Piggyback on your therapy trial

1. HYPOTHESIS AND SPECIFIC AIMS (1 page)

Primary Study Specific Aim
To assess and to characterize the kinetics of candidate quantitative imaging biomarkers (CQIBs) associated with normal tissue injury before, during, and after therapy by using serial multiparametric MRI for patients enrolled on protocol MDACC 2012-0825, “Phase II/III Randomized Trial of Intensity-Modulated Proton Beam Therapy (IMPT) versus Intensity-Modulated Photon Therapy (IMRT) for the treatment of Oropharyngeal Cancer of the Head and Neck.”

Identified Imaging Hypothesis for Primary Specific Aim
Specifically, we hypothesize that IMPT will result in a 10% difference in normalized post-therapy voxel-by-voxel organ-at-risk (OAR) region of interest (ROI) apparent diffusion coefficient (ADC) and the DCE-MRI parameters $K_{trans}$ and $v_e$ at follow-up imaging as compared with those values after IMRT, as detected by 3T MRI acquisition for uninvolved parotid and submandibular glands.
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Multi-parametric MRI - DCE (Glands)

- K-trans pre-therapy
- K-trans mid-therapy
- K-trans post-therapy
Evaluation of DCE (pre and mid – Tx)

Investigating novel MRI techniques to evaluate and monitor tumor response.
Includes non-surgical HPV patients who get chemotherapy.

Planned enrollment: n=20
MDACC2012-1128: Advanced MR for HPV-negative patients

- Investigating novel MRI techniques to evaluate interim response
- Includes non-surgical HPV- patients who get chemo and RT (induction/concurrent/re current)
- Planned enrollment n=20

MDACC 2012-1128: Assessment of the Feasibility of Acquisition of Candidate Imaging Biomarker Kinetics of Multiparametric Magnetic Resonance Imaging During Chemoradiotherapy in Human Papilloma Virus-Negative/HPV-non-Associated Head and Neck Squamous Cell Carcinomas
Pacific Northwest Annual Workshop on Methods in Radiation Oncology Clinical Trials
Clinical Endpoints

- « Vertical » Response Rate
- « Horizontal » Time to Progression

Graph showing Size over Time with markers BL, TP1, TP2, TP3, TP4, TP5 for lines A and B.
WHO Criteria - 1981

- Tumor response assessed by change in SPD of >2 lesions
- No minimum size of lesions
- No specification of number of lesions

SPD: Sum of product of diameters

\[ \text{AxB + CxD} \]
RECIST – 2000
(Response Evaluation Criteria in Solid Tumors)

SLD = Sum of diameters
When RECIST doesn’t work

Infiltrative tumor and tumor in hollow organs is hard to measure
Using RECIST 1.1 in targeted therapy trials:

1) can lead to declaration of progressive disease (PD) too early, when the treatment effect is not yet fully evident or there is "flare effect".

2) does not consider change in enhancement/density or FDG avidity, which may be the only relevant changes.
irRECIST (immune-related): Cancer progression

PERCIST (PET): Uses change
**Immune-related (ir)**

- **irRC**
  - Based on WHO (2D)
  - Up to 10 targets
  - Sum of Long Axis x Short Axis

- **irRECIST**
  - Based on RECIST (1D)
  - Up to 5 targets
  - Sum of Long Axis

**Main difference**
- New Lesions are integrated into the tumour burden.
  - When a complete response is not reached.
Immune-related (ir)

- irRC
  - Based on WHO (2D)
  - Up to 10 targets
  - Sum of Long Axis x Short Axis

- irRECIST
  - Based on RECIST (1D)
  - Up to 5 targets
  - Sum of Long Axis
What is your hypothesis?

- Always be mindful when selecting endpoints.
- You need to address your hypothesis.
- You need to be realistic in what you are asking of your patients.
- How many blood draws, biopsies, and trips to the hospital do you need to perform...
Statistical Considerations

• If this is the first time being tested
  – Training set
  – Validation set

• Continuous variable, ordinal measure, binary cut-off?
Incorporation of Novel Translational Research Endpoints in Clinical Trials
Mohamed Khan, MD, PhD, MBA
Division Chief of Radiation Oncology
Banner MD Anderson Cancer Service Line
(BMDACC-Gilbert & BMDACC-Desert, Thunderbird, Boswell)
Clifton (Dave) Fuller, MD, PhD
Assistant Professor
Head & Neck Section

And
Innovation in Radiation Oncology
Informatics and Innovation in Radiation Oncology
LET'S SOLVE THIS PROBLEM BY USING THE BIG DATA NONE OF US HAVE THE SLIGHTEST IDEA WHAT TO DO WITH
Clinical Informatics Becomes a Board-certified Medical Subspecialty Following ABMS Vote

Thursday, September 22, 2011

AMIA to offer prep courses for clinicians who sit for Board Exam

Washington, DC—Today, AMIA—the association for informatics professionals—announces the success of a multi-year initiative to elevate clinical informatics to an American Board of Medical Specialties (ABMS) subspecialty certified by an examination administered by the American Board of Preventive Medicine and available to physicians who have primary specialty certification through the American Board of Medical Specialties. Joining such subspecialties as pediatric anesthesiology, medical toxicology, sports medicine, geriatrics medicine, and cardiovascular disease, clinical informatics (CI) certification will be based on a rigorous set of core competencies, heavily influenced by publications on the...
by the American Board of Preventive Medicine and have primary specialty certification through the American Board of Medical Specialties (ABMS) subspecialty certified by an association for informatics professionals—multinational initiative to elevate clinical informatics to an area.

Joining such subspecialties as pediatric cardiology, sports medicine, geriatrics medicine, and clinical informatics (CI) certification will be based on a body of work recognized by the field, heavily influenced by publications on the topic.
Funding Opportunities

ITCR has issued four Funding Opportunity Announcements aimed at successive stages of informatics technology development.

- PAR-15-334: Development of Innovative Informatics Methods and Algorithms for Cancer Research and Management (R21)
- PAR-15-332: Early-Stage Development of Informatics Technologies (U01)
- PAR-15-331: Advanced Development of Informatics Technologies for Cancer Research and Management (U24)
- PAR-15-333: Sustained Support for Informatics Resources for Cancer Research and Management (U24)
Fellowship in Clinical Informatics: Radiation Oncology Track

Clinical informatics is the subspecialty of all medical specialties that transforms health care by analyzing, designing, implementing, and evaluating information and communication systems to improve patient care, enhance access to care, advance individual and population health outcomes, and strengthen the clinician-patient relationship.
Particle Therapy Based Clinical Trial Design: Considerations

Integral dose reduction
- Patient populations likely to benefit most: pediatrics, lymphoma
- Considerations: Small patient numbers, long-term endpoints

Improved tumor control
- Patient populations likely to benefit most: Soft tissue sarcoma, NSCLC, melanomas
- Considerations:
  - Radioresistant solid tumors historically treated with surgery
  - Dose escalation with low-LET radiation has not been successful (Carbon?)
Phase III Randomized Clinical Trial of Proton Therapy vs IMRT for Low or Low-Intermediate Risk Prostate Cancer

Study Schema

Randomize
400 men

Proton Beam Therapy (PBT) versus Intensity Modulated Radiotherapy (IMRT)

Stratify
Study site, age (< 65 years v ≥ 65 years)

Follow
Months 1, 3, 6, 9, 12, 18, 24, 36, 48, 60

Primary Endpoint
- Bowel function at 24 mo (EPIC)

Secondary Outcomes
- Urinary and erectile function
- HRQOL and Utilities
- Perceptions of care
- Adverse events
- Efficacy endpoints
- Clinical follow-up
Considerations when putting together:

- **Statistical analysis plan**
  - Primary or secondary endpoint
  - Power

- **Reporting of results**
  - Inclusion group
  - Intent to treat
  - Data complete?

- **Interpreting the Data**
  - Minimally clinically important difference
- Number/timing/costs of assessment
  - Balance between brief interval and likelihood of detecting changes
- Baseline assessment
  - To establish pre-existing differences
  - Provides reference point for other assessments
- One or more on-treatment assessments
  - Frequency will depend on research question
  - Timing will depend on when changes are expected
- Post-treatment assessments
  - Depends on research question

Penn Radiation Oncology
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<td>Timur Mitin, M.D., Ph.D.</td>
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<td>Sophia Bornstein, M.D., Ph.D.</td>
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Saturday, May 7

7:45 a.m.  Continental breakfast

8:25 a.m.  Clinical Informatics in Radiotherapy
           Dave Fuller, M.D., Ph.D.

9:05 a.m.  Particle Therapy-Based Clinical Trials
           Ramesh Rengan, M.D., Ph.D.

9:45 a.m.  QOLife Endpoints in Clinical Trial
           Lilie Lin, M.D.

10:25 a.m. Mathematical Modeling in Design
           Time-Dose-Fractionation
           Andrew Trister, M.D., Ph.D.
Measurement

- Reliability and validity depend...
  - Fact-G has 0.87 reliability in Pol, is it still reliable in Botswana?
  - Is it reliable measure in China?

- If it's to be applied in new pop.
  - What's wrong with a low reliability?
    - Poor measure implies low validity.
    - Want reliability to be above...
Adding PROs to Existing Clinical Data Warehouse

- Epic
- Aria
- Other Clinical Systems

UPHS Tumor Registry
- Detailed Diagnosis, Stage, Histology

Penn Data Store
- Visit Info
- Diagnoses
- Toxocities
- Chemotherapy
- Treatment Modality
- Dose / Fractions
- DVH Data
- Laboratory Results
- Inpatient Chemo
- Hospitalizations

PROs
Mypatientportal (EPIC)
Adding PROs to Existing Clinical Data Warehouse

- Epic
- Aria
- UPHS Tumor Registry
- Penn Data Store
- PROs
- Other Clinical Systems
- Mypatientportal (EPIC)
Overview

- Early steps
- Who is picking up the bill?
- Protocol development
- Data safety monitoring
- Case report forms & data
- Privacy & confidentiality
- IRB and supporting documentation
- Training
...and this is the form you send back to confirm you've sent back all the other forms!