Special Considerations in Combined Treatment Trials (Chemoradiation) – principles, implications for design, endpoints, and quality control

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Classic Principles of Combined Modality Therapy

- Spatial Cooperation
- Toxicity Independence
- Normal Tissue Protection from RT
- Increased anti-tumor activity within RT field due to direct interaction between modalities

Steel GG, Peckham, Int J Radiat Oncol Biol Phys 1979
Vokes EE, Weichselbaum JCO 1990
Principles of Combined Modality Therapy

♦ Spatial Cooperation
  • Independent activity of each modality
    – RT @ loco-regional site; Systemic Rx @ extra-regional or distant sites
    – Recent observations with immunotherapy have altered with classical paradigm

♦ Toxicity Independence
  • Each modality can be given in full/near full dose

♦ Normal Tissue Protection from RT

♦ Increased anti-tumor activity within RT field due to direct interaction between modalities
Multi-Modality Clinical Trials

❖ Modalities:
  • cytotoxic chemotherapy + radiation
  • Novel targeted antiproliferative agents + radiation

❖ Preclinical studies-Rationale

❖ Phase I studies

❖ Phase II studies

❖ Phase III studies
Factors Affecting Radiation Sensitivity

- **Intrinsic Factors**
  - *Ras* mutational status
  - *EGFR*
  - DNA repair capabilities
  - DNA methylation

- **Extrinsic Factors**
  - Tumor microenvironment – hypoxia
  - pH
  - Tumor vasculature – ‘normalization’
  - Immune response is altered
Expanding List of Novel Radiation Modifiers
Higgins et al, Cancer Treatment Reviews 41 (2015) 105–113

CLASS

- Hypoxic modifiers:
- VEGF inhibitors
- EGFR inhibitors
- PI3Kinase inhibitors
- mTOR inhibitors
- AKT inhibitors
- MEK, MAPK/ERK inhibitors
- c-MET inhibitors
- PARP inhibitors
- HDAC inhibitors
- Other agents
  - Aurora kinase B
Effective Survival Curve for a Multifraction Regimen

Surviving Fraction

\( D_{10} = 2.3 \times D_0 \)

Cell Survival Curve for Single Doses

Effective \( D_0 \)

Effective \( D_{10} \)
Infra-additivity (antagonistic effect)

Additivity envelope (area between the mode 1 [upper] and mode 2 [lower] curves)

Supra-additivity (‘synergism’)
Classic ED$_{50}$ - Isobologram

Normalized ED$_{50}$ - Isobologram

Cl = \frac{D_1}{(D_x)_1} + \frac{D_2}{(D_x)_2}

Cl < 1 Synergism

Cl = 1 Additive Effect

Cl > 1 Antagonism
Therapeutic Gain

Tumor control

Late normal tissue damage

Effect

Tumor Dose
Strategies to ‘open’ the therapeutic window by widening the gap between ‘local tumour control’ and ‘normal tissue complication probability’ dose–response curves.

Tumour control curve can be shifted to the left by specifically rendering tumours more sensitive to radiation.

Normal tissue complication curve may be shifted to the right by improved radiotherapy targeting and delivery, or the use of normal tissue ‘radioprotectors’.

Geoff S. Higgins, Sean M. O’Cathail, Ruth J. Muschel, W. Gillies McKenna

Drug radiotherapy combinations: Review of previous failures and reasons for future optimism: Cancer Treatment Reviews, Volume 41, Issue 2, 2015, 105 - 113
Radiosensitizers

- Classically, requires a direct interaction between radiation and chemotherapy
- The key is to exploit the differences between tumor and normal tissues
- Major goal is to improve local control
- Eradication of micrometastases may also result
Radiosensitizers

- An *ideal* radiosensitizer enhances the effect of radiation on tumor through a direct interaction and does not increase normal tissue toxicity.
Guideline for Radiation Modifier Development

Development of Investigational Radiation Modifiers
A. Dimitrios Colevas, J. Martin Brown, Stephen Hahn, James Mitchell, Kevin Camphausen, C. Norman Coleman
For the Radiation Modifier Working Group of the National Cancer Institute
Affiliations of authors: A. D. Colevas, J. Mitchell, K. Camphausen, C. N. Coleman, National Cancer Institute, Bethesda, MD; J. M. Brown, Stanford University, Stanford, CA; S. Hahn, University of Pennsylvania, Philadelphia, PA

Recommendations of the NCI Working Group

- Preclinical data are a prerequisite for clinical trials using appropriate tumor models, dosing & assays
- Attempt to elucidate the mechanism of action
- Attempt to determine target
- The appropriate design of clinical trials is critical
Recommendations of the 2011NCI Working Group

Liu F-F et al, Clin Cancer Res 2013

✦ Preclinical studies
  • Must conduct at least in-vitro clonogenic assay
  • Contact NCI Rad Res Program, coordinating preclinical/clinical studies for multiple targeted agents
  • Generate in-vivo data using different human cancer xenograft models

✦ Biomarkers
  • Develop & validate tumor microenvironment predictive biomarkers
  • Develop & validate predictive biomarkers of sensitivity to molecular-targeted therapeutics
  • Using ‘clinical-ready’ PD read-outs
  • Need for robust imaging methods for tumor ID, segmentation, & characterization across institutions
Pathway of *in-vitro* to *in-vivo* to phase I/II/III clinical trials

Development and assessment of radiation modifiers — An international consortium

- **Lab**
  - Basic science discovery
  - Simple HTP assays (generally 1 log)
  - Newer HTP assays (possibly larger range)
  - HTP clonogenic assays (multi-log)

- **In vitro**
  - Standard models
  - Tumor control
  - GEMMs—tumor, normal tissues
  - Tumor xenografts

- **In vivo**
  - Patient-derived xenografts

- **Clinic**
  - PK and PD
  - Phase 0–I
  - Phase II
  - Phase III
  - Postmarket

Mechanism of action during development and “bedside to bench”

© 2013 American Association for Cancer Research

Clinical trial design

- Simple
- Statistically powered to answer objective
- Consider use of adaptive trial design

QA

- Conduct expeditious real-time QA of RT plans (i.e. RTOG-0529)

Publication bias

- Publish results of trials regardless of outcome (see Ellis LE)

International consortium

- Establish a consortium for the evaluation of radiation modifiers to expedite the discovery & translation of effective agents that will enhance the curative outcomes of RT for pts
Preclinical Studies-Rationale

- Demonstrate *in-vitro* radiosensitization in human tumor cell lines
- Demonstrate *in-vivo* radiosensitization in human tumor models
- Demonstrate the *lack* of sensitization of normal tissues
- Preclinical studies should use clinically relevant doses and schedules of agents & XRT
Question # 1
Which of the following is not a classic hallmark of combined modality therapy?

- Toxicity Independence
- Increased Tumor Response in RT field
- Toxicity Dependence
- Spatial Cooperation
- Normal tissue protection from RT
Which of the following is not a classic hallmark of combined modality therapy?

- Toxicity Independence
- Increased Tumor Response in RT field
- *Toxicity Dependence*
- Spatial Cooperation
- Normal tissue protection from RT
Question # 2
What is the following is not a strategy to increase the therapeutic ratio?

- IGRT (image-guidance radiotherapy)
- Cytoprotectants
- Accelerated hypofractionation
- Radiosensitization agents
- IMRT (intensity-modulated radiotherapy)
What is the following is not a strategy to increase the therapeutic ratio?

- IGRT (image-guidance radiotherapy)
- Cytoprotectants
- *Accelerated hypofractionation*
- Radiosensitization agents
- IMRT (intensity-modulated radiotherapy)
Challenges

- Phase II studies of unselected patient populations
- Usually introduced in the curative setting
- Recent data on RT/immunotherapy is promising for some metastatic scenarios
- Combination with chemoradiotherapy
- Difficulty in assessing late effects
- Interval for observation may be long – results may be obsolete
- Not a priority of drug development
Phase I studies-Endpoints

- The goals of combined modality Phase I studies are similar to single agent studies.
- However, the design and application often differ.
- The primary endpoint is usually an assessment of toxicity AND to identify a RPTD, recommended Phase II dose.
- Investigate Biomarkers.
Phase I studies-Design Issues

- Think about the next step in development
  - What is the standard therapy for the tumor site being treated?
  - What is the role of conventional chemotherapy?
  - How should surgery (if appropriate) be integrated?
  - How should chemotherapy be integrated?
  - Validation of biomarker?
  - Can you avoid an unselected subject population in your eventual Phase II-III study?
RTOG 1010

- Overexpression of HER2 3+ by IHC or amplification of the HER2 gene by FISH (ratio > 2.0) centrally assessed.
  - Siewart I/II Adenocarcinoma esophagus/GEJ
  - Confirmed operable for cure and all disease in radiation field
- Stratify: + celiac nodes vs - celiac nodes
- Randomize
- Arm 1 Radiation (45 Gy), oxaliplatin, 5-FU, and trastuzumab followed by surgery 5-8 weeks after completion of radiation, then maintenance trastuzumab, q 3 weeks for 13 treatments
  or
- Arm 2 Radiation (45 Gy), oxaliplatin, and 5-FU followed by surgery 5-8 weeks after completion of radiation
- Statistics: 480 registered pts to yield 160 HER2+; DFS increases from 15 mos to 27 mos for HER2-overexpressing adenoca pts; HRatio = 0.56; 2-sided α=0.05, Power = 90%
- Accrual update: > 200 total pts registered to-date
Phase I studies

Data helpful for the design of the study

- Single agent pharmacokinetic data from the relevant scheduling regimen
  - Continuous dosing during XRT vs. once a week dosing
- Single agent pharmacodynamic data
  - Agent’s affect on a molecular target that is relevant to the interaction between XRT and radiation
- Single agent safety data
Phase I studies-Design Issues

- **Dose escalation rules**
  - Standard Phase I dose escalation rules are acceptable especially if multiple agents are being used (including conventional chemotherapy)
  - Consider using a toxicity assessment in association with clinical or biological endpoints
  - Particularly with targeted agents, defining the “optimal biologic dose” might be appropriate
  - Be careful because the biological endpoint is often considered a surrogate for therapeutic effect and this may not be completely understood during the drug development period
    - Exploit office hrs with faculty experts as this area is rapidly changing
Phase I studies-Design Issues

♦ Patient selection
  • What tumor sites?
    ○ The answer to this question impacts greatly upon the assessment of toxicity.
    ○ The selection of tumor site may also be impacted by the agent being used in combination with XRT (think C225 and HNC)
  • Curative or palliative radiotherapy?
    ○ This will affect total radiation dose and fractionation
    ○ This will affect the patient population and perhaps the ability to tolerate combined modality therapy
    ○ Neoadjuvant/Pre-operative setting
  • In general, Phase I data are generated from studies that are cancer-specific and/or site-specific
Phase I studies-Design Issues

✧ What doses and schedules of the agent should be selected?
  – If the goal is radiosensitization, then delivery of the agent during as many fractions of radiation is desirable
  – Timing may/may not be critical (i.e. Xeloda, Oxaliplatin, rectal ca)
  – The schedule and dose may also be impacted by the known characteristics and target of the agent

✧ What doses of radiation should be selected?
  – A typical approach especially in the curative setting is to start with a standard radiation dose; however escalation (or even de-escalation) of the radiation dose may be desirable in certain clinical situations
Phase I studies-Design Issues

❖ A limited dose-escalation design is typical for these studies

❖ Dose-limiting toxicity rules
  – Grade IV hematological toxicity
  – Grade III non-hematological toxicity
  – Exceptions should be considered – Grade III GI in the setting of upper abdominal XRT
  – Breaks during XRT
  – Inability to administer systemic agent
  – Surgical morbidity (pre-operative setting)
Phase I studies—Endpoints

- Toxicity assessment is typically during the entire radiation course and some defined period of time after XRT, e.g. 30 days

- How do we assess late effects?
  - There are practical and time limitations
  - TITE-CRM methodology
  - Prolonged observation time
Phase I studies-Endpoints

- Toxicity assessment

Systematic review

A systematic methodology review of phase I radiation dose escalation trials

Madelon Pijls-Johannesma a,*, Ghislaine van Mastriigt a,1, Steve M. Hahn c, Dirk De Ruysscher a, Brigitta G. Baumert a, Guido Lammering a, Jeroen Buijsen a, Soren M. Bentzen b, Yolande Lievens d, Andrew Kramar e, Philippe Lambin a

* Department of Radiation Oncology (MAASTRO), GROW-School for Oncology and Developmental Biology, Maastricht University Medical Centre, The Netherlands; b Department of Human Oncology, School of Medicine and Public Health, University of Wisconsin, WI, USA; c Department of Radiotherapy, Hospital of the University of Pennsylvania, Philadelphia, USA; d Department of Radiation Oncology, Universitaire Ziekenhuizen Leuven, Leuven, Belgium; e CRIC Val d'Aurelle – Paul Lamarque, Unité de Biostatistique, Montpellier, France

![Flowchart diagram](image_url)

Fig. 1. Flowchart design phase I trials RT. Abbreviations: ERD = excess recruitment design, TITE-CRM = time-to-event continual reassessment method.* [67,68,81].
Trial design

In series RT/PARPi and RT/Chk1i Dose Escalation

RT Dose = 20 Gy in 5#
Drug Duration = 12 days (PARPi)
Drug Duration = 2 doses (Chk1i)

RT Dose = 20 Gy in 5#
Drug Duration = 12 days (PARPi)
Drug Duration = 2 doses (Chk1i)

RT Dose = 30 Gy in 10#
Drug Duration = 12 days (PARPi) or 2 doses (Chk1i)
Drug Duration = 19 days (PARPi) or 3 doses (Chk1i)

RT Dose = 30 Gy in 10#
Drug Duration = 12 days (PARPi) or 2 doses (Chk1i)
Drug Duration = 19 days (PARPi) or 3 doses (Chk1i)

H&N and Thorax Study

Parallel Tracks

Abdomino-Pelvic Study

Kevin Harrington
ICR, UK
Phase I studies - Other Considerations

- Neo-adjuvant or pre-operative studies are currently favored

- Lead-in administration of compound(s)
  - Allows for independent assessment of toxicity
  - Allows for evaluation of a biomarker – proof of principle, explore mechanism/target

- May be particularly helpful in selecting patients for Phase II studies

- Expanded cohort at final dose may allow for a more precise evaluation of biomarker
Phase I Trial of Protease Inhibitor, Nelfinavir, With Concurrent Chemoradiotherapy For stage IIIA/IIIB inoperable NSCLC

Prior to Day -14:  
- Clinical Evaluation and Staging Studies  
- Trial Enrollment

NELFINAVIR (625 or 1250mg PO BID): 7-14 day prior to and concurrent with XRT

XRT: Day 0 to Week 7/8  
1.8 Gy/Day to 66.6 Gy  
Weekly laboratory monitoring

Day 0,7,28,35: Cisplatin 50mg/m2

Day 0-4: Etoposide 50mg/m2

Day 28-32: Etoposide 50mg/m2

3-MONTH POST-TREATMENT PET/CT

Rengan R
(a) HASTE image showing portion of metastatic NSCLC in pre-aortic lymph node. Color maps for tumor $K_{\text{trans}}$ before treatment (b), after 7 days of Nelfinavir (c). Note vascular hot spot at periphery of tumor inferiorly at baseline (B) is diminished after seven days of NFV.

Bar graph showing median pixel tumor $K_{\text{trans}}$ values prior to (blue) and post (burgundy) administration of Nelfinavir for initial four patients.
Simplified summary of the synergistic interaction between ionising radiation and immune checkpoint blockade in inducing an immune response.

(A) Tumour cell avoiding T-cell immunosurveillance due to lack of expression of stimulating ligands results in poor T-cell activation.

(B) Ionising radiation (IR) of cell leads to upregulation of RAE-1 and other radiation induced ligands (RIL) allowing recognition by T-cells. However, CTLA-4 may negatively regulate this pathway muting the T-cells ability to kill the cancer cell.

(C) Addition of CTLA-4 antibody binds CTLA-4, removing this inhibitory signal which thus allows the MHC-T cell receptor complex (TCR) to cause T-cell activation and cell killing. PD-1 and PDL-1 inhibitors are likely to exert similar effects seen with CTLA-4 inhibitors of increasing the activation of T-cell response to irradiated tumour cells.

Geoff S. Higgins, Cancer Treatment Reviews, 2015
Radiation + anti-CTLA4 promotes regression of irradiated and unirradiated tumours and is inhibited by PD-L1 on tumour cells.
Radiation + anti-CTLA4 promotes regression of irradiated and unirradiated tumours and also is inhibited by PD-L1 on tumour cells.

For Radiotherapy SGD, Session 3, Tues 16:00-17:00
Anti-Angiogenic Therapy

- Hypothesis: Can anti-angiogenic therapy augment the effect of radiation therapy and chemotherapy on rectal cancer?
- Immature and inefficient blood vessels could be pruned by eliminating excess endothelial cells --> “Normalized Vasculature” --> Improved delivery of nutrients and therapeutics
Anti-VEGF-R2 mAb enhances radiation therapy

**Tumor control probability**

<table>
<thead>
<tr>
<th>Radiation Dose, Gy</th>
<th>0</th>
<th>20</th>
<th>40</th>
<th>60</th>
<th>80</th>
<th>100</th>
<th>120</th>
<th>140</th>
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<tr>
<td><strong>U87</strong></td>
<td>![U87 Curve]</td>
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**TCD** _50_, Gy (95% CI)

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<th>Treatment</th>
<th>TCD 50</th>
<th>95% CI</th>
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<tr>
<td>RAD</td>
<td>66.2</td>
<td>(59.6-73.6)</td>
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<tr>
<td>+ 1/2mAb</td>
<td>54.8</td>
<td>(45.1-66.6)</td>
</tr>
<tr>
<td>+ mAb</td>
<td>39.1</td>
<td>(31.7-48.1)</td>
</tr>
<tr>
<td>RAD</td>
<td>97.8</td>
<td>(85.3-112.0)</td>
</tr>
<tr>
<td>+ 1/2mAb</td>
<td>86.3</td>
<td>(74.6-99.8)</td>
</tr>
<tr>
<td>+ mAb</td>
<td>74.8</td>
<td>(63.7-87.7)</td>
</tr>
</tbody>
</table>

Rectal Cancer: Phase I Study (Schema)

<table>
<thead>
<tr>
<th>Level</th>
<th>Bev (q2wk)</th>
<th>5-FU (mg/m²/d)</th>
<th>RT (Gy)</th>
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<tbody>
<tr>
<td>1</td>
<td>5 mg/kg</td>
<td>225</td>
<td>50.4</td>
</tr>
<tr>
<td>2</td>
<td>10 mg/kg</td>
<td>225</td>
<td>50.4</td>
</tr>
</tbody>
</table>

Bevacizumab: 4 Infusions
After determination of MTD, 20 additional pts to be treated
Surgery Performed 7 weeks after therapy

Willett et al. Nature Medicine, 2004
Endoscopic IFP Measurements

Mean IFP before and 12 days after the first AVASTIN infusion

Interstitial fluid pressure (mmHg)

Bars - SE, p<0.05
Question #3
When designing your Phase I trial of a radiosensitizer you should

- Always escalate drug & fix radiation dose
- Always fix drug dose & escalate radiation dose
- Ensure that drug hits the target for as many fractions of radiation as possible
- Starting drug dose should be $1/10^{th}$ the LD10 in mice
When designing your Phase I trial of a radiosensitizer you should

- Always escalate drug & fix radiation dose
- Always fix drug dose & escalate radiation dose
- *Ensure that drug hits the target for as many fractions of radiation as possible*
- Starting drug dose should be $1/10^{th}$ the LD10 in mice
Question #4
When assessing late toxicity in a drug–radiation Phase I trial you should consider all of the following except:

- Monitor subjects for 30 days after completion of treatment and consider them off study at that time
- Allow for a longer period of time (> 30 days) between dose cohorts to assess toxicity
- Follow patients for at least one year and collect late toxicity data for determination of the RPTD
- Include late radiation toxicity criteria in the definition of DLT
When assessing late toxicity in a drug–radiation Phase I trial you should consider all of the following *except*:

- Monitor subjects for 30 days after completion of treatment and consider them off study at that time
- Allow for a longer period of time (> 30 days) between dose cohorts to assess toxicity
- Follow patients for at least one year and collect late toxicity data for determination of the RPTD
- Include late radiation toxicity criteria in the definition of DLT
Phase II studies

- The decision to proceed with a combined modality Phase II study is dependent upon the safety and early efficacy results from the Phase I trial.

- Response rates are often not helpful for selecting efficacious regimens:
  - *Delayed time to response with XRT*
  - *Residual unevaluable masses vs. scarring*
  - *Progressive disease outside of the XRT field*
  - *Underlying high local response rates to XRT*
Phase II trials - Endpoints

- Consider other efficacy endpoints
  - Metabolic response rate
  - Pathological CR (neoadjuvant setting)
  - Local or locoregional control rates
  - Locoregional time to progression
  - Survival

- The endpoint selected will depend upon the tumor & the current standard therapy
Phase II trials-Endpoints

- Collecting additional toxicity data both acute and late toxicities is essential
- Collection of late toxicity data in the larger group of patients that constitutes a Phase II study will be helpful as the Phase III study is designed
Early stopping rules for toxicity (most likely acute toxicity) should be considered.

Early stopping rules for low response rates compared to historical controls may also be a useful design consideration.

Usually patients for whom XRT is a standard and definitive therapy.

If mechanisms (molecular) are known consider restricting eligibility – eg. EGFR mutations, ras mutations, altered tumor microenvironment.
A phase II multicenter randomized trial evaluating 3-year disease-free survival in patients with locally advanced rectal cancer treated with chemoradiation plus induction or consolidation chemotherapy, and total mesorectal excision or non-operative management.

Principal Investigator/Department: Julio Garcia Aguilar, MD, PhD

OBJECTIVES AND SCIENTIFIC AIMS

2.1 Primary Objective

1. To evaluate 3-year disease-free survival (DFS) in patients managed with TNT and TME or NOM, compared with standard historical controls managed according to standard of care (CRT and TME followed by adjuvant chemotherapy [ACT]).

2.2. Secondary Objectives

1. To compare outcomes between patients in the two study arms, with respect to rates of organ preservation, compliance with the neoadjuvant protocol, and adverse events.

2. To measure patient-reported functional outcomes and quality of life (QoL) in patients with distal LARC treated with TNT and NOM, and compare them to patients treated with TNT and TME.

2.3 Correlative Studies Objectives

1. To investigate the diagnostic performance of conventional and diffusion-weighted magnetic resonance imaging (DW-MRI) in identifying patients with distal LARC treated with TNT, who may benefit from NOM.

2. To evaluate the feasibility of using circulating tumor DNA and miRNA profiles in plasma to monitor tumor response to TNT in rectal cancer patients treated in both protocol arms.

3. Use of genomic analysis by next generation sequencing to profile distal rectal cancer treated with neoadjuvant chemotherapy and radiation.

A phase II multicenter randomized trial evaluating 3-year disease-free survival in patients with locally advanced rectal cancer treated with chemoradiation plus induction or consolidation therapy, and total mesorectal excision or non-operative management.

Principal Investigator/Department: Julio Garcia Aguilar, MD, PhD

OBJECTIVES AND SCIENTIFIC AIDS
2.1 Primary Objective
1. To evaluate 3-year disease-free survival (DFS) in patients managed with TTT and or NTT, chemoradiation, and total mesorectal excision, managed according to protocol, vs patients managed with induction chemotherapy (ACT).

2.2 Secondary Objectives
1. To compare outcomes between patients in the two study arms, with respect to: organ preservation, compliance with the protocol, and adverse events.
2. To measure patient-reported functional outcomes and quality of life (QOL) in patients managed with TTT and NTT, and compare them to patients treated with ACT and TME.

2.3 Correlative Studies Objectives
1. To investigate the diagnostic performance of noninvasive and diffusion-weighted magnetic resonance imaging (DW-MRI) in identifying patients with distal low rectal cancer treated with TTT vs patients who may benefit from induction chemotherapy.
2. To evaluate the feasibility of using circulating tumor DNA and mttRNA profiles in plasma to monitor tumor response to TTT in rectal cancer patients treated in both protocols.
3. Use of activity analysis by next generation sequencing to profile distal rectal cancer treated with adjuvant chemotherapy and radiation.

Distal Rectal Cancer MRI Staging

Randomization

Induction FOLFOX/CapeOx (16-18 weeks)

Interval Evaluation
DRE – Endoscopy - MRI

Chemoradiation (5.5 weeks)

Consolidation Chemoradiation (5.5 weeks)

Interval Evaluation
DRE – Endoscopy - MRI

FOLFOX/CapeOx (16-18 weeks)

Restaging
DRE - Endoscopy - MRI

Surgery
No Clinical Response

Non-Operative Management
Complete or Near Complete Clinical Response
**Daily NELFINAVIR (1250mg PO BID): Day -14 to End of XRT**

- **XRT: Day 0 to Week 7/8**
  - 1.8 Gy/Day to 66.6 Gy
  - Weekly laboratory monitoring

**Prior to Day -14:**
- Clinical Evaluation and Staging Studies
- Trial Enrollment

**Baseline DCE-MRI x2**

**Day -1: Post NFV, Pre-RT DCE-MRI**

**Day 7: DCE-MRI**

**Day 0,7,28,35: Cisplatin 50mg/m2**

**Day 0-4: Etoposide 50mg/m2**

**Day 28-32: Etoposide 50mg/m2**

**Months 3,6,12: Follow-up CT Scans**
**Phase II Evaluation of NFV**

- **DCE-MRI**
- **FDG-PET**

**Patient Enrolled**

**Nelfinavir**

**ChemoxRT**

**Randomize**

**Assess K**\(\text{trans}\) Response

**Favorable**

**ChemoxRT**

**3 MO**

**Unfavorable**

**ChemoxRT**

**3 MO**

**No Boost**

**FAVORABLE FDG-PET RESPONSE**

**3 MO**

**UNFAVORABLE FDG-PET RESPONSE**

**3 MO**

**Boost**

**3 MO**
Other Successful Examples of Systemic agents + radiotherapy

- Temozolomide and radiation for malignant gliomas
- Cetuximab and Radiation for locally advanced head and neck cancers
The Promise of Molecularly Targeted Therapy and Radiation


<table>
<thead>
<tr>
<th></th>
<th>Radiotherapy (N=212)</th>
<th>Radiotherapy plus cetuximab (N=208)</th>
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<tbody>
<tr>
<td></td>
<td>All grades</td>
<td>Grade 3/4</td>
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<tr>
<td>Skin reaction*</td>
<td>200 (94.3%)</td>
<td>45 (21.2%)</td>
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<tr>
<td>Mucositis/stomatitis†</td>
<td>199 (93.9%)</td>
<td>110 (51.9%)</td>
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<tr>
<td>Dysphagia</td>
<td>134 (63.2%)</td>
<td>63 (29.7%)</td>
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<tr>
<td>Xerostomia‡</td>
<td>150 (70.8%)</td>
<td>6 (2.8%)</td>
</tr>
<tr>
<td>Acneiform rash§</td>
<td>21 (9.9%)</td>
<td>3 (1.4%)</td>
</tr>
<tr>
<td>Infusion reaction¶</td>
<td>4 (1.9%)</td>
<td>0 (0%)</td>
</tr>
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</table>
SBRT with use of IGRT may allow radiotherapy to be tested within the confines of novel trial designs for advanced stage dx, regardless of anatomic site.
For Radiotherapy Small Group Discussion, Session 3, Tuesday 16:00 – 17:00
Schematic illustration of the SMART Trials workflow.

A. Patient presents with resistant disease
B. Bx
C. Image
D. Clinical status
E. Research analytics
F. CLIA Dx
G. Biological assessment
H. CCC informatics with clinical decision support
I. Treatment decision
J. Negotiate drug access
K. Multi-target Rx

The Collaborative Cancer Cloud (CCC)
Making Precision Medicine Mainstream
Challenges

- Phase II studies of unselected patient populations
- Usually introduced in the curative setting
- Combination with chemoradiotherapy
- Difficulty in assessing late effects
- Interval for observation may be long – results may be obsolete
- Not a priority of drug development
Challenges

- Phase II studies of unselected patient populations
- Usually introduced in the curative setting
- Combination with chemoradiotherapy
- Difficulty in assessing late effects
- Interval for observation may be long – results may be obsolete
- **Not a priority of drug development**
The lag time in initiating clinical testing of new drugs in combination with radiation therapy, a significant barrier to progress?

Median lag time-O between the opening of the phase I trial without RT and the opening of the phase I with RT was \(6\) yrs (interquartile range 5–8 yrs).

Median lag time-P between the published phase I trial without RT and the opening phase I with RT was \(3\) yrs (interquartile range 1–6 yrs).
XRT MASTER DATABASE

- Clinical data (EMR)
- Population/risk modeling (nomogram)
- SMART (Serial Multiscale ARchitecture & Theranostic) trial platform
- Omic data
- Radiomics
- Quantitative imaging
- Spatial histopathology
- Virtual tumor growth modeling
- Patient-derived xenograft
- Adaptive XRT
- Patient reported Outcomes (PRO)
- Dose-response & math modeling

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HBReview
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