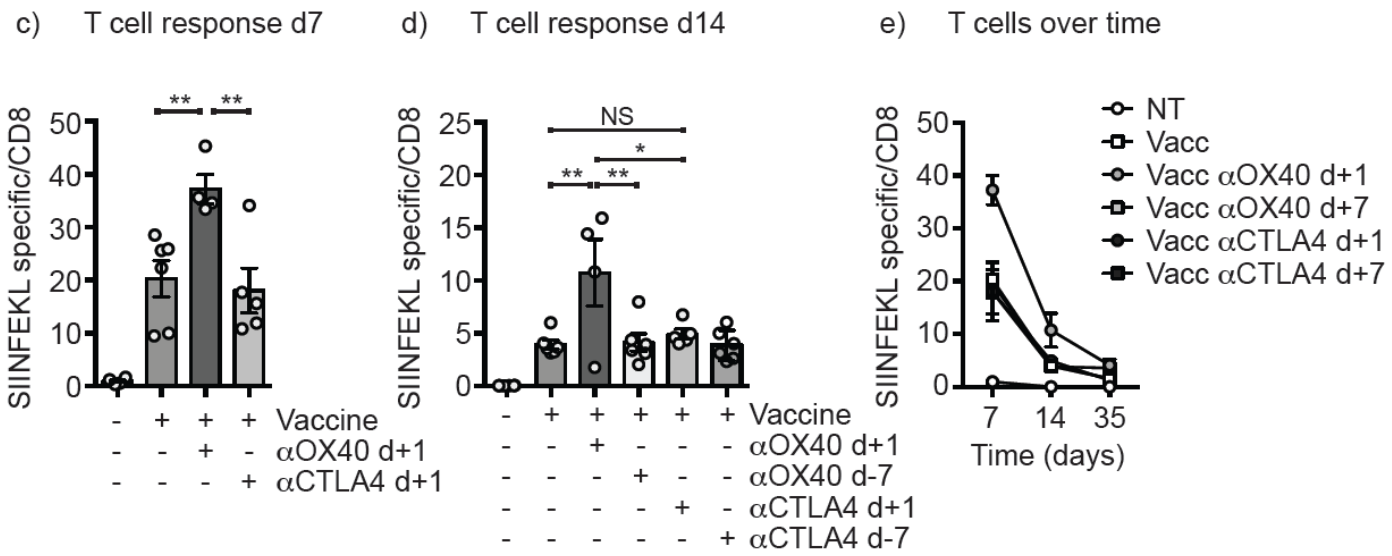
Anti-CTLA4 does not expand T cells



Shelly Bambina

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Original sin and the fall of tumor

Fall of man.
Michelangelo

PROVIDENCE Cancer Center

Bursuker and North

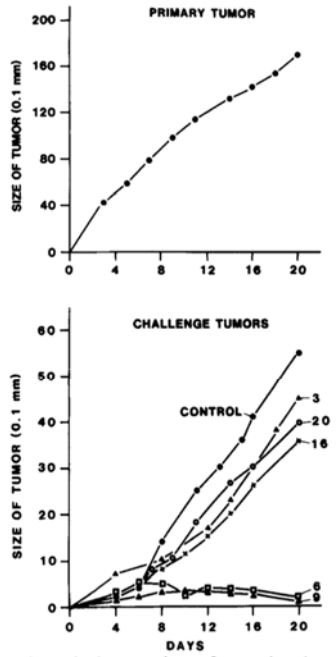

FIGURE 1. The generation and subsequent decay of concomitant immunity to growth of a tumor implant in mice bearing a progressive meth A tumor. (*Top*) Growth of the primary meth A tumor growing from an intradermal implant in the belly region. (*Bottom*) Growth of an intra-footpad implant of 10^6 meth A cells given to control mice and to tumor-bearing mice on day 3, 6, 9, 16, or 20 of tumor growth (numbers on individual graphs). Means of five mice per group.

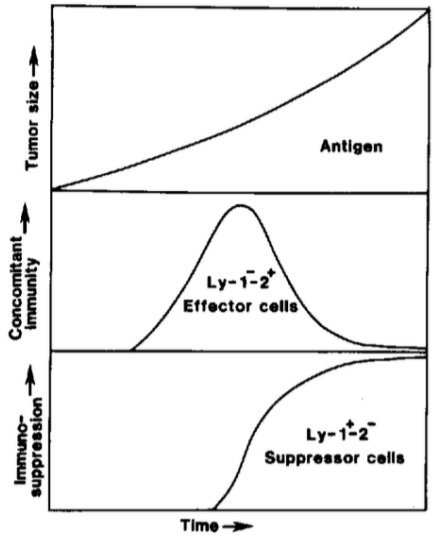

FIGURE 10. Diagrammatic representation of the immune response to a progressive immunogenic tumor of the type represented by the meth A fibrosarcoma. After the tumor reaches a critical minimum size it provides enough antigen to evoke the generation of Ly-1^-2^+ effector T cells. However, a short period of additional tumor growth provides antigenic conditions that favor the generation of Ly-1^+2^- suppressor T cells that function to down-regulate the production of Ly-1^-2^+ effector T cells. Consequently, not enough effector T cells are made to destroy the tumor.

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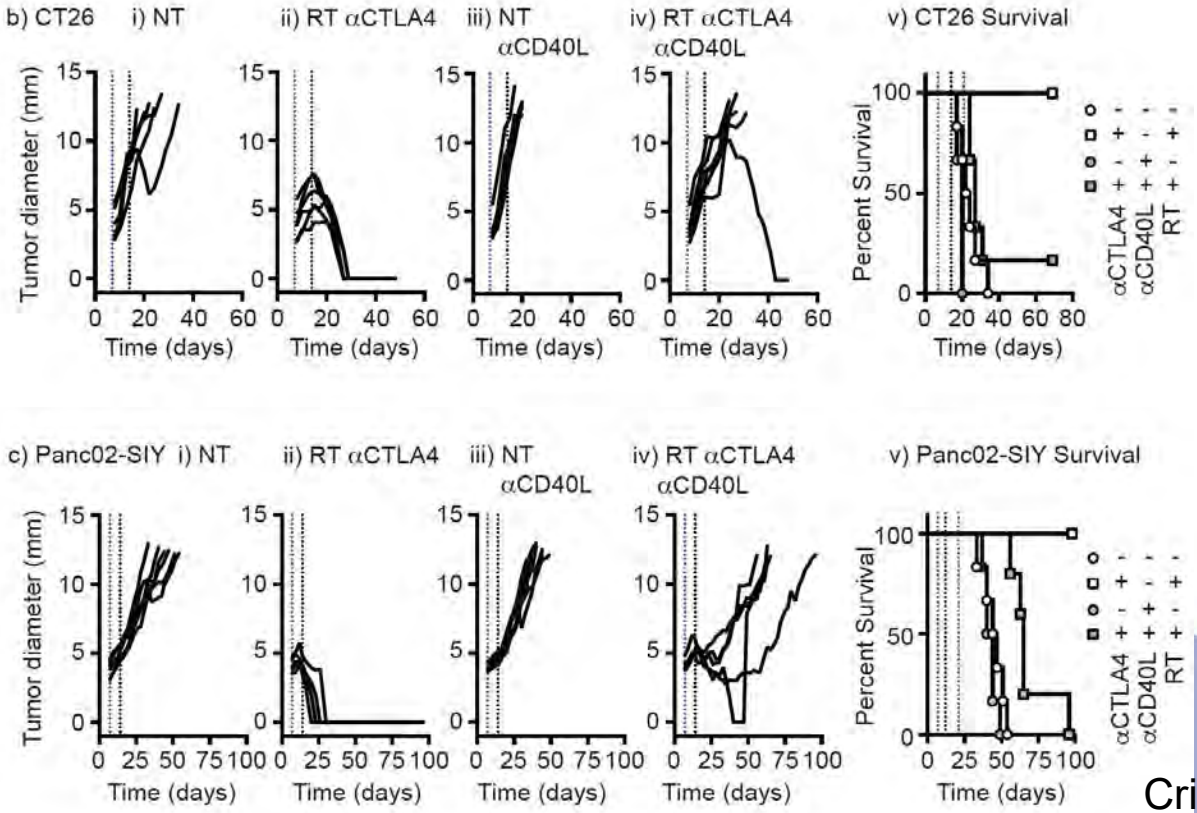
Anti-CD40L prior to challenge blocks responses



Crittenden-Gough lab

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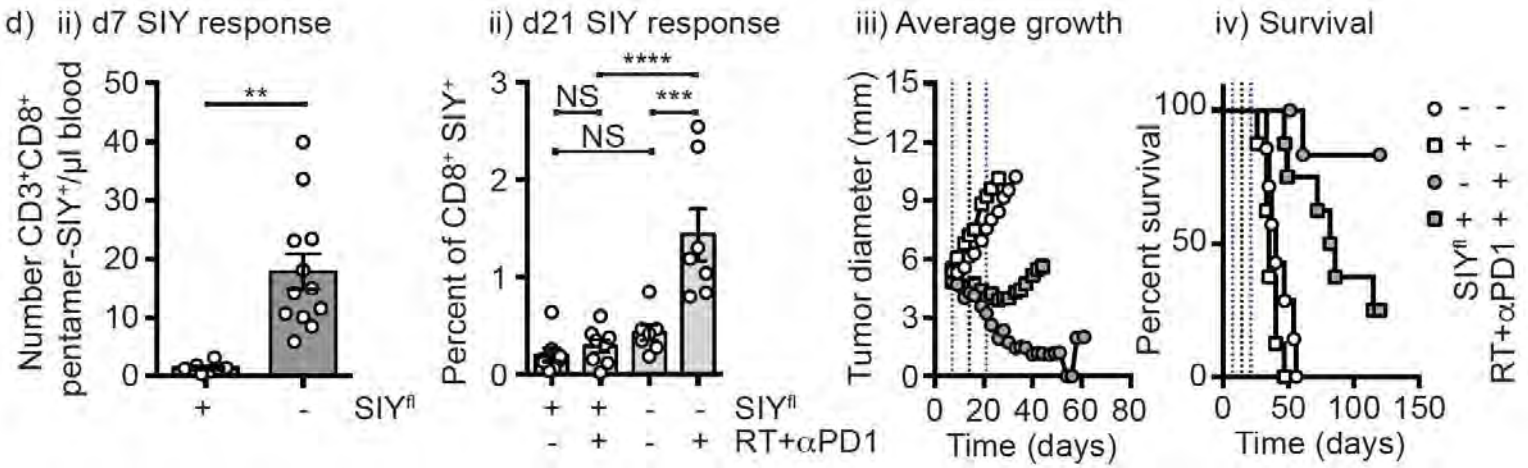
Reduced efficacy in antigen tolerant animal



Crittenden-Gough lab

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Final Thoughts

- Strong rationale for radiation and IO combinations to enhance abscopal responses.
- Dose, timing of combination and fractionation should be addressed.
- We need to exercise caution in the interpretation of some of our preclinical data
- If the abscopal response depends on generating new immune responses, there may be a number of IO agents other than checkpoints that we need to be testing in the clinic.

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THANK YOU

Toxicities of Radiation-Immunotherapy Combinations

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Center for Head and Neck Oncology
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DANA-FARBER/BRIGHAM AND WOMEN'S
CANCER CENTER
BWH

Disclosures

Employer: Brigham and Women's Physicians Organization

Potential Conflicts of Interest: research funding paid to the institution (BMS, Merck), Previous paid SAB (AstraZeneca, BMS, Debiopharm, Nanobiotix), Consulting (Tilos)

Introduction: Potential Synergy Can Be Accompanied by Increased Toxicity

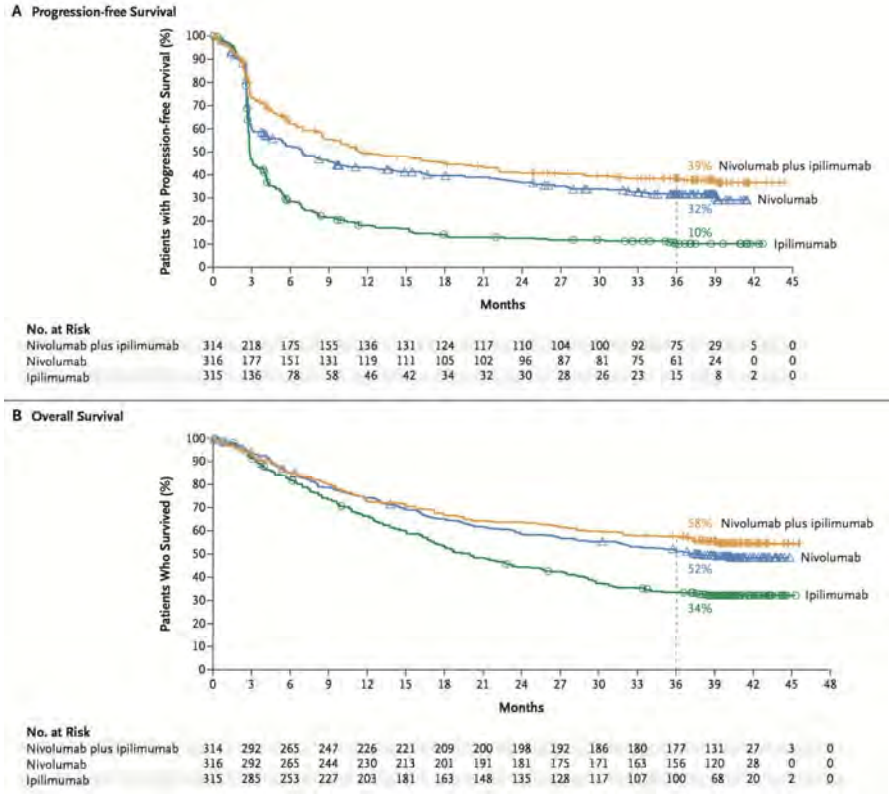

Table 2. Treatment-Related Adverse Events.*

Event	Nivolumab plus Ipilimumab (N=313)		Nivolumab (N=313)		Ipilimumab (N=311)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients with event (percent)					
Any treatment-related adverse event	300 (96)	184 (59)	270 (86)	67 (21)	268 (86)	86 (28)
Rash	93 (30)	10 (3)	72 (23)	1 (<1)	68 (22)	5 (2)
Pruritus	112 (35)	6 (2)	67 (21)	1 (<1)	113 (36)	1 (<1)
Vitiligo	28 (9)	0	29 (9)	1 (<1)	16 (5)	0
Maculopapular rash	38 (12)	6 (2)	15 (5)	2 (1)	38 (12)	1 (<1)
Fatigue	119 (38)	13 (4)	114 (36)	3 (1)	89 (29)	3 (1)
Asthenia	30 (10)	1 (<1)	25 (8)	1 (<1)	17 (5)	2 (1)
Pyrexia	60 (19)	2 (1)	21 (7)	0	21 (7)	1 (<1)
Diarrhea	142 (45)	29 (9)	67 (21)	9 (3)	105 (34)	18 (6)
Nausea	88 (28)	7 (2)	41 (13)	0	51 (16)	2 (1)
Vomiting	48 (15)	7 (2)	22 (7)	1 (<1)	24 (8)	1 (<1)
Abdominal pain	26 (8)	1 (<1)	18 (6)	0	28 (9)	2 (1)
Colitis	40 (13)	26 (8)	7 (2)	3 (1)	35 (11)	24 (8)
Headache	35 (11)	2 (1)	24 (8)	0	25 (8)	1 (<1)
Arthralgia	43 (14)	2 (1)	31 (10)	1 (<1)	22 (7)	0
Increased lipase level	44 (14)	34 (11)	27 (9)	14 (4)	18 (6)	12 (4)
Increased amylase level	26 (8)	9 (3)	20 (6)	6 (2)	15 (5)	4 (1)
Increased aspartate aminotransferase level	51 (16)	19 (6)	14 (4)	3 (1)	12 (4)	2 (1)
Increased alanine aminotransferase level	60 (19)	27 (9)	13 (4)	4 (1)	12 (4)	5 (2)
Decreased weight	19 (6)	0	10 (3)	0	4 (1)	1 (<1)
Hypothyroidism	53 (17)	1 (<1)	33 (11)	0	14 (5)	0
Hyperthyroidism	35 (11)	3 (1)	14 (4)	0	3 (1)	0
Hypophysitis	23 (7)	5 (2)	2 (1)	1 (<1)	12 (4)	5 (2)
Decreased appetite	60 (19)	4 (1)	36 (12)	0	41 (13)	1 (<1)
Cough	25 (8)	0	19 (6)	2 (1)	15 (5)	0
Dyspnea	36 (12)	3 (1)	19 (6)	1 (<1)	12 (4)	0
Pneumonitis	22 (7)	3 (1)	5 (2)	1 (<1)	5 (2)	1 (<1)
Treatment-related adverse event leading to discontinuation	123 (39)	95 (30)	37 (12)	24 (8)	49 (16)	43 (14)

Checkmate 067, Wolchok et al. NEJM 2017

Outline

- Toxicity concerns
- Existing and emerging clinical data
- Path forward, challenges

Outline

- Toxicity concerns
- Existing and emerging clinical data
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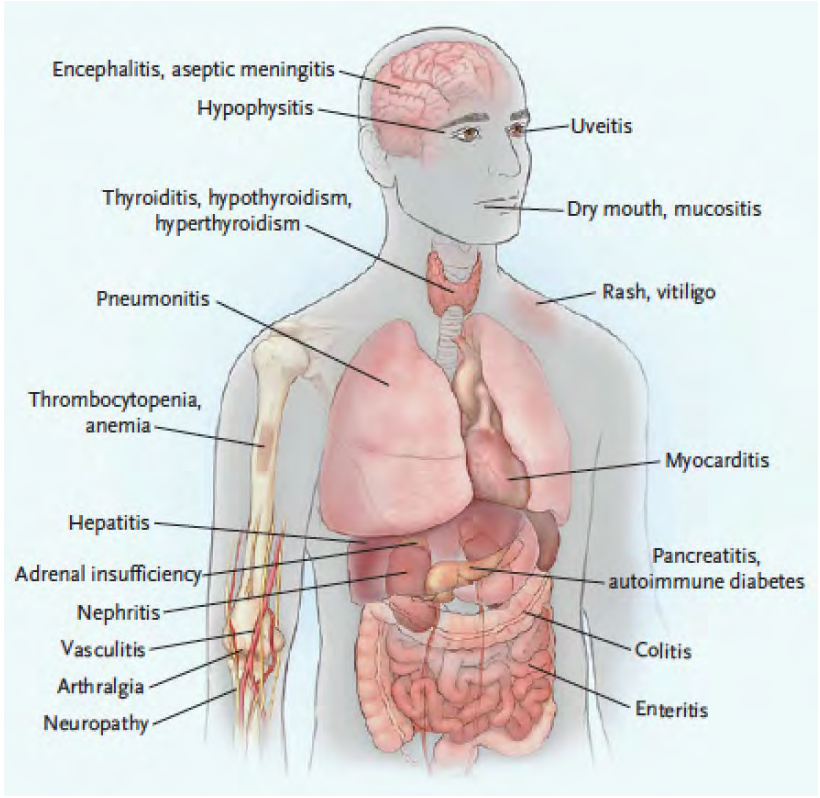
Toxicities of Immune Checkpoint Blockade

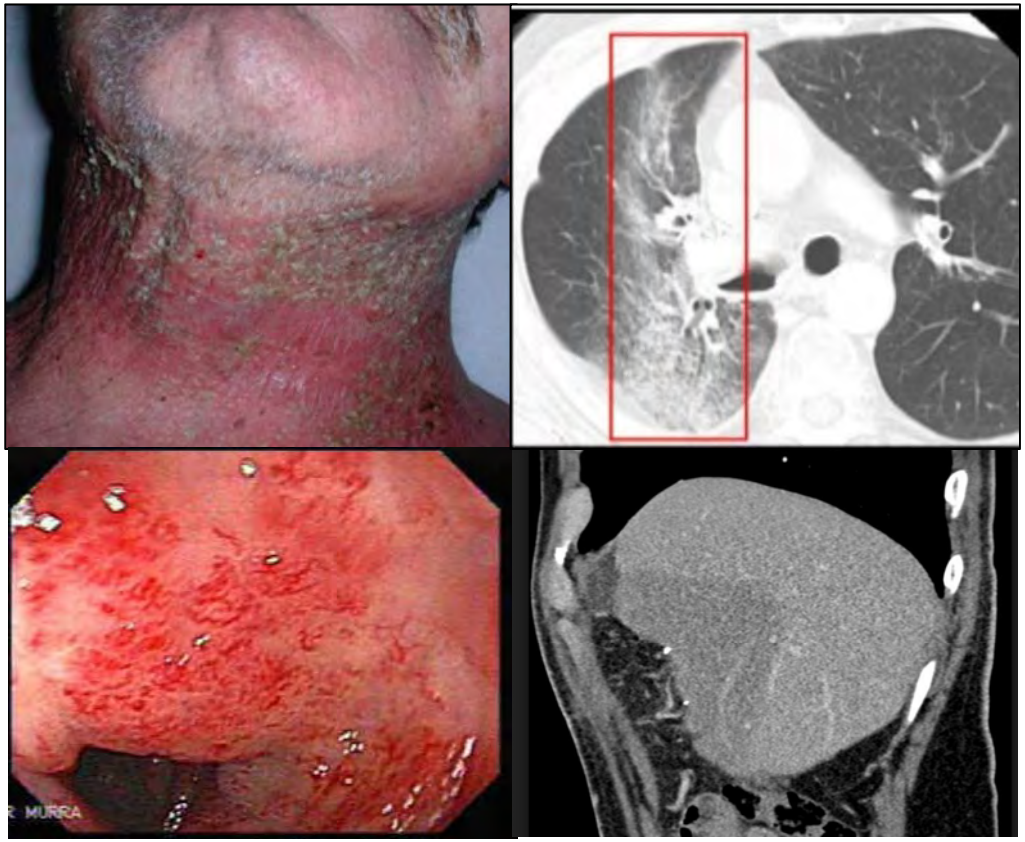


Postow, Sidlow and Hellman. NEJM 2017

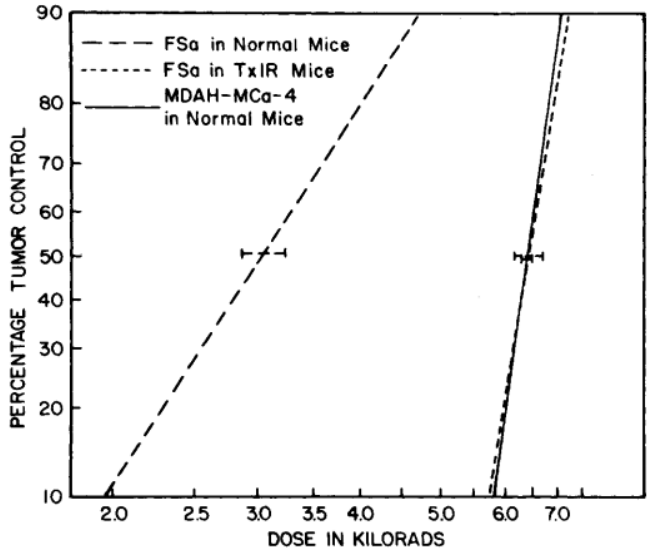
- Increased immunity can lead to inflammatory side effects
- Most commonly involves: skin, GI tract, lung, endocrine glands, liver
- Rare but serious effects also reported (e.g. fatal myocarditis)
- Frequency and distribution depends on immunologic agent used
- Early identification and appropriate treatment important
- Difficult to study in animal models

Toxicities of Radiation Therapy

- Impacts on more common / severe overlapping toxicities of particular interest
  - Dermatitis
  - Pneumonitis
  - Colitis
  - Hepatitis
- Important impact of dose/fractionation, field location/size, treatment technique, and concurrent therapy.



Potential for Enhancement of Local Radiation Effects with Immunotherapy



TEXT-FIGURE 4.—Dose-response curves for local control of the highly immunogenic FSa in normal and TxIR mice (replotted without individual data points from text-fig. 1) compared to curve for C3H mammary carcinoma MDAH-MCa-4, a tumor of little or no immunogenicity in these mice (*16*).

Preclinical Data: Control of fibrosarcoma tumors, Stone et al. JNCI 1979

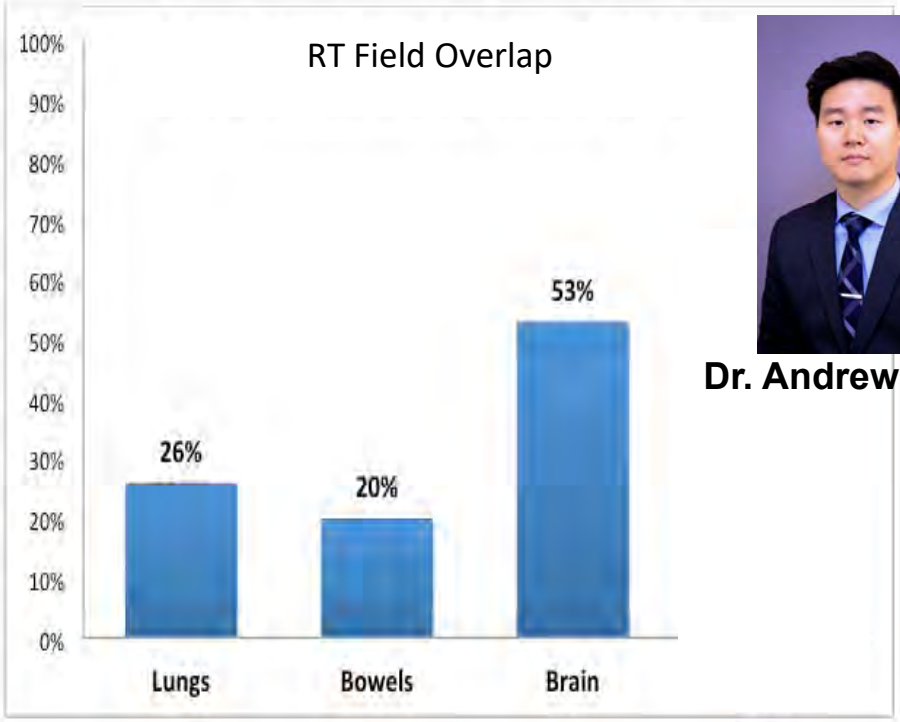
- Clinical reports of local toxicity following radiation / interferon treatment
  - Valvaara et al. Acta Oncol 1992: increased mucositis
  - Hazard et al. IJROBP 2002: neuropathy, radiation necrosis
  - Nguyen et al. Melanoma Res 2003: grade 3-4 mucositis, dermatitis
  - Perera et al. IJROBP 1997: neuropathy, stricture

Outline

- Toxicity concerns
- Existing and emerging clinical data
- Path forward, challenges

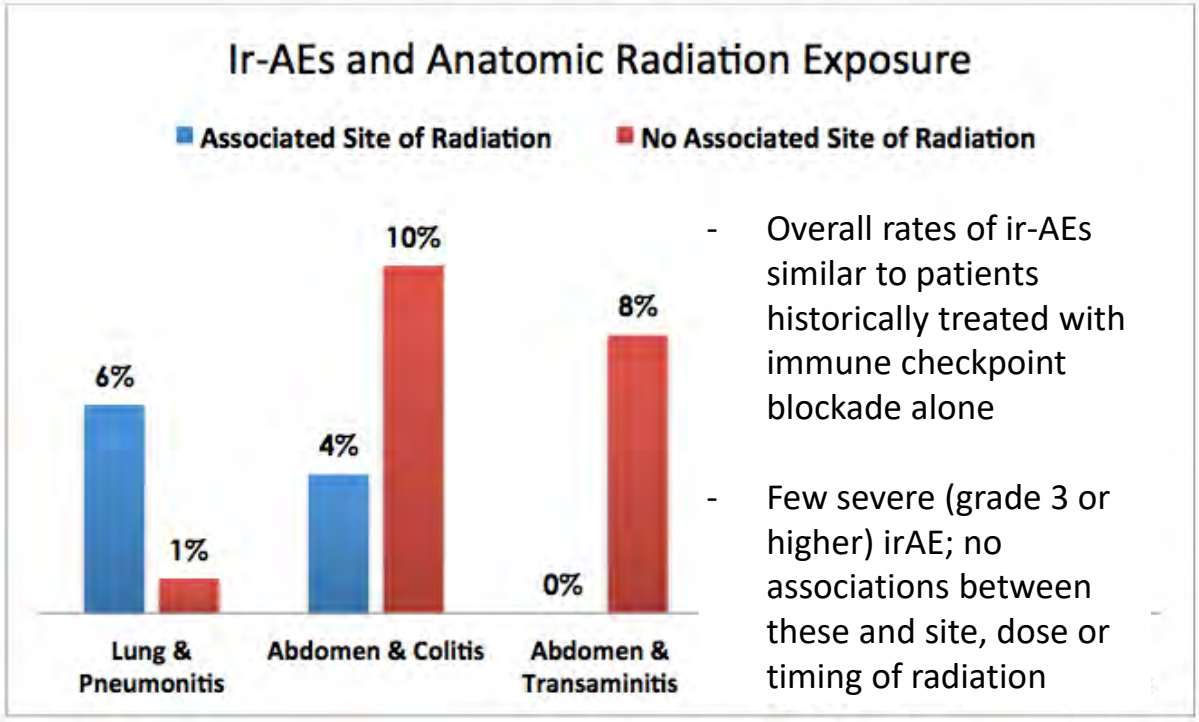
Tolerability of Radiation / Immune Checkpoint Blockade, *Bang et al. IJROBP 2017*

- Retrospective analysis of 133 consecutive patients with metastatic melanoma, renal cell cancer, and lung cancer treated at 5 affiliated centers
- Patients received standard of care palliative radiation and CTLA-4 and/or PD-1 blockade (105 patients received PD-1 inhibitors)



Dr. Andrew Bang

Tolerability of Radiation / Immune Checkpoint Blockade, *Bang et al. IJROBP 2017*



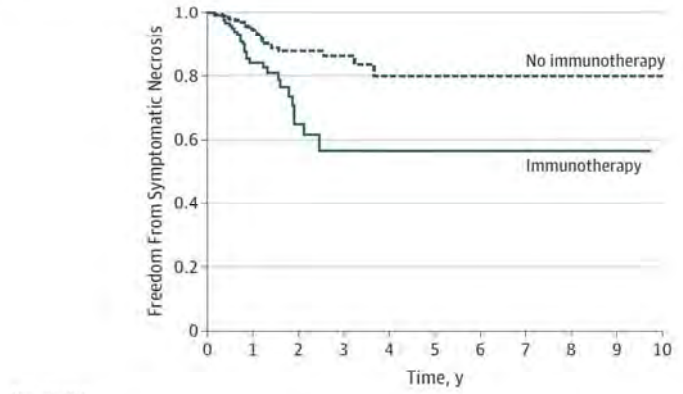
- Overall rates of ir-AEs similar to patients historically treated with immune checkpoint blockade alone
- Few severe (grade 3 or higher) irAE; no associations between these and site, dose or timing of radiation

Tolerability of Radiation / Immune Checkpoint Blockade (ICB), *Martin et al. JAMA Oncol 2018*

- Analysis of 480 patients treated with stereotactic radiosurgery to the brain, 115 of whom were also treated with ICB

- Receipt of ICB was associated with symptomatic radiation necrosis after adjusting for tumor histology (HR 2.6, 95% CI 1.4-4.9), and particularly melanoma patients who received ipilimumab (HR 4.7, 95% CI 1.4-16.2)

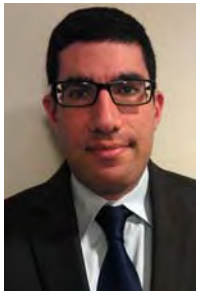
Figure. Kaplan-Meier Curves Displaying Freedom From Symptomatic Necrosis as Stratified by Receipt of Immunotherapy vs No Receipt of Immunotherapy



No. at risk

No immunotherapy	422	203	82	41	20	13	6	3	2	2	1
Immunotherapy	129	67	21	7	4	4	3	2	1	1	0

Log rank *P*<.001.



Dr. Ayal Aizer

Prospective Studies with PD-1 Directed Therapy: PD-L1 Inhibition Following Chemoradiation in Stage III NSCLC (PACIFIC), Antonia et al. NEJM 2017

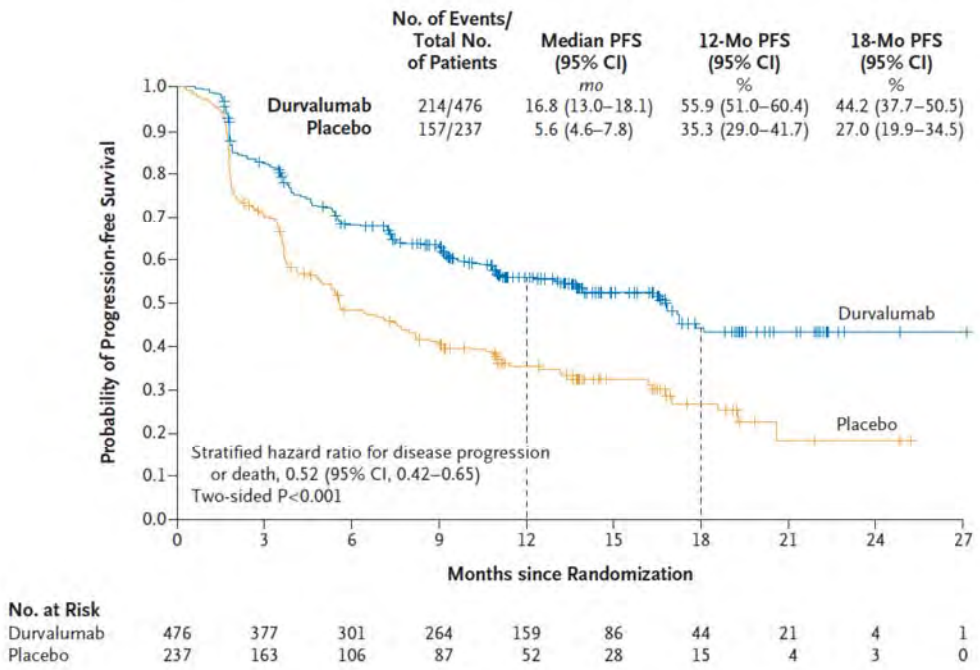
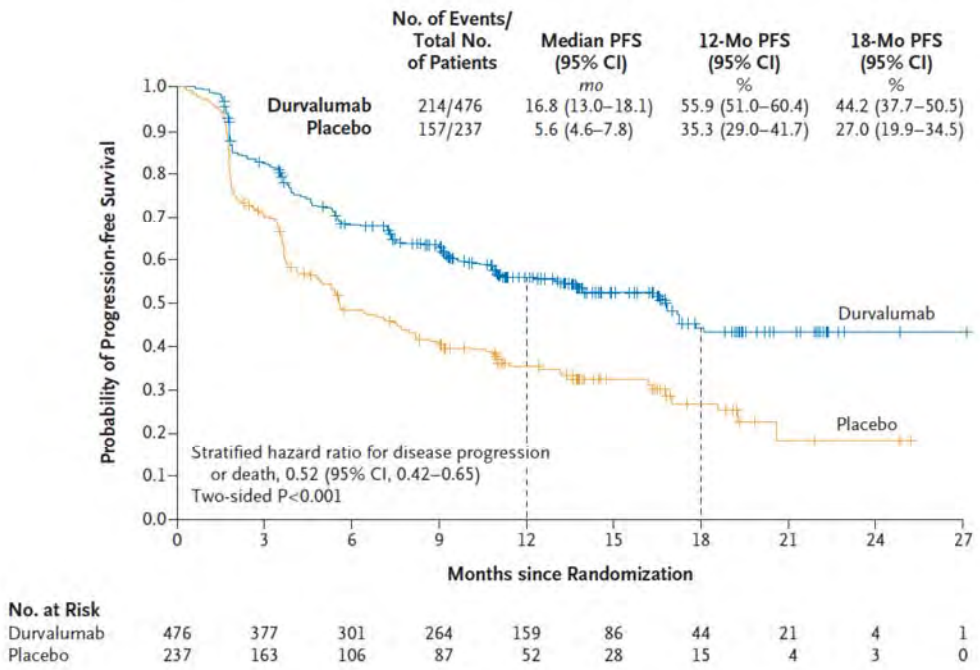


Table 3. Adverse Events of Any Cause.

Event	Durvalumab (N=475)		Placebo (N=234)	
	Any Grade*	Grade 3 or 4	Any Grade*	Grade 3 or 4
	number of patients with event (percent)			
Any event	460 (96.8)	142 (29.9)	222 (94.9)	61 (26.1)
Cough	168 (35.4)	2 (0.4)	59 (25.2)	1 (0.4)
Pneumonitis or radiation pneumonitis†	161 (33.9)	16 (3.4)	58 (24.8)	6 (2.6)
Fatigue	113 (23.8)	1 (0.2)	48 (20.5)	3 (1.3)
Dyspnea	106 (22.3)	7 (1.5)	56 (23.9)	6 (2.6)
Diarrhea	87 (18.3)	3 (0.6)	44 (18.8)	3 (1.3)
Pyrexia	70 (14.7)	1 (0.2)	21 (9.0)	0
Decreased appetite	68 (14.3)	1 (0.2)	30 (12.8)	2 (0.9)
Nausea	66 (13.9)	0	31 (13.2)	0
Pneumonia	62 (13.1)	21 (4.4)	18 (7.7)	9 (3.8)
Arthralgia	59 (12.4)	0	26 (11.1)	0
Pruritus	58 (12.2)	0	11 (4.7)	0
Rash	58 (12.2)	1 (0.2)	17 (7.3)	0
Upper respiratory tract infection	58 (12.2)	1 (0.2)	23 (9.8)	0
Constipation	56 (11.8)	1 (0.2)	20 (8.5)	0
Hypothyroidism	55 (11.6)	1 (0.2)	4 (1.7)	0
Headache	52 (10.9)	1 (0.2)	21 (9.0)	2 (0.9)
Asthenia	51 (10.7)	3 (0.6)	31 (13.2)	1 (0.4)
Back pain	50 (10.5)	1 (0.2)	27 (11.5)	1 (0.4)
Musculoskeletal pain	39 (8.2)	3 (0.6)	24 (10.3)	1 (0.4)
Anemia	36 (7.6)	14 (2.9)	25 (10.7)	8 (3.4)

Prospective Studies with PD-1 Directed Therapy: PD-L1 Inhibition Following Chemoradiation in Stage III NSCLC (PACIFIC), Antonia et al. NEJM 2017



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Back pain	50 (10.5)	1 (0.2)	27 (11.5)	1 (0.4)
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Anemia	36 (7.6)	14 (2.9)	25 (10.7)	8 (3.4)

Limited Rates of Toxicities Observed in other Retrospective / Prospective Studies

- Retrospective:
  - Aboudaram et al. Melanoma Res 2017 (anti-PD-1)
  - Ahmed et al. Annals Onc 2015 (anti-PD-1)
  - Anderson et al. JITC 2018 (anti-PD-1)
  - Barker et al. CIR 2013 (anti-CTLA-4)
  - Colaco et al. J Neurosurg 2016 (anti-CTLA-4 or PD-1)
  - Diao et al. J Neurosurg 2018 (anti-CTLA-4)
  - Fang et al. J. Neuroonc 2017 (anti-PD-1)
  - Hubbeling et al. J. Thoracic Oncol. 2018 (anti-PD-1)
  - Hwang et al. JAMA Onc 2017 (anti-PD-1)
  - Kaidar-Person et al. AntiCancer Drugs 2017 (anti-CTLA-4 or PD-1)
  - Kiess et al. IJROBP 2015 (anti-CTLA-4)
  - Liniker et al. Oncoimmunology 2016 (anti-PD-1)
  - Patel et al. Am J Clin Oncol 2015 (anti-CTLA-4)
  - Qin et al. IJROBP 2016 (anti-CTLA-4)
  - Shaverdian et al. Lancet Oncol 2017 (anti-PD-1)
- Prospective:
  - Hiniker et al. IJROBP 2016 (anti-CTLA-4 with palliative RT)
  - Katz et al. ASCO 2017 (anti-PD-1 with neoadjuvant chemoRT in pancreatic cancer)
  - Luke et al. JCO 2018 (anti-PD-1 with SBRT)
  - Papadopoulos et al. ASCO 2016 (anti-PD-1 with hypofractionated RT)
  - Powell et al. ASCO 2017 (anti-PD-1 with definitive chemoradiation in head and neck cancer)
  - Tang et al. CCR 2016 (anti-CTLA-4 with SBRT)
  - Tywan St. Victor et al. Nature 2015 (anti-CTLA-4 with hypofractionated RT)
  - Welsh et al. ASTRO 2017 (anti-CTLA-4 with SBRT)
  - Williams et al. IJROBP 2017 (anti-CTLA-4 with SRS/WBRT)

Limited Rates of Toxicities Observed in other Retrospective / Prospective Studies

- Retrospective:
  - Aboudaram et al. Melanoma Res 2017 (anti-PD-1)
  - Ahmed et al. Annals Onc 2015 (anti-PD-1)
  - Anderson et al. JITC 2018 (anti-PD-1)
  - Barker et al. CIR 2013 (anti-CTLA-4)
  - Colaco et al. J Neurosurg 2016 (anti-CTLA-4 or PD-1)
  - Diao et al. J Neurosurg 2018 (anti-CTLA-4)
  - Fang et al. J. Neuroonc 2017 (anti-PD-1)
  - Hubbeling et al. J. Thoracic Oncol. 2018 (anti-PD-1)
  - Hwang et al. JAMA Onc 2017 (anti-PD-1)
  - Kaidar-Person et al. AntiCancer Drugs 2017 (anti-CTLA-4 or PD-1)
  - Kiess et al. IJROBP 2015 (anti-CTLA-4)
  - Liniker et al. Oncoimmunology 2016 (anti-PD-1)
  - Patel et al. Am J Clin Oncol 2015 (anti-CTLA-4)
  - Qin et al. IJROBP 2016 (anti-CTLA-4)
  - Shaverdian et al. Lancet Oncol 2017 (anti-PD-1)

- Prospective:
  - Hiniker et al. IJROBP 2016 (anti-CTLA-4 with palliative RT)
  - Katz et al. ASCO 2017 (anti-PD-1 with neoadjuvant chemoRT in pancreatic cancer)
  - Luke et al. JCO 2018 (anti-PD-1 with SBRT)
  - Papadopoulos et al. ASCO 2016 (anti-PD-1 with hypofractionated RT)
  - Powell et al. ASCO 2017 (anti-PD-1 with definitive chemoradiation in head and neck cancer)
  - Tang et al. CCR 2016 (anti-CTLA-4 with SBRT)
  - Tywan St. Victor et al. Nature 2015 (anti-CTLA-4 with hypofractionated RT)
  - Welsh et al. ASTRO 2017 (anti-CTLA-4 with SBRT)
  - Williams et al. IJROBP 2017 (anti-CTLA-4 with SRS/WBRT)

Conventionally fractionated chemoradiation

Limited Rates of Toxicities Observed in other Retrospective / Prospective Studies

- Retrospective:
  - Aboudaram et al. Melanoma Res 2017 (anti-PD-1)
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  - Barker et al. CIR 2013 (anti-CTLA-4)
  - Colaco et al. J Neurosurg 2016 (anti-CTLA-4 or PD-1)
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  - Fang et al. J. Neuroonc 2017 (anti-PD-1)
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  - Hwang et al. JAMA Onc 2017 (anti-PD-1)
  - Kaidar-Person et al. AntiCancer Drugs 2017 (anti-CTLA-4 or PD-1)
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  - Liniker et al. Oncoimmunology 2016 (anti-PD-1)
  - Patel et al. Am J Clin Oncol 2015 (anti-CTLA-4)
  - Qin et al. IJROBP 2016 (anti-CTLA-4)
  - Shaverdian et al. Lancet Oncol 2017 (anti-PD-1)

- Prospective:
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  - Tang et al. CCR 2016 (anti-CTLA-4 with SBRT)
  - Tywan St. Victor et al. Nature 2015 (anti-CTLA-4 with hypofractionated RT)
  - Welsh et al. ASTRO 2017 (anti-CTLA-4 with SBRT)
  - Williams et al. IJROBP 2017 (anti-CTLA-4 with SRS/WBRT)

Higher dose stereotactic body radiotherapy (SBRT) treatment

Limited Rates of Toxicities Observed in other Retrospective / Prospective Studies

- Retrospective:
  - Aboudaram et al. Melanoma Res 2017 (anti-PD-1)
  - Ahmed et al. Annals Onc 2015 (anti-PD-1)
  - Anderson et al. JITC 2018 (anti-PD-1)
  - Barker et al. CIR 2013 (anti-CTLA-4)
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  - Kaidar-Person et al. AntiCancer Drugs 2017 (anti-CTLA-4 or PD-1)
  - Kiess et al. IJROBP 2015 (anti-CTLA-4)
  - Liniker et al. Oncoimmunology 2016 (anti-PD-1)
  - Patel et al. Am J Clin Oncol 2015 (anti-CTLA-4)
  - Qin et al. IJROBP 2016 (anti-CTLA-4)
  - Shaverdian et al. Lancet Oncol 2017 (anti-PD-1)
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  - Hiniker et al. IJROBP 2016 (anti-CTLA-4 with palliative RT)
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  - Tang et al. CCR 2016 (anti-CTLA-4 with SBRT)
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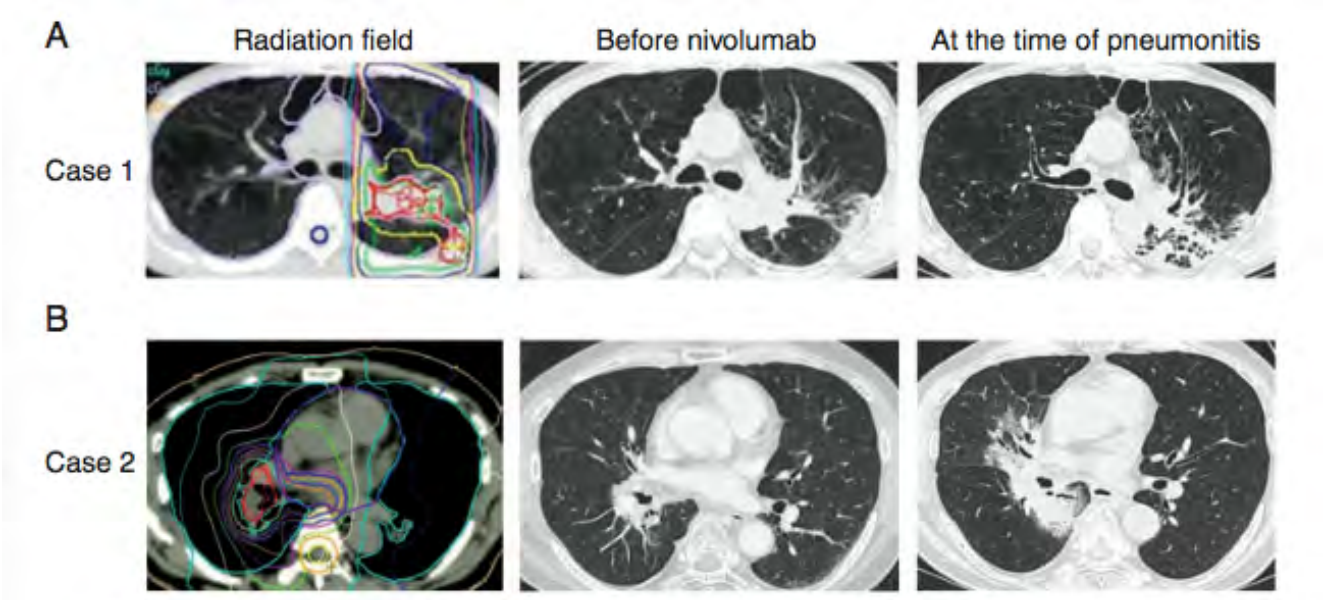
  - Welsh et al. ASTRO 2017 (anti-CTLA-4 with SBRT)
  - Williams et al. IJROBP 2017 (anti-CTLA-4 with SRS/WBRT)

Hypofractionated radiation

Attention is Needed in Future Studies and With Longer Follow up

- Nivolumab induced radiation recall pneumonitis (Shibaki et al. Annals Oncology 2017)



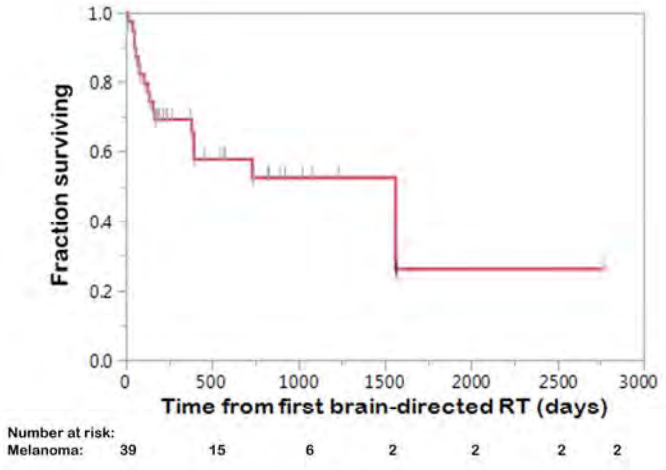
Outline

- Toxicity concerns
- Existing and emerging clinical data
- Path forward, challenges

Combining Standard of Care Radiation and Immunotherapy: Clinical Practice

- Concerns regarding theoretical and observed toxicity must be balanced by clinical benefit
  - Pike et al. Radiother Oncol 2017, median overall survival in melanoma patients treated with brain radiation/PD-1 inhibitors > 4 years
  - No evidence to support arbitrary time cutoffs between therapies

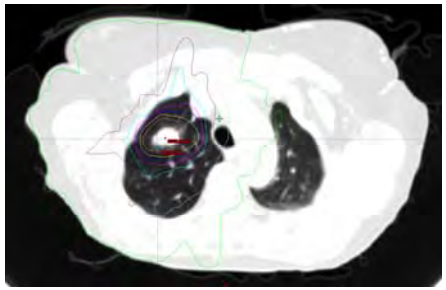
Dr. Luke Pike



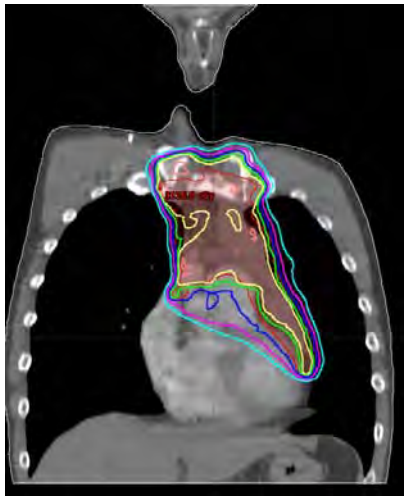
Pike et al. Radiother Oncol 2017: Survival from first brain-directed radiation therapy for melanoma patients receiving PD-1 checkpoint inhibition. Median survival 52 months.

Outstanding Questions

- Fewer data in regards to:
  - Combinations in the definitive setting (e.g. with definitive chemoradiation, larger field radiation, etc.)
  - High dose radiation – SBRT
- Novel combinations currently being explored in the clinic
  - E.g. CTLA-4/PD-1 inhibitors; CAR-T cells, IDO inhibitors, other immune checkpoint inhibitors, intratumoral immune therapies



Lung SBRT given in combination with PD-1 inhibition on protocol.



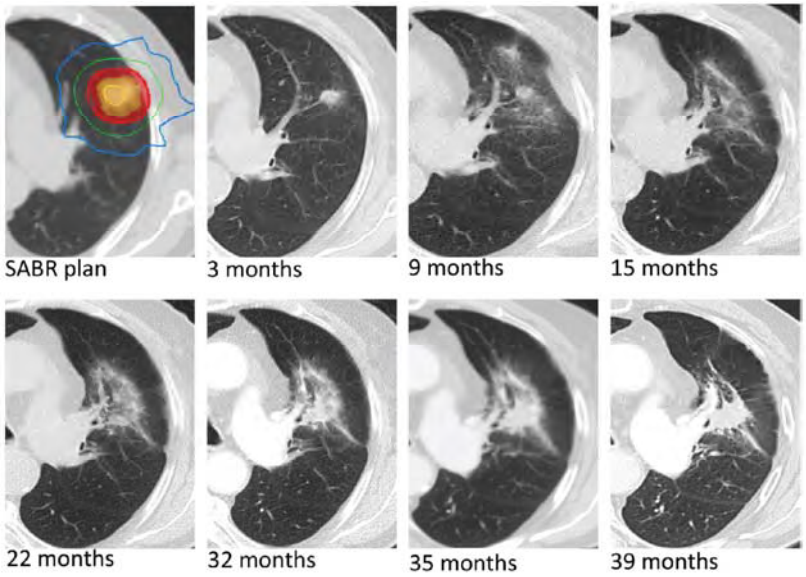
Fractionated RT for Hodgkin's Lymphoma. Image courtesy of Andrea Ng MD.

Challenges

- Time course of side effects can be delayed (both with immunotherapy and radiation)
  - Importance of multidisciplinary and extended follow-up after initiating combined therapy

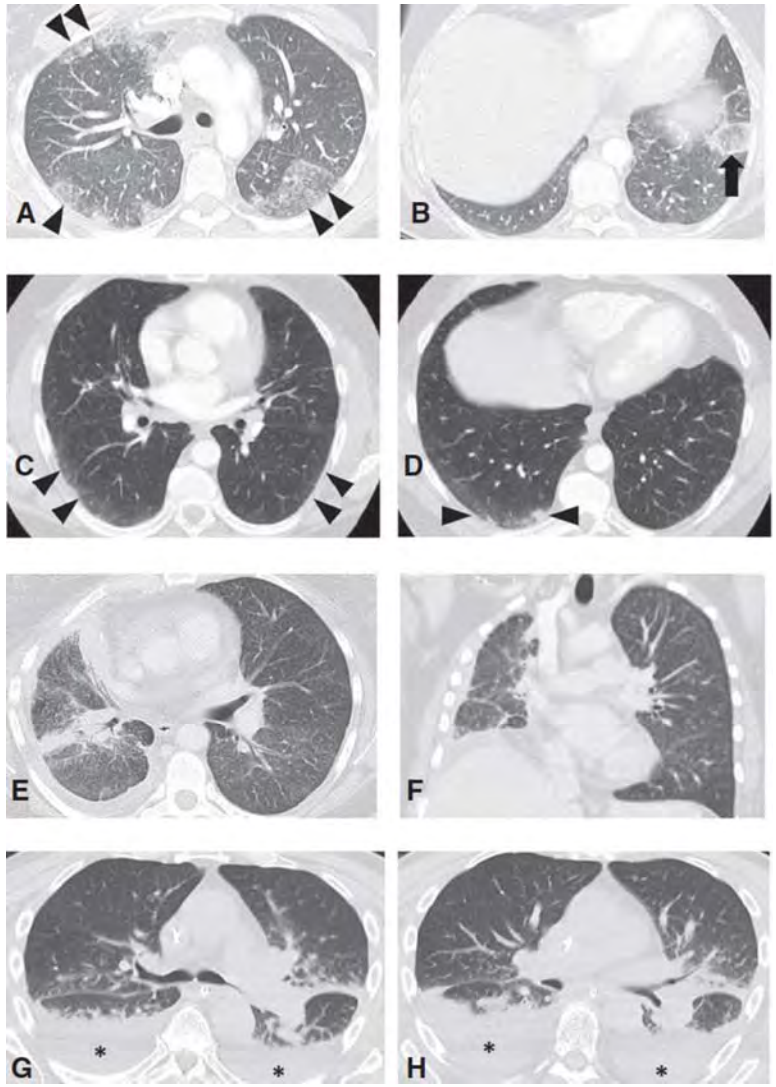
- Attribution of side effects can be difficult (e.g. pneumonitis, elevated liver function tests, etc.)

Attributing Lung Toxicity



Above: Evolving radiation induced lung injury following SABR/SBRT. Huang et al. J. Thoracic Oncology, 2015.

Right: Spectrum of radiographic manifestations of PD-1 inhibitor-related pneumonitis. Nishino et al. Clinical Cancer Research 2016.



Summary

- Immunotherapy has unique toxicities, many of which overlap with potential radiation effects
- Initial data suggests standard of care and experimental approaches that combine radiation and immune checkpoint blockade are generally safe but more data are needed
- Challenges moving forward include lack of mechanistic understanding / biomarkers, the variability and time course with which side effects develop, rapid development of new drugs and therapies

Considerations Moving Forward

- Need for evaluation of toxicity in randomized clinical trials evaluating radiation (e.g. impact of radiation dose)

- Importance of collecting radiation data on trial and also of using multi-institutional registries / databases to evaluate toxicities and rare side-effects
  - ePRO pilot to be integrated on ETCTN protocol 10021 (Durvalumab/tremelimumab +/- low or high dose RT)

- Value for education of the multidisciplinary team as more patients receive immunotherapy in the definitive setting

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AACR American Association for Cancer Research
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AMERICAN SOCIETY FOR RADIATION ONCOLOGY

SESSION III Panel Discussion:

Immunotherapy

Moderators: Marka Crittenden, MD, PhD, and Andrew B. Sharabi, MD, PhD

Panelists:

David M. Berman, MD, PhD
Michael Yellin, MD
Margaret K. Yu, MD
Andy J. Minn, MD
Steven J. Chmura, MD, PhD
Jonathan D. Schoenfeld, MD, MPhil, MPH

U.S. FOOD & DRUG ADMINISTRATION

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AMERICAN SOCIETY FOR RADIATION ONCOLOGY

SESSION IV:

Other Targeted Therapies

Session Cochairs: Theodore S. Lawrence, MD, PhD, and Ester M. Hammond, PhD

Speakers:

Kyle Cuneo, MD

Meredith A. Morgan, PhD

Ester M. Hammond, PhD

Andrew Wang, MD

FDA-AACR-ASTRO Workshop 2018

Combining Chemoradiation with Novel Kinase Inhibitors

Kyle C. Cuneo, MD

Department of Radiation Oncology

University of Michigan

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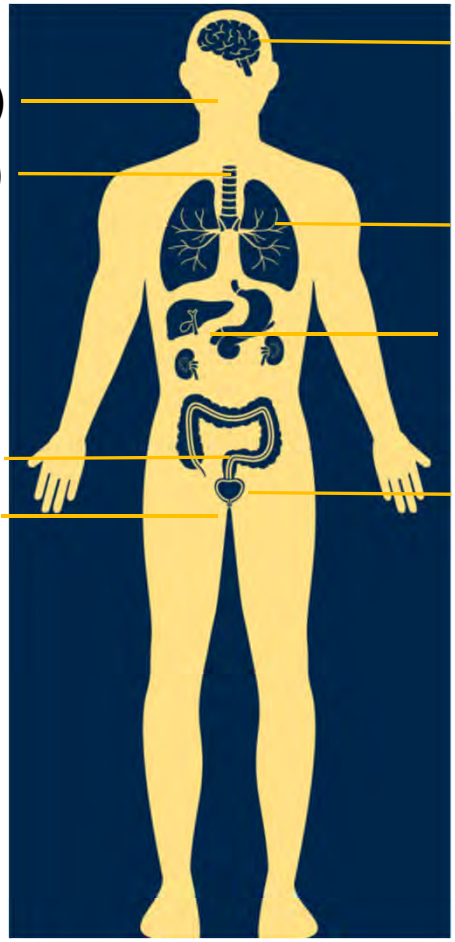
Disclosures

- **Employee at University of Michigan**
- **Grant funding from NCI/NIH**

Chemoradiation treatment for locally advanced cancers



Chemoradiation regimen (5-year survival rate)

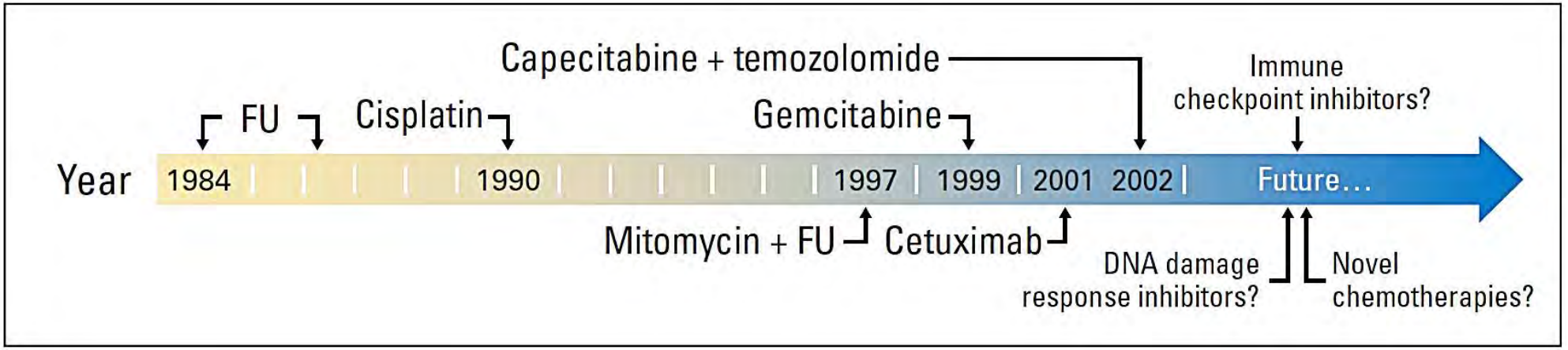
Chemoradiation is standard of care for most locally advanced cancer.

Long term outcomes remain suboptimal for most sites.

Potential areas for improvement:

- **Improve cure rates**
- **Organ preservation**
- **Reduce toxicity**

Timeline of the development of chemoradiation regimens.



Sensitizing regimens have changed minimally since introduced

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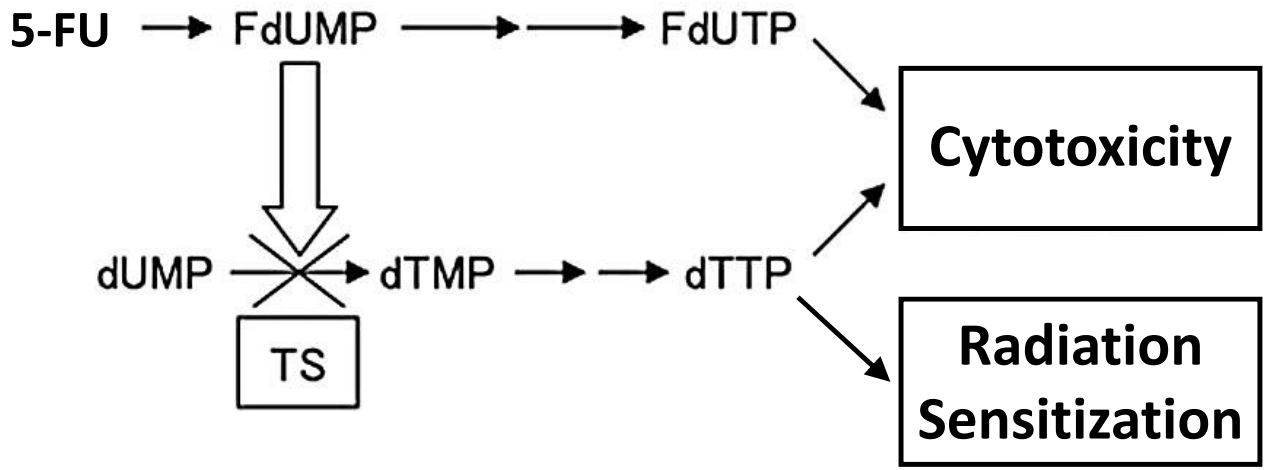
Lawrence TS, Haffty BG, Harris JR. J Clin Oncol. 2014;32(12)1173-9.

5-FU and Related Compounds



- First described by Heidelberger et al. in 1957
- FdUMP inhibits thymidylate synthase
  - Decreases dTTP leading to:
    - Inhibition of DNA synthesis
    - Accumulation in early S phase
  - FdUTP misincorporates into DNA
    - Initiates a futile repair cycle

Key
5-FU: 5-fluorouracil
dUMP: deoxyuridine monophosphate
dUTP: deoxyuridine triphosphate
dTTP: deoxythymidine triphosphate
TS: Thymidylate synthase

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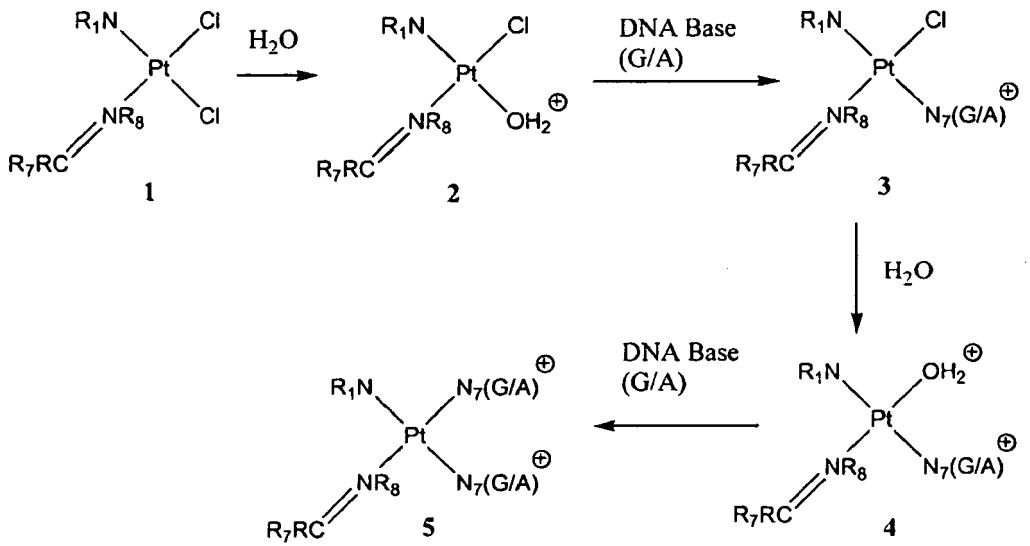
Shewach DS, Lawrence TS. J Clin Oncol. 2007;25(26)4043-50.

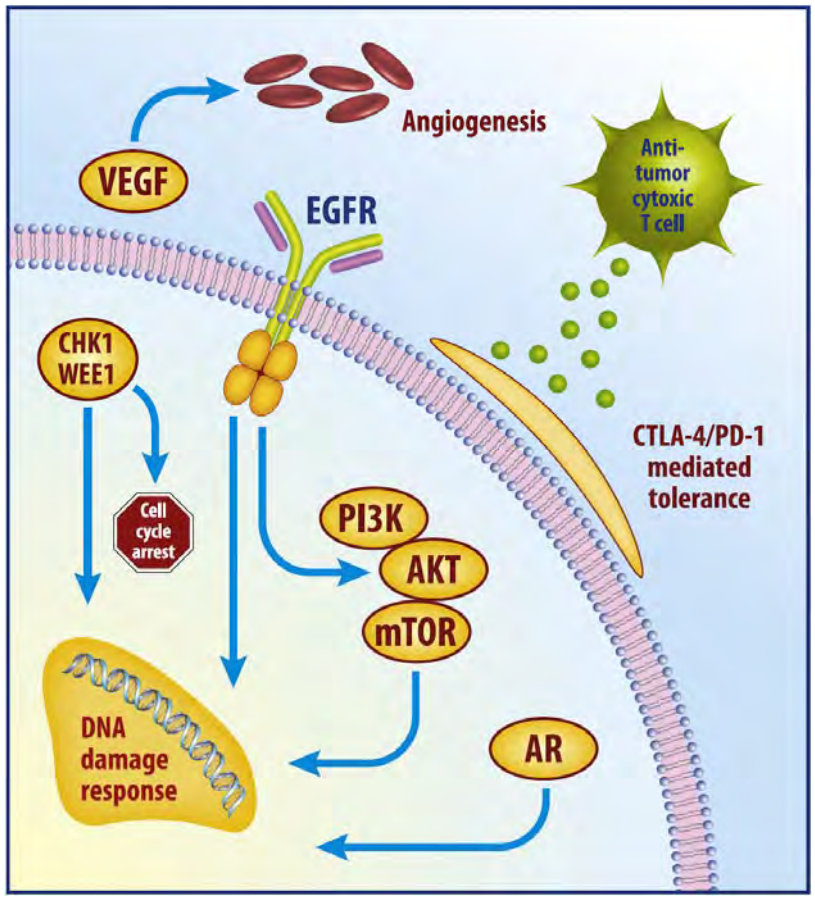
Cisplatin



- Discovered in 1845
- Licensed for medical use in 1979
- Interferes with DNA replication
- Crosslinks DNA
- Mechanism of radiation sensitization not fully understood

Improving chemoradiation with targeted therapies

- Signal transduction
  - EGFR
  - PI3K/AKT
  - MEK/ERK
  - MET
- Cell cycle checkpoints
  - WEE1
  - CHK1
- Microenvironment
  - VEGF
  - Immunotherapy



Morgan MA, Parsels LA, Maybaum J et al. Clin Cancer Res 2008;14(21):6544-50.

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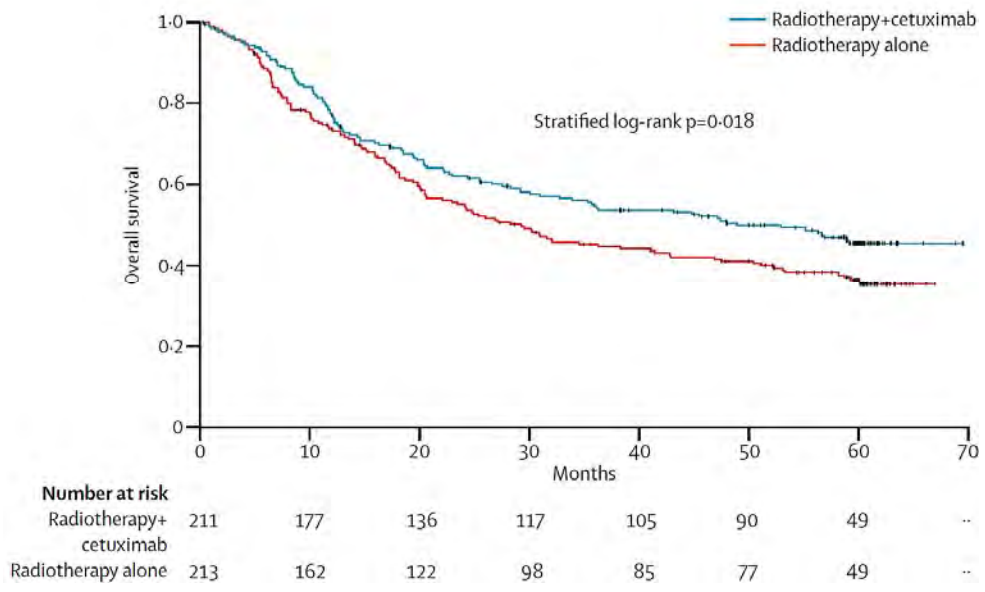
EGFR inhibition in Head and Neck Cancer

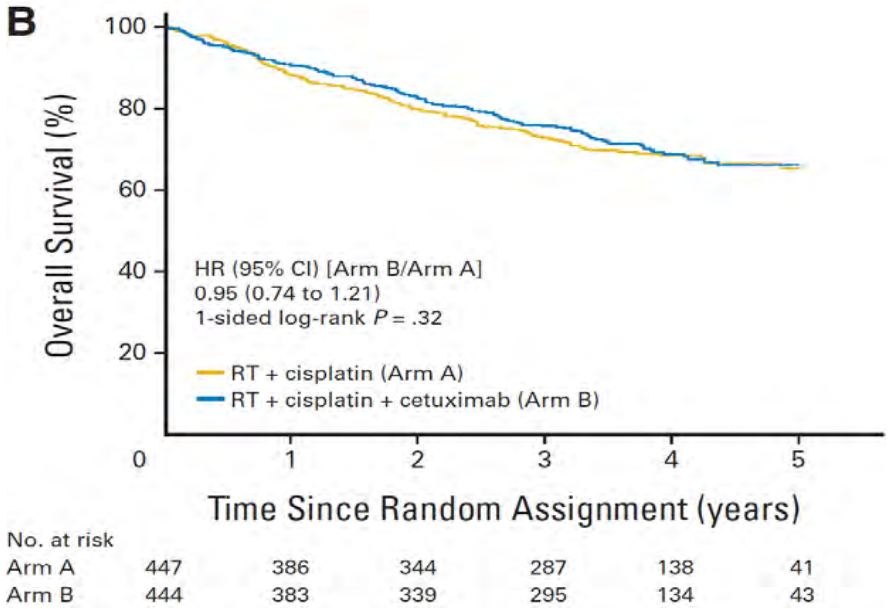
- **Cetuximab improves OS when combined with radiation alone**
- **Adding cetuximab to cisplatin has no benefit with more toxicity**

Radiation with cetuximab



Bonner JB et al. Lancet Oncol 2010. 11(1):21-8.

Chemoradiation with cetuximab

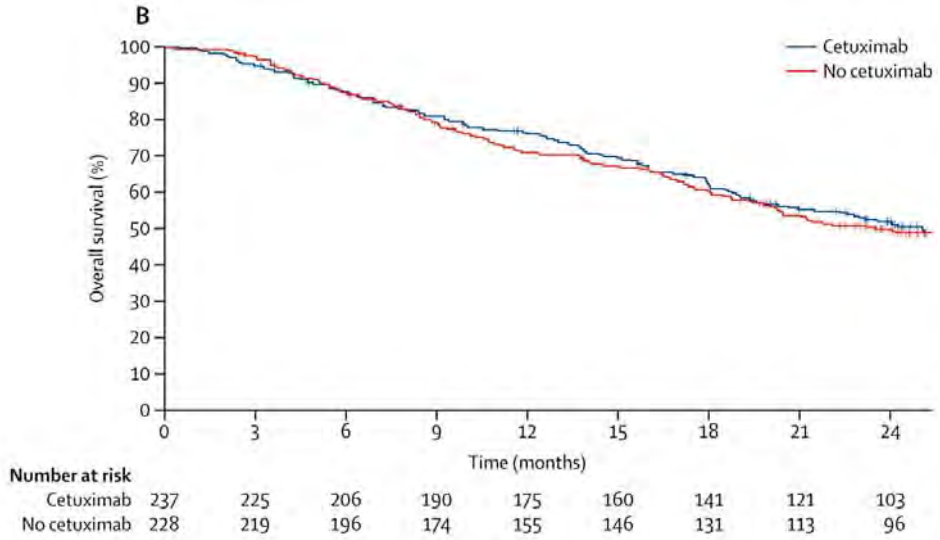


Ang KK et al. J Clin Oncol 2014. 32(27):2940-50. (RTOG0522)

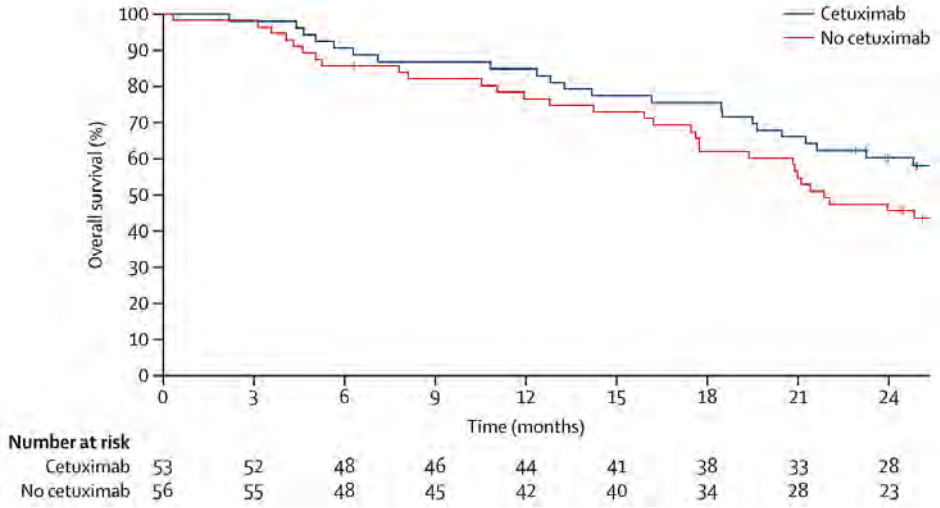
Study	Disease	Treatment arms	N	Results (red indicates statistically significant result)	Toxicity/Notes
RTOG 0522 Ang et al., 2014 Phase III	Head and neck cancer All sites	1. Radiation with cisplatin 2. Radiation with cisplatin + cetuximab	895	3 y OS: 73% chemoRT vs. 76% chemoRT + cetuximab 3 y PFS: 61% chemoRT vs. 59% chemoRT + cetuximab 3 y DM: 13% chemoRT vs. 10% chemoRT + cetuximab	Grade 3-4 mucositis higher with cetuximab More skin toxicity with cetuximab
TREMPLIN Lefebvre et al., 2013 Randomized Phase II	Head and neck cancer Larynx Hypopharynx	Induction docetaxel/cisplatin, if response: 1. Radiation with cisplatin 2. Radiation with cetuximab	116	3 mo larynx preservation: 95% RT + cisplatin vs. 93% RT + cetuximab 18 mo OS: 92% RT + cisplatin vs. 89% RT + cetuximab	Treatment compliance higher in cetuximab arm Similar results with induction chemo followed by RT alone
Italian Study Group Ghi et al. 2012, 2013 Randomized Phase II	Head and neck cancer All sites	2 x 2 factorial design A. Plus or minus induction docetaxel/cisplatin/5-FU B. Radiation with cisplatin/5-FU or cetuximab	421	Complete response: 36% chemoRT vs. 39% cetuximab-RT Median PFS: 21.6 mo chemoRT vs. 20.7 mo cetuximab-RT Median OS: 44.7 mo chemoRT vs. 44.7 mo cetuximab-RT	Primary endpoint was in field grade 3-4 toxicity: Mucositis 29% chemoRT vs. 23% cetuximab-RT Skin reaction: 11% chemoRT vs. 14% cetuximab-RT
CONCERT-1 Mesia et al., 2015 Randomized phase II	Head and neck cancer All sites	1. Radiation with cisplatin 2. Radiation with cisplatin + panitumumab	153	2 y locoregional control: 68% chemoRT vs. 61% chemoRT + panitumumab	Serious toxicity rate: 32% chemoRT vs. 43% chemoRT + panitumumab

Nonsmall cell lung cancer: RTOG 0617

All patients



High EGFR expression



Study	Disease	Treatment arms	N	Results (red indicates statistically significant result)	Toxicity/Notes
RTOG 0324 Blumenschein et al., 2011 Phase II	Nonsmall cell lung cancer	Radiation with carboplatin/paclitaxel + cetuximab	93	Response rate: 62% Median OS: 22.7 months 2 y OS: 49%	Grade 4 hematological toxicity: 22% Grade 3 esophagitis: 8%; G3-4 pneumonitis: 7% 5 treatment related deaths
CALGB 30407 Govindan et al., 2011 Randomized Phase II	Nonsmall cell lung cancer	1. Radiation with carboplatin/pemetrexed 2. Radiation with carboplatin/pemetrexed + cetuximab	101	18 mo OS: 58% chemoRT vs. 54% chemoRT + cetuximab	Grade 3+ toxicity: 76% ChemoRT vs. 85% ChemoRT + cetuximab
Netherlands van den Heuvel et al., 2014 Randomized Phase II	Nonsmall cell lung cancer	1. Radiation with cisplatin 2. Radiation with cisplatin + cetuximab	102	Local control : 84% chemoRT vs. 92% chemoRT + cetuximab 1 y OS: 82% chemoRT vs. 71% chemoRT + cetuximab	Toxicity similar between groups
RTOG 0617 Bradley et al., 2015 Phase III	Nonsmall cell lung cancer	1. Radiation with carboplatin/paclitaxel 2. Radiation with carboplatin/paclitaxel + cetuximab	544	Median OS: 24 mo chemoRT vs. 25 mo chemoRT + cetuximab High EGFR expression subset: Median OS: 21 mo chemoRT vs. 42 mo chemoRT + cetuximab	Grade 3+ toxicity increased with cetuximab: 86% vs. 70%

EGFRi with chemoradiation in Rectal Cancer

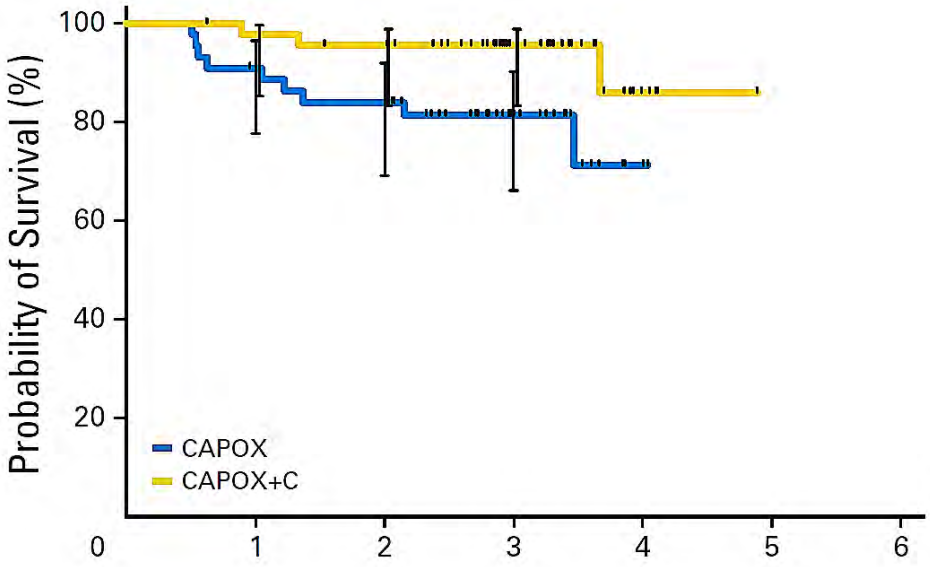
No patient selection

Variable	Arm 1 (n=49)	Arm 2 (n=49)
pCR	33%	31%
TRG		
0	2%	2%
1	14%	6%
2	10%	6%
3	35%	47%
4	33%	31%
Most frequent G3-4 toxicities		
Diarrhea	16%	24%
Rash	0%	10%
Mucositis	5%	6%
Dehydration	5%	6%

US Oncology Study
98 patients
Randomized to 5-FU RT +/- cetuximab
No difference in RR or PFS/OS
Increased toxicity

McCollum DA, Kocs DM, Chadha P, et al. J Clin Oncol. 32 (S3) 2014: 537.

KRAS/BRAF WT



EXPERT-C Trial
90 patients
KRAS/BRAF WT rectal cancer
Randomized to CAPOX then CAP-RT +/- cetuximab
Improved response rate and OS

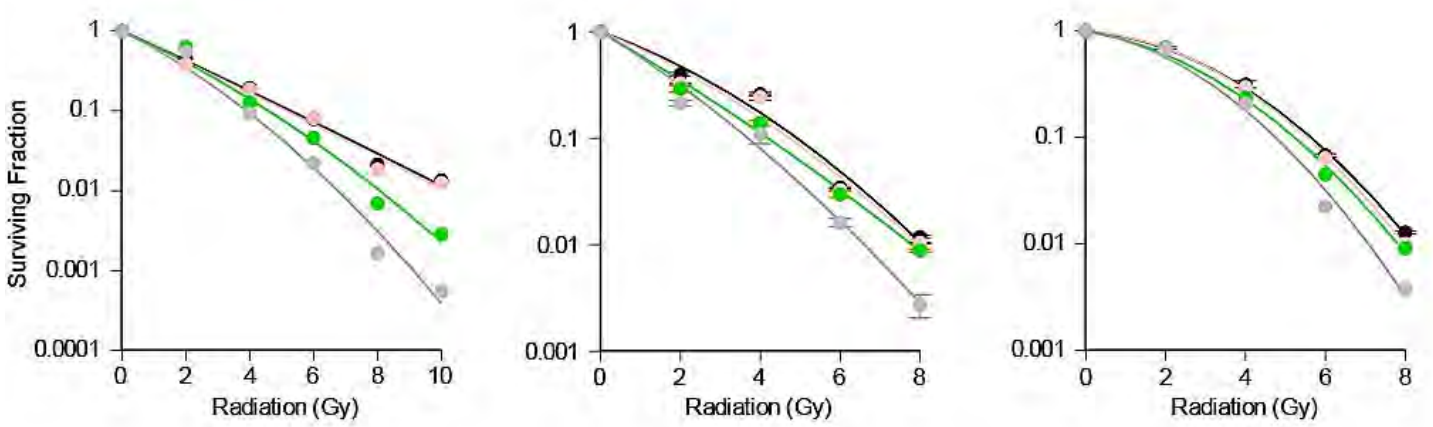
Dewdney A, Cunningham D, Tabernero J, et al. J Clin Oncol. 2012;301620-7.

Factors Associated with EGFR Response

Disease	Factors Associated with Sensitivity	Factors Associated with Resistance
Head and neck cancer	Accelerated radiation fractionation Acneiform rash (cetuximab) Oropharynx primary	HPV negative tumor Smoker Non-oropharynx primary
Nonsmall cell lung cancer	EGFR mutation: exon 19 and 12 (L858R, L861), exon 18 (G719X, G719), exon 20 (S768I) KRAS wild type EGFR overexpression Non-squamous cell histology Non-smoker Asian heritage Female sex	EGFR T790M mutation EGFR exon 20 insertion KRAS mutation Squamous cell carcinoma MET amplification/overexpression Epithelial to mesenchymal transition
Colorectal cancer	RAS wild type BRAF wild type Increased EGFR gene copy number	KRAS mutation NRAS mutation BRAF mutation MET amplification/overexpression HER2 amplification/overexpression EGFR mutation in cetuximab binding domain (rare)

Scheduling of Chemoradiation with targeted therapies

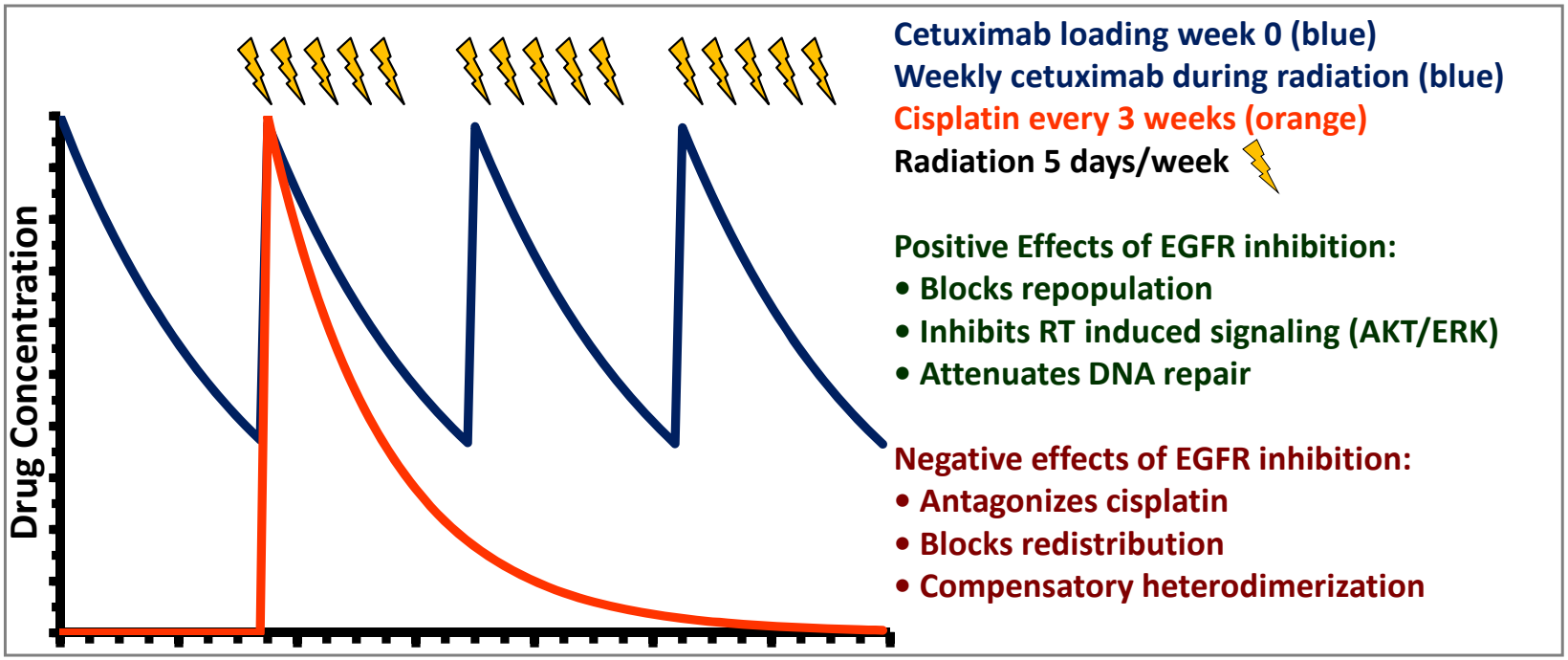
- **Drug schedule affects radiosensitivity**
- **Delivering the optimal sequence in patients is challenging**
- **Suboptimal sequencing may lead to missed opportunities for patients**



	Dose Modification Factor (DMF)		
RT			
Crizotinib 4h-Wash-RT	1.02±0.01	1.06±0.01	1.01±0.004
Crizotinib 4h RT	1.40±0.16	1.19±0.13	1.12±0.01
Crizotinib 24h RT	1.54±0.10	1.30±0.05	1.23±0.01

Cuneo et al. Unpublished data.

Scheduling Cetuximab with Chemoradiation

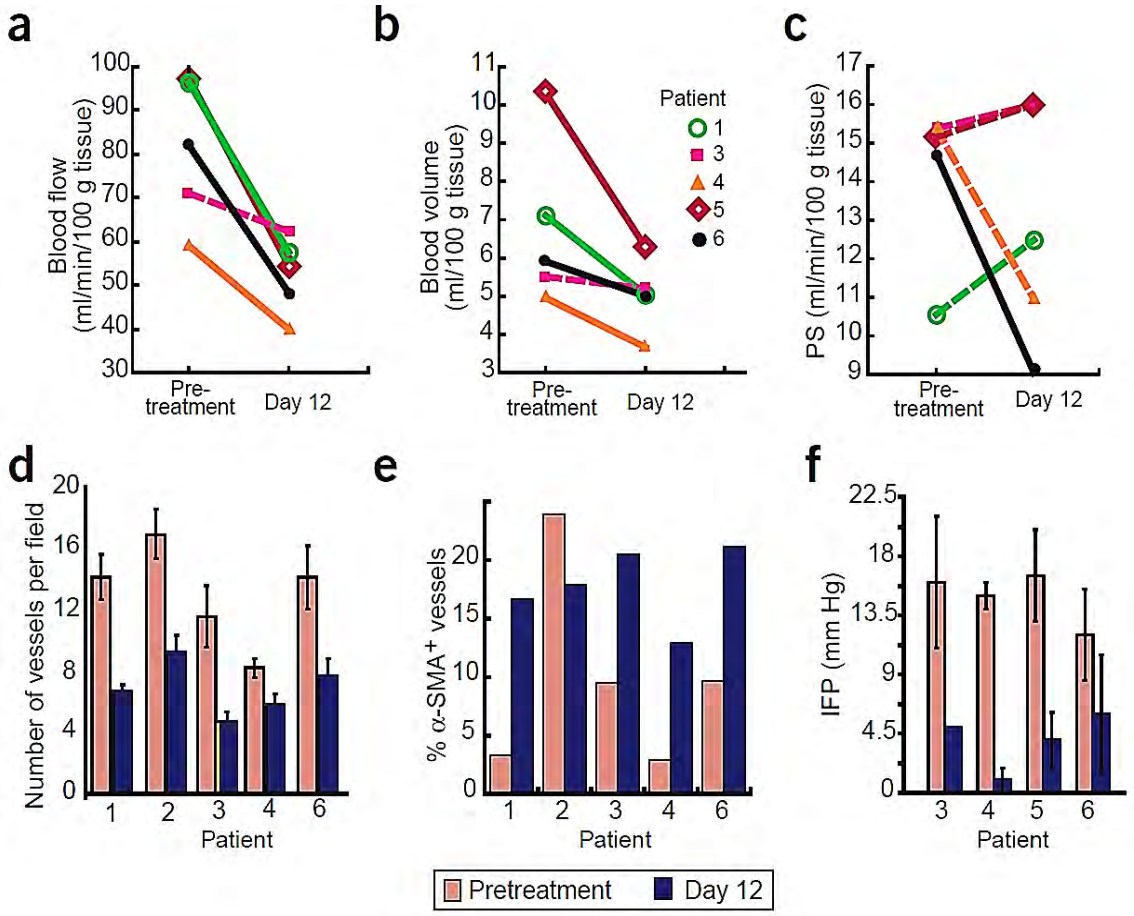


Potential issues:		Potential solutions:
Loading dose antagonizes chemotherapy	→	Eliminate loading dose
Long half life affect cell cycle redistribution	→	EGFR inhibitor with shorter half life

Cuneo KC, Nyati MK, Ray D, Lawrence TS. Pharmacol Ther. 2015;154:67-77.

VEGFi in Rectal Cancer: Impact of Scheduling

- **Rationale:**
  - VEGF/VEGFR inhibition normalizes vasculature
  - Increases delivery of systemic therapy
  - Improves oxygenation
- **Clinical Data**
  - 14 reported phase II studies in rectal cancer
  - CR rates range from 11-34%
  - Concern for postoperative complications



Willett CG, Boucher Y, di Tomaso E, et al. *Nature Med.* 2004:10, 145 - 147 .

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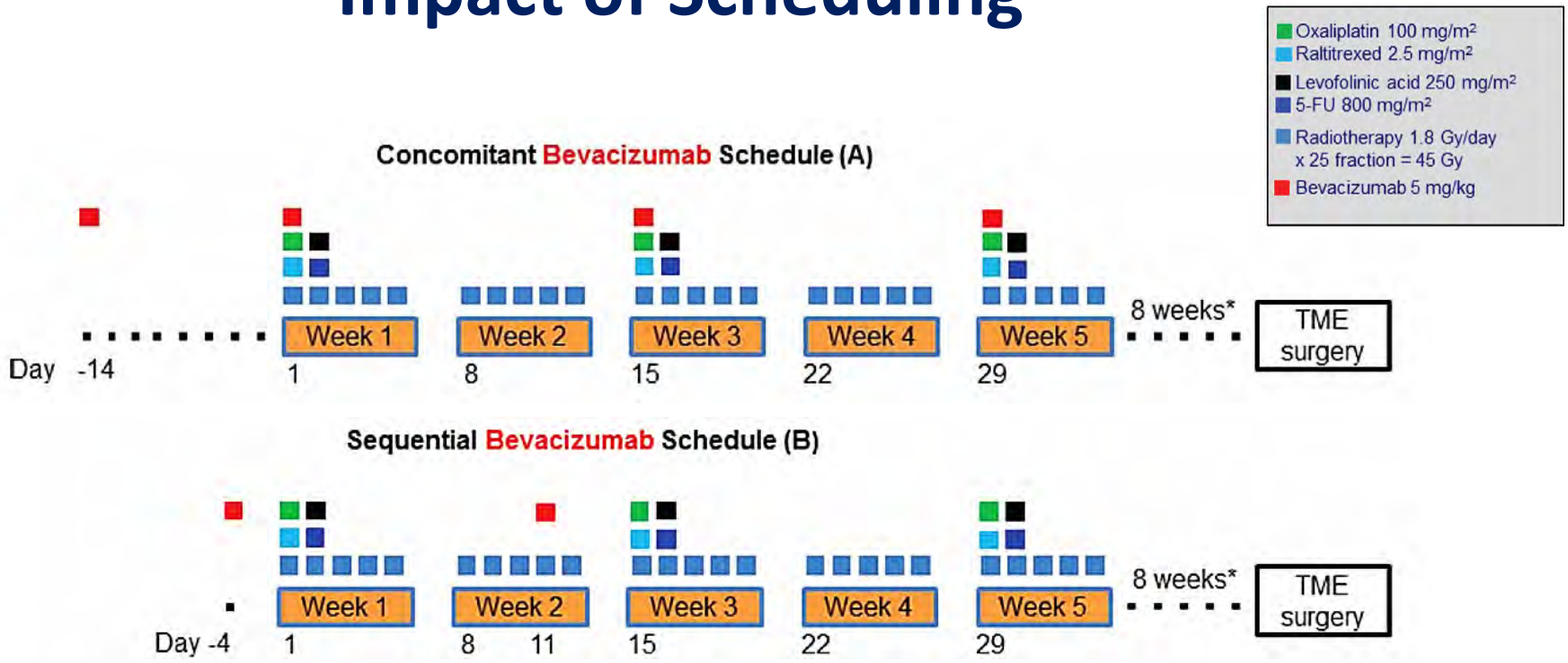
Impact of Scheduling



Complete regression rate: Schedule A 12% vs. Schedule B 50%

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Avallone A, Pecori B, Bianco F. Oncotarget. 2015 Oct 6;6(30):30394-407

Conclusions

- Chemoradiation regimens have evolved very slowly
- Novel targeted therapies can change current treatment paradigms
- Previous studies limited by scheduling and patient selection
- Optimizing scheduling and target selection is essential for success
- Need for improved preclinical models
- Need for biomarker based patient selection

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The potential of DNA damage response (DDR) inhibitors in combination with radiation treatment

Meredith Morgan, PhD

closures

- I receive research funding from AstraZeneca.
- I will not discuss any off-label uses.

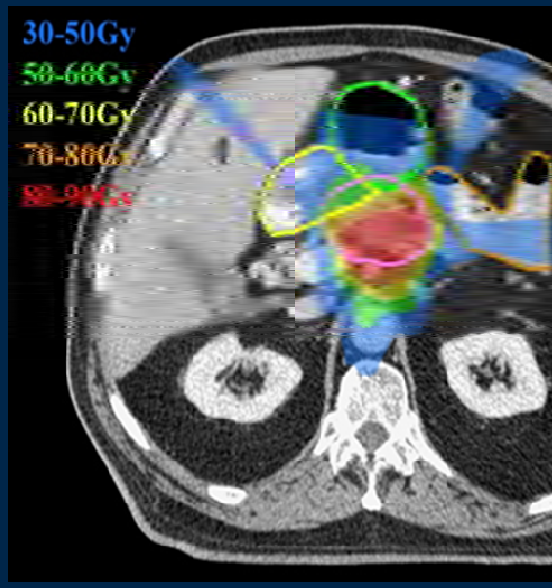
erview

- Rationale for combing DDR inhibitors with radiation

- Strategies for development of DDR inhibitors with radiation:
  - Integration with chemoradiation
  - DDR-DDR inhibitor combinations with radiation
  - DDR-immunotherapy combinations with radiation

diation Therapy

- Radiation is the most prescribed cancer therapy
- Major technological advancements in radiation delivery have maximized tumor radiation doses
- Given in combination with full systemic doses of chemotherapy for most locally advanced cancers
- Chemoradiation escalated to maximum tolerated dose; more radiation or additional chemotherapy is not feasible
- Further improvements in treatment will require tumor cell selective agents



Intensity modulated radiatio
pancreatic cancer

R is a promising target for improving chemoradiation

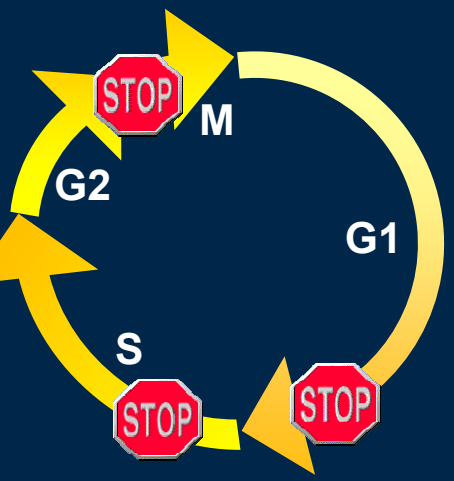
NA is the principal target of radiation.

adiation-induced cell death is caused by unrepaired DNA double-rand breaks.

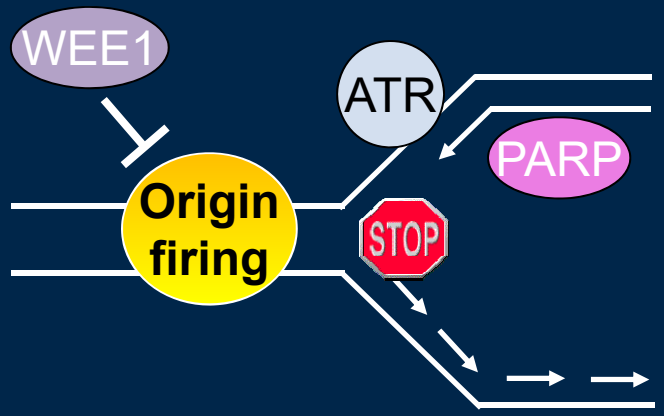
hibition of the DNA damage response improves radiation therapy fficacy and has the potential to improve survival in patients with cally advanced cancer[1, 2] .

gan et al., *Cancer Discov* 4:28-0-91, 2014
gan & Lawrence, *Clin Cancer Res* 21:2898-904, 2015

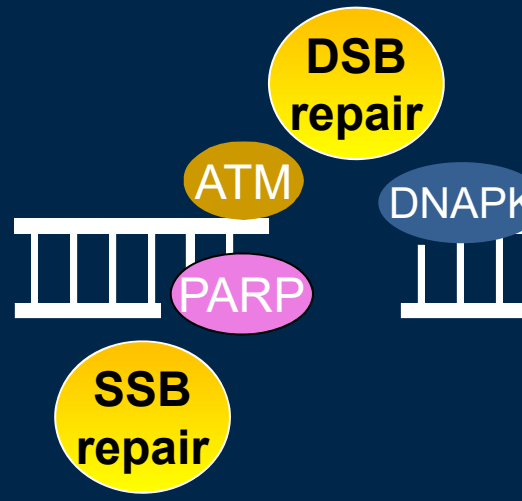
lular responses to radiation



Stop proliferation



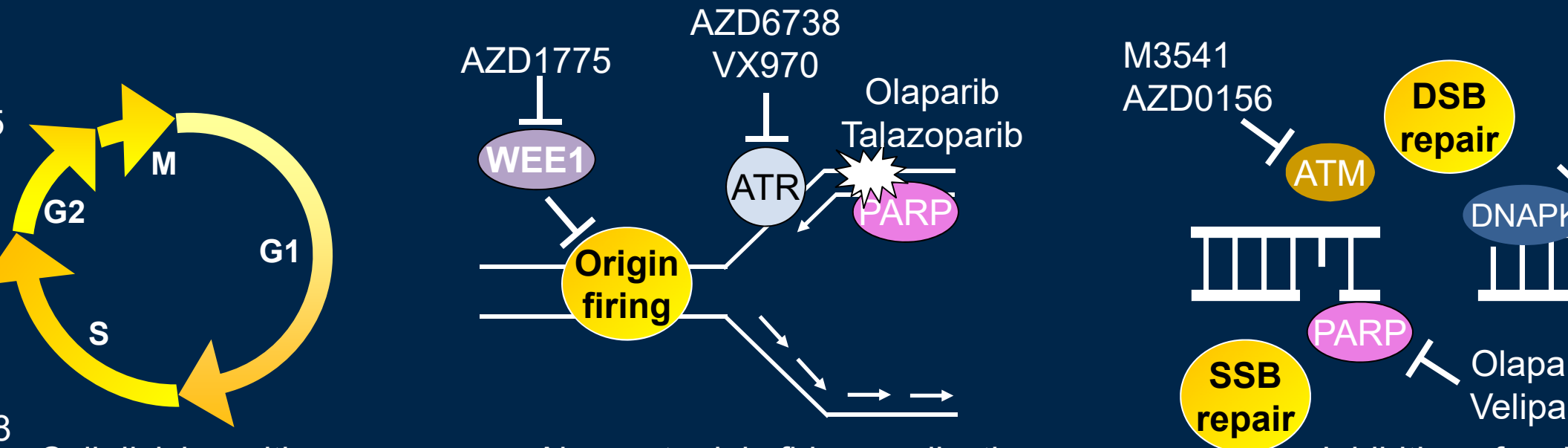
Pause DNA synthesis



Initiate DNA rep

Tumor cell survives radiation treatment

R inhibitors prevent protective cellular responses



Cell division with DNA damage

Aberrant origin firing, replication stalling & fork instability

Inhibition of maj repair pathways

Unrepaired damage & replication stress

Tumor cell dies after radiation treatment

or cell selectivity of DDR inhibitors

ations present in cancer cells but not normal cells
se replication stress and defective DNA damage
onses.

se tumor cell defects can be exploited therapeutically.
R inhibitors are *synthetically lethal* with these tumor
defects.

iation induces damage specifically in tumor cells that
entiates this process.
iation may broaden the therapeutic efficacy of DDR
bitors to tumor cells without defined mutations.

ategy 1: DDR inhibition with standard-of-care

- DDR inhibitors used to sensitize tumor cells to chemotherapy and radiation
- Potential to simultaneously improve systemic and local disease control
- As sensitizers, lower doses (relative to monotherapy) can be effective
- AZD1775 (WEE1 inhibitor) is most extensively studied

Current clinical trials

DDR inhibitor	Chemo-RT	Tumor	Phase
AZD1775	Gem-RT	Pancreatic	1
AZD1775	Tem-RT	GBM	1
AZD1775	Cis-RT	HNSCC	1

provements in pancreatic cancer therapy are urgent

- Median survival
  - Metastatic: <1 year
  - Locally advanced: 1 year
  - Resectable: 2 years
- Locally advanced refers to surgically unresectable, but not overtly metastatic
- Chemoradiation is standard-of-care
- Both local and systemic control are important.
- Effective control is the only hope for surgery and potential cure

gration of DDR inhibitors with standard-of-care in locally advance
creatic cancer

	Registration	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9-11	Wk12 -14 (1 cycle)	Wk 15	Wk 15-24	to 18 month
RT					X	X	X	X	X	Break		DLT evaluation	Optional additional cycles	F/U
Gemcitabine		X	X		X	X		X	X		X			
AZD1775		X	X		X	X		X	X		X			
Skin biopsies		X												

36 patient trial

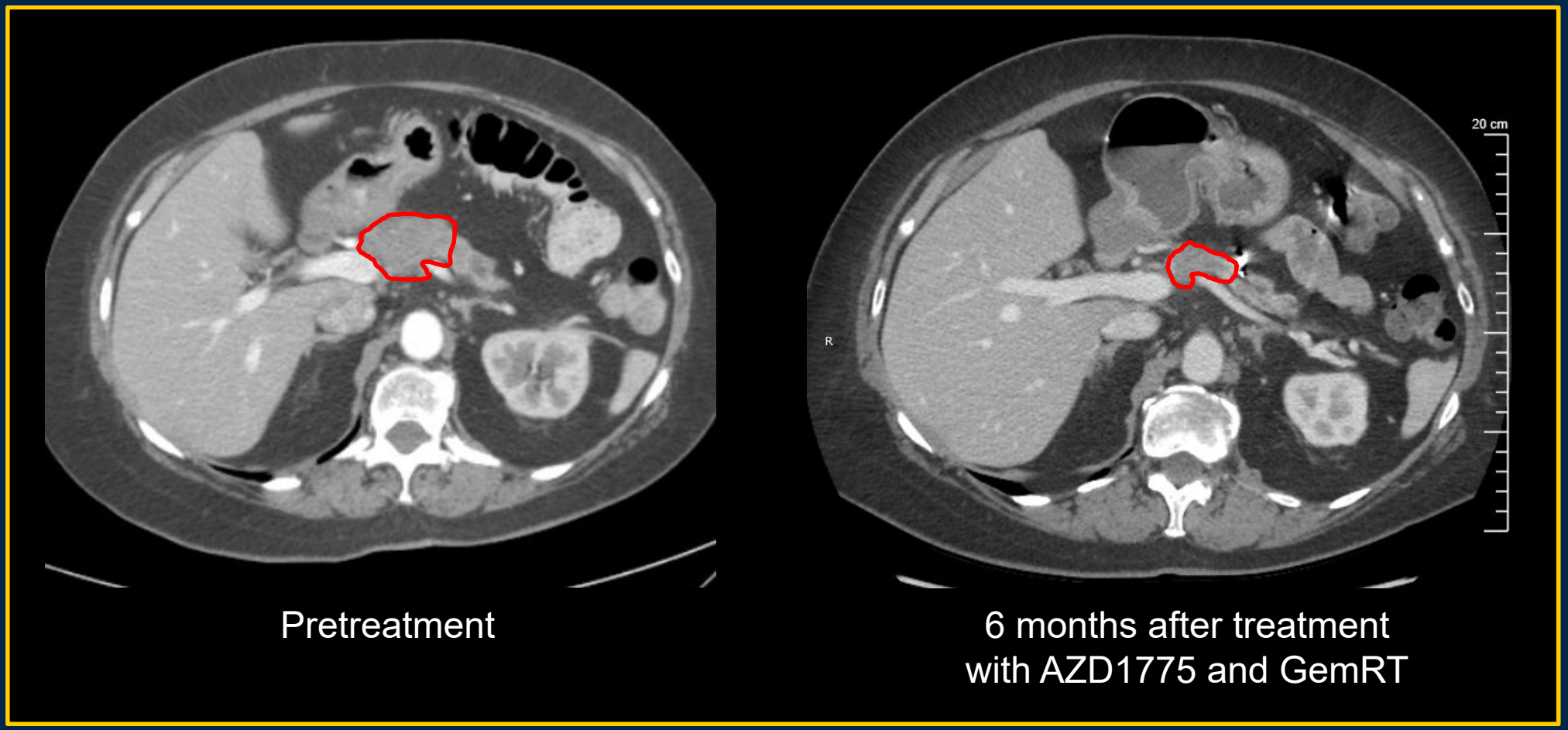
Objectives:

Determine target dose and toxicity of AZD1775 in combination with gemcitabine-radiation

Determine WEE1 inhibition by AZD1775 in surrogate biomarkers and evaluate efficacy

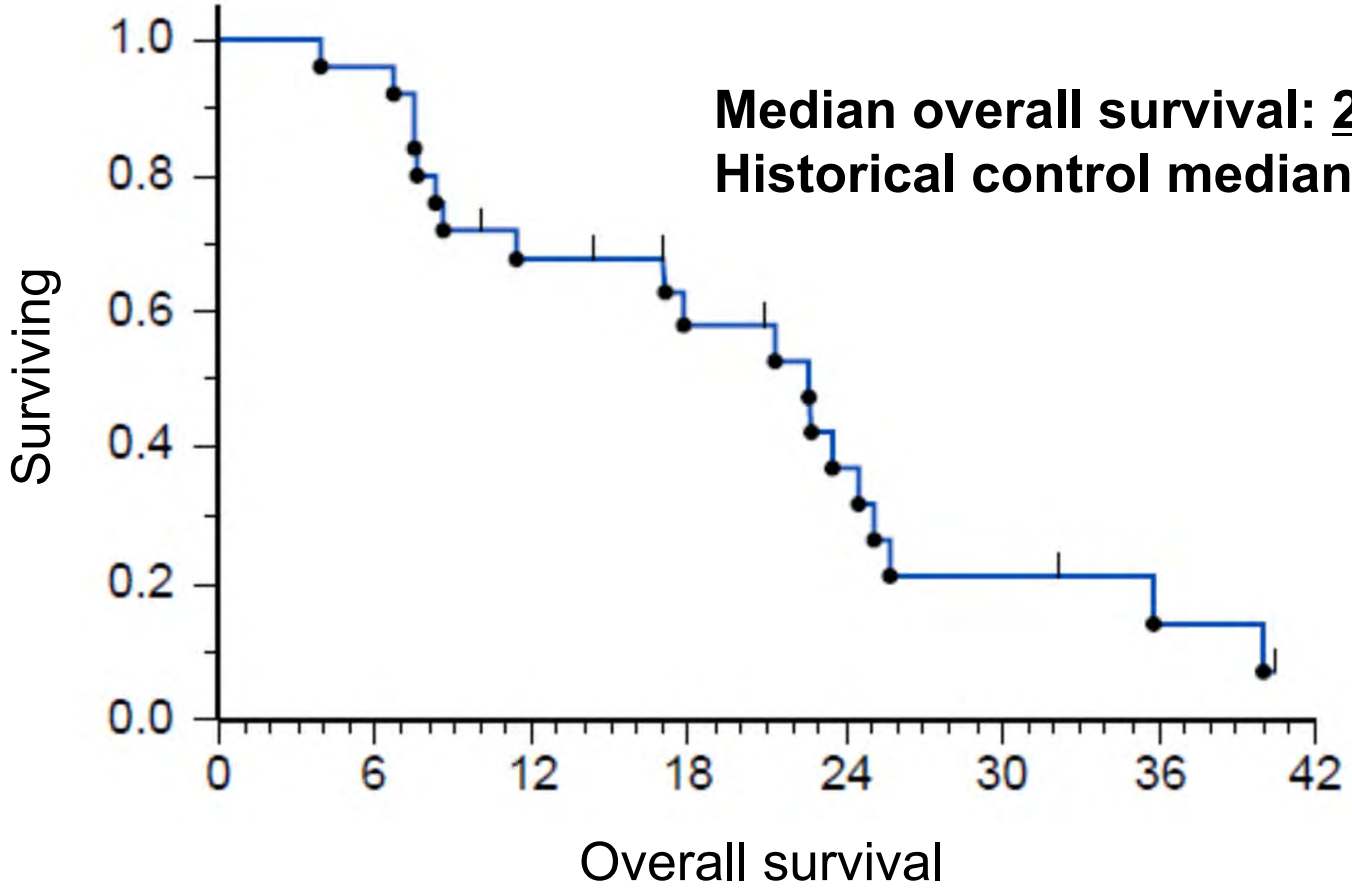
ence & Kyle Cuneo

atment of a pancreatic cancer patient with AZD1775



went on to have resection with negative margins.
y alive with no evidence of disease 2.5 years after diagnosis

D1775 with Gem-RT for locally advanced pancreatic cancer



Median overall survival: 22.6 months

Historical control median overall survival: 11 m

ategy 2: DDR-DDR inhibitor combinations

- Strategic combinations of DDR inhibitors may have greater therapeutic benefit

- Most combinations induce profound radiosensitization (e.g. WEE1-PARP)[1]

- Only some combinations are therapeutic without radiation (e.g. ATR-PARP)

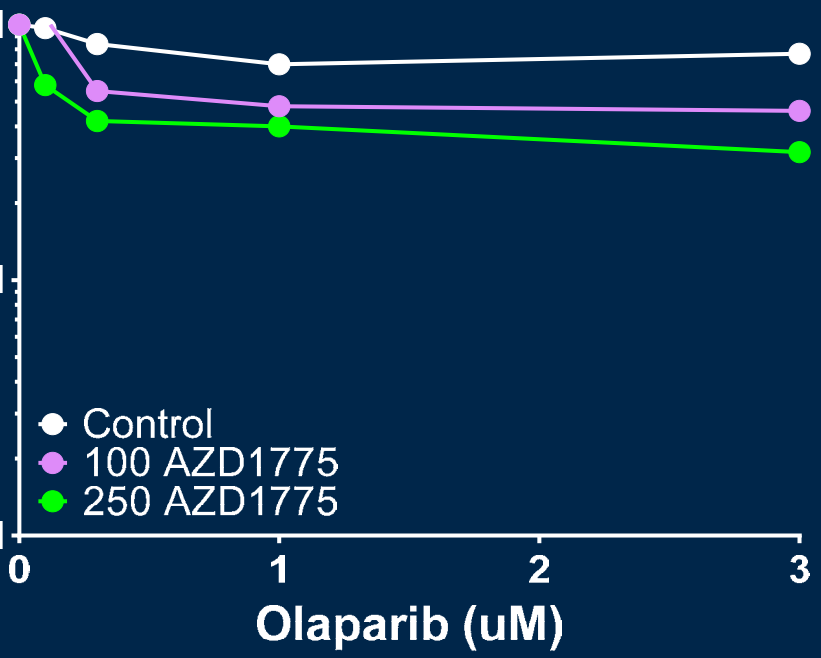
- These DDR-DDR inhibitor combinations may alleviate the need for cytotoxic chemotherapy in chemoradiation regimens and thus reduce toxicity

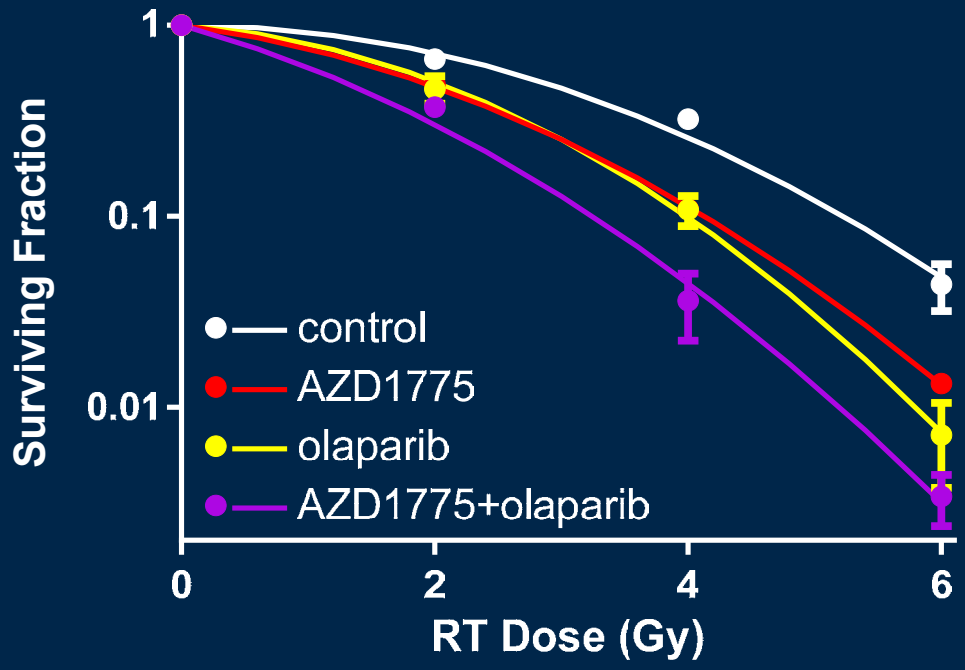
DDR inhibitor combinat		
DNAPK	PARP	Antago
ATR	PARP	Syner
WEE1	PARP	Addi

t al. *Clin Cancer Res* 20:5085-96, 2014

E1-PARP inhibitor combination

proficient MiaPaCa2 cells

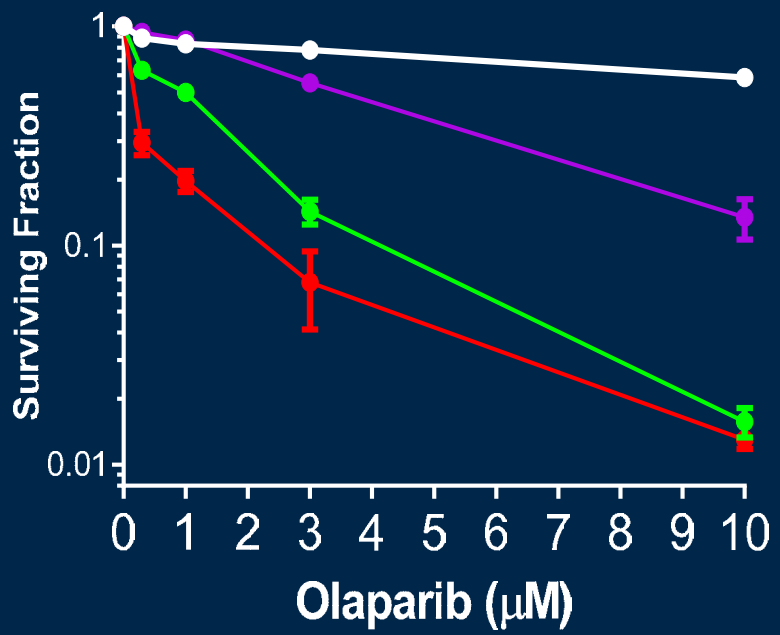




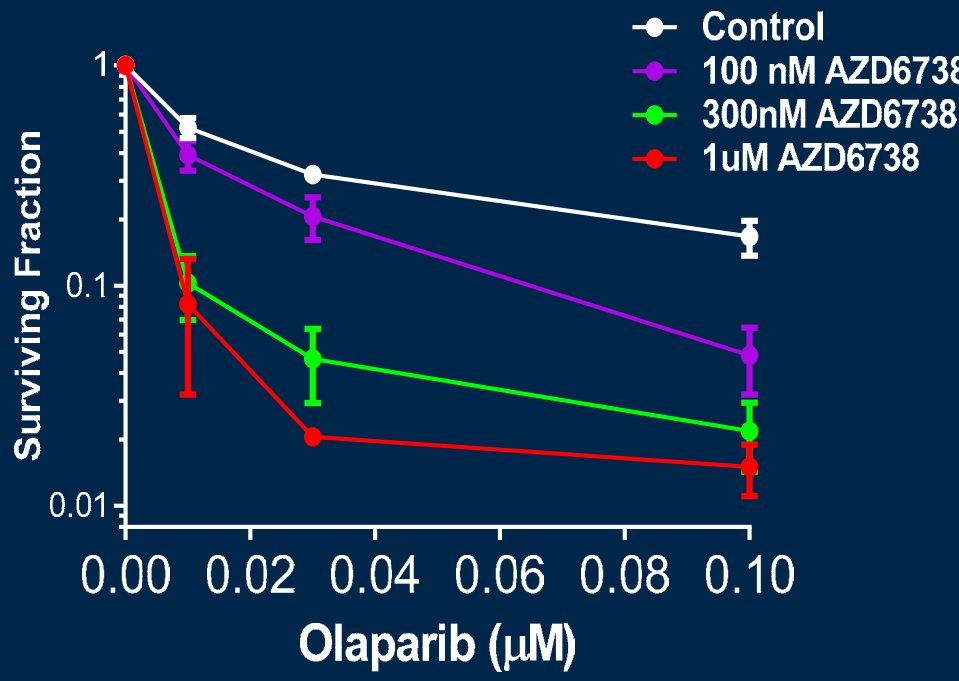
of cytotoxic activity but robust potentiation of radiosensitization

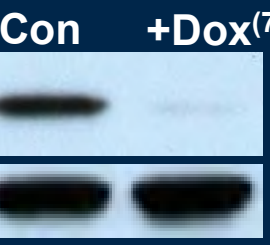
inhibition overcomes PARP inhibitor resistance

HR proficient MiaPaCa2 cells



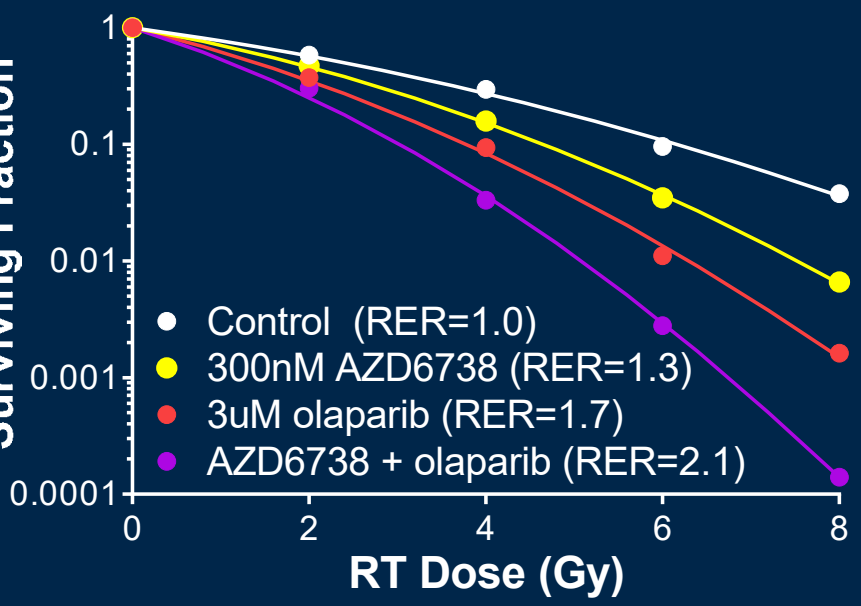
HR deficient MiaPaCa2 cells



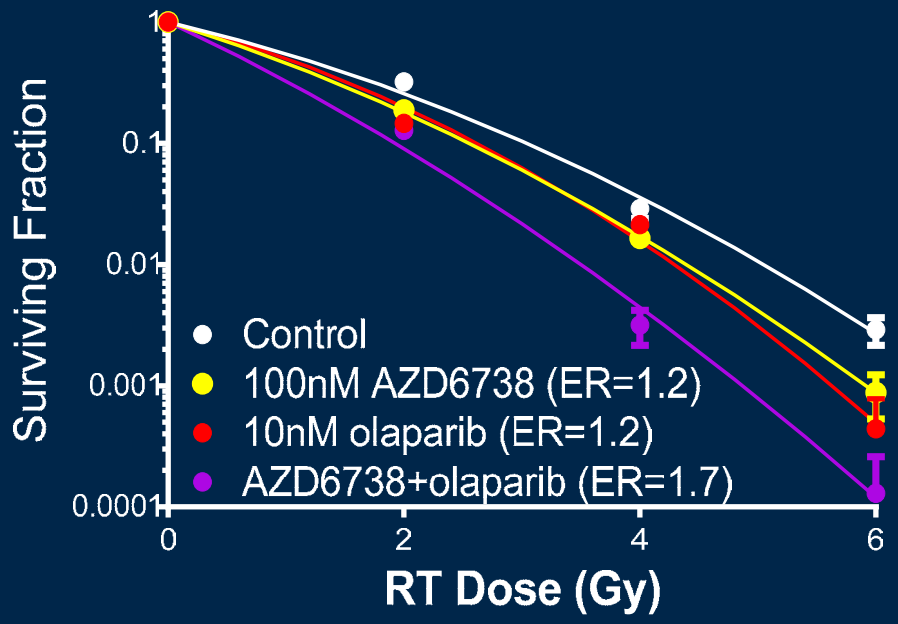


R inhibitor potentiates PARP inhibitor radiosensitization

HR proficient MiaPaCa2 cells



HR deficient MiaPaCa2 cells



PARP inhibition has synergistic cytotoxic and radiosensitizing activity.

ategy 2: DDR-DDR inhibitor combinations with radiation

- Clinical trials underway with several DDR-DDR inhibitor combinations
- Integration of radiation should increase the therapeutic benefit of these combinations

Current clinical trials

Agent 1	Agent 2	RT	Phase
AZD6738 (ATR)	Olaparib (PARP)	-	1
AZD1775 (WEE1)	Olaparib (PARP)	-	1
AZD0156 (ATM)	Olaparib (PARP)	-	1

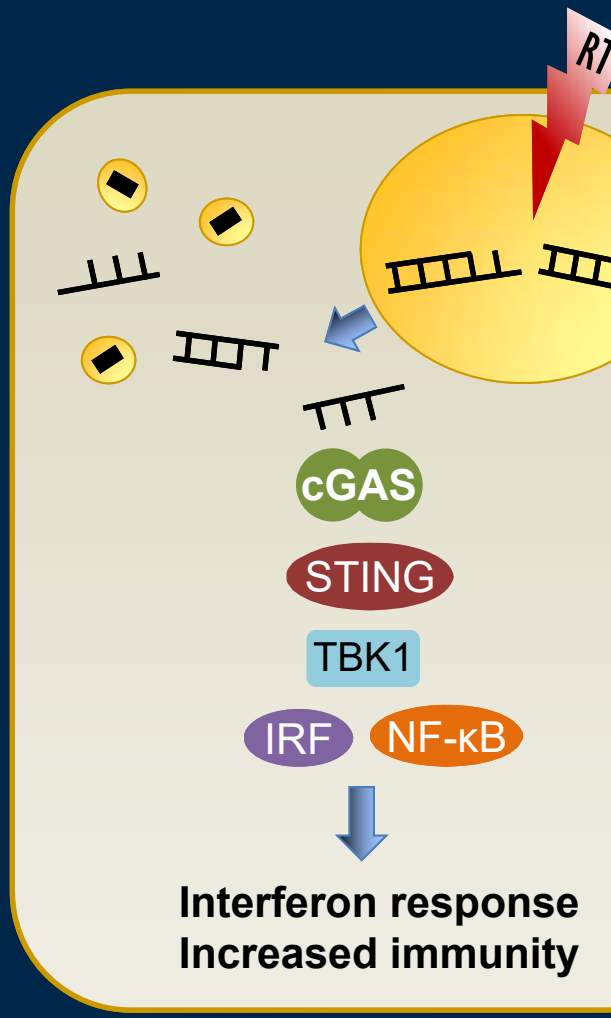
ategy 3: DDR inhibitors as sensitizers to immune checkpoint ther

Radiation causes release of damaged DNA or chromosomes from the nucleus

DNA in cytoplasm is recognized as foreign and activates an innate immune response

nhibitors of the DDR may increase this response

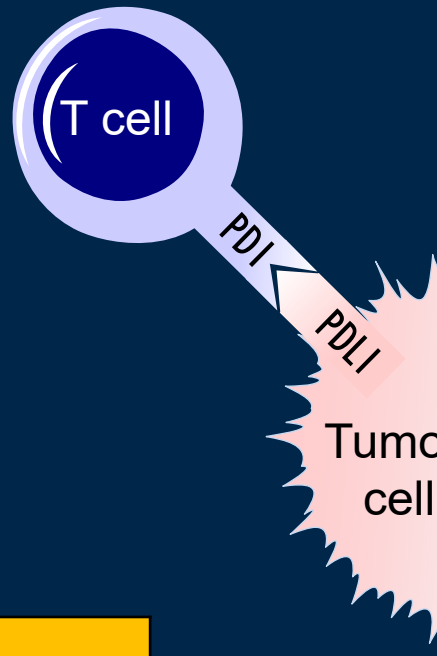
ncreased innate immunity should synergize with mmune checkpoint therapy.



al., *Nature Immunology*, 17:1142-49, 2016

ategy 3: DDR-immune checkpoint inhibitor combinations with RT

- Radiation enhances immunotherapy efficacy[1]
- Preclinical data show potential benefit of PARP inhibition[2]
- n contrast, DNA-PK inhibition may be antagonistic[3]
- DDR and immunotherapy agents are being tested clinically
- ntegration of radiation will be important in future trials



Current clinical trials

Agent 1	Agent 2	RT	Phase
AZD6738 (ATR)	MEDI4736 (PD-L1)	-	1
Olaparib (PARP)	MEDI4736 (PD-L1)	-	1
AZD1775 (WEE1)	MEDI4736 (PD-L1)	-	1, 2

[1]Twyman-Saint Victor et al., *Nature* 520:373-7
[2]Jiao et al., *Clin Cancer Res* 23:3711-20, 2017
[3]Harding et al. *Nature*, 2017

king to the future

storically very difficult to develop experimental agents as radiosensitizers
HAT IS CHANGING!

treatment of metastatic cancer improves, therapy for locally advanced
ncers will become increasingly important. The demand for new combination
liation treatment regimens will increase.

e biology of DDR (and immunotherapy) agents warrants radiation combinat
dies

egration with standard-of-care chemoradiation or radiation is the most logic
th to approval

knowledgements

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Biostatistics
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AstraZeneca
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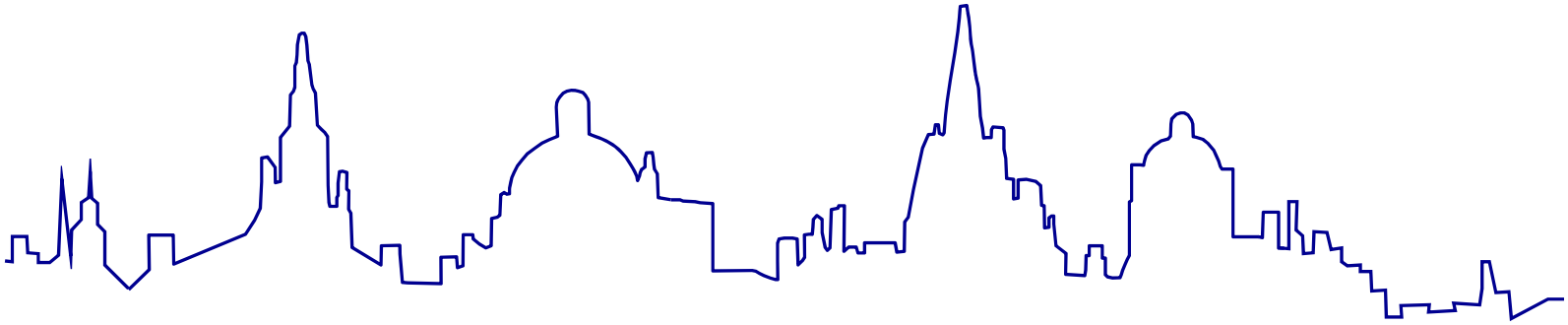
Pancreatic Cancer Research



Hypoxia – Success and Failure

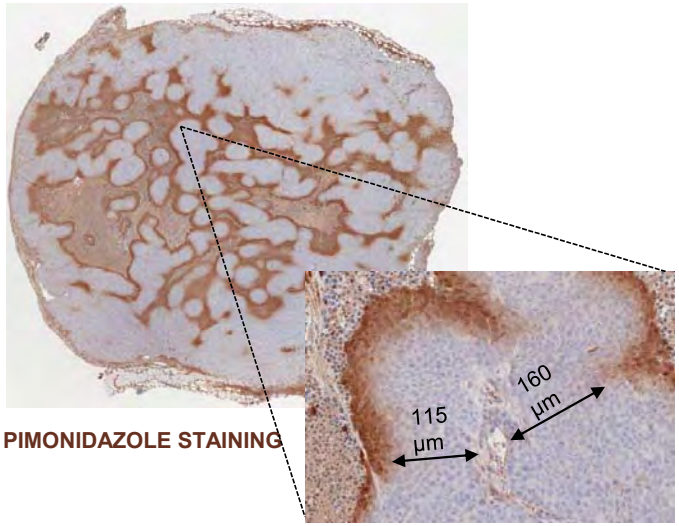
Ester M. Hammond

CANCER RESEARCH UK | MRC Medical Research Council

OXFORD INSTITUTE FOR RADIATION ONCOLOGY

FDA-AACR-ASTRO Workshop on Radiotherapy Combinations, February 2018

Hypoxia – insufficient oxygen



PIMONIDAZOLE STAINING

Normoxia	Atmospheric O_2 pressure (20.9 %). The pO2 where most pre-clinical testing is carried out
Physoxia, Physioxia, Tissue normoxia	The normal pO_2 in specific tissues/organs e.g. Brain 4.6% O_2, Intestine 8.0% O_2, Skin 2.8% O_2 liver 4.1% O_2
Hypoxia	Low O_2 levels, indicating that the tissue/organ has insufficient O_2. Associated with HIF-1 stabilisation
Radiobiological hypoxia	The level of hypoxia where significant resistance to radiation is observed (<0.13% O_2)

Hammond/Williams Clinical Oncology 2014

Why do we care about hypoxia?

Chemotherapy

Effective drug delivery and activity is compromised in hypoxic/acidic tumour regions. Adaption to hypoxia promotes chemoresistance.

Most chemotherapies are less effective

Surgery

The biological response to hypoxia includes increased motility and invasion and therefore metastasis.

Tumour is more likely to have spread at time of treatment

Radiotherapy

In the presence of oxygen, radiation leads to the formation of reactive radicals which damage DNA.

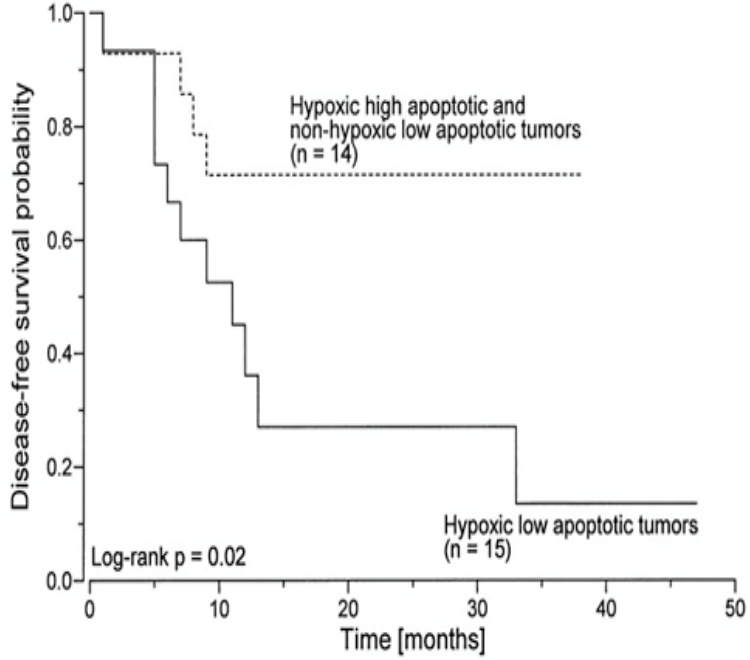
Hypoxic tumour cells receive up to 3 times less DNA damage during radiotherapy

Increased genomic instability and decreased DNA repair

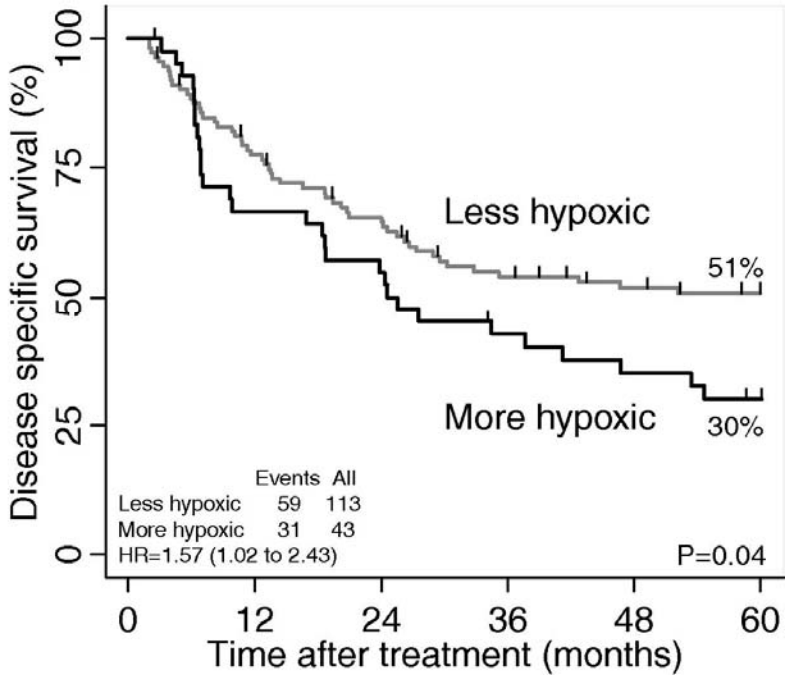
RESISTANCE TO THERAPY AND POOR PATIENT PROGNOSIS

Hammond/Williams Clinical Oncology 2014

Why do we care about hypoxia?

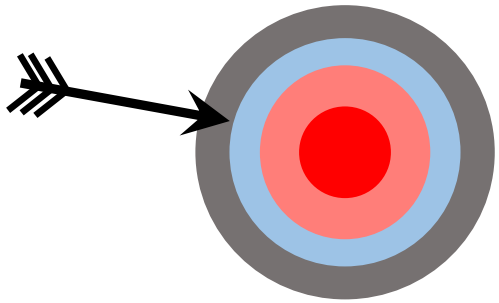


Hockel *et al*., 1999 Cancer Research



Toustrup *et al*., Radiother and Oncol 2012

Should we target tumour hypoxia?



- Many studies have demonstrated that hypoxia correlates with poor prognosis
- Hypoxic/anoxic cells are radiation resistant
- Hypoxic cells are more motile/invasive
- Hypoxia is one of the most significant differences between tumour and normal tissue

At the very least we should verify that therapies work in hypoxia

What strategies have we come up with for targeting hypoxia?

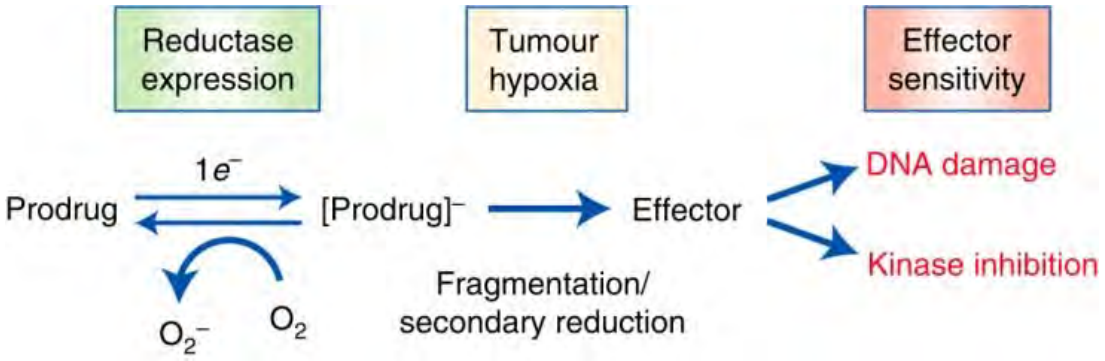
- Hyperbaric oxygen (HBO)
  - Increased radiotherapy related toxicity, oxygen seizures
  - Cumbersome and difficult to provide for all patients

- Oxygen mimics
  - Some toxicity problems but nimorazole is tolerated and used in the treatment of HNSCC in Denmark
  - NIMRAD currently testing nimorazole + IMRT in HNSCC (UK)

- CARBOGEN (95% O_2: 5% CO_2 or 98% O_2:2% CO_2)
  - BCON, phase III improved overall survival in bladder cancer
  - ARCON, phase III significant gains in regional control rates HNSCC

- Hypoxia activated prodrugs/cytotoxins
  - e.g. Tirapazamine, Evofosfamide

Hypoxia activated prodrugs – a beautifully simple concept



Drug delivery

Level of hypoxia required

Relevant enzymes must be expressed

High expression of reductases in liver

Should only work in patients with hypoxic tumours

Hunter *et al*., British Journal of Cancer 2016

Tirapazamine

TROG 02.02, HeadSTART – no evidence of benefit of adding TPZ in HNSCC

Poor radiotherapy delivery (25% of patients had noncompliant plans)

Poorly managed drug toxicity

No selection of patients based on tumour hypoxia

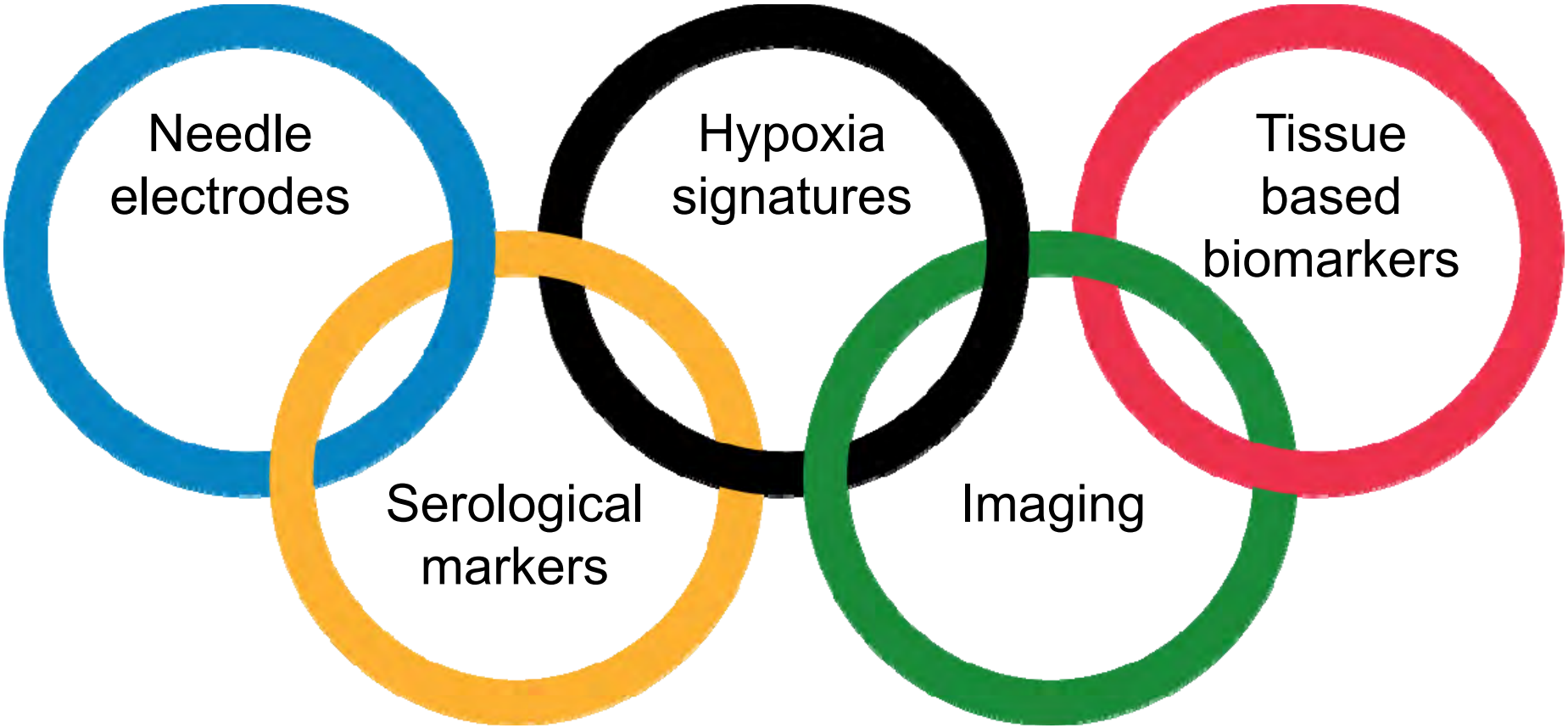
Evofosfamide (TH302)

MAESTRO trial – little to no advantage in pancreatic and soft tissue sarcoma

No selection of patients based on tumour hypoxia

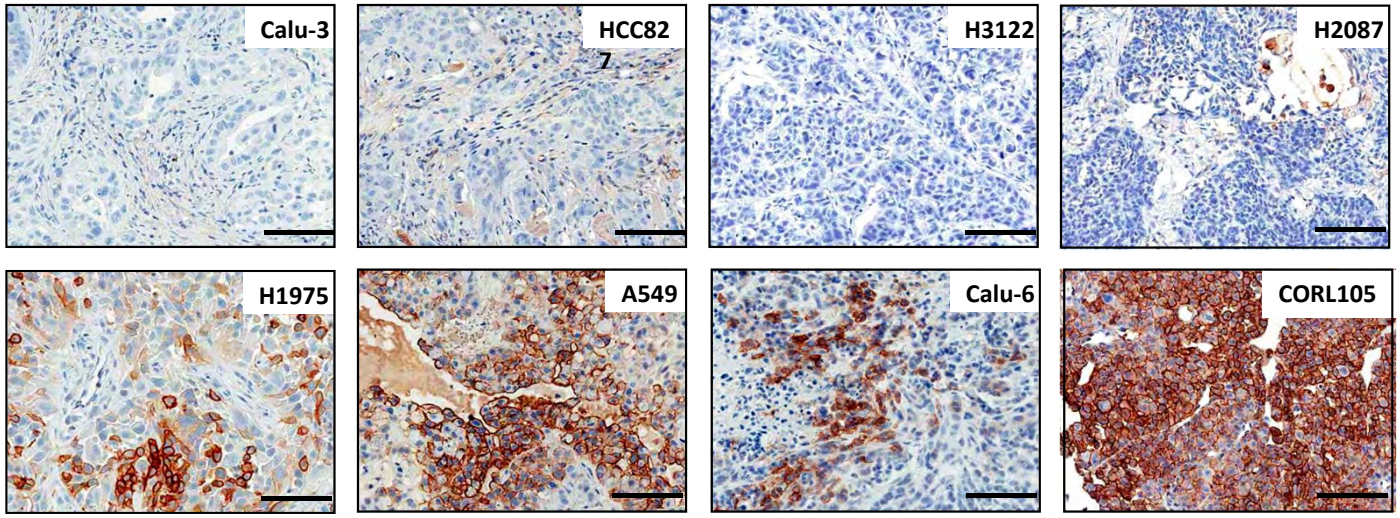
Peters *et al*., J Clin Oncol 2010

For a medal position – we need to pick the right patients



Hammond/Williams Clinical Oncology 2014

Has our preclinical testing been good enough?



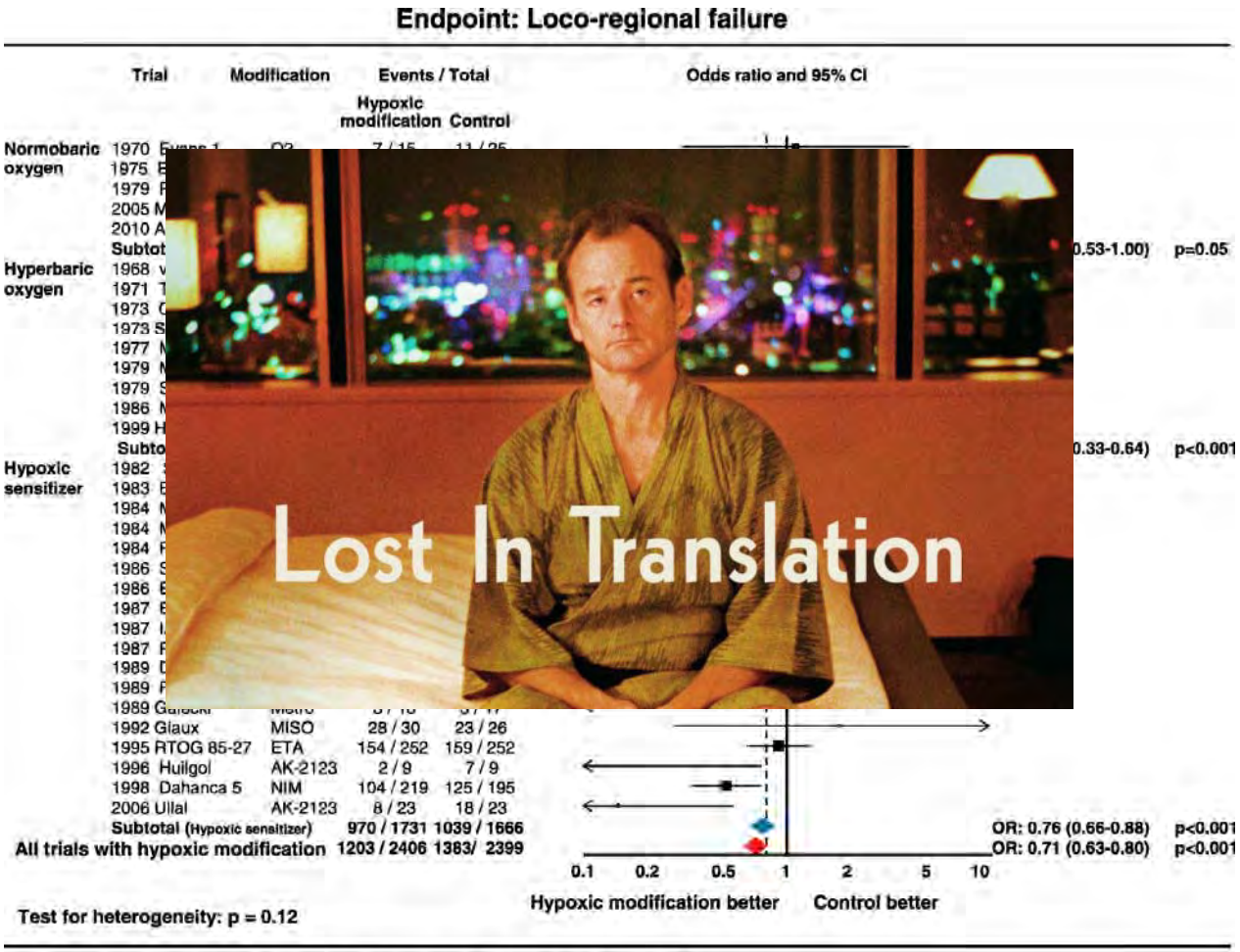
Mouse to Human

- Pharmacology
- Biology
- Are we hitting the target?
- Do we have reliable biomarkers?

Is the drug in the right place at the right time, at the right concentration?

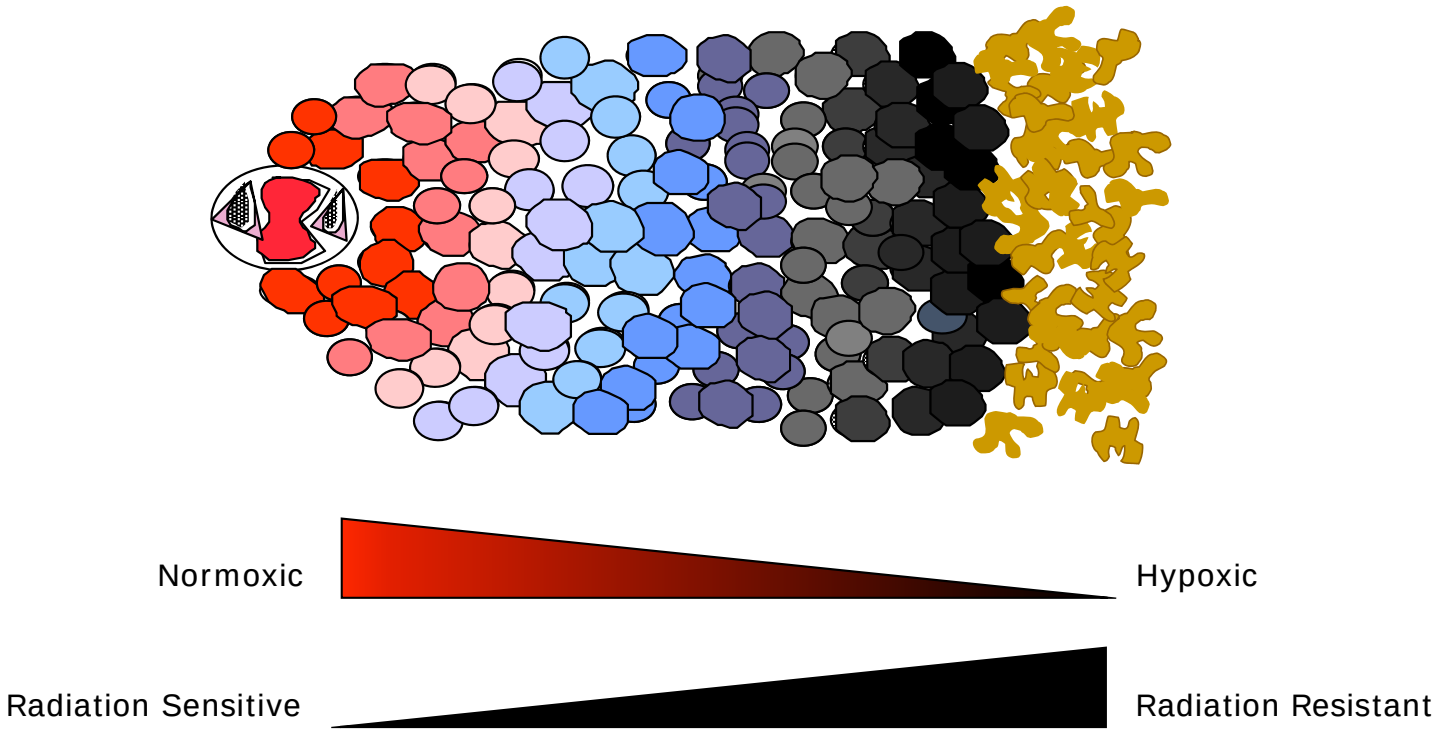
Anderson Ryan, University of Oxford

Overall indications are that hypoxia modification works but…

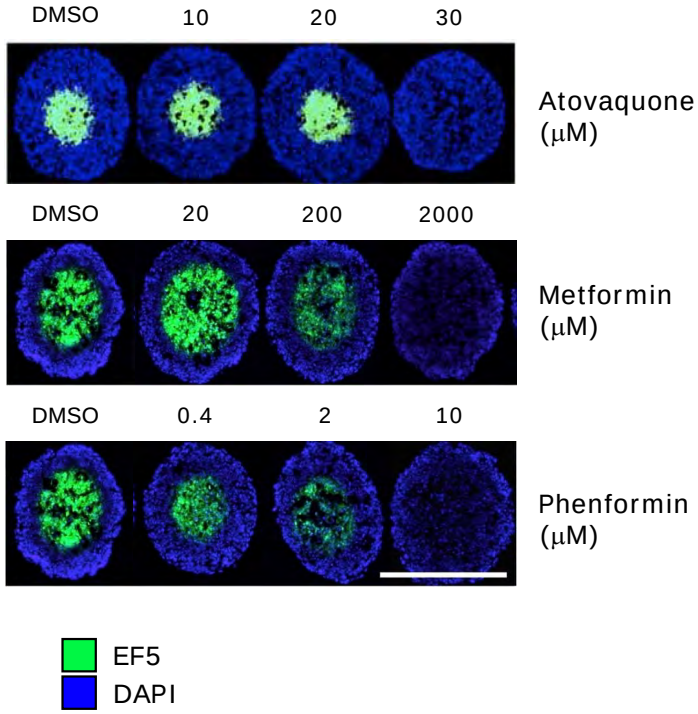


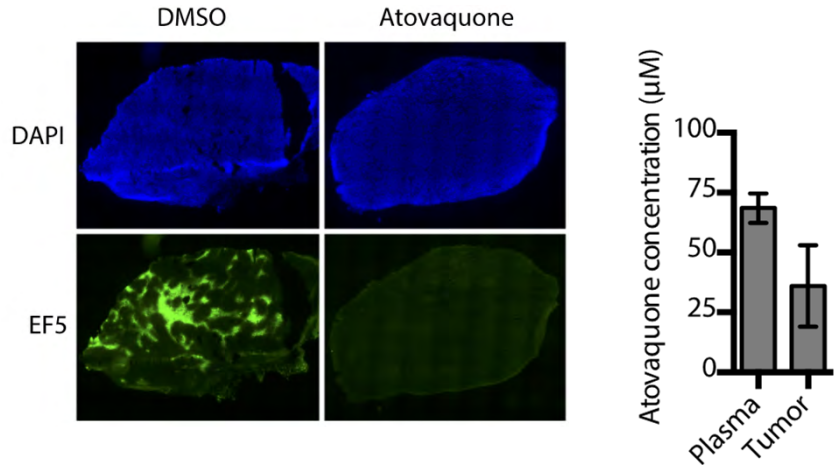
Overgaard J 2011 Radiotherapy and Oncology

New approaches: Reduce oxygen consumption



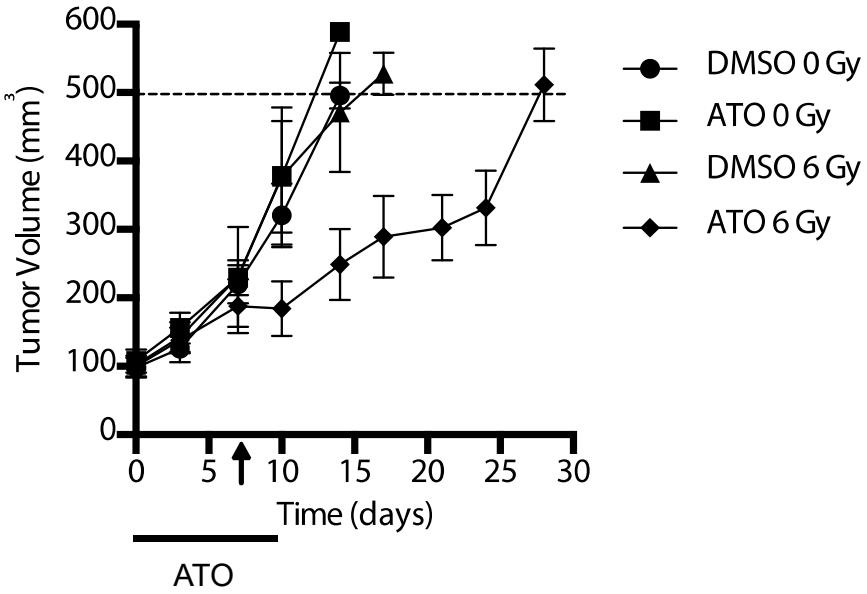
Atovaquone alleviates hypoxia in spheroid and xenograft models

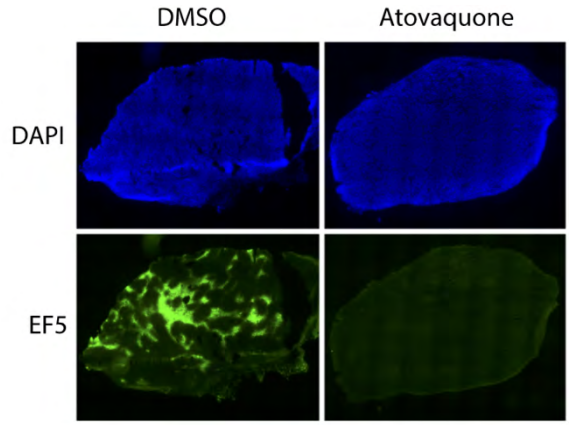


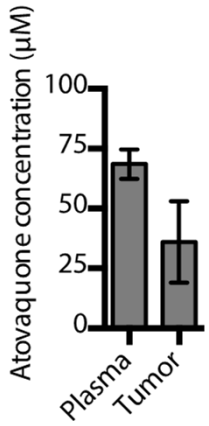


Ashton *et al*., Nat Commun 2016

Atovaquone leads to increased radiosensitivity







Ashton *et al*., Nat Commun 2016

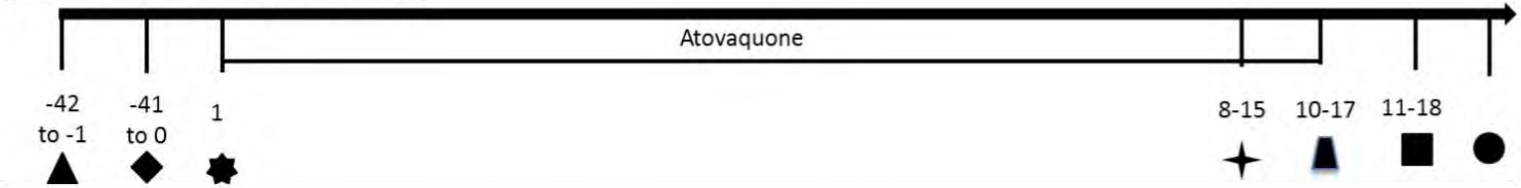
ATovaquone as **O**xygen **M**odifier

‘Window of opportunity trial’ in NSCLC patients prior to surgical resection

- **NOT** an efficacy study in unselected patients
- Biomarker driven proof of concept study
- Does atovaquone reduce tumour hypoxia in patients?
- Can we stratify patients who will respond?
- Robust, affordable biomarker?

Prof Geoff Higgins

Cohort 1 (Atovaquone group)



▲ Surgical outpatient visit. Cohort 1 Patient Information Sheet given

◆ Consent obtained. Medical history

✸ Baseline hyp-PET-CT, pCT, DWI-MRI and DCE-MRI. Baseline bloods including osteopontin, miR210, VEGF, CAIX. Start atovaquone.

✦ Repeat hyp-PET-CT, pCT, DWI-MRI and DCE-MRI. Repeat bloods including osteopontin, miR210, VEGF, CAIX, plasma atovaquone measurement.

⏢ Pimonidazole administered and atovaquone stopped

■ Tumour resected, fixed with formalin, and orientated to correlate with hyp-PET-CT imaging. In cases where orientation is difficult, MRI of the resected tumour will be performed.

● Tumour sectioned after discussion with pathology. GCP lab IHC analysis will include CAIX, pimonidazole, CD31 and CD146. Tumour mRNA extraction for gene expression quantification, tumour DNA extraction for mutational analysis, HPLC analysis of tumour atovaquone concentration.

How do we get a hypoxic cell sensitiser for use with radiation?

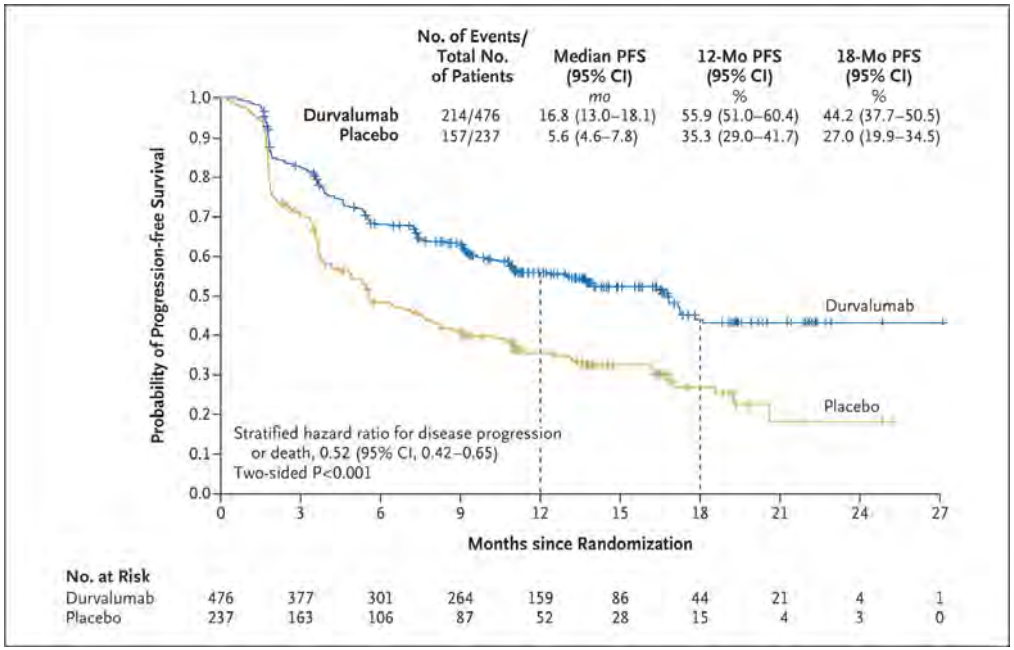
Better drugs – *must confirm activity in patients*

Better trials – *must stratify patients*

Have to **overcome negative perceptions**

Clinical champions to carry out the trials

Government and/or industrial **investors** to pay for the trials



Antonia SJ *et al*. N Engl J Med 2017

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MANCHESTER 1824

The University of Manchester

ICRR 2019

Manchester // 25-29 Aug

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AACR American Association for Cancer Research
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ASTRO
AMERICAN SOCIETY FOR RADIATION ONCOLOGY

SESSION IV Panel Discussion:

Other Targeted Therapies

Moderators: Theodore S. Lawrence, MD, PhD, and Ester M. Hammond, PhD

Panelists:

Gideon M. Blumenthal, MD
Özlem Ataman, MD, PhD
Kyle Cuneo, MD
Meredith A. Morgan, PhD
Andrew Wang, MD

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ASTRO AMERICAN SOCIETY FOR RADIATION ONCOLOGY

SESSION IV: Discussion Questions

- Why are there no novel agents registered in combination with radiotherapy in recent years despite the increase in clinical studies?
- Could the first registration of a novel agent be in combination with radiotherapy?
- Are there any specific surrogate endpoints (i.e loco-regional control, pCR) to accelerate registration in combination with radiotherapy?
- Is there a need for guidelines from regulatory agencies on the elements/design of registration for radiation combinations studies?

Prognostic and Predictive Biomarkers in (Radiation) Oncology

Daniel Spratt, MD
Associate Chair, Clinical Research
Chair, Genitourinary Division Clinical Research
Director, Spine Oncology Program

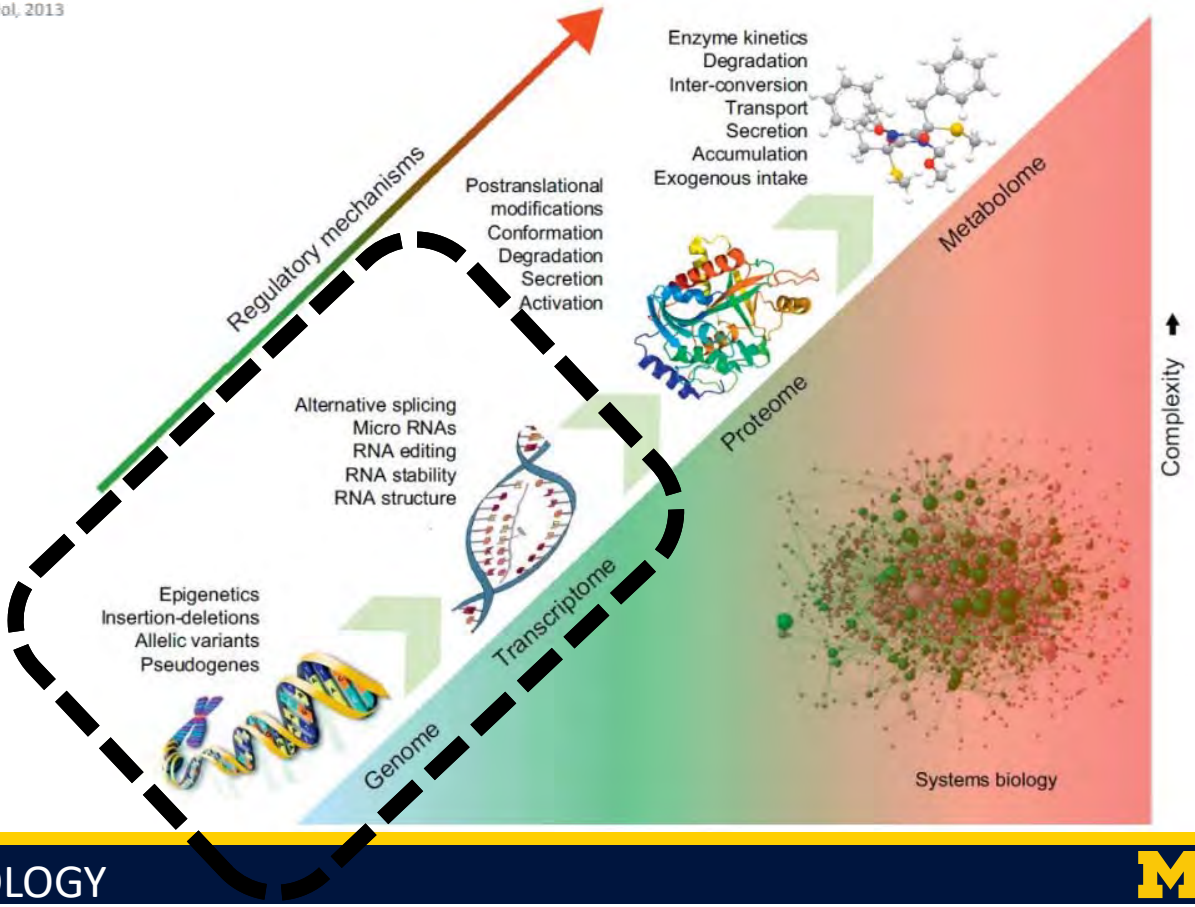
No relevant disclosures

Objectives

- Understand the difference in a prognostic and predictive biomarkers
- Understand methods to use these biomarkers for drug approval combinations with radiotherapy

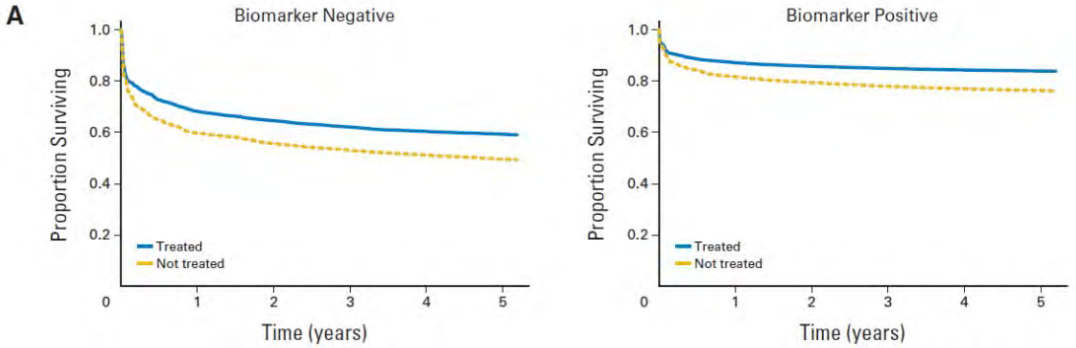
Biomarkers

Barallobre-Barreiro J et al., Rev Esp Cardiol, 2013

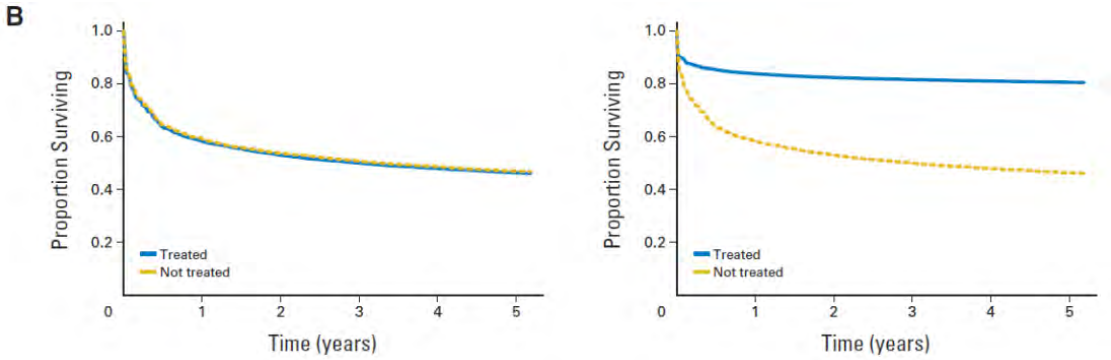


Biomarkers

- **Prognostic**: Real world personalized medicine



- **Predictive**: Ultimate personalized medicine



Ballman KV, J Clin Oncol, 2015

How do you "prove" a biomarker is predictive?

- To determine whether a biomarker is potentially predictive or prognostic, a formal **test for an interaction** between the biomarker and treatment group needs to be performed.

- Basically:
  - You are testing an interaction between the treatment group, biomarker, and outcome, and it should be statistically significant

Ballman KV, J Clin Oncol, 2015

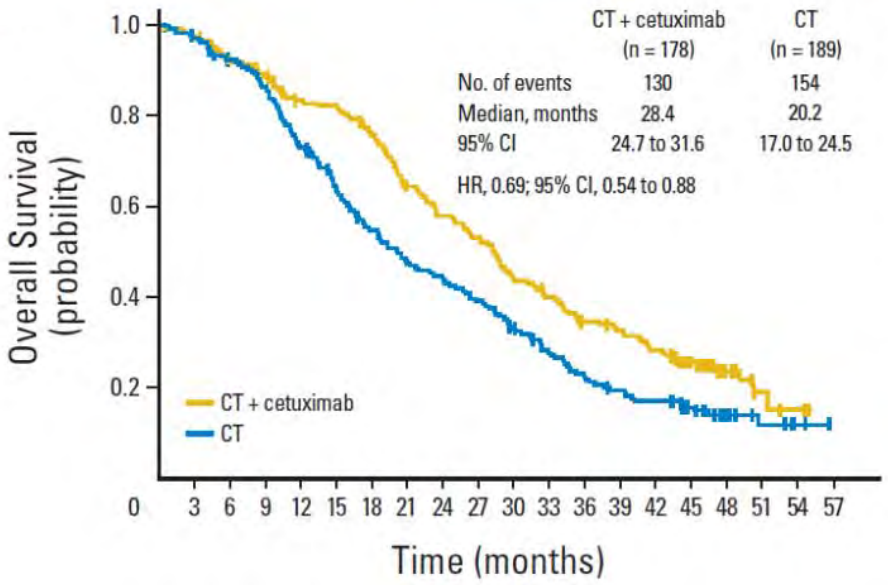
Validated Biomarkers

- **Examples of prognostic biomarkers**: **Thousands**
  - Prostate cancer: Decipher, Oncotype, Prolaris
  - Breast: Ki-67
  - GBM: MGMT

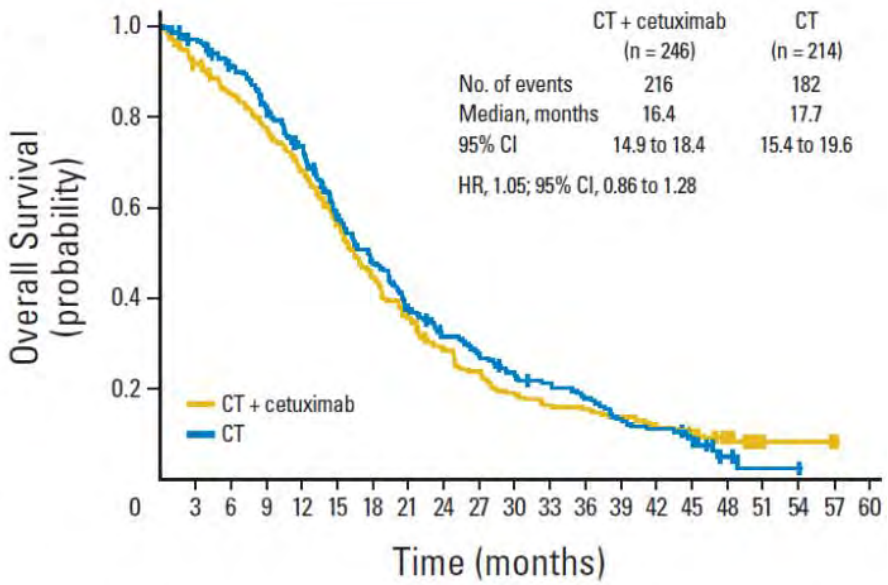
- **Examples of predictive biomarkers**: **Very few**
  - Colon: Ras
  - Lung: EGFR, ROS, Alk
  - Breast: ER, Her2
  - Melanoma: Braf
  - Mismatch repair
  - DNA damage repair

Predictive Biomarker- Colorectal Cancer and Ras

Ras wildtype



Ras mutant



TESTING MATTERS!

Van Cutsem, JCO, 2015

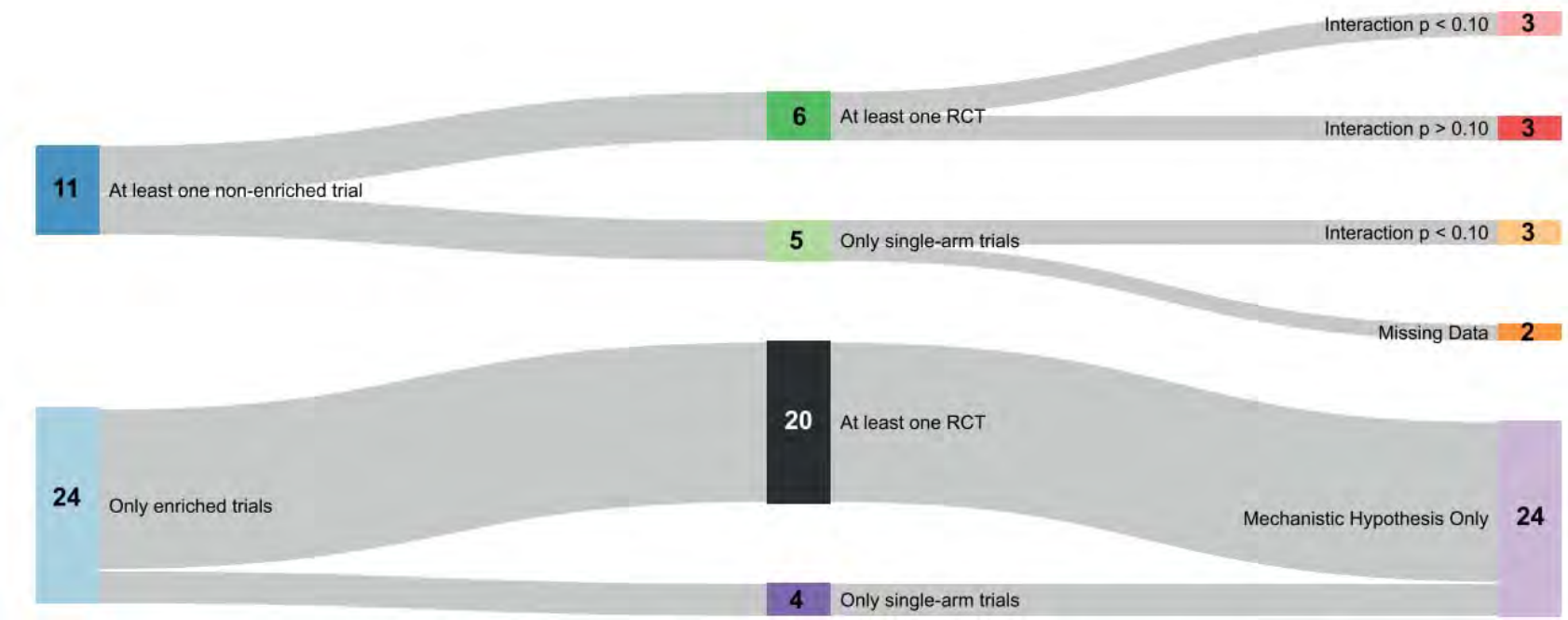
Biomarkers used for FDA Drug Approvals

Drug	Biomarker gene	Indication	Original (O) or supplemental (S) approval	Accelerated Approval or regular
Ado-Trastuzumab Emtansine	ERBB2	Breast cancer	O	regular
Afatinib	EGFR	Lung cancer	O	regular
Anastrozole	ESR1, PGR	Breast cancer (early stage)	S	accelerated
Anastrozole	ESR1, PGR	Breast cancer (advanced stage)	S	regular
Cetuximab	EGFR	Colorectal cancer	O	accelerated
Cetuximab	KRAS	Colorectal cancer	S	NA
Crizotinib	ALK	Lung cancer	O	accelerated
Dabrafenib	BRAF	Melanoma (single agent)	O	regular
Dabrafenib	BRAF	Melanoma (with trametinib)	S	accelerated
Dasatinib	BCR/ABL1	Blood cancer	O	accelerated
Denileukin Diftitox	IL2RA	Other	O	accelerated
Erlotinib	EGFR	Lung cancer	S	regular
Everolimus	ERBB2	Breast cancer	S	regular
Everolimus	ESR1	Breast cancer	S	regular
Exemestane	ESR1	Breast cancer	S	regular
Fulvestrant	ESR1	Breast cancer	O	regular
Imatinib	KIT	Blood cancer	S	regular
Imatinib	BCR/ABL1	Blood cancer (Ph + ALL, adult patients)	S	regular

Drug	Biomarker gene	Indication	Original (O) or supplemental (S) approval	Accelerated Approval or regular
Lapatinib (with capecitabine)	ERBB2	Breast cancer	O	regular
Lapatinib (with letrozole)	ERBB2	Breast cancer	S	accelerated
Letrozole	ESR1, PGR	Breast Cancer (early stage)	S	accelerated
Letrozole	ESR1, PGR	Breast cancer (advanced stage)	O	regular
Panitumumab	EGFR	Colorectal cancer	O	accelerated
Panitumumab	KRAS	Colorectal cancer	S	regular
Pertuzumab	ERBB2	Breast cancer (Metastatic)	O	regular
Pertuzumab	ERBB2	Breast cancer (Neo-adjuvant)	S	accelerated
Trametinib	BRAF	Melanoma	O	regular
Trastuzumab	ERBB2	Metastatic Breast cancer	O	regular
Trastuzumab	ERBB2	Breast cancer, adjuvant	S	regular
Trastuzumab	ERBB2	metastatic gastric adenocarcinoma	S	regular
Vemurafenib	BRAF	Melanoma	O	regular
Ceritinib	ALK	Lung cancer	O	accelerated
Lenalidomide	del (5q)	Blood cancer	O	regular

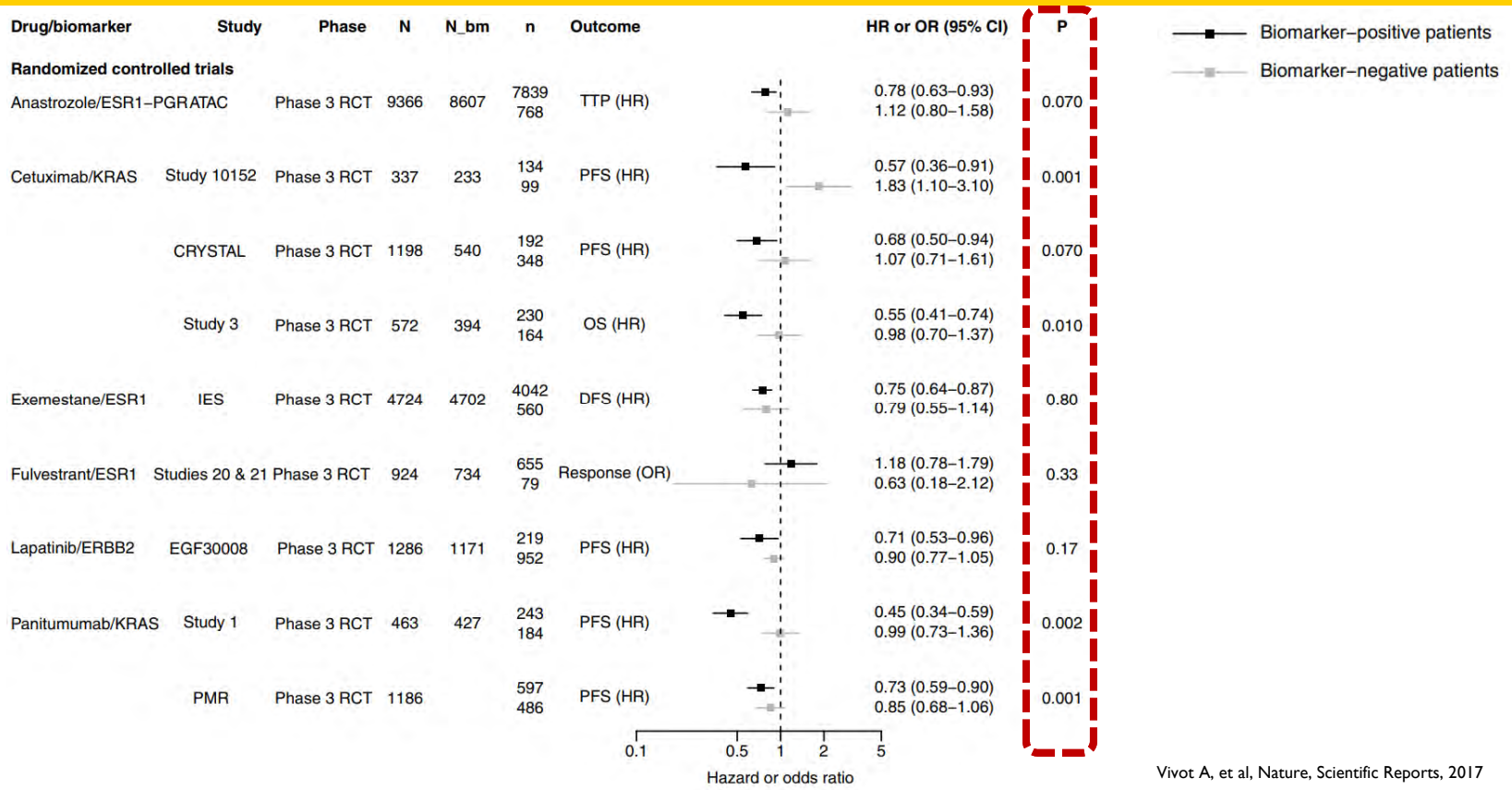
Vivot A, et al, Nature, Scientific Reports, 2017

Biomarkers used for FDA Drug Approvals



Vivot A, et al, Nature, Scientific Reports, 2017

Biomarkers used for FDA Drug Approvals



Vivot A, et al, Nature, Scientific Reports, 2017

Validated Biomarkers in Radiation Oncology

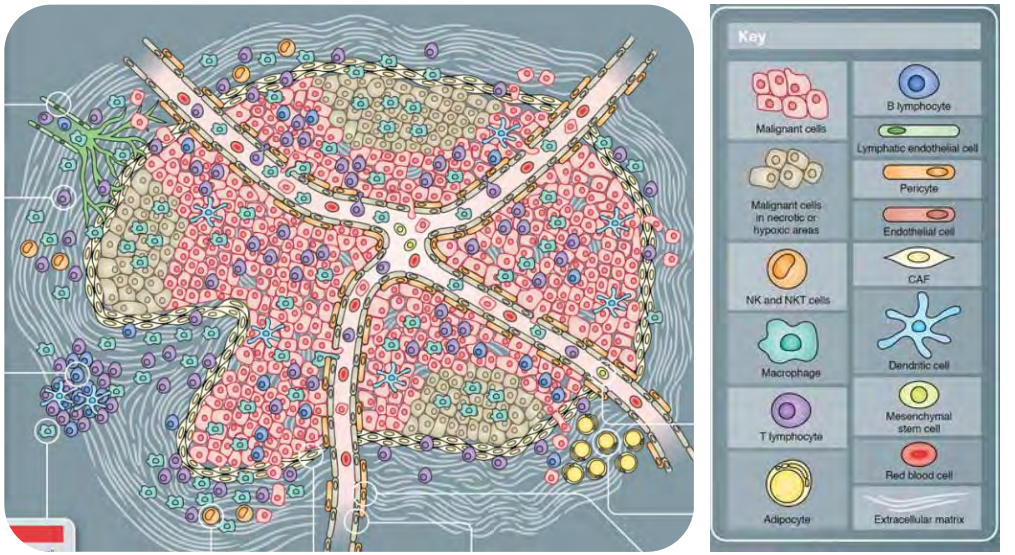
- **Examples of prognostic biomarkers**: Thousands
  - Prostate cancer: Decipher, Oncotype, Prolaris
  - Breast: Ki-67
  - GBM: MGMT

- **Examples of predictive biomarkers**:
  - NONE

Validated Biomarkers in Radiation Oncology

- There is not a single prospectively validated clinical grade biomarker that has been shown to determine who selectively benefits from radiotherapy or to guide radiotherapy dose.

The complexity of interactions of RT with tumor cells, immune cells, microenvironment, circulating disease, host, limitations of preclinical models, have been a formidable opponent.



Bottom line: Tumor cell radiosensitivity is not enough.

Validated Biomarkers in Radiation Oncology

- Another method for use of biomarkers in radiation oncology for drug approval is to leverage:
  - Prognostic biomarkers or
  - Develop predictive biomarkers for the combination agents that may have unique biological synergy with radiotherapy.

Side note: ADT may be the best example of a near pure radiosensitizer that is proven clinically AND provides synergy

	Persistently viable disease
ADT	100%
RT	40%
RT+ADT	20%

Is this synergy?

Side note: ADT may be the best example of a near pure radiosensitizer that is proven clinically AND provides synergy

	HR for PCSM
Observation vs ADT	1.0
ADT vs RT + ADT	0.44
Surgery vs Surgery + ADT	1.0
RT vs RT + ADT	~0.3-0.5

Addition of ADT to RT does not increase radiation side effects (GI/GU)
- In contrast to chemo

Using Prostate Cancer as an Example

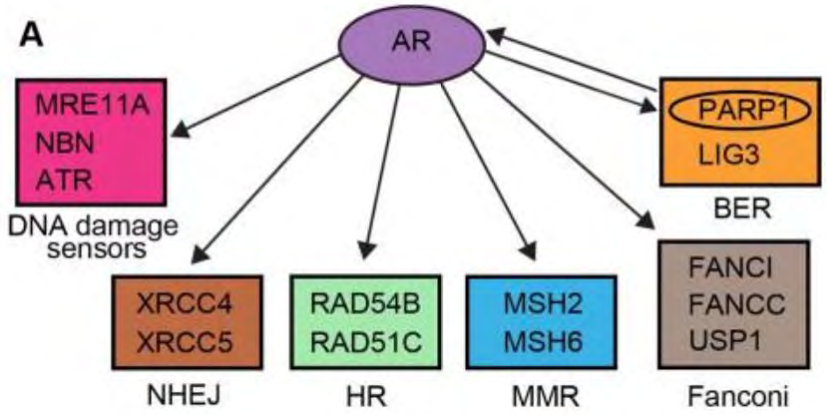
- **A story of prognostic and predictive biomarkers in prostate cancer and how they could be used for drug approval…**

Prostate Cancer as an Example

- **The most common treatments in prostate cancer include:**
  - Radiotherapy
  - Androgen deprivation therapy (ADT)
  - Taxane chemotherapy

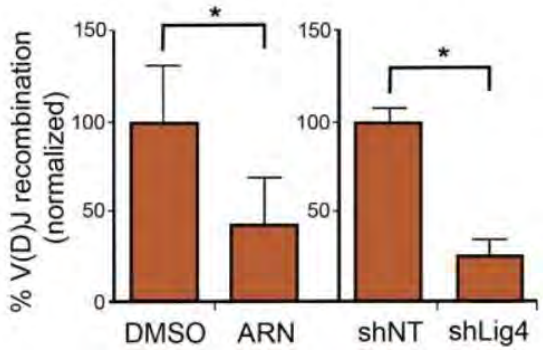
We have no predictive biomarkers to guide their use.

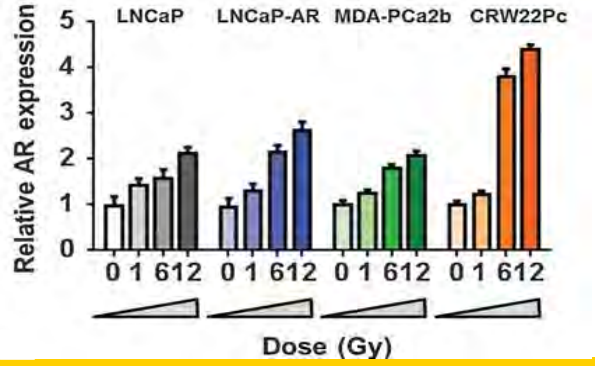
Complex interplay between DNA repair and Androgen signaling



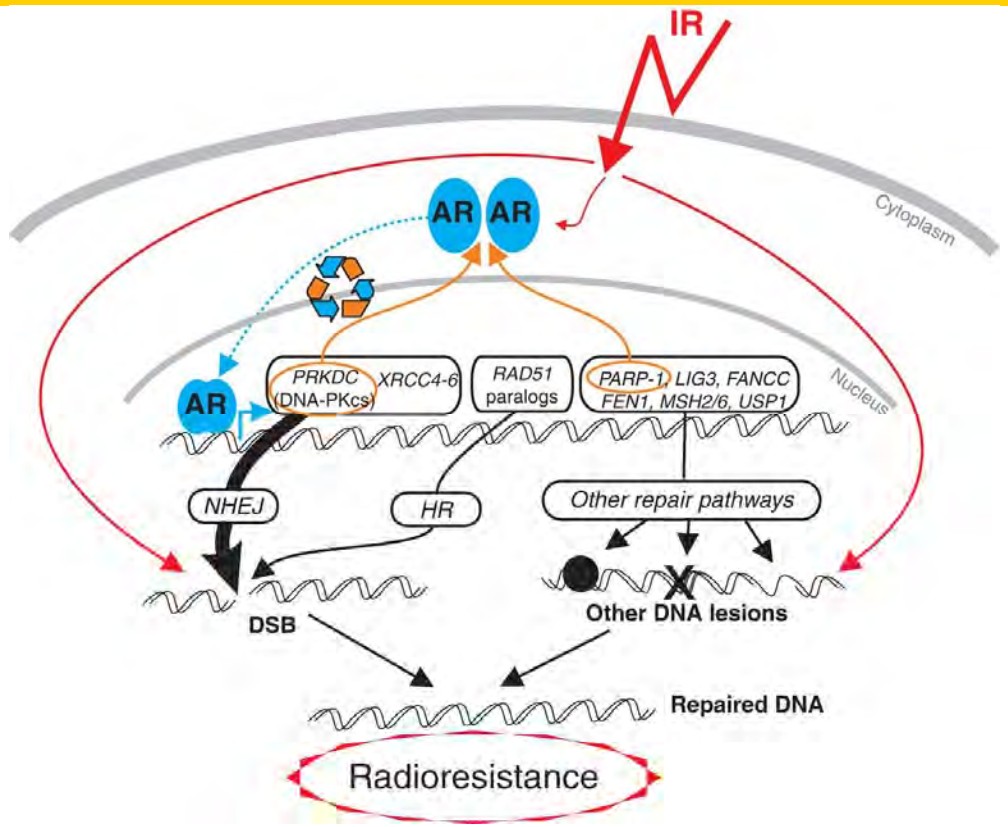
Polkinghorn W, et al, Cancer Discovery 2013

Spratt DE, et al, Cancer Research 2015





Complex interplay between DNA repair and Androgen Signaling



Opportunity to develop a predictive biomarker for ADT to benefit men receiving radiotherapy

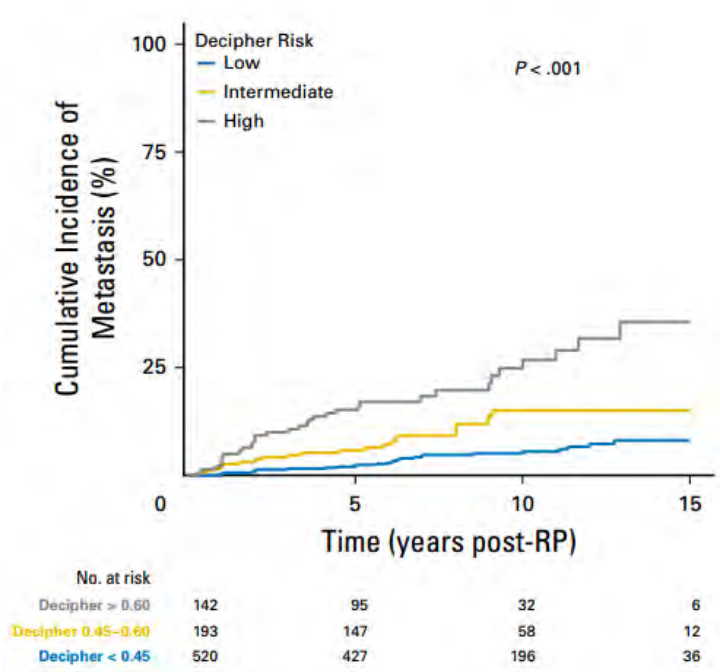
Prognostic biomarker used in Prostate Cancer

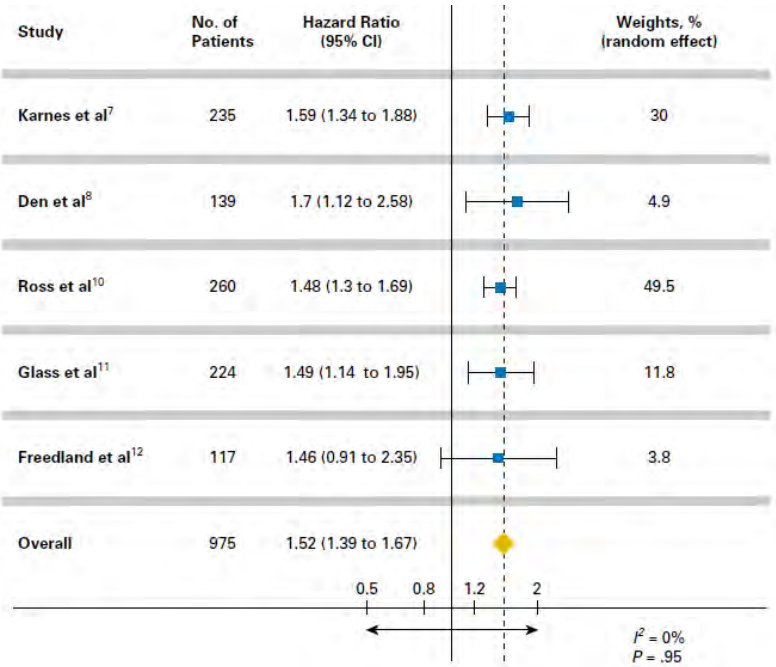
- The Decipher test, aka 22-gene expression classifier is one of the most well validated prognostic biomarkers in localized and recurrent prostate cancer.

Decipher is a robust prognostic biomarker to predict metastatic outcome

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Individual Patient-Level Meta-Analysis of the Performance of the Decipher Genomic Classifier in High-Risk Men After Prostatectomy to Predict Development of Metastatic Disease





Spratt DE et al, JCO 2017

Decipher independently predicts metastatic outcome

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

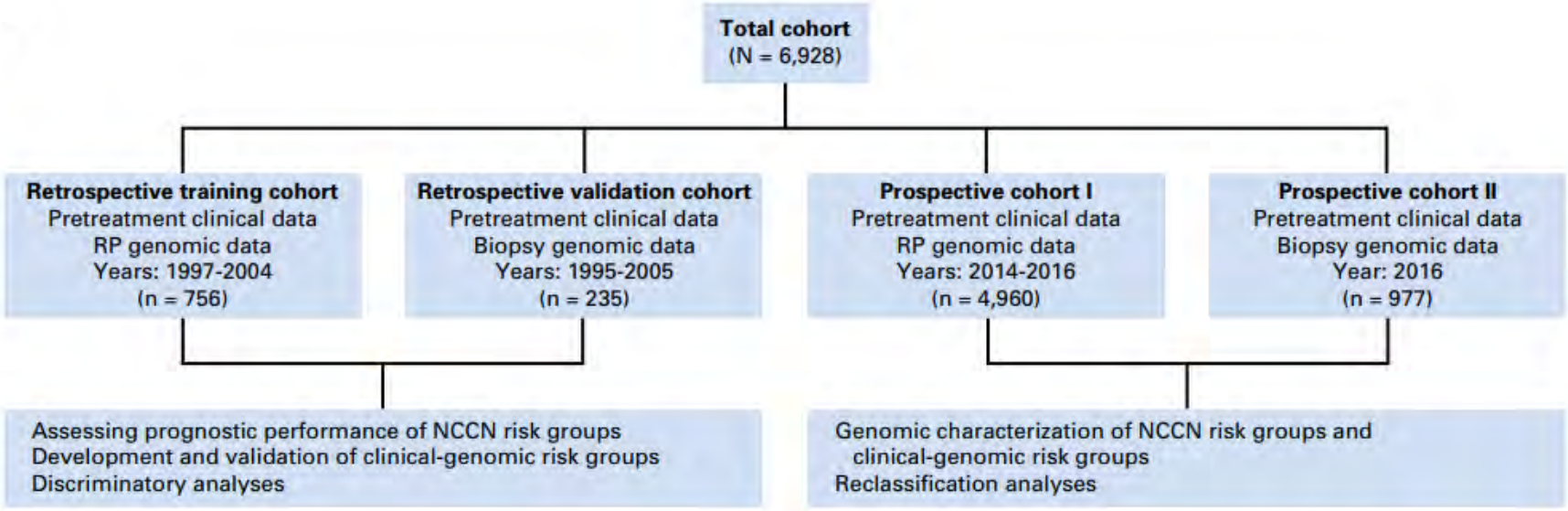
Individual Patient-Level Meta-Analysis of the Performance of the Decipher Genomic Classifier in High-Risk Men After Prostatectomy to Predict Development of Metastatic Disease

	MVA (decipher as continuous)	
Variables	Hazard Ratio (95% CI)	*P*
Log2 preoperative PSA level, ng/mL	1.10 (0.88 to 1.38)	.417
RP Gleason score ≤ 3 + 4	ref	1
RP Gleason score 4 + 3	2.40 (1.22 to 4.72)	.011
RP Gleason score ≥ 8	2.97 (1.60 to 5.51)	.001
Positive surgical margins	1.57 (0.96 to 2.58)	.075
Extraprostatic extension	1.92 (0.99 to 3.75)	.054
Seminal vesicle invasion	1.91 (1.18 to 3.11)	.009
Lymph node invasion	1.78 (0.98 to 3.26)	.06
Decipher*	1.30 (1.14 to 1.47)	< .001

Integrating prognostic biomarkers with clinicopathologic staging

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

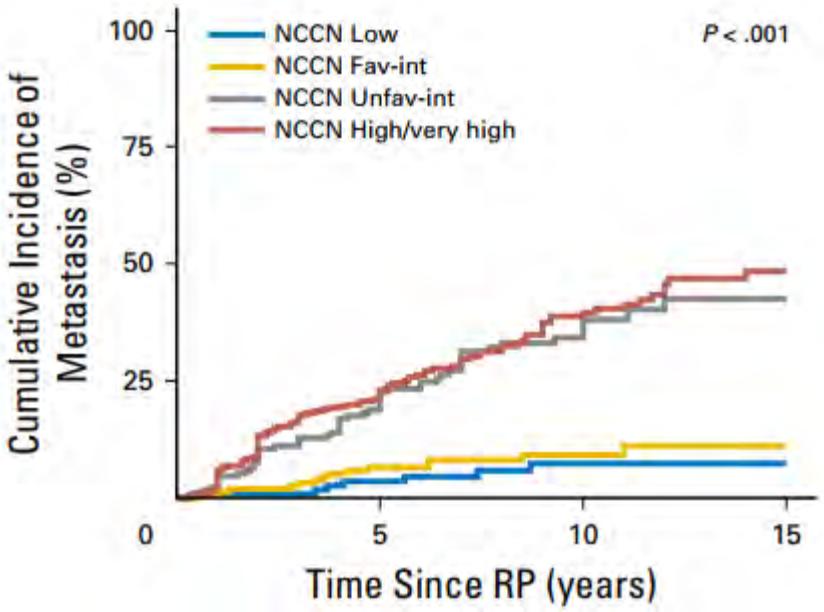
Development and Validation of a Novel Integrated Clinical-Genomic Risk Group Classification for Localized Prostate Cancer

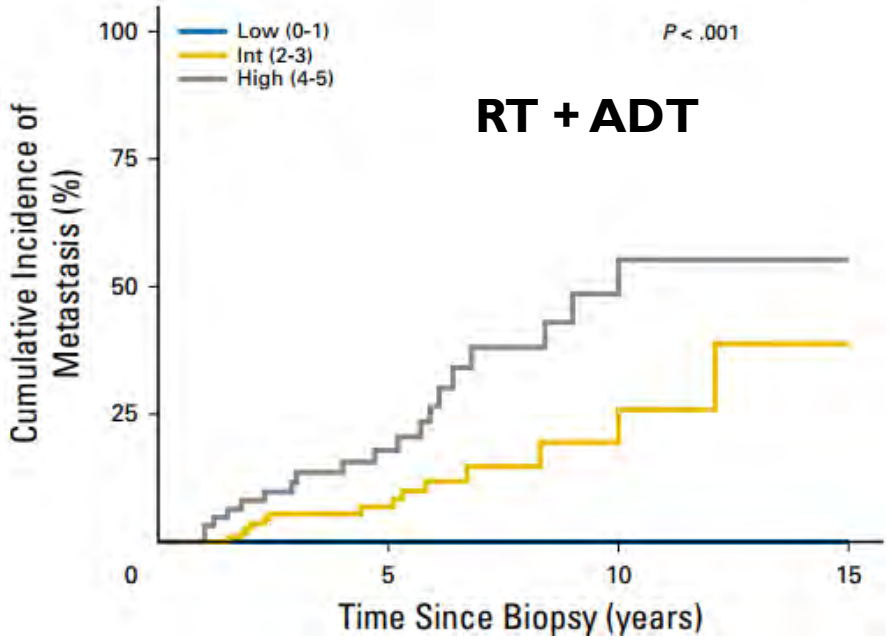


Biomarker derived risk groups are highly prognostic

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Development and Validation of a Novel Integrated Clinical-Genomic Risk Group Classification for Localized Prostate Cancer





Spratt DE et al, JCO 2017

Prognostic biomarker used in trial design for combination therapy

SCHEMA

STEP 1 REGISTRATION

Submission of tissue for DECIPHER POST-OP analysis

NOTE: Decipher analysis results must be completed before STEP 2 randomization can occur***

Androgen deprivation therapy*

↓

STEP 2 RANDOMIZATION

STRATIFY

Gleason score	PSA	Decipher risk category
1. 7 2. 8-10	1. ≥ 0.2 - < 1.0 ng/ml 2. ≥ 1.0 ng/ml	1. Low/Average 2. High

RANDOMIZE 1:1

↓

Arm 1

External Beam Radiation:
Starting 8 weeks after initiation of ADT
68.4 Gy/1.8 Gy/fraction

Plus

Androgen Deprivation Therapy:*
LHRH Agonist/antagonist
Plus
Non-Steroidal Anti-androgen
(bicalutamide)
6 months duration

↓

Arm 2

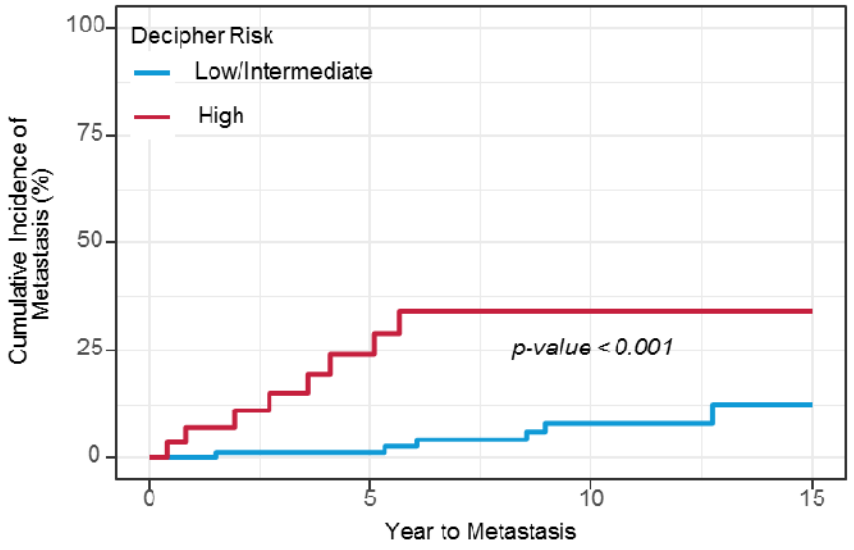
External Beam Radiation:
Starting 8 weeks after initiation of ADT
68.4 Gy/1.8 Gy/fraction

Plus

Androgen Deprivation Therapy:*
LHRH Agonist/antagonist
Plus
Non-Steroidal Anti-androgen
(bicalutamide)
6 months duration

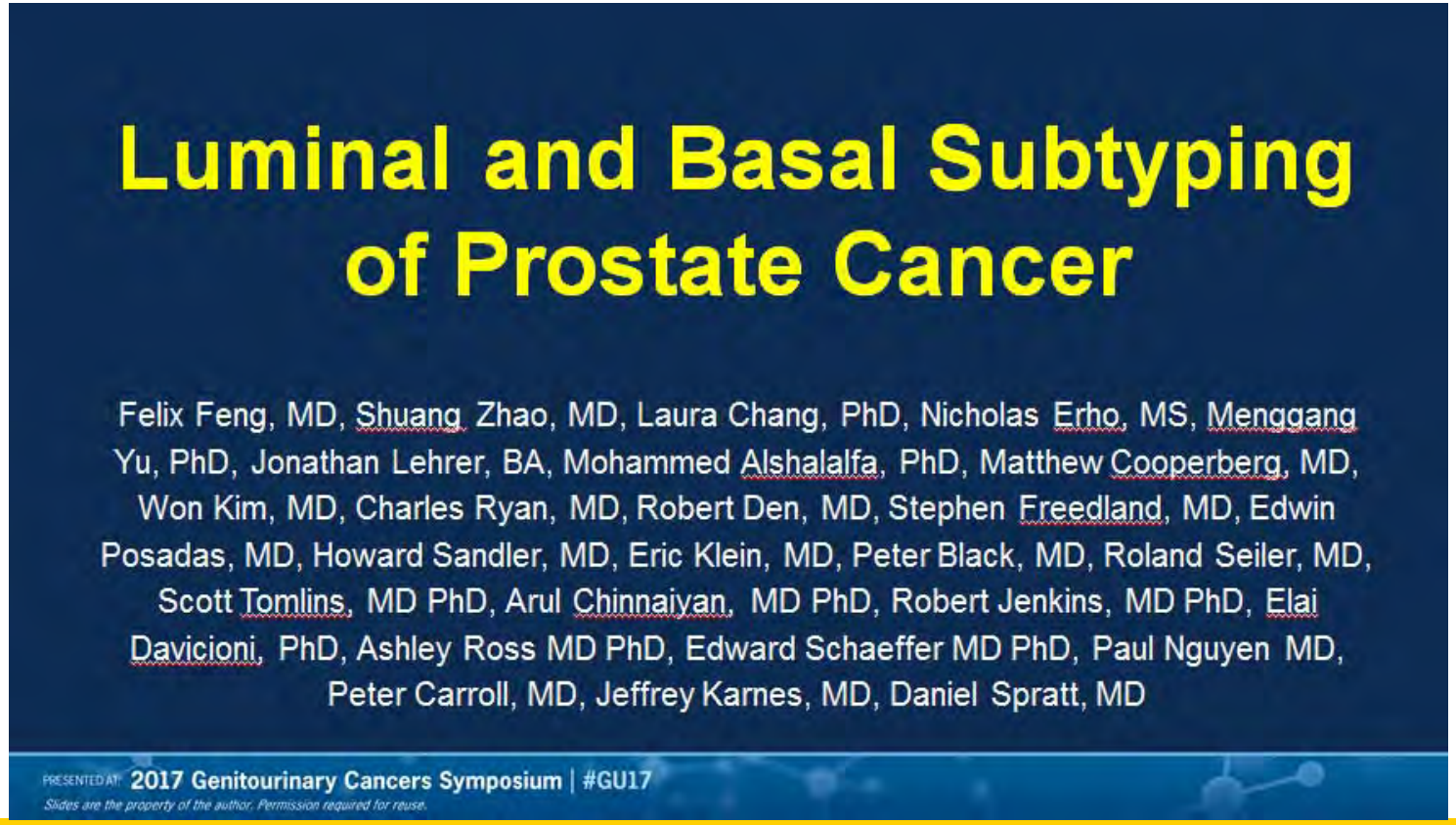
Plus
Docetaxel starting 4-6 weeks after completion of radiation
Day 1 of each 21-day cycle x 6 cycles**

- Prognostic biomarkers can be used in clinical trials to potentially identify the patient subset that will benefit most from therapy.



Spratt DE et al, Euro Urol 2017

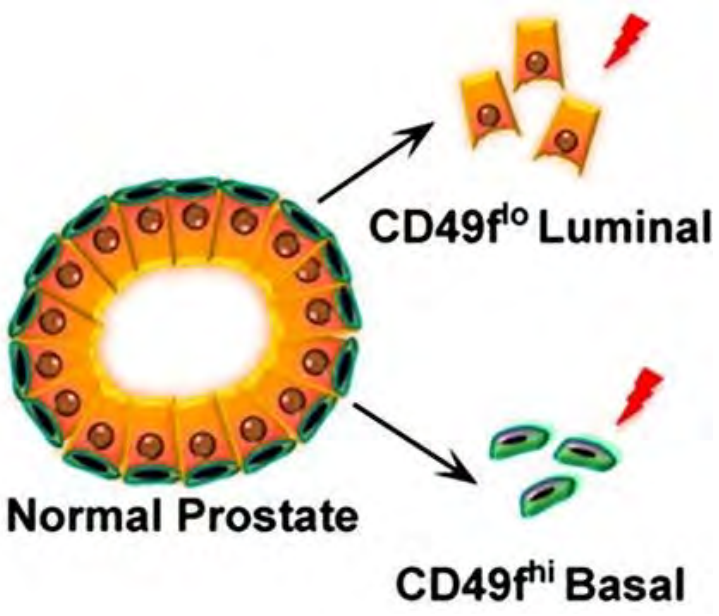
Predictive biomarkers in Prostate Cancer



Luminal and Basal Subtyping in Prostate Cancer

- The cell of origin of prostate cancer is unknown

- Prostate cancer was first thought to originate from glandular luminal cells.
- More recent evidence suggests that basal cells may play a role in prostate carcinogenesis.

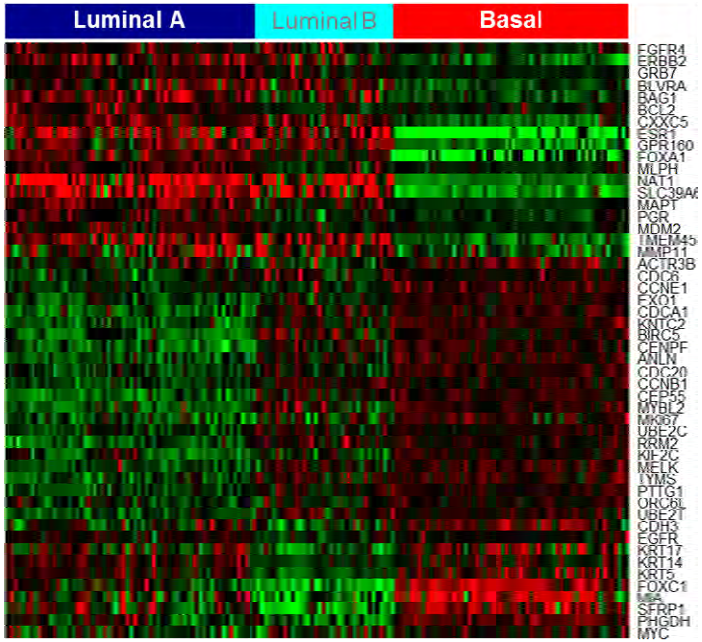


Luminal and Basal Subtyping in Prostate Cancer

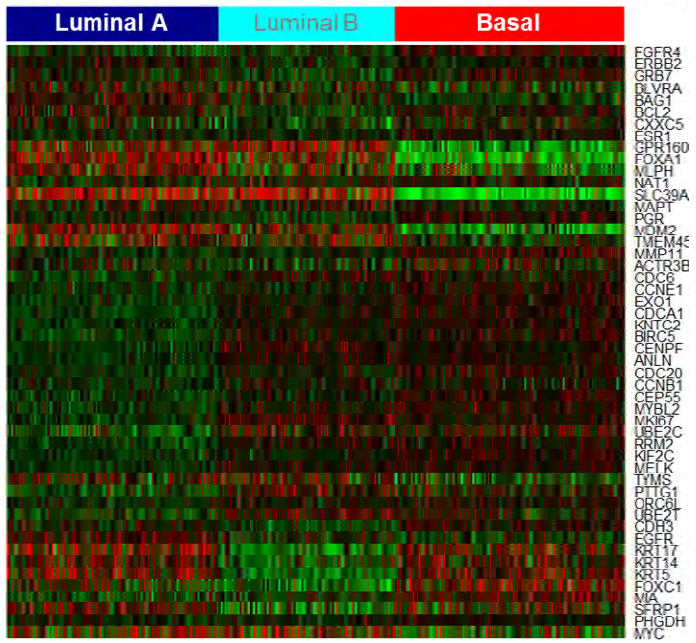
- The PAM50 test is the only clinically-utilized classifier of luminal versus basal cell-derived disease.
- The test measures the expression of 50 classifier genes and 5 control genes to identify the intrinsic subtypes of breast cancer (luminal A, luminal B, basal, and Her2)
- We hypothesized that, similar to breast cancer, subtyping can be used to guide treatment selection in prostate cancer.

Luminal and Basal Subtyping in Prostate Cancer

Breast Cohort
N=232
Expression data and PAM50 algorithm obtained from Parker et al.



Prostate Cohort
N=1567
Prostatectomy samples on a CLIA-certified platform
Studies Included: MCI, MCII, DVA, TJU, JHMI, CCF



Luminal and Basal Subtyping in Prostate Cancer

Cohorts for Matching N=780

↓

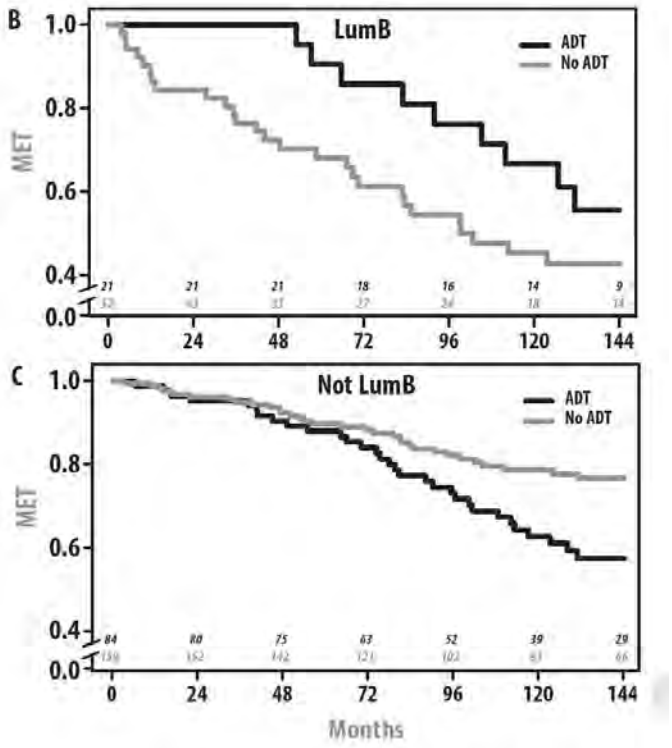
2:1 matching on ADT Covariates: Gleason, PSA, RT, LNI, ECE, SVI, SM

↓

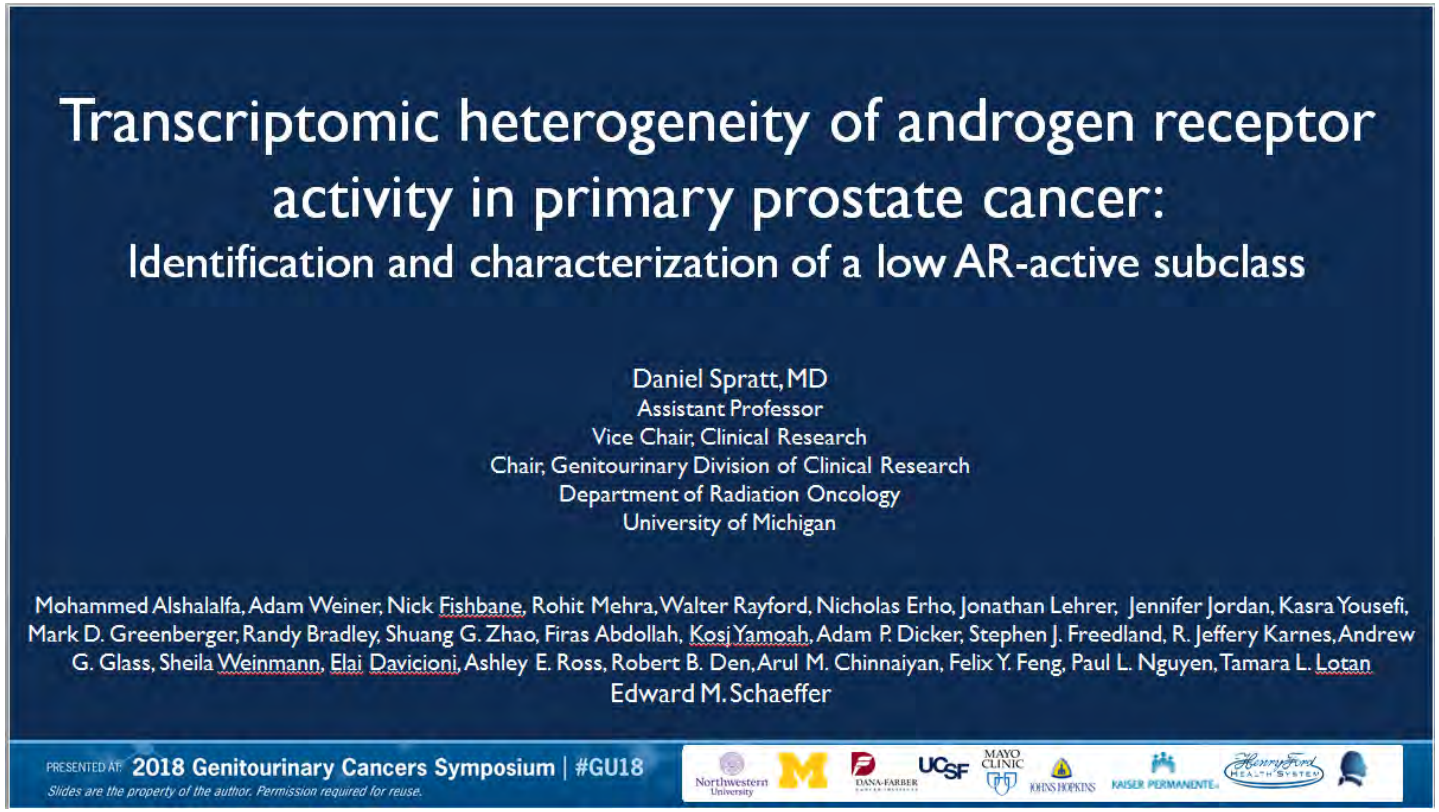
Final Matched Cohort N=315

↓

Predict response to post-operative ADT



Test for interaction was highly significant p=0.0057


Transcriptomic heterogeneity of androgen receptor activity in primary prostate cancer:
Identification and characterization of a low AR-active subclass
Daniel Spratt, MD
Assistant Professor
Vice Chair, Clinical Research
Chair, Genitourinary Division of Clinical Research
Department of Radiation Oncology
University of Michigan
Mohammed Alshalalfa, Adam Weiner, Nick Fishbane, Rohit Mehra, Walter Rayford, Nicholas Erho, Jonathan Lehrer, Jennifer Jordan, Kasra Yousefi, Mark D. Greenberger, Randy Bradley, Shuang G. Zhao, Firas Abdollah, Kosj Yamoah, Adam P. Dicker, Stephen J. Freedland, R. Jeffery Karnes, Andrew G. Glass, Sheila Weinmann, Elai Davicioni, Ashley E. Ross, Robert B. Den, Arul M. Chinnaiyan, Felix Y. Feng, Paul L. Nguyen, Tamara L. Lotan
Edward M. Schaeffer
PRESENTED AT 2018 Genitourinary Cancers Symposium | #GU18
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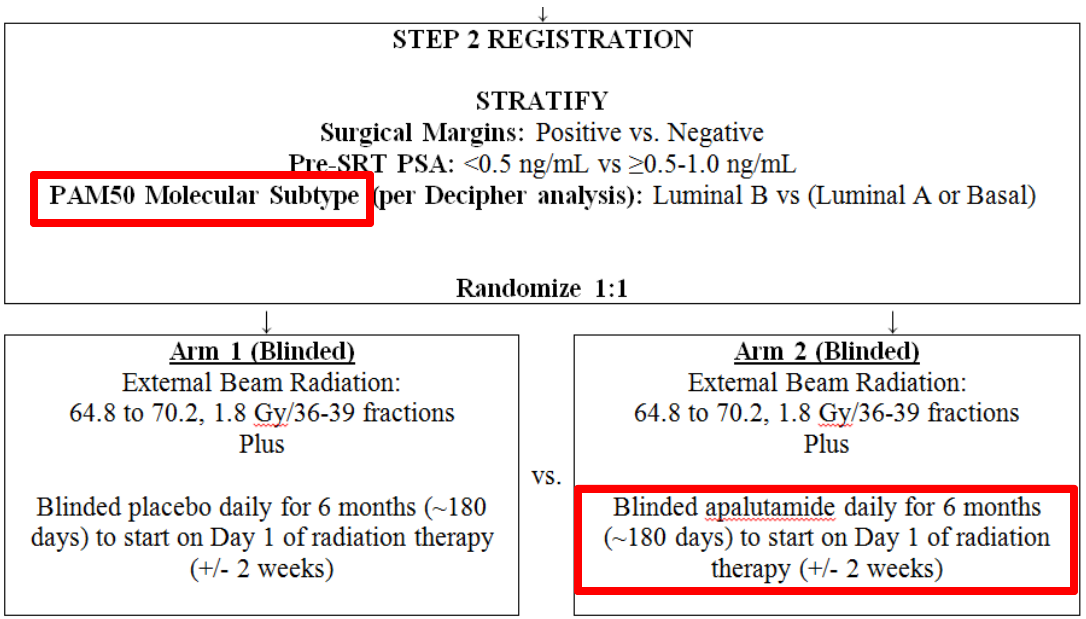
Predictive biomarker driver trials: Biomarker stratified phase IIR

NRG GU-006

A PHASE II, DOUBLE-BLINDED, PLACEBO CONTROLLED RANDOMIZED TRIAL OF SALVAGE RADIOTHERAPY WITH OR WITHOUT ENHANCED ANTI-ANDROGEN THERAPY WITH APALUTAMIDE



Co-PIs: Spratt
Feng

Predictive biomarker driven trials: Biomarker validation phase I trial

NCCN High Risk Prostate Cancer

↓

DNA: DNA repair alterations
RNA: AR activity

↓

SBRT + ADT + **PARPi**

Time-to-event continual reassessment method (TITE-CRM) design

N=38

Analyze response by biomarkers to determine if biomarker enhanced trial preferred for phase II design.

PI: Spratt

Conclusions

- There has been success in developing CLIA grade prognostic tests for many malignancies.
- There has been isolated success stories of developing predictive biomarkers for systemic therapies.
- There have been no success stories YET for a prospectively validated predictive biomarker for radiotherapy.

Conclusions

- Both prognostic and predictive biomarkers can be used to personalize treatment and to design trials to select a patient subset most likely to derive benefit from combination therapy.

- These biomarkers would be ideal candidates to be used in combination therapy trials and could increase the success of the trial and speed drug approval.

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Prostate Cancer Foundation Curing Together.

NIH Prostate Spore

Questions

 #DrSpratticus

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AMERICAN SOCIETY FOR RADIATION ONCOLOGY

The Debate:

The Next Drug Approved in Combination With Radiation Will Be…

Debaters:

"An IO Agent" - James W. Welsh, MD

"Something Else (not IO)" - Theodore S. Lawrence, MD, PhD

This House believes that the next agent to be FDA-approved with radiation therapy will be immunotherapeutic

AGAINST

Ted Lawrence, MD, PhD
University of Michigan

closure information

Sadly, I have no financial relationships to disclose that are relevant to this talk

– and –

I will mention the following off-label use and/or investigational use in my presentation:

The WEE1 inhibitor AZD1775

closure information

The views expressed in this talk do not represent those of AACR, ASTRO, the FDA or, frankly, the speaker himself

They should be received in the spirit of stimulating discussion and, hopefully, a few smiles

s wonderful, but the path to approval is filled with obstacles

Although immunotherapy (IT) will be found to cure every problem of mankind in the coming years, it has no approval path in combination with radiation therapy (RT)

Fundamental problem for IT

- **The focus is on RT stimulating the elusive abscopal effect: i.e. getting a response where we are not pointing the beam**
  - **How to differentiate the abscopal effect from the systemic effec of IT?**
- **Responses are rare**
- **Because mechanisms are mysterious, there are too many differen approaches**

e approval path for RT+ drugs is slow but straightforward

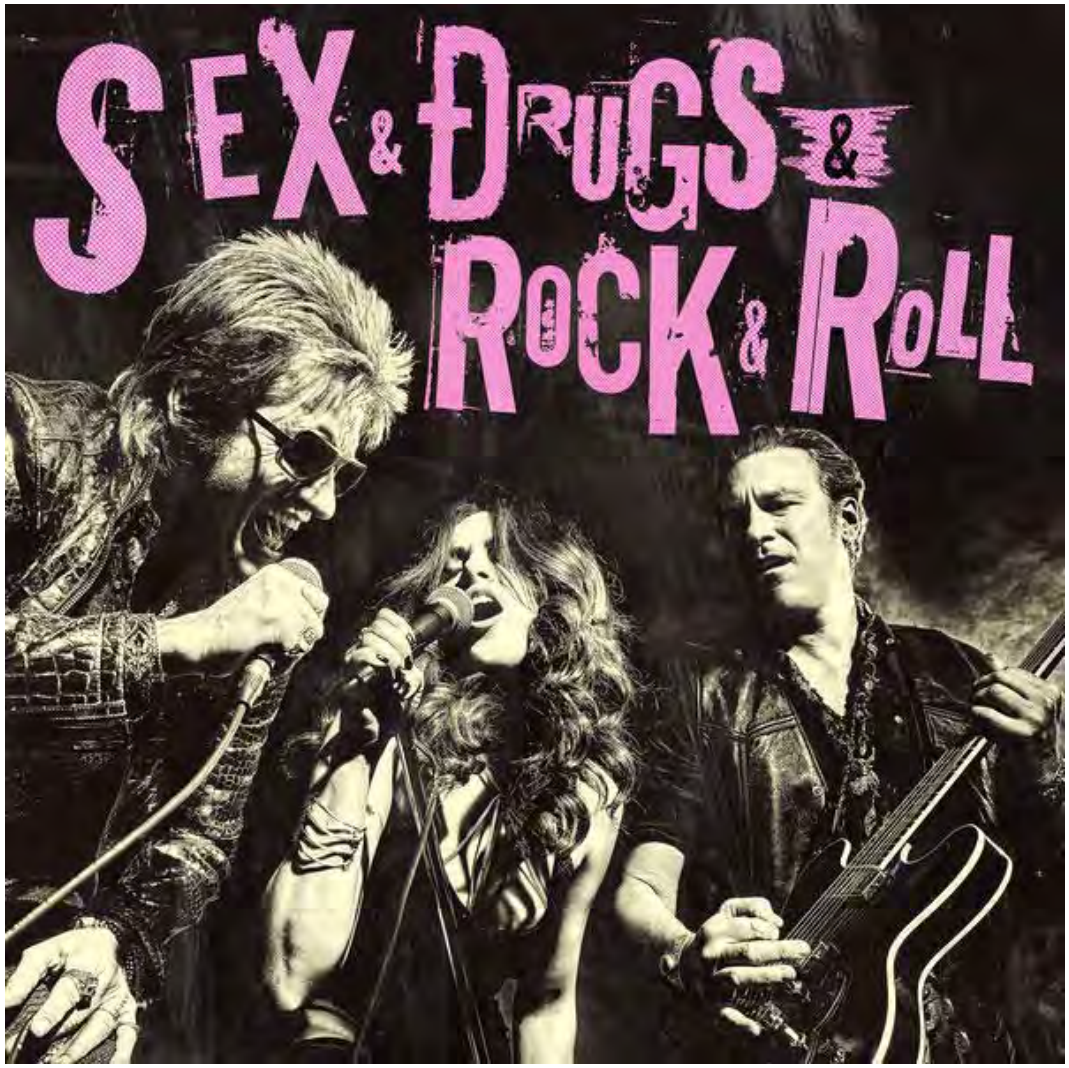
Drugs work by increasing the response or producing protection where we are pointing the beam

- **Responses are easily measurable**
- **Responses are common**
- **Because mechanisms are clearer, easier to get agreement on dose and schedule**

Our side has successes

- **And more in the wings**

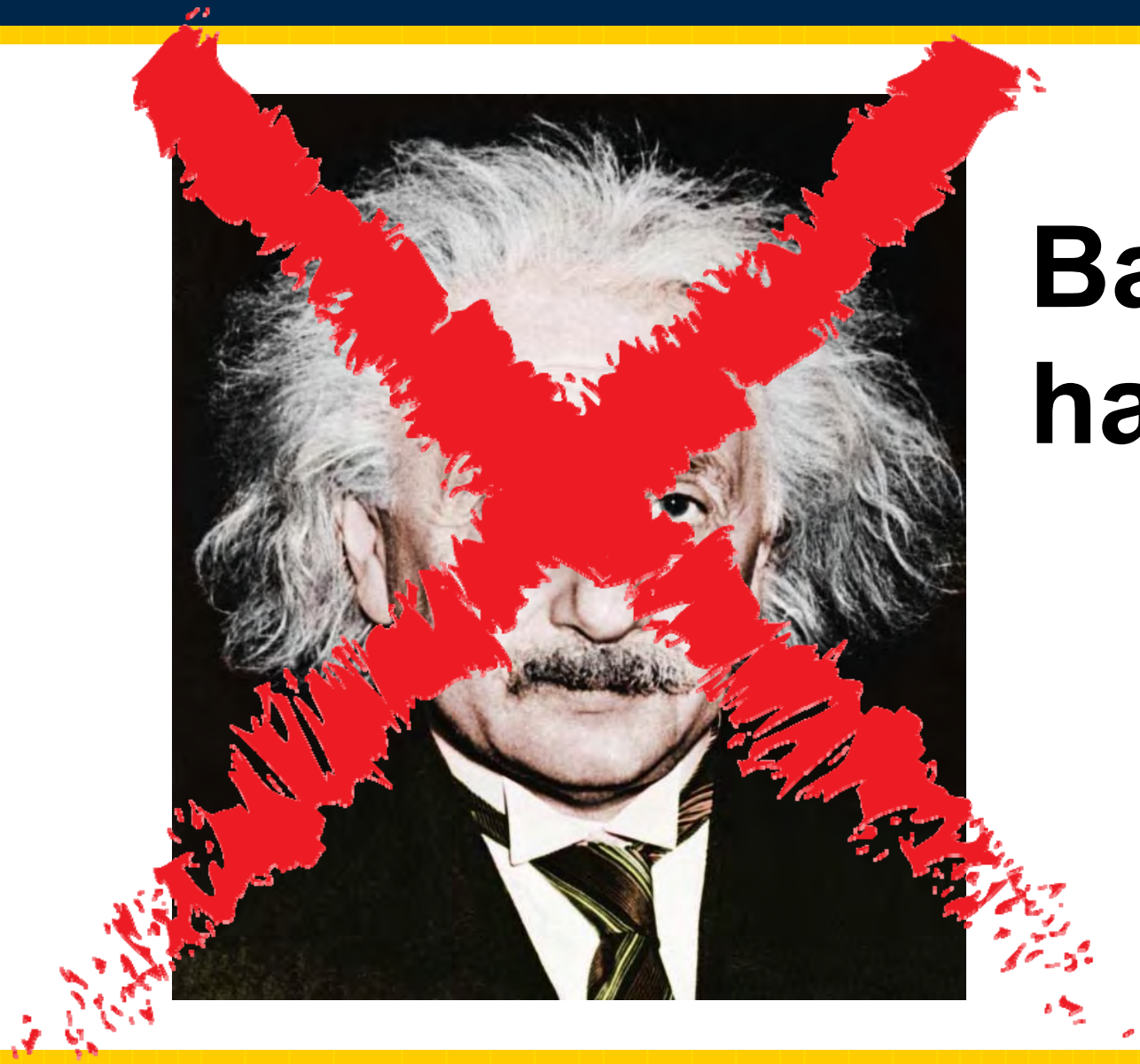
nunotherapy Cures- Hope and Hype



Better than...

nunotherapy Cures- Hope and Hype

nunotherapy Cures- Hope and Hype



Bad hair

nunotherapy Cures- Hope and Hype

Bad taste

to get FDA approval in combination with RT

IT is counting on the “Elusive Abscopal Effect”

The abscopal effect is a phenomenon in which local radiotherapy is associated with the regression of metastatic cancer at a distance from the irradiated site.

e Elusive Abscopal Effect

The patient was treated with two cycles of ipilimumab, followed by stereotac
adiotherapy to two of eight hepatic metastases and two additional cycles of
ilimumab. Remarkably, subsequent positron-emission tomography–comput
omography showed that all metastases, including the nonirradiated liver lesi
nd a nonirradiated axillary lesion, had completely resolved…"

He was treated with intracranial stereotactic radiosurgery (SRS) and
mmunotherapy with ipilimumab…This patient received palliative radiation to
rimary melanoma, yet there was a delayed but robust response in all untrea
utaneous metastases. This type of response in distant tumors after local
adiotherapy is known as the abscopal effect."

Hinniker et al NEJM 366: 2035, 2012
Stamell et al Red Journal 85: 293, 2013

e Elusive Abscopal Effect… IS IT EVEN REAL?

he patient was treated with two cycles of ipilimumab, followed by stereotactic diotherapy to two of eight hepatic metastases and two additional cycles of ipilimum markably, subsequent positron-emission tomography–computed tomography sho t all metastases, including the nonirradiated liver lesions and a nonirradiated axill ion, had completely resolved…"

e was treated with intracranial stereotactic radiosurgery (SRS) and immunotherap imumab…This patient received palliative radiation to his primary melanoma, yet th s a delayed but robust response in all untreated cutaneous metastases. This type sponse in distant tumors after local radiotherapy is known as the abscopal effect."

NO IT DOES NOT!!

IT SHOWS A SYSTEMIC EFFECT OF IMMUNOTHERAPY

1. *Hinniker et al NEJM 366: 2035, 2012.* 2. *Stamell et al Red Journal 85: 293, 2013.*

The NEW ENGLAND JOURNAL of MEDICINE

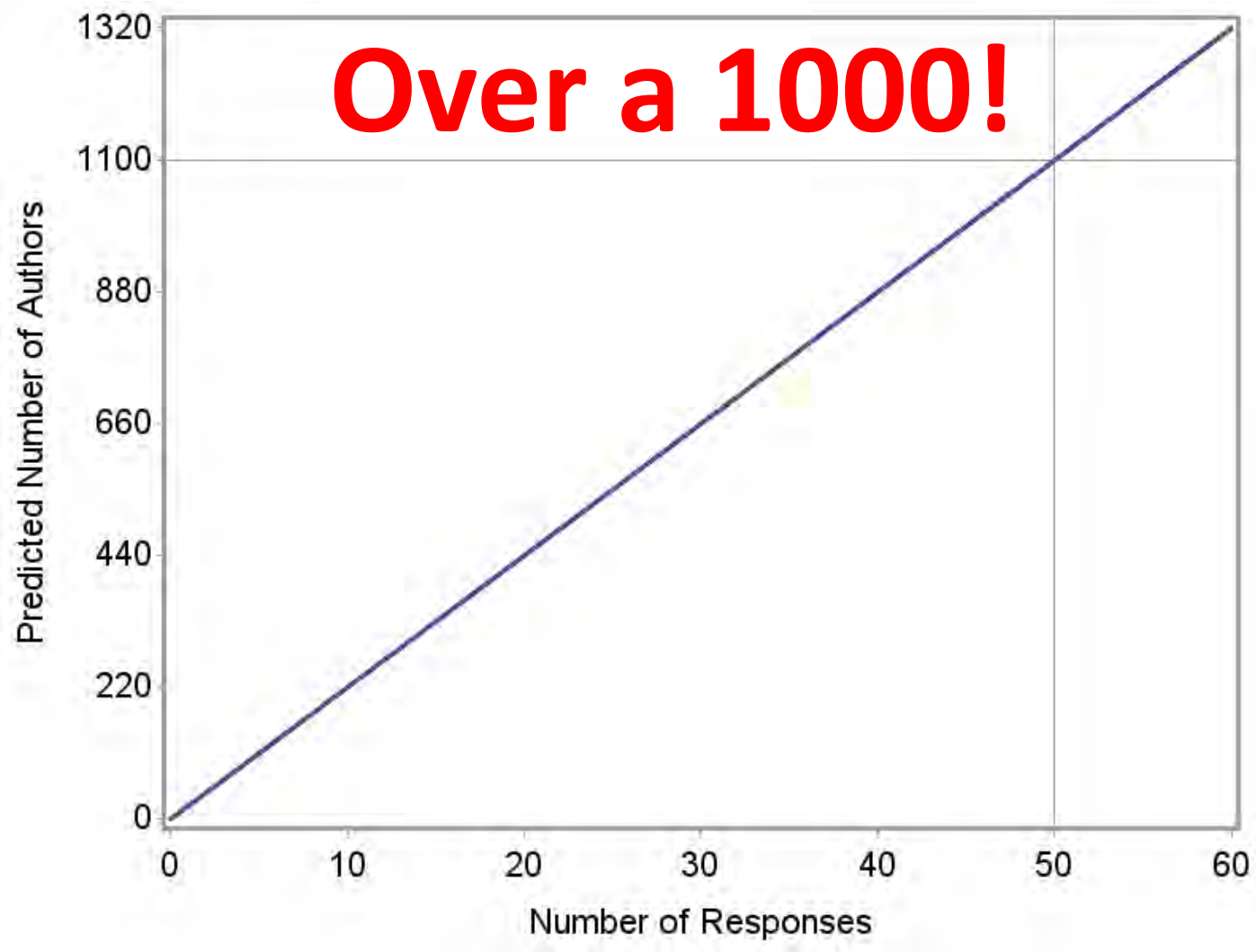
Immunologic Correlates of the Abscopal Effect in a Patient with Melanoma

Michael A. Postow, M.D., Margaret K. Callahan, M.D., Ph.D., Christopher A. Barker, M.D., Yoshiya Yamada, M.D., Jianda Yuan, M.D., Ph.D., Shigehisa Kitano, M.D., Ph.D., Zhenyu Mu, M.D., Teresa Rasalan, B.S., Matthew Adamow, B.S., Erika Ritter, B.S., Christine Sedrak, B.S., Achim A. Jungbluth, M.D., Ramon Chua, B.S., Arvin S. Yang, M.D., Ph.D., Ruth-Ann Roman, R.N., Samuel Rosner, Brenna Benson, James P. Allison, Ph.D., Alexander M. Lesokhin, M.D., Sacha Gnjatic, Ph.D., and Jedd D. Wolchok, M.D., Ph.D.

22 authors for 1 response

N Engl J Med 2012;366:925

v many radiation oncologists does it take……



Schipper, M soon t
published observa

00 Unhappy Radiation Oncologists

rials are incredibly disorganized!

	Vaccination	CTLA-4	PD-1	Others*	Total
Estimated enrollment	3310	692	692	667	5252†
No. of trials	30	20	15	18	81†
No. primarily sponsored by industry‡	15	0	2	1	18
Phase					
0	0	1	1	2	4
1	9	9	7	3	26†
1/2	1	3	2	8	14
2	16	7	5	5	32†
3	4	0	0	0	4
Cancer type					
Breast	1	0	1	6	8
GBM	5	0	1	0	6
Melanoma	1	14	2	1	17†
NSCLC	2	1	4	1	7
Pancreatic	9	1	2	1	12†
Prostate	6	0	0	1	7
Others	6	4	6	9	25
Year of initiation					
Before 2011	8	0	0	3	11
2011	3	3	0	3	9
2012	4	4	0	1	9
2013	6	3	0	5	14
2014	3	8	3	1	14†
2015	6	2	12	6	25†
Dose per fraction§					
0-2.9 Gy	22	3	6	2	33
3-5.9 Gy	4	3	0	2	9
6-10 Gy	5	10	8	9	31
>10 Gy	2	7	1	7	17
Fractionation§					
1 fraction	4	5	2	5	16
2-5 fractions	6	11	7	14	38
6-10 fractions	0	3	0	3	6
10-27 fractions	0	0	0	0	0
>27 fractions	22	1	6	1	30
RT timing§					
RT >1 wk before IT	9	5	3	0	17
RT within 1 wk of IT	9	10	7	12	38
RT >1 wk after IT	7	4	3	4	18

Abbreviations: CTLA-4 = cytotoxic T-lymphocyte-associated protein 4; GBM = glioblastoma multiforme; IT = immunotherapy; NSCLC = non-small cell lung cancer; PD-1 = programmed cell death protein 1; RT = radiation therapy.

We queried ClinicalTrials.gov for ongoing trials involving IT and RT.

* The "Others" category includes immunotherapies such as interleukin 2, toll-like receptor agonists, tumor necrosis factor receptor superfamily, member 4 agonists, and transforming growth factor β–targeted agents, as well as other immune modifiers.

† Row totals are lower than the sum of the trials because 2 trials combining CTLA-4 and PD-1 blockade were included in both columns.

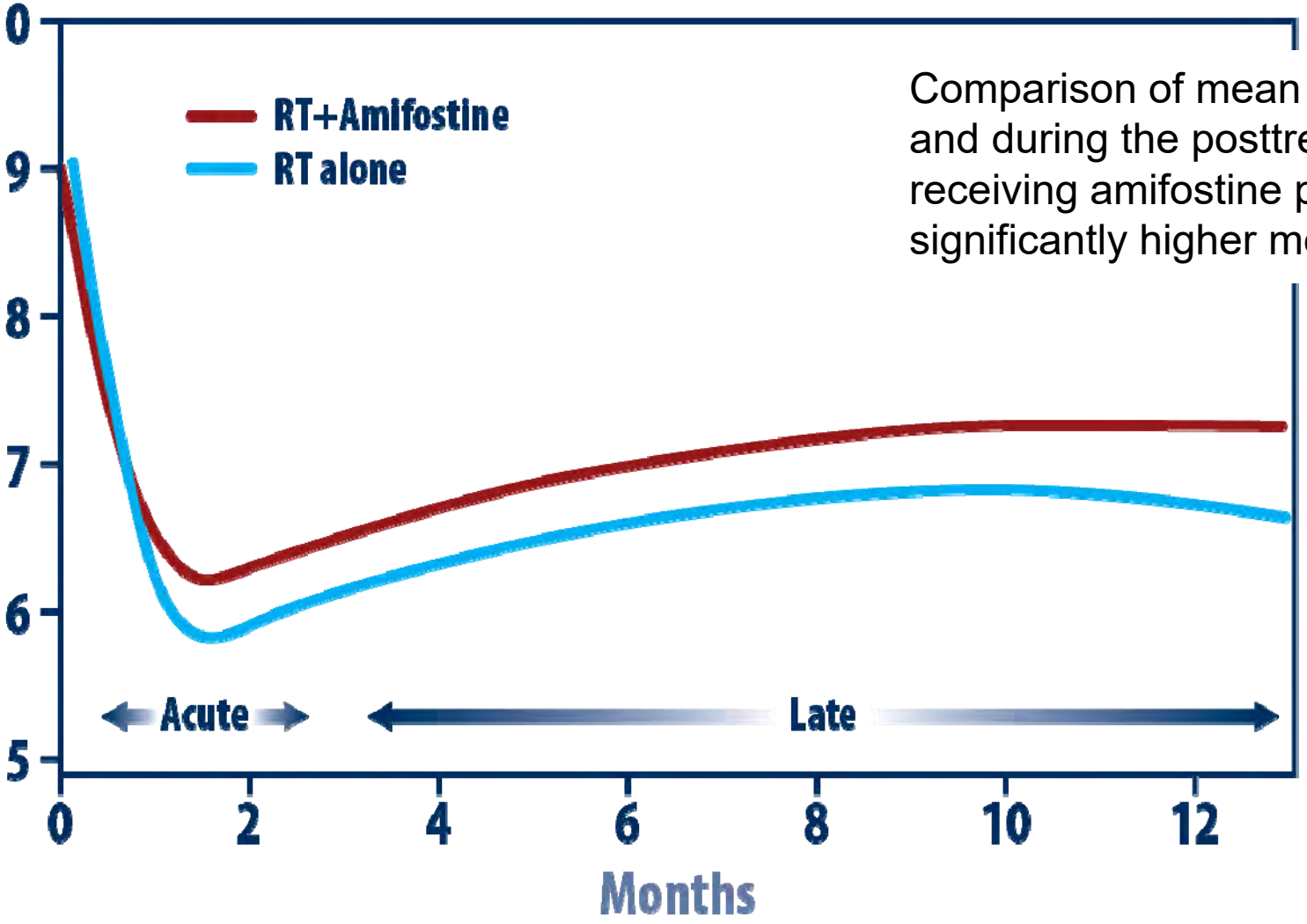
‡ Studies co-sponsored by industry were not included.

§ The sums of these categories may not equal the actual number of trials reported because trials using multiple dose, fractionation, or timing schemes were included in the totals for each category and/or some trials did not report exact schemes.

Overview of ongoing clinical trials combining RT with IT

Johnson CB and Jagsi J, Red Journal 95:1254, 2016

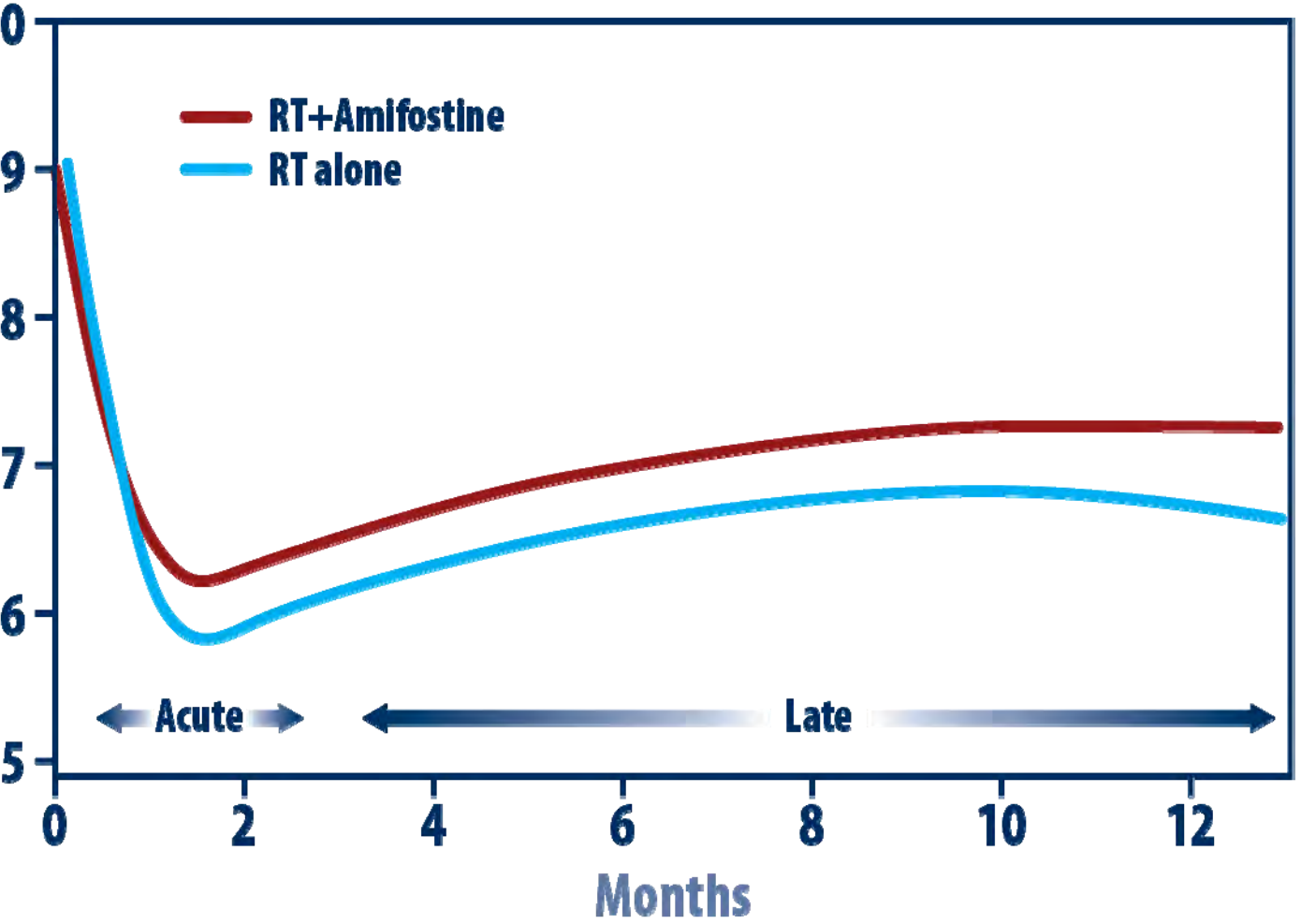
ifostine Protects Against Xerostomia



Comparison of mean scores on PBQ during treatm
and during the posttreatment follow-up period; patie
receiving amifostine plus radiotherapy had a
significantly higher means score *(p=0.008).*

Brizel, DM et al J. Cl
Oncology 18: 3339,

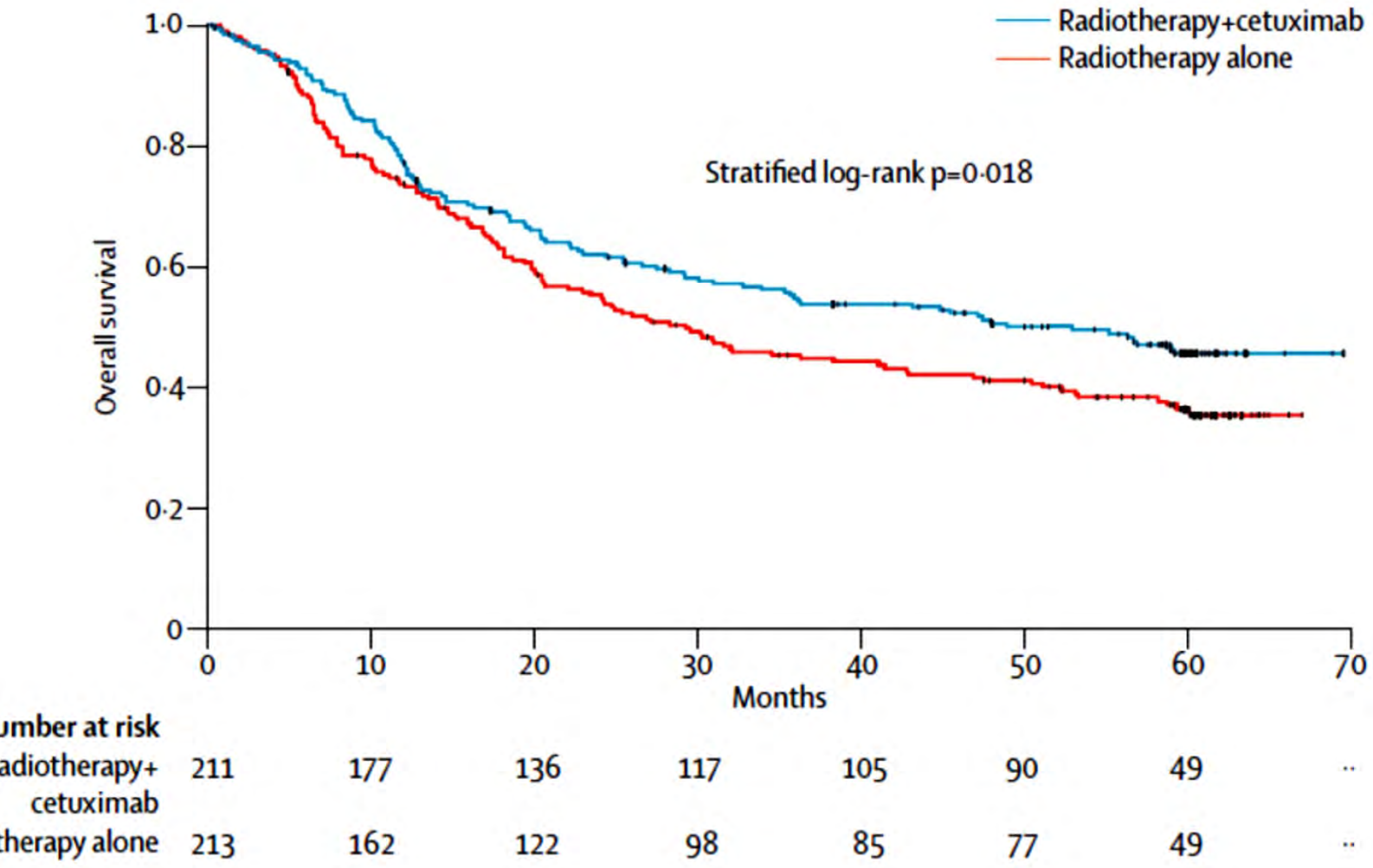
ifostine Protects Against Xerostomia



Amifostine with RT FDA Approved!

izel, DM et al J. Clin. Oncology 18: 3339, 2000

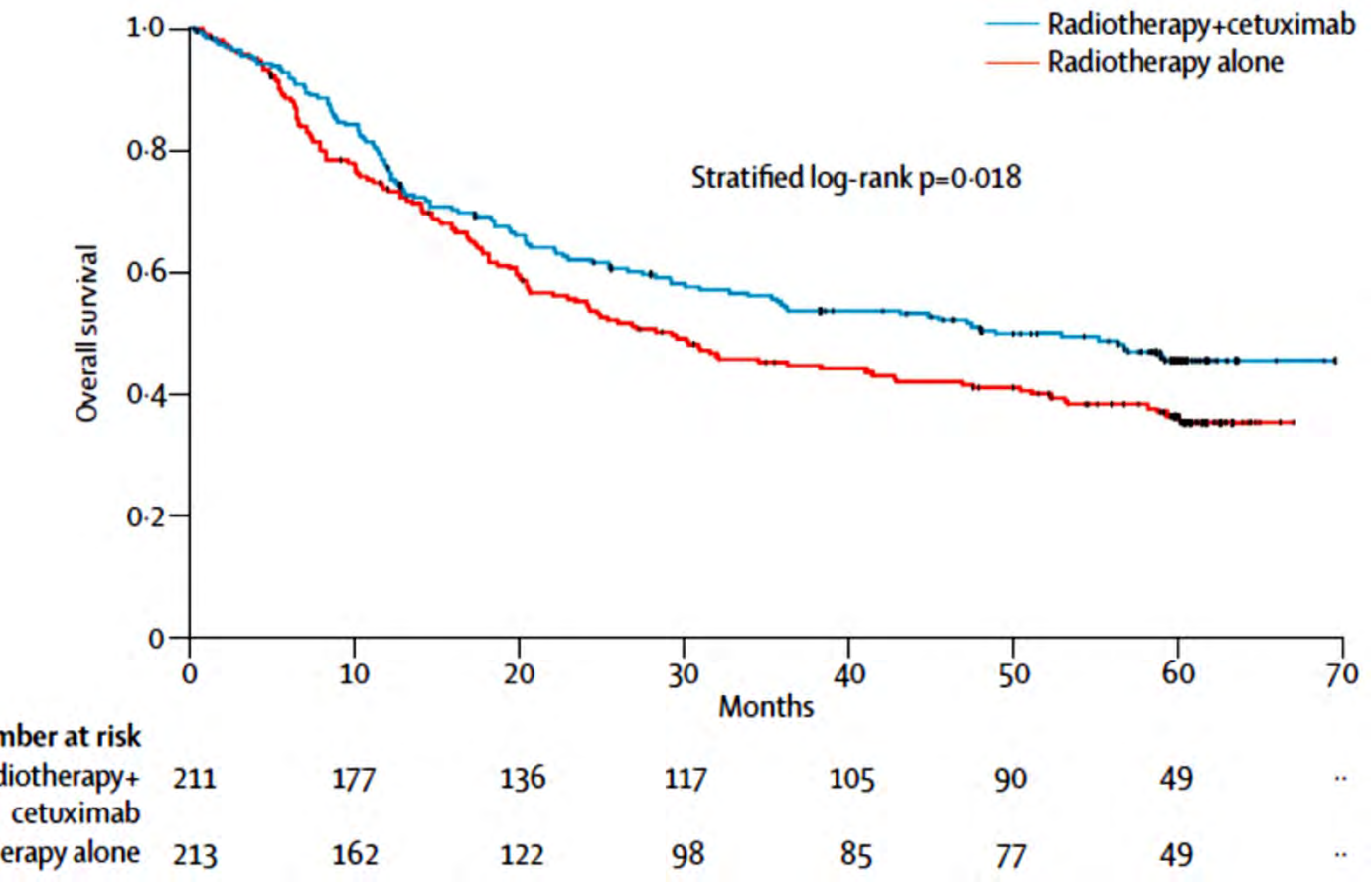
uximab + Radiation is Superior to Radiation for HN Cancer



Overall survival by treatment: 5-year update (median follow-up 60 month

Bonner JA et al Lancet Oncology 11: 21, 2010

uximab + Radiation is Superior to Radiation for HN Cancer



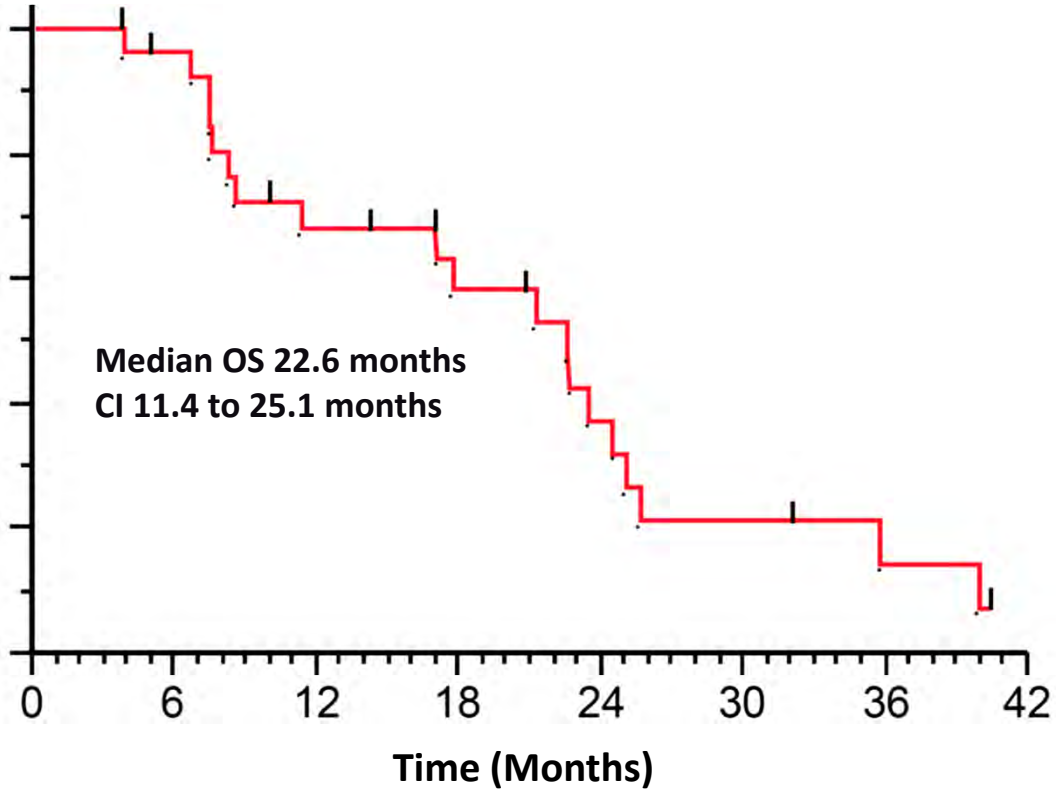
mber at risk								
diotherapy+ cetuximab	211	177	136	117	105	90	49	..
erapy alone	213	162	122	98	85	77	49	..

Cetuximab with RT FDA Approved!

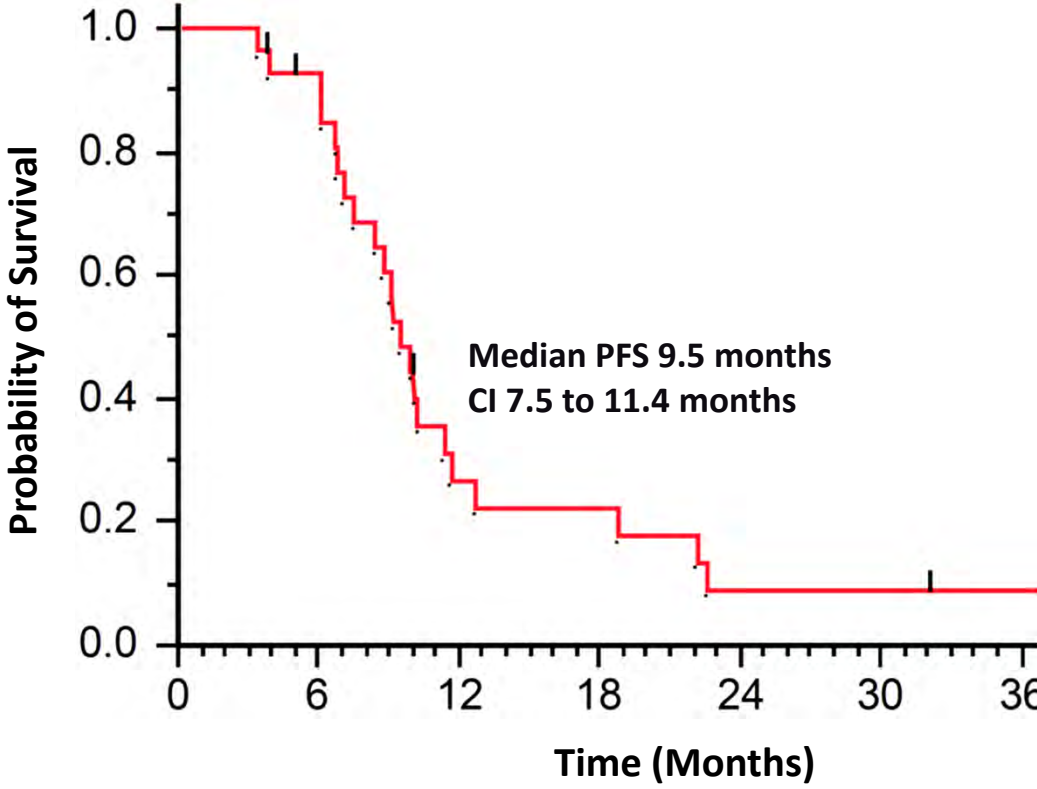
Bonner JA et al Lancet Oncology 11: 21, 2010

D1775 with Gem/RT may increase OS in Pancreatic Cancer

Overall Survival

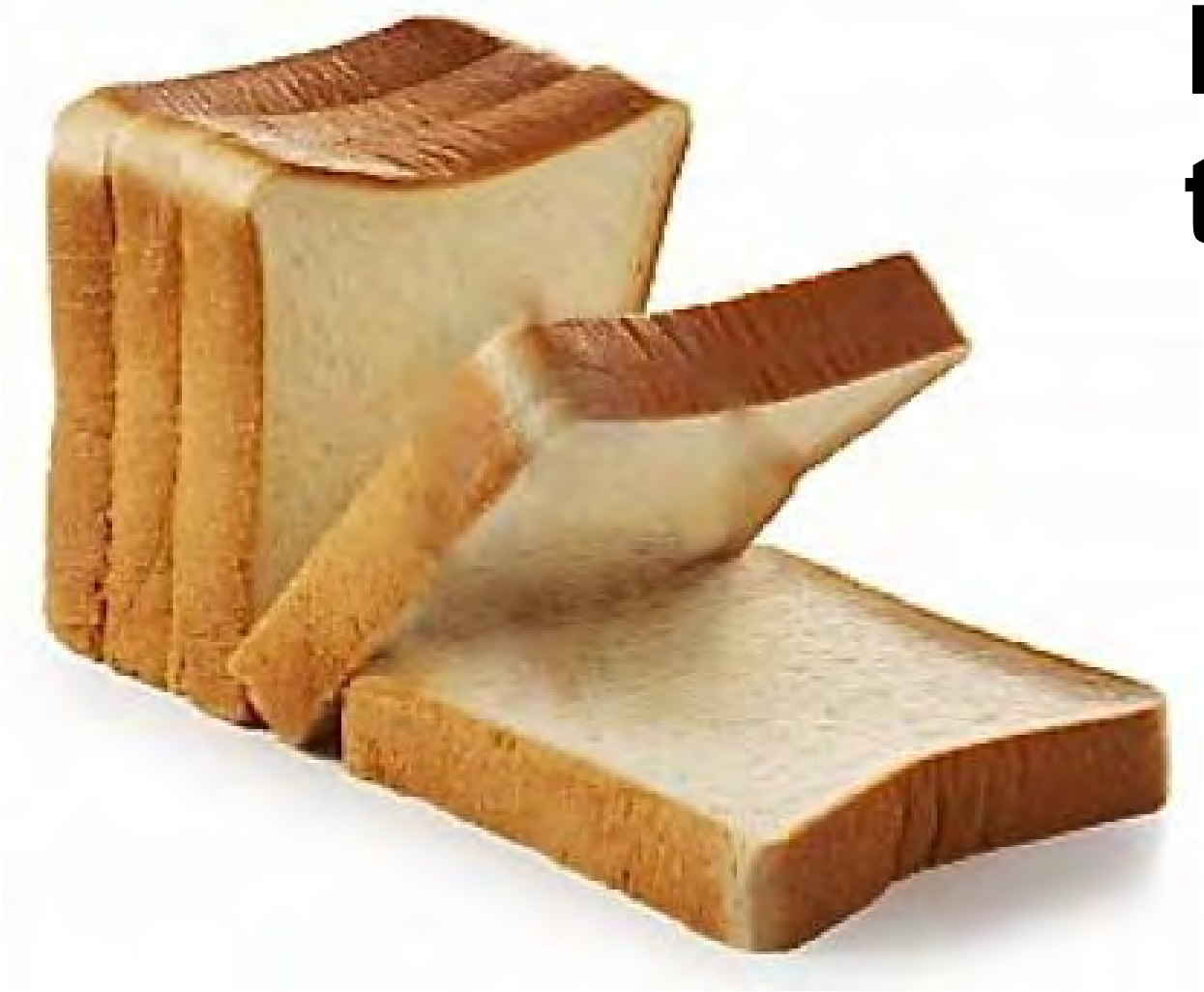


Progression Free Survival



Cuneo K, et al (preliminary results of an ongoing clinical trial)

nunotherapy Cures- Hope and Hype



Better than…

s Cool but Drugs will Rule!

Category	Immunotherapy	Drugs
Ease of assessing response	**Hard: is it a systemic response or the elusive abscopal effect?**	**Easy: Look inside in the beam!**
Responses rate	**Rare: needs 1000 physicians**	**Common**
Getting agreement on the right trial	**Hard: every cytokine and T cell has its own fan club**	**Easy: Targeted therapies are….targeted**
Successes	**None**	**Drugs are already FDA approved with RT**

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The next agent that will be FDA approved combined with RT will be: A DRUG

Final Panel Discussion:

Moderator: Amanda Walker, MD

Panelists:

Paul G. Kluetz, MD

Helen Bulbeck, PhD

Robert Iannone, MD

Quynh-Thu Le, MD, FACR, FASTRO

Ricky Sharma, MD, PhD

U.S. FOOD & DRUG ADMINISTRATION

AACR American Association for Cancer Research
FINDING CURES TOGETHER℠

ASTRO
AMERICAN SOCIETY FOR RADIATION ONCOLOGY

Summary & Future Directions

Speaker:
Amanda Walker, MD