



Clinical Development of Drug-Radiotherapy Combinations

February 22-23, 2018 | Bethesda, MD

@FDAOncology

@AACR

@ASTRO_org

@CR_UK



Join the conversation with #RxRTCombos18



Workshop Cochairs:

Amanda Walker, MD

Stephen M. Hahn, MD

Theodore S. Lawrence, MD, PhD

Marka Crittenden, MD, PhD

Phuoc T. Tran, MD, PhD

Introduction

Speakers:

AACR Cochair

Amanda Walker, MD

Yaacov Richard Lawrence, MD

Ricky Sharma, MD, PhD



FDA AACR ASTRO workshop



**Radiation and Immunotherapy,
Improving Collaboration with Industry
or
Drug-RT combos, a missed opportunity, and
how to fix it**

Yaacov Lawrence, Sheba Medical Center, Israel
Bethesda, Feb 2018

Ideas presented do not reflect

- FDA
- AACR
- ASTRO

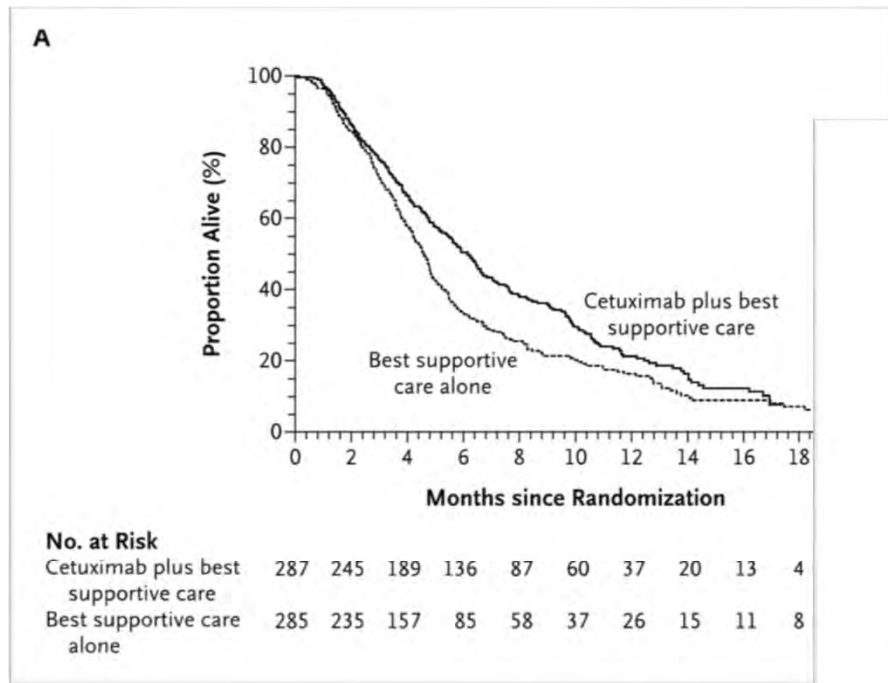
Conflicts of interest, Research funding

- Karyopharm Therapeutics
- Checkmate Pharmaceuticals
- Bristol-Myers Squibb
- Gateway for Cancer Research

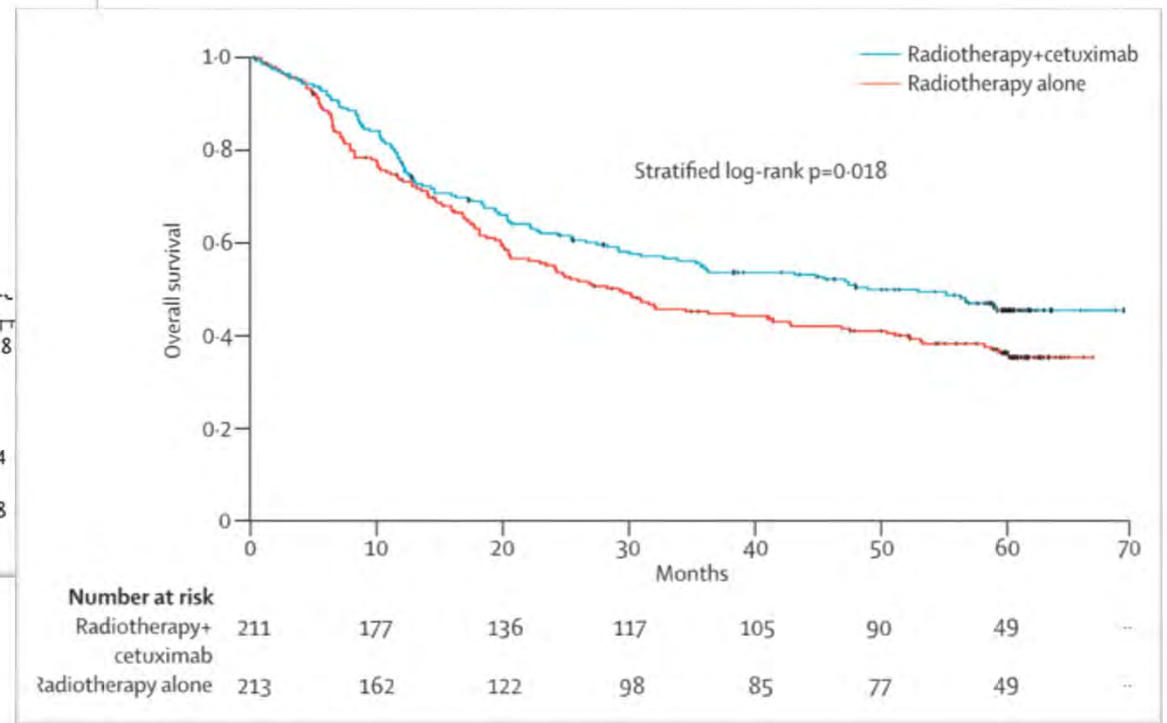
Overview of talk

- 1. RT- Drug combinations - a missed opportunity**
2. Pharma – Society: interdependence
3. Pharma – Society: Difficulties
4. Life-and-Death of a drug
5. Previous governmental attempts to influence drug development
6. Game theory approach

RT-drug combinations, the missed opportunity



Colon cancer, Jonker et al NEJM 2007



Head and Neck cancer, Bonner et al Lancet 2010

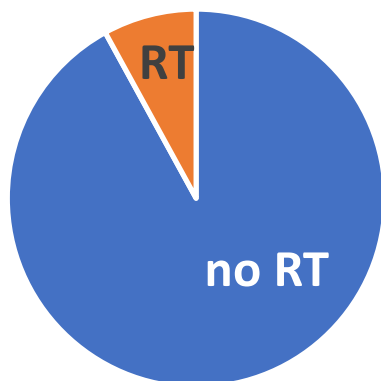
Drug – RT combo , locally advanced disease

Drug	Clinical indication with radiation	Year Phase III published
5-FU / mitomycin	Anal cancer	1974 (not phase III)
Cisplatin	Head and neck; cervical cancer	2000s
5-FU / capecitabine	Gastric cancer	2001
Temozolomide	Glioblastoma	2005
Cetuximab	Head and neck	2006
Carboplatin + paclitaxel	Esophageal cancer	2012

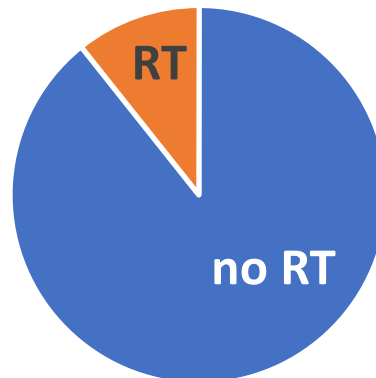
We are not hitting the target, because we are not throwing enough arrows



Phase I cancer trials



Phase III cancer trials



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Interdependence





The Golden age of academic medicine?

BRITISH MEDICAL JOURNAL

LONDON SATURDAY OCTOBER 30 1948

STREPTOMYCIN TREATMENT OF PULMONARY TUBERCULOSIS

A MEDICAL RESEARCH COUNCIL INVESTIGATION

The following gives the short-term results of a controlled investigation into the effects of streptomycin on one

The Control Scheme

Determination of whether a patient would be treated by streptomycin and bed-rest (S case) or by bed-rest alone (C case) was made by reference to a statistical series based on random sampling numbers at each centre by Professor Bradford Hill. The series were unknown to any of the co-ordinators and were contained in sealed envelopes, each bearing on the back the name of the hospital and a number. At the time of the trial, by the panel, and before admission to the centre, the appropriate number was selected from the central office; the card inside

FT Magazine

Home World Companies Markets Global Economy Lex

Arts Magazine Food & Drink House & Home Lunch with the FT Style Books Pursuits

April 18, 2009 1:11 am

Defining Moment: British scientists conduct the first randomised clinical trial, 1948

By Clive Cookson

Austin Bradford Hill

Society and Pharma need each other

Pharma needs society

- Universities- basic research
- Physicians to accrue patients
- FDA to approve drug
- Physicians to prescribe
- Insurance to pay
- Clinical knowledge

Society needs pharma

- Perform high throughput drug discovery / compound screens
- Chemical optimization
- Manufacture safe products
- Fund clinical trials
- Produce the drug
- Solve acute medical problems

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Both Society and Pharma have difficulties

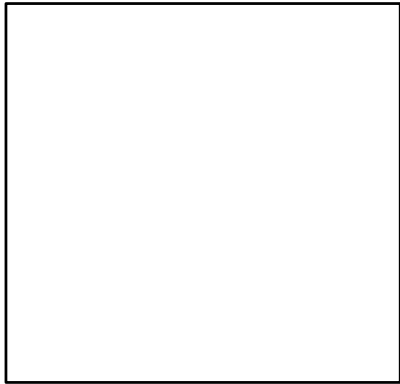
Industry

- High cost of developing drugs
- Costly regulatory requirements
- Low level of success at phase III level “product drought”
- Few new blockbusters
- Short patent terms limit profits
- Changing payer behaviors

Society

- Lack of innovation
 - Children
 - Elderly
 - Rare disease
 - Radiation
- High cost of drugs
- Popular pressure to approve and purchase drugs with limited efficacy

The Stakeholders



Government



Pharma



Physicians



Patients

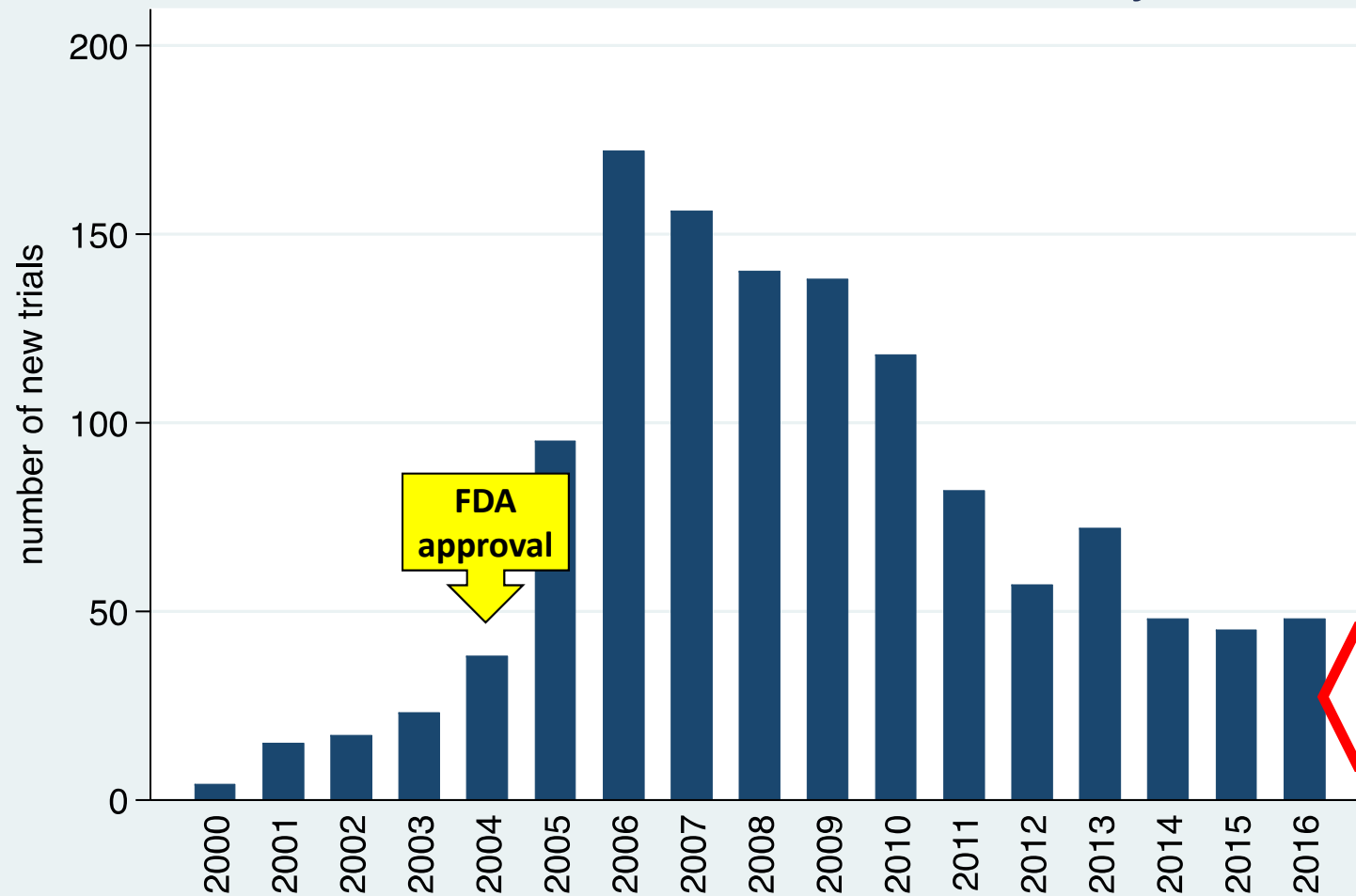


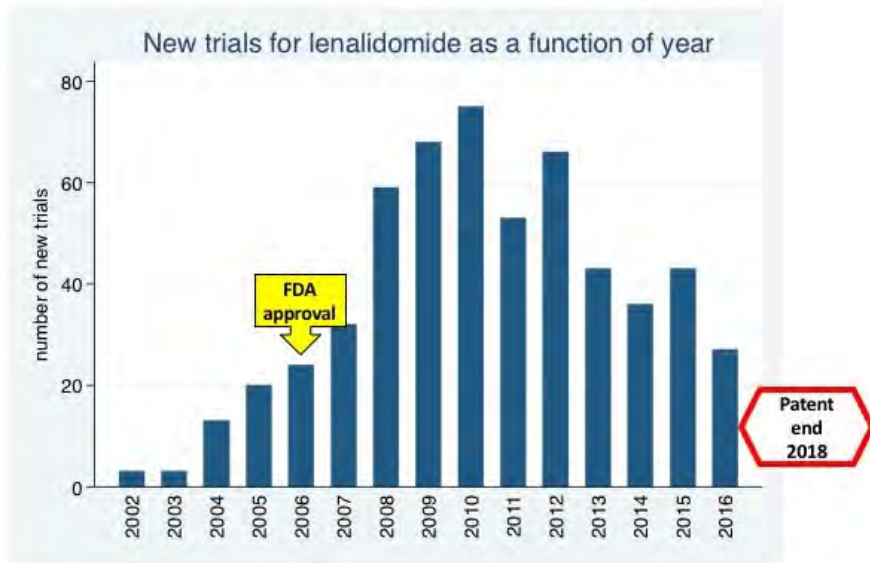
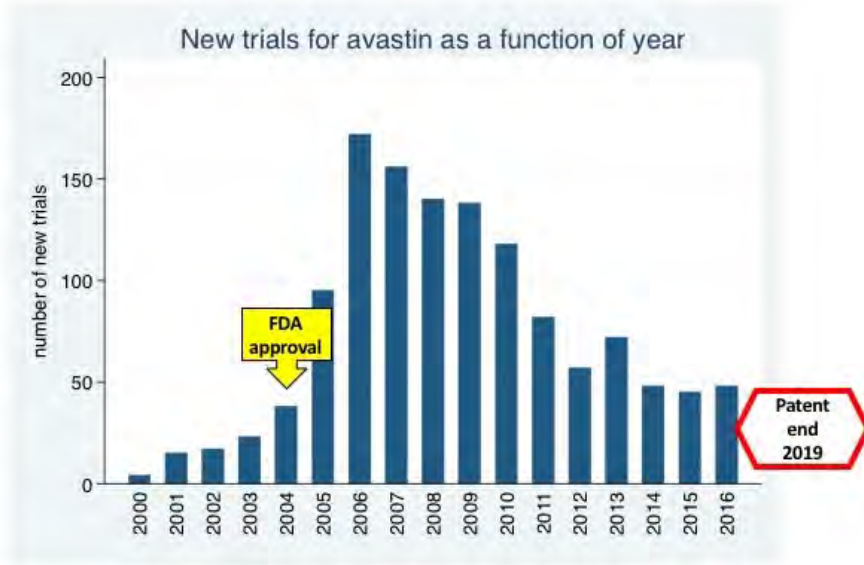
**HMOs /
Payers**

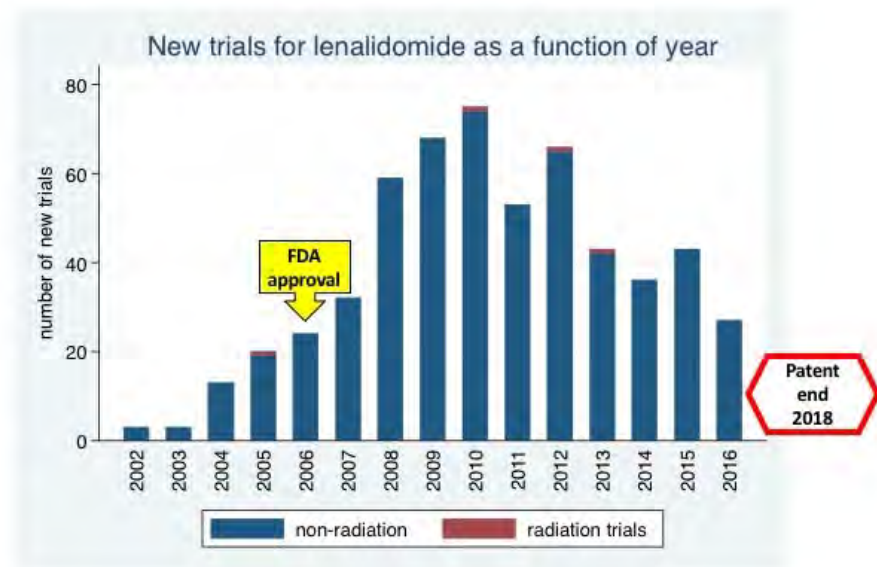
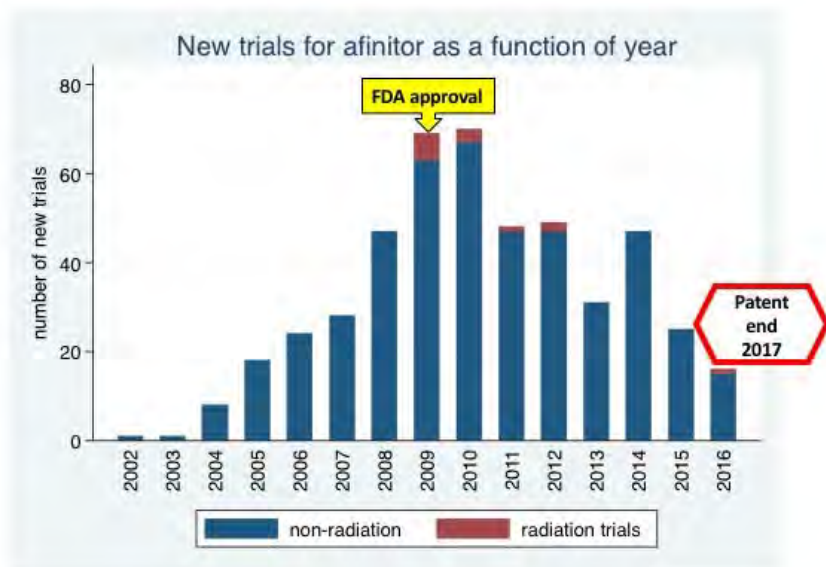
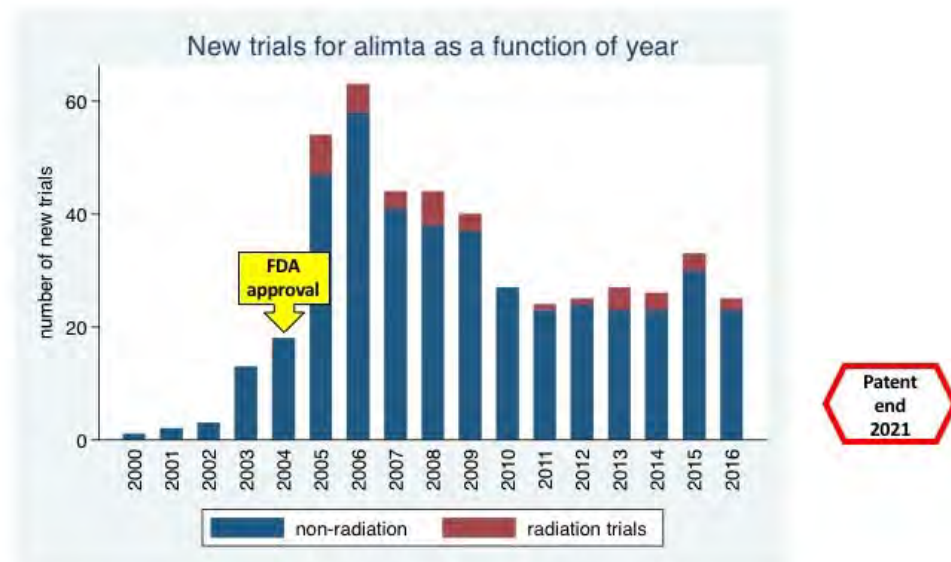
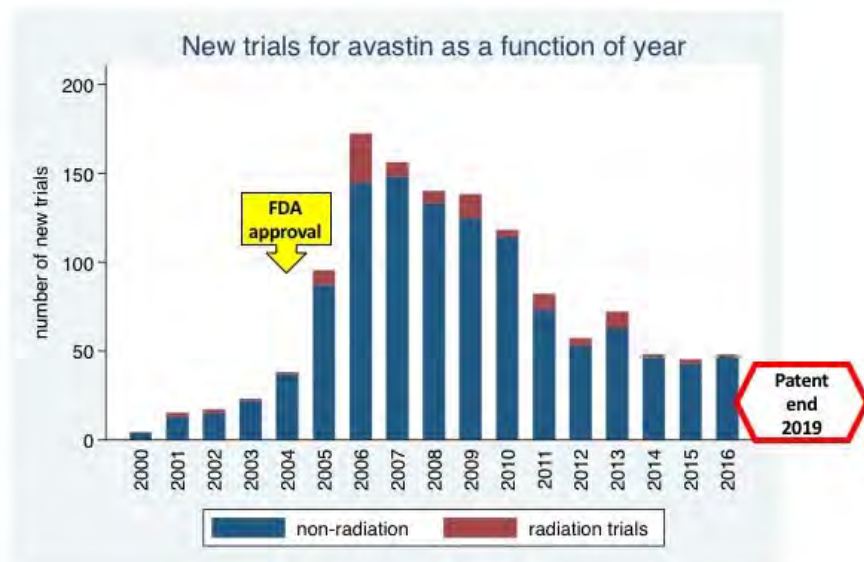
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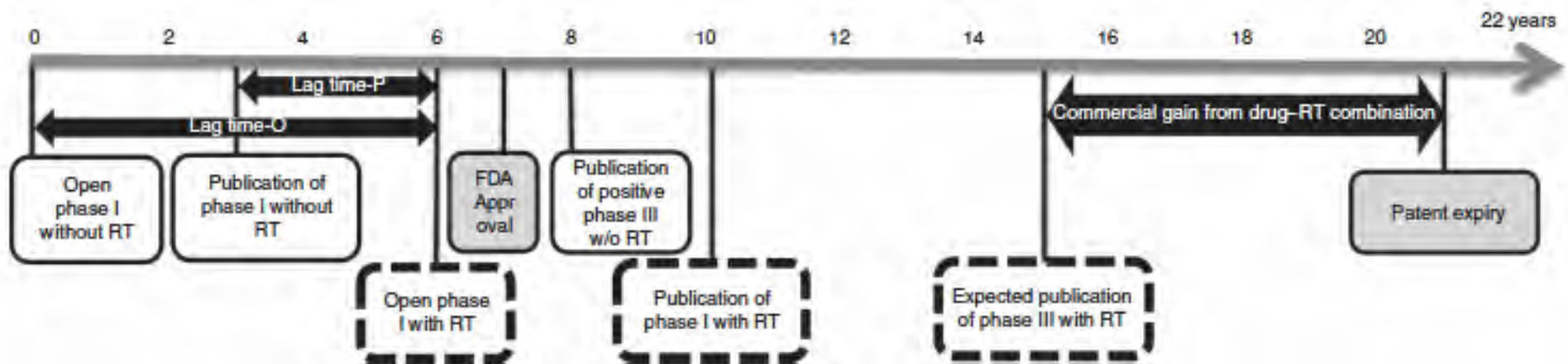
New trials for avastin as a function of year







RT drug combos are started (too) late



B J Cancer 2014, Blumenfeld et al

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Key legislation to promote drug development.

“provide market exclusivity to promote public health goals”

1980	Bayh-Dole Act	Encourage commercial development based on federal research funding
1983	Orphan Drug Act	Conditions for which “no reasonable expectation” that U.S. sales could support drug’s development. Provides: (1) grants to support clinical trials (2) tax credits (3) exclusive marketing rights for 7 years post FDA approval.
1984	Hatch-Waxman Act	• Extend drug patent to compensate for premarket development • Approve generics on basis of bio-equivalence • 180 days of generic market exclusivity.
1997	Pediatric exclusivity provisions of FDA Modernization Act	6 months of market exclusivity , from end of the drug’s, in exchange for conducting pediatric studies , regardless of the outcome of the trial;

Key legislation : critiques

1980	Bayh-Dole Act	• Encouraged a “web of patents”
1983	Orphan Drug Act	• Drug approvals often based on small poor-quality clinical trials • Still leads to many disease to be ignored • Some almost developed drugs repositioned for “orphan diseases”
1984	Hatch-Waxman Act	• no evidence has linked market exclusivity extensions to enhanced drug development • It has been said that patent expiration is a greater driver of innovation than are extended monopolies,
1997	Pediatric exclusivity provisions of FDA Modernization Act	• six-month exclusivity period overcompensated manufacturers • the drugs most frequently used by children were underrepresented • largely irrelevant medications tested, e.g. Lipitor • <50% trials published in peer review journals • The costs fall nearly exclusively on patients and insurers

“These incentive programs.. have been characterized by misuse and may contribute to harmful secondary consequences.. “

The Milbank Quarterly, Vol. 89, No. 3, 2011 (pp. 450–502)

Incentives for Drug Development — The Curious Case of Colchicine

Aaron S. Kesselheim, M.D., J.D., and Daniel H. Solomon, M.D., M.P.H.

In July 2009, the Food and Drug Administration (FDA) officially announced what physicians have long known — that the drug colchicine can effectively treat acute flares of gouty arthritis. The plant

a combination pill containing colchicine and probenecid (Col-Probenecid, Watson Laboratories) for use in gout.

In 2007, URL Pharma organized pharmacokinetic studies

Strategies that delay or prevent the timely availability of affordable generic drugs in the United States

Gregory H. Jones, Michael A. Carrier, Richard T. Silver and Hagop Kantarjian

Subverting the Hatch-Waxman Act

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Companies take advantage of complex patent / antitrust laws to extend drug lifetimes:

- reverse payment (or “pay-for-delay”) patent settlements;
- authorized generics;
- product hopping;
- lobbying against cross-border importation
- buying out competitors

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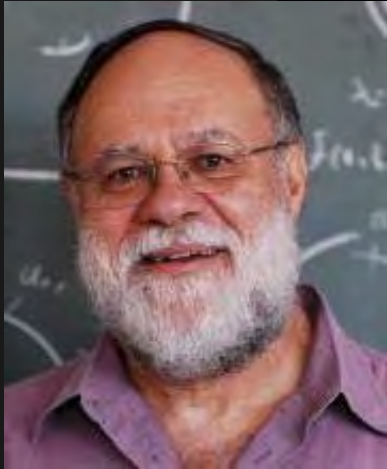
<http://www.ascopost.com/issues/may-25-2016/the-arrival-of-generic-imatinib-into-the-us-market-an-educational-event/>

How persuade drug companies to develop drug-RT combinations

	technique	How to apply to RT-drug combinations
1	Avoid paradox of choice	give a clear simple pathway for drug development with RT
2	Give one simple reason	Explain why important
3	Loss aversion	Post FDA approval, required to continue drug development
4	The scarcity principle	there are 4 FDA “golden approvals” with RT waiting to be taken
5	Personalize the message	speak pharma’s language
6	Reach out, overcome fear of unknown	seminars on RT for pharma executives / researchers
7	Throw more darts	More chance of success....

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Sergiu Hart



Kobi Glazer

GAME Theory



Tenants of economic game theory

- Acknowledge everybody has an agenda
- Companies are
 - driven for their own benefit
 - exploit the rules for their own benefit
- Create rules that encourage companies to address society's needs



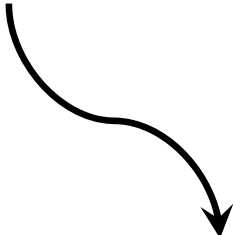
The world of Pharma



“Pharmaceutical companies are in the business of making money by selling pharmaceuticals.”

Profit = Sales – cost

[West J Med](#). 2001 Dec; 175(6): 422–423.

- 
- R + D
 - risk
 - distractions
 - need external expertise
 - QA for Radiation treatments
 - psychological cost (comfort zone)

Implications of Pharma's profit model

- Pharma makes money through selling tablets
- Therefore:
 - Pharma tries to sell a lot of tablets
 - Encourage prescribing medication for a long duration
- Dream drug “40mg b.i.d. for 30 years”



How long are new drugs given for?

PMID	Experimental agent	Disease	median duration of treatment / months
29231133	Daratumumab	Myeloma	14.7
29224502	Brentuximab	Hodgkin's	6
29151359	osimertinib	NSCLC	16.2
29141164	Bevacizumab	Glioblastoma	4.5
28976863	Obinutuzumab	Follicular Lymphoma.	29.4
28953447	Rituximab	Mantle-Cell Lymphoma.	?
28891423	Nivolumab	Melanoma	12
28891408	Dabrafenib plus Trametinib	Melanoma	12
		median	12 months

Most recent clinical trials of systemic agents published in NEJM, Feb 2018

PubMed [1]

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Search results

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PubMed [1]

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Search results

Items: 1 to 20 of 99

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Search results

Items: 1 to 20 of 54

ASCO Meeting Library

Search Results

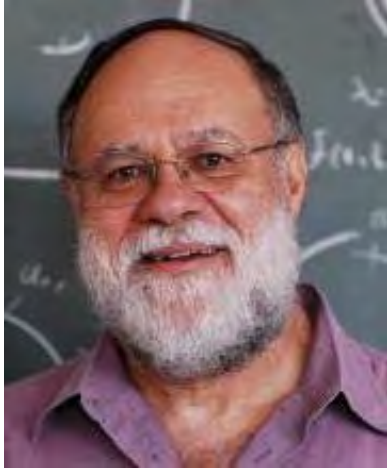
"cancer cure"

7 results found for "cancer cure"

75 results found for "beyond progression"

- **Paul Ehrlich's magic bullet for cancer:**
 - Is is biologically possible?
 - Is it economically viable?





Sergiu Hart

Cancer drug development 'a market failure'

An inefficient allocation of goods & services, leading to a net social loss



Kobi Glazer

The individualized incentive model

- The incentive should closely match the desired end point

Key legislation : critiques

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2016 127: 1398-1402
doi:10.1182/blood-2015-11-680058 originally published online January 27, 2016

Strategies that delay or prevent the timely availability of affordable generic drugs in the United States

Gregory H. Jones, Michael A. Carrier, Richard T. Silver and Hagop Kantarjian

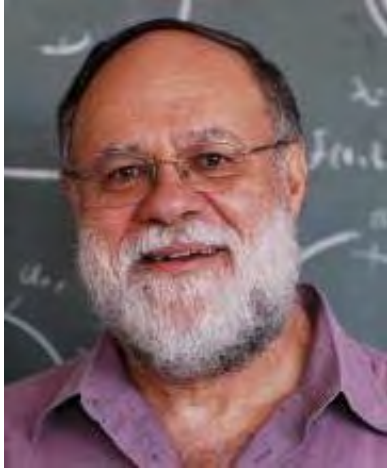
Subverting the Hatch-Waxman Act

Unfortun... compar... extend... (or “pa... border... in canc...

Companies take advantage of complex patent / antitrust laws to extend drug lifetimes:

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- authorized generics;
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- lobbying against cross-border importation
- buying out competitors

http://www.ascopost.com/issues/may-25-2016/the-arrival-of-generic-imatinib-into-the-us-market-an-educational-event/



Sergiu Hart



Kobi Glazer

The Individualized Incentive Model to promote treatments that increase long-term survival

1. Do not change regulation or pricing
2. If patients are progression-free at three years, the company receives a substantial payment, say \$60,000

The 'Individualized Incentive Model'*, Expected outcomes

- Increased attempt to create therapies that drive long-term PFS survival
- More emphasis on locally-advanced disease
- Indirectly, RT-drug combinations

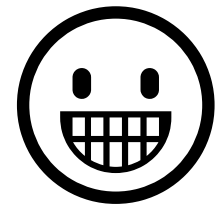
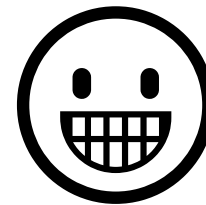
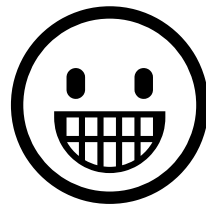
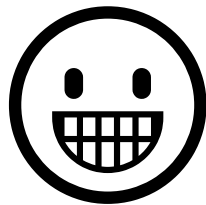
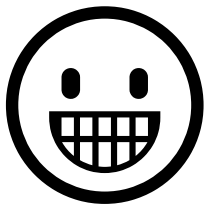
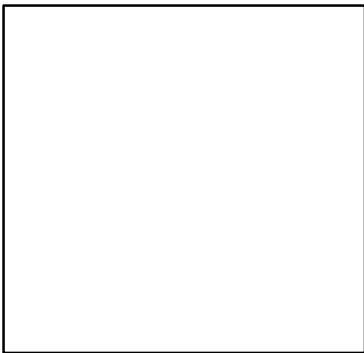
*If patients are progression-free at three years, the company receives a substantial payment, say \$60,000

Questions regarding 'Individualized Incentive Model'

- Who will drive the change (Medicare, HMOs)
- How big does the bonus need to be?
- Would the payers be willing to pay?
- What happens with people that die from co-morbidities?
- How could incentives be subverted?
 - Over treat early disease?
- Stress test – take a bunch of smart people



Who benefits?



Summary

- Described essential yet imperfect relationship between Pharma and society
- Previous attempts to correct the situation
- Proposed **Individualized Incentive Model** to reward pharma
 - Game-theory principles
 - a 'win-win' , for everyone's benefit

Questions?

NCRI CTRad Recommendations for New Drug-Radiotherapy Combinations

Professor Ricky Sharma, University College London



CENTRE
FOR DRUG
DEVELOPMENT



Disclosures

Honoraria:

- BTG, Sirtex, Roche, Cancer Research UK

Advisory Boards/Consultancy:

- Astra Zeneca, DeepMind, Vertex, BTG, Sirtex, Terumo, Affidea, Boston Scientific, Varian, Cancer Research Technology

Research Funding:

- Sirtex, BTG, Cancer Research UK

Open access paper in *Nature Reviews Clinical Oncology*



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A triumph for collaboration in radiotherapy research: landmark paper published by NCRI CTRad Working Group

CONSENSUS STATEMENT

OPEN

Clinical development of new drug–radiotherapy combinations

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Sharma RA et al. *Nat Rev Clin Oncol* 2016; 13: 627-42

Clinical Need for New Approaches to Cancer Therapy



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RESEARCH
UK

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1 in 2 people in the UK will get cancer

Category: [Press release](#)

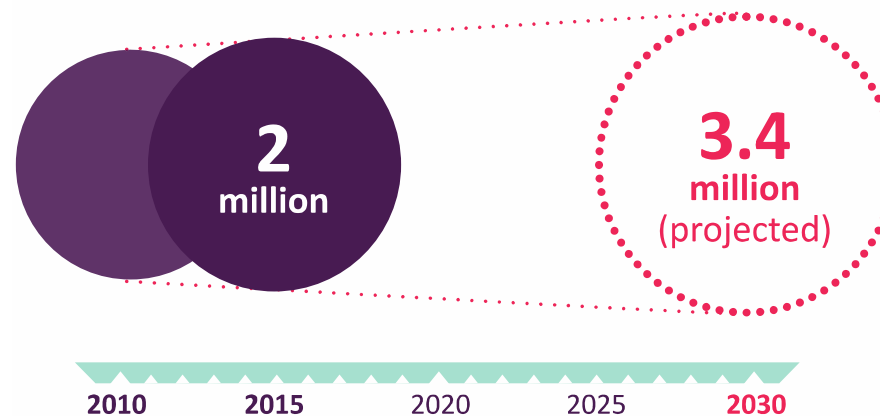


4 February 2015

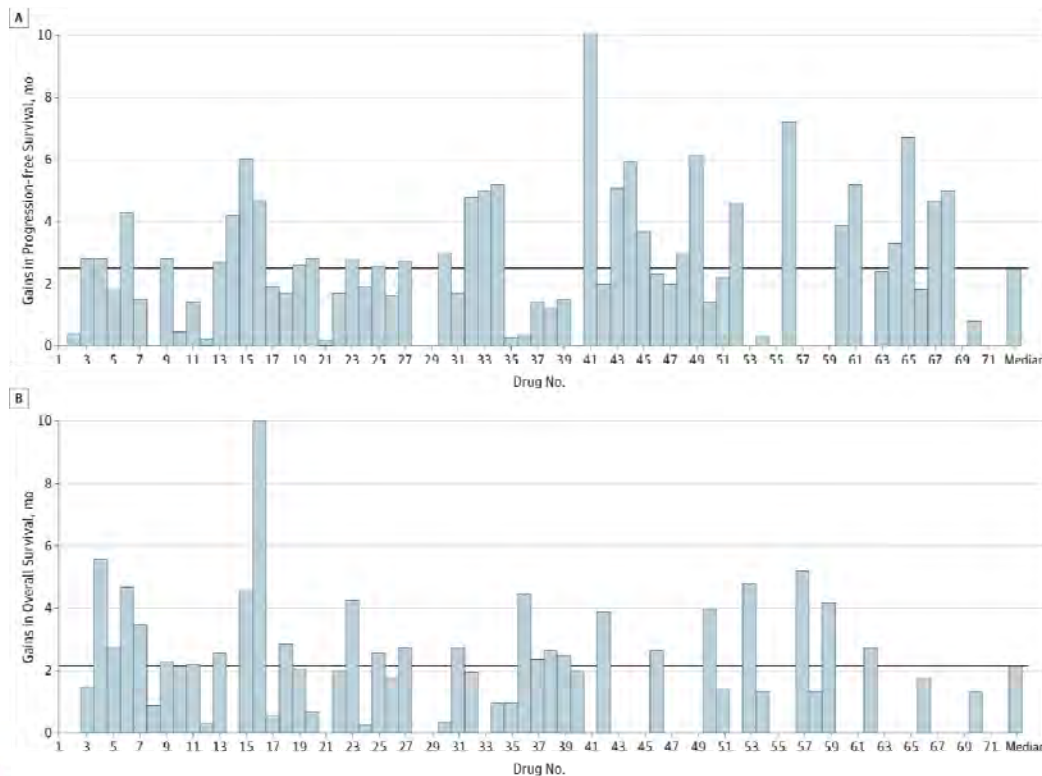


Cancer Research UK

People in the UK with a cancer diagnosis



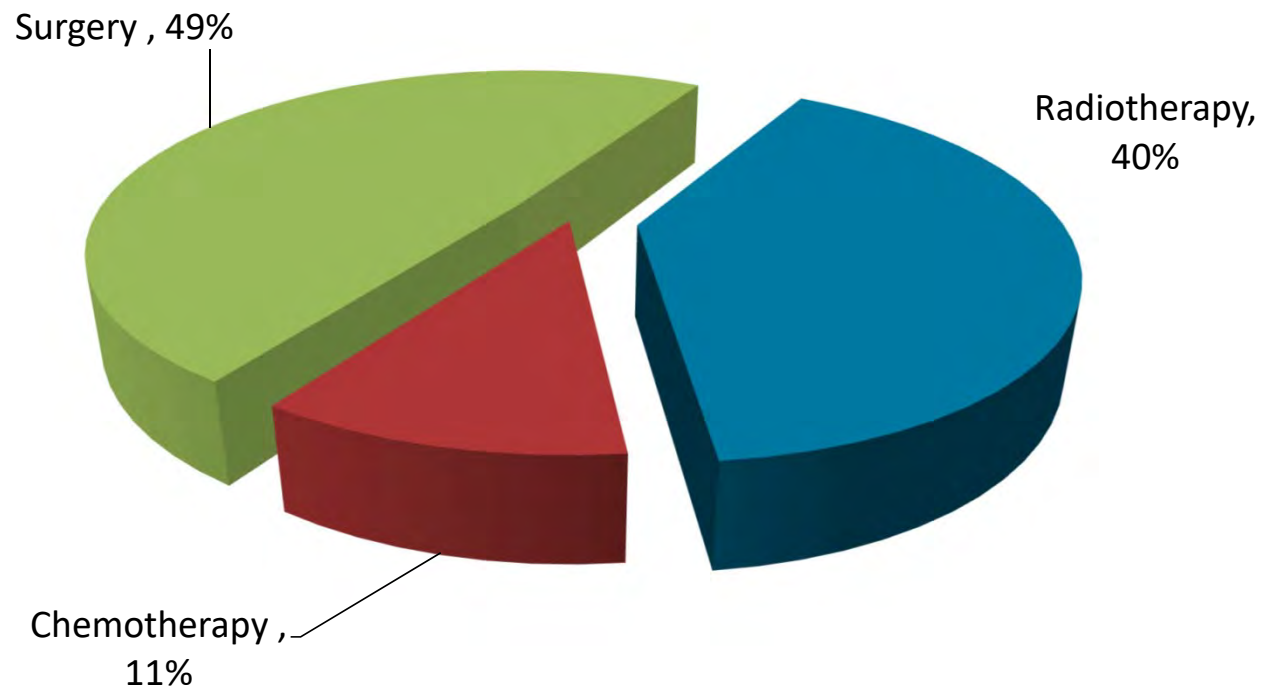
71 drugs for all solid cancers approved by the FDA from 2002 to 2014



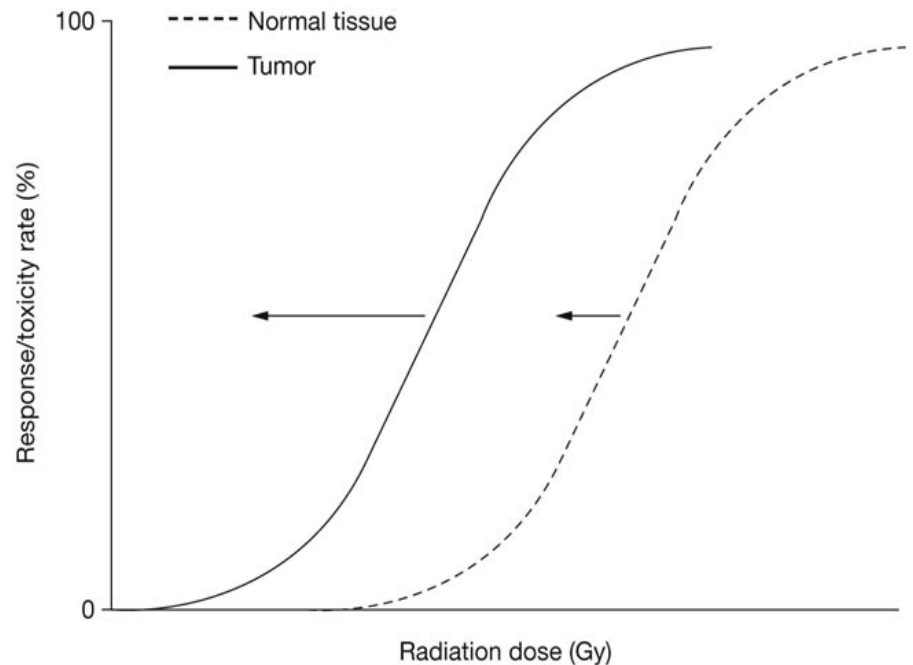
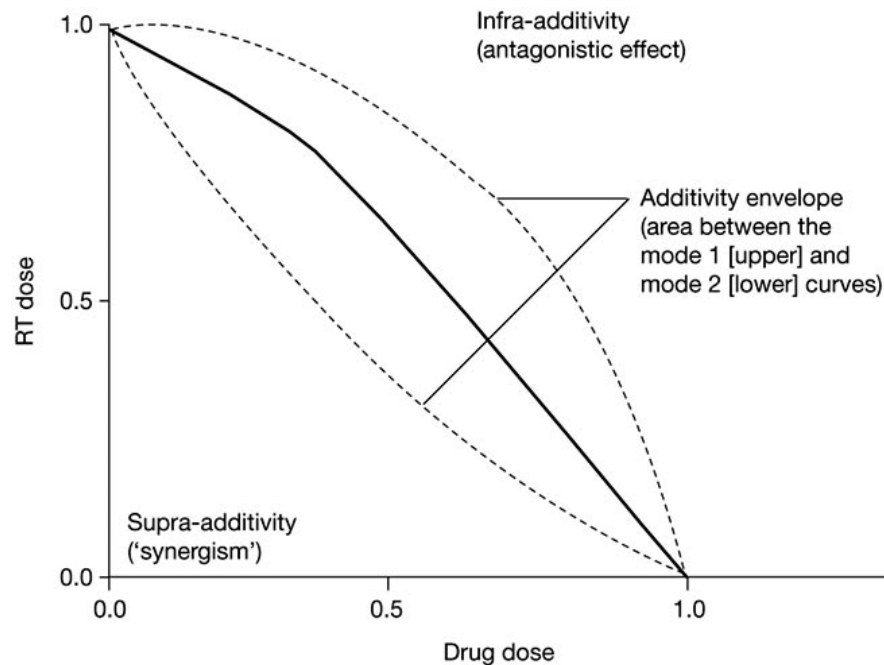
Improvement in median PFS
= 2.5 months

Improvement in median overall
survival = 2.1 months

Curative Treatments for All Cancers



Supra-Additivity can Improve the Therapeutic Index



Steel G et al. *Int J Radiat Oncol Biol Phys*, 1979

Effective Surgical Adjuvant Therapy for High-Risk Rectal Carcinoma

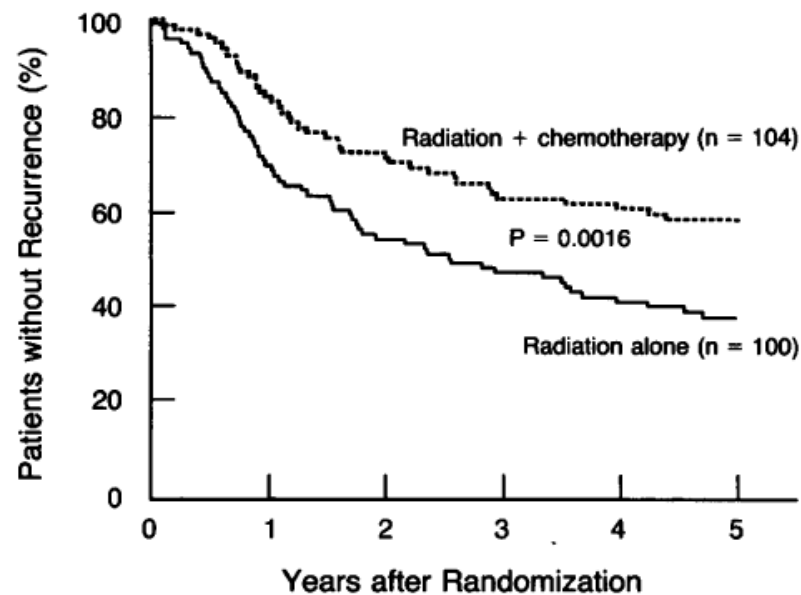


Figure 1. Recurrence-free Interval According to Treatment Group.

Krook J, et al. *New Eng J Med* 1991

Level 1 Evidence for Chemo-radiotherapy

Table 1. Combination of radiation and systemic therapy, level 1 evidence*

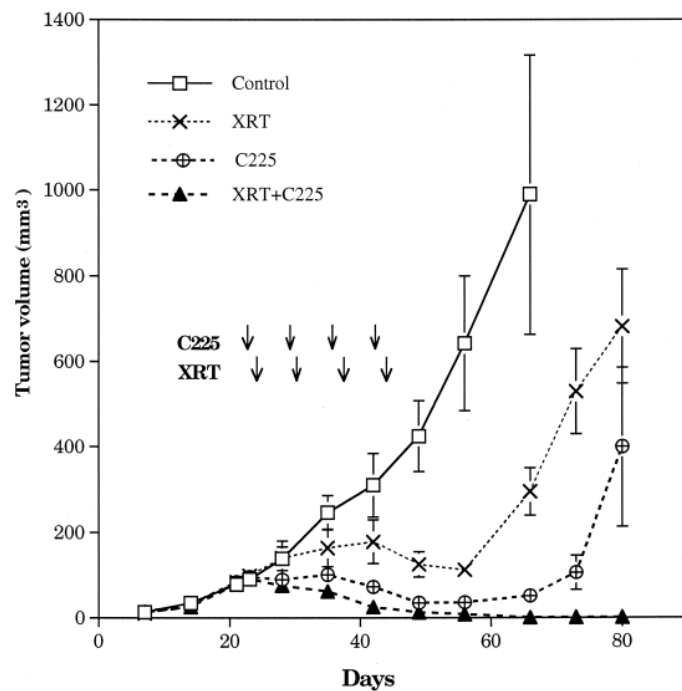
Primary	Systemic agent	Advantage of combined treatment compared with radiation alone
Glioblastoma (brain)	Temozolomide	Improved OS
Head and neck	Cisplatin, cetuximab	Improved OS
Lung	Cisplatin	Improved OS
Esophagus	5FU + cisplatin	Improved OS
Stomach	5FU + leucovorin	Improved OS compared with no treatment
Rectum	5FU	Improved OS
Anus	5FU + mitomycin	Improved local control
Cervix	Cisplatin	Improved OS
Prostate	Androgen deprivation therapy	Improved OS
Bladder	5FU + mitomycin	Improved local control

* OS = overall survival; 5FU = 5-fluorouracil.

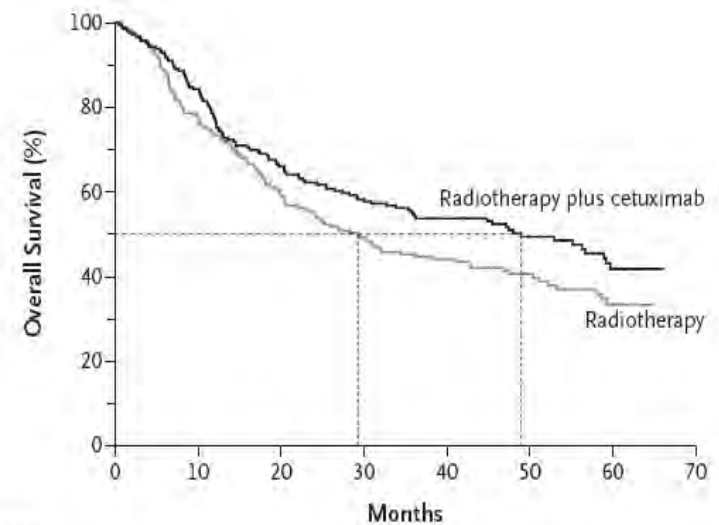
Rollercoaster



Cetuximab + Radiotherapy in Head and Neck



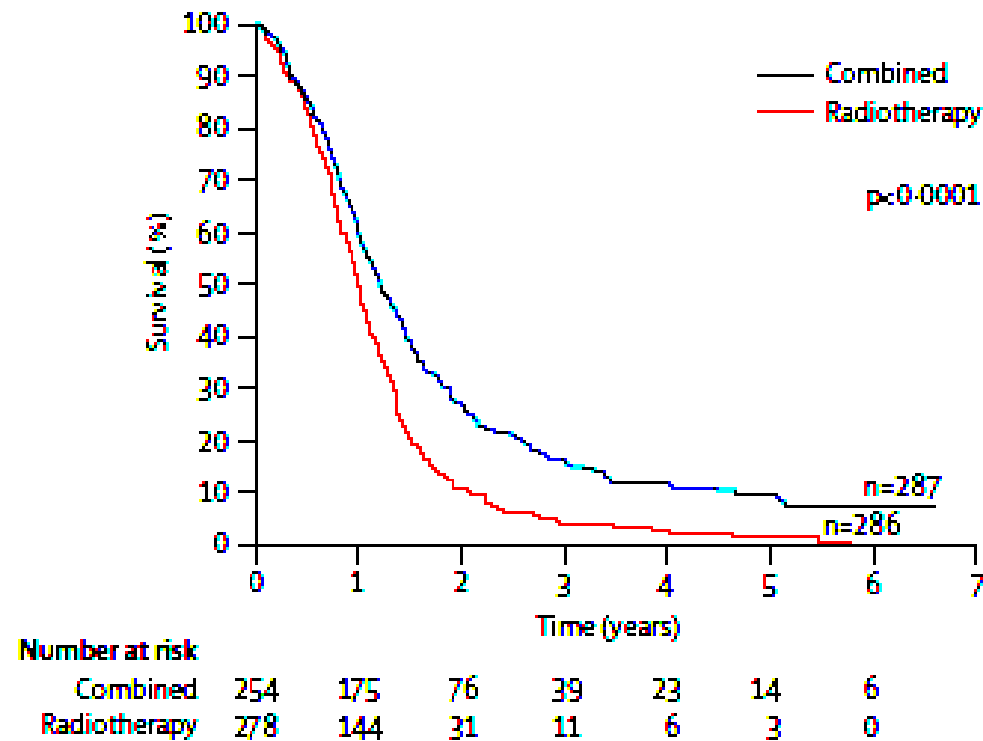
Harari and Huang. *Int. J. Radiation Oncology Biol. Phys*, 2001



No. at Risk							
Radiotherapy	213	162	122	97	73	47	22
Radiotherapy plus cetuximab	211	177	136	116	98	61	24

Bonner, et al *N Engl J Med*, 2006.

Temozolomide plus RT for Glioblastoma Multiforme

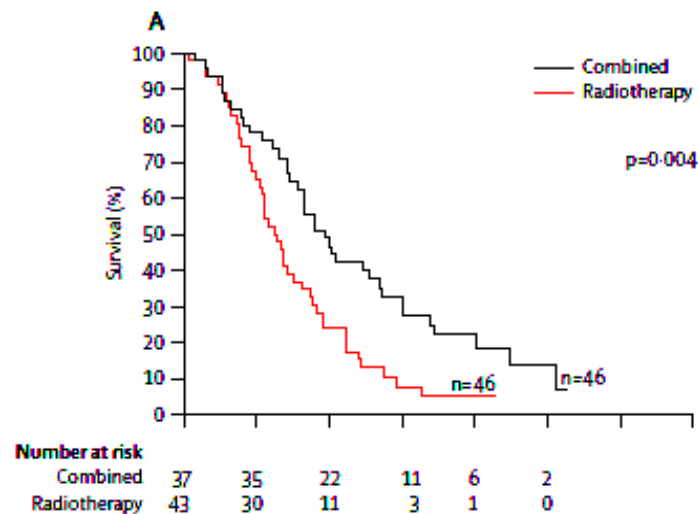


Stupp R, et al. *Lancet Oncol*, 2009

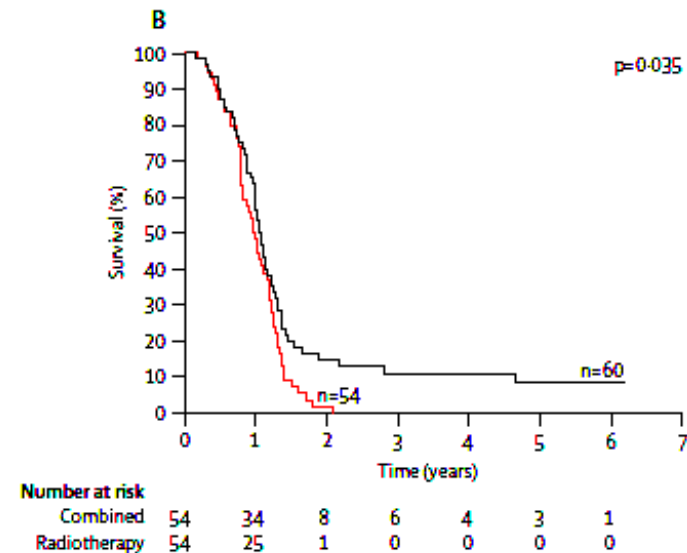
MGMT as a Biomarker for Temozolomide Resistance

Promoter region of *O*-6-methylguanine-DNA methyltransferase (MGMT) gene

MGMT silenced



MGMT functional

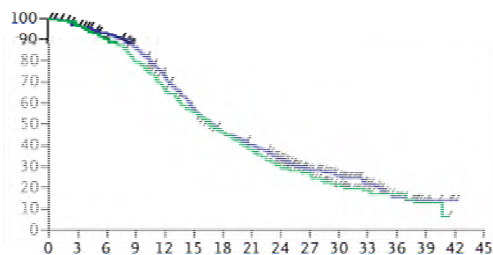


Hegi M, et al. *J Clin Oncol*, 2008

Subsequent High Profile Negative Results

Newly diagnosed GBM:
Superior PFS and QoL

■ Bevacizumab + RT-TMZ
■ Placebo + RT-TMZ

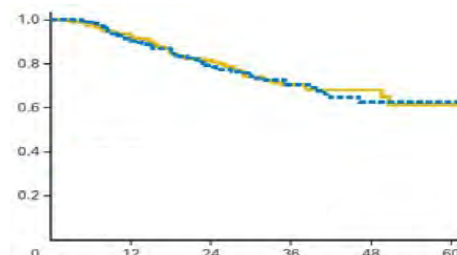


Time (months)

Chinot O et al.
NEJM 2014

Cervical cancer:
3-year OS 70%

■ Cis-RT
■ Cis-RT + tirapazamine

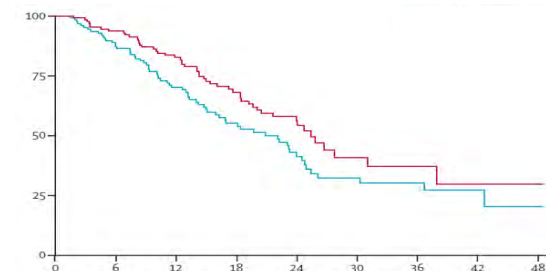


Time (months)

DiSilvestro P et al.
J Clin Oncol 2014

Oesophageal cancer:
Stopped early

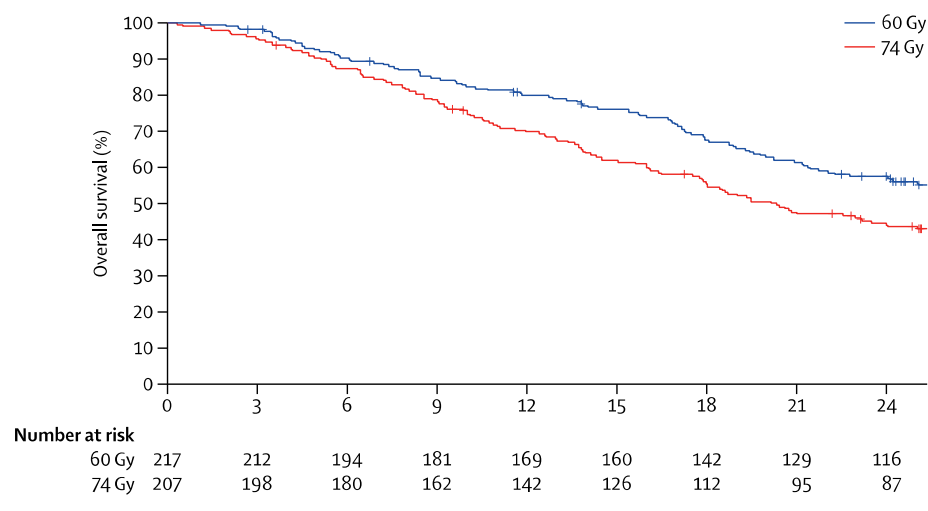
■ Cis-Cape-RT + cetuximab
■ Cis-Cape-RT



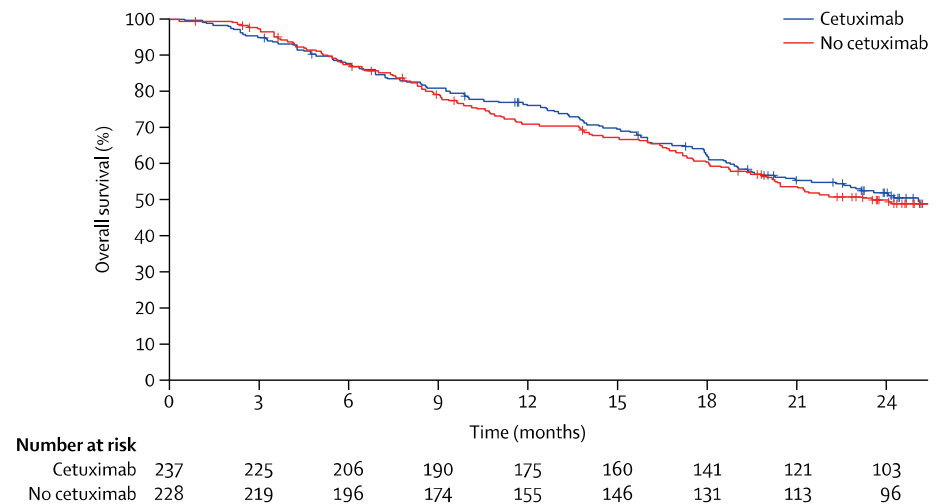
Time (months)

Crosby T et al.
Lancet Oncol 2013

RTOG 0617: 2x2 factorial phase III trial in patients with stage IIIA/B NSCLC (n=544)



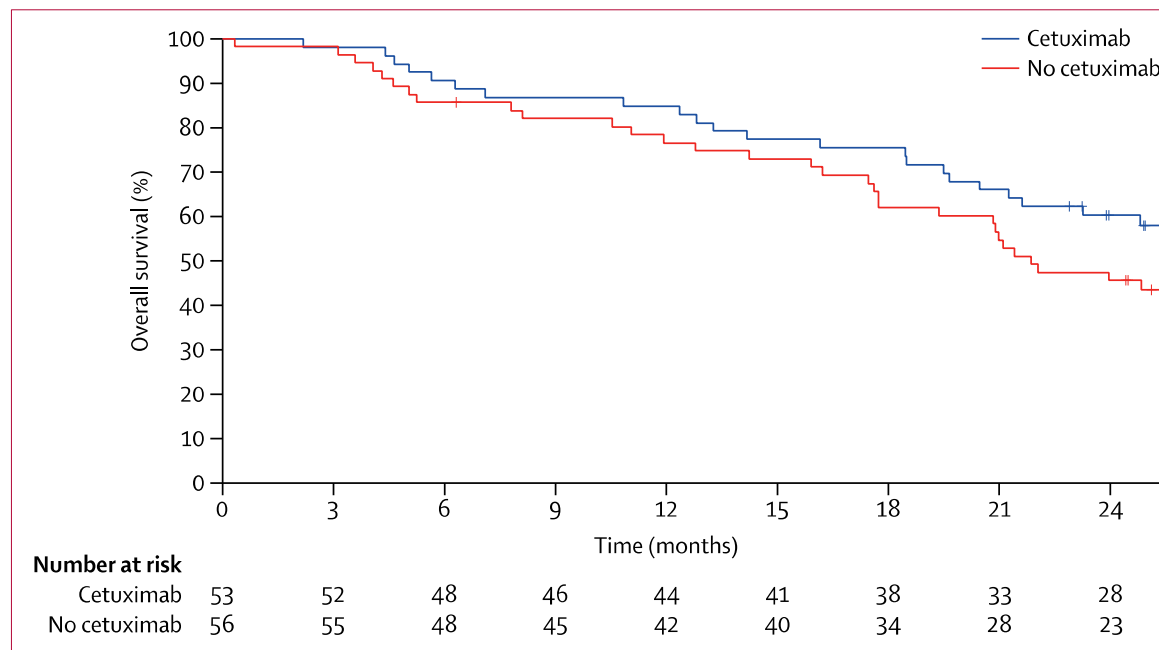
74 Gy total dose worse than 60 Gy



No benefit from adding cetuximab to paclitaxel-carboplatin-RT

Why the failures to meet primary endpoint?

- Number of agents being combined
- Toxicity: Dose constraints for critical organs
- Patient selection, e.g. EGFR expression



Can we do better?

Critical Review

The Clinical Development of Molecularly Targeted Agents in Combination With Radiation Therapy: A Pharmaceutical Perspective

Ozlem U. Ataman, MD, PhD,^{*} Sally J. Sambrook, PhD,^{*} Chris Wilks, BSc,[†]
Andrew Lloyd, BSc,^{*} Amanda E. Taylor, PhD,[‡] and Stephen R. Wedge, PhD[†]

^{*}Global Medicines Development, AstraZeneca, Alderley Park, Macclesfield, Cheshire, United Kingdom; [†]Innovative Medicines, AstraZeneca, Alderley Park, Macclesfield, Cheshire, United Kingdom; and [‡]Yellow Delaney Communications Ltd, Wilmslow, Cheshire, United Kingdom

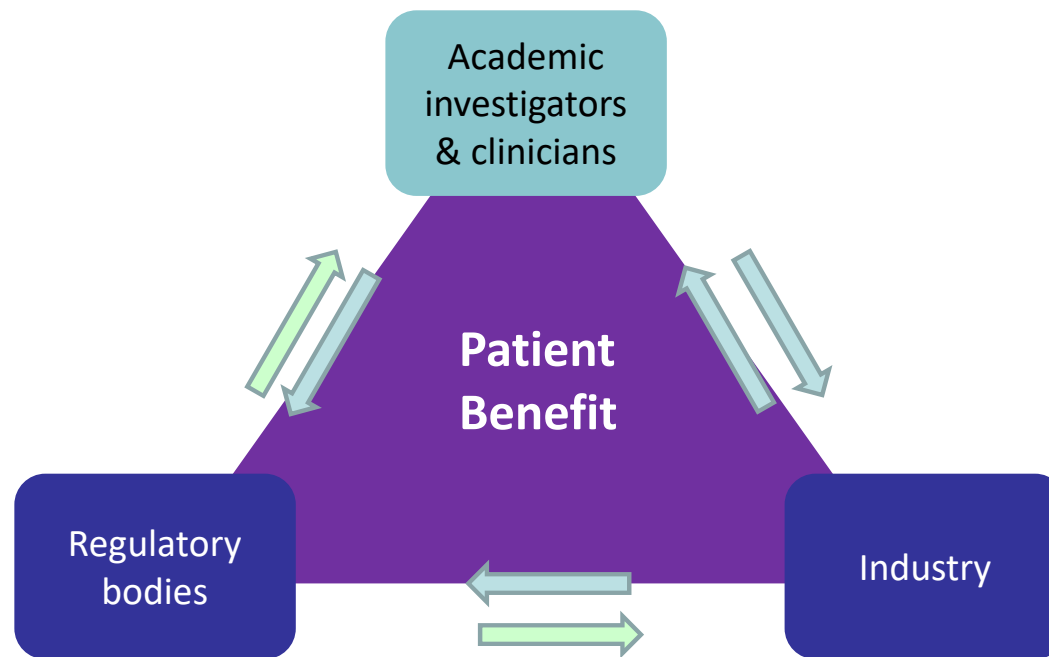


2012; 84: e447-54

Summary of findings:

- Pharmaceutical industry sponsorship is limited
- Phase III studies: mainly sponsored by cooperative groups
- Majority of RT combination trials not initiated until after drug approval
- No consensus on study endpoints

Stakeholders for New Drug-RT Combinations



Strengths of 37 members: Diversity, knowledge and expertise

**10 Radiation
Oncologists**

3 Medical Oncologists

**2 Scientists from
Academia**

1 Clinical Radiologist

3 Regulatory Experts

**2 Consumer
representatives**

**13 Scientists/
Clinicians from
Pharma**

3 Statisticians

“Route to Registration” Working Group

WORKSHOP 1: 25TH SEPT 2014; WORKSHOP 2: 25TH SEP 2015

- Develop concept, discuss and write draft guidance

EIGHT WORK PACKAGES/CONSENSUS STATEMENTS:

1. Drug-radiotherapy combinations
2. Route to registration
3. Clinical endpoints
4. Changing the standard of care
5. Clinical trial methodology
6. Radiotherapy quality assurance
7. Preclinical dataset and target population
8. Patient and consumer involvement and raising awareness

Drug-radiotherapy combinations

Collaboration between industry and academia is essential

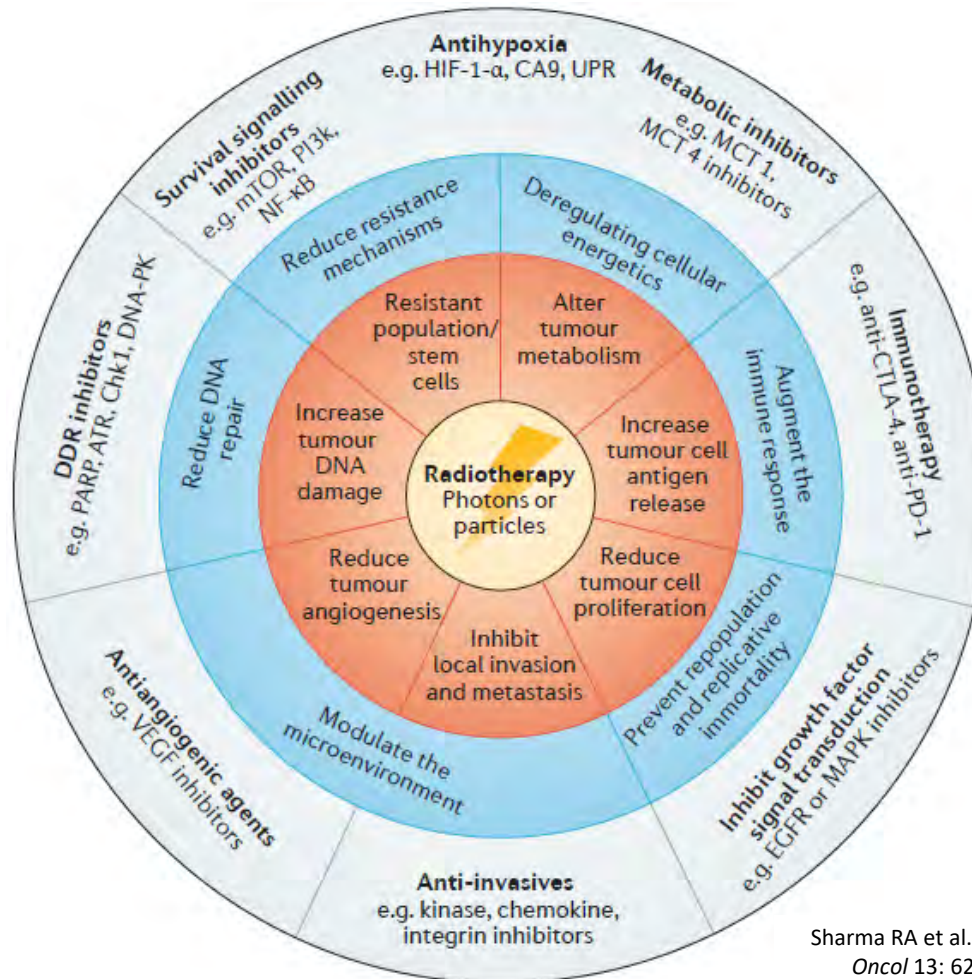
Occur as early as possible in drug development (e.g. RaDCom)

Consider drug-radiotherapy combinations as important as drug-drug combinations

Robust scientific basis for the combination in preclinical models

Line of sight to registration

Strong Basic Science



Sharma RA et al. *Nature Rev Clin Oncol* 13: 627-642, 2016



British Journal of Cancer (2011) 105, 628–639
© 2011 Cancer Research UK All rights reserved 0007–0920/11

www.bjcancer.com

Guideline

Guidelines for preclinical and early phase clinical assessment of novel radiosensitisers

KJ Harrington^{*,1}, LJ Billingham², TB Brunner³, NG Burnet⁴, CS Chan⁵, P Hoskin⁶, RI Mackay⁷, TS Maughan⁸, J Macdougall⁵, WG McKenna³, CM Nutting¹, A Oliver⁵, R Plummer⁹, IJ Stratford¹⁰ and T Illidge¹¹ NCRI Clinical and Translational Radiotherapy Research Working Group

NCI–RTOG Translational Program Strategic Guidelines for the Early-Stage Development of Radiosensitizers

Yaacov Richard Lawrence, Bhadrasain Vikram, James J. Dignam, Arnab Chakravarti, Mitchell Machtay, Boris Freidlin, Naoko Takebe, Walter J. Curran Jr, Soren M. Bentzen, Paul Okunieff, C. Norman Coleman, Adam P. Dicker

Manuscript received August 15, 2012; revised September 15, 2012; accepted October 02, 2012.

Correspondence to: Yaacov Richard Lawrence, MRCP, Department of Radiation Oncology, Sheba Medical Center, Tel HaShomer 52621, Israel (e-mail: yaacovla@gmail.com).

Radiotherapy-Drug Combinations Consortium (RaDCom) in the UK

Providing preclinical evidence for early phase clinical trials

- Collaborative network of labs delivering quality preclinical efficacy data
- Partnership with industry, CRUK and other funding bodies
- Key point for industrial partners seeking appropriate expertise

Active Collaborations



Clinical end points: Questions

Which end points to select to represent local control of disease?

How best demonstrate the benefit for patients – e.g. patient reported outcomes?

Organ sparing as a clinical end point?

Composite and co-primary end points?

Clinical end points: Recommendations

Include clinically relevant early and intermediate end points

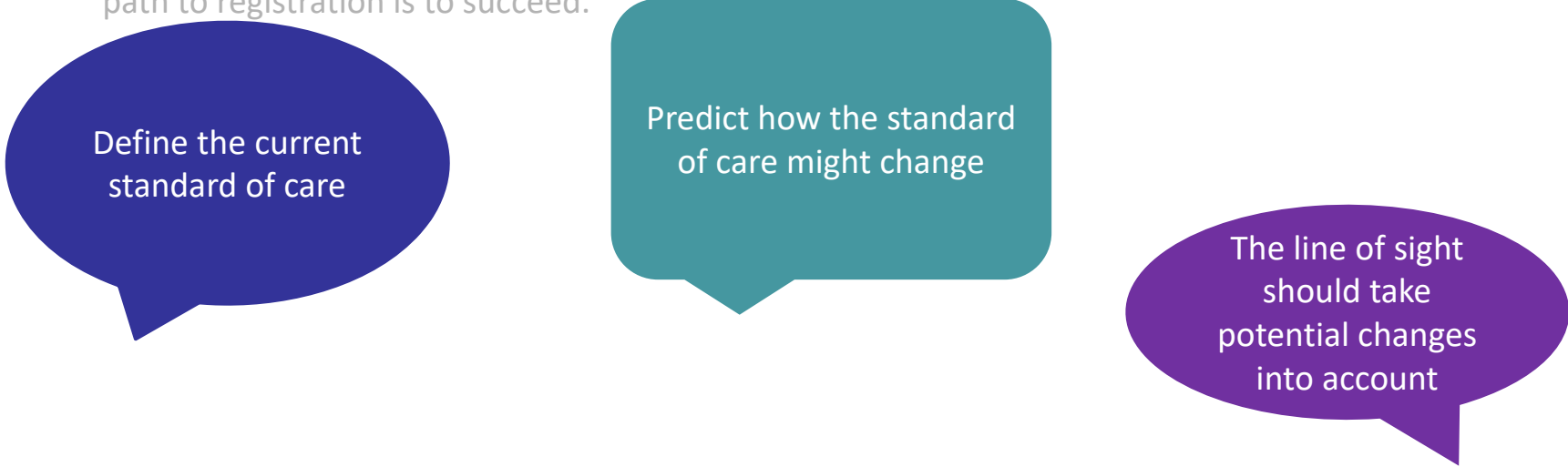
End points must be pragmatic, relevant to patients and applicable in a 'real world' setting

Loco-regional control matters to patients

Secondary end points should include normal tissue toxicity

Changing the standard of care

The treatment intent and the current standard of care for each disease being treated must be defined by the investigators, including any potential variation across countries. Potential changes in the standard of care must be predicted by clinical experts if the path to registration is to succeed.



Define the current
standard of care

Predict how the standard
of care might change

The line of sight
should take
potential changes
into account

Changing the standard of care

RT combinations with good biological/therapeutic rationale should be considered in preclinical studies and as part of design of early-phase studies

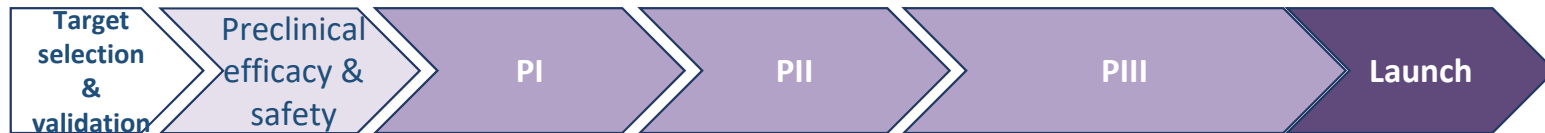
Ensure access to new treatments are achieved in the shortest possible timeframe

Limited / no guidelines for RT-drug combinations

Early discussion with regulatory agencies

Adaptive design to support early initiation of combinations once a MTD or BED is defined

Core Programme



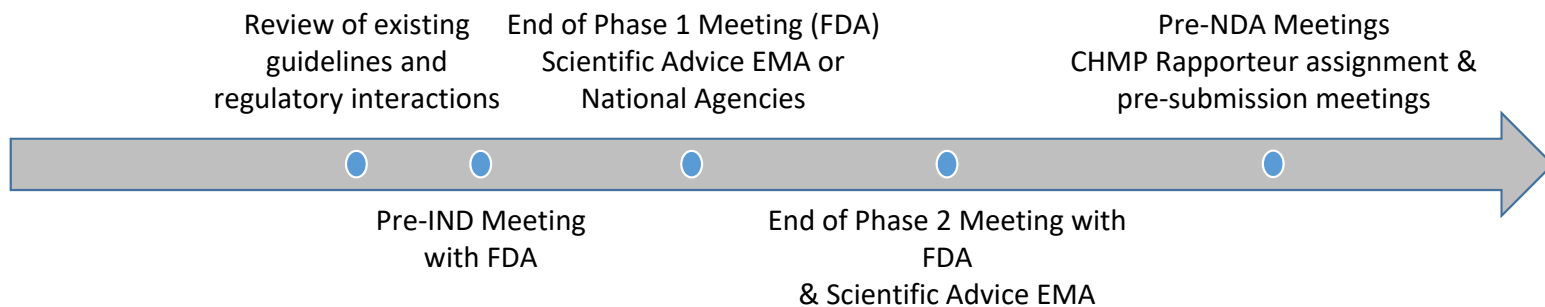
Monotherapy/
chemo MTD

Radiotherapy Program



RT-combined
MTD

Potential Regulatory Interactions



COMMENTARY

Clinical Development of Cancer Drugs in Combination With External Beam Radiation Therapy: US Food and Drug Administration Perspective



Amanda J. Walker, MD, Hyun Kim, MD, Haleh Saber, PhD,
Paul G. Kluetz, MD, Geoffrey Kim, MD, and Richard Pazdur, MD

*Office of Hematology and Oncology Products, Center for Drug Evaluation and Research, US Food and
Drug Administration, Silver Spring, Maryland*

“It is critical that sponsors engage with the FDA early and often in the process of drug development through meeting requests and special protocol assessments”

Existing Regulatory Guidance

1. EMA - Guideline on the evaluation of anticancer medicinal products in man
2. EMA - Guideline on clinical development of fixed combination medicinal products
3. FDA - Early Development Considerations for Innovative Combination Products
4. FDA - Classification of Products as Drugs and Devices & Additional Product Classification Issue
5. FDA - Guidance for industry: Co-development of two or more new investigational drugs for use in combination

Perceived Regulatory Barriers

1. Lack of guidance on combination between a loco-regional therapy and a systemic therapy
2. Limited regulatory experience of successful drug-RT registrations
3. Guidance on preclinical data package required to be submitted
4. Specific case studies:
 - Repurposing drugs/expansion of indications
 - Radiosensitisation using sub-therapeutic doses of drug
 - Identification of sub-populations most likely to benefit from a drug-RT combination
 - Immuno-radio-oncology

Consumer involvement and raising awareness

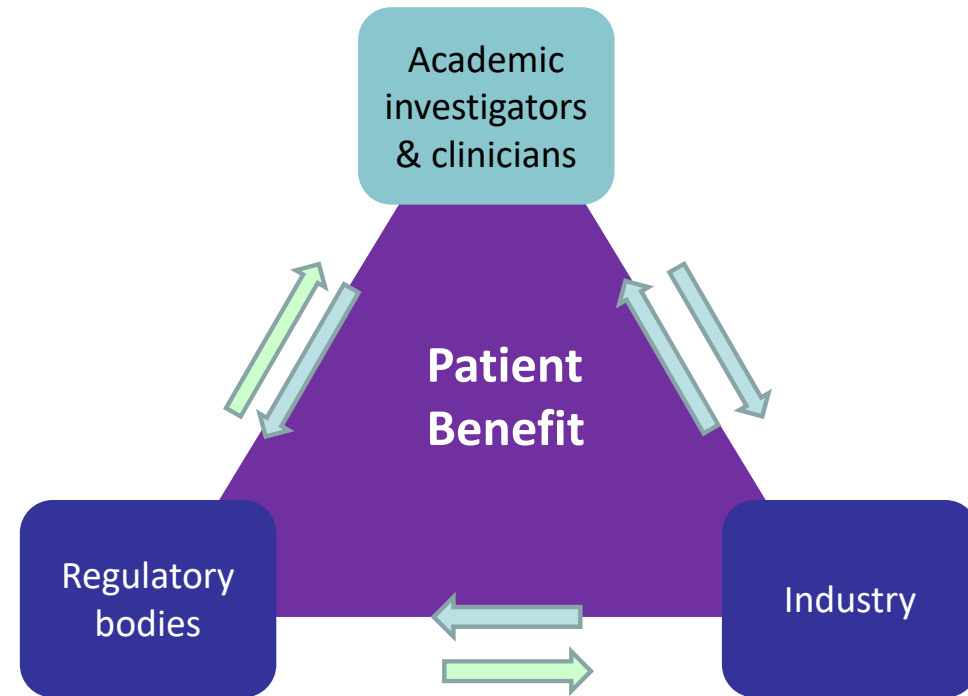
Patients/consumers should be involved from the concept stage of development

Patients/consumers need to define what will or will not be acceptable to trial participants

Include clear statements about the potential benefit for future patients from conducting this research

Conclusions

1. The NCRI CTRad Joint Academia-Pharma Working Group and the AACR-FDA-ASTRO Workshop have brought together academics, industry, consumer groups and regulators to make progress on New Drug-Radiotherapy Combinations
2. There is an opportunity to build on consensus statements from 2016 on how to combine new drugs with RT, with specific reference to regulatory guidance to overcome perceived barriers



NCRI CTRad Joint Academia-Pharma Working Group

E-mail: ricky.sharma@ucl.ac.uk

Supported by:

- **CANCER RESEARCH UK COMBINATIONS ALLIANCE**
 - PARTNERING TO DRIVE NEW COMBINATION THERAPIES



- **RADIOTHERAPY-DRUG COMBINATIONS CONSORTIUM (RADCOM)**
 - PROVIDING NECESSARY PRECLINICAL EVIDENCE FOR EARLY PHASE CLINICAL TRIALS





SESSION I: Preclinical Considerations

Session Cochairs:

C. Norman Coleman, MD, and Kaye J. Williams, PhD

Speakers:

Paul M. Harari, MD

Tim M. Illidge, MD, PhD

Kevin A. Camphausen, MD

Kaye J. Williams, PhD

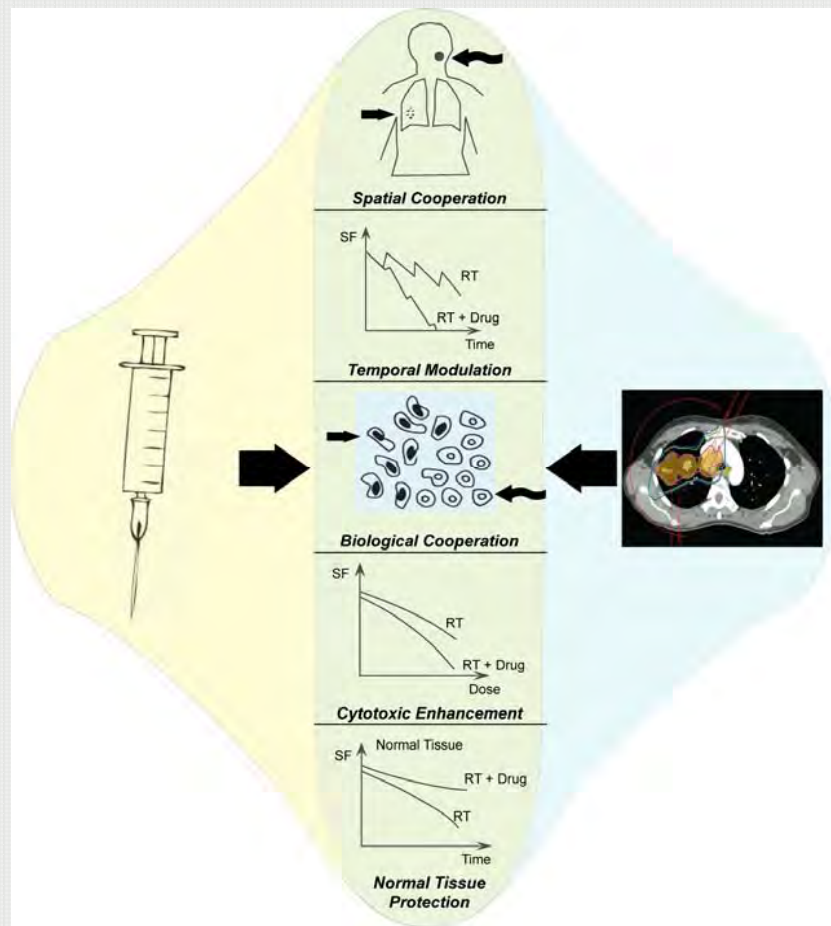
Todd R. Palmby, PhD

Past Successes and Failures of Radiation-Drug Combinations

Paul M. Harari, M.D., FASTRO
Jack Fowler Professor and Chairman
Department of Human Oncology
University of Wisconsin School of Medicine

Drug-Radiotherapy Combinations Workshop
Bethesda, Maryland, Feb 22, 2018

Rationale for combination therapies with radiation:

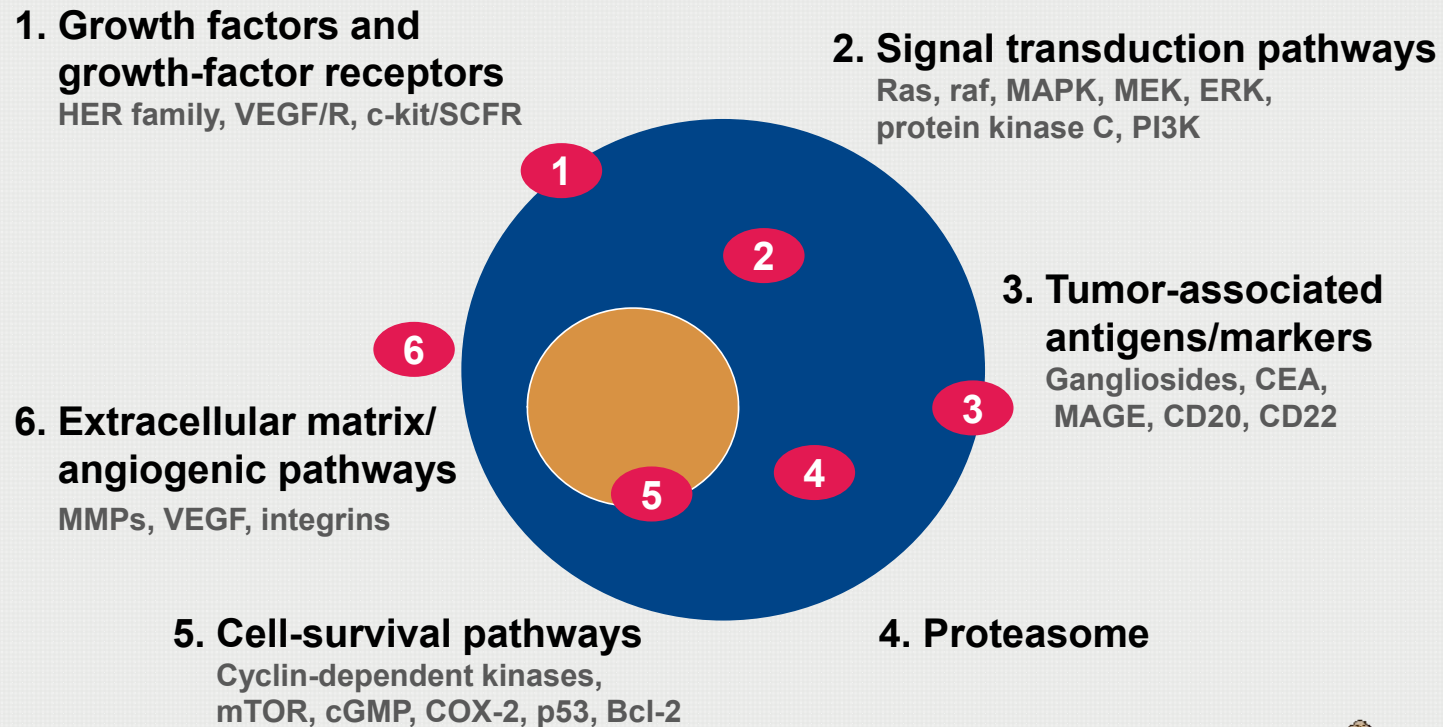


Modified Steel Hypothesis

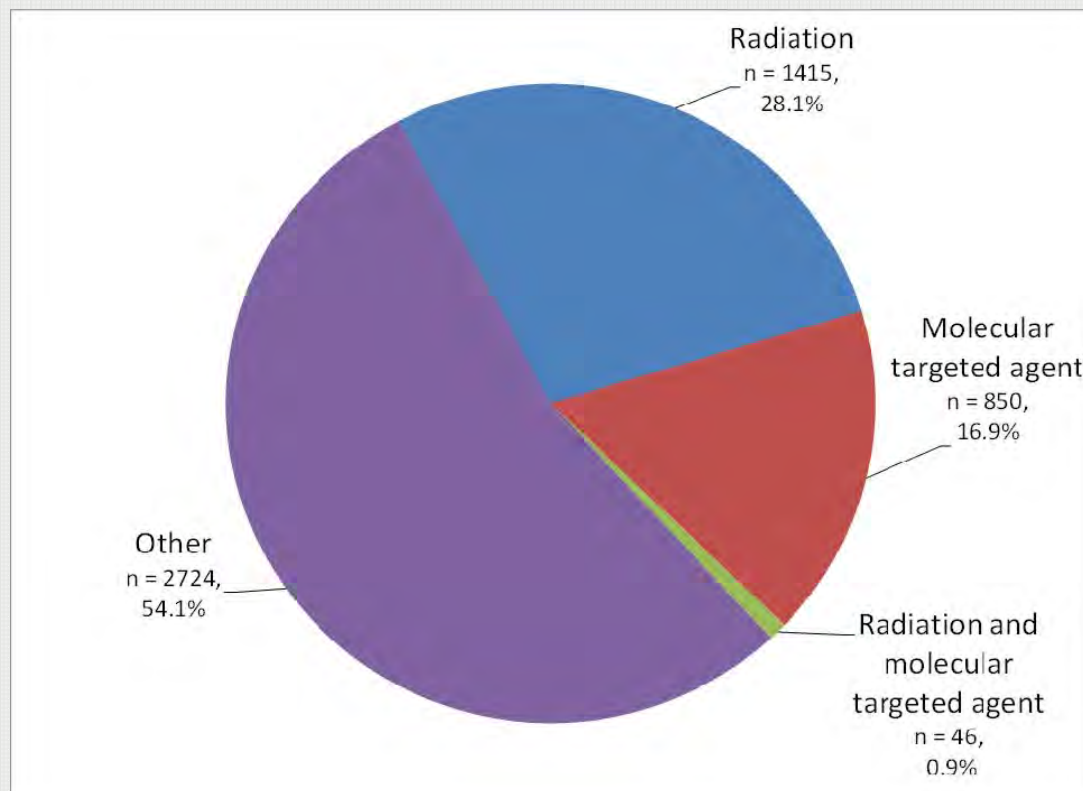
Steel and Peckham, IJROBP, 1979
Bentzen et al, Nat Clin Pract Oncol, 2007

Molecular Targets

Tumor cell

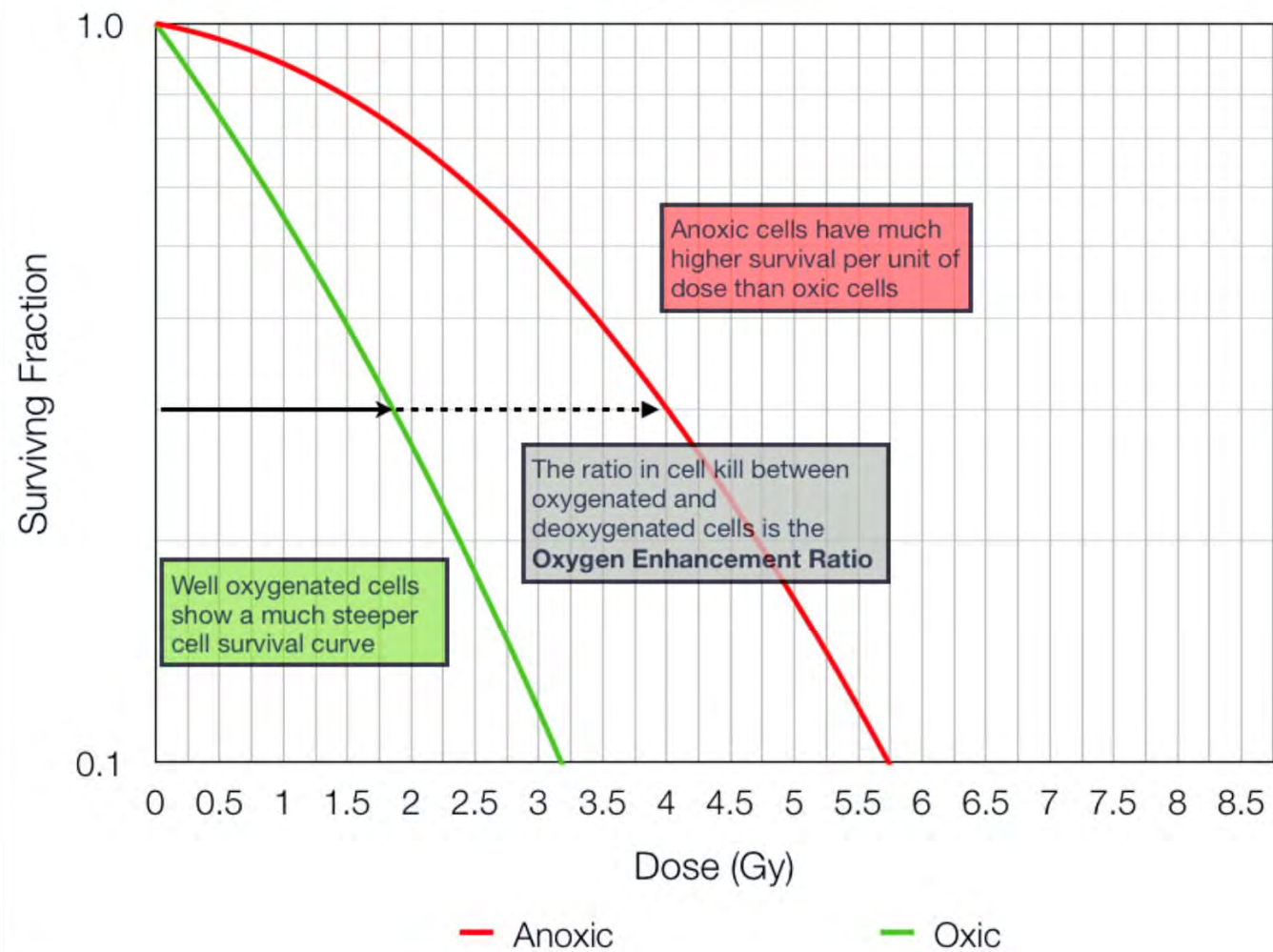


Distribution of Phase III Clinical Trials in Oncology

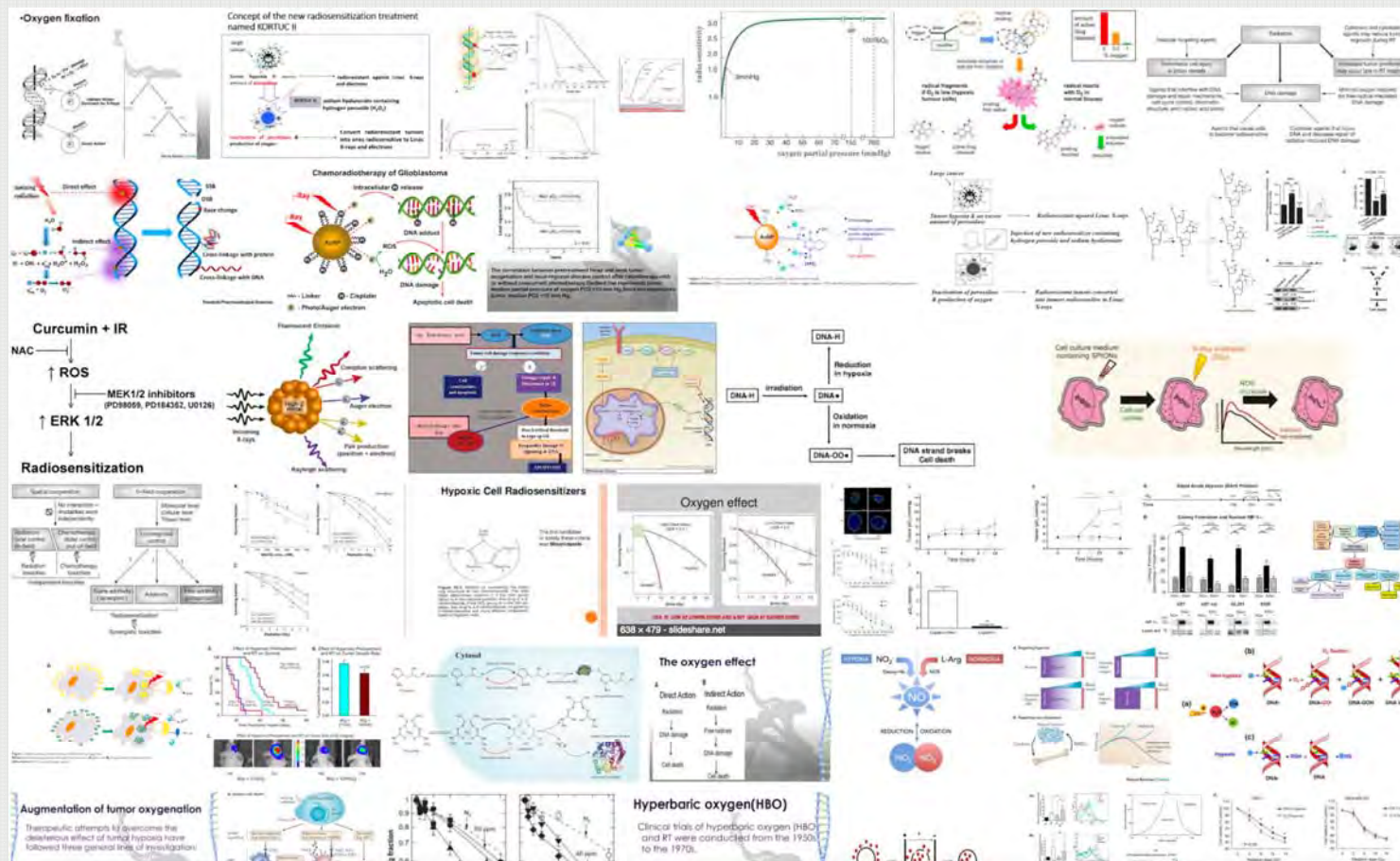


Morris & Harari: J Clin Oncol 2014

Oxygen Effect

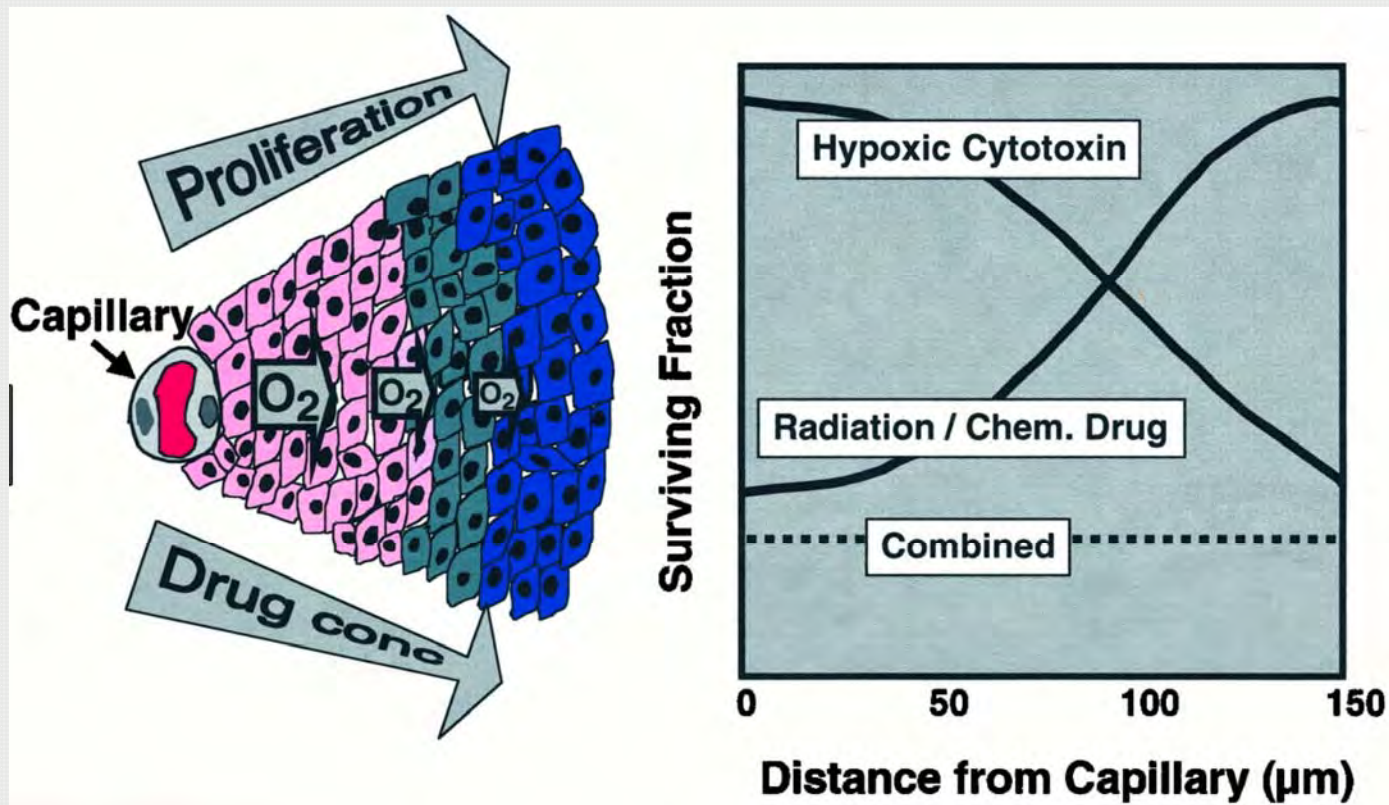


Oxygen as a Radiosensitizer



Tumor Hypoxia

Thomlinson and Gray: 1955





● *Clinical Investigation*

**ANEMIA IS ASSOCIATED WITH DECREASED SURVIVAL AND INCREASED
LOCOREGIONAL FAILURE IN PATIENTS WITH LOCALLY ADVANCED
HEAD AND NECK CARCINOMA: A SECONDARY ANALYSIS OF RTOG 85-27**

W. ROBERT LEE, M.D.,* B. BERKEY, M.S.,† V. MARCIAL, M.D.,‡ K.K. FU, M.D.,§
J.S. COOPER, M.D.,|| B. VIKRAM, M.D.,¶ L.R. COIA, M.D.,# M. ROTMAN, M.D.,J AND
H. ORTIZ, M.D.‡

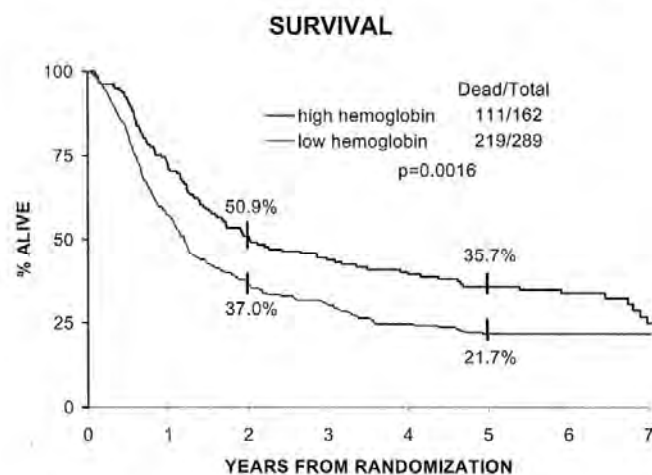


Fig. 1. Overall survival for all patients according to hemoglobin level.

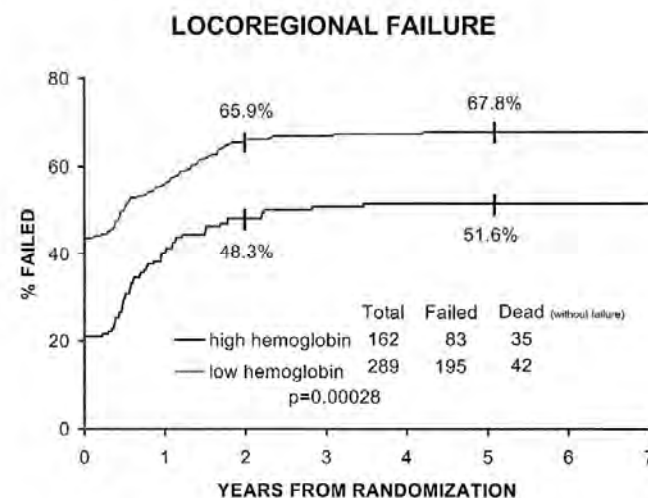


Fig. 2. Locoregional failure for all patients according to hemoglobin level.

Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: randomised, double-blind, placebo-controlled trial

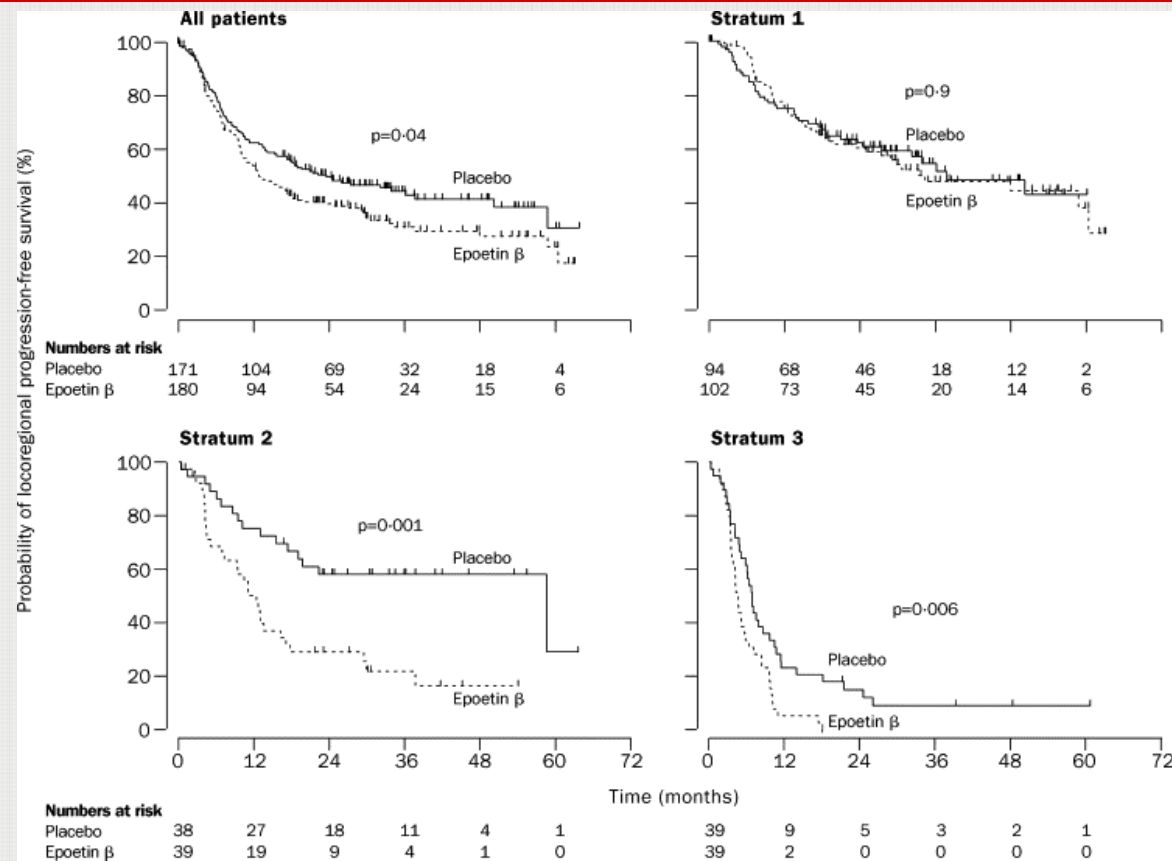
Dr Michael Henke, MD, Prof Roland Laszig, MD, Prof Christian Rübe, MD, Ulrich Schäfer, MD, Klaus-Dieter Haase, MD, Prof Burkhard Schilcher, MD, Stephan Mose, MD, Karl T Beer, MD, Ulrich Burger, PhD, Chris Dougherty, MD, Prof Hermann Frommhold, MD

The Lancet
Volume 362, Issue 9392, Pages 1255-1260 (October 2003)



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Locoregional Progression Free Survival



The Lancet 2003 362, 1255-1260 DOI: (10.1016/S0140-6736(03)14567-9)
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**School of Medicine
and Public Health**
UNIVERSITY OF WISCONSIN-MADISON

Radiotherapy With or Without Erythropoietin for Anemic Patients With Head and Neck Cancer: A Randomized Trial of the Radiation Therapy Oncology Group (RTOG 99-03)

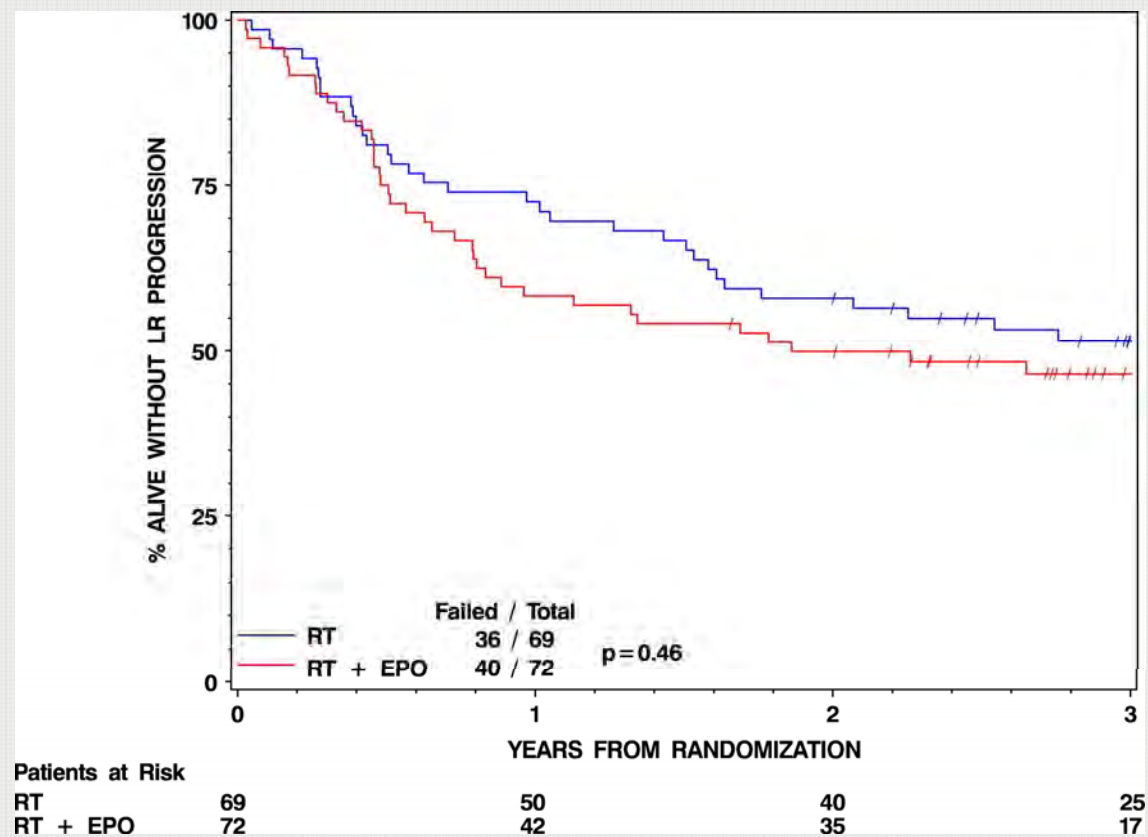
Mitchell Machtay, M.D., Thomas F. Pajak, Ph.D., Mohan Suntharalingam, M.D., George Shenouda, M.B.B.Ch., Ph.D., F.R.C.P.(C), Diane Hershock, M.D., Diana C. Stripp, M.D., Anthony J. Cmelak, M.D., Alan Schulsinger, M.D., Karen K. Fu, M.D.

International Journal of Radiation Oncology • Biology • Physics
Volume 69, Issue 4, Pages 1008-1017 (November 2007)



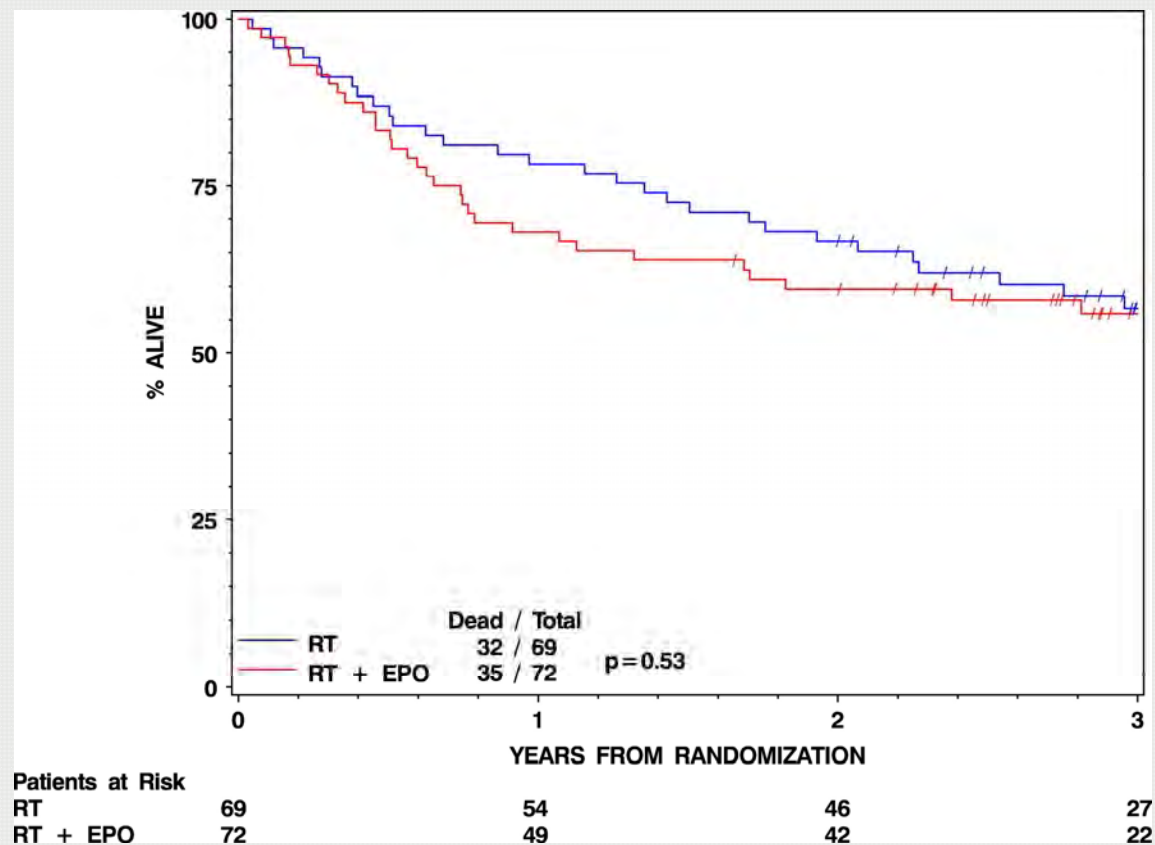
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Locoregional progression free survival in RTOG 99-03

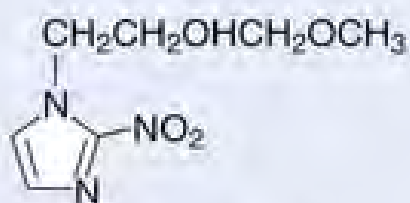


International Journal of Radiation Oncology • Biology • Physics 2007 69, 1008-1017
Copyright © 2007 Elsevier Inc.

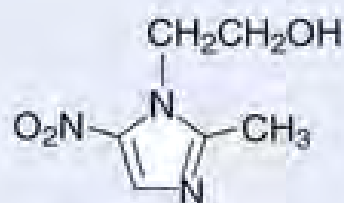
Overall Survival in RTOG 99-03



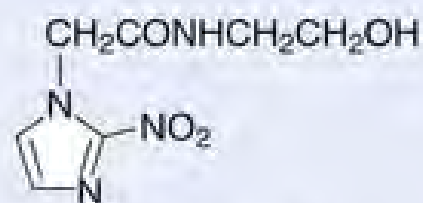
Hypoxic Radiosensitizers



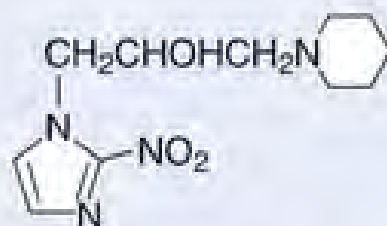
Misonidazole



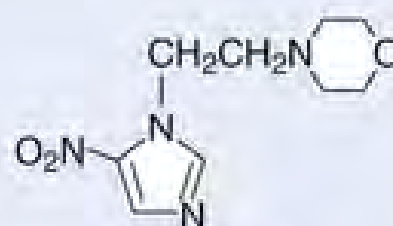
Metronidazole



Etanidazole



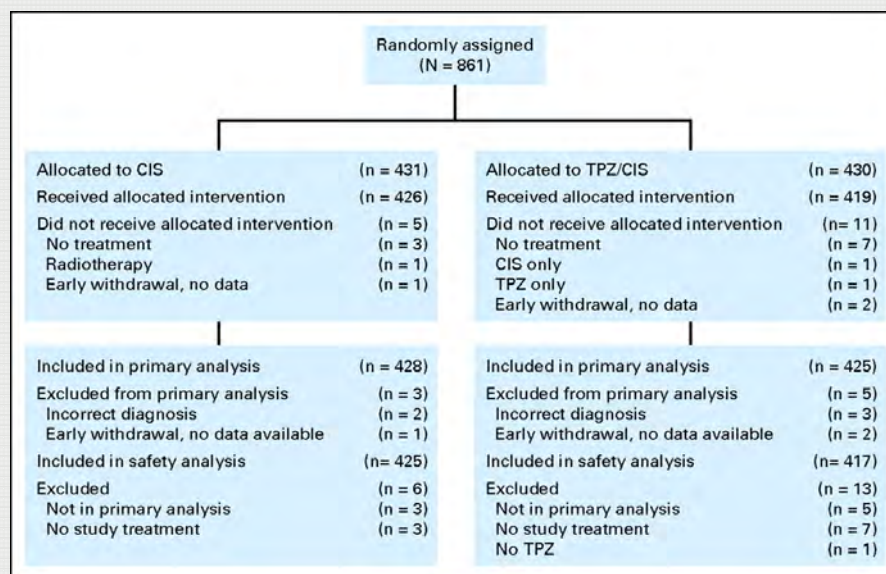
Pimonidazole



Nimorazole

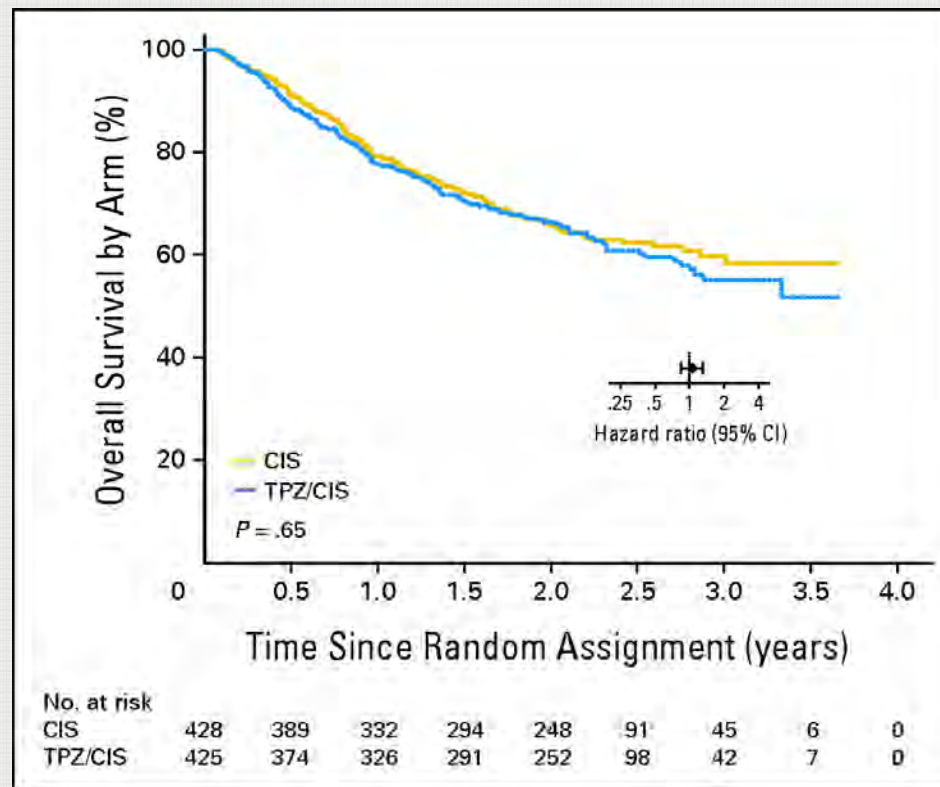
Tirapazamine, Cisplatin, and Radiation Versus Cisplatin and Radiation for Advanced Squamous Cell Carcinoma of the Head and Neck (TROG 02.02, HeadSTART): A Phase III Trial of the Trans-Tasman Radiation Oncology Group

Danny Rischin, Lester J. Peters, Brian O'Sullivan, Jordi Giralt, Richard Fisher, Kally Yuen, Andy Trotti, Jacques Bernier, Jean Bourhis, Jolie Ringash, Michael Henke, and Lizbeth Kenny



Overall survival by arm

CIS, cisplatin; TPZ, tirapazamine



Rischin D et al; JCO 2010, 28, 2989-2995

Why so much preclinical promise and so little clinical trial success?

- ◆ Anemia likely a surrogate for other comorbidities
- ◆ Not every tumor is hypoxic
- ◆ Drugs delivered at inadequate concentrations
- ◆ Drugs not well distributed within tumors
- ◆ Drugs not as effective as advertised
- ◆ Drug limiting toxicities: ie neurotoxicity for imidazoles
- ◆ Lack of drug/radiation selectivity for tumors
- ◆ Reoxygenation during fractionated radiation
- ◆ Many Others...

Science strong, clinical trials confirmation weak However...

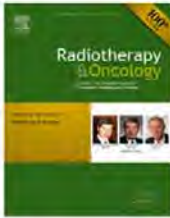
J Overgaard: “Hypoxic radiosensitization adored and ignored”

Radiotherapy and Oncology 100 (2011) 22–32

Contents lists available at [ScienceDirect](#)

 **Radiotherapy and Oncology**

journal homepage: www.thegreenjournal.com



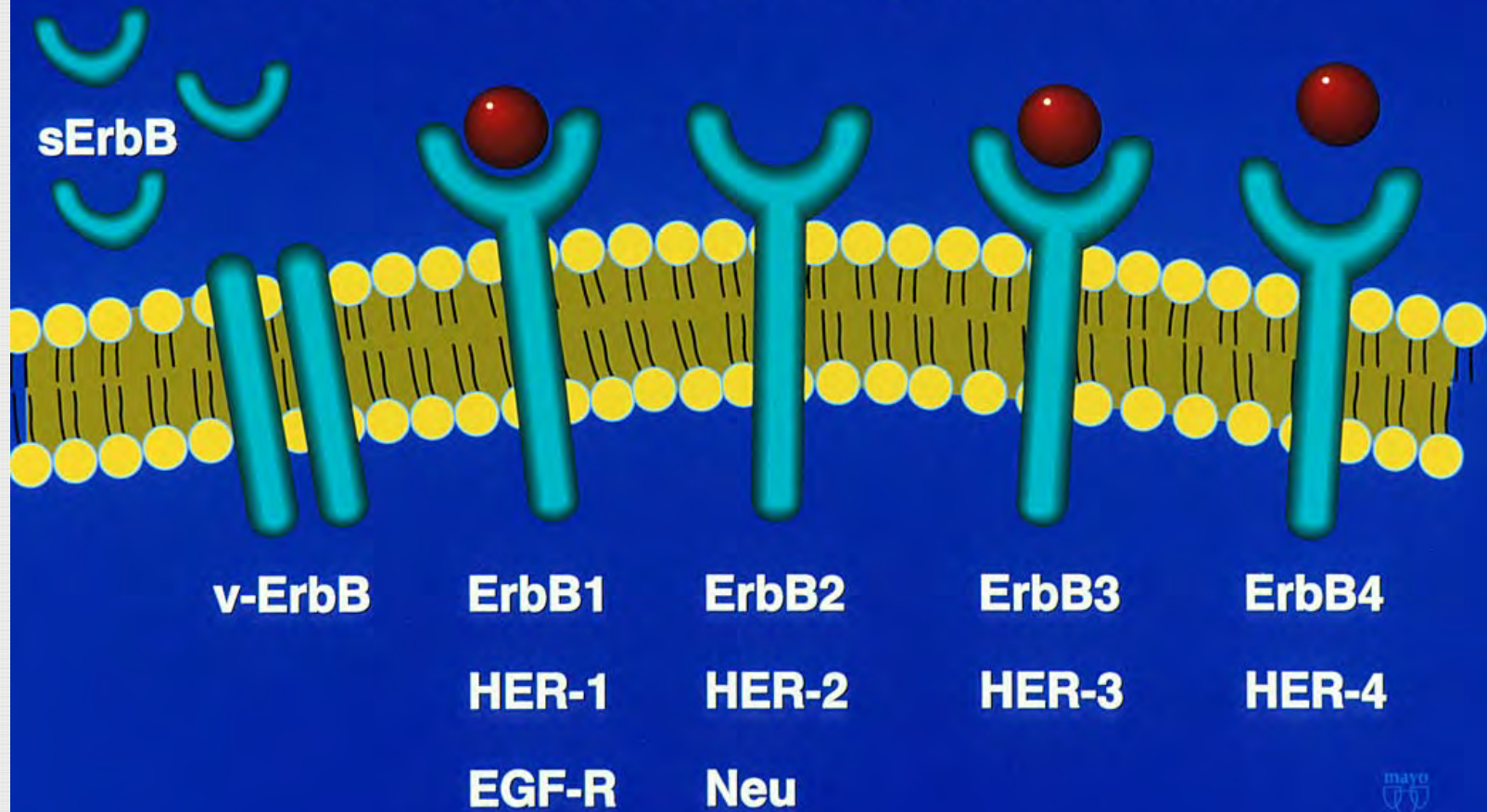
Meta-analysis of hypoxia in HNSCC

Hypoxic modification of radiotherapy in squamous cell carcinoma of the head and neck – A systematic review and meta-analysis

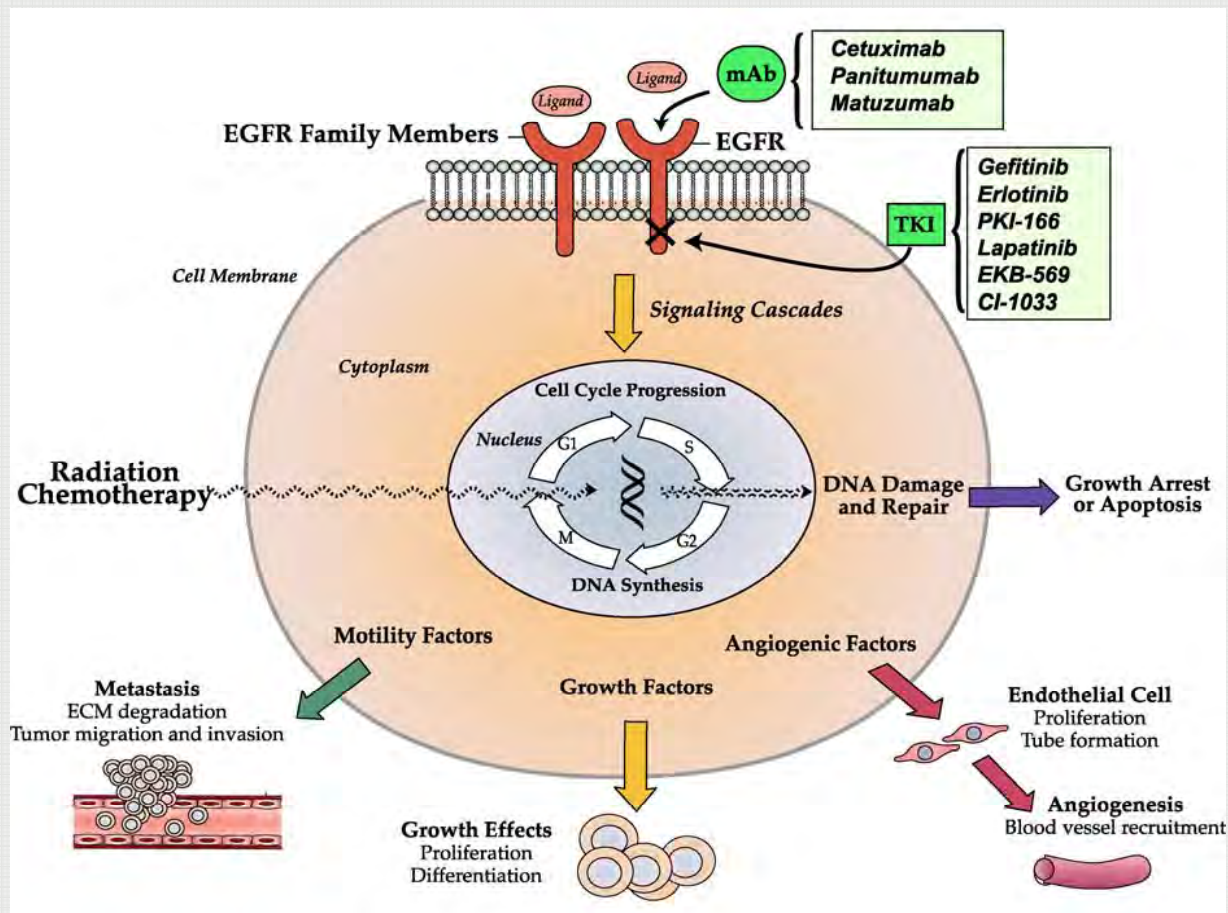
Jens Overgaard *

Department of Experimental Clinical Oncology, Aarhus University Hospital, Aarhus, Denmark

ErbB Family of Receptor Tyrosine Kinases

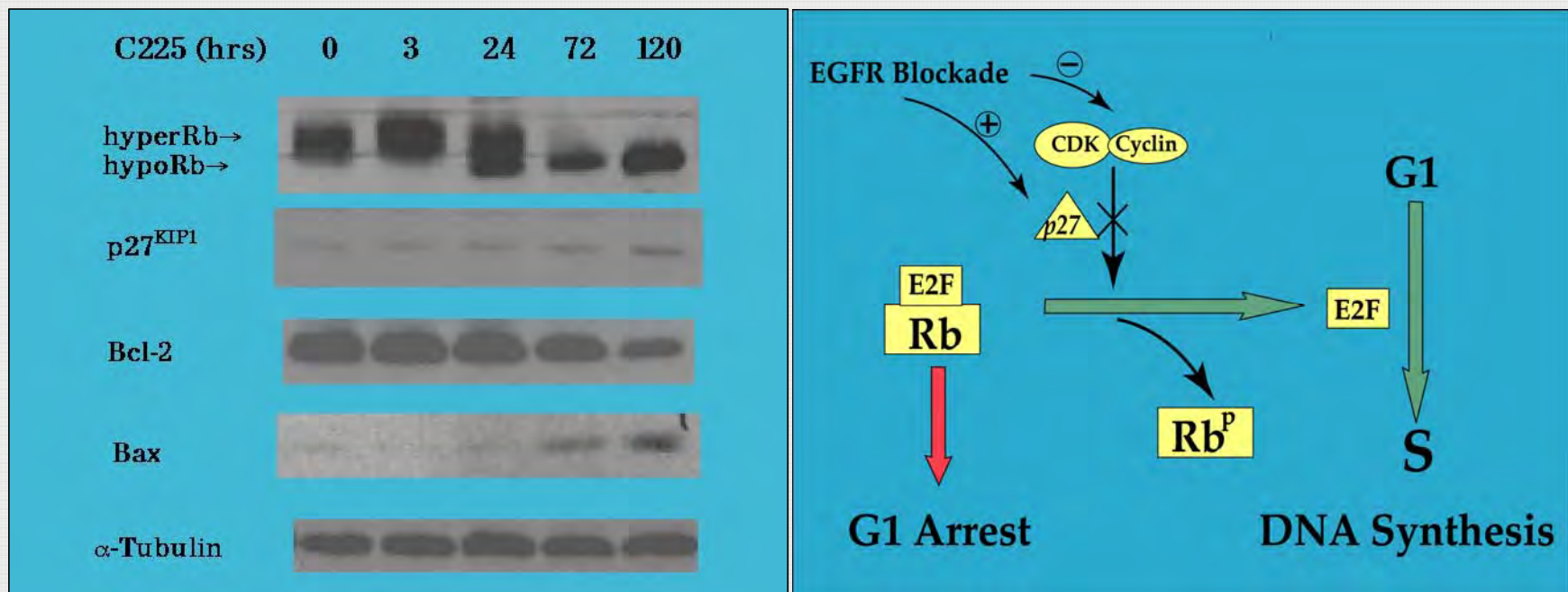


Schematic of EGFR signaling interactions



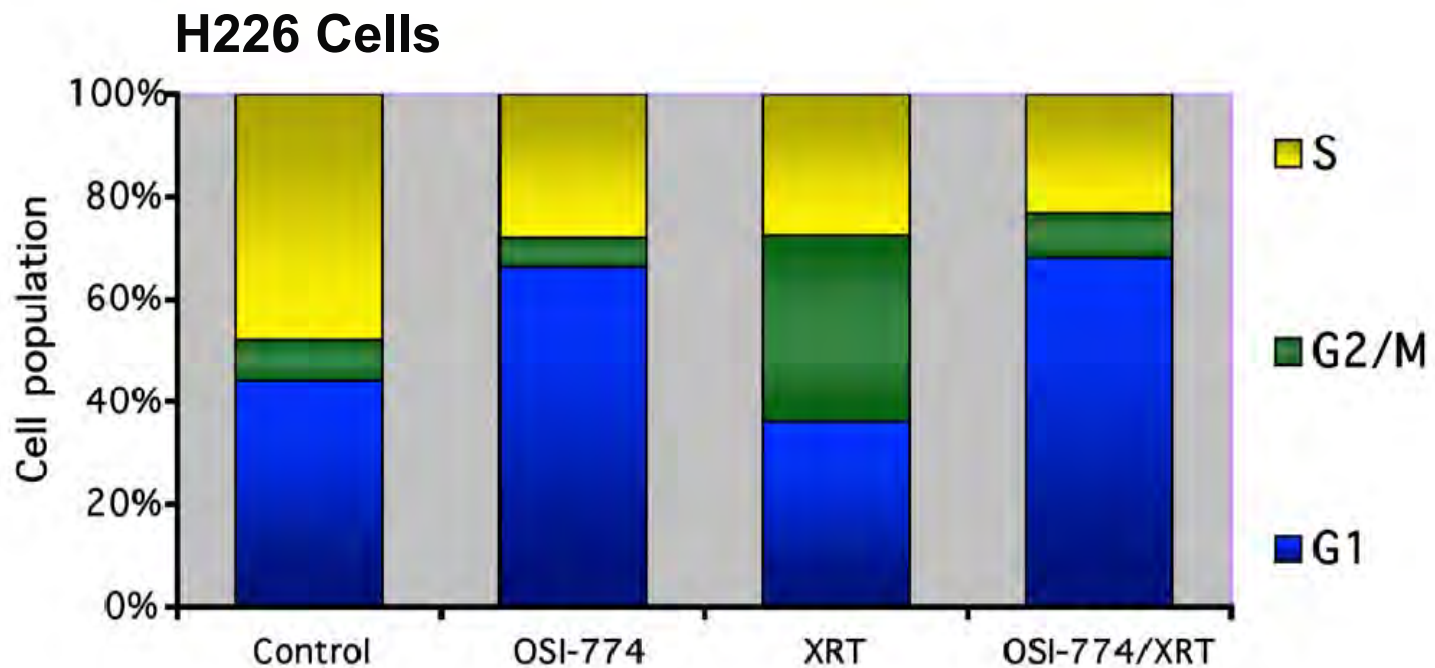
Harari & Huang:
Clin Cancer Res 2004

Effect of Cetuximab on G1 Cell Cycle & Apoptosis Regulatory Proteins



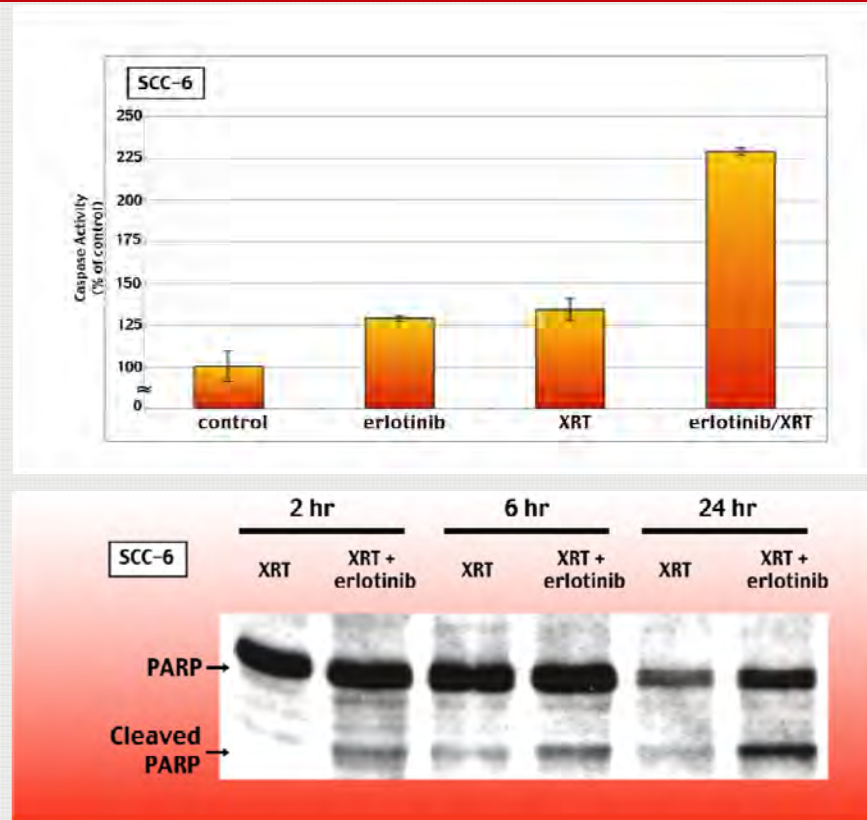
Huang et al, Cancer Res. 59:1935, 1999

Effect of Erlotinib and Radiation on Cell Cycle Phase Distribution



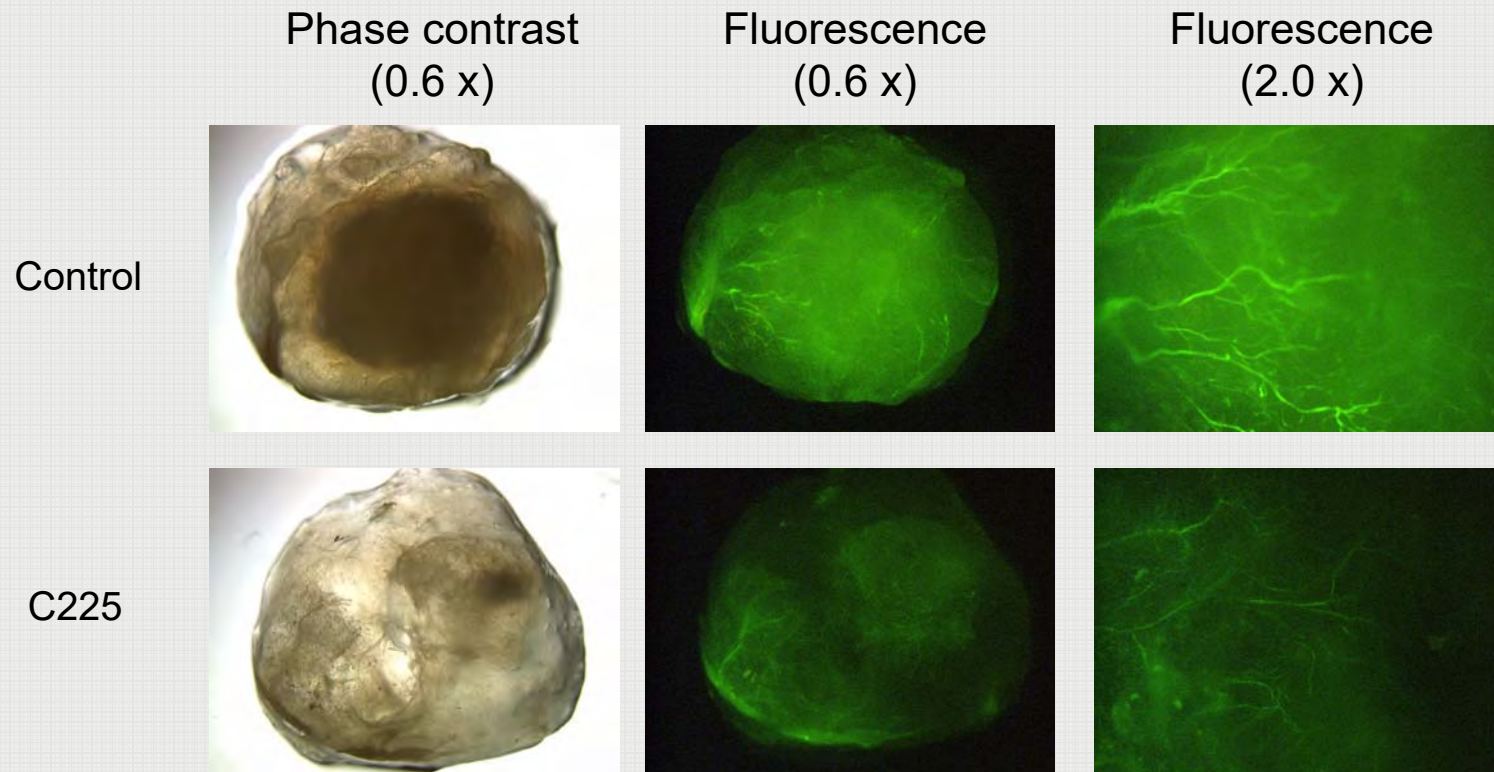
Chinnaiyan et al, Cancer Res. 65: 3328-35, 2005

Erlotinib enhances XRT induced apoptosis

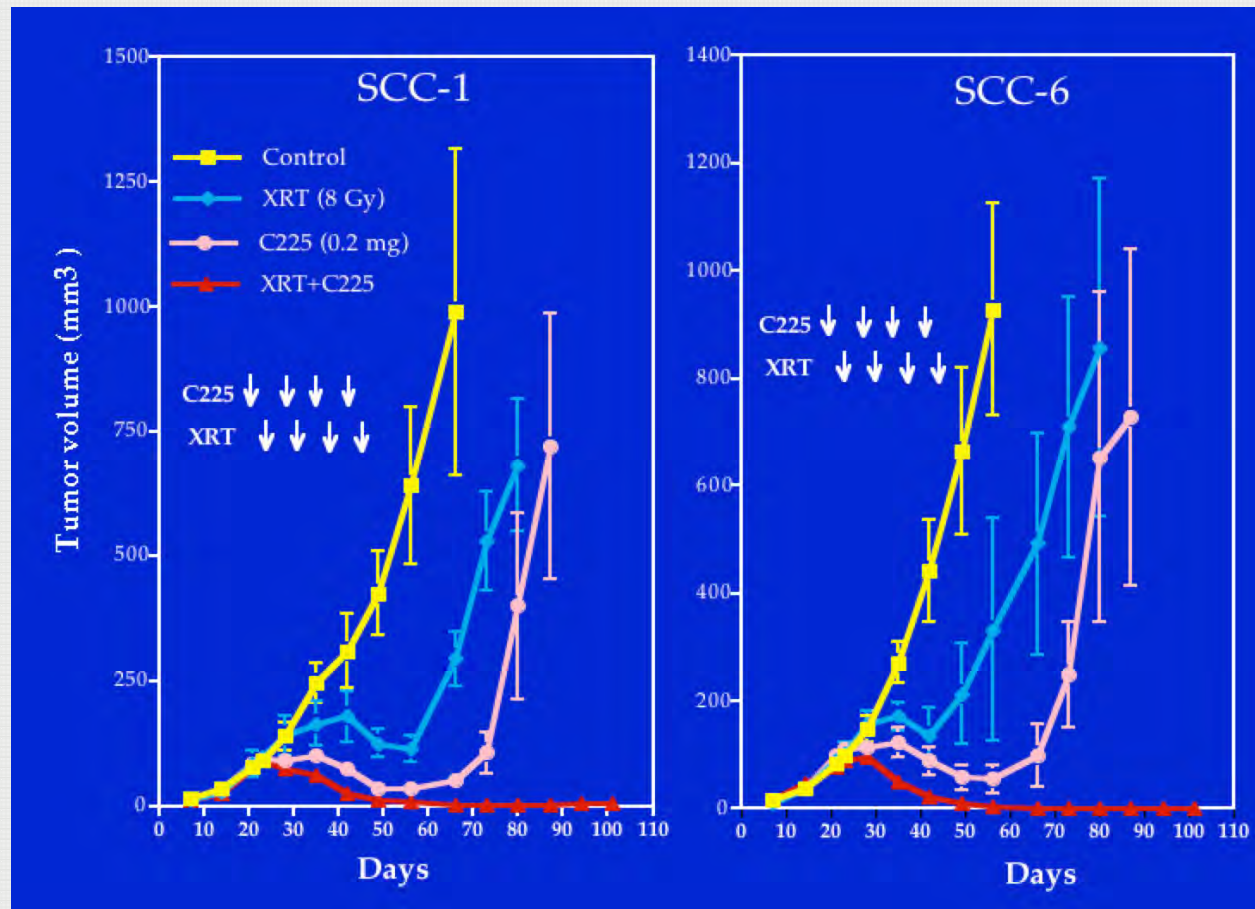


Chinnaiyan et al, Cancer Res. 65:3328-35, 2005

Anti-Angiogenic Effect of Cetuximab on Tumor-Induced Vascularization



Antitumor Activity of Cetuximab in Combination with Radiation in SCC Xenografts



Huang et al,
Clin Cancer Res 6:2166, 2000

EGFR Preclinical Summary

EGFR blockade plus radiation

- Antiproliferative effects
- Multiple cell cycle checkpoints
 - Radiation:G2 EGFR blockade:G1
- Apoptosis induction
- Inhibition of DNA damage repair
- Anti-angiogenic effects
- Anti-metastatic effects

Which served as a definitive rationale for EGFR inhibition with RT?

RT + Cetuximab: Phase III Study Design

Stratify by

- Karnofsky score:
90-100 vs. 60-80
- Regional Nodes:
Negative vs. Positive
- Tumor stage:
AJCC T1-3 vs. T4
- RT fractionation:
Concomitant boost
vs. Once daily
vs. Twice daily

R
A
N
D
O
M
I
Z
E

Arm 1 (RT)

Radiation therapy

Arm 2 (RT+Cetux)

Radiation therapy +
Cetuximab

Study accrual 1998-2002
424 patients randomized

February 9th, 2006

The NEW ENGLAND JOURNAL of MEDICINE

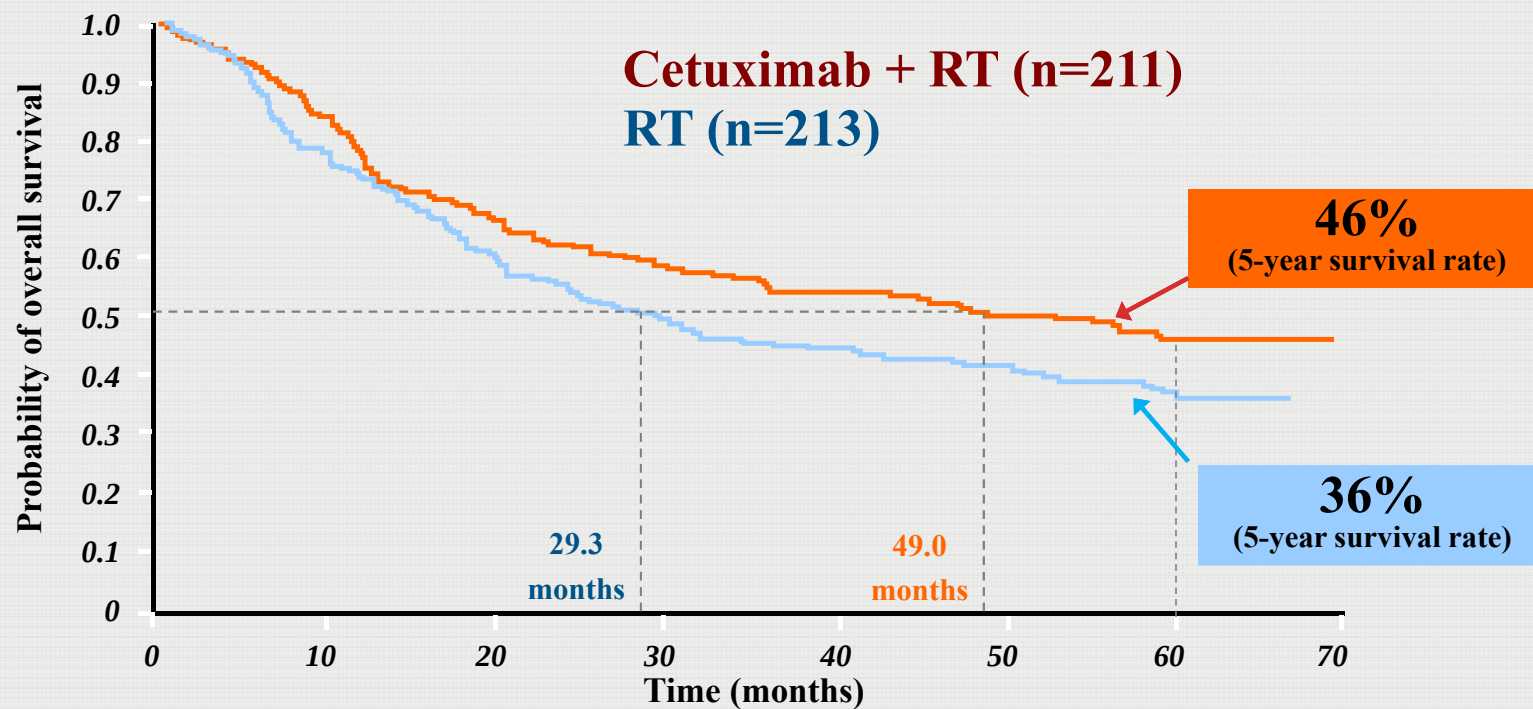
N Engl J Med 2006;354:567-78.

ORIGINAL ARTICLE

Radiotherapy plus Cetuximab for Squamous-Cell Carcinoma of the Head and Neck

James A. Bonner, M.D., Paul M. Harari, M.D., Jordi Giralt, M.D.,
Nozar Azarnia, Ph.D., Dong M. Shin, M.D., Roger B. Cohen, M.D.,
Christopher U. Jones, M.D., Ranjan Sur, M.D., Ph.D., David Raben, M.D.,
Jacek Jassem, M.D., Ph.D., Roger Ove, M.D., Ph.D., Merrill S. Kies, M.D.,
Jose Baselga, M.D., Hagop Youssoufian, M.D., Nadia Amellal, M.D.,
Eric K. Rowinsky, M.D., and K. Kian Ang, M.D., Ph.D.*

Radiation + Cetuximab: Overall survival Five-year update



Hazard ratio=0.73 (95% CI: 0.56–0.95); p=0.018

Bonner, Harari, Giralt et al. Lancet Oncology 2010

Radiation plus Cetuximab in H&N Cancer

- **First phase III trial to demonstrate survival increase using a molecular targeted agent combined with radiation**
- Benefits achieved without notable increase in overall toxicity
- Addition of cetuximab (90% compliance) did not delay completion of radiation

Drug registration in combination with radiation

How many agents followed the cetuximab example for FDA registration in combination with radiation since 2006?

Drug registration in combination with radiation

How many agents followed the cetuximab example for FDA registration in combination with radiation since 2006?

Zero

What was the scope of the clinical data supporting a phase III RCT?

A single phase I trial of 16 H&N cancer patients

Cetuximab heralded as a modern day radiosensitizer

Are we sure?

Virtually all HNSCC express EGFR.
We have no biomarker for response.

Potential role of vascular, HPV, immune and other effects?

RTOG 0522: Stage III-IV Phase III

Stage III & IV* SCC of :

- Oropharynx
- Hypopharynx
- Larynx

Stratify :

- Larynx ~ Others
- N0~N1,2a,2b~N2c-3
- KPS
60-80 ~ 90-100
- 3-D vs IMRT*

R
A
N
D
O
M
I
Z
E



1. Accelerated FX* +
CDDP: 100 mg/m², q3W X 2

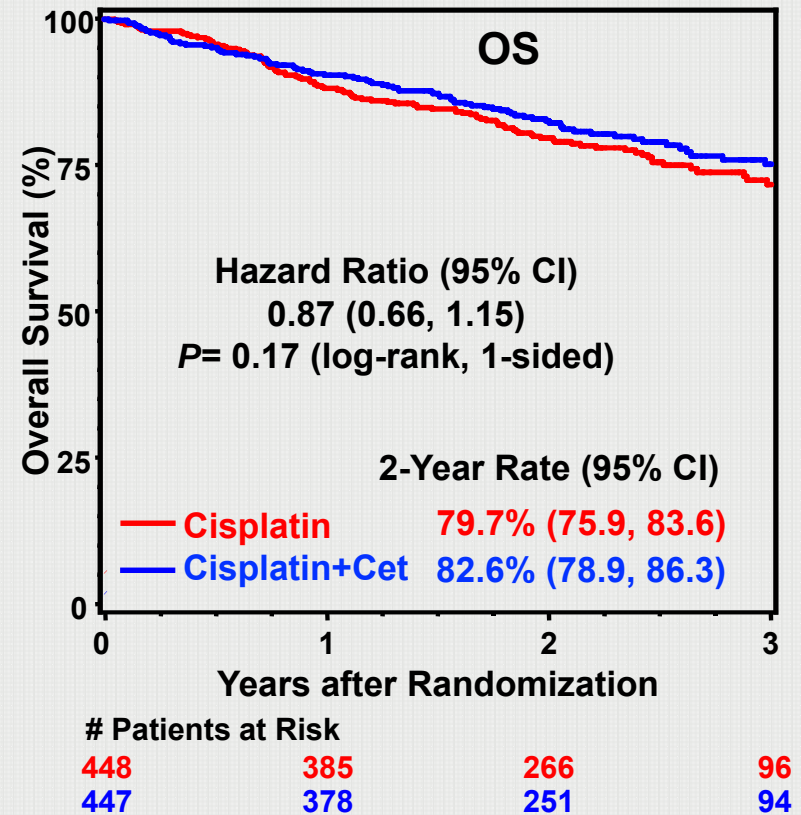
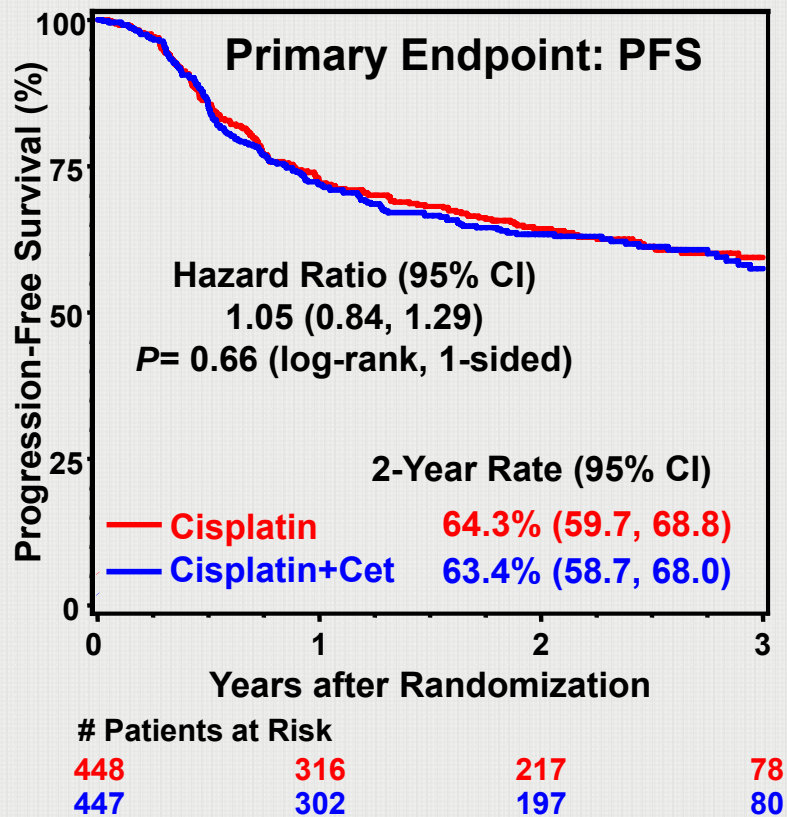


2. Accelerated FX* +
CDDP: 100 mg/m², q3W X 2
C225: 400 mg/m², Week -1
250 mg/m²/w, Wks 2-8

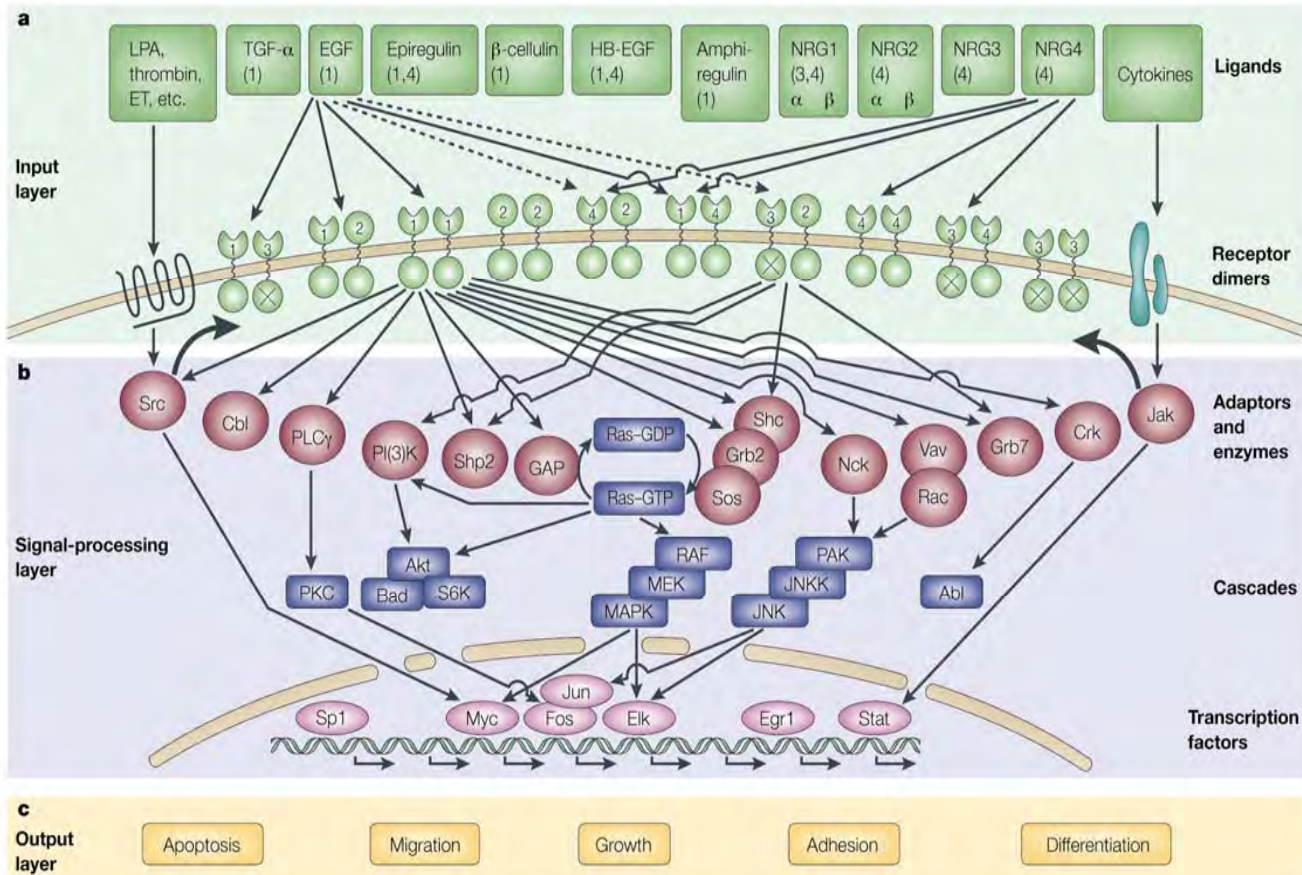
*3-D: AFX-CB (72 Gy/42 F/6 W)
IMRT: 70 Gy/35 F/6W (BID x 5d)

RTOG 0522
N~1000

RTOG 0522: Tumor Control Endpoints



The HER/ErbB Signaling Network



Yarden & Sliwkowski, Nature Reviews MCB (2001)

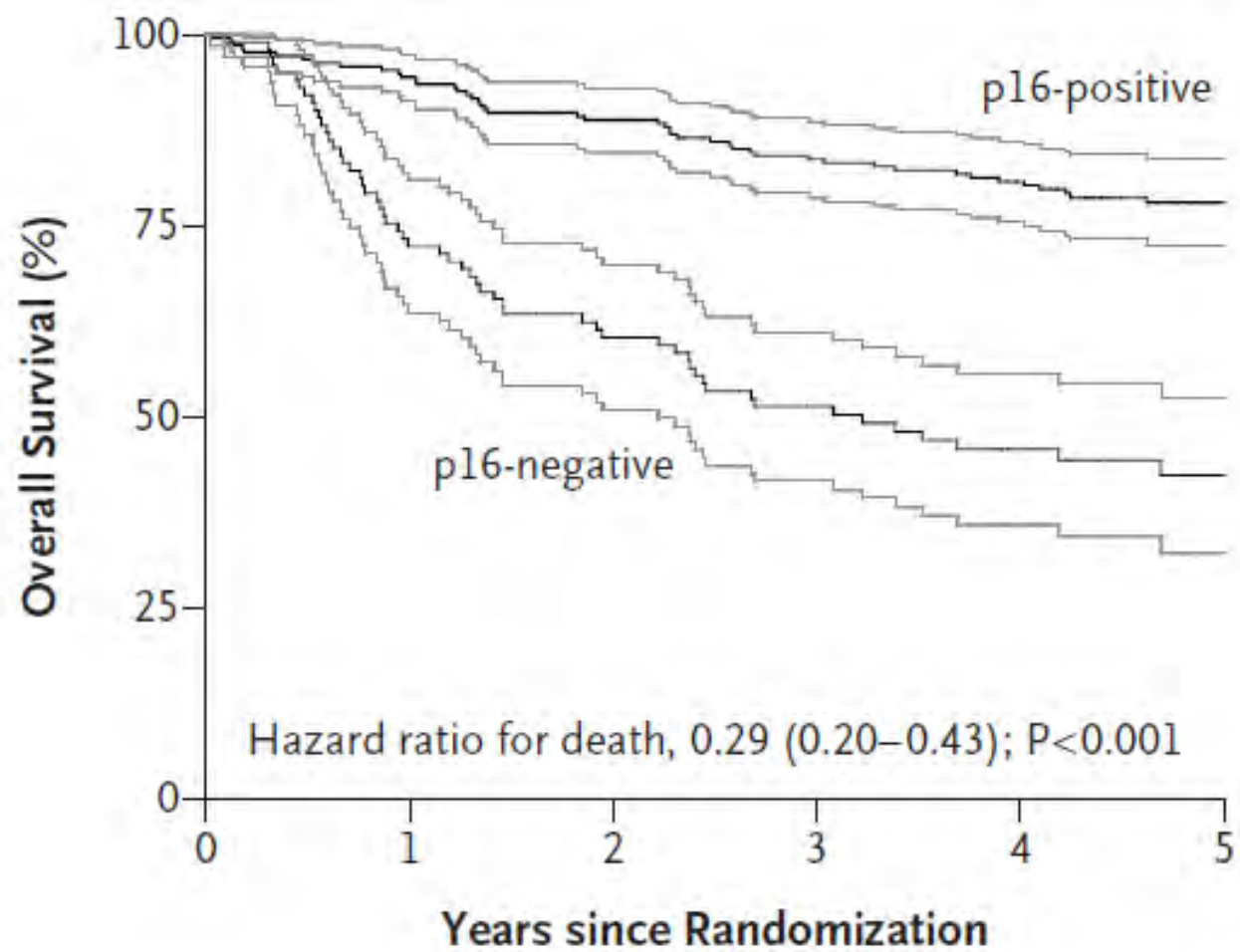
The NEW ENGLAND JOURNAL *of* MEDICINE

ORIGINAL ARTICLE

Human Papillomavirus and Survival of Patients with Oropharyngeal Cancer

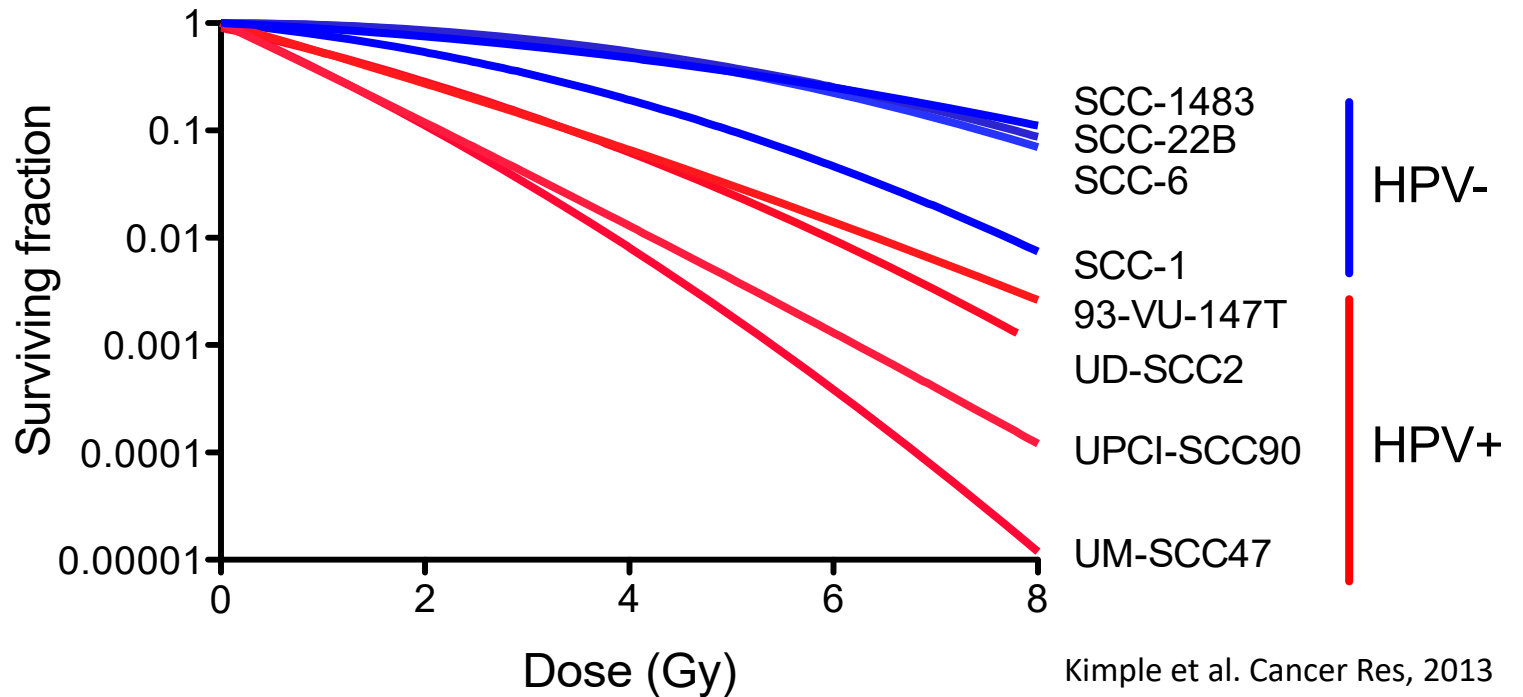
K. Kian Ang, M.D., Ph.D., Jonathan Harris, M.S., Richard Wheeler, M.D.,
Randal Weber, M.D., David I. Rosenthal, M.D., Phuc Felix Nguyen-Tân, M.D.,
William H. Westra, M.D., Christine H. Chung, M.D.,
Richard C. Jordan, D.D.S., Ph.D., Charles Lu, M.D., Harold Kim, M.D.,
Rita Axelrod, M.D., C. Craig Silverman, M.D., Kevin P. Redmond, M.D.,
and Maura L. Gillison, M.D., Ph.D.

June 2010



Enhanced Radiation Sensitivity in HPV-Positive Head and Neck Cancer

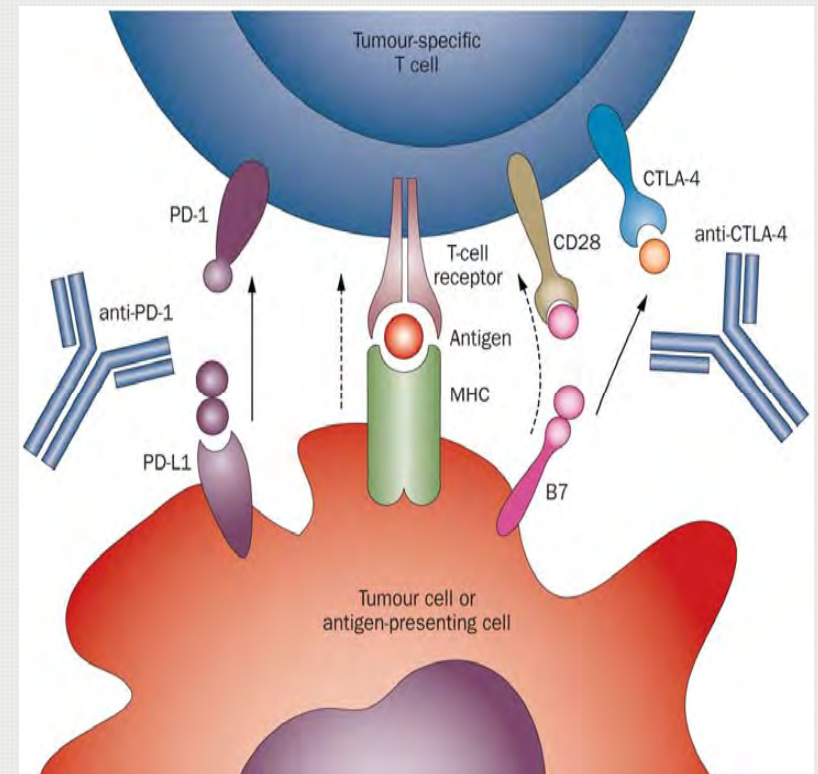
Randall J. Kimple^{1,3}, Molly A. Smith¹, Grace C. Blitzer¹, Alexandra D. Torres^{1,2}, Joshua A. Martin^{1,2}, Robert Z. Yang^{1,2}, Chimera R. Peet¹, Laurel D. Lorenz², Kwangok P. Nickel¹, Aloysius J. Klingelhutz⁴, Paul F. Lambert^{2,3}, and Paul M. Harari^{1,3}



Immunotherapy: a revolution in oncology

- Recombinant cytokines (IFN, IL2)
- Tumor-specific mAbs (dinutuximab, rituximab)
- Cell therapies (Sipuleucel-T, CAR-T's, adoptive cell transfer)
- Tumor vaccines
- Oncolytic viruses
- T cell checkpoint inhibitors (anti-CTLA-4, anti-PD-1)
- Emerging molecular targeted immunotherapies

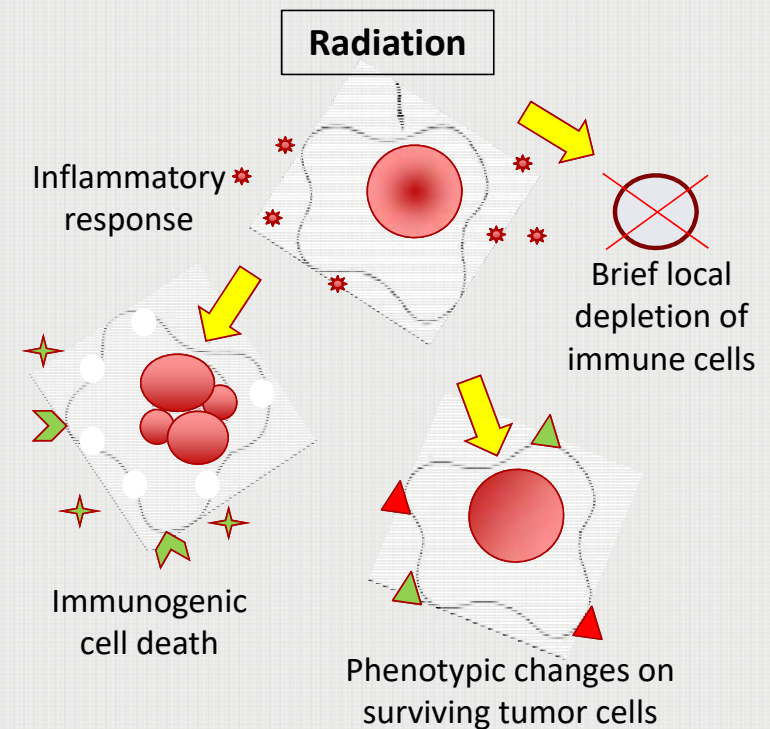
Drake *et al.*, Nat Rev Clin Oncol, 2014



Slide courtesy Dr. Zach Morris

Effect of radiation on tumor immune susceptibility

- **Stress response (Seconds to minutes)**
 - Pro-inflammatory cytokines released
- **Immunogenic cell death (Hours to weeks)**
 - Cell surface translocation of calreticulin
 - Extracellular release of HMGB1
 - Release of ATP
- **Tumor cell phenotypic changes (Days)**
 - MHC1
 - Fas
 - PDL1
 - NKG2D ligand
 - Toll-like receptors
- **Temporary local eradication of suppressive immune cells**
 - Myeloid-derived suppressor cells
 - Regulatory T cells



Slide courtesy Dr. Zach Morris

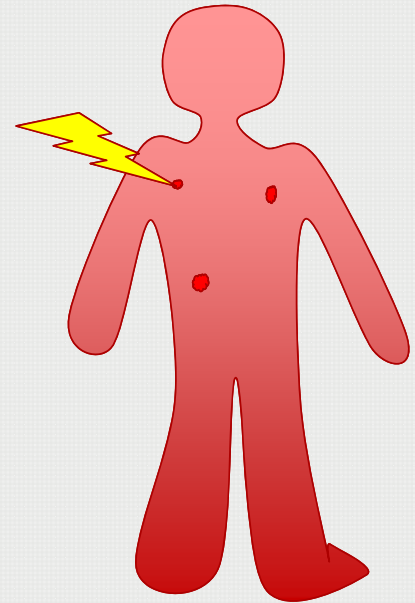
Interaction of radiation with immune response is not a new concept

- Influence of host immune competence on radiation response in animal models

- Stone et al., JNCI 1979

- The abscopal effect

- Mole, Br J Radiology 1953



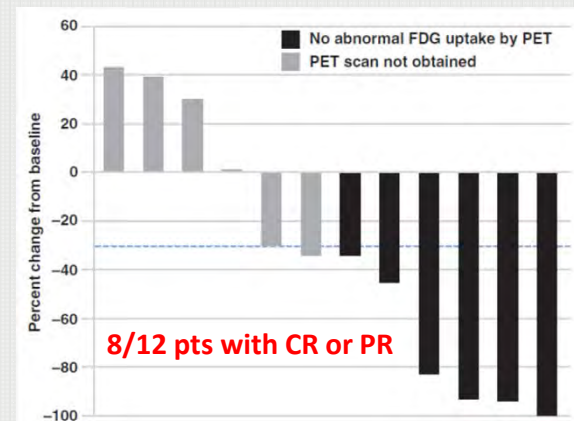
Early prospective studies of radiation + immunotherapy

Seung et al. Sci Transl Med, 2012

Eligibility: Met RCC or Melanoma w/no prior Tx

Treatment: 20 Gy x 1-3 + IL2 (600kU/kg Q8hrs x14)

Endpoint: Response rate and toxicity



Golden et al., Lancet Oncology, 2015

Eligibility: Stable/progressing solid tumor mets

Treatment: 35 Gy/10 fx + systemic GM-CSF

Endpoint: Abscopal response

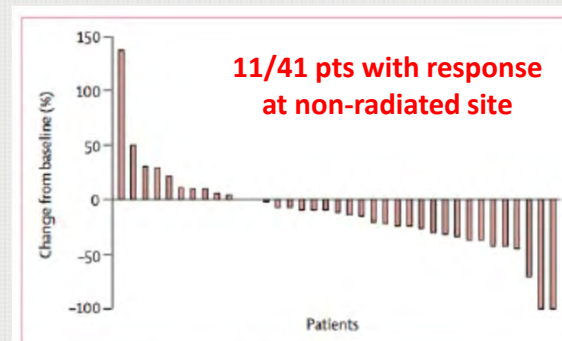
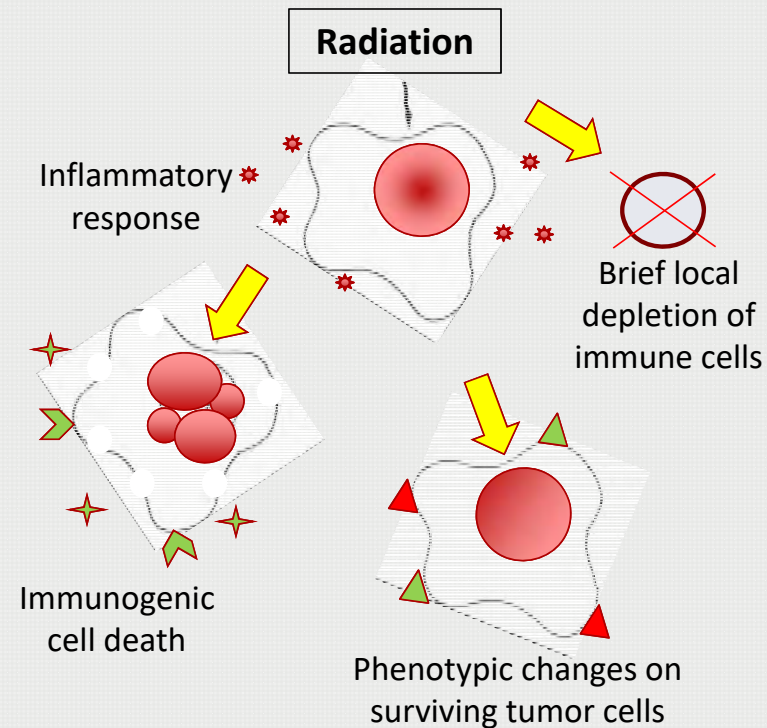


Figure 2: Waterfall plot of best abscopal responses

The plot shows the percent change from baseline in the best responding abscopal lesions. Each bar represents the best abscopal response for one patient.

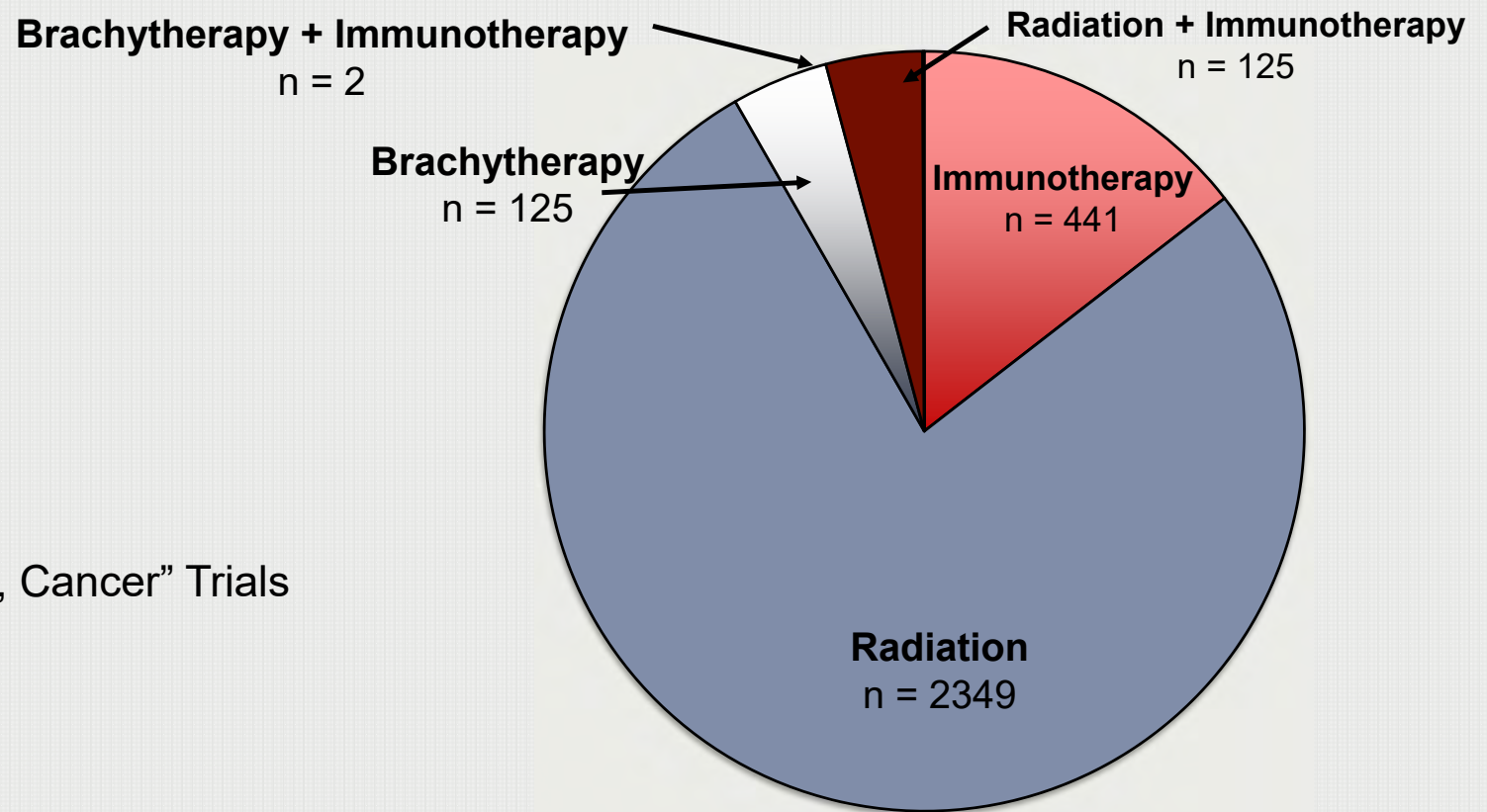
Optimizing radiation to enhance immunotherapy

- Timing/sequencing
- Dose
- Fractionation
- Quality (high vs low LET)
- Dose rate
- Heterogeneity
- Coverage within tumor
- Coverage of metastatic sites
- Regional LNs



Slide courtesy Dr. Zach Morris

Current trials with radiation + immunotherapy



ClinicalTrials.gov
“Open, Interventional, Cancer” Trials

Slide courtesy Dr. Zach Morris

Why so challenging to study new drugs with RT?

- **Phase I paradigm was designed for drugs**
 - Easy to study new agents in met/rec setting
- **Half of RT patients are treated for cure**
 - Need to respect standard of care Rx
- **RT yields local tumor response most of the time**
 - Good for patients, tough for RT/drug testing

**We commonly don't know
why trials fail...and**

**We commonly don't know
why trials succeed**

Vast majority of explaining comes after the results are in

Recommendation for Radiotherapy-Drug Studies 2018 and Beyond

**Robust preclinical testing AND strong
increase in the number of clinical trials that
combine radiation with drugs**

Promote Multidisciplinary Team Science

Opportunities to Study Radiation Combined with Drug

- **Tumors where RT plays a key treatment role**
 - Opportunity to augment curative therapy
 - Opportunity to enhance palliation
- **Consider also oligometastatic disease**
 - Radiation for symptomatic metastases
 - Systemic agents for microscopic disease

When to study radiation combined with drug in oncology?

**When to study radiation
combined with drug in oncology?**

Far More Frequently!

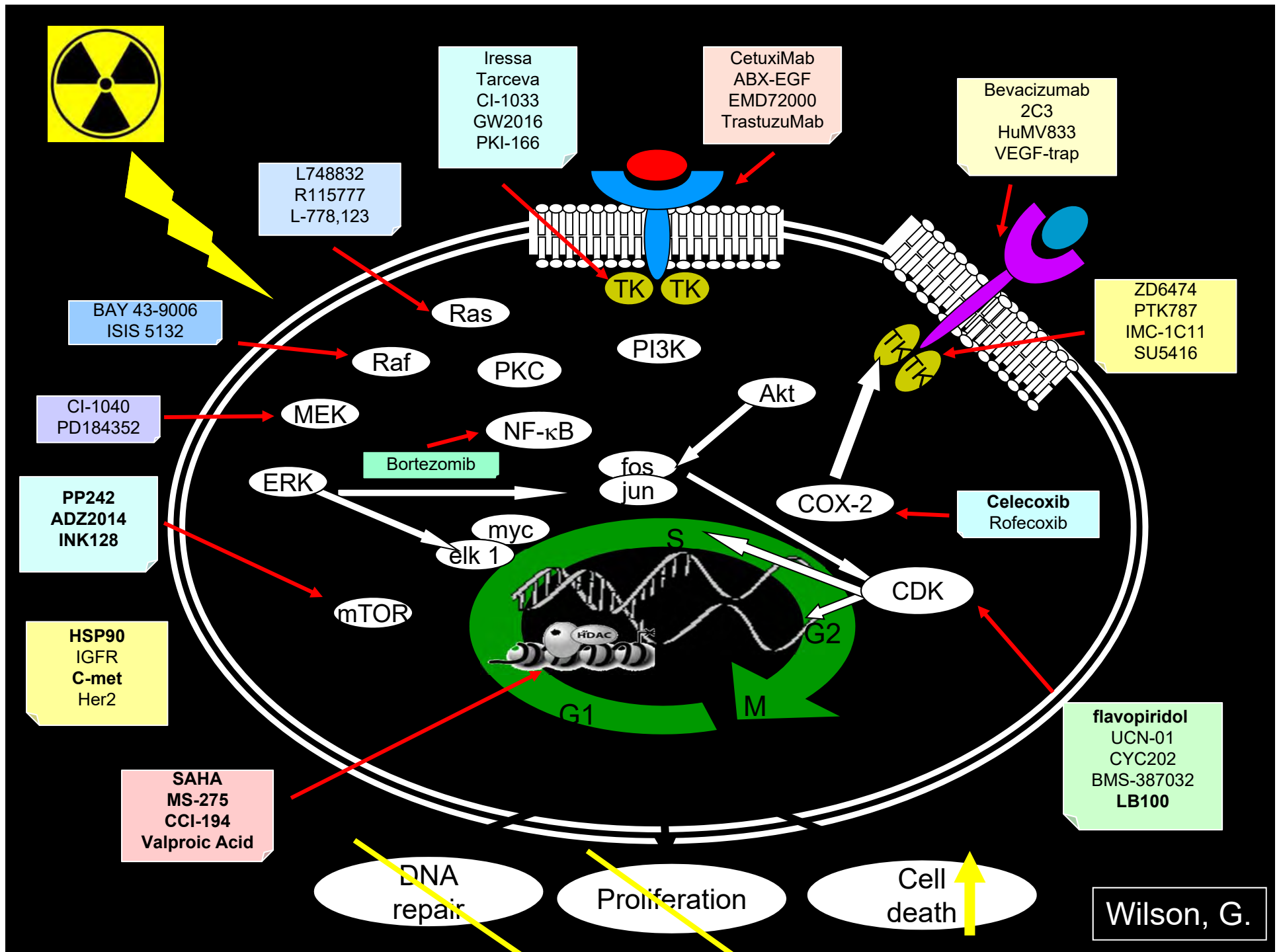
**When to study radiation
combined with drug in oncology?**

Far More Frequently!

Thank You

Preclinical Approach to “Repurposing”

Kevin Camphausen
Radiation Oncology Branch
National Cancer Institute



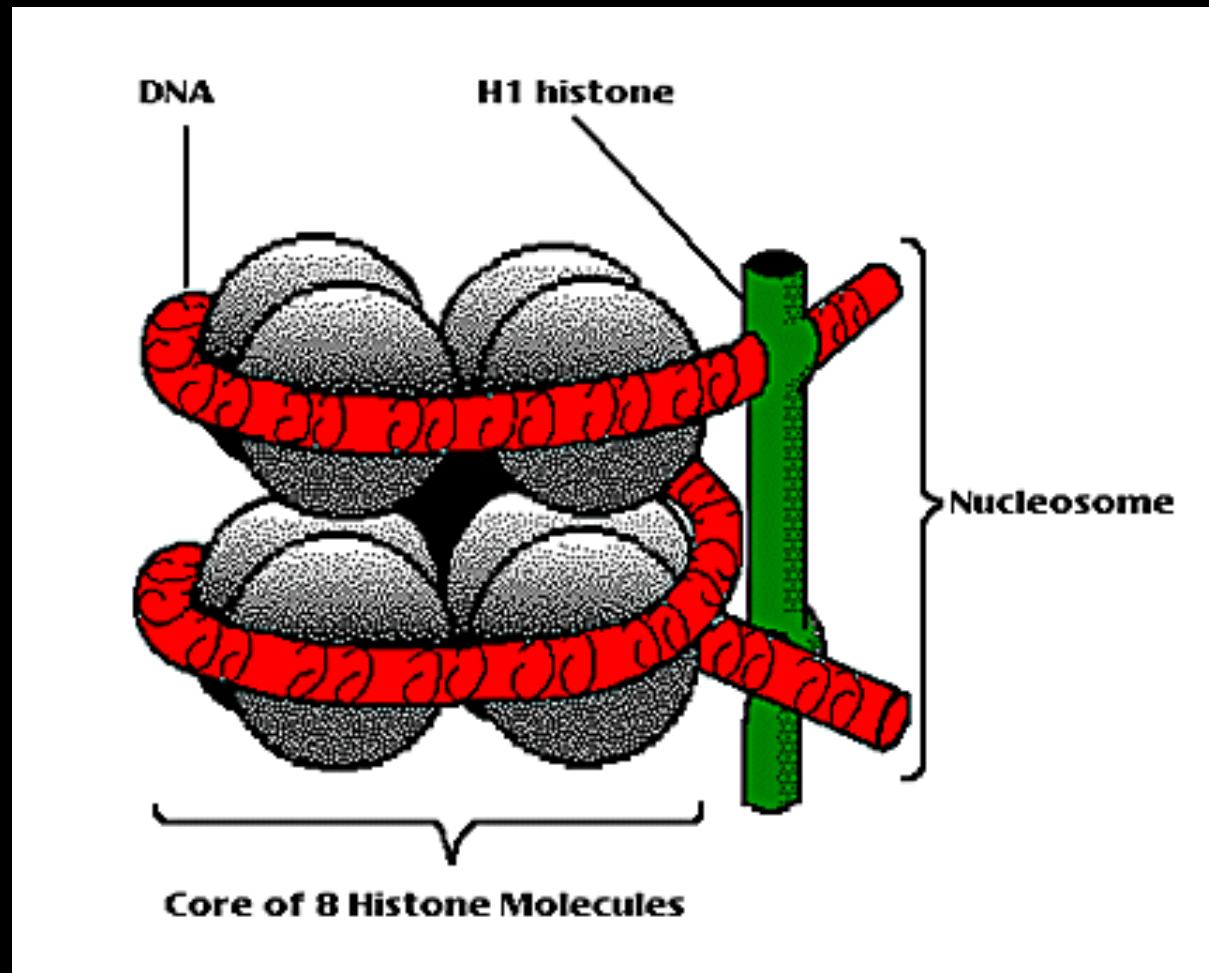
Radiation Targets

- Single Target Agents
 - Growth factor receptors (EGFR, VEGFR)
 - DNA repair proteins (DNA-PK, Rad51)
 - Transcription factors (NFkB, p53)
 - Signal transduction proteins (Ras, PI3K, c-Abl)
- Multi-target Inhibition
 - Chaperone proteins (HSP90 inhibition)
 - Microenvironment (angiogenesis, vasculature)
 - Epigenetic modification (HDACi, methyltransferase inh)
- Radiation Inducible Targets
 - Antigens or receptors (Fas, CEA)

Issues for Target/Agent Development

- Mechanism
 - Cell type or condition specific (cross BBB)
- Method of Targeting
 - Antibodies (EGFR, VEGFR)
 - Small molecules (Gleevec, Flavopiridol)
 - Gene therapy (TNFerade)
- Therapeutic ratio
 - Tumor > normal cells (Rad51)

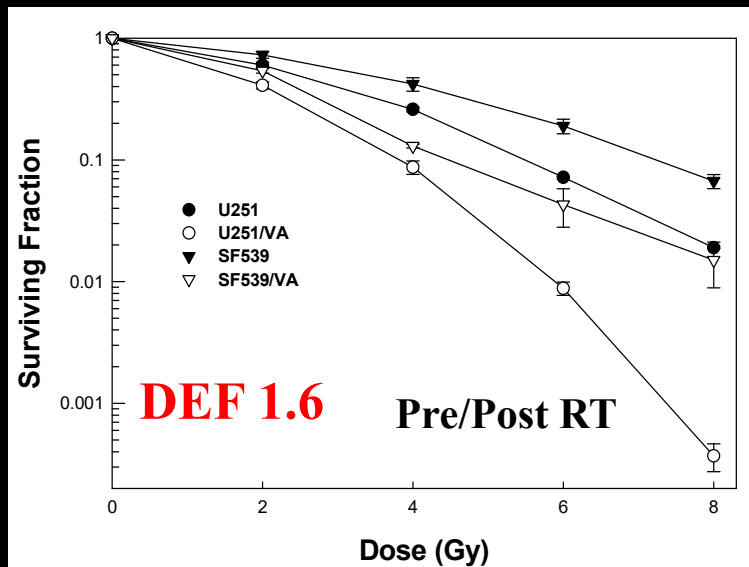
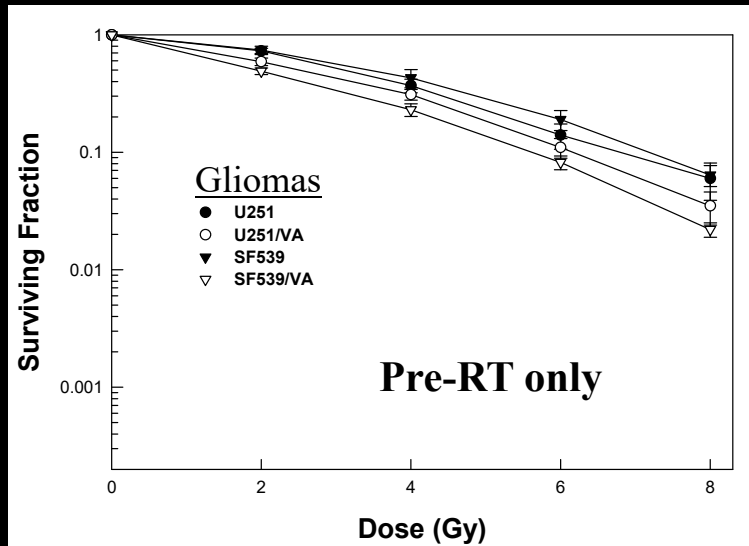
HDAC inhibition: Nucleosome



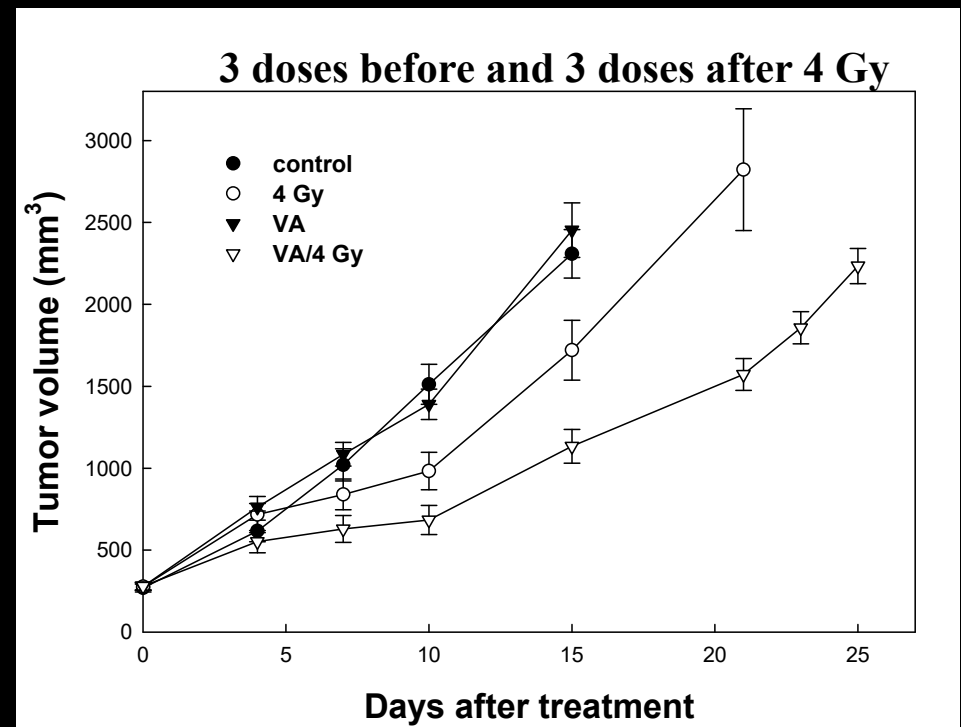
HDAC inhibition

- Histone Deacetylase Inhibitors
 - Modify chromatin structure and gene expression
 - Dynamic process involving HATs and HDACs
 - Tumors have reduced HATs and aberrant HDACs
 - Historical: sodium butyrate sensitized cells
- Hypothesis: HDAC inhibition will modify the tumor cell response to irradiation

Valproic Acid sensitizes glioma cells



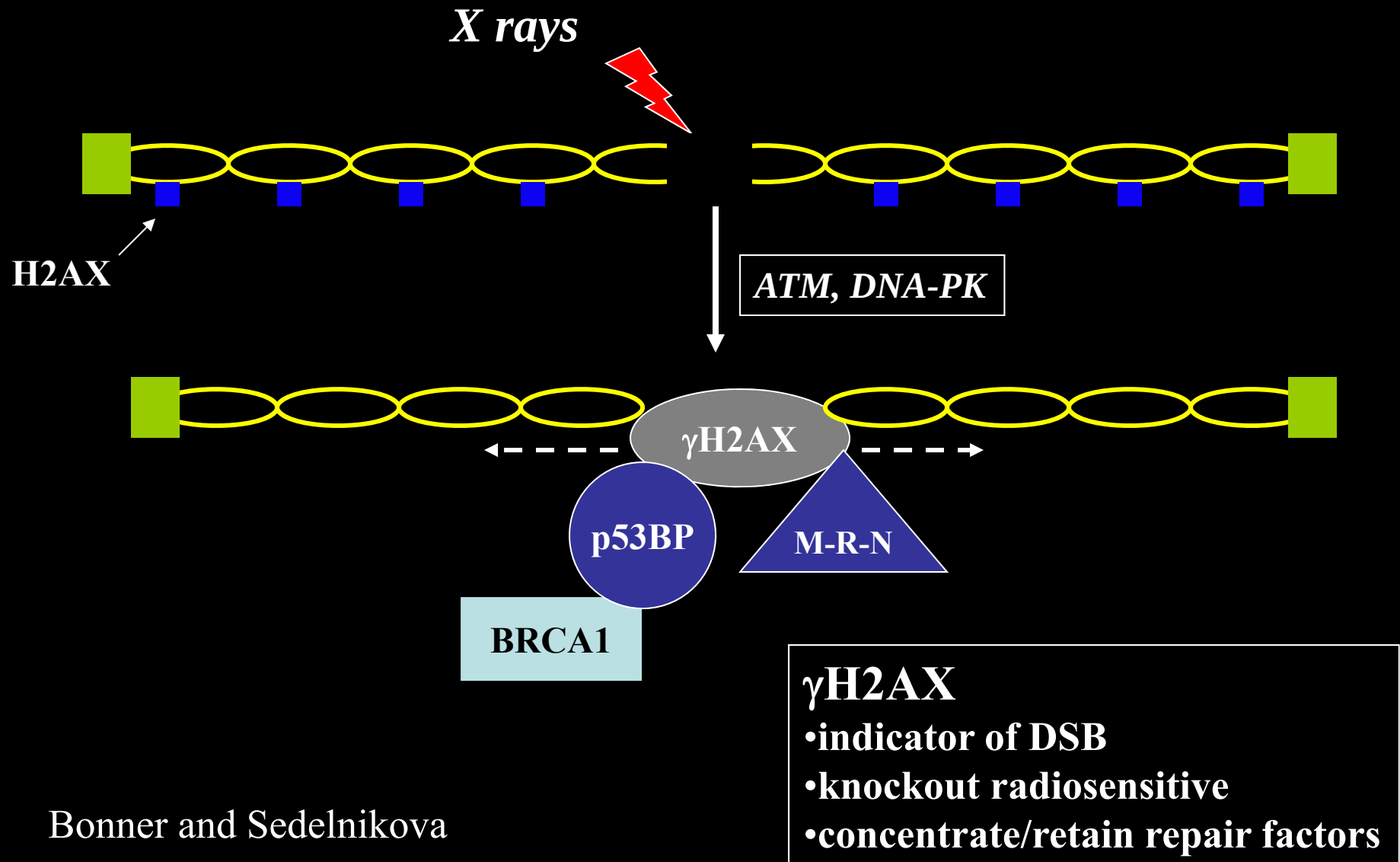
Tumor Growth Delay Assay



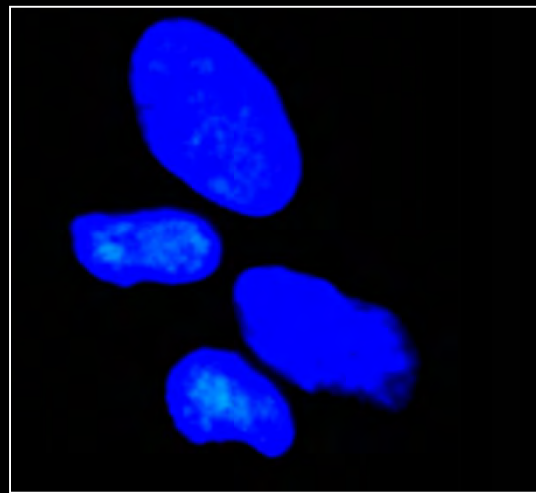
VA 0d, 4 Gy IR 4.2d, Combination 11d: $p < 0.01$

Camphausen Int'l. J. Can. 2005

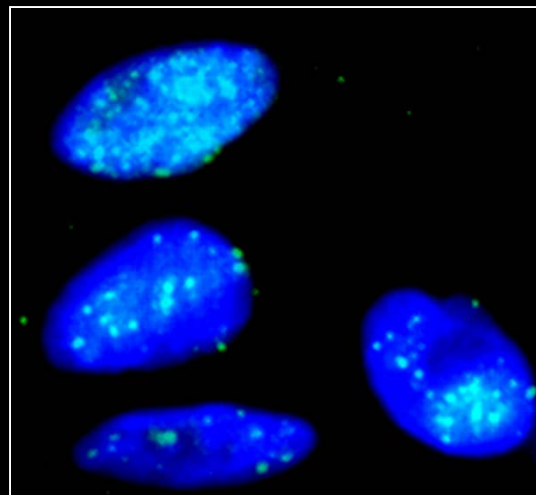
γ H2AX as a marker for DSB



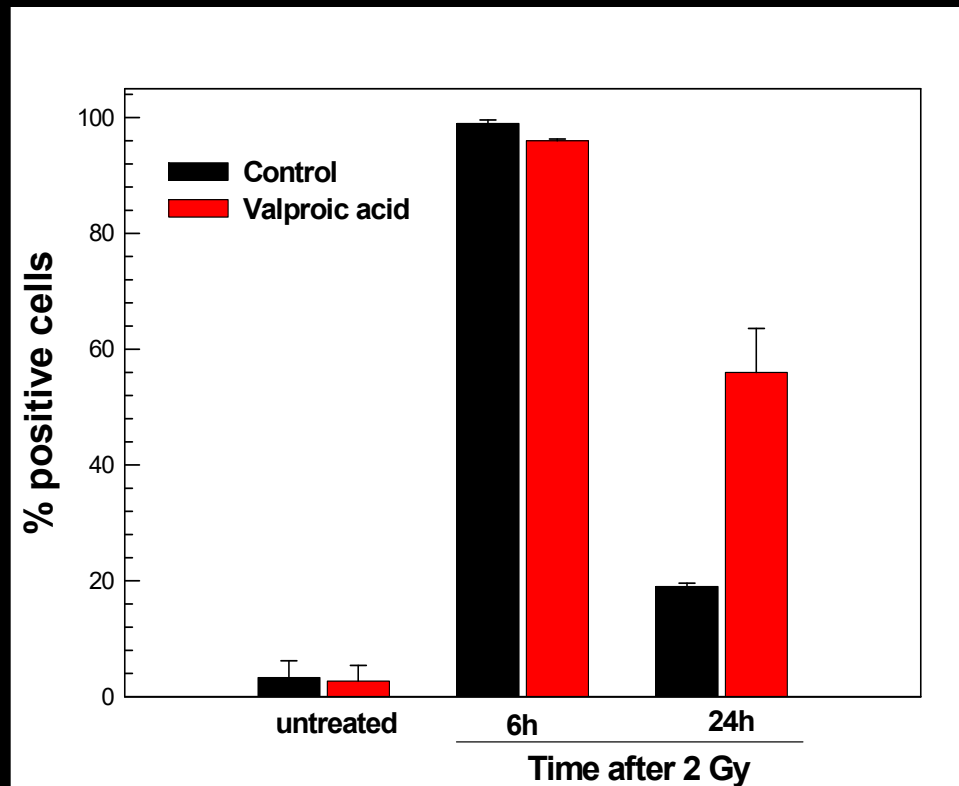
γ H2AX foci



untreated

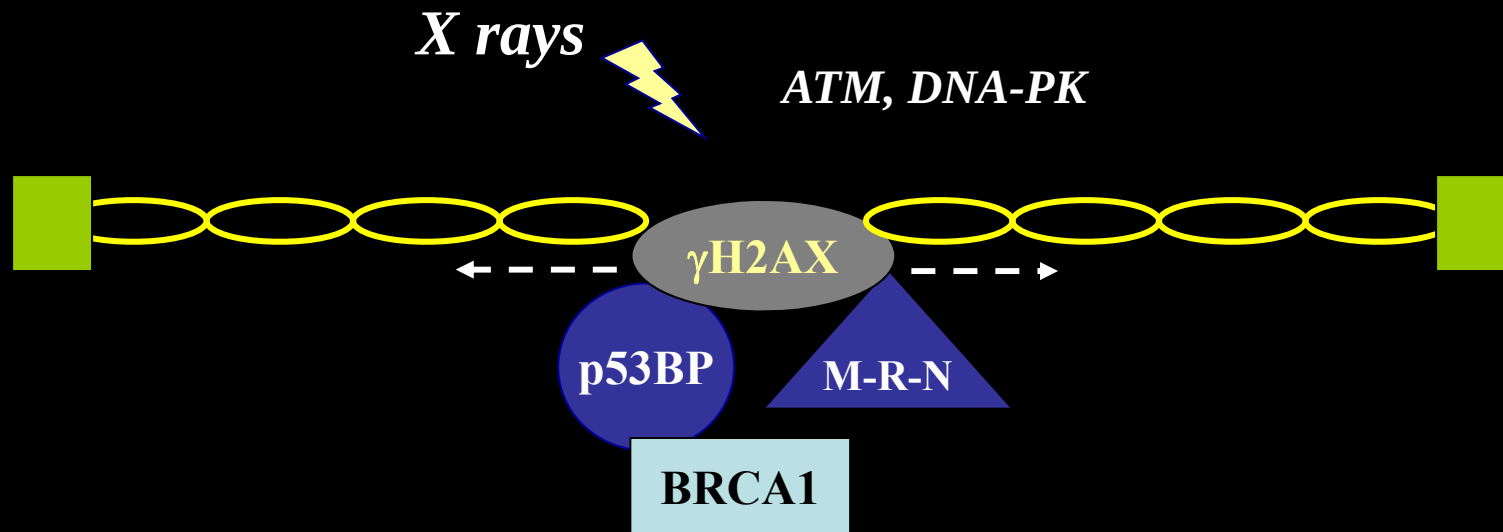


2 Gy/6h

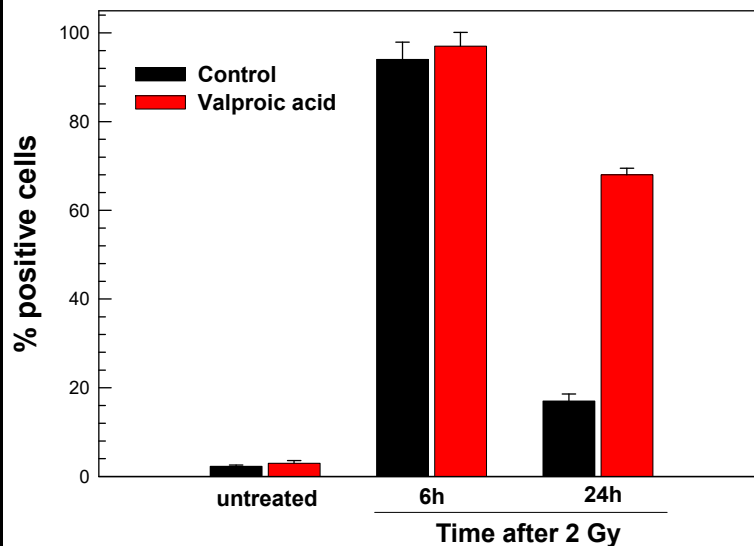


- No difference in foci induction at 6h
- Retention of foci at 24h
- No greater number of DSBs initially instead an accumulation of unrepaired DSBs

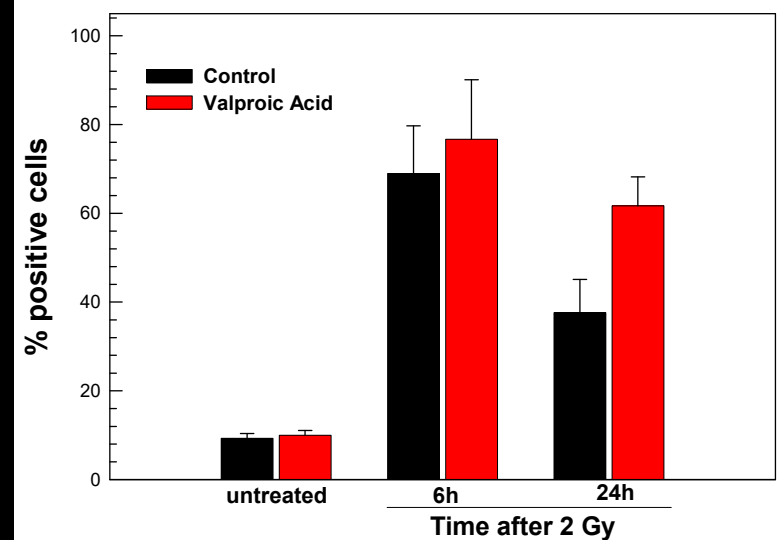
Mechanistic: Inhibition of Recruitment of Repair Molecules?



U251, p53BP1 foci, 2 Gy

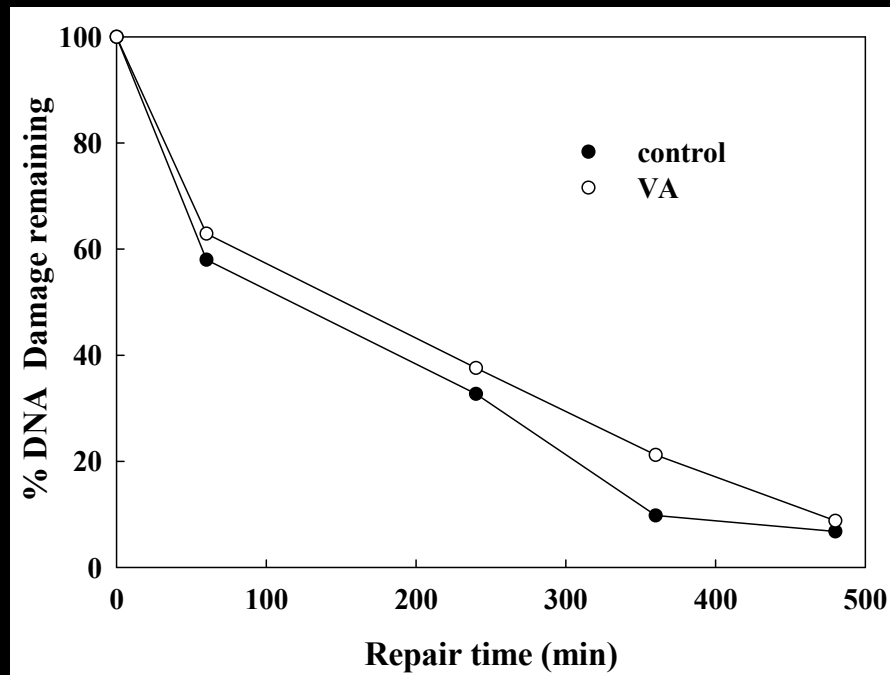


U251, BRCA1 foci, 2 Gy

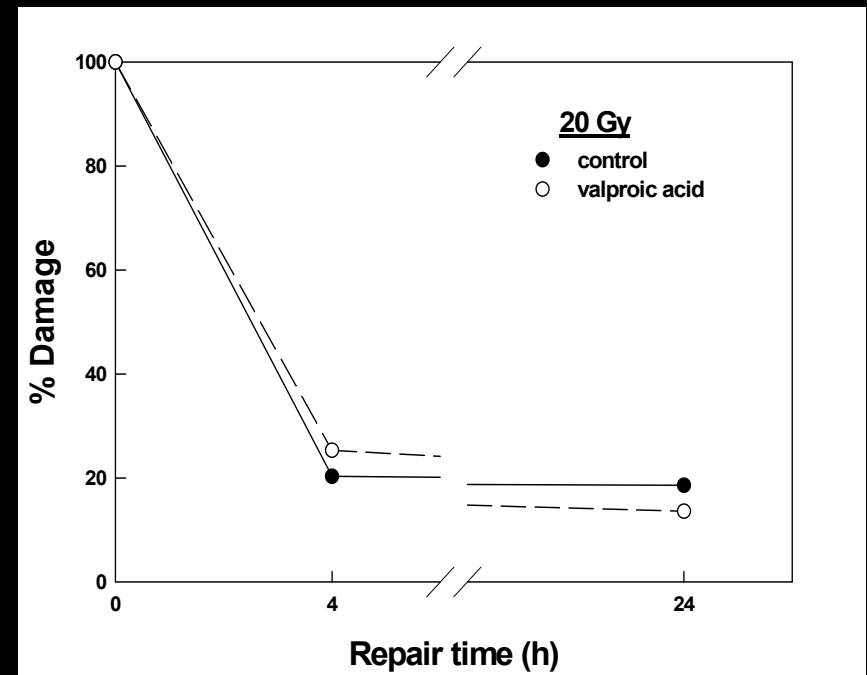


Valproic acid and DSB repair

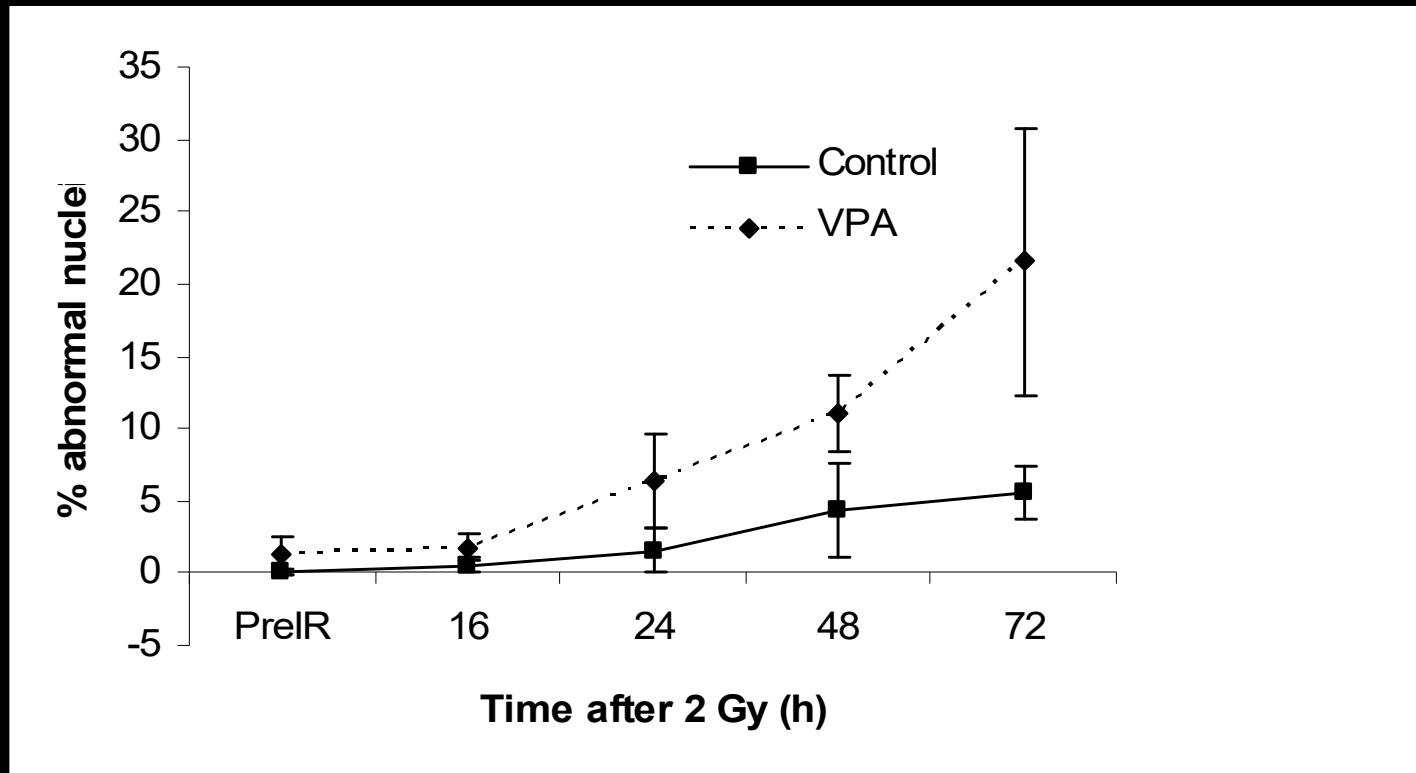
Neutral Comet (10Gy)



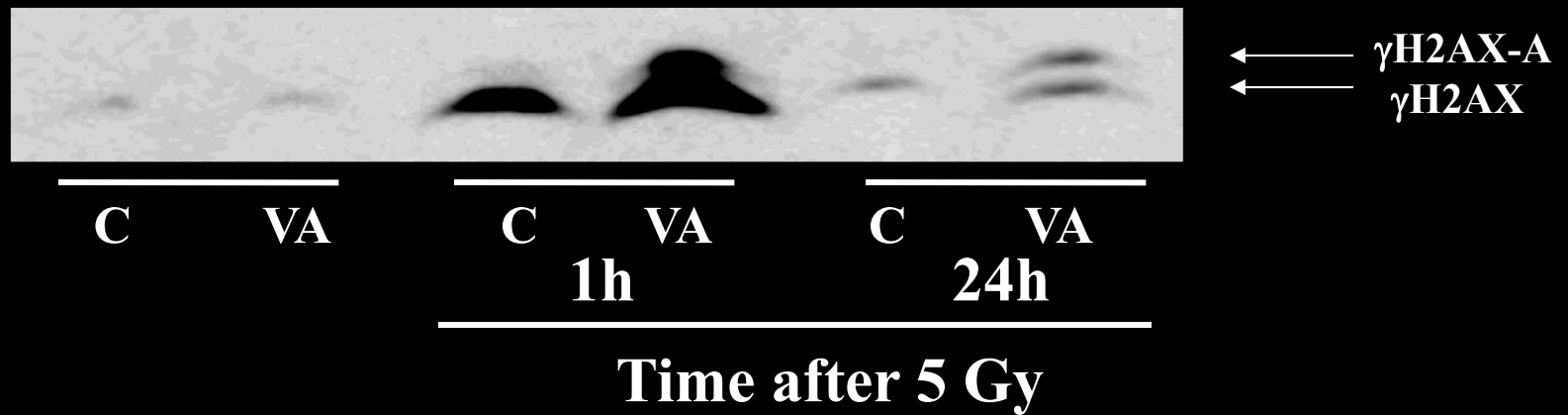
PFGE (20 Gy)



VA-induced Mitotic Catastrophe



HDACi and acetylated- γ H2AX



- “constitutive” acetylated γ H2AX
- VA increases acetylated γ H2AX
- retained γ H2AX is acetylated

HDACi Preclinical Conclusions

- prolongs expression of γ H2AX
 - other repair proteins
- acetylates γ H2AX therefore not dispersed
- no apparent effect on nucleic acid rejoining
- Inhibition of chromatin remodeling

Translation Bench to Bedside

NCI 05-C-
IRB Submission Date:

**A PHASE II CLINICAL TRIAL OF THE HISTONE DEACETYLASE
INHIBITOR VALPROIC ACID IN COMBINATION WITH TEMODAR AND
RADIATION THERAPY IN PATIENTS WITH HIGH GRADE GLIOMAS**

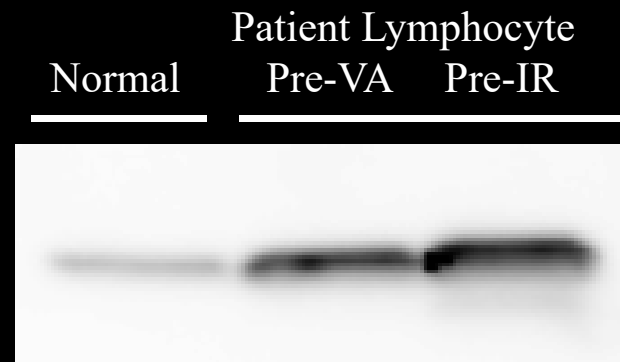
Principal Investigator: Kevin Camphausen, M.D.¹
Protocol Chairperson: Howard Fine, M.D.²
Associate Investigators: Anurag Singh, M.D., ROB
Shervin Karimpour, M.D., ROB
Edward Oldfield, M.D., S.N.³
John Park, M.D.³
Cheryl Royce, RN, NP²
Sharon Smith, RN¹
Linda Sciuto, RN¹

¹Radiation Oncology Sciences Program
Radiation Oncology Branch, NCI
Bldg. 10/ Rm. B3B69
10 Center Drive
Bethesda, MD 20892
Phone (301) 496-5457
Fax: (301) 480-5439

²NCI, NOB
³NINDS

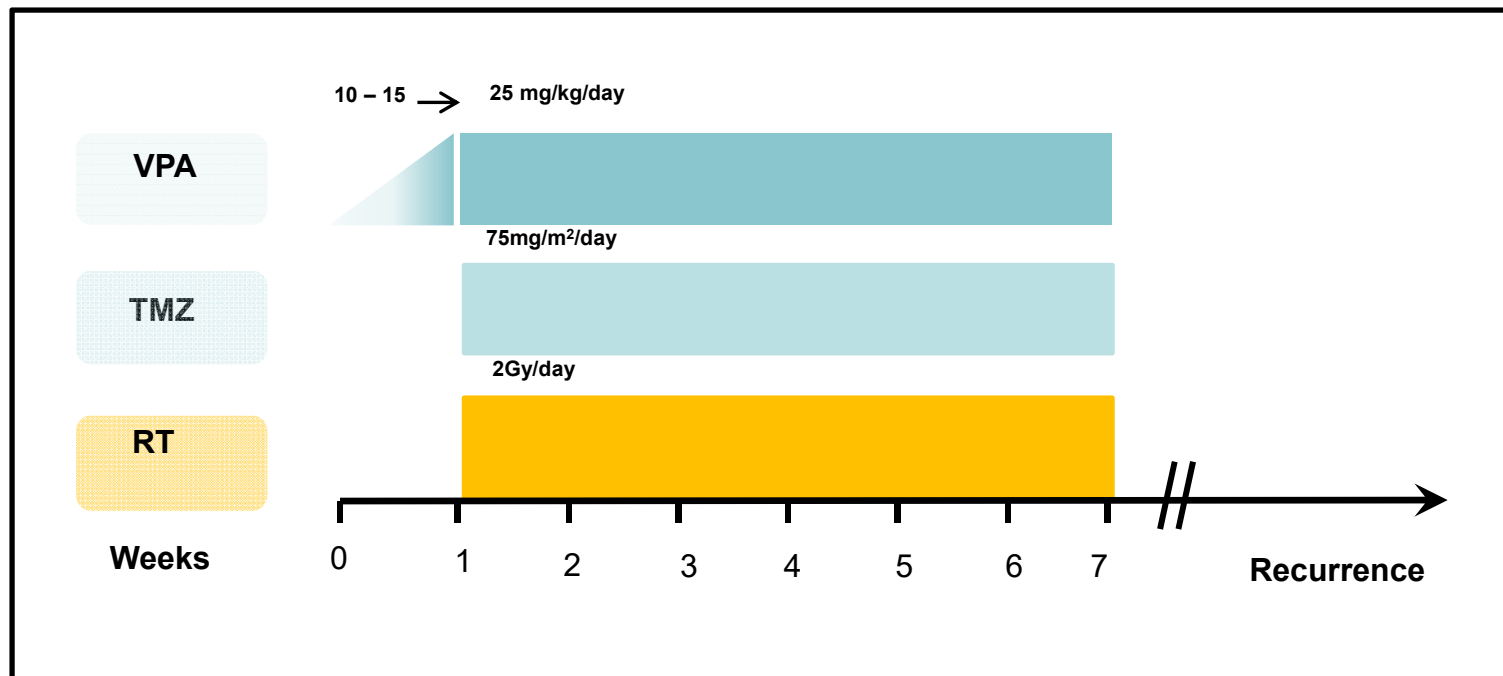
Complete

- Primary GBM
 - Temodar, 60Gy, VA
 - 6m Temodar
 - 41 pts.
 - Lymphocytes for acetyl-H4



Acetyl-H4

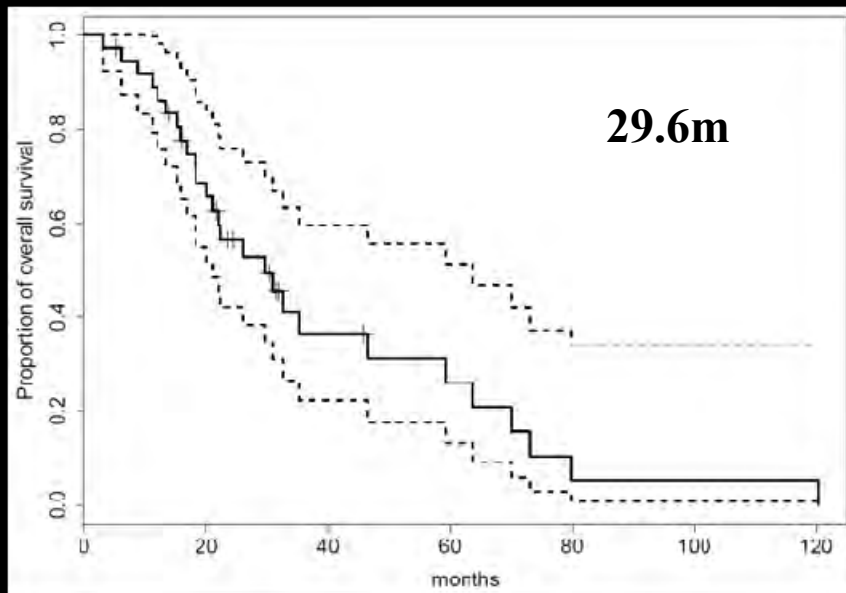
Trial Schema



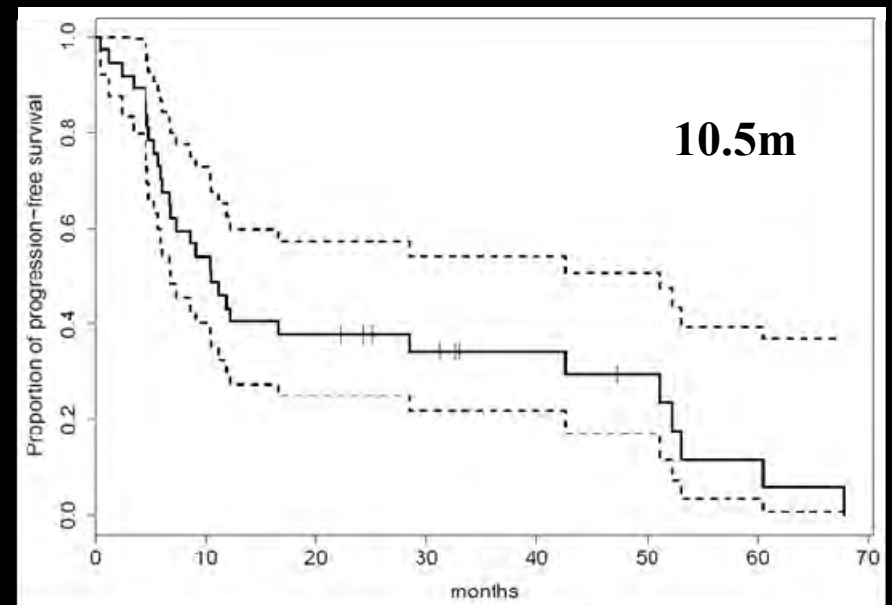
\$20/patient for VPA for total course

Valproic Acid Results

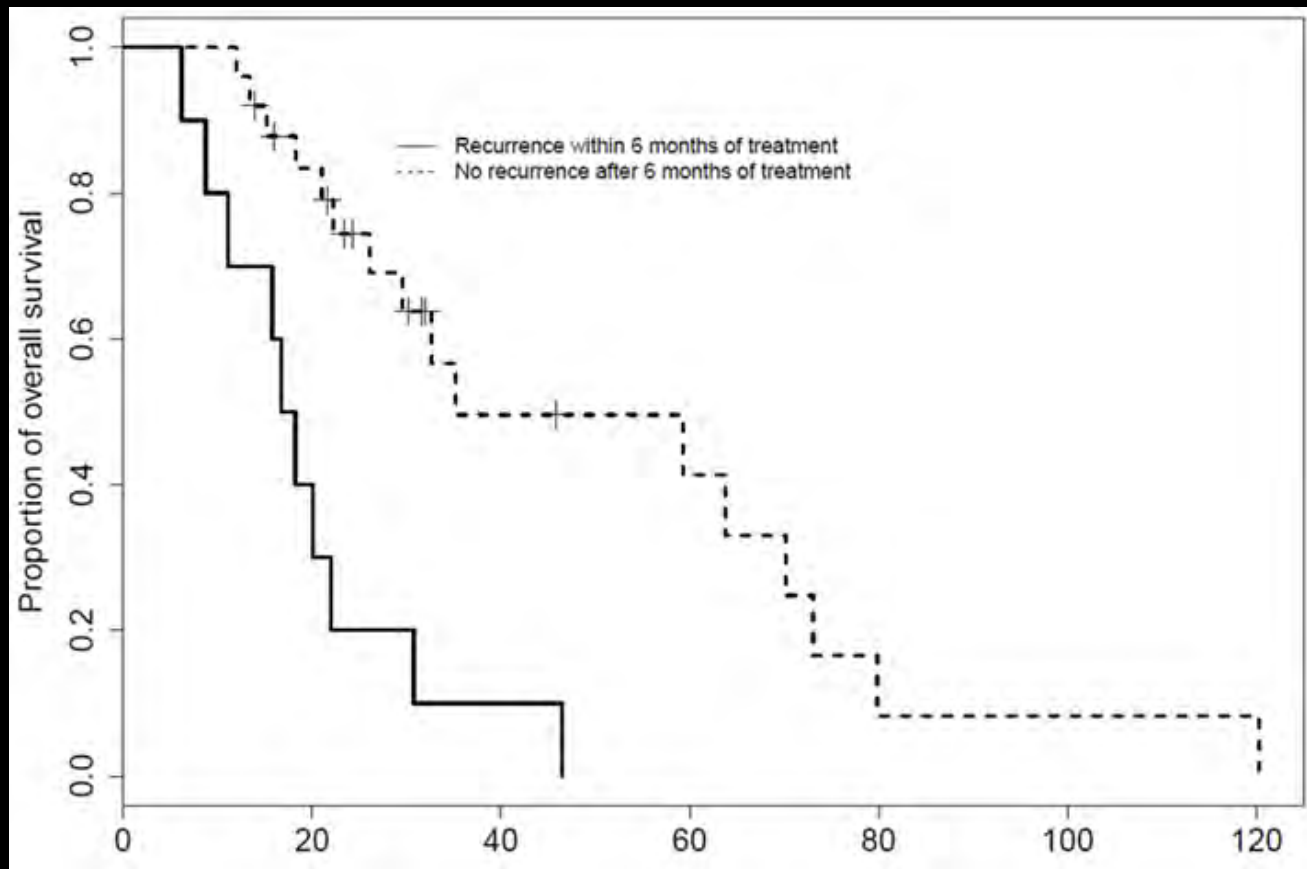
A



B

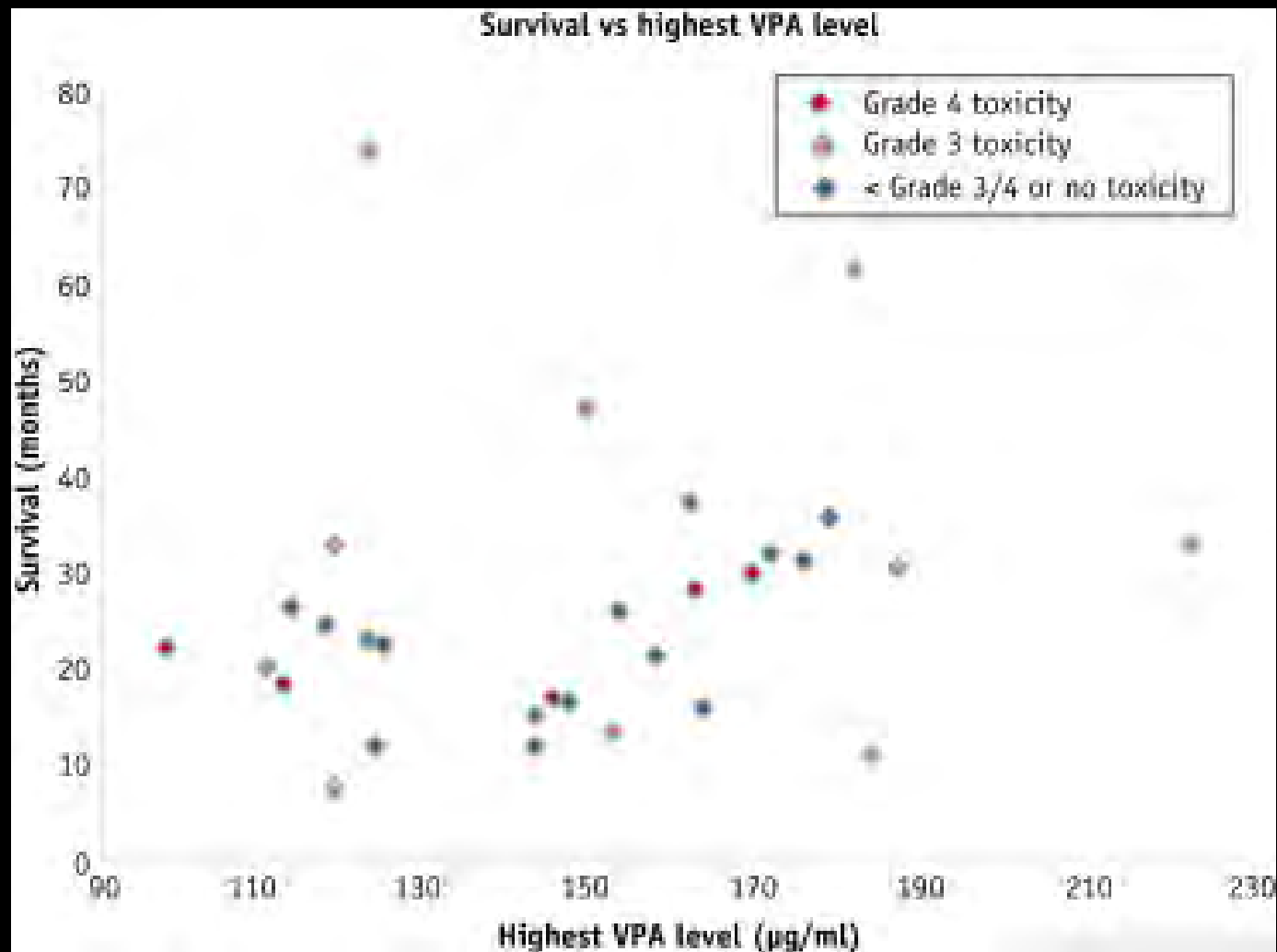


Kaplan-Meier analysis of (A) **overall survival** and (B) **progression-free survival**.
Dotted lines represent 95% confidence limits.



Landmark Analysis of time to progression versus overall survival: Kaplan-Meier survival estimate vs. timing of recurrence using landmark analysis setting the landmark time at 6 months. The survival difference based on the log-rank is highly significant ($p=0.0002$). The hazard ratio is 4.7.

VPA Toxicity



Problems with Study

- No TMZ in pre-clinical models
- MGMT status of pts unknown
- Accrual took too long
- Pts may have gotten Avastin
- No Genetic Sequencing
 - MGMT status
 - IDH status
- Drug no longer under patent
- Reviewers odd comments

Problems with Analysis

First Author	# of Patients	% Complete Study Drug	Grade 3 Toxicity	Grade 4 Toxicity	Grade 5 Toxicity	% delayed RT	6m PFS	median OS	Reference
Brown, P.	97	82%	105	24	2	-	-	15.3m	27
Peereboom, D.	28	74%	31	5	4	-	30%	8.6m	28
Prados, M.	66	-	43	5	-	-	73%	19.3m	29
Rosenfeld, M.	97	-	45	15	-	-	-	17.2m	30
Butowski, N.	66	-	66% grade 3/4		-	-	65%	16.5m	31
Chakravarti, A.	147	74%	122	31	1	-	40%	11.5m	32
Stupp, R.	64	85%	22	40	-	30%	-	-	33
Stupp, R.	287	85%	7% grade 3/4			32%	54%	14.6m	16
This Trial	37	67%	16	6		0%	70%	29.6m	Current Study

97%

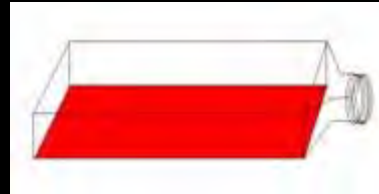
60%

Acknowledgments

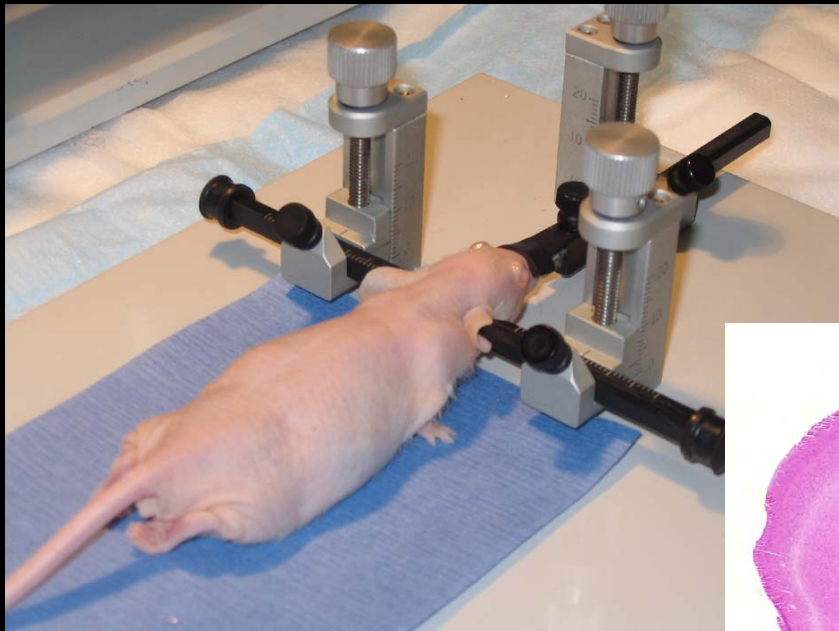
- Phil Tofilon
- Tamalee Kramp
- Mary Sproull
- Uma Shankavaram

Model Comparison: gene expression analysis

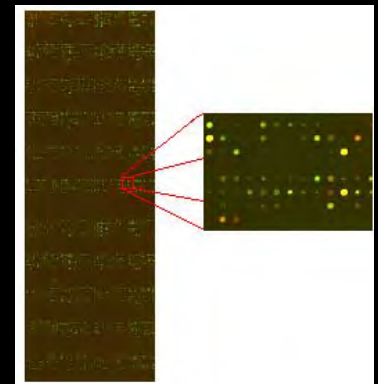
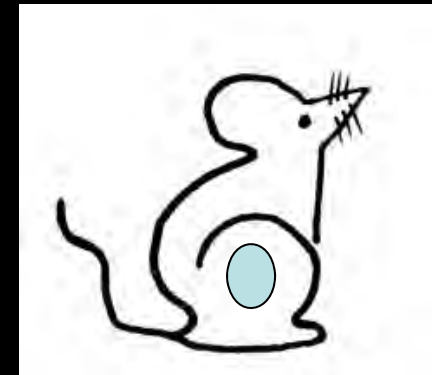
Tissue culture



Ic xenograft



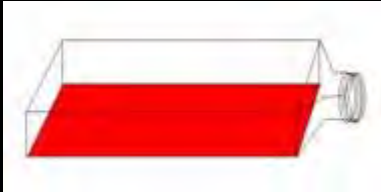
Sc xenograft



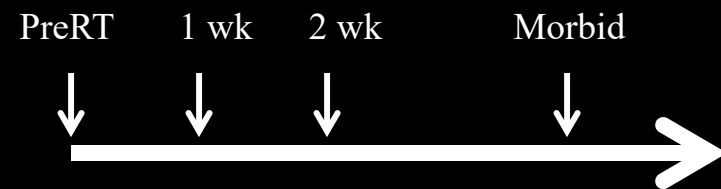
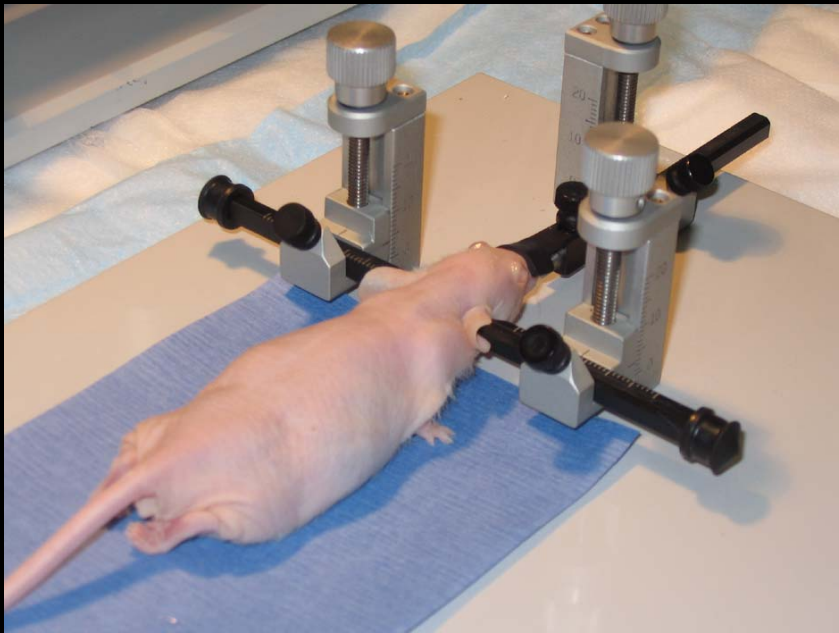
Current Experimental Design

- *Orthotopic* Implants
 - Luciferase imaging
 - MR imaging (DEMRI, c13 pyruvate)
 - Urine/Serum collection (biomarkers)
 - Tumor collection (omics)
 - Drug/RT combinations (survival benefit)
 - Imaging
 - Biomarkers
- Clinical Correlation

Preclinical GSC Biomarker



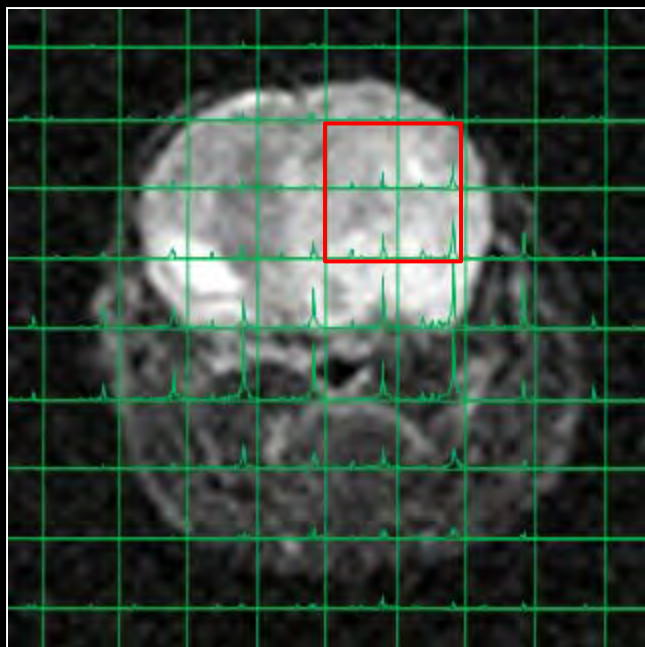
GSCs



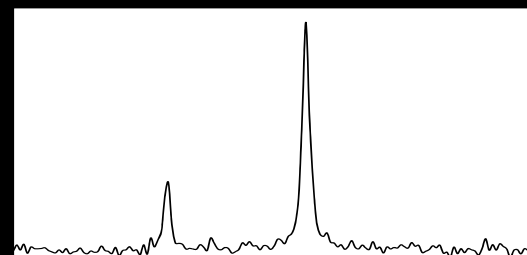
Collections:

- Plasma, serum, urine
- Imaging
- Tumor
 - Histology
 - Genomics
 - Proteomics
 - TMA production

Imaging GSC: NSC11

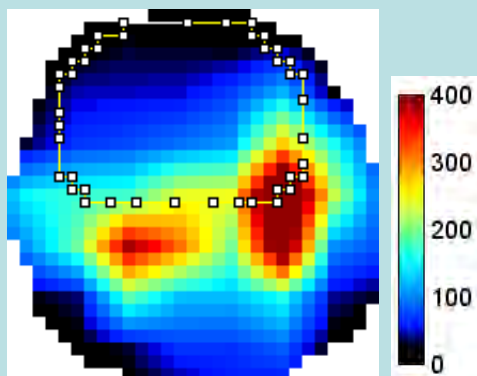


NCS11 ic hyper-polarized ^{13}C -pyruvate
7 T, Body coil
30 sec after injection
Voxel size: 2mm x 2mm x 8mm

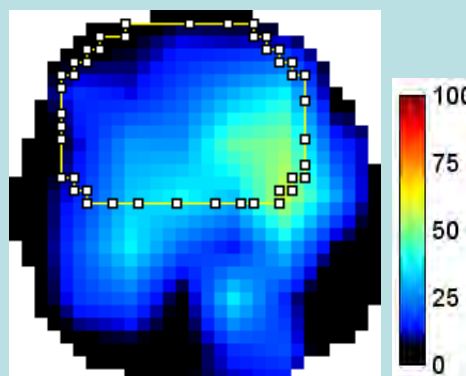


Total ^{13}C -pyruvate and ^{13}C -lactate in tumor (red 4 voxels)

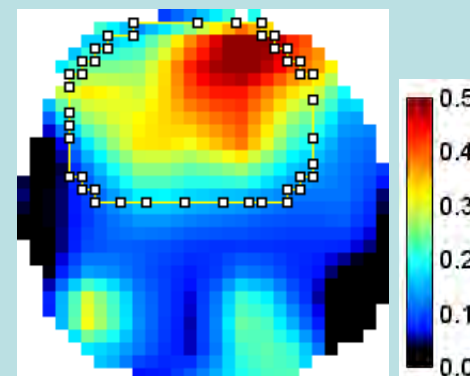
^{13}C -pyruvate map



^{13}C -lactate map



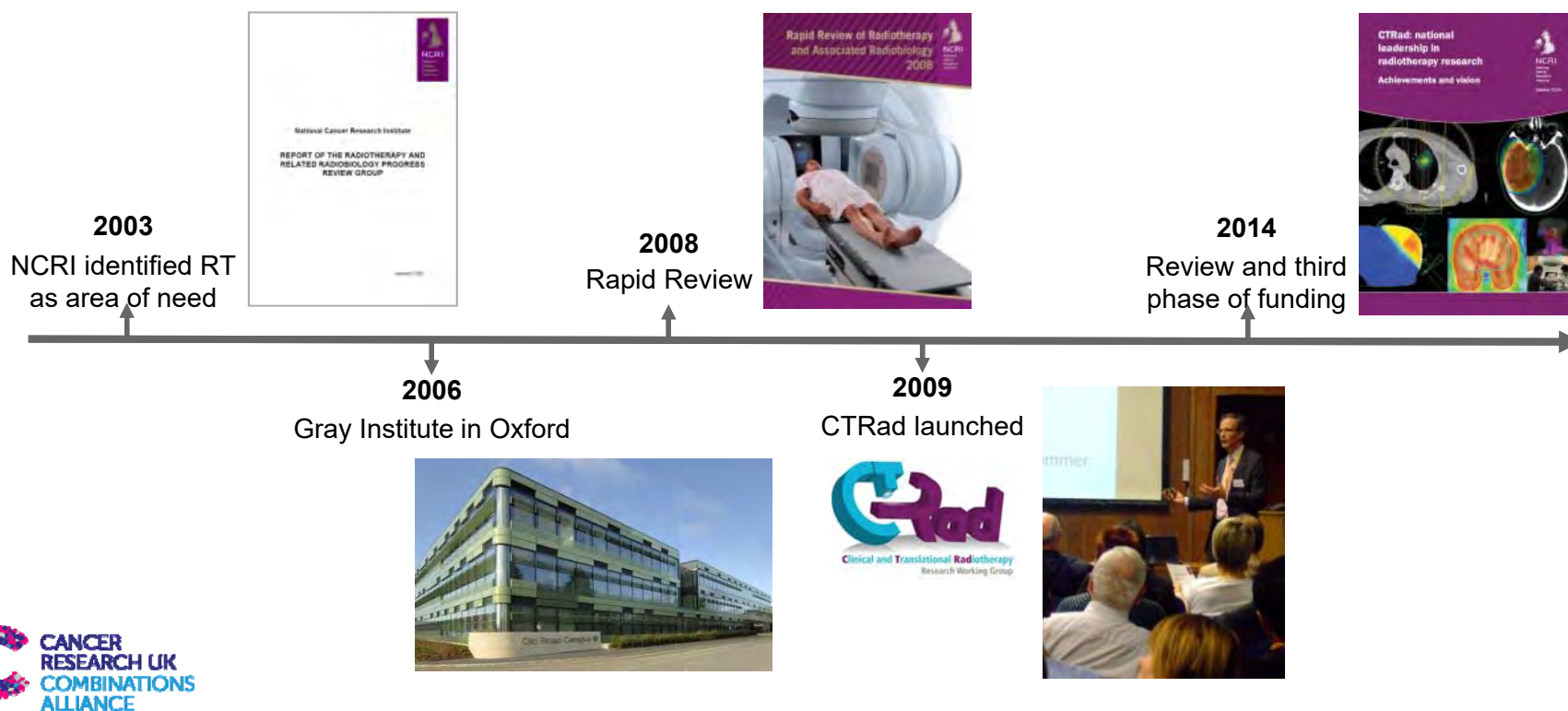
Lactate/Pyruvate map



Radiotherapy-Drug Combination Consortium



THE NEED FOR NATIONAL COORDINATION IN RADIOTHERAPY



CTRAD'S MISSION STATEMENT

To maximise quantity and quality of life for patients receiving radiotherapy
by optimising tumour control and minimising toxicity





CTRad Executive Group

Chair
Deputy Chair
Workstream co-chairs
Consumer representatives
Ex-officio members
NCRI Secretariat



Workstream 1 Science base

- Preclinical studies
- Radiation-drug interactions
- Radiobiology
- Biomarkers & imaging
- Physics & imaging

Workstream 2 Phase I/II trials

- Phase I/II studies
- Experimental Cancer Medicine
- Biomarkers & imaging
- Systemic therapies and RT

Workstream 3 Phase III trials and methodology

- Phase III trials
- Linking with CSGs
- Trials methodology development for evaluating novel RT approaches

Workstream 4 New Technology, Physics, QA

- New technologies (e.g. proton therapy, SABR, functional imaging)
- Quality assurance
- Radiotherapy Physics
- Databases



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RaDCom

Workstream 1 Science base

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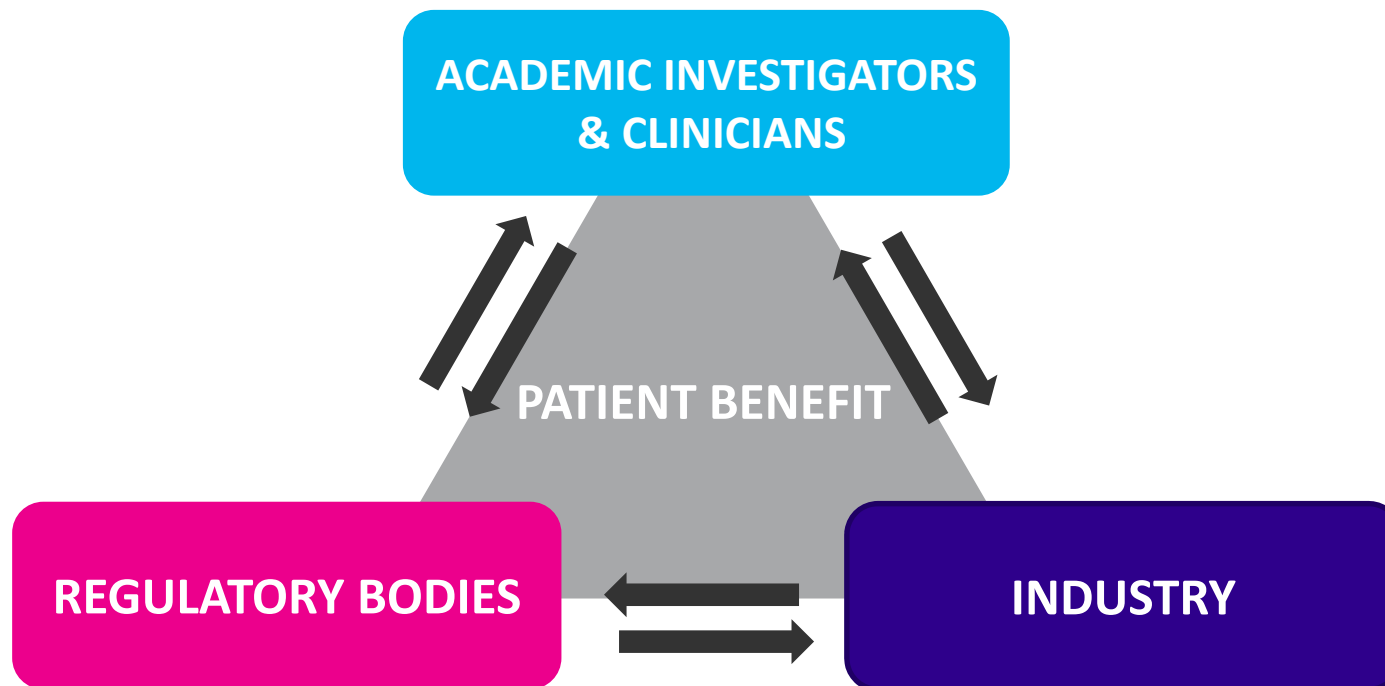
Workstream 3 Phase III trials and methodology

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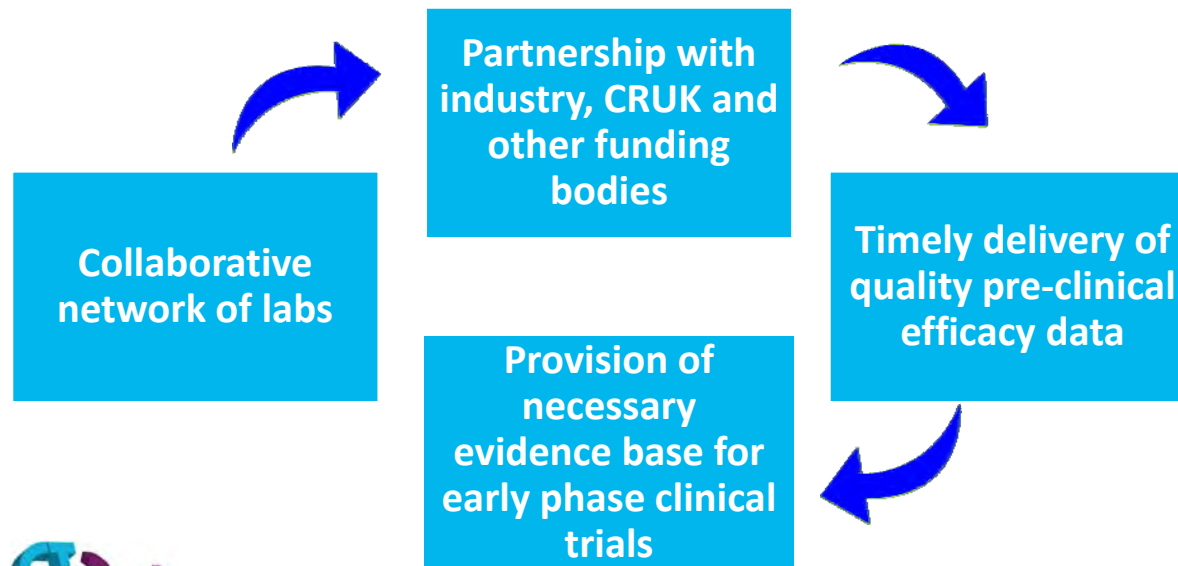
- New technologies (e.g. proton therapy, SABR, functional imaging)
- Quality assurance
- Radiotherapy Physics
- Databases

STAKEHOLDERS FOR NEW DRUG-RT COMBINATIONS



RADIOTHERAPY – DRUG COMBINATIONS CONSORTIUM **(RaDCom)**

Established 2013, developed by CTRad, CRUK Drug Development Office with support from the ECMC Programme Office

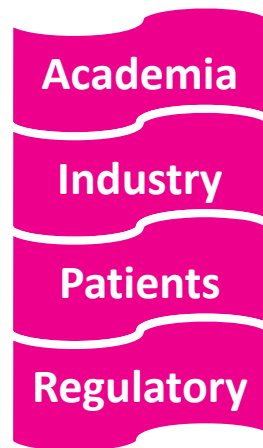


Pharma challenges:

- Route to clinic perceived as long and complex
- Differentiation and prioritisation of agents within same class to specific disease types
- Need for therapeutic index assessment
- Models for assessing immune targeting



“ROUTE TO REGISTRATION” WORKING GROUP (led by Ricky Sharma)



CONSENSUS STATEMENT

OPEN

Clinical development of new drug–radiotherapy combinations

Ricky A. Sharma¹, Ruth Plummer², Julie K. Stock³, Tessa A. Greenhalgh⁴, Ozlem Ataman⁵, Stephen Kelly⁶, Robert Clay⁷, Richard A. Adams⁸, Richard D. Baird⁹, Lucinda Billingham¹⁰, Sarah R. Brown¹¹, Sean Buckland⁶, Helen Bulbeck¹², Anthony J. Chalmers¹³, Glen Clack¹⁴, Aaron N. Cranston¹⁵, Lars Damstrup¹⁶, Roberta Ferraldeschi¹⁷, Martin D. Forster¹, Julian Golec¹⁸, Russell M. Hagan¹⁹, Emma Hall²⁰, Axel-R. Hanauske²¹, Kevin J. Harrington²⁰, Tom Haswell¹², Maria A. Hawkins⁴, Tim Illidge²², Hazel Jones³, Andrew S. Kennedy²³, Fiona McDonald²⁰, Thorsten Melcher²⁴, James P. B. O'Connor²², John R. Pollard¹⁸, Mark P. Saunders²², David Sebag-Montefiore¹¹, Melanie Smitt²⁵, John Staffurth⁸, Ian J. Stratford²² and Stephen R. Wedge² on behalf of the NCRI CTRad Academia-Pharma Joint Working Group

Written by **Working Group:**

- 22 members from Pharma
- 15 members from academia
- 3 other

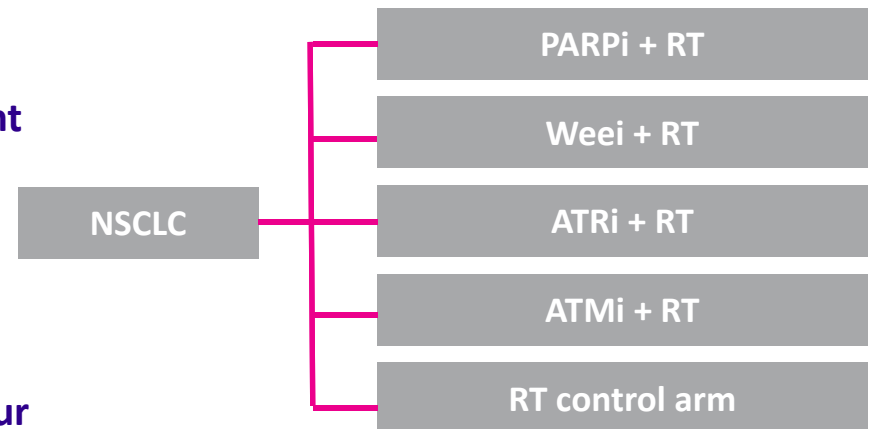
Open-access, publication coincided with ASCO

Published in Nature Reviews Clinical Oncology: June 2016

Eminence-based consensus recommendations, presenting a balanced review of the field

Multi-centre multi-arm platform studies: CONCORDE

- Continuous and rapid recruitment of patients to the different arms, greater efficiency than multiple phase I studies.
- TITE-CRM (time-to-event continuous reassessment model) statistical design: accelerates recruitment and dose escalation, with incorporation of subacute and late radiation effects into decision making.
- Radiotherapy protocol with clearly defined tumour and normal tissue dose constraints: ensure that radiosensitising effects of DDRi accurately measured.



Harrow S, et al., The Challenges Faced in Developing Novel Drug Radiation Combinations in Non-small Cell Lung Cancer, Clinical Oncology (2016), <http://dx.doi.org/10.1016/j.clon.2016.08.004>

Disease site specific reviews

- Highlighting areas of unmet need and opportunity
- Resource is enhanced by trial design expertise from clinicians with proven track records in the development and delivery of early phase clinical studies of RT-drug combinations

Considerations: tumour-site dependent signalling pathways, mutations that may favour specific targeted therapy, RT requirements



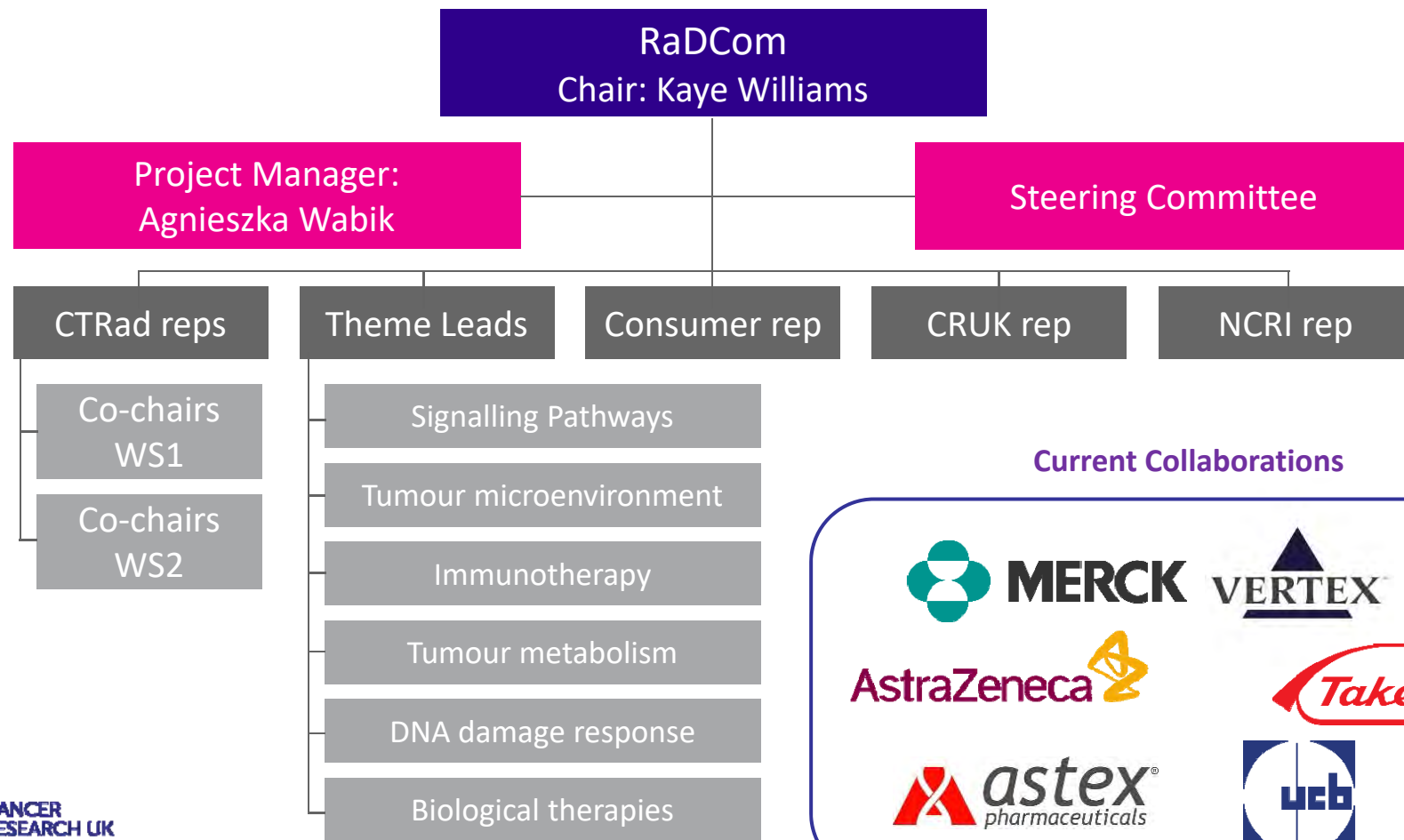
UK WIDE PRECLINICAL RADIOTHERAPY CAPABILITY AND FACILITY MAPS

- Create a database of preclinical models and facilities for radiotherapy and radiobiology research (including both in vitro and in vivo models)
- **enables immediate identification of groups and centres that, working together, could deliver high quality pre-clinical studies**

Why?

- Expand studies to broader range of tumour types, including immune competent
- Incorporate normal tissue expertise for evaluation of therapeutic index
- Promote collaboration within RT community
- Contribute to improving RT quality assurance by working with National Physics Lab





Current Collaborations



RaDCom Steering Committee

Chair: **Prof Kaye Williams** (Manchester)

Clinical Deputy Chairs: **Prof Tim Illidge*** (Manchester) and **Prof Ricky Sharma*** (UCL)

Workstream 1 Co-chairs: **Prof Susan Short*** (Leeds) and **Prof Nicola Curtin** (Newcastle)

Workstream 2 Co-chairs: **Prof Ricky Sharma*** (Oxford) and **Dr Richard Adams*** (Cardiff)

Theme Leads:

DNA damage response:

Prof Anthony Chalmers* (Glasgow)

Signalling pathways:

Dr Andy Ryan (Oxford)

Tumour microenvironment:

Prof Kaye Williams (Manchester)

Tumour metabolism:

Prof Ian Stratford (Manchester)

Immunotherapy:

Prof Tim Illidge* (Manchester)

Biological therapies:

Prof Kevin Harrington* (ICR)/ **Prof Susan Short*** (Leeds)

Patient representatives:

Dr Helen Bulbeck / Mr Tom Haswell

Additional WS2 members:

Prof Ruth Plummer* (Newcastle) / **Dr Geoff Higgins*** (Oxford)

RaDCom Project Manager:

Dr Agnieszka Wabik



RaDCom PORTFOLIO

PRECLINICAL PROJECTS

16

PHARMA COMPANIES

11

INVESTIGATORS

18

INSTITUTIONS

9

TARGETS TESTED

13

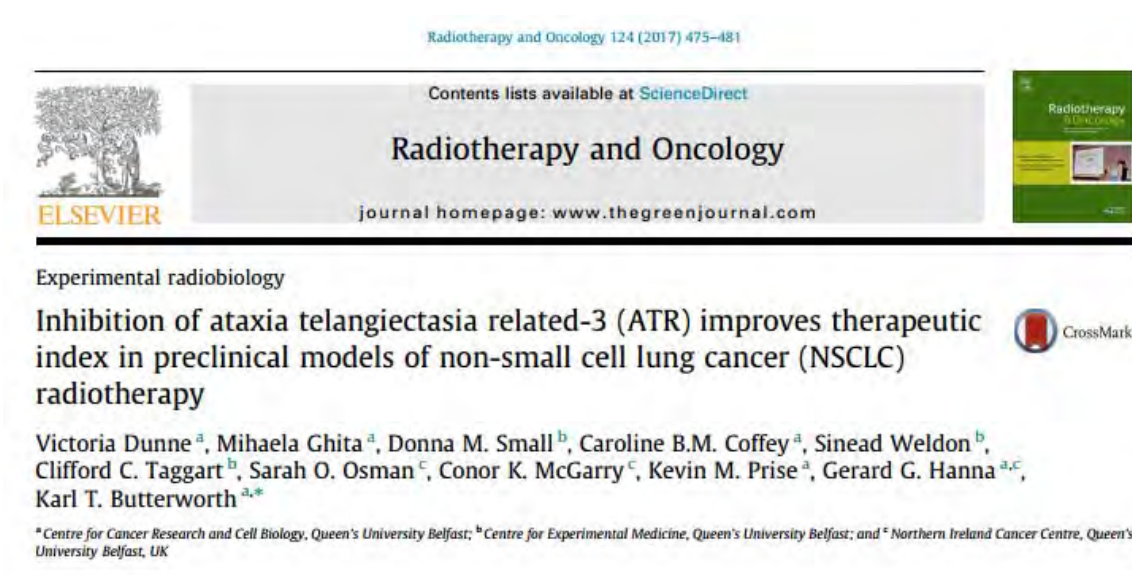
Projects include external beam and molecular radiotherapy and investigate tumour efficacy, normal tissue damage and radio-protection.



RaDCom portfolio: exemplars

Therapeutic index study to support CONCORDE

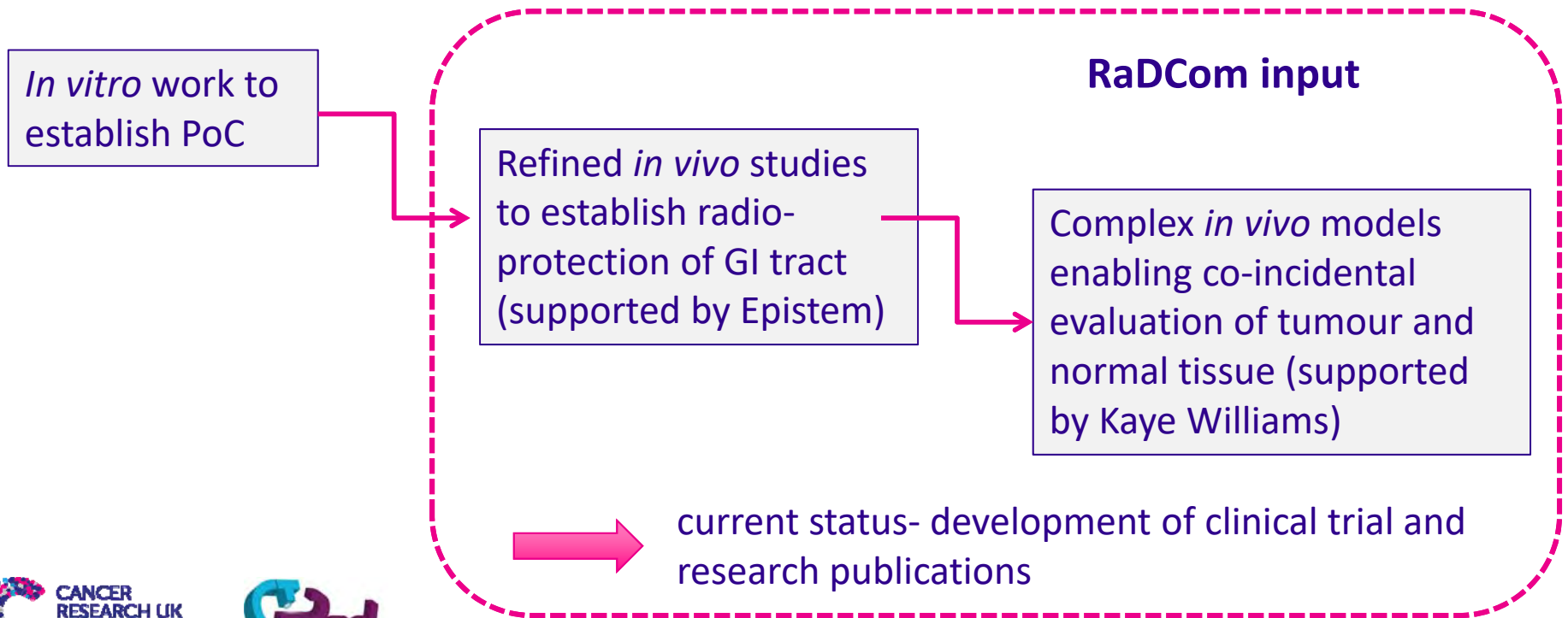
- Impact of RT + ATRi in NSCLC and normal tissue models *in vitro* and *in vivo* (lead researcher, Dr Karl Butterworth, Belfast)



RaDCom portfolio: exemplars

Drug “repurposing” for radioprotection

- lead researcher, Dr Ilaria Bellantuono, Sheffield



FUNDING OPTIONS FOR PRECLINICAL STUDIES

Preclinical data to support RT-drug combinations

CRUK NAC Preclinical Combination funding stream

- 6-12 months, up to £50k
- Associated clinician and phase I outline
- Potential access to novel molecules via Combinations Alliance

MRC

Medical
Research
Council

Other funding
opportunities (including
CRUK partnering with
disease site charities)



CANCER
RESEARCH UK
COMBINATIONS
ALLIANCE



Clinical and Translational Radiotherapy
Research Working Group

WITH SUPPORT FROM

CANCER RESEARCH UK COMBINATIONS ALLIANCE

PARTNERING TO DRIVE NEW COMBINATION THERAPIES



RADIOTHERAPY-DRUG COMBINATIONS CONSORTIUM (RADCOM)

PROVIDING NECESSARY PRECLINICAL EVIDENCE FOR EARLY PHASE CLINICAL TRIALS



- RaDCom project manager contact: agnieszka.wabik@cancer.org.uk

Thank you



SESSION I Panel Discussion: Preclinical Considerations

Moderators:

C. Norman Coleman, MD, and Kaye J. Williams, PhD

Panelists:

Özlem Ataman, MD, PhD
Melinda Merchant, MD, PhD
Paul M. Harari, MD
Tim M. Illidge, MD, PhD
Kevin A. Camphausen, MD
Todd R. Palmby, PhD

SESSION I: Discussion Questions

- What is the minimum needed for preclinical data so that a committee will pass it along to a study and FDA will accept that as sufficient?
- What good are the models for prediction and need they be efficacy and toxicity?
- What data would you want to see before you would ask a person to join a clinical trial?



SESSION IIA: Clinical Considerations

Session Cochairs: Fei-Fei Liu, MD, and Ricky Sharma, MD, PhD

Speakers:

Andrew B. Sharabi, MD, PhD

Jessica Lowenstein, MS

Fei-Fei Liu, MD

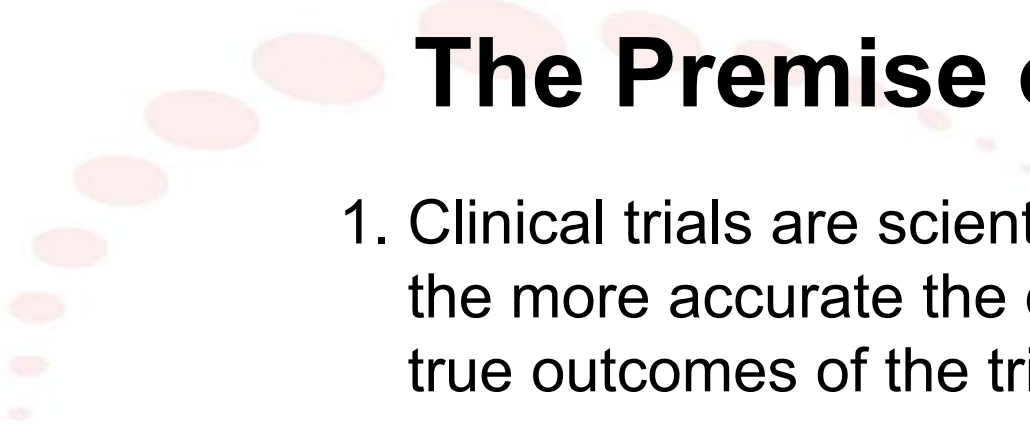
Tatiana M. Prowell, MD



Radiation Therapy Quality Assurance in Clinical Trials: Why and How



Jessica Lowenstein
Assoc. Director of IROC - Houston
February 22, 2018



The Premise of my Talk

1. Clinical trials are scientific research where the more accurate the data, the clearer the true outcomes of the trial can be determined.
2. It is not acceptable to permit mediocre patient care. We should all strive to do better.
3. Radiation Oncology is based on the physical sciences and as such is quantifiable.

Single Institution vs. Multi-institution

The inclusion of trial data from many institutions increases variability in the delivery of a therapeutic radiation dose regardless of the protocol specifications.

1. contouring targets and healthy tissue
2. different dose calculation algorithms
3. different delivery machines
4. human interpretation and errors, etc.

Best example: RTOG 0617 std dose vs higher dose in the lung
single inst – higher dose better survival
multi institution – lower dose better survival

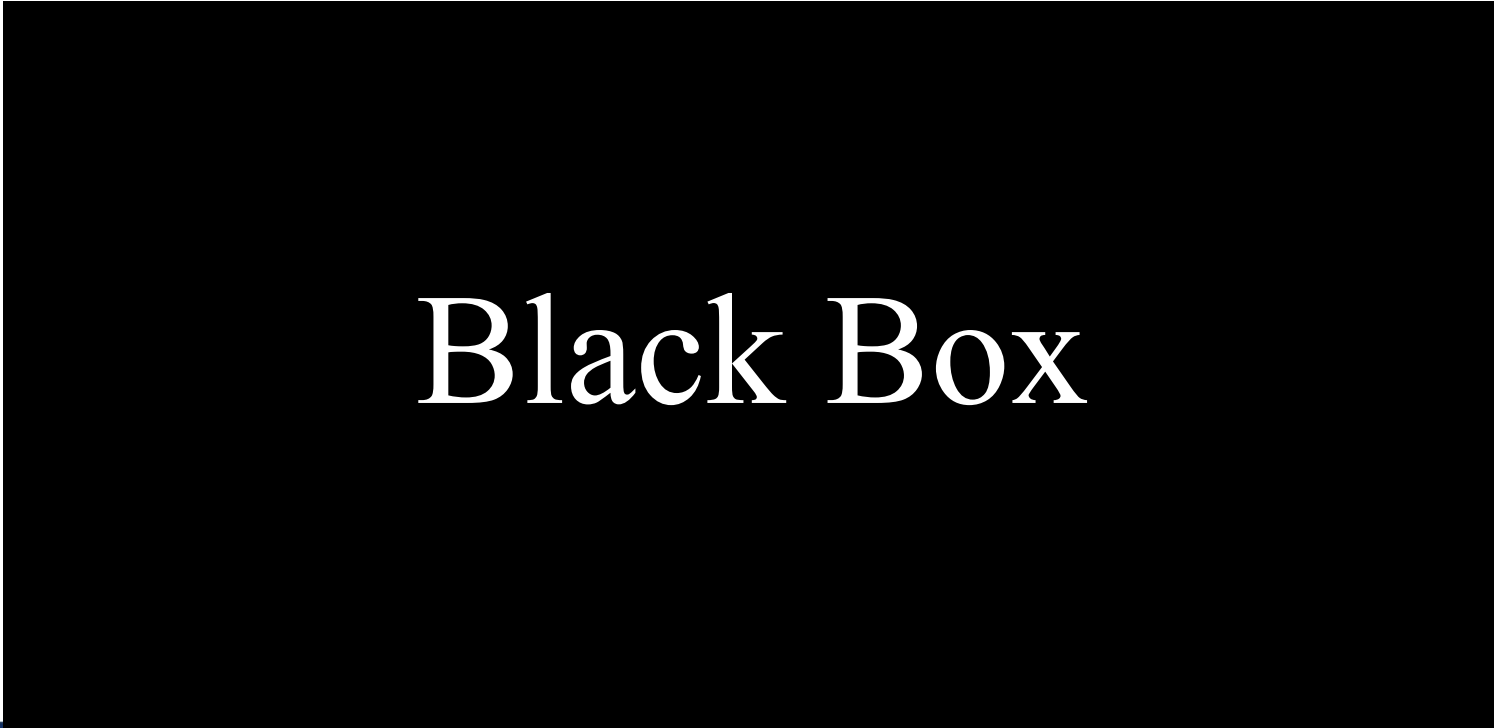
There's a need for consistency that QA can bring.

Quality in Radiation Oncology

- Radiation Oncology is versatile, complicated and important for many patients
- Intuitively, quality is very important
 - deliver the correct dose to the correct place
- Achieving optimal quality can be challenging as complexity increases
- Yet in Radiation Oncology we can quantify the delivery and its quality

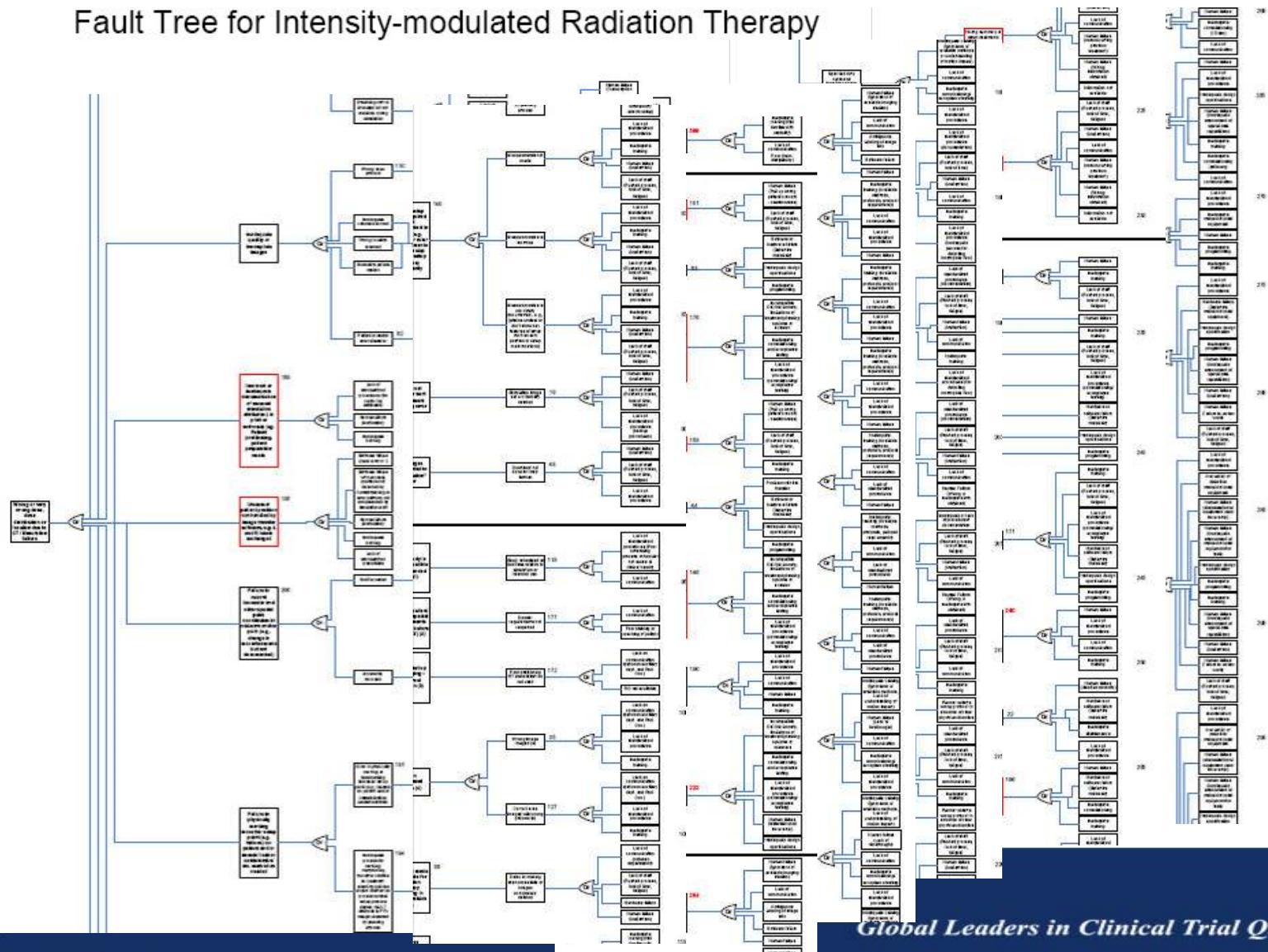


Imaging, Planning and Delivery - QA required at each step



Black Box

Fault Tree for Intensity-modulated Radiation Therapy



What accuracy is necessary?

- What is the right dose?
 - ICRU Report 24 (1976)
 - “...the available evidence... points to the need for an accuracy of +/- 5% in the deliver of an absorbed dose to a target volume if the eradication of the primary tumor is sought.”
 - Biological variability in an endpoint is <5%

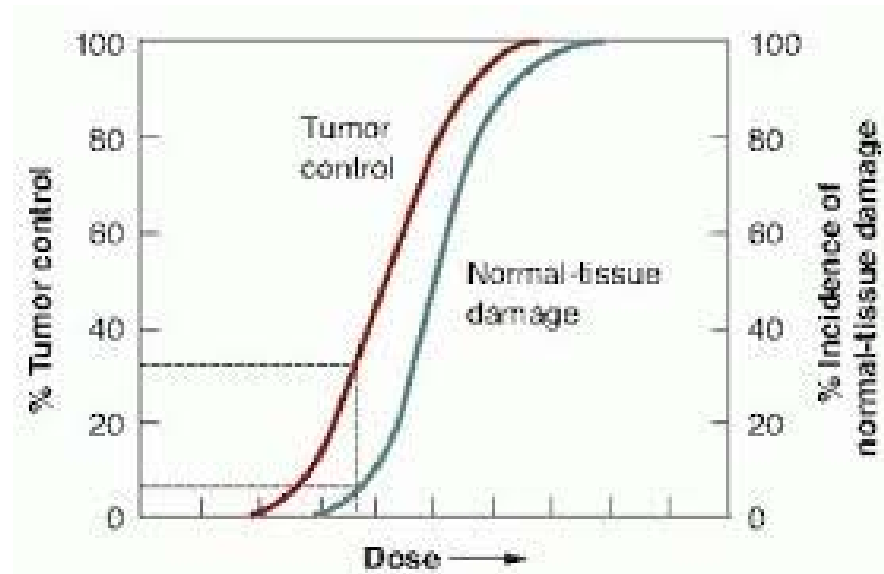
Further evidence:

- Tumor control: Randomized photon vs electron treatment
 - Same nominal dose, but significantly poorer tumor control with electrons
 - Turned out there was a 7%-low calibration error in the electrons
- Normal tissue complication: GYN reactions
 - Excessive GI and skin reactions observed
 - Investigation identified a 7-10%-high output calibration error
 - Other patients without dose delivery error did not develop skin reactions

Reported in Dutreix Radiother Oncol 1984

Dose response

- Variations make sense in terms of basic dose response biology
- Sensitivity depends on where we are on the dose response curve
 - if we are on the shoulder, not as sensitive
- Usually we're somewhere on the steep slope and therefore sensitive to dose variations

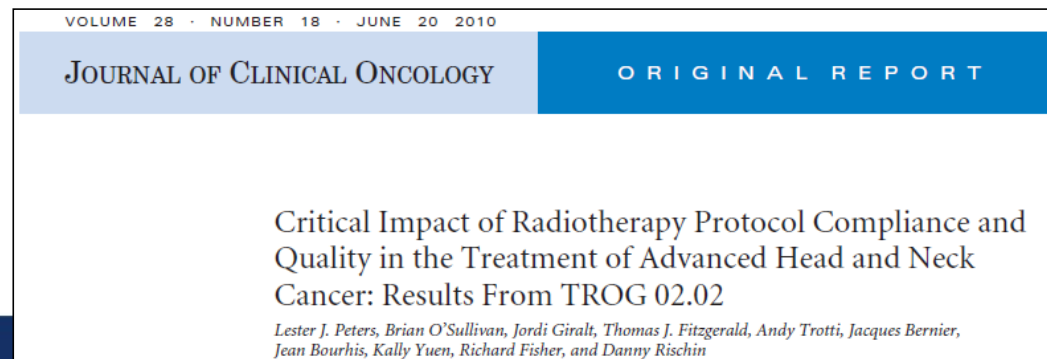


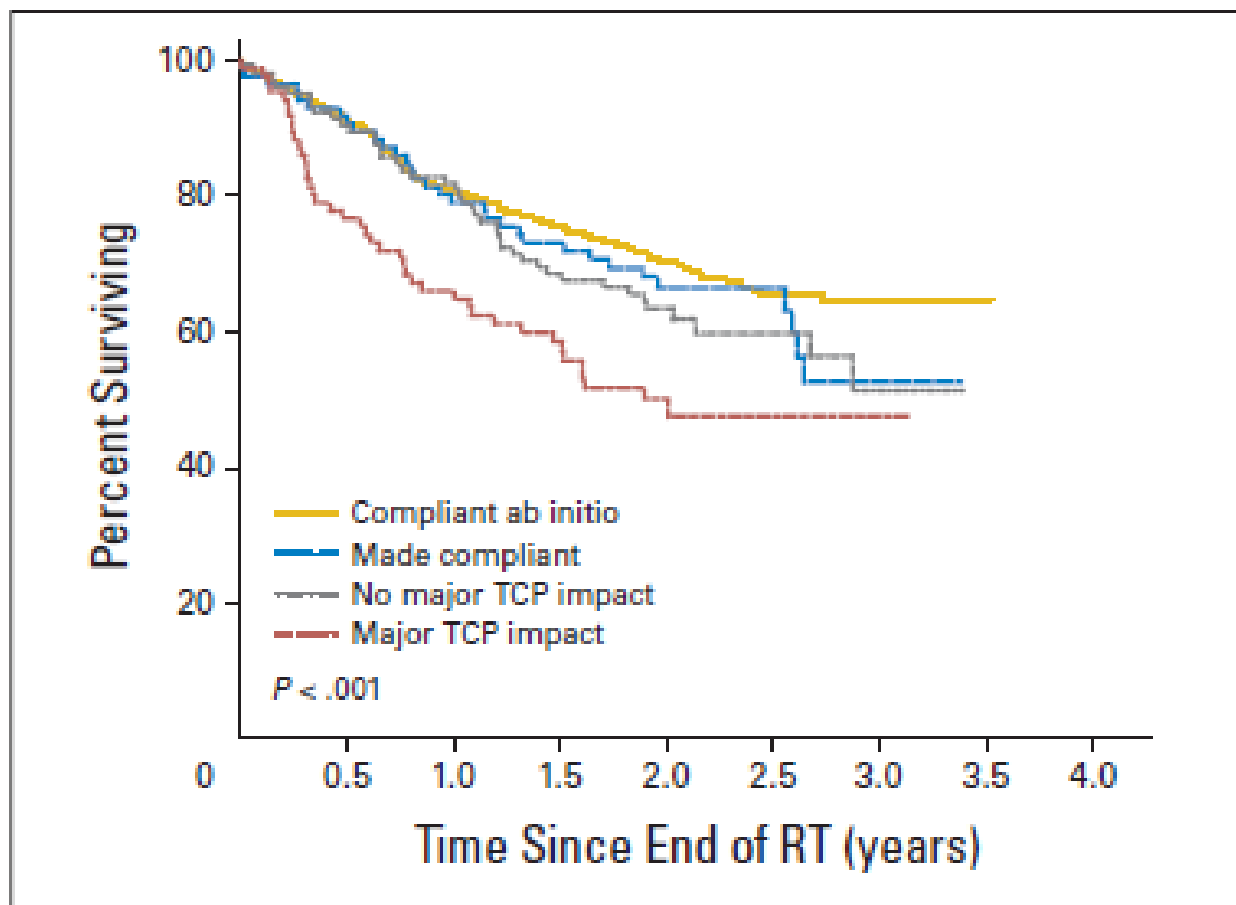
How important is good quality?

- Because of the steepness of the dose response curve, we need to be within 5%
- Previous slides showed observable effects from very specific conditions of dose variation
- What about the bigger question of how quality affects radiotherapy outcomes in contemporary RT?

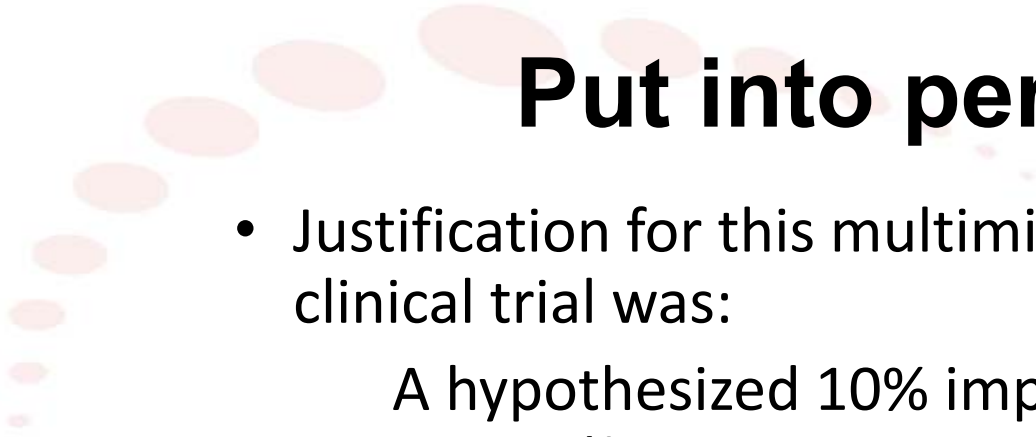
A contemporary example: TROG 02.02

- Cisplatin (CIS) vs Cisplatin + tirapazamine (TPZ)
- All patients: 70 Gy in 35 fx using a shrinking field technique
- Hypothesis: 10% improvement in 2 year overall survival
- 861 patients





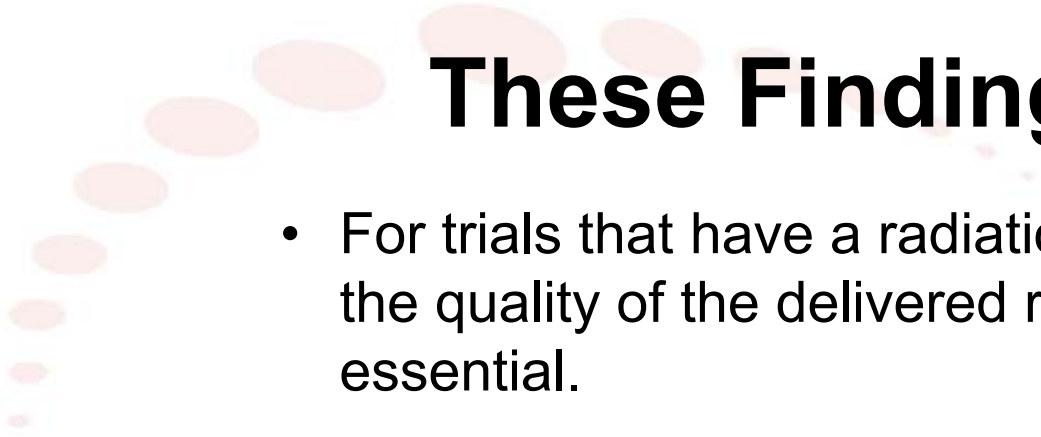
2 year overall survival: 70% vs 50%



Put into perspective

- Justification for this multimillion dollar phase 3 clinical trial was:
 - A hypothesized 10% improvement in 2 y overall survival!
- What we really learned retrospectively
 - A 20% difference in survival based on the quality of RT delivered!

The quality of RT is critical to patient survival

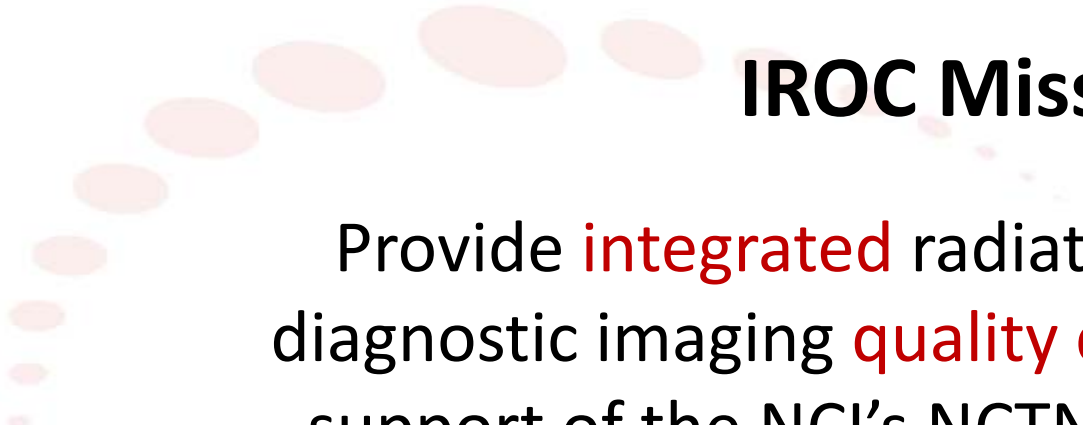


These Findings support

- For trials that have a radiation dose question or not, the quality of the delivered radiation therapy is essential.
- Variability in radiation therapy delivery creates uncertainty that can obscure true outcomes.
- Poor radiation therapy quality has been shown to result in poorer survival and complication outcomes

What do we hope to achieve with Quality Assurance and Peer Review?

- Improve the accuracy of dose delivery to the intended location
- Compliance with protocol specifications
- Ensure the best possible treatment for our patients
- Improve outcomes from clinical trials
- Avoid errors and enhance patient safety
- Learn from our mistakes



IROC Mission

Provide **integrated** radiation oncology and diagnostic imaging **quality control programs** in support of the NCI's NCTN Network thereby **assuring high quality data** for clinical trials designed to improve the clinical outcomes for cancer patients worldwide

IROC-H Dose Verification Program

Reference calibration
(NIST traceable)

Evaluated by
IROC Dosimeters

×

Correction Factors:
Field size & shape
Depth of target
Transmission factors
Treatment time

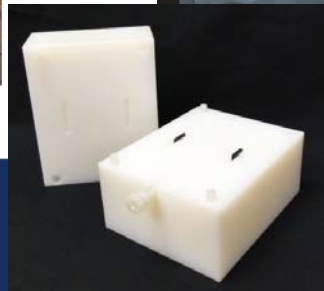
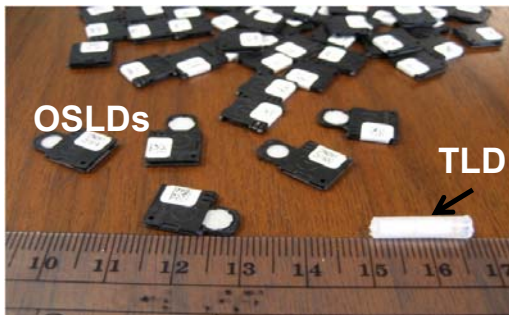
Evaluated by
IROC visits and
chart review

Tumor Dose

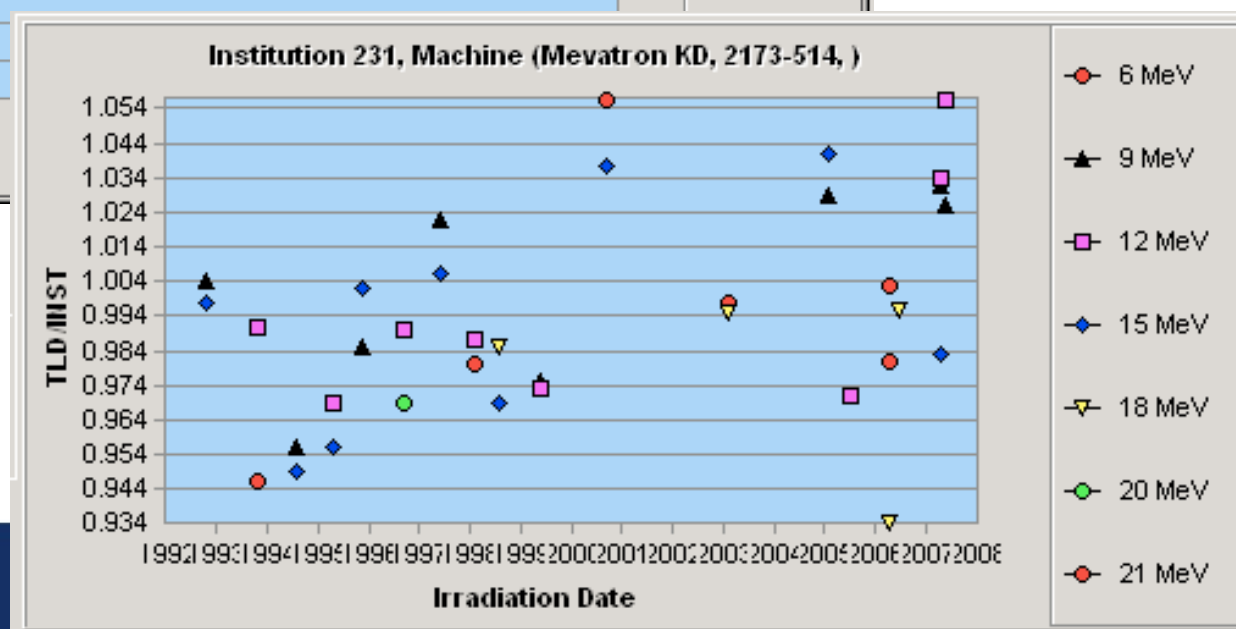
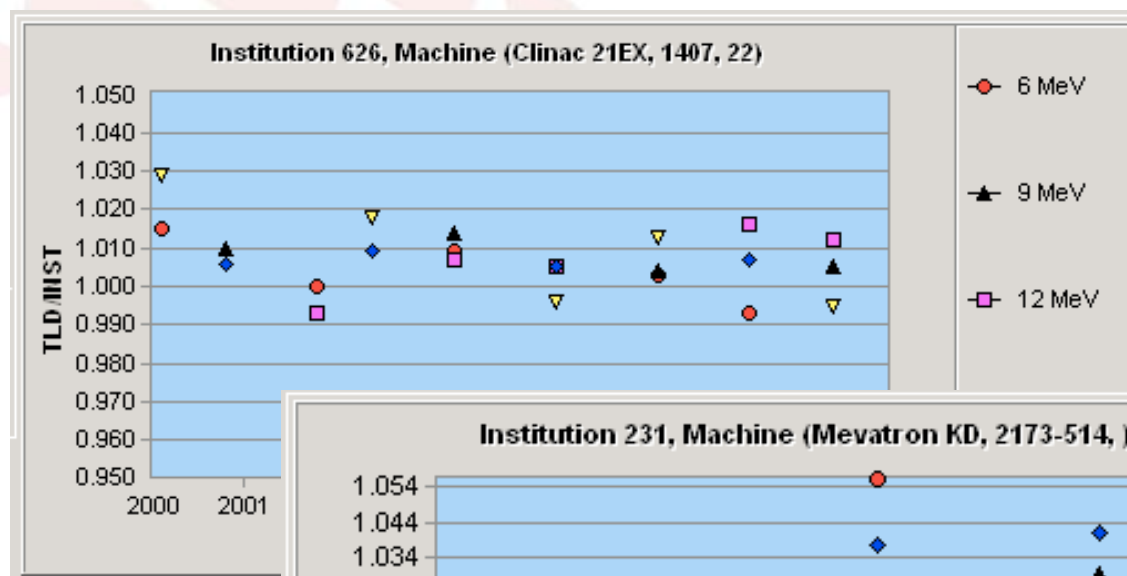
Evaluated by
IROC phantoms

Remote Audits of Machine Output

- Verification of Reference Calibration for photon and electron beams
- Units of special design
(Gamma Knife, CyberKnife, Tomotherapy)



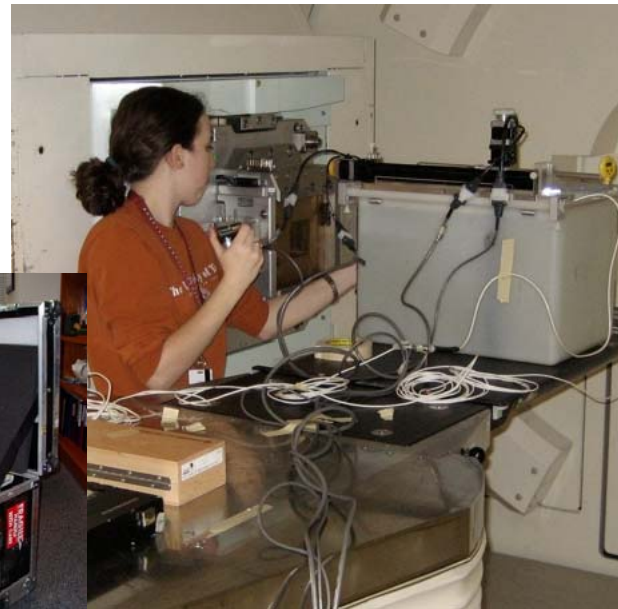
Electronic review & reporting of TLD results



On-Site Dosimetry Review Visit

The only completely independent comprehensive radiotherapy quality audit in the USA and Canada with measurements

1. Identify errors in dosimetry and QA and suggest improvements.
2. Collect and verify dosimetry data for chart review.
3. Improve quality of patient care.



On-Site Dosimetry Review Audit

Discrepancies Discovered (Jan. '05 – Mar. '11)

<u>Discrepancies Regarding:</u>	<u>Number of Institutions Receiving rec. (n = 156)</u>
Review QA Program	115 (74%)
Photon Field Size Dependence (FSD)	62 (40%)
Wedge Factor (WF)	50 (32%)
Off-axis Factors (OAF)/Beam symmetry	46 (29%)
Electron Calibration	27 (17%)
Photon Depth Dose	25 (16%)
Electron Depth Dose	18 (12%)
Photon Calibration	13 (8%)

Results of Chart Review

- **1% Systematic errors**
Potential to impact every patient treated by institution
- **11% Individual errors**
 - **Impacts study groups and institution**
- **27% Reporting errors**
 - **Impacts study group and institution**

Without IROC review 39% of the doses used by the NCTN groups would be incorrect

What is credentialing?

- Verifying an appropriate level of competency and ability to provide a basis for confidence
- Analogous to independent peer review
- Applies to
 - Institutions
 - Specific protocols
 - Radiation Oncologists, Med. Physicists
 - Treatment Planning Systems/algorithms
 - Treatment machine
 - Treatment modality

Purpose of Credentialing

- Educate
- Improve understanding of protocol
- Evaluate ability to use new technologies in clinical trials to deliver dose to only the intended treatment site
- Evaluate ability to calculate accurate dose to treatment site
- Evaluate ability to not irradiate critical healthy tissues near tumor
- Improve treatment delivery/patient safety

REDUCE THE NUMBER OF PROTOCOL DEVIATIONS

None Credentialed Protocols

(closed studies)

Study	Major Deviations	Minor Deviations	Number of Patients
GOG 0184	44 (7%)	114 (17%)	654
GOG 0122	29 (15%)	37 (19%)	197
NSABP B14	135 (9%)	214 (15%)	1460
NSABP R01	72 (44%)	0	163
RTOG 9001	43 (14%)	76 (24%)	315
RTOG 9003	75 (7%)	188 (18%)	1073

Results of Credentialing

(closed studies)

Study	Major Deviations	Minor Deviations	Number of Patients
GOG 165 <u>HDR Cervix</u>			
Credentialed inst	0	15 (21%)	70
Non-credentialed	57 (21%)	87 (32%)	275

Results of Credentialing

<u>Study</u>	<u>Disease Site</u>	<u>Major Deviations</u>	<u>Minor Deviations</u>	<u>Number of Patients</u>
COMS	Eye	43 (5%)	47 (3.6%)	1166
GOG 165	Cervix	0	15 (21%)	70
RTOG 95-17 HDR & LDR	Breast	0	4 (4%)	100
RTOG 0019 LDR	Prostate	0	6 (5%)	117
NSABP B39/RTOG 0413				
3D	Breast	3 (0.3%)	121 (10%)	1171
MammoSite		0	42 (12%)	348
MultiCatheter		0	8 (9%)	93

Use of Advanced Technologies in clinical trials?



TRACKING

TPS

HETERO CORRECTION

GATING

IGRT
KV OR MV

IMRT

SBRT

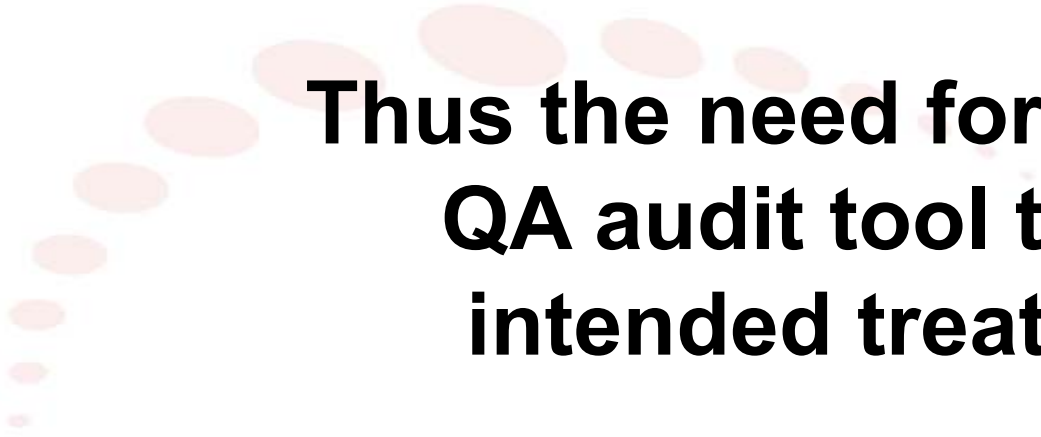
Respiratory
Control





Now we are back to the “Black Box”

Black Box



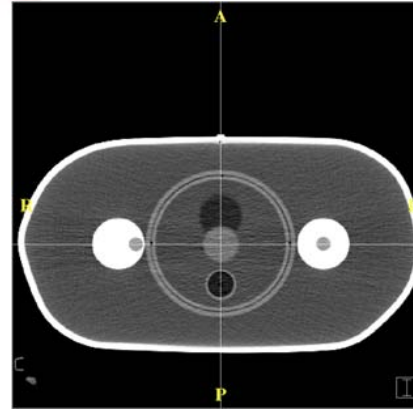
**Thus the need for an end-to-end
QA audit tool to verify the
intended treatment goal.**

**Deliver the correct dose
to correct location
as planned**

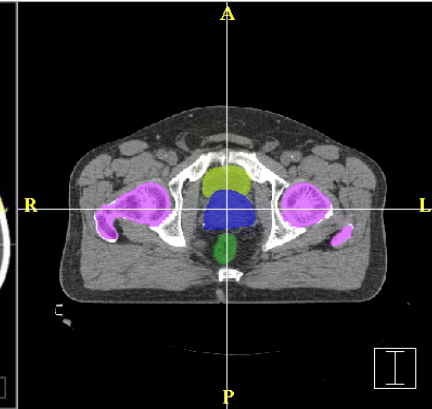
IROC-H Phantom Design

- Anthropomorphic shape
 - Water filled or solid targets and organs at risk
- Point and planar dosimeters
- Purpose is to evaluate the complete treatment process
- Benefits
 - Uniform phantoms/dosimeters
 - Standardized analysis
 - Uniform pass/fail criteria
 - Inst to inst comparison
 - Established infrastructure

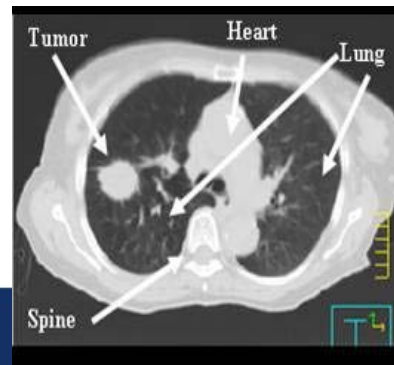
Phantom



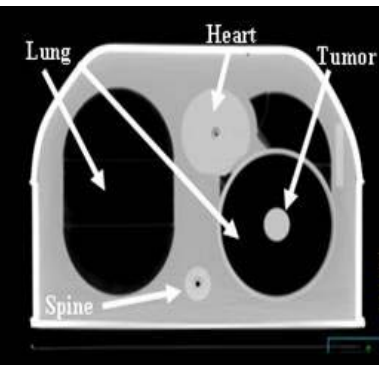
Patient



Patient



Phantom



Global Leaders in Clinical Trial Quality Assurance

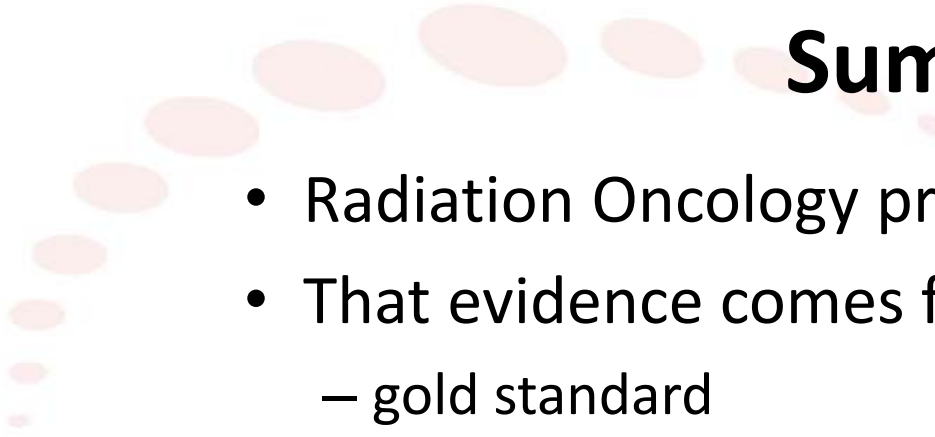
Photon Phantom Results

Comparison between institution's plan and delivered dose.

Phantom	H&N	Liver insert	Lung	Prostate	Spine
Irradiations	2052	165	1109	566	336
Pass	1755 (86%)	120 (71%)	921 (85%)	484 (85%)	261 (78%)
Fail	297	45	188	82	75
Criteria	7%/4mm	7%/4mm	5%/5mm	7%/4mm	5%/3mm

Some Key Findings from Credentialing

- Deficient treatment planning computer modeling for IMRT delivery
- Incorrect lung tumor dose calculations for Stereotactic Body Radiation Therapy (SBRT)
- Deficient dose calculation algorithms for both protons and x-rays
- Incorrect institutional modeling of their treatment x-ray beams



Summary

- Radiation Oncology practice is evidence based
- That evidence comes from clinical trials
 - gold standard
- Low quality undermines these trials which may conceal the true outcome
- Therefore a continued need for Radiation Oncology QA within clinical trials is essential

**Thank You
Questions?**





IROC Resources

IROC Houston

713-745-8989 / fax 713-745-1364

irochouston@mdanderson.org

IROC Ohio

614-293-2929 / fax 614-293-9275

help@irocoho.org

IROC Philadelphia- DI

215-940-8820 / fax 215-923-1737

irocphila-di@acr.org

IROC Philadelphia- RT

215-574-3219 / fax 215-923-1737

irocphila-rt@acr.org

IROC Rhode Island

401-753-7600 / fax 401-753-7601

irocri@garc.org

IROC St. Louis

314-747-5415 / fax 314-747-5423

irocstl@radonc.wustl.edu

Relevant Clinical End-points for RT Combination Trials

Fei-Fei Liu MD

*Chief and Chair Radiation Medicine Program
Princess Margaret Cancer Center, University of Toronto
Senior Scientist, Ontario Cancer Institute*

*FDA/AACR/ASTRO Workshop
Feb 22-23, 2018
Bethesda, MD*

Disclosure

**I have no actual or potential conflict
of interest to declare.**

Gold Standard End-Points

Overall Survival

- Hard, quantifiable, indisputable end-point
- Meaningful to patients
- Large number of patients & long f/up

Quality of Life

- Validated tools
- Meaningful for patients

RT Combination Trials

Other end-points need to be considered

- RT is a local therapy
- Curative treatments - loco-regional control (LRC), or end-points reflective of LRC are important
- Should translate into increased OS/DFS
- Similar to neo-adjuvant/adjuvant approaches

RT Combination Trials

Relevant end-points considerations:

- Site-dependent
- Target patient population
- Stage of disease
- Emerging end-points
- PRO

RT Combination Trials

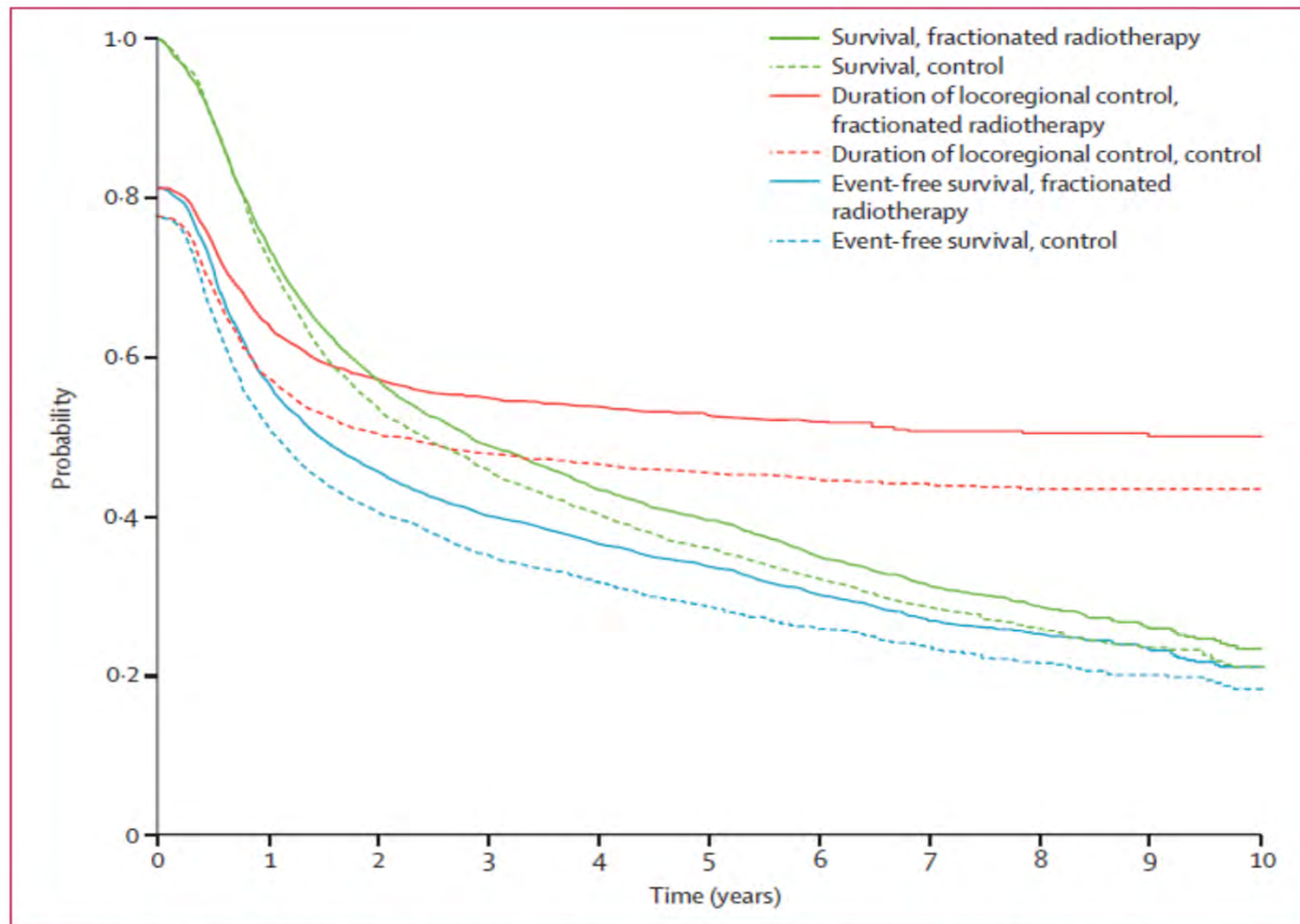
1. HNC
2. Lung
3. Breast
4. GI
5. GU
6. CNS

RT Combination Trials

1. HNC

- OS
- EFS (LRC)
- PFS
- QoL

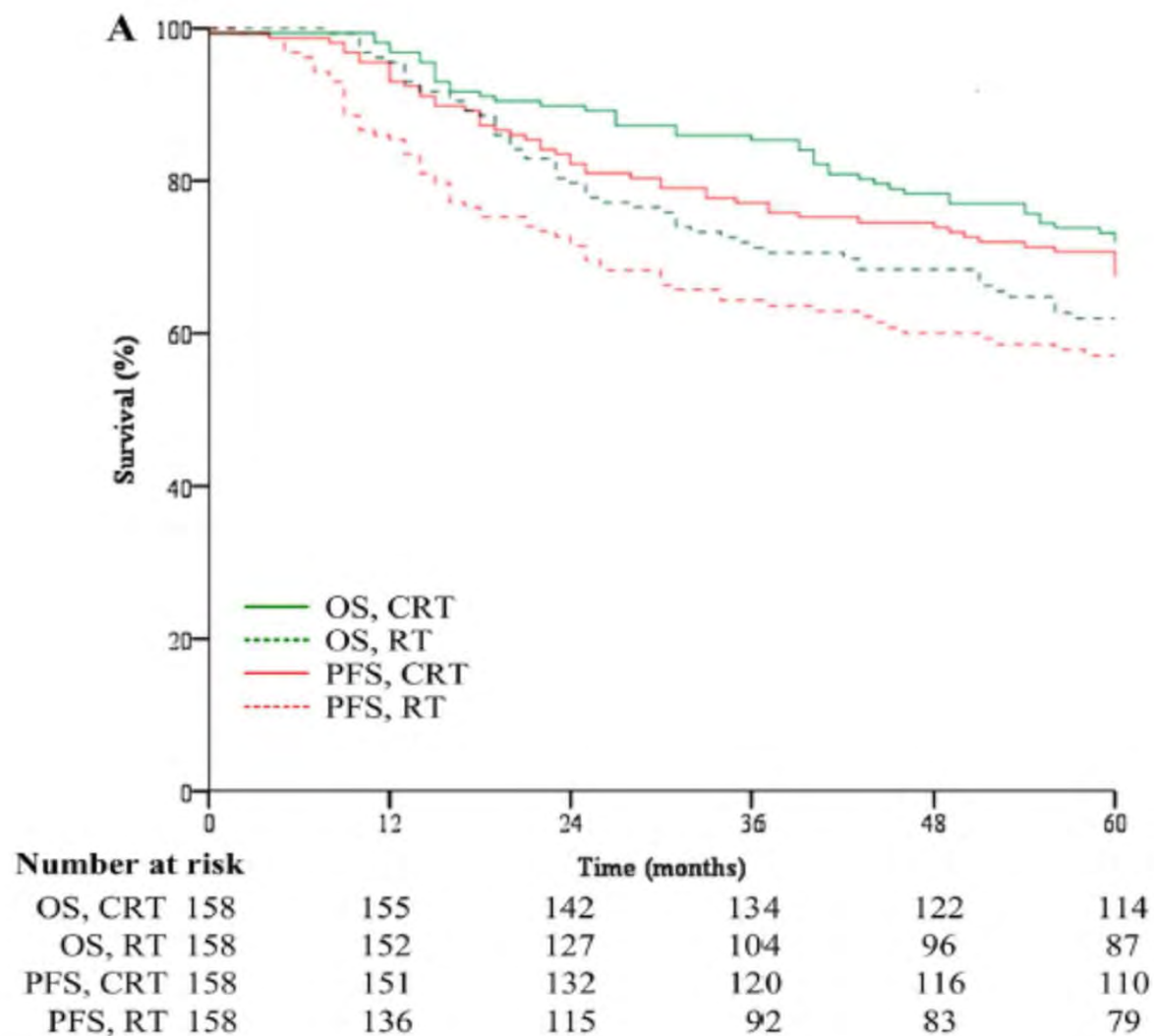
EFS (Event-Free Survival) for HNSCC RT Combination Trials



- 22,774 patients
- 116 treatment comparisons
- EFS: randomization to any event

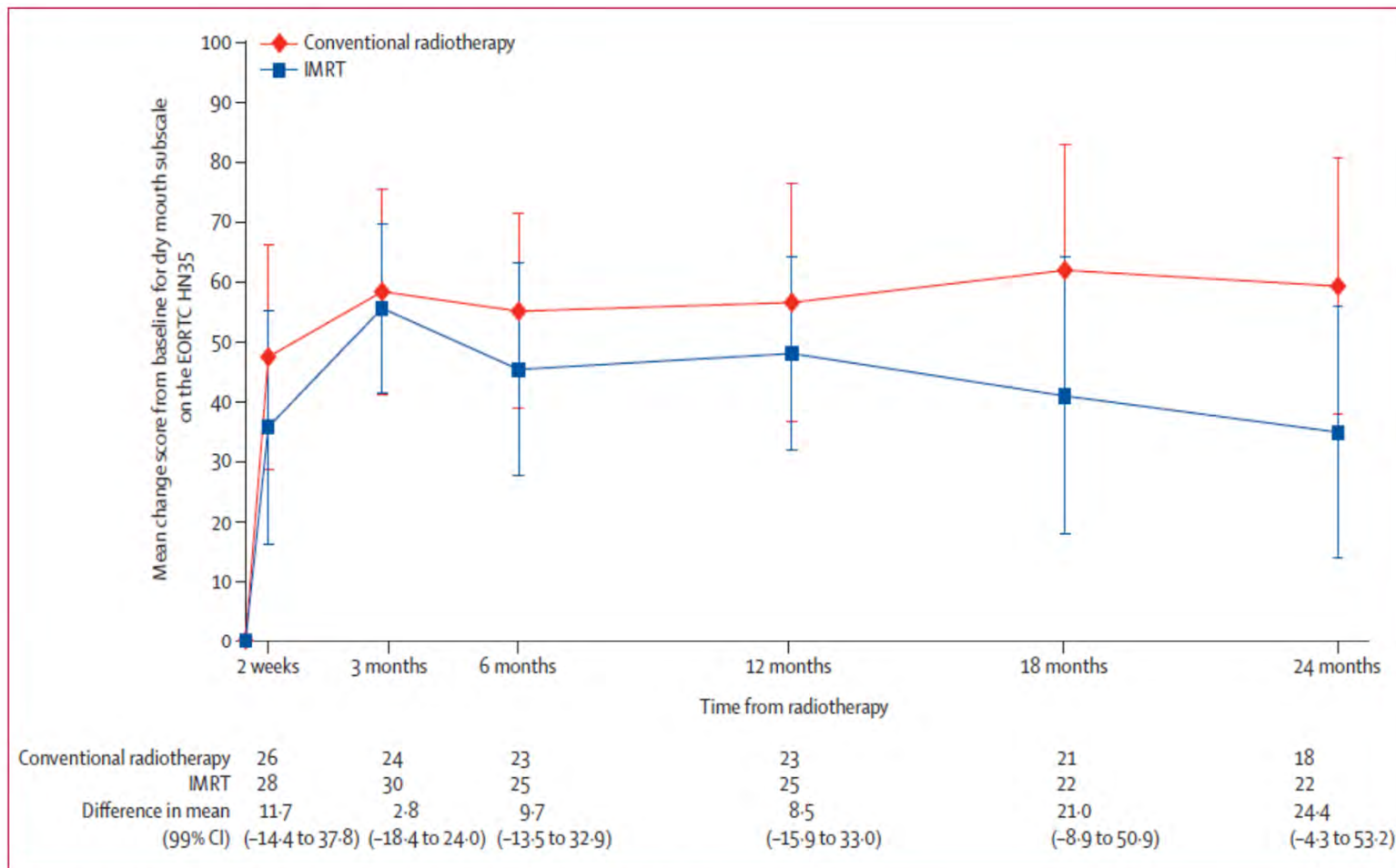
Figure 1: Locoregional control, event-free survival, and overall survival in the radiotherapy trials

PFS (Progression-Free Survival) for NPC RT vs. CRT Trial



- 316 NPC patients

QoL & Normal Tissue Toxicity End-point for HNC



- Conventional vs. parotid-sparing IMRT
- $\geq$ grade 2 xerostomia
- LENT-SOMA

Figure 3: Mean EORTC HN35 dry mouth subscale score changes from baseline

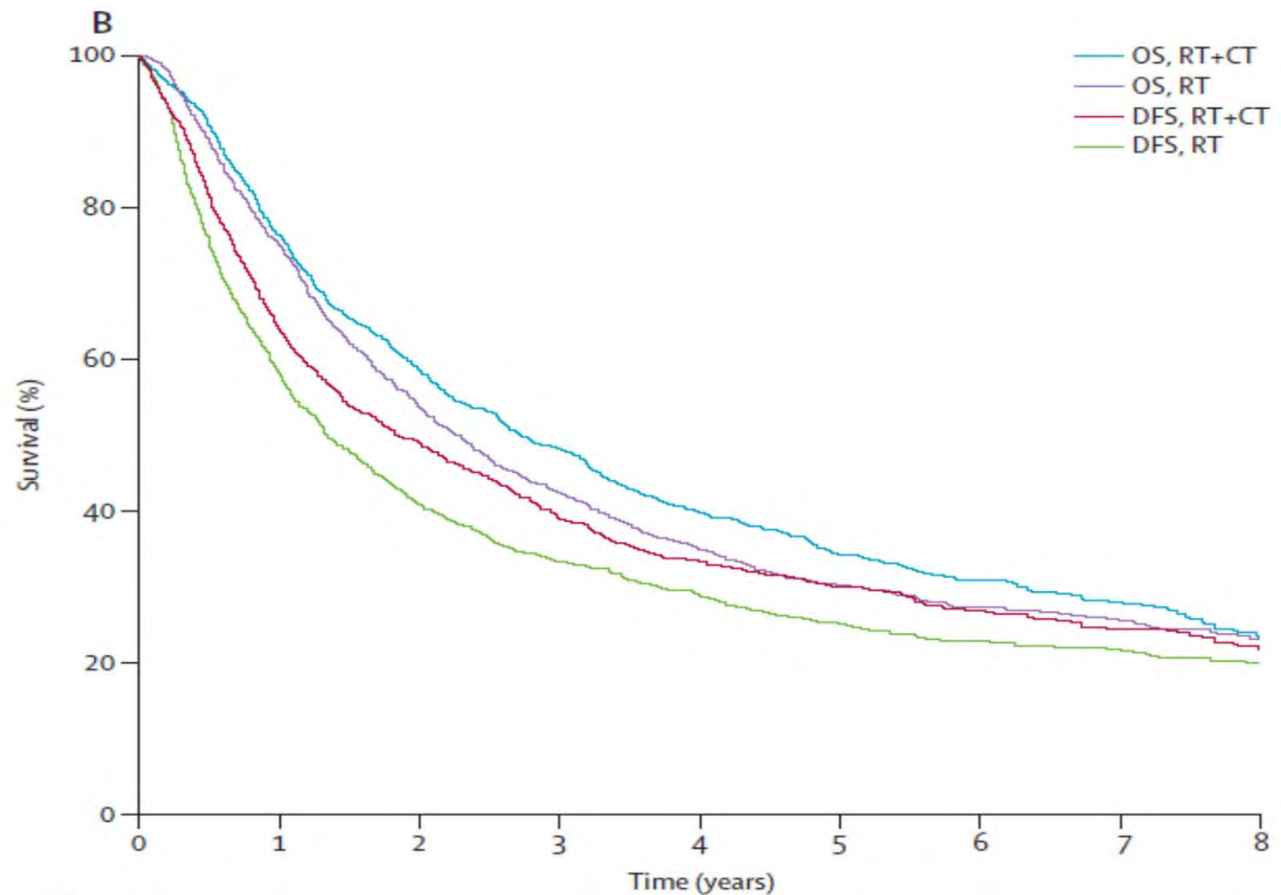
IMRT=intensity-modulated radiotherapy. EORTC HN35=European Organization for Research and Treatment of Cancer head and neck specific module HN35.

RT Combination Trials

2. Lung

- OS
- PFS
- DFS
- ?FDG-PET

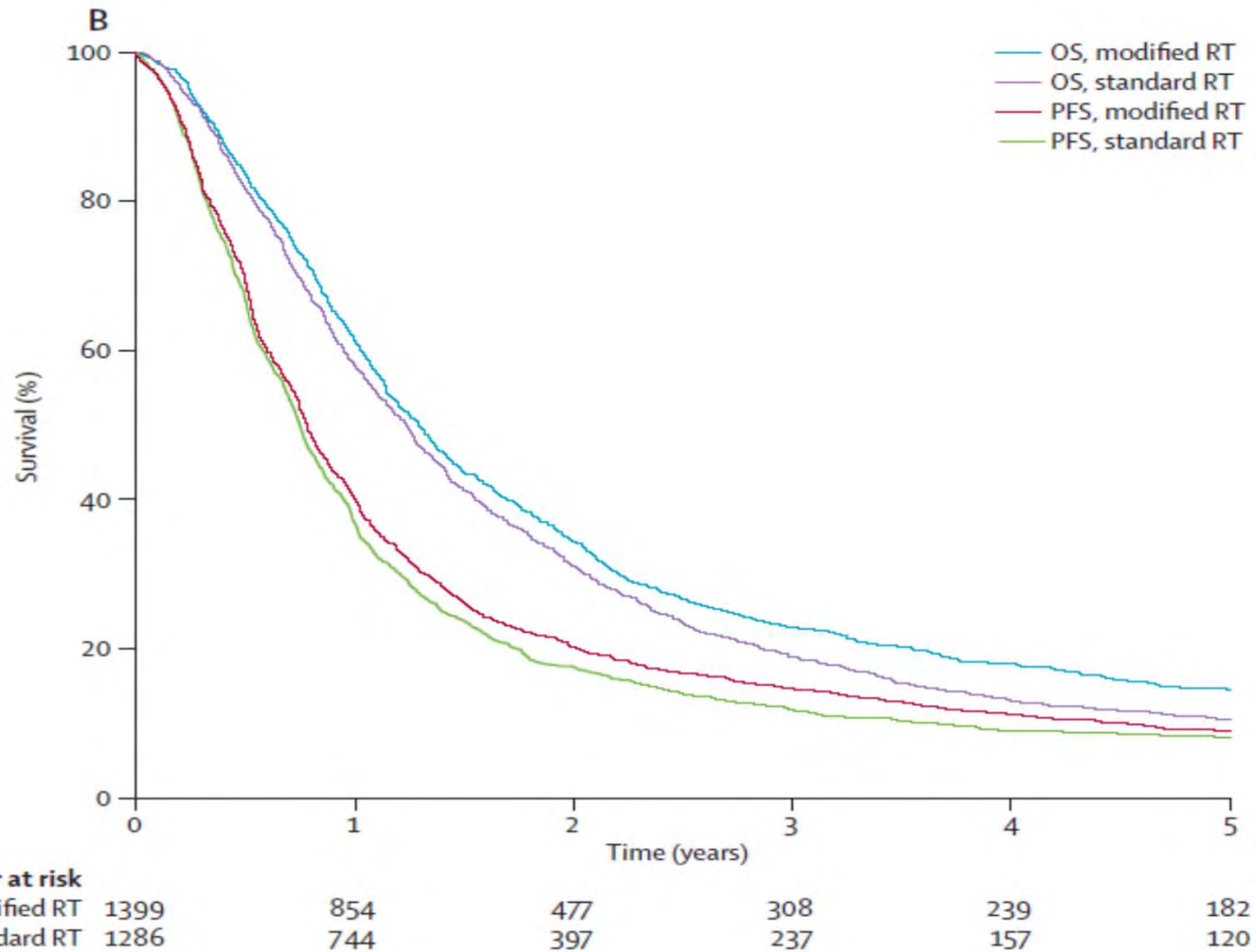
DFS ~ OS for NSCLC



Number at risk									
OS, RT+CT	1115	834	630	484	351	254	184	129	74
OS, RT	1132	837	585	445	328	249	178	127	73

- 60 RCTs
- 15,071 patients

PFS ~ OS for NSCLC



- 60 RCTs
- 15,071 patients

Potential Role for FDG-PET in NSCLC

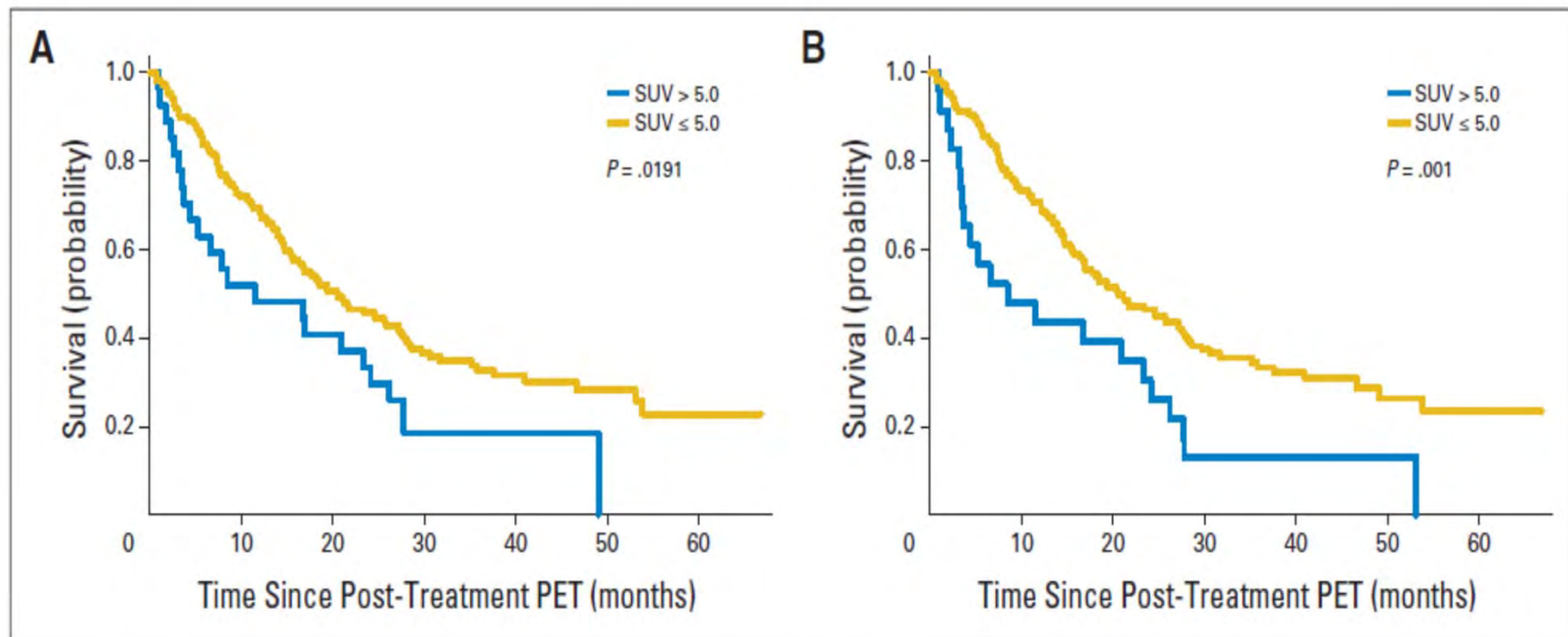


Fig 3. Overall survival based on a peak standardized uptake value (SUV) cutoff of 5.0. (A) Results based on local institutional read. (B) Results based on central review read. PET, positron emission tomography.

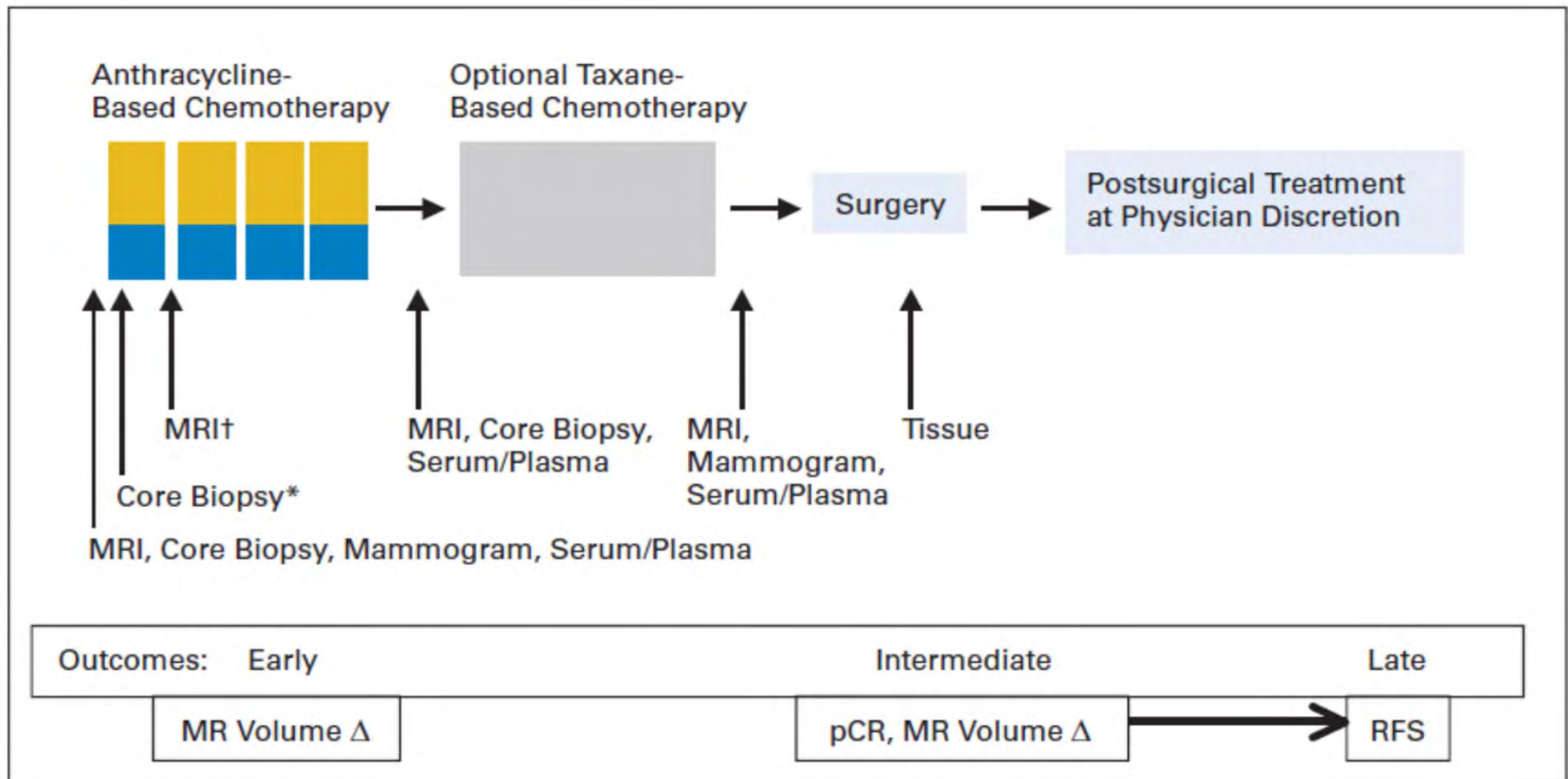
- 173 evaluable FDG-PET scans/250 NSCLC
- Concurrent platinum-based CRT

RT Combination Trials

3. Breast

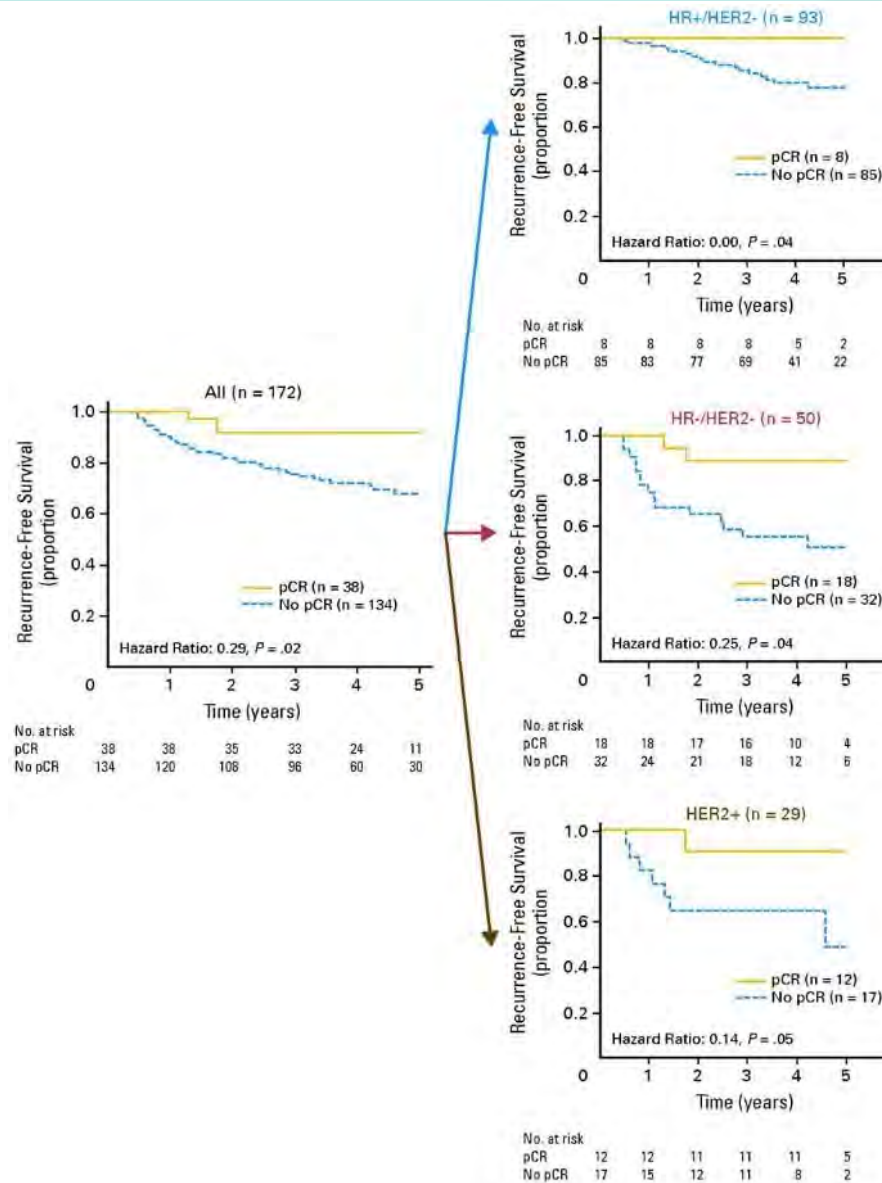
- OS
- DFS
- QoL
- pCR & RFS

pCR for Breast Cancer & Neo-adjuvant Chemotherapy (NAC) – Sx + RT



- 221 LABC, NAC

pCR Associated with Improved RFS

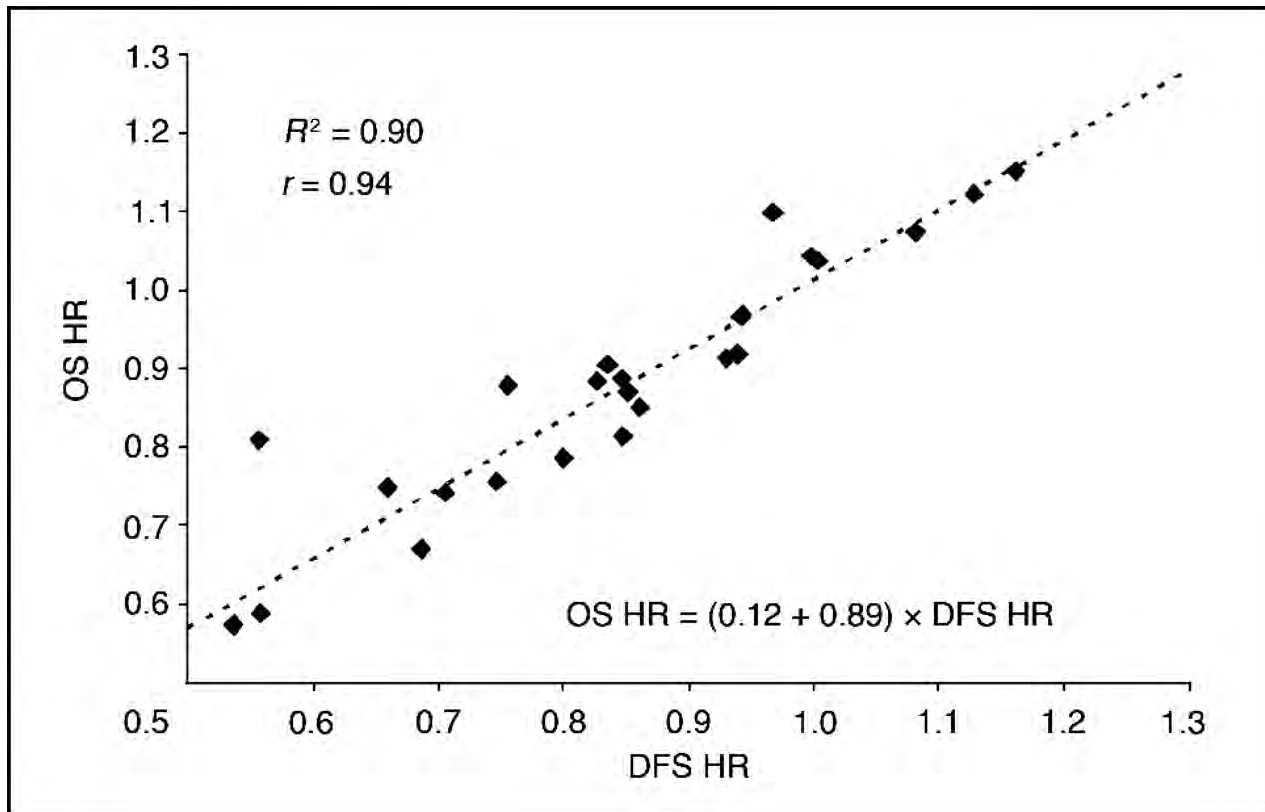


RT Combination Trials

4. GI

- OS
- DFS
- QoL
- pCR & R0

DFS & OS in Cancer End-points

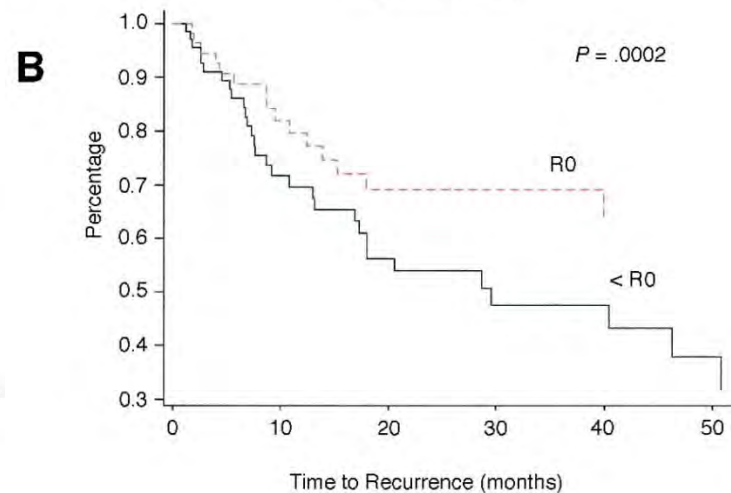
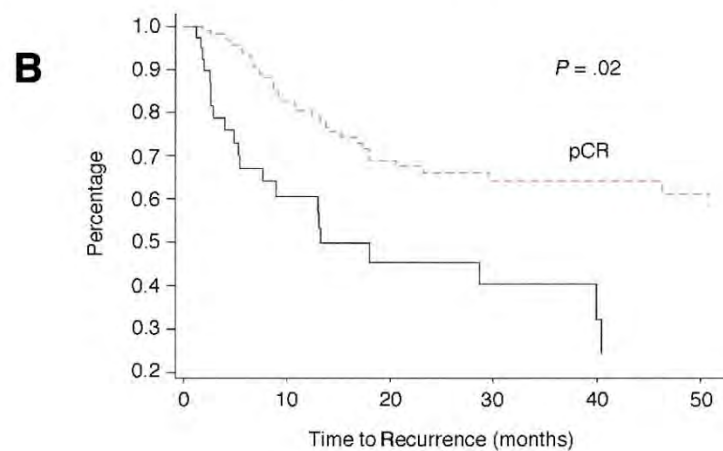
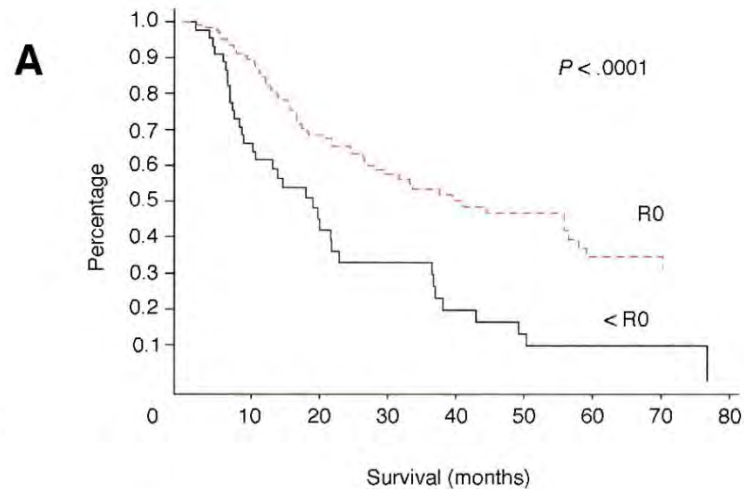
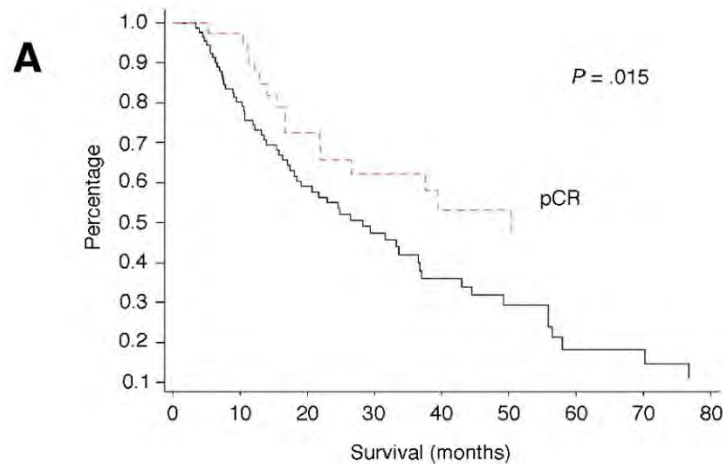


- 18 RCTs (CT)
- 20,898 CRC

Fig 2. Disease-free survival (DFS) versus overall survival (OS) hazard ratios (HR) by trial.

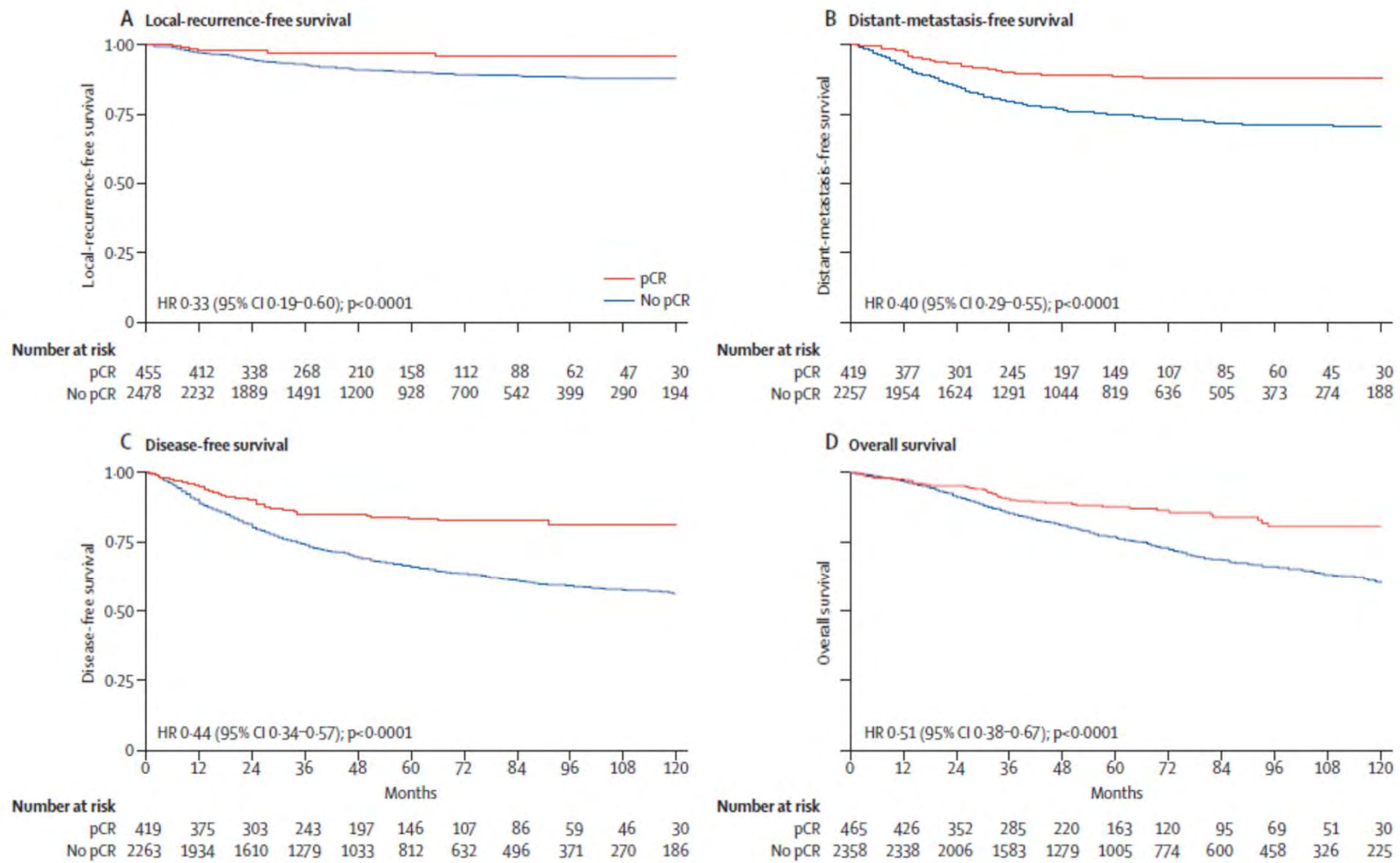
pCR & R0 Associated with Improved OS & DFS

- 131 patients with esophageal CA
- Pre-op CRT (Cisplatin + 5-FU + RT)



pCR in Rectal Carcinoma

- 2823 patients with rectal CA; treated with pre-op CRT

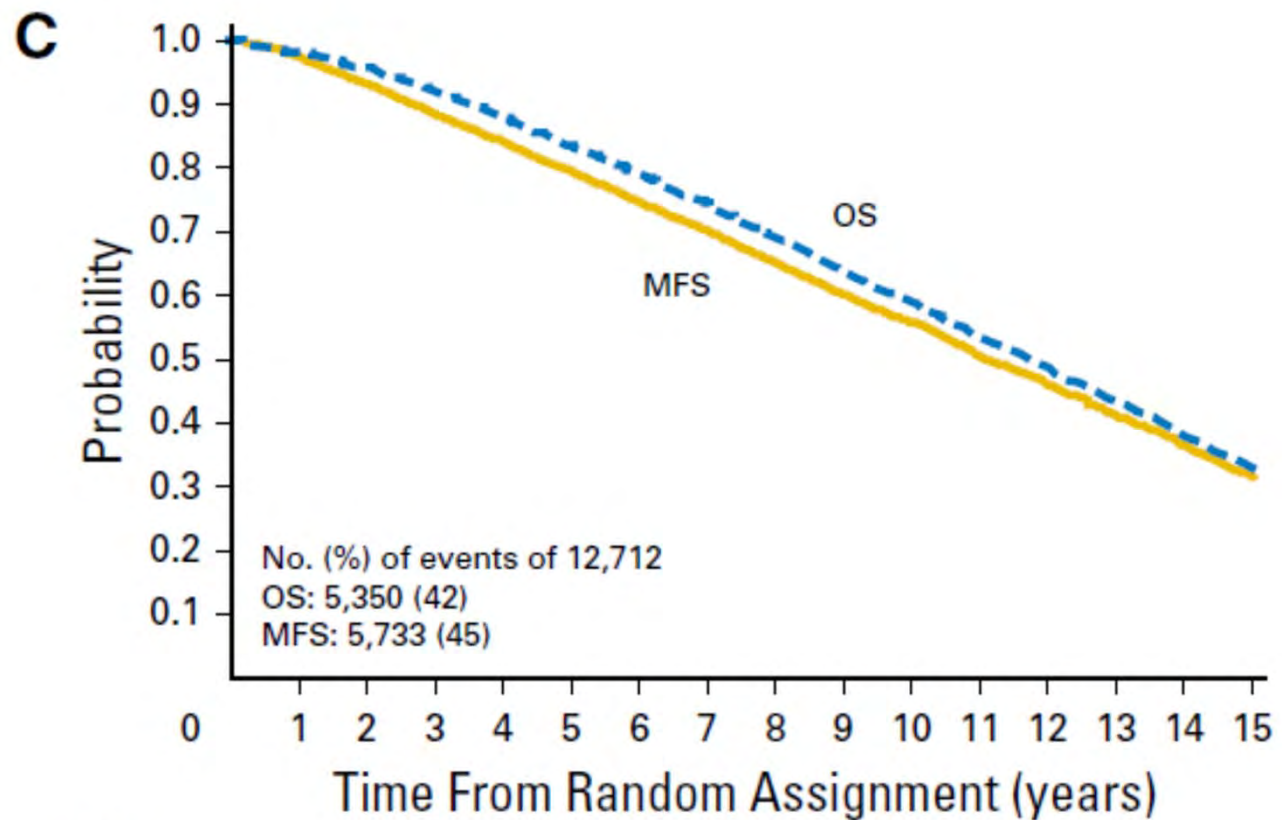


RT Combination Trials

5. GU

- OS
- DFS
- MFS (metastasis-free survival)
- QoL
- PSA nadir

MFS is Strong Surrogate for OS in Localized Prostate Cancer

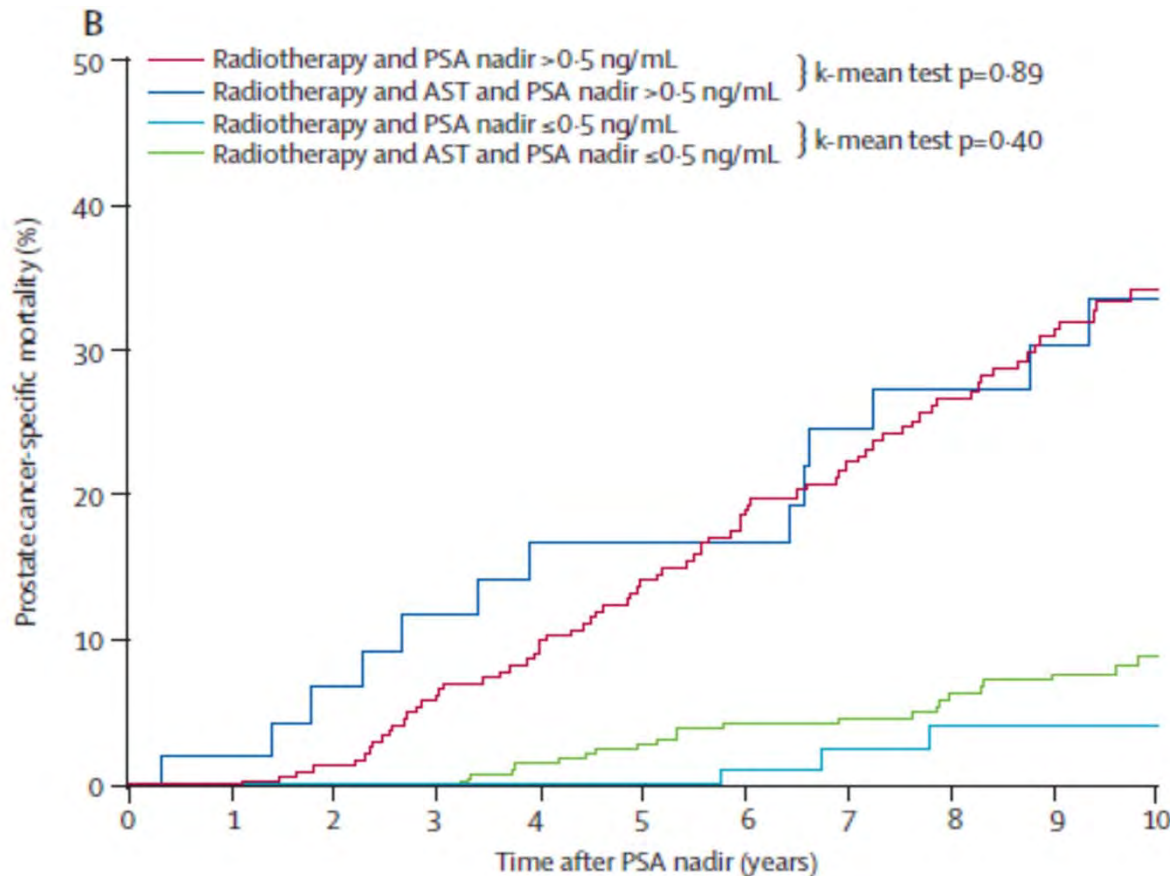


- 28,905 men with localized prostate CA from 28 RCTs
- Up to 90% were RT patients
- MFS strongly correlated with OS

No. at risk

--- OS 12,712	11,321	8,162	4,714	1,853	726
— MFS 12,712	10,831	7,656	4,394	1,711	668

PSA Nadir/End in Prostate Cancer



- 743 men with prostate CA in 2 RCTs
- PSA nadir (and end) strongly correlated with PCSM

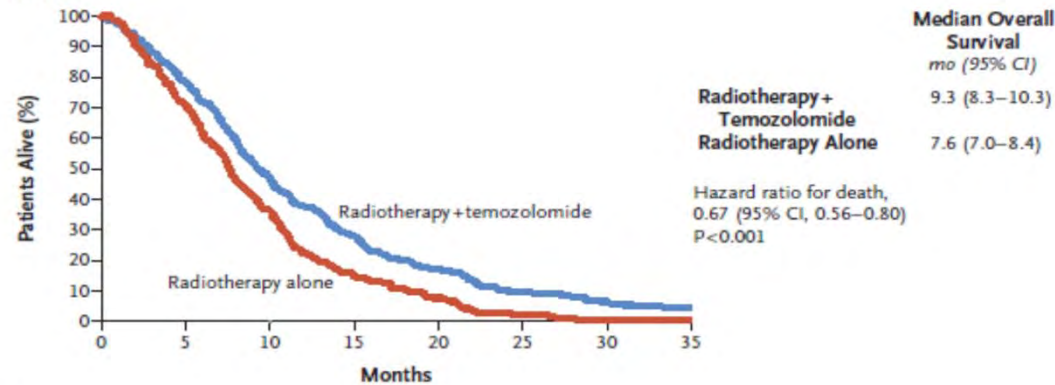
RT Combination Trials

6. CNS

- OS
- PFS
- Cognitive-deterioration-free survival
- QoL

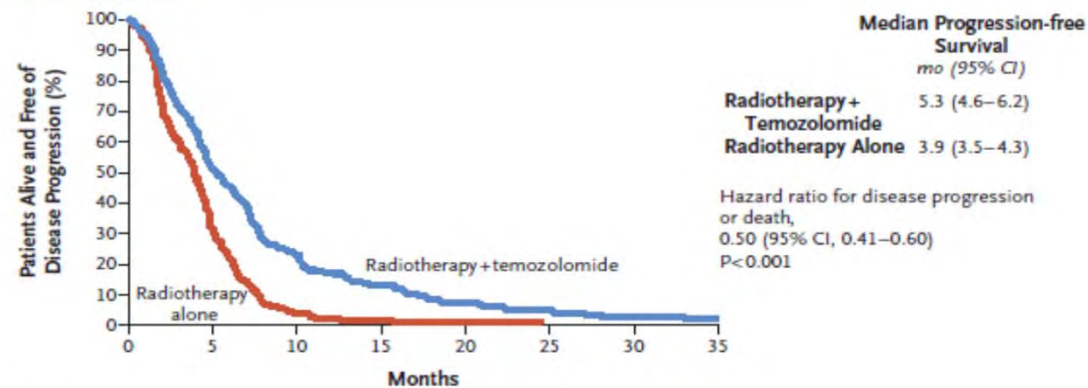
OS & PFS GBM

A Overall Survival



No. at Risk							
Radiotherapy + temozolomide	281	217	129	77	43	23	15
Radiotherapy alone	281	196	100	40	19	5	1

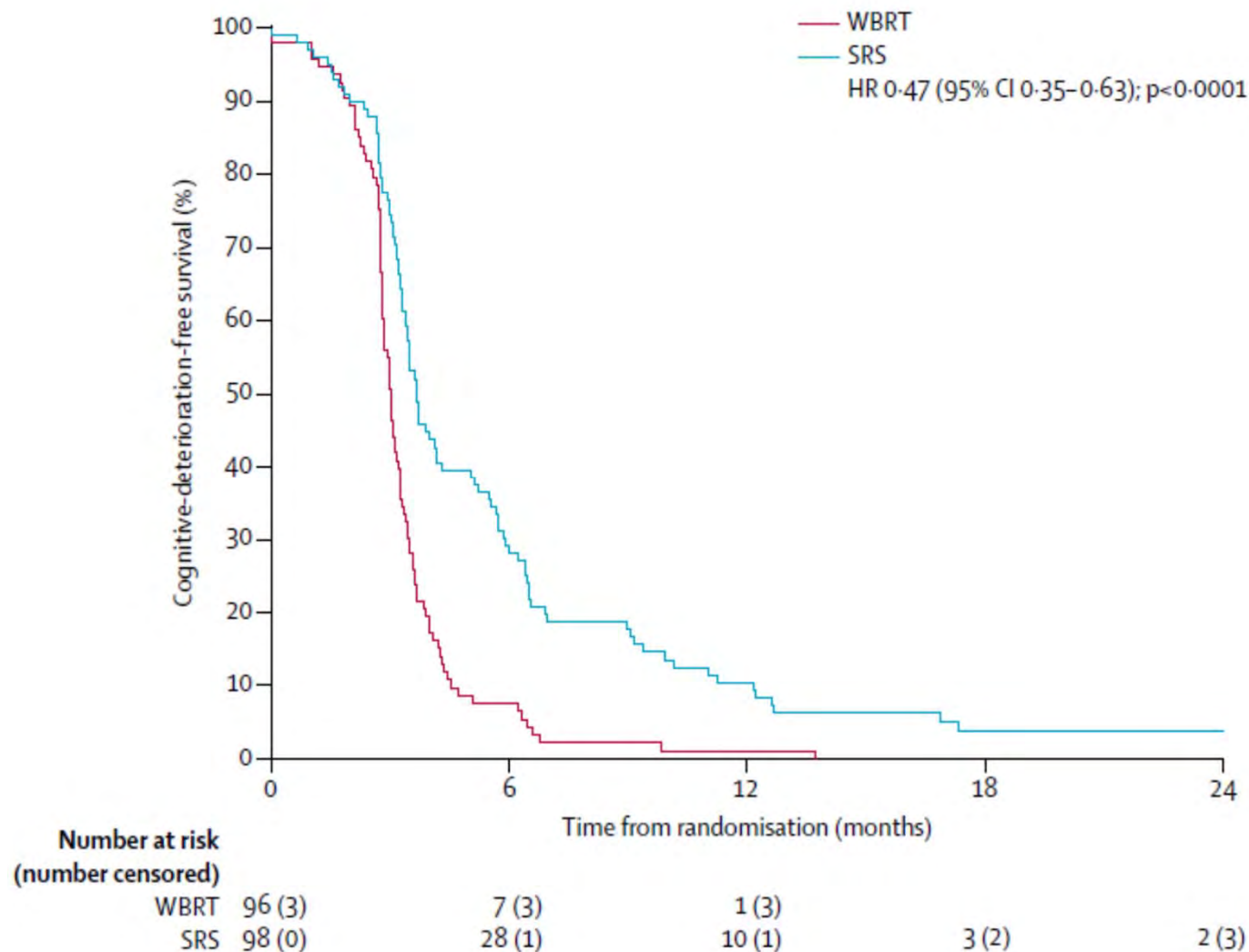
B Progression-free Survival



No. at Risk							
Radiotherapy + temozolomide	281	141	62	32	17	11	6
Radiotherapy alone	281	87	10	5	2	0	0

- 562 patients $\geq$ age 65
- RT + TMZ vs. RT alone

Cognitive End-point for Brain Metastasis



- 195 patients post resection for brain mets
- WBRT vs. SBRT
- 1 SD drop in 1/6 cognitive tests

RT Combination Trials

Other end-points need to be considered

➤ **Organ preservation**

- **Larynx/hypopharynx (time to tracheotomy; survival with functional larynx/esophagus)**
- **Bladder**
- **Rectum**

RT Combination Trials

Toxicity end-points obviously need to be considered

- **CTCAE v5.0 (2017/18)**
- **Breast cosmesis (global cosmetic score)**
- **Prostate cancer RT**
 - **Early proctoscopy, and VRS (Vienna Rectoscopy Score)**

Olivotto et al; JCO 31:4038, 2013
Peterson et al; IJROBP; 91:968, 2014
Ippolito et al; IJROBP; 83:e191, 2012
Wachter et al; Rad Oncol; 54:11, 2000

Conclusions

- 1. OS, DFS, QoL end-points are gold standard**
- 2. Additional end-points for combined RT trials need to be considered**
 - **LRC, EFS, PFS, MFS**
 - **Organ-preservation**

Conclusions

3. Site/stage/treatment-dependent end-points

- pCR, R0, PSA-nadir
- Neuro-cognitive evaluations

4. Late normal tissue toxicity end-points

- CTCAE v5.0
- LENT-SOMA
- Cosmesis, proctoscopy

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The Route to Registration: Regulatory Perspective

Tatiana M. Prowell, MD

Breast Cancer Scientific Liaison, FDA
Asst. Prof. of Oncology, Johns Hopkins



Disclosures

- I have no financial interests to disclose.
- I will not discuss off-label use of unapproved agents.



US Drug Approval Pathways

	Regular Approval	Accelerated Approval
Diseases	Any	Serious/life-threatening
Comparative Efficacy Required	No	Yes
Endpoint	Clinical benefit	“Surrogate” endpoint [†]
Confirmatory Trial Required	No	Yes

[†]Accelerated approval relies upon an endpoint that is “reasonably likely to predict clinical benefit.”



US Drug Approval Pathways

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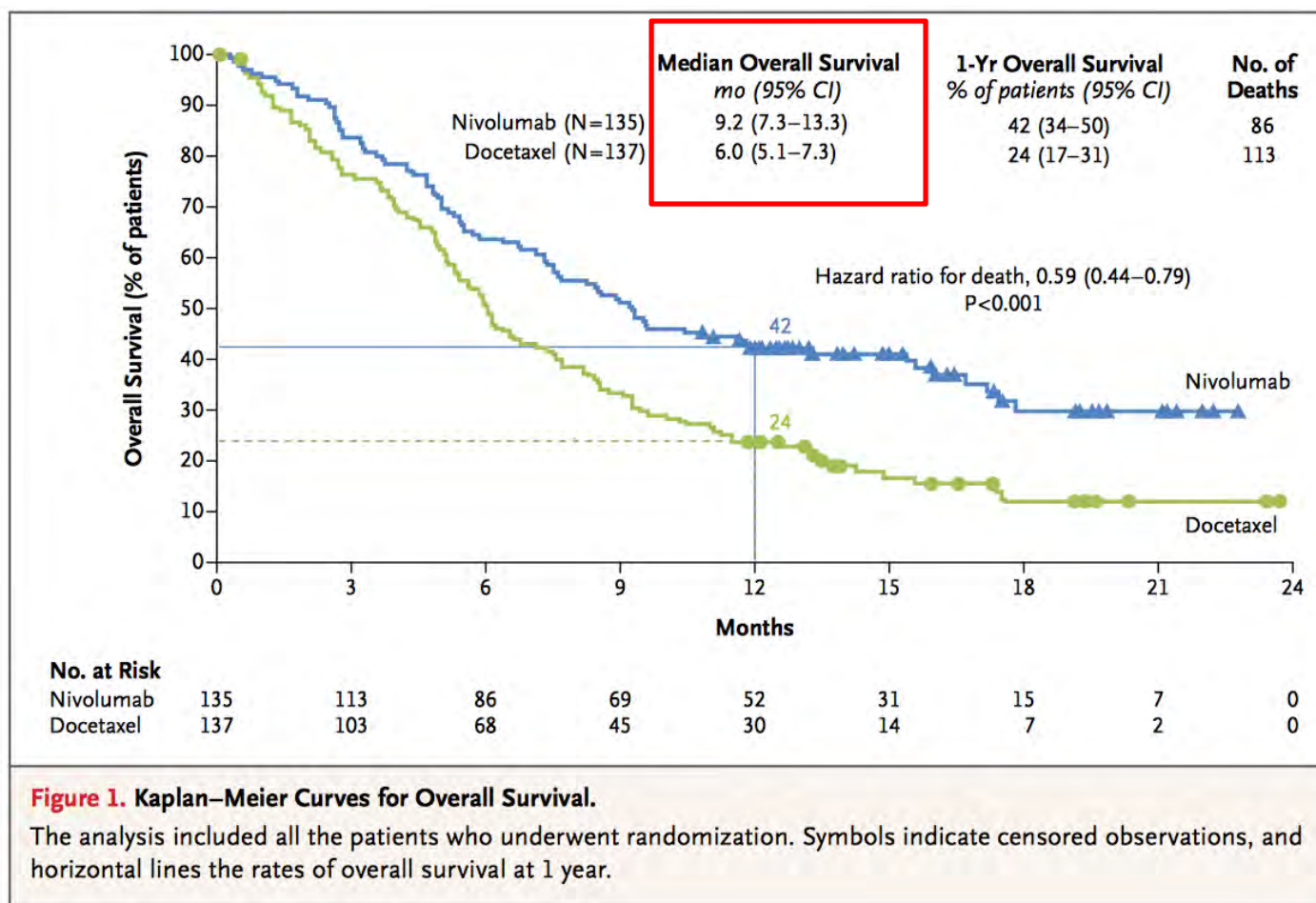
What Constitutes Clinical Benefit?

- Clinical benefit has a U.S. regulatory definition: a direct measure of “how a patient feels, functions, or survives”
- In the advanced cancer setting, “clinical benefit” has historically most often meant improved:
 - Overall survival
 - Progression-free survival, when of sufficient magnitude

Why Overall Survival Still Matters

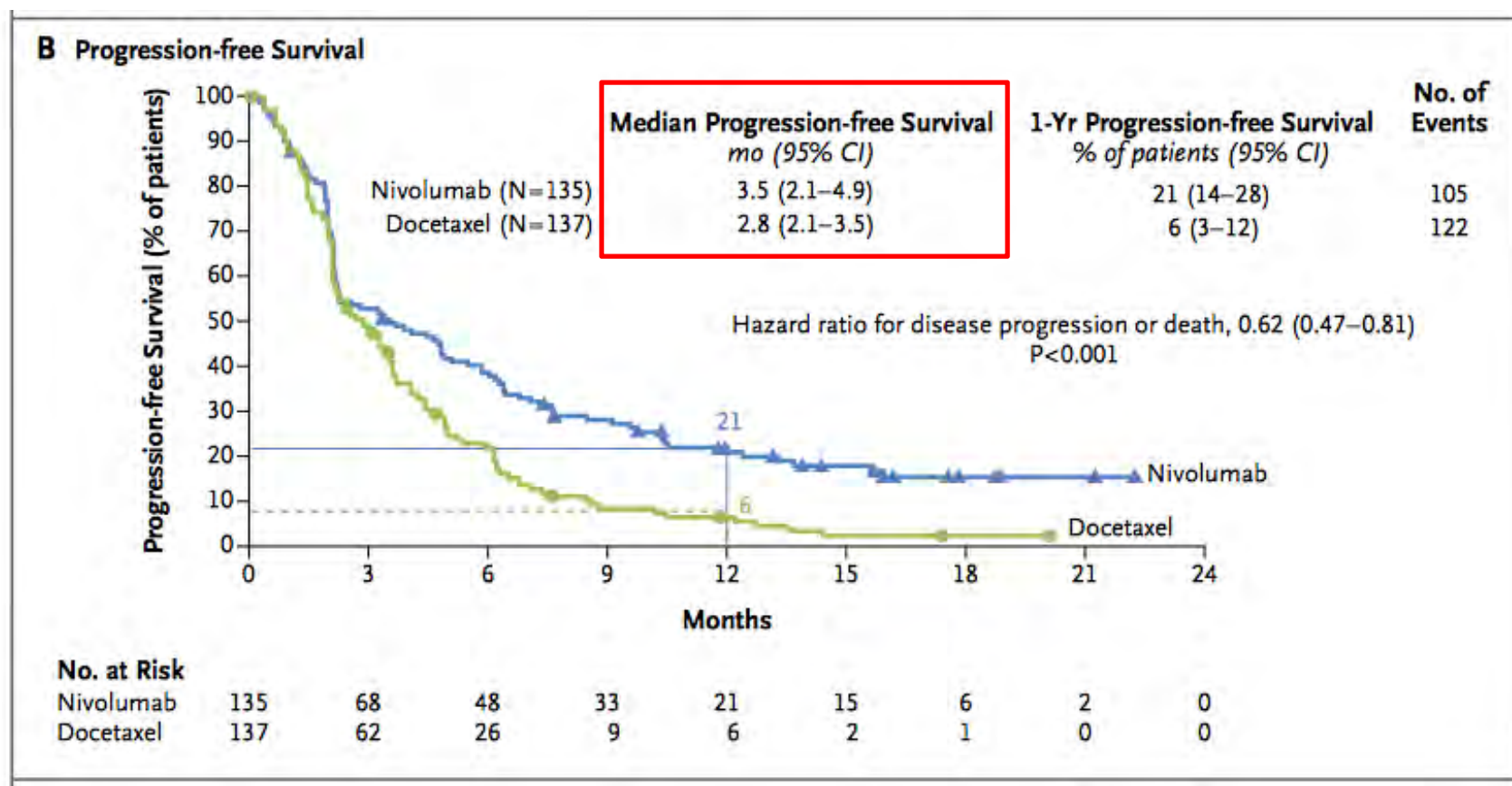
- Despite well-known challenges of using OS as an endpoint, it will always matter to regulators:
 - Captures bottom line of both safety and efficacy
 - It matters to patients!
- Measured precisely
- No need for interpretation
- Data rarely missing and easily source-verifiable
- May better reflect treatment compared to PFS or other endpoints in certain settings

Nivolumab: Median OS in Advanced Squamous Cell Lung Cancer



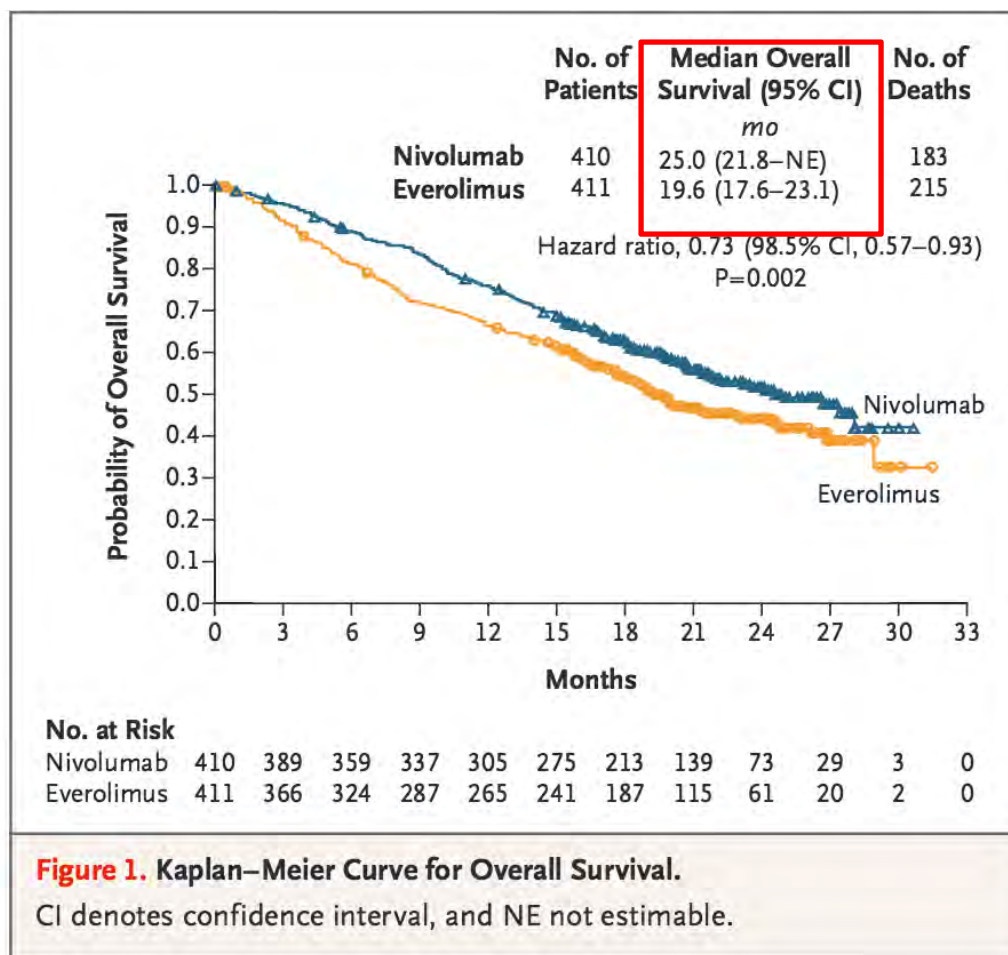
Brahmer et al. N Engl J Med 2015; 373:123-135

Nivolumab: Median PFS in Advanced Squamous Cell Lung Cancer



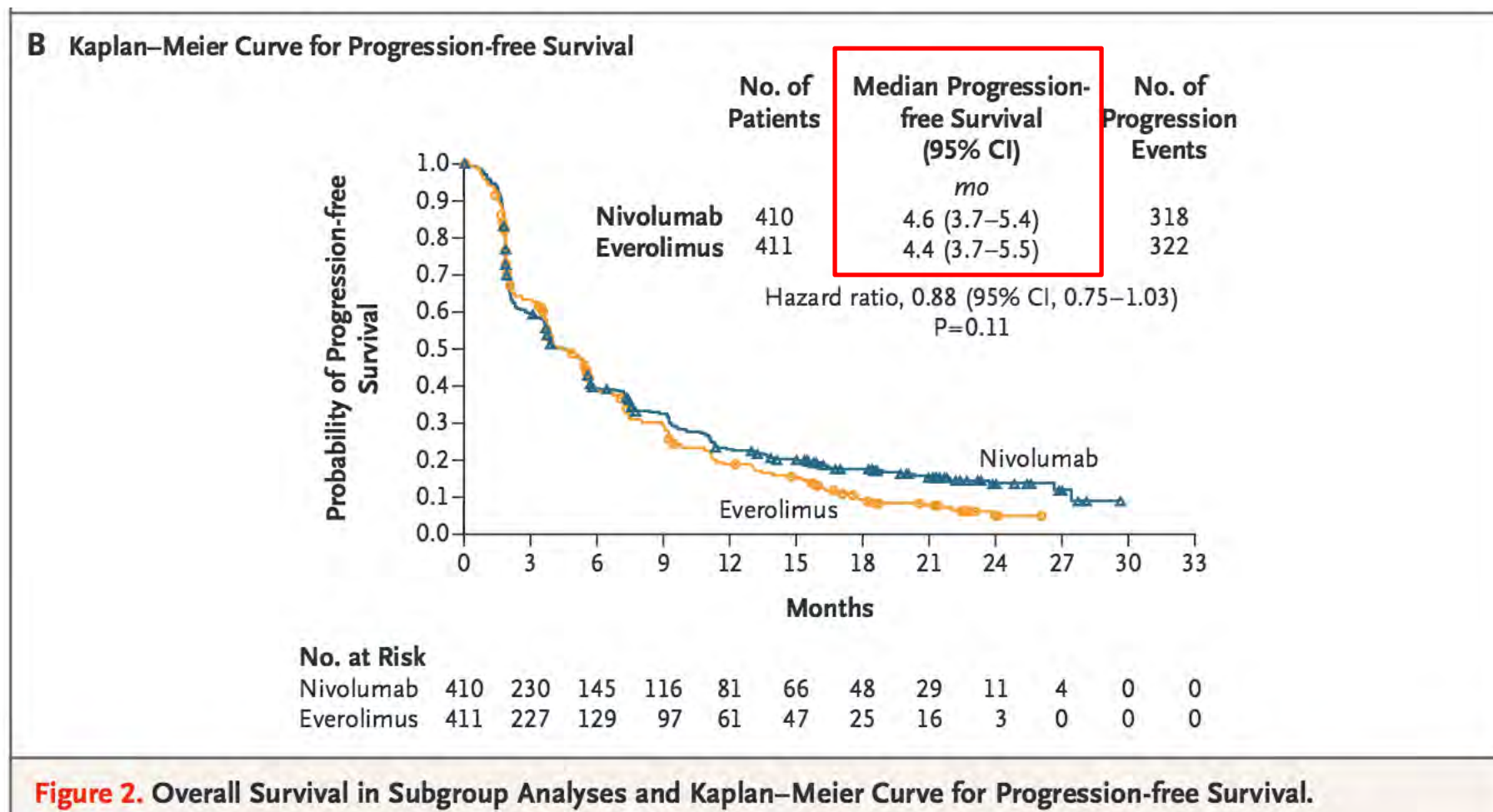
Brahmer et al. N Engl J Med 2015; 373:123-135

Nivolumab: Median OS in mRCC



Motzer et al. N Engl J Med 2015;373:1803-13

Nivolumab: Median PFS in mRCC



Motzer et al. N Engl J Med 2015;373:1803-13

OS as an Endpoint in 2018

- Time-to-event endpoints are almost impossible to interpret in a single arm trial
- Randomized trials require equipoise
 - Ethical considerations
 - Feasibility considerations
- Cross-over will confound interpretation of OS
 - OS benefit, if large, may still be observed
 - Sensitivity analyses can help
 - Industry has expressed concerns about compromising global drug approval/reimbursement if OS improvement is not demonstrated

Objective Response Rate

- Isolates treatment effect from natural history of disease
- Lends itself well to use in single-arm trials
- Does not account for stable disease
- Poses unique advantages and challenges in certain settings
 - Bone metastases
 - Peritoneal carcinomatosis
 - Immuno-oncology agents
- Commonly used for accelerated approval and in some recent examples has served as basis for regular approval

Features of the Response Matter

- Duration of response
- Persistence of response after treatment discontinuation
- Depth of response
- Association with symptomatic improvement

Nature and Extent of Response Matters

Response seen from across the room

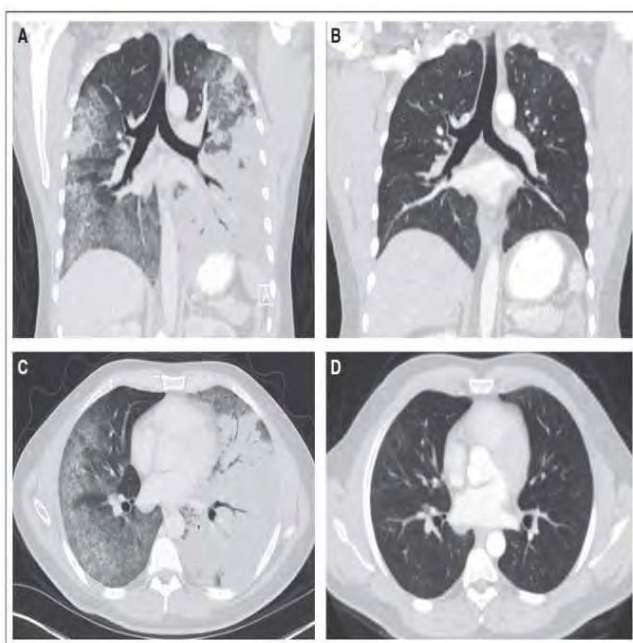
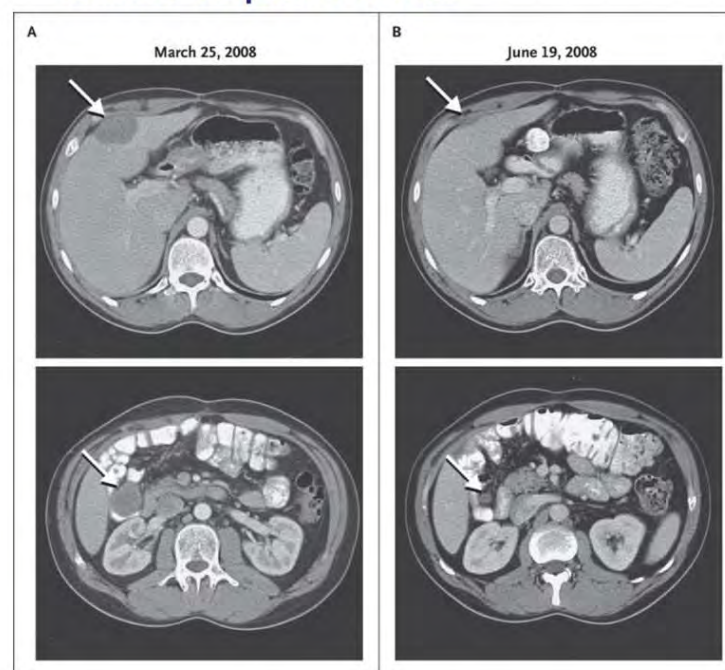


Fig 4. Response of an ROS1-positive patient with advanced non-small-cell lung cancer to crizotinib. Computed tomography scans of the chest were obtained (A and C) at baseline and (B and D) after 12 weeks of crizotinib. Shown are (A and B) coronal reconstructions and (C and D) axial slices.

Bergethon et al., JCO, 2012;
30(8): 863-70

Response where you need an arrow to point it out

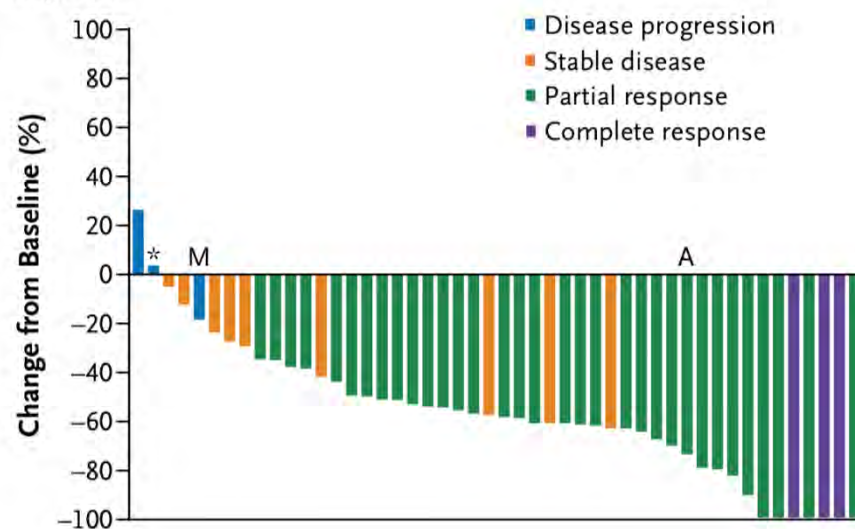


Butrynski et al., NEJM, 2010;
363: 1727-1733

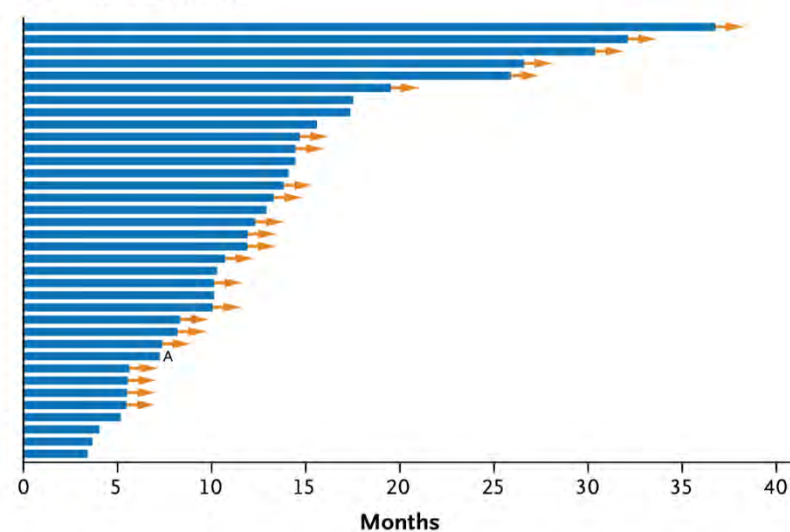
Slide courtesy, G. Blumenthal

Depth, Durability, & Persistence of Response

A Best Response



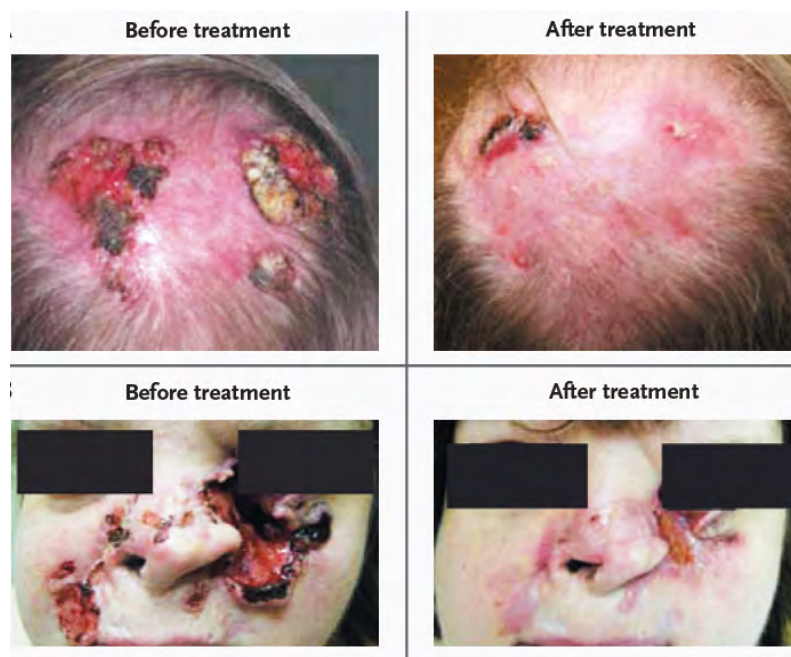
C Duration of Response



Shaw et al. NEJM, 2014; 371: 1963-1971

When Is Response Clinical Benefit?

Regular approval granted based on **clinical** response rate (and duration), the cosmetic improvement and the high likelihood of tumor related symptomatic relief



Vismodegib Response

Von Hoff et al., NEJM, 2009;
361: 1164-72



Romidepsin Response

Piekarz et al., JCO, 2009; 27:
5410-5417

Slide courtesy, J. Beaver

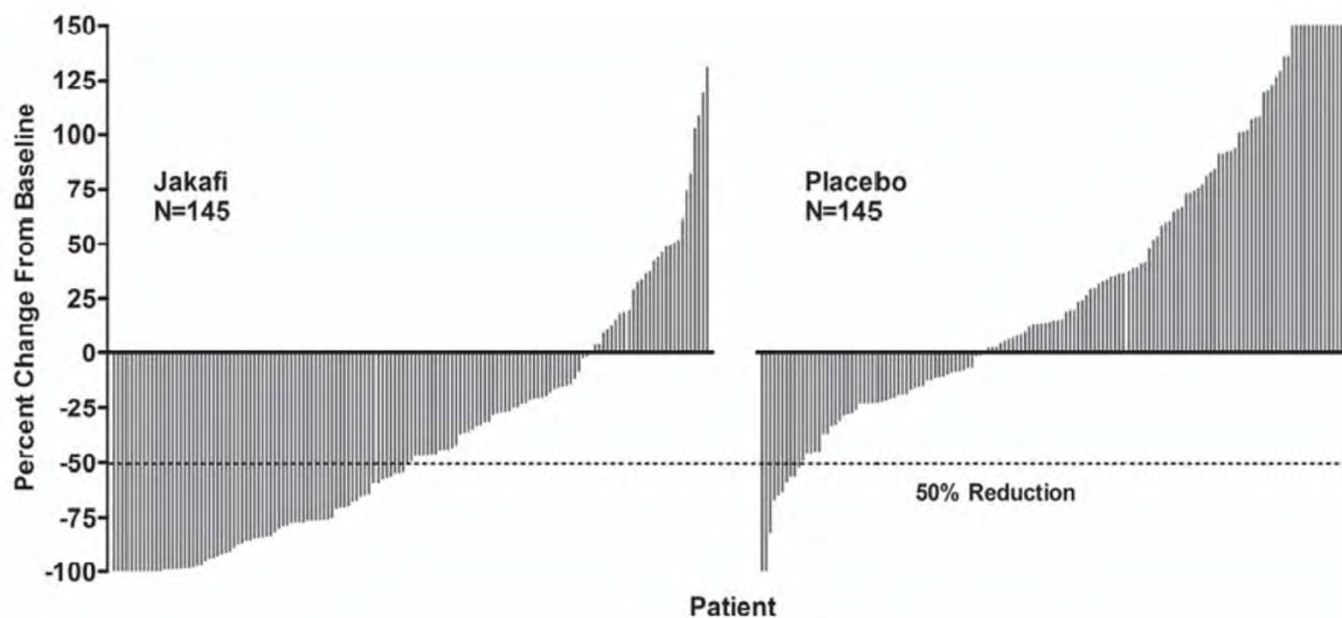
Ruxolitinib for Myelofibrosis: Response + Symptomatic Relief

	Study 1	
	Jakafi (N=155)	Placebo (N=154)
Time Points	Week 24	
Number (%) of Patients with Spleen Volume Reduction by 35% or More	65 (41.9)	1 (0.7)
P-value	< 0.0001	

	Jakafi (N=148)	Placebo (N=152)
Number (%) of Patients with 50% or Greater Reduction in Total Symptom Score by Week 24	68 (45.9)	8 (5.3)
P-value	< 0.0001	

Ruxolitinib: Change in Total Symptom Score

Figure 2: Percent Change from Baseline in Total Symptom Score at Week 24 or Last Observation for Each Patient (Study 1)



Worsening of Total Symptom Score is truncated at 150%.

Ruxolitinib Development: Lessons Learned

- Enrolled patients who were symptomatic from their disease (i.e. something to improve)
- Engaged early with FDA to discuss trial endpoints and registration strategy
- Developed a simple PRO tool with a limited number of items of importance to patients
- Captured and submitted real-time PRO data electronically (not burdensome, minimal missing data)
- Assessed response rate AND change in the symptom score and relationship of the two, which was plausible
- Aimed for superiority and had a real statistical analysis plan

Conclusions

- Regular approval requires demonstration of clinical benefit or improvement in a validated surrogate for it.
 - Overall survival
 - Progression-free survival of sufficient magnitude
 - Objective response rate in some cases
 - Organ preservation?
- Accelerated approval relies upon demonstration of an endpoint that is reasonably likely to predict clinical benefit and requires improvement over available therapy & continued study in postmarketing setting.
- The most appropriate design & endpoint will vary based by the disease, pt population, and context of available therapy.



Acknowledgments

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 - Julia Beaver
 - Gideon Blumenthal
 - Richard Pazdur



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Thanks for your attention!
Questions?



SESSION IIA Panel Discussion: Clinical Considerations

Moderators: Fei-Fei Liu, MD, and Ricky Sharma, MD, PhD

Panelists:

Helen Bulbeck, PhD
Zelanna Goldberg, MD, MA
Geoffrey Kim, MD
Andrew B. Sharabi, MD, PhD
Jessica Lowenstein, MS
Tatiana M. Prowell, MD



SESSION IIB: Clinical Considerations

Session Cochairs: Fei-Fei Liu, MD, and Ricky Sharma, MD, PhD

Speakers:

Paul G. Kluetz, MD

Patty Spears

Adam P. Dicker, MD, PhD



Clinical Outcome Assessments

- Quantifying symptoms and function

Paul Kluetz, MD
FDA Oncology Center of Excellence

February 22, 2018
FDA-AACR-ASTRO Workshop on Radiotherapy Combinations



- I have no financial interests to disclose
- I will not discuss off-label use



Traditional (“Regular”) Approval

- Regular approval requires
 - Substantial evidence of Safety and Efficacy
 - Well-controlled clinical trials (usually 2 or more)
 - based on **prolongation of life, a better life or an established surrogate for either of the above**



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COA Glossary & Abbreviations

Clinical Outcome Assessment (COA)

Assessment of a clinical outcome made through report by a clinician, a patient, a non-clinician observer or through a performance-based assessment

Patient Reported Outcome (PRO)

A measurement based on a report that comes directly from the patient about the status of a patient's health condition without amendment or interpretation of the patient's response by a clinician or anyone else.

Ex. Numeric rating scale of pain intensity

1

Clinician Reported Outcome (ClinRO)

A measurement based on a report that comes from trained health-care professional after observation of a patient's health condition.

Ex. Psoriasis Area and Severity Index

2

Observer Reported Outcome (ObsRO)

A measurement based on a report of observable signs, events or behaviors related to a patient's health condition by someone other than the patient or a health professional.

Ex. Observer-completed log of seizure episodes

3

Performance Outcome (PerfO)

A measurement based on a task(s) performed by a patient according to instructions that is administered by a health care profession.

Ex. 6-Minute Walk Test

4



PRO assessments should be held to same standard as other trial measures

Measures in adequate and well-controlled trials:

- Clear statement of objectives
- Distinguish effect of the drug from other influences
- Well-defined and reliable assessments

Reference 21 CFR 314.126, 21 CFR 201.57(c)(7)



What is your PRO Trial Objective?

- **What is your PRO Trial Objective?**
 - Describe the patient experience on treatment?
 - Inform Safety / Tolerability?
 - Inform Efficacy?
- **What is your U.S. regulatory goal for the PRO data?**
 - Supportive data for overall benefit:risk assessment?
 - Descriptive patient experience data in product label?
 - Make a claim of treatment benefit in product label?
 - Substantial evidence of efficacy or improved safety



Using PRO for Efficacy

- **Ruxolitinib for myelofibrosis**
 - Primary endpoint: Radiographic Surrogate Endpoint
 - Reduction in spleen size by (MRI) (Splenic Response Rate)
 - Key secondary endpoint: PRO **Total Symptom Score**
 - Abdominal discomfort, pain under left ribs, night sweats, itching, bone/muscle pain and early satiety
- **Is shrinking a patient's spleen clinical benefit?** The total symptom score was very helpful in correlating the anti-tumor effect with improvements in how patients were feeling (symptoms) and Jakafi™ was granted traditional approval.

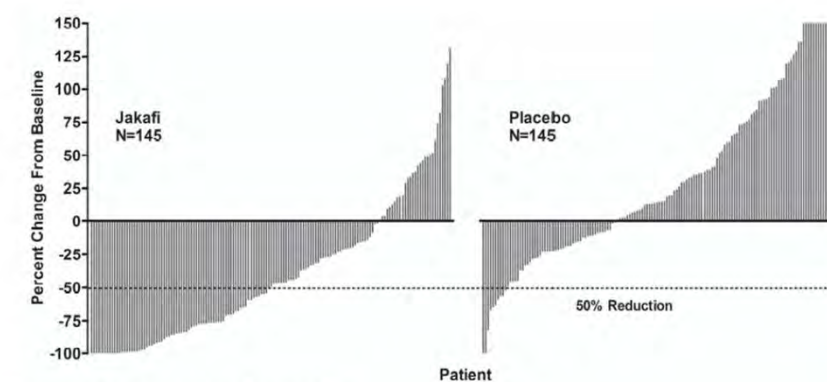


Ruxolitinib FDA Product Label

Table 8: Improvement in Total Symptom Score

	Jakafi (N=148)	Placebo (N=152)
Number (%) of Patients with 50% or Greater Reduction in Total Symptom Score by Week 24	68 (45.9)	8 (5.3)
P-value	< 0.0001	

Figure 2: Percent Change from Baseline in Total Symptom Score at Week 24 or Last Observation for Each Patient (Study 1)



Worsening of Total Symptom Score is truncated at 150%.



Using PRO for Safety/Tolerability

- 2013 Crizotinib Visual Symptoms- VSAQ-ALK
- “The majority of patients on the XALKORI arm in Study 1 (> 50%) reported visual disturbances; these visual disturbances occurred at a frequency of 4-7 days each week, lasted up to 1 minute, and had mild or no impact (scores 0 to 3 out of a maximum score of 10) on daily activities as captured in a patient questionnaire.”



Using PRO for Patient Preference

- **FDA Label for Rituxan Hycela (Subcutaneous delivery)**
- **14.4 Patient Experience**
- After Cycle 8, 477 of 620 patients (77%) reported preferring subcutaneous administration of RITUXAN HYCELA over intravenous rituximab and the most common reason was that administration required less time in the clinic. After Cycle 8, 66 of 620 patients (11%) preferred rituximab intravenous administration and the most common reason was that it felt more comfortable during administration. Forty eight of 620 patients (7.7%) had no preference for the route of administration. Twenty nine subjects of 620 (4.7%) received Cycle 8 but did not complete the preference questionnaire.



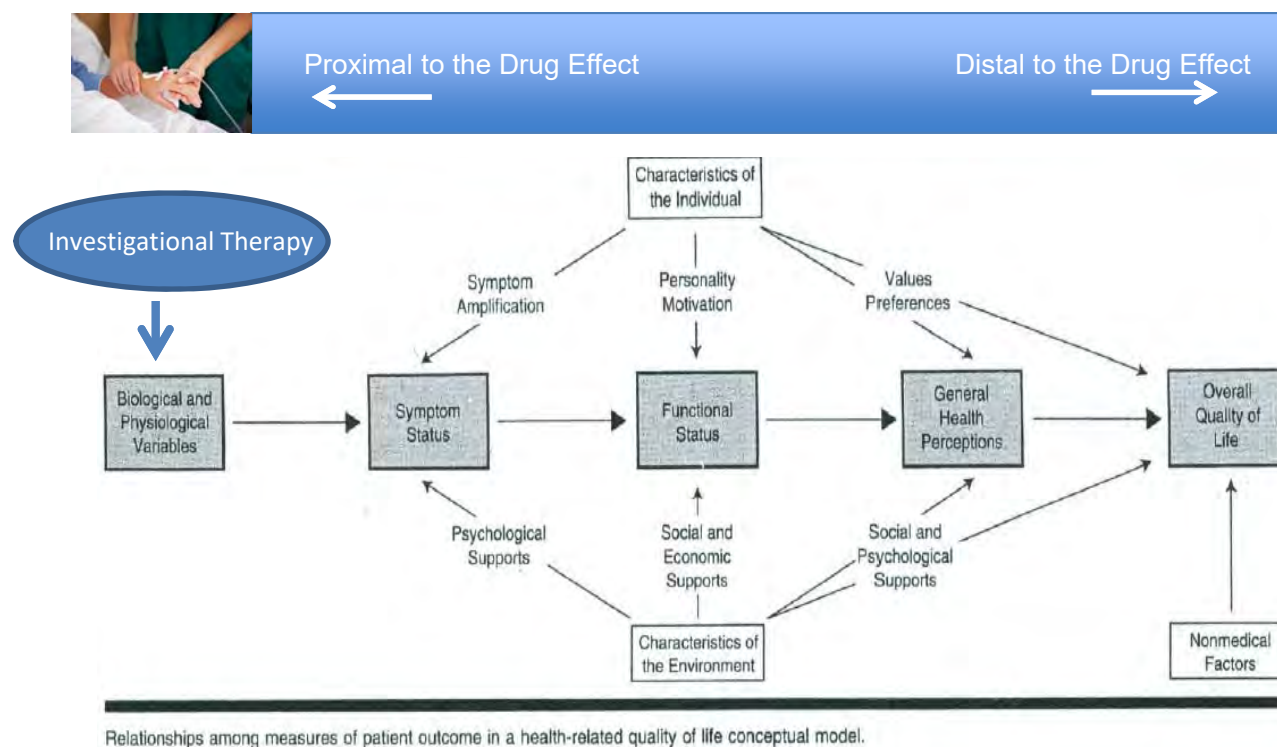
WHAT PRO measures for U.S. regulatory purposes?

Measures in adequate and well-controlled trials:

- Clear statement of objectives
- **Distinguish effect of the drug from other influences**
- Well-defined and reliable assessments

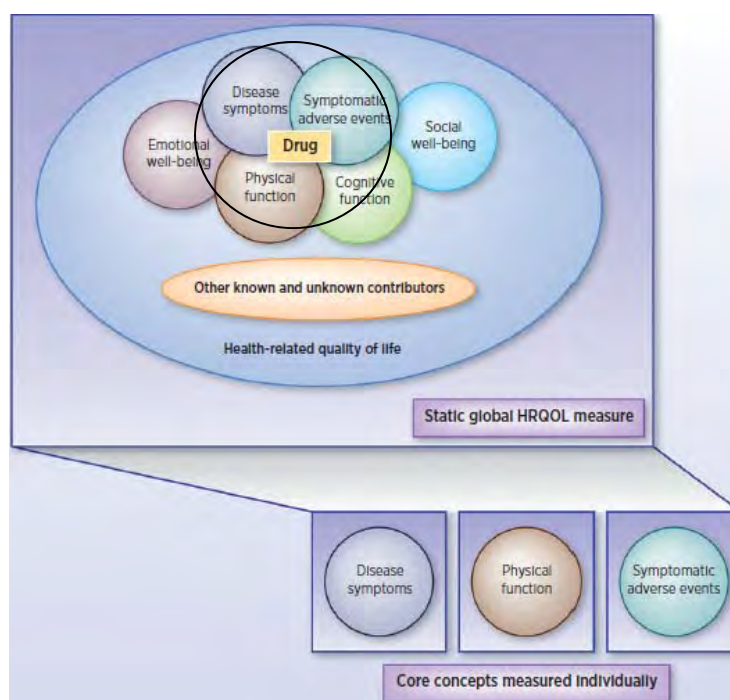
Reference 21 CFR 314.126, 21 CFR 201.57(c)(7)

Distinguishing the Effect of the Drug: The Challenge of Overall Quality of Life



Adapted from Wilson et al., Linking Clinical Variables with HRQOL. *JAMA*, 1995, (273): 59-65.

“Proximal” symptom and functional outcome assessments (Proximal to the Therapy’s Effect)



Proximal symptom and functional assessments are favored for drug labeling

Other aspects of HRQL can still be important to describe the patient experience (but may be more susceptible to bias and non-drug contributors)

Proximal concepts may not be the only PRO data to assess or measure

Focusing on core patient-reported outcomes in cancer clinical trials. *Clin Can Res* 22.7 (2016): 1553-1558.



HOW can I measure a patient-reported symptom or functional outcome...

Measures in adequate and well-controlled trials:

- Clear statement of objectives
- Distinguish effect of the drug from other influences
- **Well-defined and reliable assessments**



What is a “Fit For Purpose” PRO Instrument?

1

Appropriate for its intended use

- Study design, Patient population, Therapy under study

2

Validly and reliably measures concepts that are:

- Clinically relevant
- Important to patients

3

Can be communicated in labeling in a way that is accurate, interpretable, and not misleading (i.e., **well-defined**)

What is meant by “well-defined”?

Physical Function Score

All questions within the PF domain score are measuring physical function (A person’s assessment of his/her ability to carry out important and meaningful day-to-day activities (e.g., self care, domestic) that require physical effort¹⁾

Two reasonable examples include:

PROMIS PF

Are you able to do chores such as vacuuming or yard work?.....

Are you able to go up and down stairs at a normal pace?

Are you able to go for a walk of at least 15 minutes?

Are you able to run errands and shop?

EORTC QLQC30 PF Domain

Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?

Do you have any trouble taking a long walk?

Do you have any trouble taking a short walk outside of the house?

Do you need to stay in bed or a chair during the day?

Do you need help with eating, dressing, washing yourself or using the toilet?

¹Painter, P. & Marcus, R.L. (2013).CJASN, 8(5): 861-872

What is meant by “well-defined”?

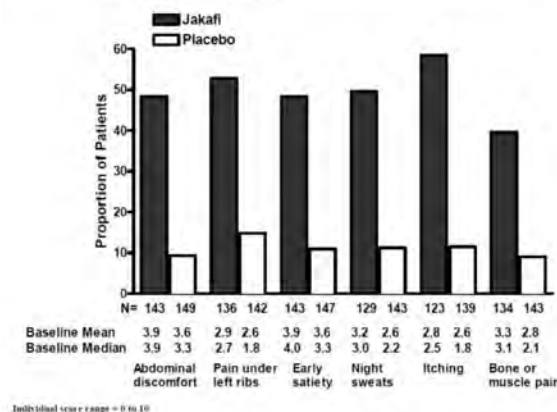
Disease Symptom Score

All questions within the symptom scale are measuring symptoms of the disease (to the extent feasible).

One reasonable example is the Myelofibrosis Symptom Assessment Form

- Abdominal Discomfort
- Pain under left ribs
- Early satiety
- Night sweats
- Itching
- Bone or Muscle Pain

Figure 3: Proportion of Patients With 50% or Greater Reduction in Individual Symptom Scores at Week 24



Source: FDA product label, ruxolitinib-

https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202192lbl.pdf



What is meant by “well-defined”?

Individual Symptoms

Individual symptoms are often considered well-defined and more easily interpretable

One reasonable example is this item from the PRO-CTCAE™ library below:

, what was the SEVERITY of your DRY MOUTH at its WORST?

Also, single item pain questions are commonly used and considered well-defined:

3. Please rate your pain by marking the box beside the number that best describes your pain at its **worst in the last 24 hours.**

☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
No Pain										Pain As Bad As You Can Imagine

NCI website for PRO-CTCAE, <http://healthcaredelivery.cancer.gov/pro-ctcae>

MD Anderson Brief Pain Inventory, <https://www.mdanderson.org/research/departments-labs-institutes/departments-divisions/symptom-research/symptom-assessment-tools.html>



What is NOT well-defined?

- A score where one or more items are not measuring the concept of interest
- Hypothetical example: A fictitious **Fatigue Score**
 - How tired are you?
 - How much weakness do you have?
 - What is your energy level
 - What level of pain do you have?
 - How much numbness and tingling do you have?
 - How would you rate your quality of life?



What is NOT well-defined?

- Hypothetical example: A fictitious **Fatigue Score**
 - How tired are you?
 - How much weakness do you have?
 - What is your energy level
 - What level of pain do you have?
 - How much numbness and tingling do you have?
 - How would you rate your quality of life?

While pain and neuropathy may contribute to one's fatigue, they are not components of fatigue itself. While HRQL may be impacted by fatigue, it is not a component of fatigue.



PRO Instruments

- You can develop your own... However it takes time and MANY measurement tools exist
- Consult with FDA to confirm a PRO measure is “fit for purpose” to maximize your potential for product labeling



Reasonable PRO strategy for typical cancer trial?

“We favor a thoughtful combination of **static questionnaires** and **item banks** or **libraries** to create a balanced, flexible, and modular approach to PRO assessment to address targeted trial objectives and accommodate the needs of multiple stakeholders.”

"Focusing on Core Patient-Reported Outcomes in Cancer Clinical Trials—Response." Clinical Cancer Research 22.22 (2016): 5618-5618.



“The Totality of the Data”

- Standard set of data from Serum Markers, Imaging and Survival with clinician reported adverse events (CTCAE)
- Clinical outcomes to complement the above
 - PRO measures of disease symptoms, treatment symptoms and function are direct measures of important clinical outcomes
 - Increasing interest in cognitive performance tests and wearable devices
- Healthcare utilization have limitations but also can complement our understanding of the risks and benefits



Healthcare Utilization	Baseline		Assessment Period 1		Assessment Period 2		Assessments Period X....	
	Arm A N(%)	Arm B N(%)	Arm A N(%)	Arm B N(%)	Arm A N(%)	Arm B N(%)	Arm A N(%)	Arm B N(%)
ED Visits	n/a	n/a						
Hospitalizations	n/a	n/a						
Opiates								
Antiemetics								
Antidiarrheals								
Oral or IV Steroids								
Transfusions								
- PRBC								
- Platelet								
Growth Factors								
Palliative Procedures (e.g. EBRT, venting g tubes, etc.)								
Other: (describe)								
	N=	N=	N=	N=	N=	N=	N=	N=



Further Considerations: Strength of Endpoint Results

- **What** is being Measured? (**Endpoint Selection**)
 - Direct Benefit (Feels/Functions/Survives) or a Surrogate?
- **How** accurately is it being measured? (**Measurement Characteristics**)
 - How certain can we be regarding the result and magnitude?
 - Susceptibility to Bias
 - Accuracy of the Timing of the Event (When did the event Occur?)
- **How Much** effect on the endpoint is observed? (**Magnitude of Effect**)
 - Large effects seen in trial results can mitigate uncertainty
 - Small effects even in survival can question clinical relevance



Summary

- Clinical outcomes can complement standard efficacy and safety measures
- Combination of generic well-defined functional domains supplemented by disease and treatment symptoms using item libraries and symptom scales
- Instruments should be well-defined to allow for clear communication to patients and providers in labeling
- Additional data on healthcare utilization, mobile device data, etc. can help to support a favorable risk:benefit for patients

A Patient's Perspective on PRO Assessments

Patty Spears
Cancer Patient Research Advocate
University of North Carolina at Chapel Hill
Lineberger Comprehensive Cancer Center
Raleigh, NC
@paspears88

Why PROs?

PROs Consider:

Not only **WHAT IS THE MATTER** with the patient
But also **WHAT MATTERS** to the patient

~~Sandra Finestone

“A PRO is any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else.”

Assessing harms and benefits are very subjective and needs to be done consistently and reliably to actually predict benefits and harms that **ARE IMPORTANT** to patients.



PRO Assessments

Can be used during:

◆ **Clinical Care** – in the Real-World

- This is being tested now and a 2017 ASCO presentation showed a survival advantage (Basch)

◆ **Registration Clinical Trials** (Kluetz)

- To use as an endpoint for **REGISTRATION**
- To collect descriptive information for **PATIENTS**

◆ **Clinical Trials answering an intervention question**

- PRO-CTCAE should be in every trial to measure tolerability
- Other assessments can provide information important for patients about how other patients felt and functioned during a new intervention.

Aid in Decision Making: Benefits vs. Harms

- ◆ Once a drug is approved, patients are faced with treatment decisions.
- ◆ Decision making on the part of the physician and patient is important and very complex.
- ◆ What is necessary to make that decision?



- ☐ **BENEFITS**

What **benefits** are being measured and **are they important to patients?**

- ☐ **HARMS**

What **harms** are being measured and **are they important to patients?**

The best decision is made when everyone is fully informed of the actual benefits and harms that are **important to patients!**

The Clinical Trial Landscape is Changing

- ◆ **Patients** are more involved in research, in clinical trials and in their own healthcare.
 - ◆ **Patients** want to have a voice.
 - ◆ **Patients** need the information from other patients on trials to make **Patient Informed Decisions** about their treatment.
 - ◆ **The process to approve drugs is changing** – accelerated approval, breakthrough designations.
 - ◆ **Precision Medicine Initiative** – it's changing the way we do trials.
- 

So, what's the problem?

◆ **Historically:**

- ❑ QOL questionnaire's have been around since the '70s
- ❑ HR-QOL questionnaire's have been around since the '90s
- ❑ Short forms have been developed for diseases (FACT-B, FACT-P, etc)
- ❑ Specific forms for certain side effects have been developed (Anxiety, Depression, etc)

Why is it still so challenging?

Challenges

- ❑ One size fits all approach (chemotherapy vs targeted therapy, immunotherapy, combination therapies)
- ❑ Although health-related focused, the questions are still very broad
- ❑ New short forms are added on top of each other
- ❑ Measuring items not associated DIRECTLY with the patient experience as it relates to disease and treatment
- ❑ Not a primary objective and not often a secondary objective
- ❑ Analysis and reporting is not done at the same time as the efficacy clinical trial results (later and different journals)
- ❑ Information of HR-QOL is not getting back to the patient and is not aiding patients decision-making.

What do Patients Think are barriers?

◆ **Redundancy**

- ☐ Being asked the same question over and over
- ☐ Redundant questions irritate patients

◆ **Complexity**

- ☐ Vague or unclear questions
- ☐ The answer isn't there and no write in options
- ☐ Not fully understanding the question

◆ **Time**

- ☐ The time it takes to fill them out – too long
 - ☐ The pressure they feel to do it quickly - rushed
 - ☐ Too many questions
- 

What do patients think will help?

◆ **What is being asked is important**

- ☐ Asking about what matters to them
- ☐ Relevant questions to what they are experiencing

◆ **Knowing why the questions are being asked**

- ☐ Knowing what the results are being used for
- ☐ Relevance to them and other patients

◆ **Feedback is important**

- ☐ That their responses are being used in their personal care
- ☐ Being informed about the results and how they were used

◆ **Length/Time matters!**

- ☐ The number of questions and/or the time required
 - ☐ Less questions can be asked more often, more questions less often
- 

What Changes are needed?

Now

- Used in phase 3 trials
- Analyzed separate from efficacy and published at different times
- Information is not shared with patients
- Instrument validation
- Combination of multiple instruments
- Global HR-QOL

Future

- Use in early phase trials (1,2 and 3)
- Analyzed along with efficacy and published together
- Information is shared with public and patients
- Item (question) validation
- Combination of specific items
- Targeted measurements

How do you effectively collect PRO data in trials?

- ◆ **Start Early** - collecting PRO data in early trials (Phase I and II) to better inform the collection of PROs in larger later trials (Phase III)
- ◆ **Develop targeted (precision) PROs for ALL trials**
 - ❑ Asks patients to report what matters to them
 - ❑ Make PROs acceptable to patients to complete
 - ❑ Make PROs an important part of the trial with well-defined purpose and use
 - ❑ Make the PRO endpoints meaningful to patients
 - ❑ Make the PRO information available to patients

Patient Informed PROs - ASKING:
The Right Question ~ at The Right Time ~ in The Right Way

What do you do with PRO data?

◆ **How is the analysis conducted?**

- ☐ Toxicity over Time (ToxT)
- ☐ Percentages
- ☐ Averages or individual items
- ☐ By item category or by patient?

◆ **When is the analysis conducted?**

- ☐ When the primary analysis is done?
- ☐ After the primary is done and published?

◆ **Who sees the data?**

- ☐ Clinicians read journals – which journal is it published in?
- ☐ Patients – how can we get the information to patients?

Patient Informed PROs - ASKING: The Right Question ~ at The Right Time ~ in The Right Way

How can we get PRO information to clinicians and patients?

◆ **Clinicians**

- Publish with primary objective – then everyone will see the information
- Publish with secondary objectives
- Publish in a journal well-read by clinicians

◆ **Patients**

- Identify what patients want or need to hear about
- Present it in a way patients can understand
- Dissemination?
 - ▣ Drug information sheets (for drugs)
 - ▣ Comprehensive Cancer Centers and Oncology Clinic Patient Resources
 - ▣ Non-profits with large constituents with the disease

Patient Informed PROs - ASKING: The Right Question ~ at The Right Time ~ in The Right Way

What would I like to know about a new intervention?

- ◆ How will I feel, but more importantly can I function at a normal level while experiencing a side effect.
- ◆ Can I still work during this treatment? Can I still do all the things I normally do?
- ◆ Does everyone experience a side effect?
- ◆ Is there a chance I will not experience any side effects? Is there a chance I will experience all the side effects?
- ◆ What is the most severe side effect?
- ◆ What is the most burdensome side effect?
- ◆ How did other patients handle the side effects?
- ◆ How long did each side effect last? Was it limited or extended a long time?
- ◆ Are there available medications to help with side effects?

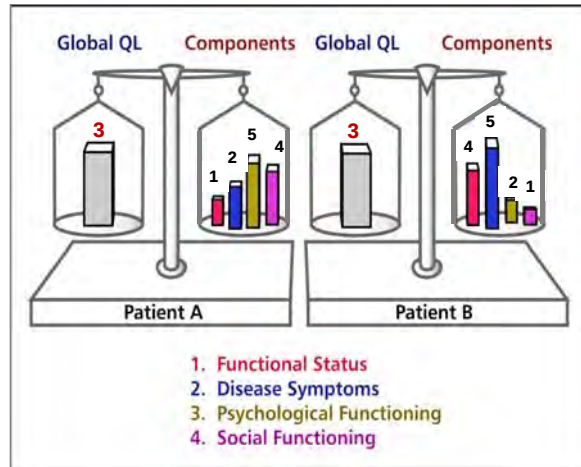
Patient Informed PROs - ASKING: The Right Question ~ at The Right Time ~ in The Right Way

The problem with current analysis methods

- ◆ The problem with averaging
- ◆ What you measure matters
- ◆ Can we get away from 'grouping' everyone in one large group and start looking at:
 - Patient level data
 - Patterns to side effects by patient
 - How certain side effects contribute to physical function
 - Using all the data

Examples....

The problem with averaging



Patient A has a QoL average of **3** of 5
and

Patient B has a QoL average of **3** of 5

	A	B
Functional Status	1	4
Disease Symptom	2	5
Psychological Function	5	2
Social Function	4	1

However, each Patient is having a very different experience!

Adapted from Patti Ganz, Komen Webinar, 2016

What is being measured matters...

- ◆ Time to deterioration (arrows)
 - **Treatment B is best**
 - Treatment A declines rapidly but recovers.
- ◆ Group means across time (dashed lines)
 - **Both treatments A and B are the same**
- ◆ Group means at a single time point (42 weeks)
 - **Treatment A is best**

Such inconsistencies cast doubt on HRQOL and other patient-reported outcome findings in publications from randomised trials, and could affect the overall risk or benefit assessment of drugs and the decisions to register, reimburse, or use these agents in the clinic.

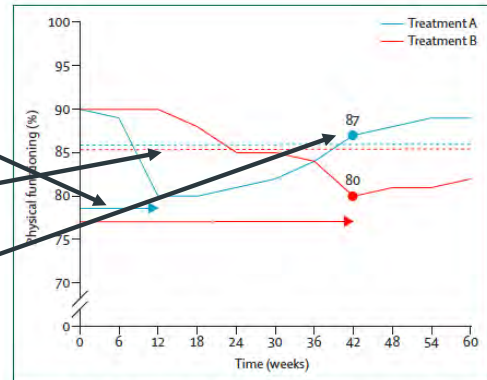
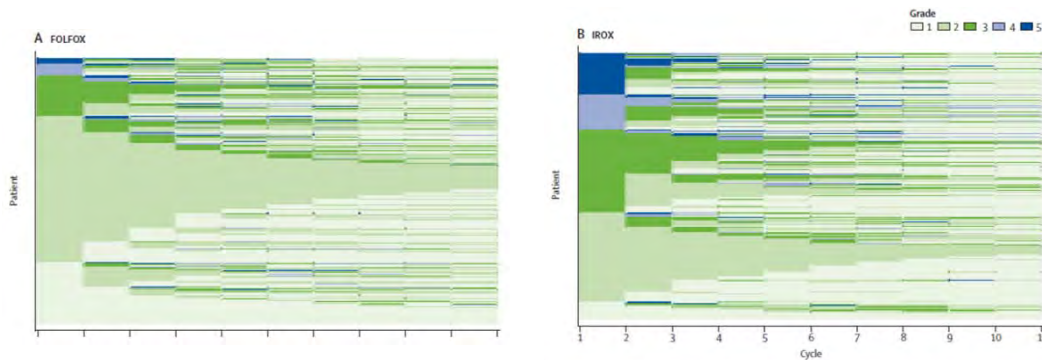


Figure: Hypothetical mean physical functioning scores at every assessment point for two treatment groups
Results from a time to deterioration analysis are represented with arrows. A comparison of group means across time are represented with dashed lines, and a comparison of group means at a single timepoint are represented by values above points at 42 weeks.

Bottomley, Lancet Oncol, 2016

Can we do something different?

- ◆ Examine Adverse events BY PATIENT?
- ◆ Examine Adverse Events as Toxicity over Time (ToxT)



Diarrhea
By patient
FOLFOX vs IROX

**Using all the data
Patient level**

figure 5: Event charts for severity and timing of diarrhoea on an individual patient level in NCCTG N9741
OLFOX=5-fluorouracil plus oxaliplatin. IROX=irinotecan plus oxaliplatin. Each horizontal line represents one
patient. (A) Event chart of diarrhoea in patients given FOLFOX. (B) Event chart of diarrhoea in patients given IROX

Thanarajasingam et al, *Lancet Oncol* 2016; 17: 663–70

Considerations of PRO assessments in combination therapies

- ◆ Drugs and Radiation Therapy are given by different clinicians, usually in different areas. **Coordination of Care**
- ◆ New drugs used in combination with Radiation Therapy are Immunotherapies. These come with very different side effects than typical well-known cancer therapies. **IO side effects and their management is important (ASCO & SITC Guidelines on IO AE management 2018)**
- ◆ Abscopal effects – what to look for is getting harder to determine in combination therapies. **Knowing what to measure and look for is getting harder.**

What can be done to ensure the right PROs are measured at the right time in the right patient?

Patient Informed PROs - ASKING: The Right Question ~ at The Right Time ~ in The Right Way

As was stated earlier...

- ◆ **Start Early** - collecting PRO data in early trials (Phase I and II) to better inform the collection of PROs in larger later trials (Phase III)
 - ▣ ***Epecially considering logistics (2 disciplines and unknown toxicities)***
- ◆ **Develop targeted (precision) PROs for ALL trials**
 - ▣ Asks patients to report what matters to them
 - ▣ ***Find out what to measure – more complex treatment regimens – ask patients***
 - ▣ Make PROs acceptable to patients to complete
 - ▣ ***Where and when PROs filled out during combination treatments – ask patients***
 - ▣ Make PROs an important part of the trial with well-defined purpose and use
 - ▣ Make the PRO information available to patients
 - ▣ ***Measure and let them know what is important to them – ask patients***

Patient Informed PROs - ASKING: The Right Question ~ at The Right Time ~ in The Right Way

Targeted PRO measurements

- ◆ **Rigor** in development and incorporation of PROs in trials
- ◆ **Include patients** and other stakeholders in discussions about relevance, timing and construction of PROs
- ◆ **Process of PRO inclusion during trial development**
 - What is the Treatment (chemo, immuno, biological, radiation, surgery)?
 - What is the Disease (Stage, type)?
 - What is the Endpoint?
 - ▣ What measures are needed?
 - ▣ How often will they be collected?
 - ▣ When will they be analyzed?

Patient Informed PROs - ASKING: The Right Question ~ at The Right Time ~ in The Right Way

Potential Benefits - Gains

- ◆ **Less missing data** (potentially)

- ☐ Patients more likely to fill out the questionnaires that are relevant, take less time and they understand their importance.

- ◆ **Relevant information for Informed decision-making**

- ☐ Physicians and patients will have access to the results to make a more informed decision.

- ◆ **Value will be added**

- ☐ New agents can be approved based upon improving how a patient feels and functions in addition to efficacy and safety.

Patient Informed PROs - ASKING: The Right Question ~ at The Right Time ~ in The Right Way

Incorporation of Digital Health and PROs in Cancer Clinical Trials

Sidney Kimmel Cancer Center

UNTIL EVERY CANCER IS CURED

Adam P Dicker, MD, PhD

Disclosures:

Dr. Dicker is an employee of Thomas Jefferson University

- Additional support from:
 - National Cancer Institute
 - Prostate Cancer Foundation
 - Prostate Cancer Research Program (Dept. of Defense)
 - NRG Oncology

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- Percy Ivy, MD
- Christine Tran, MS
- Stephen Blattner, MD
- Mark Tykocinski, MD



Internet Use

U.S. ADULTS 2015

73% Online Daily

Device Ownership

U.S. ADULTS 2015

Health Information Seeking
U.S. ADULTS 2015

70% Search Internet First for Health or Medical Information



1 in 20
Google Searches
Are for Health-Related
Information

A web-based version of this report is available at: <https://PresCancerPanel.cancer.gov/report/connectedhealth>

What is Digital Health?

- Digital health uses technology to deliver care and information to patients and providers that is more convenient, cost effective, and personalized.
- It takes advantage of a variety of hardware (cell phones, computers, cameras, and sensors) and software (including mobile apps, games, computer programs; and social media).
- Digital health has the potential to improve outcomes, decrease costs, improve efficiency, and deliver care and information in entirely new ways.

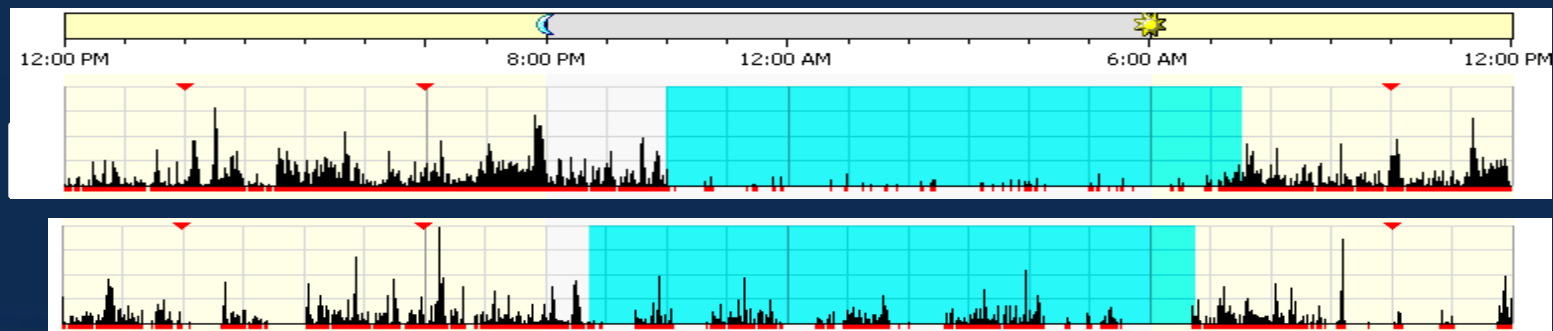
Passive Activity and Sleep Monitoring



MiniMitter Actiwatches



Actigraph Link





U.S. Department of Health and Human Services



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The guidance documents listed here are FDA guidances with Digital Health content and are intended to help industry and FDA staff understand FDA's regulation of digital health products.

Please note that the 21st Century Cures Act (12/13/2016) clarified FDA's **regulation of medical software**. The new law amended the definition of "device" in the Food, Drug and Cosmetic Act to exclude certain software functions, including some of those in the guidance documents below.

If you have questions about how the 21st Century Cures Act affects your products, or if you have comments on how the FDA should regulate medical software, please email digitalhealth@fda.hhs.gov.

Journals focused on Digital Health (partial list)

Article | 19 February 2018 | **OPEN**

Delivering digital cognitive behavioral therapy for insomnia at scale: does using a wearable device to estimate sleep influence therapy?

Annemarie I. Luik, Pedro Farias Machado & Colin A. Espie

Article | 12 February 2018 | **OPEN**

Frequent discussion of insomnia and weight gain with glucocorticoid therapy: an analysis of Twitter posts

Rikesh Patel, Maksim Belousov [...] William G. Dixon

Article | 25 January 2018 | **OPEN**

Highly flexible, wearable, and disposable cardiac biosensors for remote and ambulatory monitoring

Stephen P. Lee, Grace Ha [...] Roozbeh Ghaffari

Perspective | 25 January 2018 | **OPEN**

Mobile and pervasive computing technologies and the future of Alzheimer's clinical trials

P. Murali Doraiswamy, Vaibhav A. Narayan & Hussein K. Manji

Perspective | 15 January 2018 | **OPEN**

Population measurement for health systems

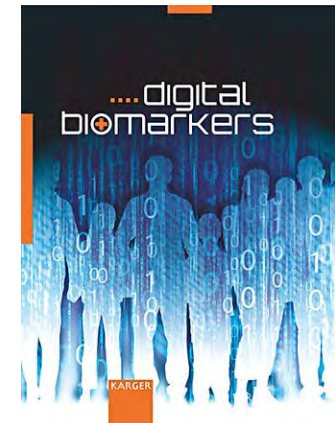
Bruce R. Schatz

Review Article | 15 January 2018 | **OPEN**

Impact of remote patient monitoring on clinical outcomes: an updated meta-analysis of randomized controlled trials

Benjamin Noah, Michelle S. Keller [...] Brennan M. R. Spiegel

[All Articles >>](#)



**JCOTM | CLINICAL CANCER
INFORMATICS**
An American Society of Clinical Oncology® journal

npj | Digital Medicine



JMIR
Publications
The Leading eHealth Publisher

[Journal of Medical Internet Research](#)

Four Questions:

- How do we develop PROs with new drugs?
 - example: citizen science with patients
- What are the opportunities for wearables and/or ePROs?
 - example: prediction of toxicity
- How can ePROs & Apps improve adherence
 - example: mitigation of drug toxicity
- What can remote monitoring provide for disease management?
 - example: NSCLC
- How to we nurture and develop this space
 - example: Sidney Kimmel Medical College & Cancer Center,
Thomas Jefferson University, Phila, PA



BONNIE J. ADDARIO
LUNG CANCER
FOUNDATION

***Transform lung cancer into a
chronically managed disease***





The Lung Cancer Registry



- **Overview:**
 - Patient community-powered resource that drives discovery based on patient data and reported outcomes
 - The Registry gives patients a “voice” and access to view how patients are approaching their treatment and managing their care
 - Researchers and clinicians can register for a professional account and access the de-identified data. You can view and search the data, learn how patients report their lung cancer history from diagnosis, through treatment and more & submit proposals for conducting research in the registry.
- **Goals/Objectives/Strategy**
 - Launched in 2017 the Registry already has nearly 600 patients in more than a dozen countries
 - The goal of the registry is to grow by adding more patients and to engage with researchers & clinicians to learn about their needs as we expand the registry capabilities.
 - First registry study launched in January 2018 on *Immunotherapy PRO*
 - As we collaboratively build this comprehensive patient database, we encourage you to invite all your patients to participate.
- The Lung Cancer Registry - <https://vimeo.com/187115666>

***Participate in the Lung Cancer Registry. A community powered by patients and the patient voice.
Together moving lung cancer developments forward.***



The Lung Cancer Registry



Lung Cancer Patients to Help Medical Community Understand the Side Effects of Immunotherapy Treatment

Study designed to help doctors better understand and educate patients with non-small cell lung cancer on what to expect when undergoing immunotherapy treatment.

"Immunotherapy, along with targeted therapy, has helped transform the treatment of lung cancer over the past decade ,said Bonnie J. Addario, 14-year lung cancer survivor and founder of the ALCF. Gathering information from patients and passing that knowledge on to other lung cancer patients accurately and quickly is helping patients live longer, which is our goal."

"We're inspired by the opportunity to put the Lung Cancer Patient Registry to innovative use," said Harold P. Wimmer, National President and CEO of the American Lung Association. "The patient-provided data used in this new trial will allow us to gain knowledge from patients directly and better inform treatment."

"Patient-reported outcomes (PRO's) can help show clinical benefit in reducing disease related symptoms, provide more accurate estimates of toxicity, help model treatment costs and improve symptom management," said Adam P. Dicker, M.D., PhD, Sidney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA . "These toxicities really do have costs, and it's important for patients to know how much out-of-pocket costs they might incur."

Participate in the Lung Cancer Registry. A community powered by patients and the patient voice. Together moving lung cancer developments forward



The Lung Cancer Registry



Who can join?

- Anyone diagnosed with lung cancer. Information can be submitted by a caregiver on behalf of the patient.
- Researchers and clinicians get access to information on participants as an open-access repository as well as a research tool

How do I join?

- Log into and sign up at: www.lungcancerregistry.org
- Patients – register under the “Sign-Up” link.
- Researchers and Clinicians – apply for a professional account under the “Researcher” link.

How to participate in/engage with Patient Registry?

- Contact Sandra S. Shaw – Director of the Lung Cancer Registry at sandra@lungcancerfoundation.org
- Learn about resources for patients as well as for clinicians and researchers

Our Members:



INTERNATIONAL
ASSOCIATION
FOR THE STUDY
OF LUNG CANCER
Conquering Thoracic Cancers Worldwide



Participate in the Lung Cancer Registry. A community powered by patients and the patient voice. Together moving lung cancer developments forward

LUNG CANCER PATIENT SURVEY: CONTENTS

1. Registered Users: Heat Maps
2. Registered Users
3. Participant Status
4. Deceased Information
5. Symptoms
6. Non Lung Cancer Treatment
7. Diagnosis
8. Other Cancer History
9. Testing
10. Molecular Testing
11. Treatment-Therapy
12. Current Treatment or Therapy
13. Current Surgery
14. Current Chemotherapy
15. Current Targeted Molecular Therapy
16. Current Radiation Therapy
17. Current Immunotherapy
18. Prior Treatment
19. Prior Treatment- Surgery
20. Prior Treatment- Chemotherapy
21. Prior Treatment- Targeted Molecular Therapy
22. Prior Treatment- Radiation Therapy
23. Prior Treatment- Immunotherapy
24. Physician
25. Family Members
26. General Questions

I. REGISTERED PATIENTS: WORLD HEAT MAP

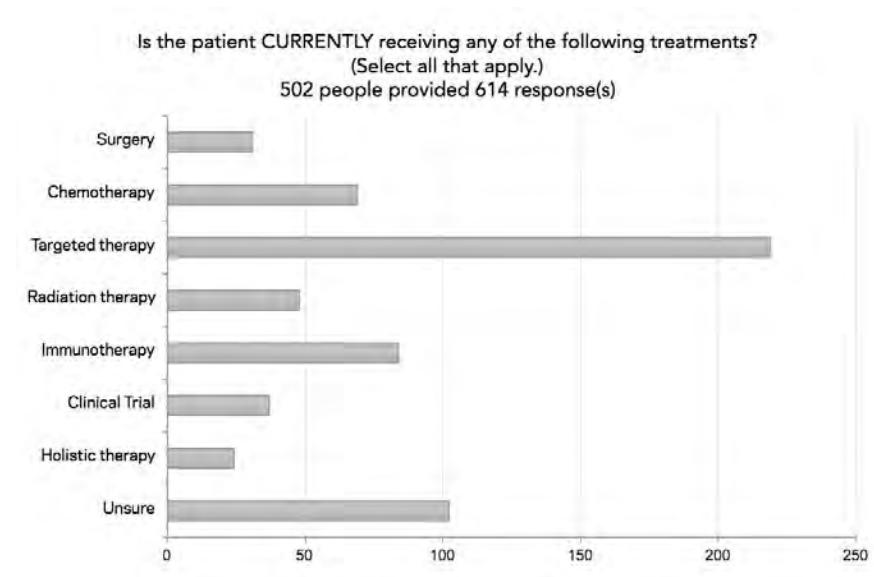
EXPLORE DATA

Select from the left menu to view the responses to surveys you have completed.

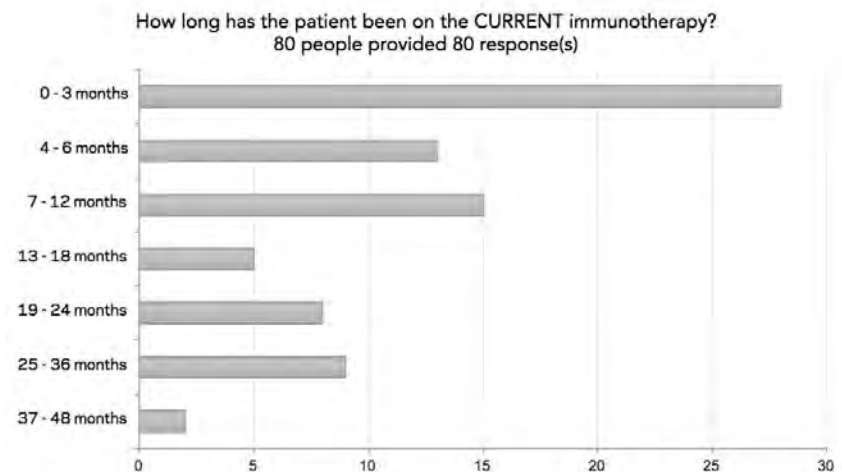
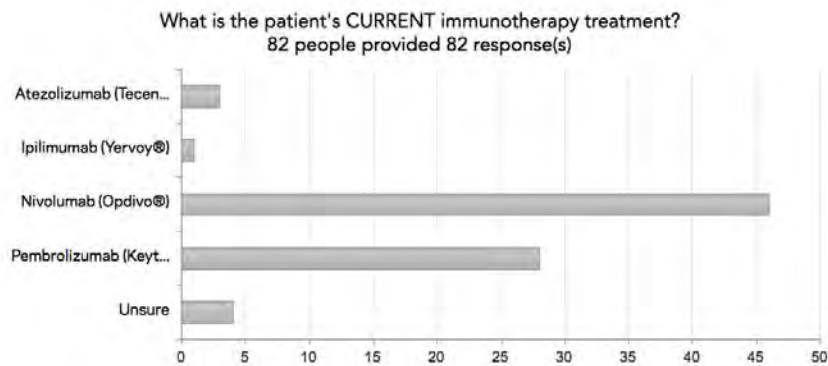


Registered Patients. Click on the map to zoom in or use the map controls to navigate.

12. CURRENT TREATMENT OR THERAPY



17. CURRENT IMMUNOTHERAPY



Abstract submitted to ASCO

Four Questions:

- How do we develop PROs with new drugs?
 - example: citizen science with patients
- What are the opportunities for wearables and/or ePROs?
 - example: prediction of toxicity
- How can ePROs & Apps improve adherence
 - example: mitigation of drug toxicity
- What can remote monitoring provide for drug development?
 - example: NSCLC
- How to we nurture and develop this space
 - example: Sidney Kimmel Medical College, Sidney Kimmel Cancer Center, Thomas Jefferson University, Phila, PA

Unmet need: Lung Cancer

- In early stage and locally advanced lung cancer patients, we lack a tool to remotely monitor patients who are at risk for developing radiation pneumonitis (RP).
- In patients with metastatic lung cancer, we lack a tool to remotely monitor patients at risk for decline in functional status.

Hypothesis:

- A combination of electronic patient reported outcomes and remote monitoring will improve the lives of patients

ePROs +



Our Unique Wearable Symptom Acquisition System

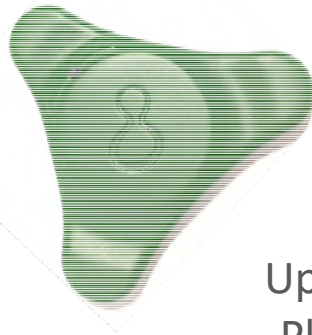
All-In-One Wearable Cough Counter for Consumer

Full Onboard Processing for:

- **Cough Counting**
- Respiration
- Wheeze
- Heart Rate
- Temperature
- Activity

Alerts

Inhaler Detection



Upper Torso
Placement

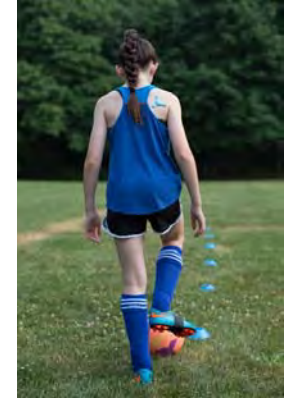
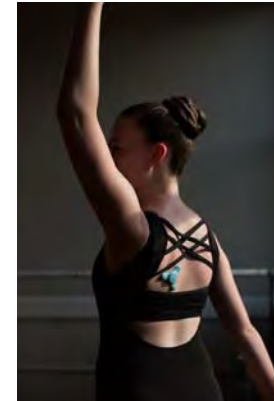
Rechargeable
Battery

Bedside Monitoring

Adhesive Backing

Activity Proof

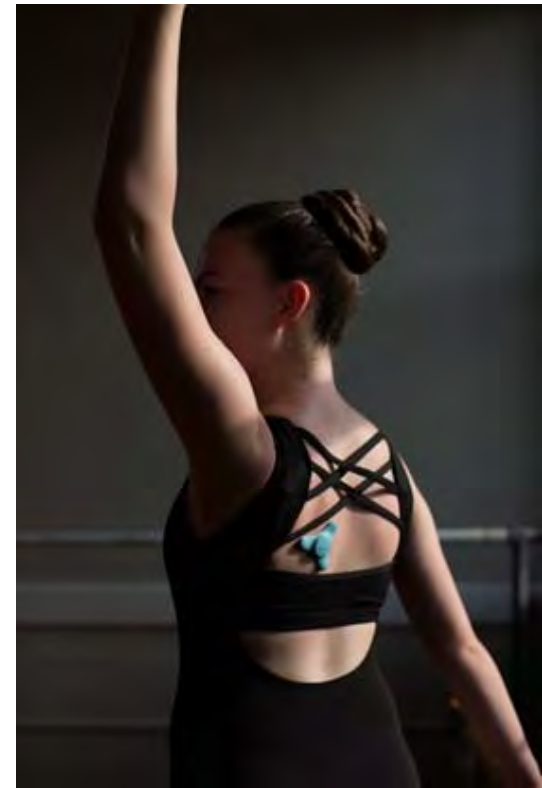
Wireless



User Centric Features

Unique Symptom Acquisition System Wearable

- Flexible and Comfortable
- Upper Torso Placement
- Rechargeable Battery
- Bedside Monitoring
- Adhesive Backing
- Activity Proof
- Wireless



RSM Data Acquisition Platform

Wearable



AI driven symptom trend and awareness features

Full on-board processing of:
cough, wheeze, activity, respiration, heart rate and skin temperature

App



Behavioral change metrics

Additional metrics
personalization
Notifications

Web Portal



Data Science leveraged portal

Identifying population level metrics, while factoring individual responses

Clinical Trial Benefits of Wearable

- Designed to reduce cost in major areas of clinical trials
- Complete and accurate respiratory monitoring for clinical trials
- Events not previously monitored now can be monitored including respiratory responses, abnormal chest sounds and other significant events
- Understand the impact and responses continuously in real-time and receive unparalleled access to objective data on participant's individual responses
- Unique algorithm technology that is customizable to clinical trial's needs

Clinical Trial Benefits of App

- Journaling is compiled in the easy-to-navigate app, eliminating the need to wade through reams of paper to decipher participants' journals or logs
- Set medication and reporting schedules for trial participants with general trial reminders
- Trial participants push data to their phones or to the cloud (yours or HCO's)
- Study data can be blinded from participants or shared with them
- Data is transmitted using encrypted secure transmission services either from the wearable to a smartphone via BLE or directly from the wearable to the cloud via Wi-Fi

A pilot study investigating the feasibility of ADAMM (Automated Device for Asthma Monitoring and Management) in combination with electronic patient-reported outcomes in adult patients with lung cancer

Primary Study Endpoint

Percentage of hours per day and percentage of days per study period that patients wear the device (**compliance**)

Secondary Study Endpoints

1. Percentage of eligible patients who agree to participate in this study (recruitment feasibility)
2. Percentage of patients who deem ADAMM acceptable/tolerable (via acceptance score of ≥ 28) (acceptability/tolerability)
3. Percentage of patients who complete ePRO at defined intervals (compliance with ePROs)

**A pilot study investigating the feasibility of ADAMM
(Automated Device for Asthma Monitoring and Management) in combination
with electronic patient-reported outcomes in adult patients with lung cancer**

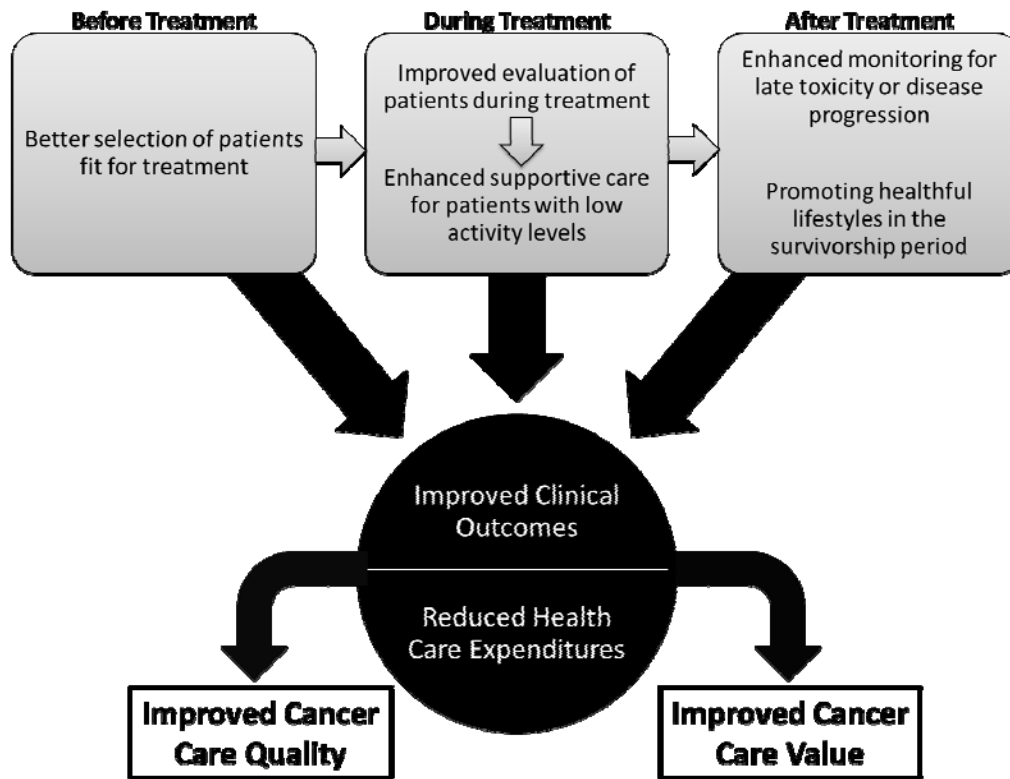
Inclusion Criteria

1. Patients are capable of giving informed consent
2. Patients are being treated with RT or chemoRT
3. Patients have either metastatic or non-metastatic lung cancer
4. Speak English

ePRO tools (via clinic ipad weekly):

1. MDASI-Lung
2. UCSD Shortness of Breath Questionnaire
3. PROMIS Dyspnea short form
4. Brief fatigue inventory

Why Study Activity Monitoring in Cancer Care?

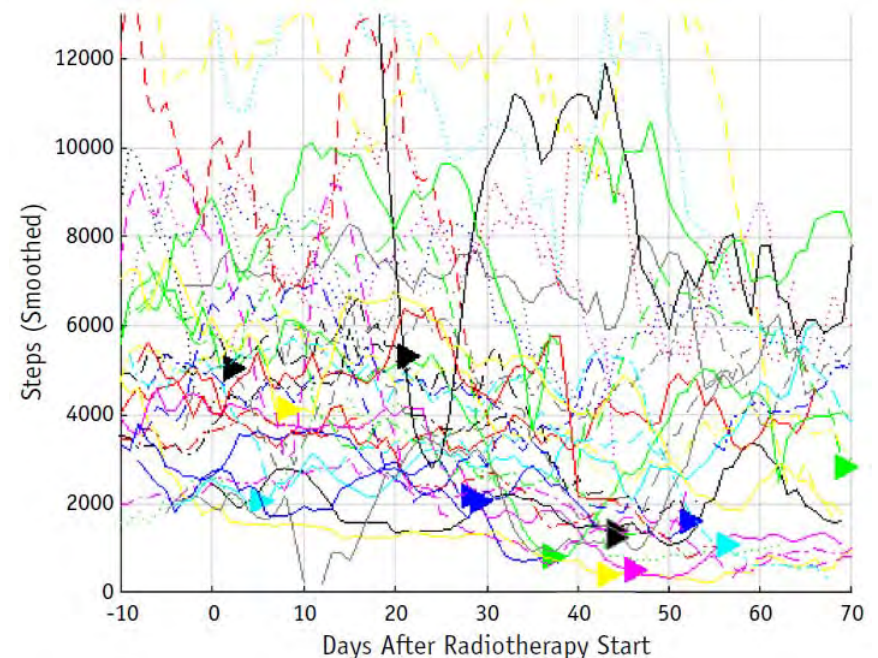


Nitin Ohri, MD
Albert Einstein

Continuous Activity Monitoring During Concurrent Chemoradiotherapy

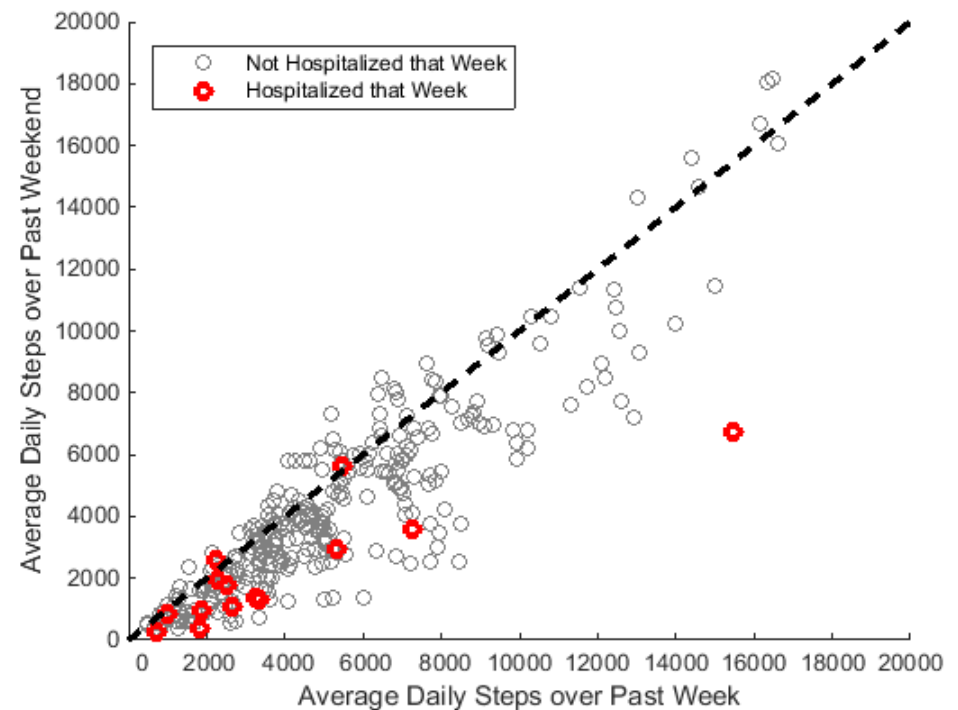
Nitin Ohri, MD,* Rafi Kabarriti, MD,* William R. Bodner, MD,*
Keyur J. Mehta, MD,* Viswanathan Shankar, DrPH,[†]
Balazs Halmos, MD,[‡] Missak Haigentz, Jr, MD,[‡] Bruce Rapkin, PhD,[†]
Chandan Guha, MBBS, PhD,* Shalom Kalnicki, MD,*
and Madhur Garg, MD*

- Key findings:
 - Step counts were obtained for 94% of days during patients' treatment courses.
 - 14/38 subjects were hospitalized due to acute toxicities (triangles).
 - 38% reduction in the risk of hospitalization for every 1,000 steps taken each day (HR=0.62, $p<0.001$)



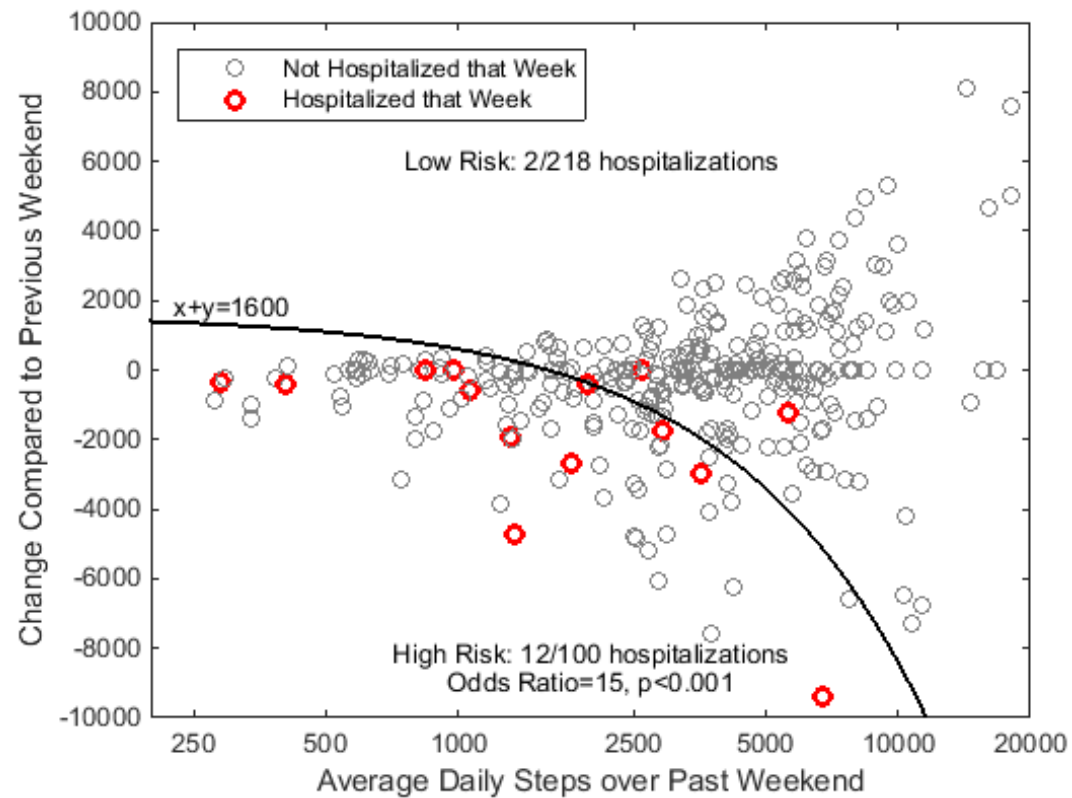
Weekend Step Counts

- Multivariable analysis revealed that patients average 1,400 fewer steps/day on weekends compared with weekdays.
- Weekend step counts were the best predictors of short-term hospitalization risk.



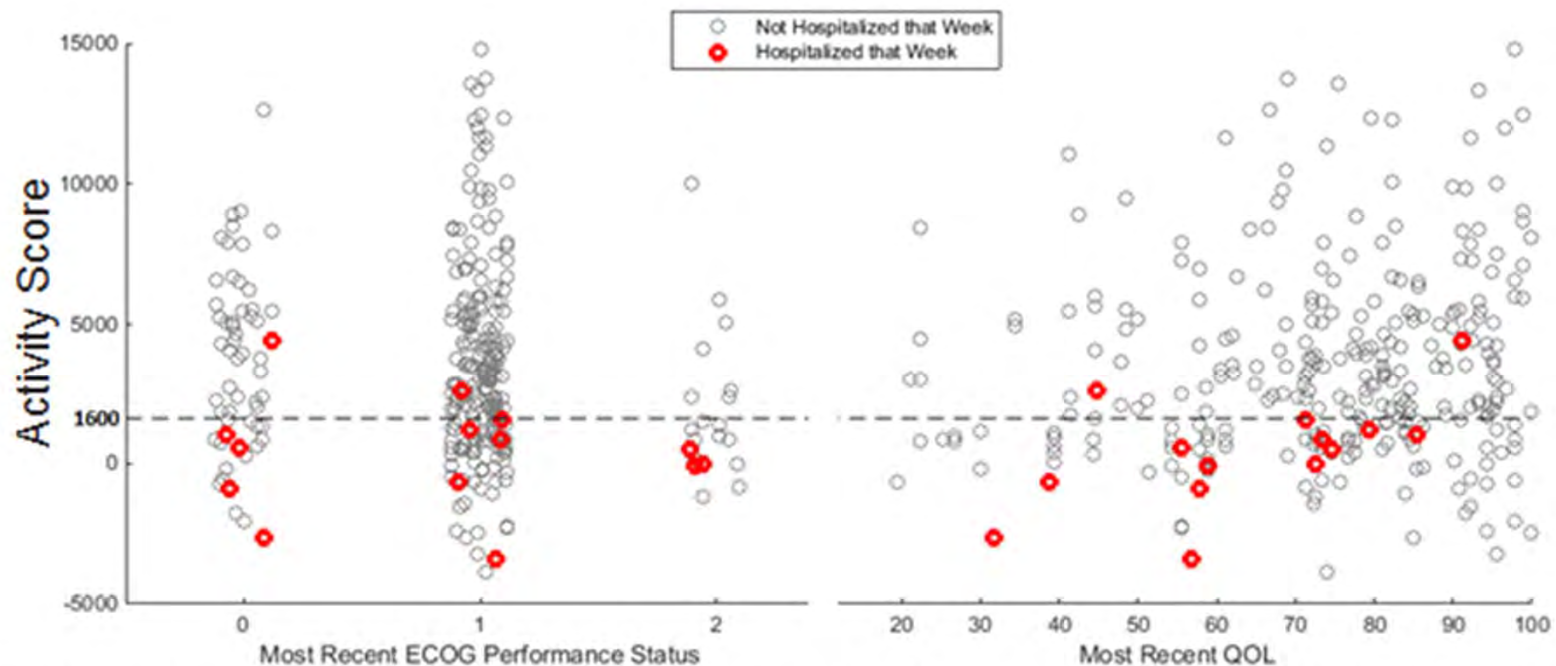
Nitin Ohri, MD
Albert Einstein

“Activity Score” Predicts Hospitalizations



Nitin Ohri, MD
Albert Einstein

Predicting Hospitalization: Activity Score v. PS and QoL



Recent step counts are better predictors of hospitalization risk than physician-rated performance status (left, where 4 patients with PS=0 were hospitalized) and patient reported QoL (average score on EORTC QLC-C30, right).

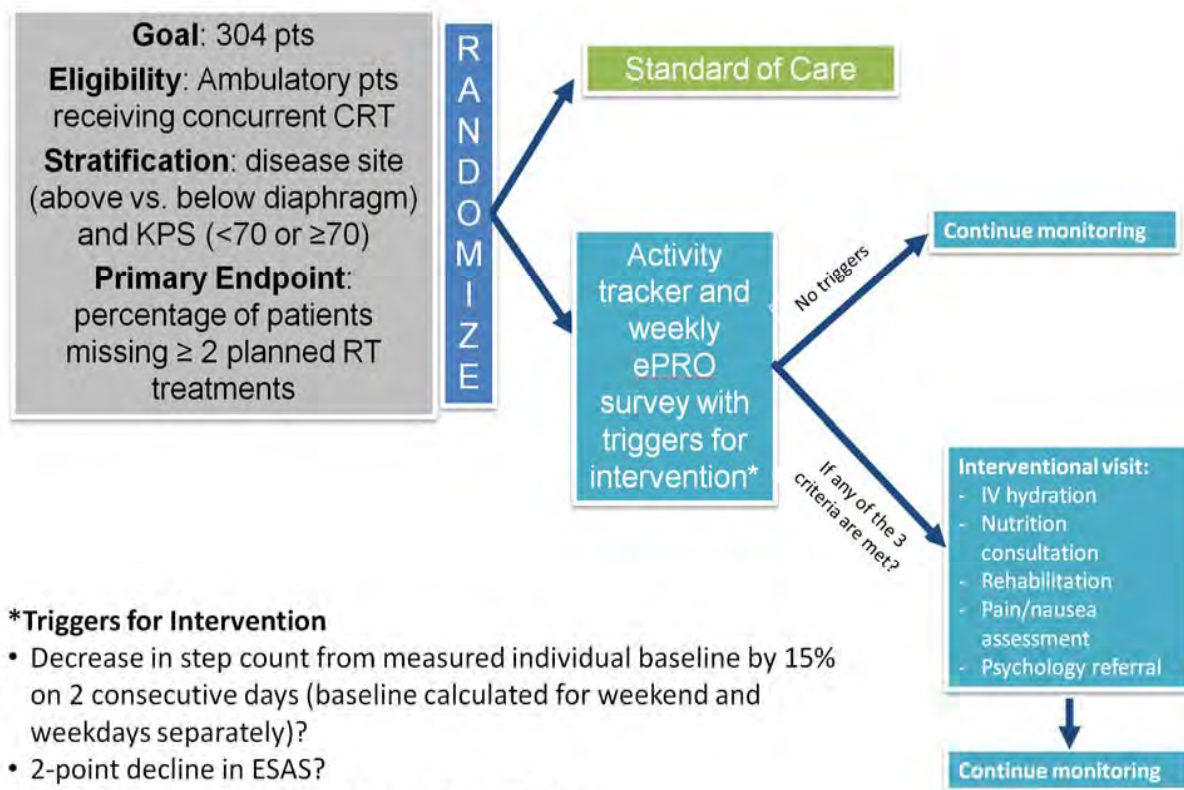
PRO-RAM: The investigation of remote electronic Patient-Reported Outcomes in combination with Remote Activity Monitoring to reduce missed treatments in patients receiving concomitant chemoradiotherapy



Noelle Williams

- Aim 1: To investigate compliance rates with the activity trackers (% wearing / syncing the device over total prescribed time) and ePRO completion.
- Aim 2: To explore correlations between validated ePROs (Edmonton Symptom Assessment Tool and EQ-5D-5L) and activity tracker data and to characterize types and costs of interventions initiated by our care team that were triggered by declining step data and/or ePRO scores.
- Aim 3: To prospectively demonstrate that an early targeted intervention system (triage visit with subsequent outpatient supportive care measures) as triggered by remote ePRO scores and activity tracker data for patients receiving chemoradiotherapy (CRT) will reduce the rates of patients missing ≥ 2 RT treatment visits when compared to the usual model of care.

Randomized phase II study investigating remote activity monitoring with remote electronic patient-reported outcomes to reduce missed treatments in patients receiving concomitant chemoradiotherapy



***Triggers for Intervention**

- Decrease in step count from measured individual baseline by 15% on 2 consecutive days (baseline calculated for weekend and weekdays separately)?
- 2-point decline in ESAS?
- 10% decline in EQ5D visual analogue scale?

Four Questions:

- How do we develop PROs with new drugs?
 - example: citizen science with patients
- What are the opportunities for wearables and/or ePROs?
 - prediction of toxicity
- **How can ePROs & Apps improve adherence**
 - mitigation of drug toxicity
- What can remote monitoring provide for drug development?
 - example: NSCLC
- How to we nurture and develop this space
 - example: Sidney Kimmel Medical College, Sidney Kimmel Cancer Center, Thomas Jefferson University, Phila, PA

Technology APPLications: Use of digital health technology to enable drug development

"A pilot study to evaluate the feasibility, usability, and perceived satisfaction with eCO (eCediranib-Olaparib), a mobile application for side effect monitoring and reporting, in women with recurrent ovarian cancer."

eCO (an investigational medical device) consists of:

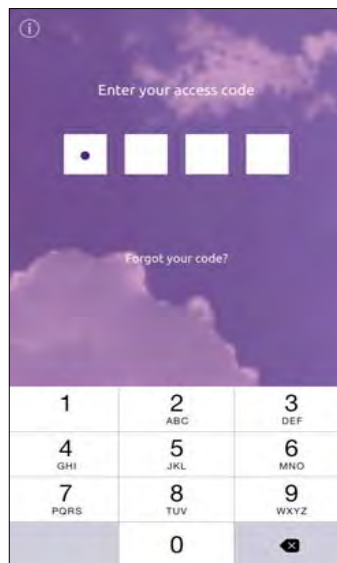
- **A mobile device allowing patients to:**
 - Record blood pressure checks manually or using a Bluetooth BP monitor
 - Report diarrhea episodes when needed
 - Report symptoms-related data
 - Receive side-effect management recommendations
 - Contact study team
- **A web portal allowing the study team to:**
 - Monitor patients' side effects (hypertension/diarrhea)
 - Receive notifications based on pre-determined criteria
 - View study protocol sections related to hypertension and diarrhea recommendations



Web Portal View of Patient Data



Secure Access for Patients

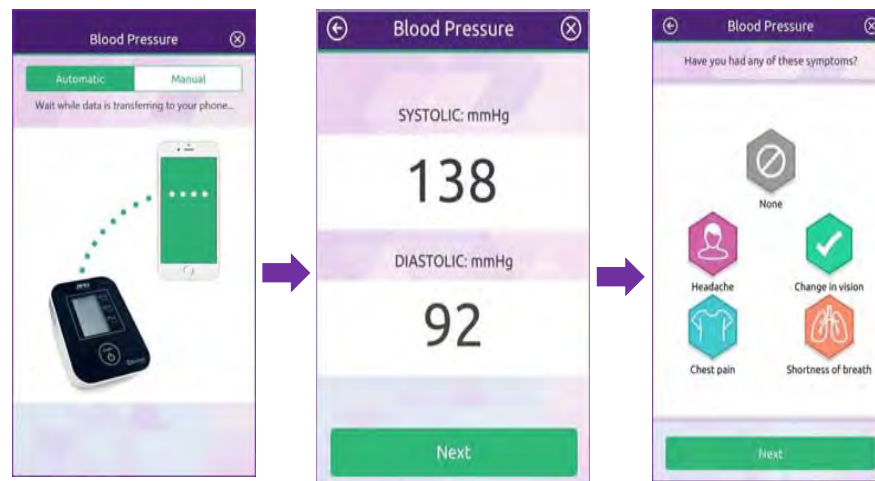


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- Data is stored on a secure server and not on patient phone
- Access is prescription only
- Access code entry adds additional layer of security for patients



Blood Pressure



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Diarrhea

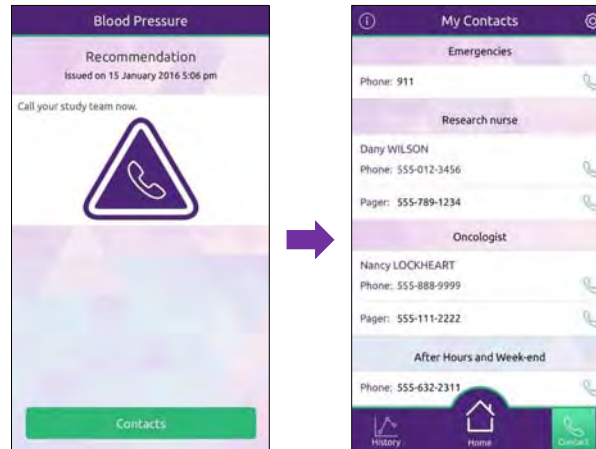
The image displays three sequential screenshots of a mobile application titled "Diarrhea".

Screenshot 1: Record your bowel movements
The screen shows a header "Record your bowel movements" and a sub-header "My usual number of stools/day is 3". Below this, it asks "Over the past 24h, my number of bowel movements was:" and features a numeric keypad with a minus sign, the number "4", and a plus sign. A green "Next" button is at the bottom.

Screenshot 2: Have you had any of these symptoms?
The screen shows a header "Have you had any of these symptoms?". It features four hexagonal icons: "None" (top), "Diarrhea feels uncontrollable" (left), "Severe cramping" (right), and "Blood in stools*" (bottom). A green "Next" button is at the bottom.

Screenshot 3: Recommendation
The screen shows a header "Recommendation" with a timestamp "Issued on 15 January 2016 5:08 pm". It lists four numbered recommendations: 1. "Take 1 loperamide (Imodium®) after each loose bowel movement. Do not take more than 8 pills in 24 hours.", 2. "Drink fluids.", 3. "Start BRAT diet." (accompanied by images of bananas, rice, applesauce, and toast), and 4. "If your diarrhea gets worse, call your study team." A green "OK" button is at the bottom.

Real Time Collaboration When Needed



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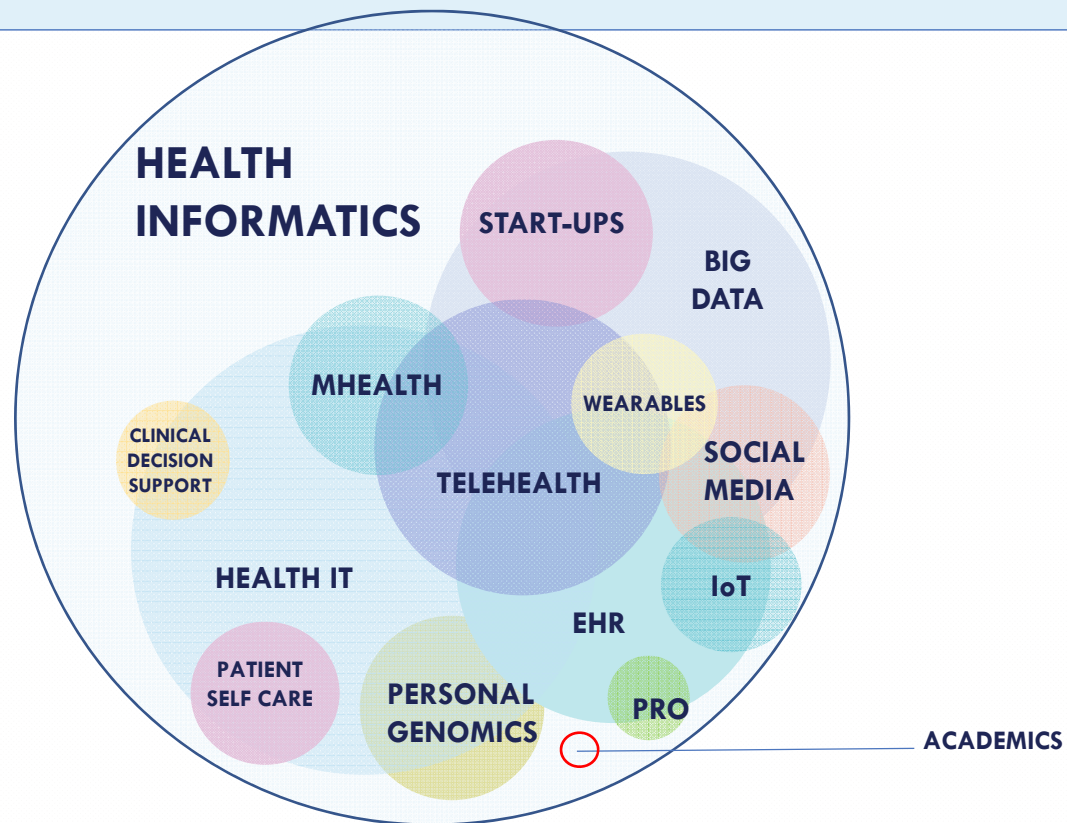
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Manuscript accepted to JCO Clinical Cancer Informatics

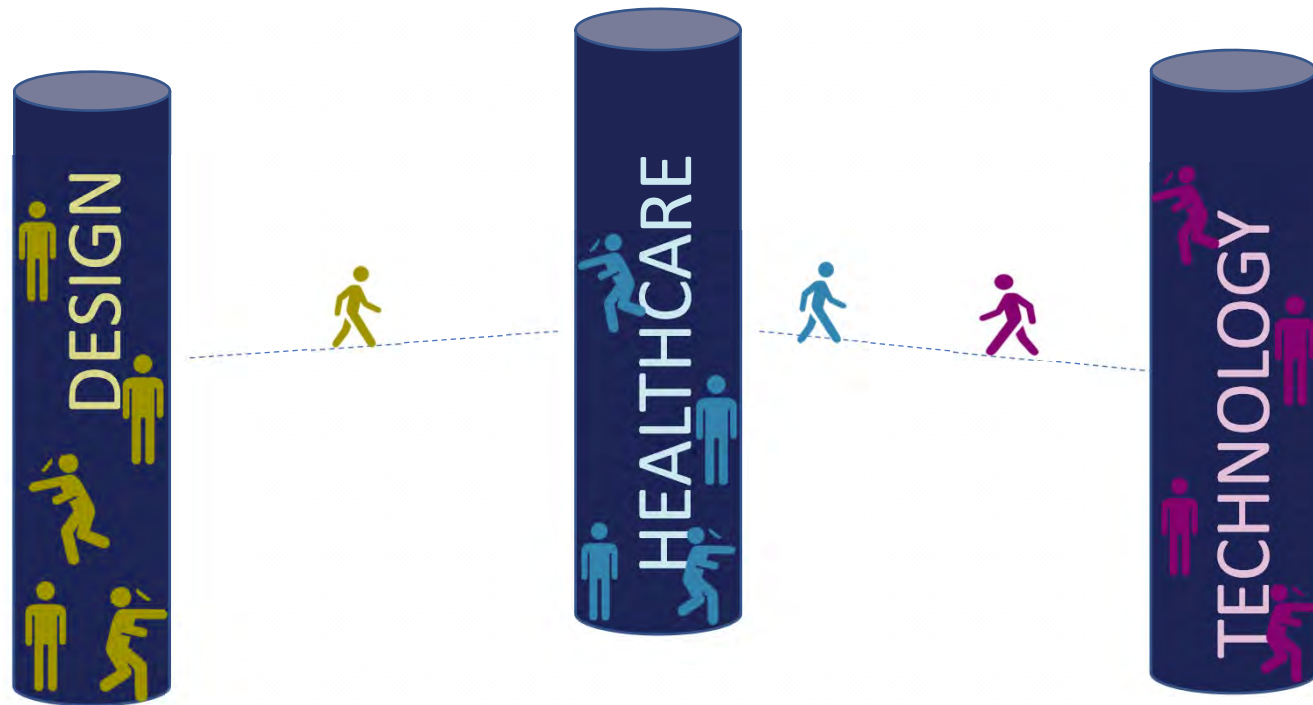
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THE DIGITAL HEALTH LANDSCAPE



PROBLEM



SOLUTION



Jefferson Institute of Digital Health

Approach, Sample Curriculum and Degrees

APPROACH

Interdisciplinary/ Cross
Professional Teams

Industry Infused

Practicum Centered

Real and Virtual

Hybrid Faculty

Co-Ops

CURRICULUM

Technology / Cybersecurity

Health/Biology

Health Care Systems

Design for Health

Data Analytics

Business Intelligence

Interdisciplinary Innovation Entrepreneurship

Computational Thinking

Health System Sciences (HSS)

DEGREES

BS/MS - Healthcare Innovation

BS/MS – Digital Applications

MS – Digital Health

MS - Applied Health Technology

Executive Masters –
Digital Health

Executive Masters –
Healthcare Practice in the Digital Age

PhD - Health Innovation & Design

ExMDHMS Digital Health

Sample/Proposed Foundational Courses

Course Clusters – all Masters’ Level	Anticipated Participants		
	Healthcare Learners	Tech Learners	Design Learners
Healthcare system overview: Evolution, Organization, Delivery, Culture, Finance, Architecture, Design, Innovation History, HSS		X	X
Introduction to Design Thinking and Innovation: Fundamentals of functional design and materials	X		
Comparative technology architecture	X		X
Fundamentals of clinical and basic research: Design, interpretation, funding, operations and management		X	X
Fundamentals of biologic and physiologic monitoring		X	X
Fundamentals of population science and population health		X	X
Healthcare safety and quality management: Systems, measurement, reporting, improvement science		X	X
Principles of user experience	X	X	X
Fundamentals of health information technology and clinical informatics: Health tech, data and systems, interoperability, information exchange	X	X	X
Seminars in cross disciplinary teams: Function, leadership, effectiveness	X	X	X
Clinical and econometric outcomes analysis	X	X	X
Organization of the biotechnology industry and markets	X	X	X
Introduction to business and legal issues for entrepreneurs: IP law and practices, contracts, funding sources, business structures	X	X	X
Fundamentals of digital and mobile design methods	X		
Leadership: Seminar Organizational Integration of Innovation	X	X	X

JeffMD Digital Health



Robert Bloom



Cassra Clarke



Justin Dang



Lillian Flashner



Jeffrey Lu



Sara Long



Marissa Ruggiero



Abhishek Surampudy



Brendan Gleason



Taylor Jones



George Titomihelakis



Christine Wamsley



Ji-Hui (Gavyn) Ooi



Sabrina Lefcochilos-
Fogelquist

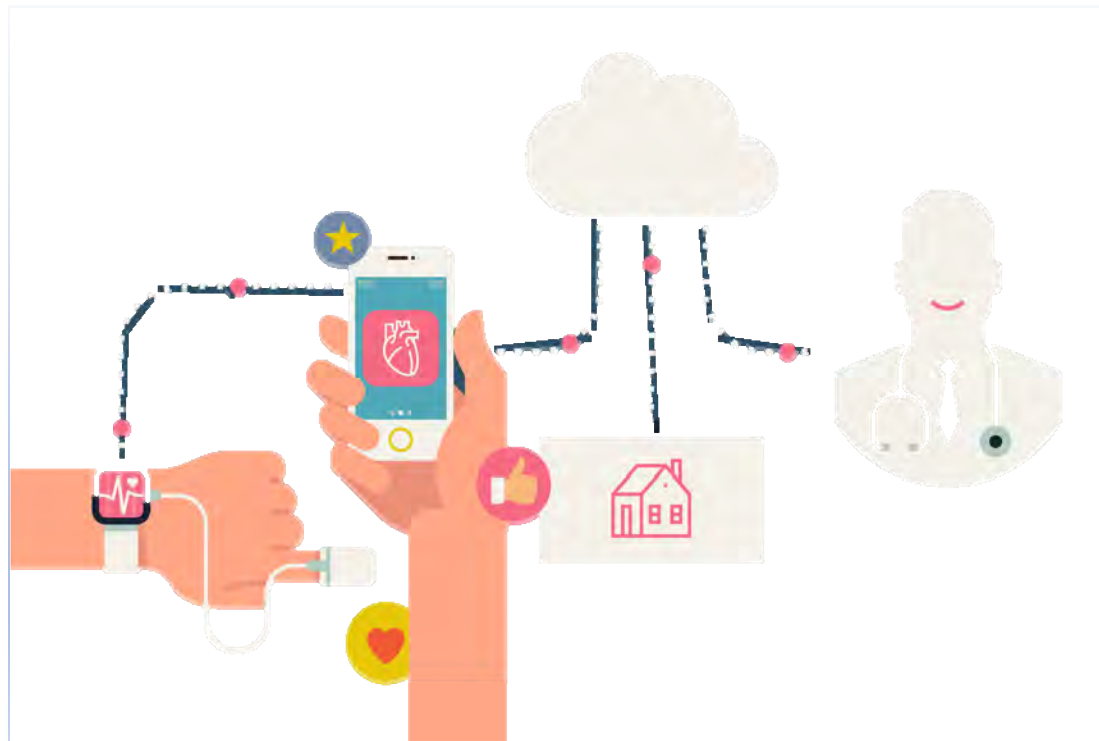


Chaim Miller



Victoria Nguyen

NRG Oncology Digital Health Working Group



Adam Dicker
Heather Jim



a National Cancer Institute program

- Meeting with NRG Oncology Alliance, SWOG, COG, ECOG-ACRIN, CCTG (Sept 2017)
- **Creation of NCTN Digital Health Steering Committee**
 - Representation will include participants from:
 - Children's Oncology Group, ECOG-ACRIN, Alliance for Clinical Trials, and Canadian Cancer Clinical Trials Network (3CTN)
- Alliance May 2018 meeting
 - Mini-symposium on digital health
- NRG Oncology July 2018 meeting
 - NCORP mini-symposium on digital health

Integration of data will result in clinical benefit

Patients eligible for early phase clinical trials



Analysis of tumor and other tissues for pathway activation or resistance / other



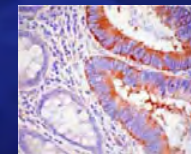
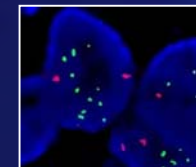
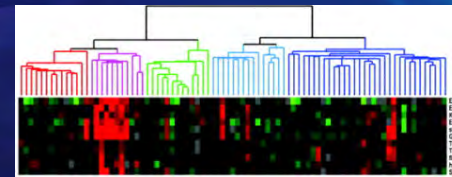
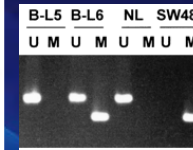
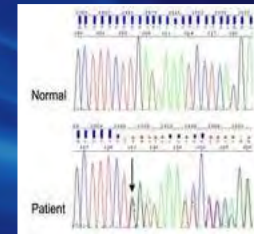
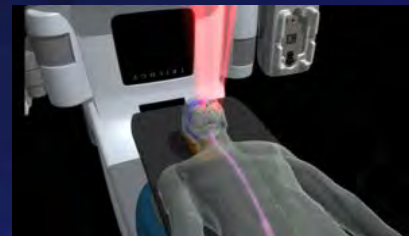
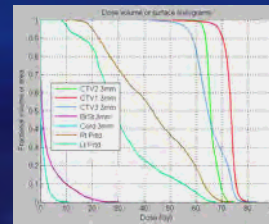
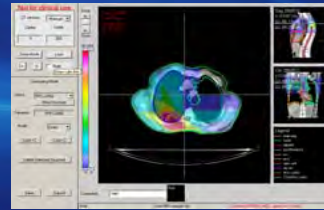
Patient assigned to trial based on molecular characterization of tumor



Patient monitoring



Patient monitoring:
Post-treatment molecular reanalysis



Translational slide, Percy Ivy, MD
National Cancer Institute

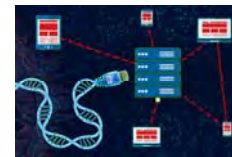
A tiered approach for a comprehensive, personalized, molecular, patient centered perspective

Imaging Data

-Functional
-Spatial



**Translational
molecular profile**

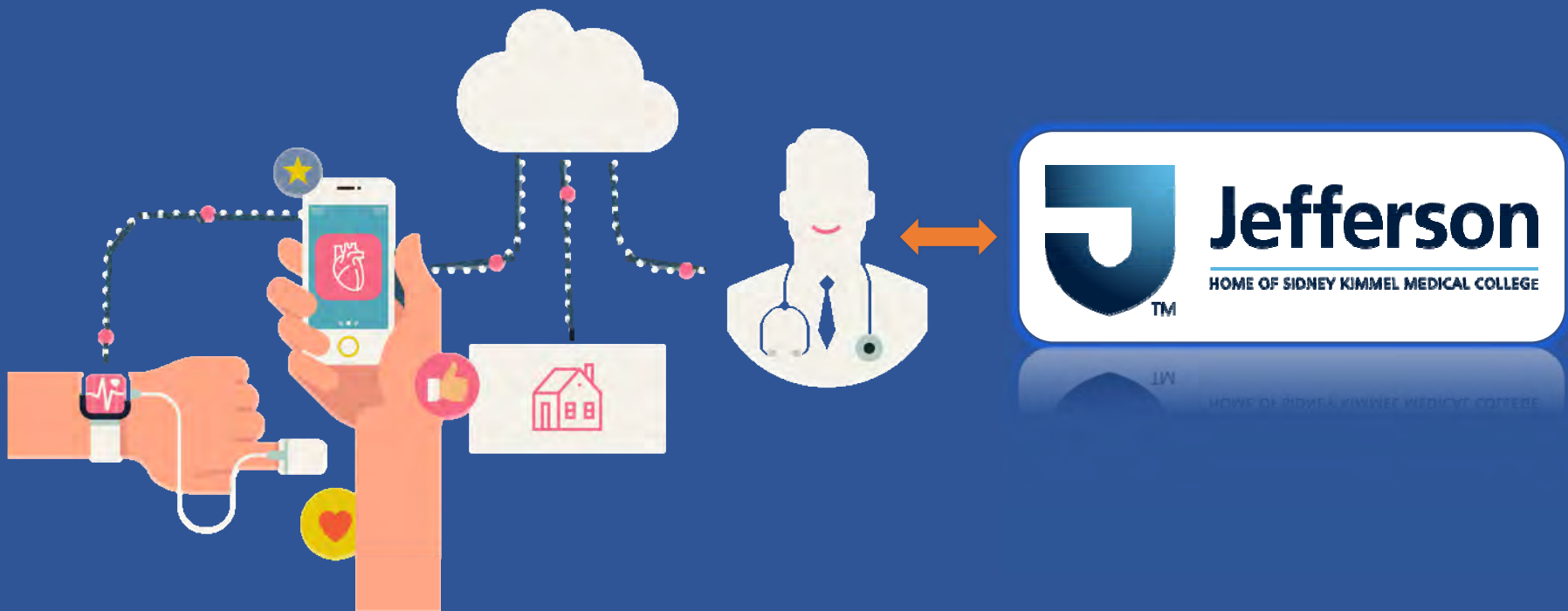


**Patient Reported
Outcomes +
Wearable data**



- PRO-CTCAE
- Remote collection
- Weekly
- Shared with patient

Thank you!



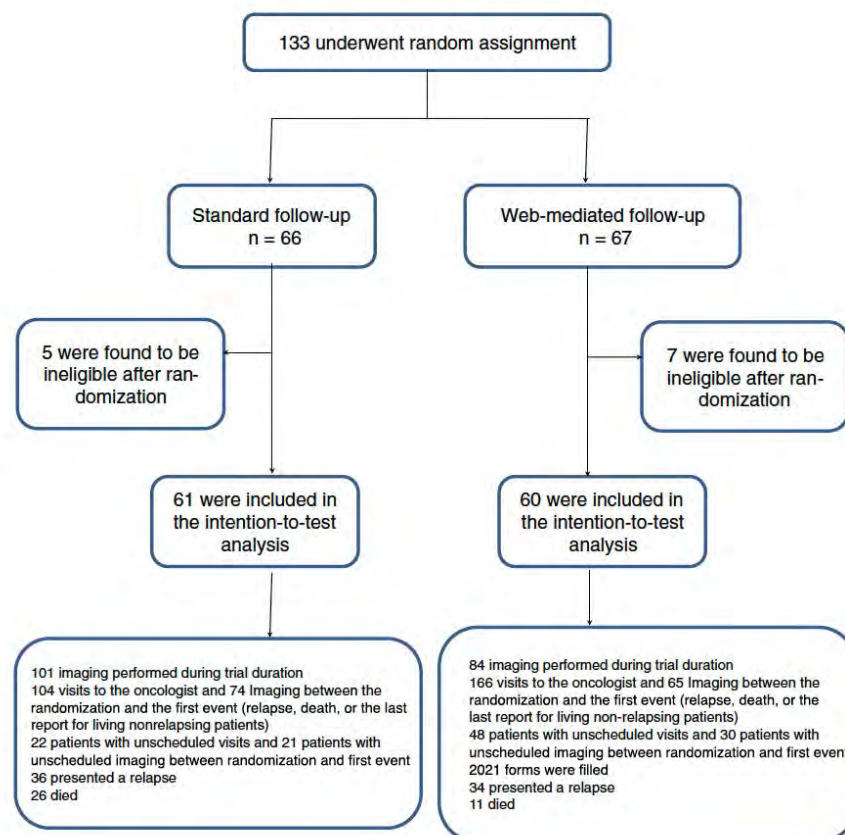
Backup

Four Questions:

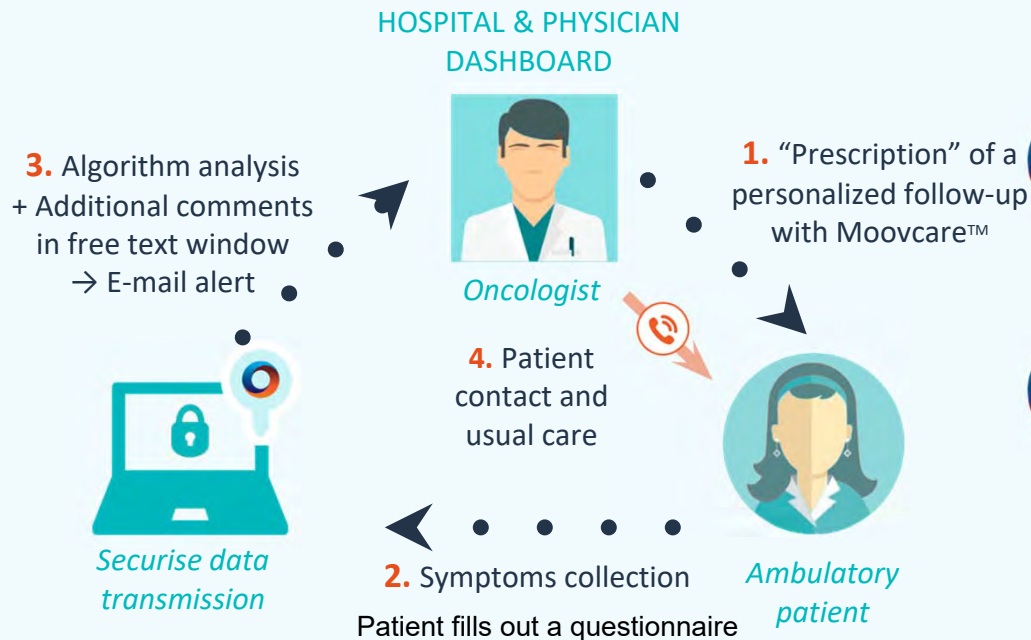
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Randomized Trial Comparing a Web-Mediated Follow-up With Routine Surveillance in Lung Cancer Patients

Fabrice Denis, Claire Lethrosne, Nicolas Pourel, Olivier Molinier,
Yoann Pointreau, Julien Domont, Hugues Bourgeois, H  l  ne Senellart,
Pierre Tr  moli  res, Thibaut Liz  e, Jaafar Bennouna, Thierry Urban,
Claude El Khouri, Alexandre Charron, Anne-Lise Septans, Magali Balavoine,
S  bastien Landry, Philippe Solal-C  ligny, Christophe Letellier



Moovcare™ : A revolutionary web-application



Based on European regulation

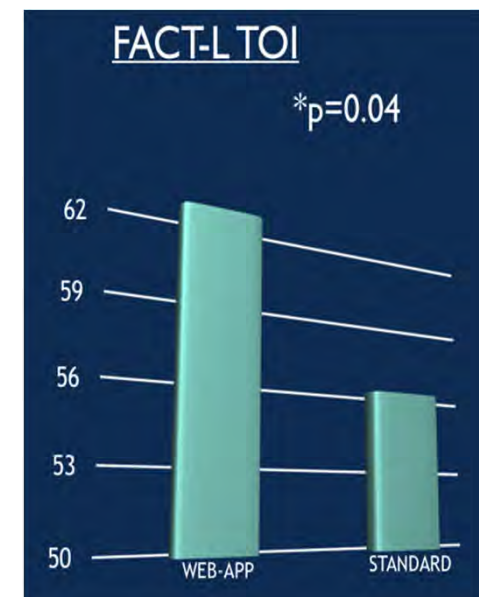
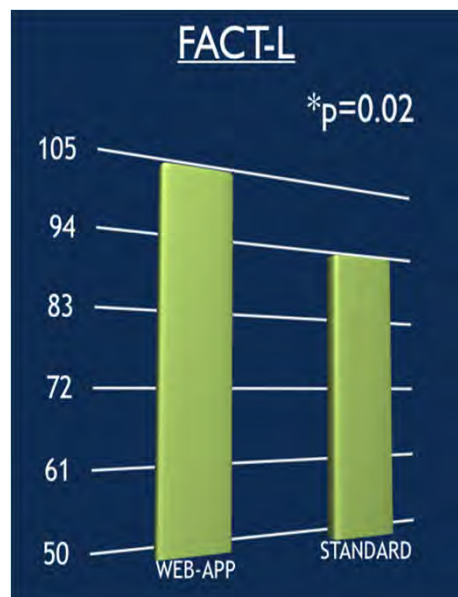
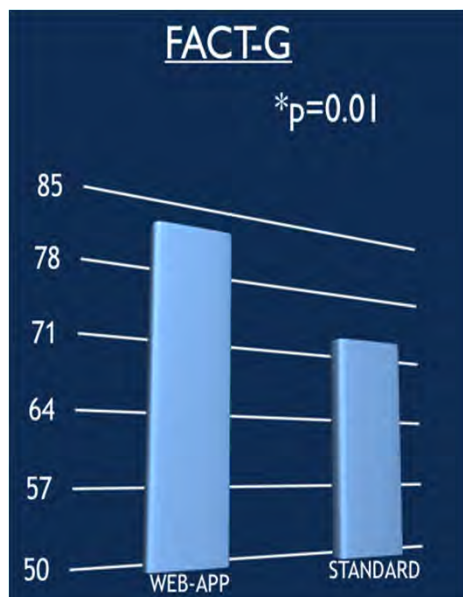


Web-application based on **an algorithm analyzing the dynamics of clinical symptoms** to detect clinical signs of relapses and complication

The physician send a questionnaire to the patient. The algorithm analyses the answers to the questionnaire and generates an alert to the physician when it detects a risk of relapse

Validated in Phase II and multicenter Phase III trials
(primary endpoint: overall survival)

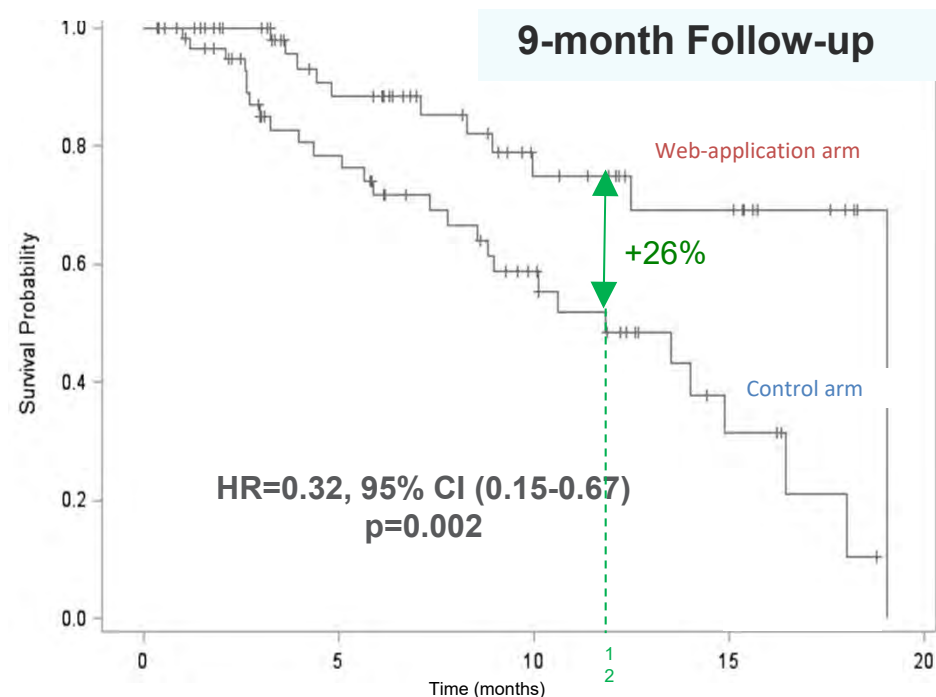
Moovcare™ : Phase III - Quality of Life (mean score at 6 months)



Moovcare™: Median follow-up at 9 months



- Pre-Planned interim analysis
- 28% of death (37/133)
- Median OS : 19 [95% CI (12.5-NC)] vs 12 months [95% CI (8.6-16.4)], $p=0.001$
- 1-year OS improvement : 75% vs 49% (+26%)
- Trends are kept at 2 years follow up



Digital Health, fast moving area....

- FDA on Digital Biomarkers: <https://www.karger.com/Article/FullText/481274>
- Former FDA Commissioner, Dr. Robert Califf: <https://www.karger.com/Article/FullText/479861>
- **FDA: Digital Health Innovation Action Plan:**
<https://www.fda.gov/downloads/MedicalDevices/DigitalHealth/UCM568735.pdf> and some updates: <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm577480.htm>
- Coverage: <https://rockhealth.com/what-you-need-to-know-about-fdas-game-changing-digital-health-innovation-action-plan/>

AEs Underestimate Presence of Severe PROs

anorexia by

50%

diarrhea by

24%

nausea by

26%

vomiting by

13%

Di Maio et al., *J Clin Oncol* 2015; 33: 910-5.

PRESENTED AT: **ASCO ANNUAL MEETING '17** | **#ASCO17**

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SESSION IIB Panel Discussion:

Clinical Considerations

Moderators: Fei-Fei Liu, MD, and Ricky Sharma, MD, PhD

Panelists:

Zelanna Goldberg, MD, MA

Paul G. Kluetz, MD

Patty Spears

Adam P. Dicker, MD, PhD



Summary & Future Directions

Speaker:

Stephen M. Hahn, MD