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
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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Clinical indication with radiation</th>
<th>Year Phase III published</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-FU / mitomycin</td>
<td>Anal cancer</td>
<td>1974 (not phase III)</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>Head and neck; cervical cancer</td>
<td>2000s</td>
</tr>
<tr>
<td>5-FU / capecitabine</td>
<td>Gastric cancer</td>
<td>2001</td>
</tr>
<tr>
<td>Temozolomide</td>
<td>Glioblastoma</td>
<td>2005</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>Head and neck</td>
<td>2006</td>
</tr>
<tr>
<td>Carboplatin + paclitaxel</td>
<td>Esophageal cancer</td>
<td>2012</td>
</tr>
</tbody>
</table>
We are not hitting the target, because we are not throwing enough arrows
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3. Pharma – Society: Difficulties
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6. Game theory approach
Interdependence

Pharma  Society
The Golden age of academic medicine?

Austin Bradford Hill
<table>
<thead>
<tr>
<th>Pharma needs society</th>
<th>Society needs pharma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Universities- basic research</td>
<td>Perform high throughput drug discovery / compound screens</td>
</tr>
<tr>
<td>Physicians to accrue patients</td>
<td>Chemical optimization</td>
</tr>
<tr>
<td>FDA to approve drug</td>
<td>Manufacture safe products</td>
</tr>
<tr>
<td>Physicians to prescribe</td>
<td>Fund clinical trials</td>
</tr>
<tr>
<td>Insurance to pay</td>
<td>Produce the drug</td>
</tr>
<tr>
<td>Clinical knowledge</td>
<td>Solve acute medical problems</td>
</tr>
</tbody>
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Both Society and Pharma have difficulties

<table>
<thead>
<tr>
<th>Industry</th>
<th>Society</th>
</tr>
</thead>
<tbody>
<tr>
<td>• High cost of developing drugs</td>
<td>• Lack of innovation</td>
</tr>
<tr>
<td>• Costly regulatory requirements</td>
<td>• Children</td>
</tr>
<tr>
<td>• Low level of success at phase III level “product drought”</td>
<td>• Elderly</td>
</tr>
<tr>
<td>• Few new blockbusters</td>
<td>• Rare disease</td>
</tr>
<tr>
<td>• Short patent terms limit profits</td>
<td>• Radiation</td>
</tr>
<tr>
<td>• Changing payer behaviors</td>
<td>• High cost of drugs</td>
</tr>
<tr>
<td></td>
<td>• Popular pressure to approve and purchase drugs with limited efficacy</td>
</tr>
</tbody>
</table>
The Stakeholders

Government | Pharma | Physicians | Patients | HMOs / Payers
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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”

<table>
<thead>
<tr>
<th>Year</th>
<th>Act</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980</td>
<td>Bayh-Dole Act</td>
<td>Encourage <strong>commercial development</strong> based on federal research funding</td>
</tr>
<tr>
<td>1983</td>
<td>Orphan Drug Act</td>
<td><strong>Conditions for which “no reasonable expectation”</strong> 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.</td>
</tr>
</tbody>
</table>
| 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

<table>
<thead>
<tr>
<th>Year</th>
<th>Legislation</th>
<th>Critiques</th>
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<td>Drug approvals often based on small poor-quality clinical trials&lt;br&gt;Still leads to many disease to be ignored&lt;br&gt;Some almost developed drugs repositioned for “orphan diseases”</td>
</tr>
<tr>
<td>1984</td>
<td>Hatch-Waxman Act</td>
<td>no evidence has linked market exclusivity extensions to enhanced drug development&lt;br&gt;It has been said that patent expiration is a greater driver of innovation than are extended monopolies,</td>
</tr>
<tr>
<td>1997</td>
<td>Pediatric exclusivity provisions of FDA Modernization Act</td>
<td>six-month exclusivity period overcompensated manufacturers&lt;br&gt;The drugs most frequently used by children were underrepresented&lt;br&gt;largely irrelevant medications tested, e.g. Lipitor&lt;br&gt;&lt;50% trials published in peer review journals&lt;br&gt;The costs fall nearly exclusively on patients and insurers</td>
</tr>
</tbody>
</table>

“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)
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
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

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

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

- 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?

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

Most recent clinical trials of systemic agents published in NEJM, Feb 2018
PubMed | "cancer cure" [TI]

Format: Summary  Sort by: Most Recent

Search results
Items: 1 to 20 of 99

PubMed | "beyond progression" [TI]

Format: Summary  Sort by: Most Recent

Search results
Items: 1 to 20 of 54
7 results found for "cancer cure"

75 results found for "beyond progression"
Paul Ehrlich’s magic bullet for cancer:
- Is it biologically possible?
- Is it economically viable?
An inefficient allocation of goods & services, leading to a net social loss

Cancer drug development ‘a market failure’

Sergiu Hart

Kobi Glazer
The individualized incentive model

• The incentive should closely match the desired end point

Key legislation : critiques

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

Big Pharma
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
Disclosures

Honoraria:
- BTG, Sirtex, Roche, Cancer Research UK

Advisory Boards/Consultancy:

Research Funding:
- Sirtex, BTG, Cancer Research UK
A triumph for collaboration in radiotherapy research: landmark paper published by NCRI CTRad Working Group

Clinical Need for New Approaches to Cancer Therapy

1 in 2 people in the UK will get cancer

People in the UK with a cancer diagnosis

- 2 million (current)
- 3.4 million (projected)

2010 2015 2020 2025 2030
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

- Surgery: 49%
- Radiotherapy: 40%
- Chemotherapy: 11%

Sir Mike Richards,
NCRI Annual Cancer Conference 2011
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.

- Radiation + chemotherapy (n = 104)
- Radiation alone (n = 100)

\[ P = 0.0016 \]
# Level 1 Evidence for Chemo-radiotherapy

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

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

* OS = overall survival; 5FU = 5-fluorouracil.
Rollercoaster
Cetuximab + Radiotherapy in Head and Neck


Temozolomide plus RT for Glioblastoma Multiforme

MGMT as a Biomarker for Temozolomide Resistance

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

MGMT silenced

MGMT functional

Subsequent High Profile Negative Results

**Newly diagnosed GBM:**
Superior PFS and QoL
- Bevacizumab + RT-TMZ
- Placebo + RT-TMZ

**Cervical cancer:**
3-year OS 70%
- Cis-RT
- Cis-RT + tirapazamine

**Oesophageal cancer:**
Stopped early
- Cis-Cape-RT + cetuximab
- Cis-Cape-RT

Chinot O et al.
*NEJM* 2014

DiSilvestro P et al.
*J Clin Oncol* 2014

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

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

- Academic investigators & clinicians
- Regulatory bodies
- Industry
- Patient Benefit
Strengths of 37 members:
Diversity, knowledge and expertise

10 Radiation Oncologists
1 Clinical Radiologist
2 Consumer representatives
3 Statisticians

3 Medical Oncologists
2 Scientists from Academia
3 Regulatory Experts
13 Scientists/Clinicians from Pharma

UCL Cancer Institute
“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

Collaborative groups involving academia and pharmaceutical companies should prioritise the evaluation of appropriate novel drug-radiotherapy combinations early in a drug's clinical development plan. This should include a scientific basis in radiobiology, immuno-oncology, molecular biology and pharmacology.
Strong Basic Science

Guideline

Guidelines for preclinical and early phase clinical assessment of novel radiosensitisers

KJ Harrington, LJ Billingham, TB Brunner, NG Burnet, CS Chan, P Hoskin, RI Mackay, TS Maughan, J Macdougall, WG McKenna, CM Nutting, A Oliver, R Plummer, IJ Stratford and T Illidge NCRI Clinical and Translational Radiotherapy Research Working Group

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


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

Correspondence to: Yaakov Richard Lawrence, MRCP, Department of Radiation Oncology, Sheba Medical Center, Tel HaShomer 52211, 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

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[Logos of collaborating companies]
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
- Loco-regional control matters to patients
- End points must be pragmatic, relevant to patients and applicable in a ‘real world’ setting
- Secondary end points should include normal tissue toxicity

Regulators and researchers should define meaningful clinical endpoints for a specific tumour type to accelerate development of novel combination therapies. Including early and relevant early and intermediate endpoints will accelerate clinical development by generating compelling data in a timely and cost-effective manner. Regulators should recognise that endpoints must be pragmatic, relevant to patients and applicable in a ‘real world’ setting, and should reflect (i) the important clinical benefits of durable locoregional control and (ii) the balance of effects on tumour control and normal tissue toxicity. Composite or co-primary end points may be necessary or advantageous.
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

Currently, there are no published guidelines on how to design studies using novel drug-radiotherapy combinations and there is limited guidance on regulatory aspects. In the absence of specific guidance, drug-radiotherapy combinations should be viewed as similar in concept to novel drug-novel drug combinations. There should be a strong scientific rationale for the combination based on understanding of mechanisms of action and a clear line of sight to registration for the combination, based on clinical need.

- **Limited / no guidelines for RT-drug combinations**
- **RT combinations with good biological/therapeutic rationale should be considered in preclinical studies and as part of design of early-phase studies**
- **Early discussion with regulatory agencies**
- **Ensure access to new treatments are achieved in the shortest possible timeframe**
- **Adaptive design to support early initiation of combinations once a MTD or BED is defined**
Core Programme

- Target selection & validation
- Preclinical efficacy & safety
- PI
- PII
- PIII
- Launch

Preclinical efficacy & safety

PI

PII

PIII

Launch

Potential Regulatory Interactions

- Review of existing guidelines and regulatory interactions
- End of Phase 1 Meeting (FDA)
- Scientific Advice EMA or National Agencies
- Pre-NDA Meetings
- CHMP Rapporteur assignment & pre-submission meetings

Radiotherapy Program

- RT MOA
- Hypothesis
- Preclinical efficacy & safety
- PI
- PII/III
- Launch

Monotherapy/chemo MTD

RT-combined MTD

Pre-IND Meeting with FDA

End of Phase 2 Meeting with FDA & Scientific Advice EMA
“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 onwards for a clearer understanding of patient priorities and what will be considered acceptable by patients who may or may not wish to participate in a clinical trial. Efforts to raise public awareness of the efficacy of radiotherapy and drug–radiotherapy combinations should include clear statements of the potential benefits of the research to improve cancer treatment.

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
Molecular Targets

Tumor cell

1. Growth factors and growth-factor receptors
   HER family, VEGF/R, c-kit/SCFR

2. Signal transduction pathways
   Ras, raf, MAPK, MEK, ERK, protein kinase C, PI3K

3. Tumor-associated antigens/markers
   Gangliosides, CEA, MAGE, CD20, CD22

4. Proteasome

5. Cell-survival pathways
   Cyclin-dependent kinases, mTOR, cGMP, COX-2, p53, Bcl-2

6. Extracellular matrix/angiogenic pathways
   MMPs, VEGF, integrins
Distribution of Phase III Clinical Trials in Oncology

- Radiation: n = 1415, 28.1%
- Molecular targeted agent: n = 850, 16.9%
- Radiation and molecular targeted agent: n = 46, 0.9%
- Other: n = 2724, 54.1%

Morris & Harari: J Clin Oncol 2014
Oxygen Effect

- Anoxic cells have much higher survival per unit of dose than oxic cells.
- Well oxygenated cells show a much steeper cell survival curve.
- The ratio in cell kill between oxygenated and deoxygenated cells is the Oxygen Enhancement Ratio.
Oxygen as a Radiosensitizer
Tumor Hypoxia
Thomlinson and Gray: 1955

[Diagram showing proliferation, capillary, drug cone, and a graph depicting surviving fraction as a function of distance from capillary (μm)]
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.,‖ 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)
Locoregional Progression Free Survival

All patients

Stratum 1

Stratum 2

Stratum 3

Numbers at risk

Time (months)

Probability of locoregional progression-free survival (%)

Placebo

Epoetin β
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 Hershack, 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)
Locoregional progression free survival in RTOG 99-03

![Graph showing locoregional progression free survival](image)

- **RT**
  - Failed: 36 / 69
  - Patients at Risk: 69
- **RT + EPO**
  - Failed: 40 / 72
  - Patients at Risk: 72

Years from randomization:
- 0
- 1
- 2
- 3

% Alive without LR progression:
- 100
- 75
- 50
- 25
- 0

Failed / Total:
- RT: 36 / 69 (p=0.46)
- RT + EPO: 40 / 72

International Journal of Radiation Oncology • Biology • Physics 2007 69, 1008-1017
Copyright © 2007 Elsevier Inc.
Overall Survival in RTOG 99-03
Hypoxic Radiosensitizers
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

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”
ErbB Family of Receptor Tyrosine Kinases

sErbB

v-ErbB  ErbB1  ErbB2  ErbB3  ErbB4
HER-1  HER-2  HER-3  HER-4
EGF-R  Neu
Schematic of EGFR signaling interactions
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

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<tr>
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<th>Phase contrast (0.6 x)</th>
<th>Fluorescence (0.6 x)</th>
<th>Fluorescence (2.0 x)</th>
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<td>C225</td>
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<td><img src="image6" alt="C225 Fluorescence 2.0x" /></td>
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</table>
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

**Study accrual 1998-2002**
- 424 patients randomized

**Arm 1 (RT)**
- Radiation therapy

**Arm 2 (RT+Cetux)**
- Radiation therapy + Cetuximab
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?
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?
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*

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: Tumor Control Endpoints

**Primary Endpoint: PFS**

- Hazard Ratio (95% CI): 1.05 (0.84, 1.29)
- 2-Year Rate (95% CI):
  - Cisplatin: 64.3% (59.7, 68.8)
  - Cisplatin+Cet: 63.4% (58.7, 68.0)

**Overall Survival (OS)**

- Hazard Ratio (95% CI): 0.87 (0.66, 1.15)
- 2-Year Rate (95% CI):
  - Cisplatin: 79.7% (75.9, 83.6)
  - Cisplatin+Cet: 82.6% (78.9, 86.3)

# Patients at Risk:

- PFS: 448 316 217 78
- OS: 448 385 266 96
The HER/ErbB Signaling Network

Yarden & Sliwkowski, Nature Reviews MCB (2001)
Human Papillomavirus and Survival of Patients with Oropharyngeal Cancer

Overall Survival (%)

Hazard ratio for death, 0.29 (0.20–0.43); P<0.001

Years since Randomization
Enhanced Radiation Sensitivity in HPV-Positive Head and Neck Cancer

Randall J. Kimple\textsuperscript{1,3}, Molly A. Smith\textsuperscript{1}, Grace C. Blitzer\textsuperscript{1}, Alexandra D. Torres\textsuperscript{1,2}, Joshua A. Martin\textsuperscript{1,9}, Robert Z. Yang\textsuperscript{1,2}, Chimera R. Peet\textsuperscript{1}, Laurel D. Lorenz\textsuperscript{2}, Kwangok P. Nickel\textsuperscript{7}, Aloysius J. Klingelhutz\textsuperscript{4}, Paul F. Lambert\textsuperscript{2,3}, and Paul M. Harari\textsuperscript{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

Slide courtesy Dr. Zach Morris
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
  - 8/12 pts with CR or PR

**Golden et al., Lancet Oncology, 2015**
- **Eligibility:** Stable/progressing solid tumor mets
- **Treatment:** 35 Gy/10 fx + systemic GM-CSF
- **Endpoint:** Abscopal response
  - 11/41 pts with response at non-radiated site
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

n = 2
n = 2349
n = 441
n = 125

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 oligometastastic 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

DNA

H1 histone

Nucleosome

Core of 8 Histone Molecules
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
γH2AX as a marker for DSB

X rays

H2AX

ATM, DNA-PK

γH2AX

p53BP

M-R-N

BRCA1

γH2AX
• indicator of DSB
• knockout radiosensitive
• concentrate/retain repair factors

Bonner and Sedelnikova
\( \gamma H2AX \) foci

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

\[ \text{untreated} \quad \text{2 Gy/6h} \]
Mechanistic: Inhibition of Recruitment of Repair Molecules?

$X$ rays

ATM, DNA-PK

U251, p53BP1 foci, 2 Gy

% positive cells

Control  Valproic acid

untreated  6h  24h

Time after 2 Gy

U251, BRCA1 foci, 2 Gy

% positive cells

Control  Valproic Acid

untreated  6h  24h

Time after 2 Gy
Valproic acid and DSB repair

Neutral Comet (10Gy)

PFGE (20 Gy)

repair time (h)

% Damage

0 20 40 60 80 100

control valproic acid

repair time (min)

% DNA Damage remaining

0 20 40 60 80 100

control VA

repair time (h)

% Damage

0 20 40 60 80 100

control valproic acid

20 Gy
VA-induced Mitotic Catastrophe

% abnormal nuclei

Time after 2 Gy (h)

Control
VPA
HDACi and acetylated-γH2AX

- “constitutive” acetylated γH2AX
- VA increases acetylated γH2AX
- retained γH2AX is acetylated
HDACi Preclinical Conclusions

• prolongs expression of γH2AX
  – other repair proteins
• acetylates γH2AX therefore not dispersed
• no apparent effect on nucleic acid rejoining
• Inhibition of chromatin remodeling
Translation Bench to Bedside

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

Patient Lymphocyte

<table>
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<tr>
<th>Normal</th>
<th>Pre-VA</th>
<th>Pre-IR</th>
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<td>Complete</td>
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</table>

Acetyl-H4
Trial Schema

$20/patient for VPA for total course
Valproic Acid Results

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

Survival vs highest VPA level

- Grade 4 toxicity
- Grade 3 toxicity
- < Grade 3/4 or no 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

<table>
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<tr>
<th>First Author</th>
<th># of Patients</th>
<th>% Complete Study Drug</th>
<th>Grade 3 Toxicity</th>
<th>Grade 4 Toxicity</th>
<th>Grade 5 Toxicity</th>
<th>% delayed RT</th>
<th>6m PFS</th>
<th>median OS</th>
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<td>32%</td>
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<td>This Trial</td>
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<td>67%</td>
<td>16</td>
<td>6</td>
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<td>70%</td>
<td>29.6m</td>
<td>Currant Study</td>
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- **97%**
- **60%**
Acknowledgments

• Phil Tofilon
• Tamalee Kramp
• Mary Sproull
• Uma Shankavaram
Model Comparison: gene expression analysis

- Tissue culture
  ![Tissue culture](image)
- Ic xenograft
  ![Ic xenograft](image)
- Sc xenograft
  ![Sc xenograft](image)
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)
Radiotherapy-Drug Combination Consortium
THE NEED FOR NATIONAL COORDINATION IN RADIOTHERAPY

2003
NCRI identified RT as area of need

2006
Gray Institute in Oxford

2008
Rapid Review

2009
CTRad launched

2014
Review and third phase of funding
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
CTRad Executive Group
Chair
Deputy Chair
Workstream co-chairs
Consumer representatives
Ex-officio members
NCRI Secretariat

RaDCom

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
STAKEHOLDERS FOR NEW DRUG-RT COMBINATIONS

ACADEMIC INVESTIGATORS & CLINICIANS

PATIENT BENEFIT

REGULATORY BODIES

INDUSTRY
RADIOTHERAPY – DRUG COMBINATIONS CONSORTIUM (RaDCom)

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

- **Collaborative network of labs**
- **Partnership with industry, CRUK and other funding bodies**
- **Provision of necessary evidence base for early phase clinical trials**
- **Timely delivery of quality pre-clinical efficacy data**
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)

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
RaDCom
Chair: Kaye Williams

Project Manager:
Agnieszka Wabik

CTRad reps
Co-chairs WS1
Co-chairs WS2

Theme Leads
- Signalling Pathways
- Tumour microenvironment
- Immunotherapy
- Tumour metabolism
- DNA damage response
- Biological therapies

Consumer rep
CRUK rep
NCRI rep

Steering Committee

Current Collaborations
- MERCK
- VERTEX
- AstraZeneca
- Takeda
- astex pharmaceuticals
- UCB
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
INVESTIGATORS 18
TARGETS TESTED 13

PHARMA COMPANIES 11
INSTITUTIONS 9

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

*In vitro* work to establish PoC

Refined *in vivo* studies to establish radio-protection of GI tract (supported by Epistem)

RaDCom input

Complex *in vivo* models enabling co- incidental evaluation of tumour and normal tissue (supported by Kaye Williams)

current status- development of clinical trial and research publications
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

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

[Cancer Research UK Combinations Alliance] [Clinical and Translational Radiotherapy Research Nursing 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
What accuracy is necessary?

• What is the right dose?
  – “…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

Global Leaders in Clinical Trial Quality Assurance
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)

<table>
<thead>
<tr>
<th>Discrepancies Regarding:</th>
<th>Number of Institutions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Review QA Program</td>
<td>115 (74%)</td>
</tr>
<tr>
<td>Photon Field Size Dependence (FSD)</td>
<td>62 (40%)</td>
</tr>
<tr>
<td>Wedge Factor (WF)</td>
<td>50 (32%)</td>
</tr>
<tr>
<td>Off-axis Factors (OAF)/Beam symmetry</td>
<td>46 (29%)</td>
</tr>
<tr>
<td>Electron Calibration</td>
<td>27 (17%)</td>
</tr>
<tr>
<td>Photon Depth Dose</td>
<td>25 (16%)</td>
</tr>
<tr>
<td>Electron Depth Dose</td>
<td>18 (12%)</td>
</tr>
<tr>
<td>Photon Calibration</td>
<td>13 (8%)</td>
</tr>
</tbody>
</table>
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)

<table>
<thead>
<tr>
<th>Study</th>
<th>Major Deviations</th>
<th>Minor Deviations</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG 0184</td>
<td>44 (7%)</td>
<td>114 (17%)</td>
<td>654</td>
</tr>
<tr>
<td>GOG 0122</td>
<td>29 (15%)</td>
<td>37 (19%)</td>
<td>197</td>
</tr>
<tr>
<td>NSABP B14</td>
<td>135 (9%)</td>
<td>214 (15%)</td>
<td>1460</td>
</tr>
<tr>
<td>NSABP R01</td>
<td>72 (44%)</td>
<td>0</td>
<td>163</td>
</tr>
<tr>
<td>RTOG 9001</td>
<td>43 (14%)</td>
<td>76 (24%)</td>
<td>315</td>
</tr>
<tr>
<td>RTOG 9003</td>
<td>75 (7%)</td>
<td>188 (18%)</td>
<td>1073</td>
</tr>
</tbody>
</table>
# Results of Credentialing (closed studies)

<table>
<thead>
<tr>
<th>Study</th>
<th>Major Deviations</th>
<th>Minor Deviations</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG 165 HDR Cervix</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Credentialed inst</td>
<td>0</td>
<td>15 (21%)</td>
<td>70</td>
</tr>
<tr>
<td>Non-credentialed</td>
<td>57 (21%)</td>
<td>87 (32%)</td>
<td>275</td>
</tr>
</tbody>
</table>
## Results of Credentialing

<table>
<thead>
<tr>
<th>Study</th>
<th>Disease Site</th>
<th>Major Deviations</th>
<th>Minor Deviations</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMS Eye</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GOG 165 Cervix</td>
<td></td>
<td></td>
<td>15 (21%)</td>
<td>70</td>
</tr>
<tr>
<td>RTOG 95-17 HDR &amp; LDR</td>
<td>Breast</td>
<td>0</td>
<td>4 (4%)</td>
<td>100</td>
</tr>
<tr>
<td>RTOG 0019 LDR</td>
<td>Prostate</td>
<td>0</td>
<td>6 (5%)</td>
<td>117</td>
</tr>
<tr>
<td>NSABP B39/RTOG 0413</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3D MammoSite Breast</td>
<td>3 (0.3%)</td>
<td>121 (10%)</td>
<td>348</td>
<td></td>
</tr>
<tr>
<td>3D MultiCatheter</td>
<td>0</td>
<td>42 (12%)</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td>3D</td>
<td>0</td>
<td>8 (9%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Use of **Advanced Technologies** in clinical trials?

**Tracking**

**TPS**

**Hetero Correction**

**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
## Photon Phantom Results

Comparison between institution’s plan and delivered dose.

<table>
<thead>
<tr>
<th>Phantom</th>
<th>H&amp;N</th>
<th>Liver insert</th>
<th>Lung</th>
<th>Prostate</th>
<th>Spine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irradiations</td>
<td>2052</td>
<td>165</td>
<td>1109</td>
<td>566</td>
<td>336</td>
</tr>
<tr>
<td><strong>Pass</strong></td>
<td>1755 (86%)</td>
<td>120 (71%)</td>
<td>921 (85%)</td>
<td>484 (85%)</td>
<td>261 (78%)</td>
</tr>
<tr>
<td><strong>Fail</strong></td>
<td>297</td>
<td>45</td>
<td>188</td>
<td>82</td>
<td>75</td>
</tr>
<tr>
<td><strong>Criteria</strong></td>
<td>7%/4mm</td>
<td>7%/4mm</td>
<td>5%/5mm</td>
<td>7%/4mm</td>
<td>5%/3mm</td>
</tr>
</tbody>
</table>
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@irocohio.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
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
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
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
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

Michiels et al; Lancet Oncol 10:341, 2009
PFS (Progression-Free Survival) for NPC RT vs. CRT Trial

- 316 NPC patients

Chen et al; Sci Reports doi 10.1038; July 2015
QoL & Normal Tissue Toxicity End-point for HNC

- Conventional vs. parotid-sparing IMRT
- > 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.

2. Lung
   - OS
   - PFS
   - DFS
   - ?FDG-PET
DFS ~ OS for NSCLC

- 60 RCTs
- 15,071 patients

Mauguen et al; Lancet Oncol; 14:619, 2013
PFS ~ OS for NSCLC

- 60 RCTs
- 15,071 patients

Mauguen et al; Lancet Oncol; 14:619, 2013
Potential Role for FDG-PET in NSCLC

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

Machtay et al; JCO; 31:3823, 2013
3. Breast
  - OS
  - DFS
  - QoL
  - pCR & RFS
pCR for Breast Cancer & Neo-adjuvant Chemotherapy (NAC) – Sx + RT

- 221 LABC, NAC

Esserman et al; JCO; 30:3242, 2012
pCR Associated with Improved RFS

Esserman et al; JCO; 30:3242, 2012
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.

\[ R^2 = 0.90 \]
\[ r = 0.94 \]

\[ \text{OS HR} = (0.12 + 0.89) \times \text{DFS HR} \]
pCR & R0 Associated with Improved OS & DFS

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

Berger et al; JCO; 23:4330, 2005
pCR in Rectal Carcinoma

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

Maas et al; Lancet Oncol; 11:835, 2010
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

Xie et al; JCO; 35:3097, 2017
• 743 men with prostate CA in 2 RCTs
• PSA nadir (and end) strongly correlated with PCSM

6. CNS

- OS
- PFS
- Cognitive-deterioration-free survival
- QoL
• 562 patients ≥ 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

Brown et al; Lancet Oncol; 18:1049, 2017
Other end-points need to be considered

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

Lefebvre & Ang; *IJROBP*; 73:1293, 2009
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
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
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
Precision Radiation Medicine.
Personalized Care. Global Impact.
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

<table>
<thead>
<tr>
<th></th>
<th>Regular Approval</th>
<th>Accelerated Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diseases</strong></td>
<td>Any</td>
<td>Serious/life-threatening</td>
</tr>
<tr>
<td><strong>Comparative Efficacy</strong></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Required</strong></td>
<td></td>
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</tr>
<tr>
<td><strong>Endpoint</strong></td>
<td>Clinical benefit</td>
<td>“Surrogate” endpoint†</td>
</tr>
<tr>
<td><strong>Confirmatory Trial</strong></td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

†Accelerated approval relies upon an endpoint that is “reasonably likely to predict clinical benefit.”
### US Drug Approval Pathways

<table>
<thead>
<tr>
<th></th>
<th>Regular Approval</th>
<th>Accelerated Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diseases</strong></td>
<td>Any</td>
<td>Serious/life-threatening</td>
</tr>
<tr>
<td><strong>Comparative Efficacy Required</strong></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Endpoint</strong></td>
<td><strong>Clinical benefit</strong></td>
<td><strong>“Surrogate” endpoint”†</strong></td>
</tr>
<tr>
<td><strong>Confirmatory Trial Required</strong></td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

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

Presented at FDA-AACR-ASTRO Workshop on Clinical Development of Drug-Radiotherapy Combinations. tatiana.prowell@fda.hhs.gov or Twitter: @tmprowell
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

Figure 1. Kaplan–Meier Curves for Overall Survival.
The analysis included all the patients who underwent randomization. Symbols indicate censored observations, and horizontal lines the rates of overall survival at 1 year.

Nivolumab: Median PFS in Advanced Squamous Cell Lung Cancer

Nivolumab: Median OS in mRCC

Nivolumab: Median PFS in mRCC


**Figure 2.** Overall Survival in Subgroup Analyses and Kaplan–Meier Curve for Progression-free Survival.

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

Presented at FDA-AACR-ASTRO Workshop on Clinical Development of Drug-Radiotherapy Combinations. tatiana.prowell@fda.hhs.gov or Twitter: @tmprowell
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

Response where you need an arrow to point it out

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

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

Slide courtesy, G. Blumenthal
Depth, Durability, & Persistence of Response

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

Pre
Post Cycle 1

Slide courtesy, J. Beaver

Presented at FDA-AACR-ASTRO Workshop on Clinical Development of Drug-Radiotherapy Combinations. tatiana.prowell@fda.hhs.gov or Twitter: @tmprowell
# Ruxolitinib for Myelofibrosis: Response + Symptomatic Relief

<table>
<thead>
<tr>
<th>Study 1</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Jakafi (N=155)</td>
<td>Placebo (N=154)</td>
</tr>
<tr>
<td>Time Points</td>
<td>Week 24</td>
<td></td>
</tr>
<tr>
<td>Number (%) of Patients with Spleen Volume Reduction by 35% or More</td>
<td>65 (41.9)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt; 0.0001</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Jakafi (N=148)</th>
<th>Placebo (N=152)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%) of Patients with 50% or Greater Reduction in Total Symptom Score by Week 24</td>
<td>68 (45.9)</td>
<td>8 (5.3)</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt; 0.0001</td>
<td></td>
</tr>
</tbody>
</table>

Presented at FDA-AACR-ASTRO Workshop on Clinical Development of Drug-Radiotherapy Combinations. Please contact tatiana.prowell@fda.hhs.gov for permission to reuse or distribute.
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

• Thanks to the following individuals for sharing insights, slides, & feedback:
  – Julia Beaver
  – Gideon Blumenthal
  – Richard Pazdur
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
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**
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

1. 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*

2. 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*

3. 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*

4. 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*
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.
Table 8: Improvement in Total Symptom Score

<table>
<thead>
<tr>
<th></th>
<th>Jaks6 (N=148)</th>
<th>Placebo (N=152)</th>
</tr>
</thead>
<tbody>
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<td>Number (%) of Patients with 50% or Greater Reduction in Total Symptom Score by Week 24</td>
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</tr>
</tbody>
</table>

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)

FDA Label for Ruxolitinib [https://www.accessdata.fda.gov/](https://www.accessdata.fda.gov/)
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.”

FDA Label for Crizotinib [https://www.accessdata.fda.gov/](https://www.accessdata.fda.gov/)
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.

FDA Label for Rituxan Hycela [https://www.accessdata.fda.gov/](https://www.accessdata.fda.gov/)
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

“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

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

Reference 21 CFR 314.126, 21 CFR 201.57(c)(7)
### What is a “Fit For Purpose” PRO Instrument?

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
</table>
| **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 effort\(^1\))

Two reasonable examples include:

<table>
<thead>
<tr>
<th>PROMIS PF</th>
<th>EORTC QLQC30 PF Domain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are you able to do chores such as vacuuming or yard work?</td>
<td>Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?</td>
</tr>
<tr>
<td>Are you able to go up and down stairs at a normal pace?</td>
<td>Do you have any trouble taking a long walk?</td>
</tr>
<tr>
<td>Are you able to go for a walk of at least 15 minutes?</td>
<td>Do you have any trouble taking a short walk outside of the house?</td>
</tr>
<tr>
<td>Are you able to run errands and shop?</td>
<td>Do you need to stay in bed or a chair during the day?</td>
</tr>
</tbody>
</table>

\(^1\)Painter, 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

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.

No Pain

Pain As Bad As You Can Imagine

NCI website for PRO-CTCAE, [http://healthcaredelivery.cancer.gov/pro-ctcae](http://healthcaredelivery.cancer.gov/pro-ctcae)
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.”

“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
<table>
<thead>
<tr>
<th>Healthcare Utilization</th>
<th>Baseline</th>
<th>Assessment Period 1</th>
<th>Assessment Period 2</th>
<th>Assessments Period X...</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Arm A N(%)</td>
<td>Arm B N(%)</td>
<td>Arm A N(%)</td>
<td>Arm B N(%)</td>
</tr>
<tr>
<td>ED Visits</td>
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<td>Hospitalizations</td>
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<td>Opiates</td>
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<td>Antiemetics</td>
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<td>Antidiarrheals</td>
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<td>Oral or IV Steroids</td>
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<td>Transfusions</td>
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<td>- PRBC</td>
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<td>- Platelet</td>
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<tr>
<td>Growth Factors</td>
<td></td>
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</tr>
<tr>
<td>Palliative Procedures</td>
<td></td>
<td></td>
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<tr>
<td>Other: (describe)</td>
<td></td>
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</tbody>
</table>
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?

<table>
<thead>
<tr>
<th>Now</th>
<th>Future</th>
</tr>
</thead>
<tbody>
<tr>
<td>Used in phase 3 trials</td>
<td>Use in early phase trials (1, 2 and 3)</td>
</tr>
<tr>
<td>Analyzed separate from efficacy and published at different times</td>
<td>Analyzed along with efficacy and published together</td>
</tr>
<tr>
<td>Information is not shared with patients</td>
<td>Information is shared with public and patients</td>
</tr>
<tr>
<td>Instrument validation</td>
<td>Item (question) validation</td>
</tr>
<tr>
<td>Combination of multiple instruments</td>
<td>Combination of specific items</td>
</tr>
<tr>
<td>Global HR-QOL</td>
<td>Targeted measurements</td>
</tr>
</tbody>
</table>
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?
## 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?
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.

<table>
<thead>
<tr>
<th>Functional Status</th>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease Symptom</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Psychological Function</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Social Function</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

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.

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

Thanasisingam 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)
  - Especially 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*
## 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.
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
Acknowledgments:

- Heather Jim, PhD
- Nitin Ohri, MD
- Percy Ivy, MD
- Christine Tran, MS
- Stephen Blattner, MD
- Mark Tykocinski, MD
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.

Naomi Fried, PhD
Passive Activity and Sleep Monitoring

MiniMitter Actiwatches

Actigraph Link

12:00 PM | 6:00 PM | 12:00 AM | 6:00 AM | 12:00 PM

Jim et al. Health Psychol 2013; 32: 768-774
Guidances with Digital Health Content

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)
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
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](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.*
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.”

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](http://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](mailto:sandra@lungcancerfoundation.org)
- Learn about resources for patients as well as for clinicians and researchers.

**Our Members:**

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

Is the patient CURRENTLY receiving any of the following treatments?
(Select all that apply.)
502 people provided 614 response(s)
17. CURRENT IMMUNOTHERAPY

What is the patient's CURRENT immunotherapy treatment?
82 people provided 82 response(s)

- Atezolizumab (Tecentriq®)
- Ipilimumab (Yervoy®)
- Nivolumab (Opdivo®)
- Pembrolizumab (Keytruda®)
- Unsure

How long has the patient been on the CURRENT immunotherapy?
89 people provided 89 response(s)

- 0 - 3 months
- 4 - 6 months
- 7 - 12 months
- 13 - 18 months
- 19 - 24 months
- 25 - 36 months
- 37 - 48 months

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
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**)

*Sidney Kimmel Cancer Center at Thomas Jefferson University*
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?

Better selection of patients fit for treatment

Improved evaluation of patients during treatment
Enhanced supportive care for patients with low activity levels

Enhanced monitoring for late toxicity or disease progression
Promoting healthful lifestyles in the survivorship period

Improved Clinical Outcomes

Reduced Health Care Expenditures

Improved Cancer Care Quality

Improved Cancer Care Value

Nitin Ohri, MD
Albert Einstein
• 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.
“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).

Nitin Ohri, MD
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

• 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

Goal: 304 pts
Eligibility: Ambulatory pts receiving concurrent CRT
Stratification: disease site (above vs. below diaphragm) and KPS (<70 or ≥70)
Primary Endpoint: percentage of patients missing ≥ 2 planned RT treatments

**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

- 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

© Voluntis, all rights reserved

© Voluntis
Blood Pressure

© Voluntis, all rights reserved
Diarrhea

Record your bowel movements:
- 4 +

Over the past 24 hours, my number of bowel movements was:

- Bright red or dark brown color, blood, tarry stools
- Dehydration

Diarrhea severity:
- None
- Severe cramping

Recommendation:
1. Take 1 loperamide (Imodium) after each loose bowel movement. Do not take more than 8 pills in 24 hours.
2. Drink fluids.
4. If your diarrhea gets worse, call your study team.

© Voluntis, all rights reserved
Real Time Collaboration When Needed
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
  – 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, Sidney Kimmel Cancer Center, Thomas Jefferson University, Phila, PA
PROBLEM
A NEW CROSS-TRAINED INDIVIDUAL
Jefferson Institute of Digital Health
Approach, Sample Curriculum and Degrees

<table>
<thead>
<tr>
<th>APPROACH</th>
<th>CURRICULUM</th>
<th>DEGREES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interdisciplinary/ Cross Professional Teams</td>
<td>Technology / Cybersecurity</td>
<td>BS/MS - Healthcare Innovation</td>
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<tr>
<td>Industry Infused</td>
<td>Health/Biology</td>
<td>BS/MS – Digital Applications</td>
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<tr>
<td>Practicum Centered</td>
<td>Health Care Systems</td>
<td>MS – Digital Health</td>
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<tr>
<td>Real and Virtual</td>
<td>Design for Health</td>
<td>MS - Applied Health Technology</td>
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<tr>
<td>Hybrid Faculty</td>
<td>Data Analytics</td>
<td>Executive Masters – Digital Health</td>
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<td>Co-Ops</td>
<td>Business Intelligence</td>
<td>Executive Masters – Healthcare Practice in the Digital Age</td>
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<td>Interdisciplinary Innovation Entrepreneurship</td>
<td>PhD - Health Innovation &amp; Design</td>
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<td></td>
<td>Computational Thinking</td>
<td></td>
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<td></td>
<td>Health System Sciences (HSS)</td>
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</table>
### ExMDHMS Digital Health

#### Sample/Proposed Foundational Courses

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

Integration of data will result in clinical benefit
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:

• 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, Sidney Kimmel Cancer Center, Thomas Jefferson University, Phila, PA
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, Hélène Senellart, Pierre Trémolières, Thibaut Lizée, Jaafar Bennoua, Thierry Urban, Claude El Khouri, Alexandre Charron, Anne-Lise Septans, Magali Balavoine, Sébastien Landry, Philippe Solal-Céligny, Christophe Letellier

133 underwent random assignment

Standard follow-up  
$n = 66$

5 were found to be ineligible after randomization

61 were included in the intention-to-test analysis

101 imaging performed during trial duration
104 visits to the oncologist and 74 imaging between the randomization and the first event (relapse, death, or the last report for living non-relapsing patients)
22 patients with unscheduled visits and 21 patients with unscheduled imaging between randomization and first event
36 presented a relapse
26 died

Web-mediated follow-up  
$n = 67$

7 were found to be ineligible after randomization

60 were included in the intention-to-test analysis

84 imaging performed during trial duration
166 visits to the oncologist and 65 imaging between the randomization and the first event (relapse, death, or the last report for living non-relapsing patients)
48 patients with unscheduled visits and 30 patients with unscheduled imaging between randomization and first event
2021 forms were filed
34 presented a relapse
11 died
Moovcare™: A revolutionary web-application

**HOSPITAL & PHYSICIAN DASHBOARD**

1. “Prescription” of a personalized follow-up with Moovcare™

2. Symptoms collection
   - Patient fills out a questionnaire
   - Ambulatory patient

3. Algorithm analysis + Additional comments in free text window → E-mail alert

4. Patient contact and usual care
   - Oncologist

Web-application based on an algorithm analysing the dynamics of clinical symptoms to detect clinical signs of relapses and complications.

The physician sends 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)

Based on European regulation

Securise data transmission

"Prescription" of a personalized follow-up with Moovcare™

"Examination" of a personalized follow-up with Moovcare™

"Prescription" of a personalized follow-up with Moovcare™

"Examination" of a personalized follow-up with Moovcare™

"Prescription" of a personalized follow-up with Moovcare™

"Examination" of a personalized follow-up with Moovcare™
Moovcare™: Phase III - Quality of Life (mean score at 6 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](https://www.karger.com/Article/FullText/481274)
- Former FDA Commissioner, Dr. Robert Califf: [https://www.karger.com/Article/FullText/479861](https://www.karger.com/Article/FullText/479861)
AEs Underestimate Presence of Severe PROs

- anorexia by 50%
- diarrhea by 24%
- nausea by 26%
- vomiting by 13%

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