Lessons Learned from Radiation Oncology Clinical Trials

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This paper is dedicated to the memory of Dr. Kian Ang, a leader in radiation oncology, who was continuously improving outcome for our cancer patients; through the methodical conduct of high impact clinical trials.
ABBREVIATIONS

AFX  Accelerated fractionated radiation therapy
Akt  Serine/Threonine specific protein kinase and oncogene (protein kinase B)
ASCO  America Society of Clinical Oncology
CNS  Central nervous system
CDDP  Cisplatin
Cre  Causes Recombination
CT  Computed tomography
DCE  Dynamic contrast enhanced
DFS  Disease-free survival
DWI  Diffusion-weighted imaging
EGFR  Epidermal growth factor receptor
EML4-ALK  Echinoderm microtubule-associated protein-like 4 – ALK (anaplastic lymphoma kinase)
EORTC  European Organization for Research and Treatment of Cancer
FTI  Farnesyltransferase inhibitor
GBM  Glioblastoma multiforme
GEMM  Genetically-engineered mouse model
γ-H2AX  Gamma-histone 2AX
HNSCC  Head and neck squamous cell carcinoma
HPV  Human papilloma virus
ICGC  International Cancer Genome Consortium
IDH1  Isocitrate dehydrogenase 1
IGF1R  Insulin-like growth factor-1 receptor
IGRT  Image-guided radiation therapy
IMRT  Intensity-modulated radiation therapy
K-ras  Kirsten rat sarcoma viral oncogene
LA HNSCC  Locally-advanced head and neck squamous cell carcinoma
MRI  Magnetic resonance imaging
MMCT  O-6-Methylguanine-DNA-Methyltransferase
MMC  Mitomycin-C
MTT  3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
NCCTG  North Central Cancer Treatment Group
NCI  National Cancer Institute
NF1  Neurofibromin 1
NF-kBIA  Nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha
NSCLC  Non-small cell lung cancer
OPC  Oropharyngeal cancer
OS  Overall survival
P-Akt  Phosphorylated Akt
PAR  Poly-ADP-ribose
PBMC  Peripheral blood mononuclear cell
PD  Pharmacodynamic
PK  Pharmacokinetics
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tr>
<td>PDGFRA</td>
<td>Platelet-derived growth factor receptor, alpha polypeptide</td>
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<tr>
<td>PET</td>
<td>Positron emission tomography</td>
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<tr>
<td>PTEN</td>
<td>Phosphatase and tensin homolog</td>
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<td>QA</td>
<td>Quality assurance</td>
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<td>QIN</td>
<td>Quantitative Imaging Network</td>
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<tr>
<td>RT</td>
<td>Radiation therapy</td>
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<tr>
<td>RCT</td>
<td>Randomized clinical trial</td>
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<tr>
<td>RECIST</td>
<td>Response evaluation criteria in solid tumors</td>
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<tr>
<td>RTOG</td>
<td>Radiotherapy and Oncology Group</td>
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<tr>
<td>siRNA</td>
<td>Short-interfering RNA</td>
</tr>
<tr>
<td>SRC</td>
<td>Tyrosine kinase proto-oncogene “sarcoma”</td>
</tr>
<tr>
<td>STK33</td>
<td>Serine/threonine-protein kinase 33</td>
</tr>
<tr>
<td>TCGA</td>
<td>The Cancer Genome Atlas</td>
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<tr>
<td>TKI</td>
<td>Tyrosine kinase inhibitor</td>
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<tr>
<td>TMZ</td>
<td>Temozolomide</td>
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<tr>
<td>TPZ</td>
<td>Tirapazamine</td>
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ABSTRACT

A Workshop entitled “Lessons Learned from Radiation Oncology Trials” was held on December 7-8th, 2011 in Bethesda, MD, to present and discuss some of the recently conducted Radiation Oncology clinical trials with a focus on those that failed to refute the null hypothesis. The objectives of this Workshop were to summarize and examine the questions that these trials provoked, to assess the quality and limitations of the preclinical data that supported the hypotheses underlying these trials, and to consider possible solutions to these challenges for the design of future clinical trials.

Several themes emerged from the discussions, including: a) opportunities to learn from null-hypothesis trials through tissue and imaging studies; b) value of preclinical data supporting the design of combinatorial therapies; c) significance of validated biomarkers; d) necessity of quality assurance in radiotherapy delivery; e) conduct of sufficiently-powered studies to address the central hypotheses; and f) importance of publishing results of the trials regardless of the outcome.

The fact that well-designed hypothesis-driven clinical trials produce null or negative results is expected given the limitations of trial design, and complexities of cancer biology. It is important to understand the reasons underlying such null results however, in order to effectively merge the technological innovations with the rapidly evolving biology for maximal patient benefit, through the design of future clinical trials.
INTRODUCTION

Clinical trials involving RT for cancer are initiated to identify novel technological and biological approaches that can improve local tumor control, DFS, OS, reduce toxicity, and/or enhance quality of life. The design of these trials should be based on solid preclinical evidence supporting such approaches; however, oftentimes, patients participating in the experimental arm fare no better than control subjects (1). A similar trend is currently being reported for drug combination trials (2). To identify possible reasons for these negative outcomes, and to propose pathways to increase the likelihood of “success”, a Workshop entitled “Lessons Learned from Radiation Oncology Trials” was held on December 7-8th, 2011 in Bethesda, MD, sponsored by the Radiation Research Program of the NCI. The objectives of the Workshop were to assess the quality, quantity, and limitations of the preclinical data that supported the hypotheses underlying a few recently completed trials, and to consider potential improvements in methods generating these trials. Attendees included radiation and medical oncology clinical trialists, radiation biologists, clinician-scientists, radiation physicists, statisticians, and representatives from the pharmaceutical industry. To provide common ground for dialogue, results from ten recent Phase III RCTs from several different malignancies were discussed (Table 1), which included the spectrum of positive, negative, and null outcomes.

SUMMARY OF CLINICAL TRIALS
Central Nervous System Tumors

Two studies focused on GBMs were presented and discussed. The RTOG 0525/EORTC 26052-22053 was an international Phase III RCT determining whether dose-intensifying adjuvant TMZ could improve OS (3). The overall conclusion was “no evidence for improvement”, although the prognostic value of MGMT promoter methylation status was confirmed.

The second Phase I/II RTOG 0211 trial examined the addition of an EGFR TKI (Gefitinib, Iressa™) to RT for GBM patients, which failed to demonstrate any OS benefit with the combinatorial approach (4). In fact, tumors with elevated SRC or PTEN expression fared worse with the TKI, illustrating the complex signalling cascades underlying most GBMs.

Head and Neck Squamous Cell Carcinoma

Despite the success of the landmark Cetuximab plus RT for patients with LA HNSCC (5, 6), more recent trials have been disappointing. The RTOG 0129 asked whether AFX plus CDDP will improve OS for LA HNSCC patients (7); in fact, no difference was observed between the standard vs. AFX group, suggesting that CDDP likely offsets tumor cell repopulation during fractionated RT.

The TROG 02.02 trial examined the value of adding a hypoxic cytotoxic agent TPZ to CDDP-RT for LA HNSCC patients (8). Disappointingly, this study also demonstrated no difference in outcome, but underscored the importance of QA in RT delivery (9), as well as questioning the clinical importance of tumor hypoxia (10). A third trial (RTOG 0522) asked whether the addition of Cetuximab to CDDP-RT could improve progression-free survival (11); this study not only failed to demonstrated an advantage
to the triple-modality, but observed greater acute toxicities. Furthermore, Cetuximab and CDDP appeared to have overlapping mechanisms of action; hence, utilizing complementary tumoricidal agents would likely be more effective.

**Lung**

The four-arm RTOG 0617 trial compared OS differences between high- vs. standard-dose conformal RT with concurrent chemotherapy (Carboplatin and Paclitaxel), with or without Cetuximab for patients with stage IIIA/IIIB NSCLC. The results demonstrated no difference in OS between the high- (74 Gy) vs. standard-dose (60 Gy) patients (12), even suggesting an inferior survival with the high-dose arm, possibly related to treatment-related deaths, which may underscore the importance of QA in RT planning and delivery (13).

**Gastrointestinal**

The RTOG 9811 Phase III RCT addressed the efficacy of substituting CDDP for MMC, in the standard 5-FU/MMC/RT regimen for anal canal carcinoma. The results demonstrated no difference in DFS between the two treatment arms, but the CDDP group experienced a significantly higher colostomy rate (14). The major design flaw related to two new hypotheses of drug and sequence, both being addressed simultaneously; the new drug being CDDP, delivered in an induction manner. Consequently, it remained unclear if the negative results were related to an ineffective drug, an ineffective sequence, or both.

The RTOG 0020 Phase II randomized trial of Gemcitabine/Paclitaxel/RT, followed by an FTI (R115777) for unresectable pancreatic cancer demonstrated that maintenance FTI failed to improve clinical outcome, yet was associated with increased
toxicities, highlighting the challenges to inhibiting K-ras, an established oncogenic target in this disease (15).

**Genitourinary**

The RTOG 94-13 trial, a complex four-arm randomization of whole pelvis vs. prostate-only RT, with secondary randomization of neo-adjuvant vs. concurrent hormone scheduling (16, 17) reported no significant difference in progression-free survival for any group. This was an under-powered 4-arm trial, and failed to address the issues of field size, or timing of androgen suppression. There might also have been an unpredicted biological interaction between concurrent androgen suppression with RT, arguing for the importance of companion translational studies to acquire biological insights.

The EORTC 22961 trial demonstrated that longer-term androgen suppression (total of 3 years) was marginally superior to shorter-term (6 months) when patients were also treated with RT (18). The effect size was small; 5-year cumulative prostate-specific mortality differed by only 2.5%, plus the majority of patients had low Gleason scores. Hence, it still remained unclear if long-term androgen ablation is beneficial for most patients.

**EMERGING THEMES (See Table 2 for summary)**

1. **Preclinical Studies**

Many reasons could account for the success of the Cetuximab plus RT RCT for HNSCC (5, 6), including: a) the universally reported prognostic value for EGFR over-expression (19-21); b) the role of EGFR in mediating radiation resistance (22-24); c) the
demonstration of efficacy of EGFR inhibitors in several different preclinical cancer models (25-27); d) a well-designed drug (28) which was highly efficacious and well-tolerated (29); and e) a well-constructed and efficiently-executed clinical trial (5).

Based on the above success, and corroborating the framework for preclinical studies as outlined by the UK group (30), it is recommended that before any combinatorial treatments are considered with RT, one must start with an in vitro clonogenic assay of novel drug-of-interest plus RT in relevant preclinical cancer models. The MTT and apoptotic assays are simple, but are poor substitutes for the more quantitative clonogenic survival assays, which until demonstrated otherwise, will remain the gold standard for the evaluation of any radiation sensitizer, DNA repair modification, or combinations of RT with drug.

The Molecular Radiation Therapeutics Branch within the Radiation Research Program of the NCI (rrp.cancer.gov/aboutRRP/mrtb.htm) has already generated extensive data for multiple targeted agents combined with RT in panels of human cancer cell lines; therefore, this resource should be the first point of contact before embarking on any combinatorial therapies. Next is the generation of in vivo data using different human cancer xenograft models, which have their limitations by only partially reflecting human tumor heterogeneity; furthermore, the tumor microenvironment (e.g. hypoxia), stromal factors, or the human metastatic patterns are not completely recapitulated. Some orthotopic models might address such limitations (31, 32), as well as early-passaged human tumor xenografts. An alternative is the utilization of GEMMs of human cancers (33), which could be useful for lung cancer (34, 35), and soft tissue sarcomas (36). Recently, Robert Kerbel’s group at the Sunnybrook Research Institute
developed a clinically-relevant murine model of postsurgical advanced metastatic breast cancer, which could be an improved model on evaluating efficacy of anti-angiogenic agents (37). This and other similar works highlight the need to focus on developing and utilizing better preclinical models, which in turn might lead to higher success rates in clinical trials.

Many of these xenograft models are readily available within the Radiation Oncology community including CNS (38); lung (39, 40), breast (41), head and neck (42), pancreas (32, 43), and cervix (31). Funding for these studies remains challenging, although some pharmaceutical companies could be interested since such data will inform the design of early-phase clinical trials. Finally, another potential solution could be the utilization of a panel of molecularly annotated first generation xenografts harboring high and low levels of the putative target (44); this could guide clinically realistic RT and drug doses for subsequent clinical trials.

II. Microenvironment as a Target

Over 60 years of research on hypoxia and RT tumor response can be summarized as: a) rodent and human tumors contain hypoxic cells; b) rodent tumors are more hypoxic than human tumors; thus, will model only the most hypoxic of human tumors; c) hypoxic human tumors are RT-resistant; d) methods to overcome hypoxia in human tumors are less than perfect but are beneficial (45); and e) the ideal methods to identify or treat hypoxic tumors do not yet exist.

Three limitations of the TROG 02.02 trial (8) relate to: administration of TPZ, QA of RT plans, and HPV status. The TPZ dose was sufficiently high to potentiate CDDP; however, it was administered with only 9 of 35 fractions, which could have compromised
the anticipated benefit. Tumors were not selected for hypoxia, and 12% of these patients had non-compliant RT plans that adversely affected tumor control (9), who were disproportionally distributed to the TPZ arm. Finally, TROG 02.02 was designed before the full appreciation of HPV-associated OPC, which appear not to benefit from hypoxic modifications (46), thereby diluting the potential benefit of TPZ.

Other tumor microenvironment properties such as extracellular pH, angiogenesis, and interstitial fluid pressure might also influence tumor response to RT, as well as targeting stromal cells, cytokines, and oxidative stress. To date however, other than hypoxia, no Phase III RCTs have evaluated such strategies with RT outcome.

In summary, hypoxia is a negative predictor in some tumors treated with RT. Despite clear benefits in multiple trials of hypoxia modifiers with RT, the results have not been sufficiently dramatic to change clinical practice (47). Improved agents are being developed (48), and will be evaluated with hypoxia imaging conducted at critically important times (49), which will help to improve selection of appropriate patients for such therapeutic strategies and hopefully improve the likelihood of positive clinical trials.

III. Biomarker Studies

Biomarkers are germane to categorizing patients into distinct risk groups for prognostic or predictive value, enriching cohorts for clinical trials, and tracking longitudinal response to therapies. With the emergence of data derived from the ICGC (www.icgc.org/) and TCGA (cancergenome.nih.gov) deep-sequencing projects, this is an opportune moment to capitalize on such resources to triage patients into genetically- or proteomically-defined groups, to identify novel targets, and actionable mutations for RT-combinatorial trials, although tumor heterogeneity will remain challenging (50). Many
of the ICGC/TCGA clinical data are not yet sufficiently mature to identify robust prognostic markers; the role of RT might also be difficult to discern, if such treatment details are lacking. Consequently, the value of well-annotated biospecimens linked to RT RCTs cannot be overstated.

The landmark observation of the benefit of TMZ to RT for GBM (51) changed practice, and led to the evaluation of TMZ dose intensification (RTOG 0525), corroborating the prognostic value of MGMT methylation status. A translational study evaluating primary GBM tissues from participants in multiple clinical trials demonstrated a potential 2-gene signature ($\Delta NF-kBIA$ plus $MGMT$ methylation), as well as suggesting a biological explanation for the lack of efficacy of Erlotinib (52), since $NF-kBIA$ deletion and EGFR amplification emerged to be mutually exclusive aberrations in GBM. Similar important insights have been derived from RCT tissue studies for HNSCC, not only corroborating the superior outcome for HPV-associated HNSCC (7), but also their limited benefit by hypoxic modifiers (46), which might in part account for the negative TROG 02.02 trial (8, 10). These data clearly illustrate the value of correlative tissue studies in providing biological insights, and informing the design of future trials.

Another approach is the utilization of an adaptive trial design (53); in these trials, data gathered during trial progression is used to change an aspect of the trial midway. In the Biomarkers-Integrated Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE) trial, 40% of the patients were randomly assigned to receive one of four treatments during the first phase of the trial (54). In the second adaptive phase, treatments were based on the results of previous biomarker testing during the first phase. This trial highlighted the potential advantage of an adaptive design, especially
during complex trials that assessed multiple drugs and biomarkers, and require tissue collection and biomarker analysis (53). This is a very promising area of investigation that should influence the design of future RT-drug trials for lung cancer, which requires the analysis of multiple known mutations such as KRAS, EGFR, and EML4-ALK.

Yet another critically important consideration is the utilization of “clinical-ready” PD read-outs. PD assays of DNA damage such as γ-H2AX in tumor tissues (55), or quantifying PAR levels in PBMCs (56) might be highly applicable for RT clinical studies, as opposed to P-Akt, which is notoriously unstable. This is an area of active investigation by the Frederick National Laboratory for Cancer Research; an important resource for the Radiation Oncology research community.

IV. Imaging Biomarker Studies

Tumor response assessment in clinical trials has typically been derived from longitudinal assessments of anatomically-based diagnostic images (CT, MRI), using RECIST, which could be subject to observer bias, differences in scanning techniques, or lack of quantitative rigor (57). In an effort to address these shortcomings, an NCI-led Quantitative Imaging Network was established, to develop robust automated and semi-automated methods for tumor identification, segmentation and characterization. Each institution in this Network has engaged teams of clinicians and researchers to develop enhanced QA methods for image acquisition and data analysis, and to improve inter-institutional reproducibility.

The ability to quantify a metabolic tumor volume on PET/CT scans across institutions will be critical, which will provide biological information, in addition to achieving an added level of consistency. This will also expand the use of molecular
imaging via an array of novel PET tracers, as well as application of advanced MRI methods including spectroscopy, DCE, and DWI. The synergy between the QIN and cooperative groups will be crucial for the future of RT research.

V. Designs of Clinical Trials

In designing complex clinical trials, there needs to be a deep appreciation of the characteristics of the targeted population, and competing risks. For example, if the proportion of patients in a hypothetical “hypoxic cytotoxic” trial is only 15%, depending on the anticipated benefit of the intervention, up to 1000 patients might be required to demonstrate a difference in outcome (as hypothesized by Dr. Quynh-Thu Le). Similarly, if the targeted population has competing risks (e.g. lung or HNSCC patients); the sample size needs to be increased significantly, if OS was the primary end-point.

Alternatively, if the design of clinical trials is complex (e.g. RTOG 94-13 had a complex 2x2 design), and if the interaction between the modalities is not fully appreciated, then this could lead to a potentially under-powered study. In the RTOG 94-13 trial, at the time of its design, the interaction of hormonal therapy with RT for prostate cancer was not yet fully elucidated (58), underscoring the importance of preclinical evaluations to better understand such potentially complex biology.

VI. Importance of Radiation Therapy Quality Assurance

The critical importance of QA in RT was succinctly illustrated in the aforementioned TPZ trial, wherein deficient RT plans were associated with a 20% reduction in OS (9), which far outweighed any potential benefits from biologically-targeted agents. The fundamental principle is that if the tumor is not irradiated, it will not be controlled. Many international efforts have been undertaken to conduct pre-reviews.
of IMRT plans (59, 60), plus QA programs for IGRT protocols (61, 62). These are critically important endeavors to ensure patient safety, treatment fidelity, and quality of RT.

The recently completed RTOG 0617 trial for NSCLC was a null trial, failing to demonstrate a benefit for the higher-dose radiotherapy arm. Multiple reasons might explain this observation, but there was a higher incidence of treatment-related deaths in the latter arm (discussed during Workshop), posing dosimetric considerations as one possible explanation. Similarly, a review of RTOG gastrointestinal trials uncovered a significant minority of unacceptable RT plans (discussed by Dr. Chris Willett) which might also in part, account for their null results (63). Importantly, in trials where unacceptable RT plans were corrected, positive results were then observed (63). By harnessing the capabilities of digital technology, pre-treatment reviews of RT plans could be undertaken in an expeditious and resource-efficient manner. Several reports have highlighted that RT QA is a critically important step in the clinical trials process, which should result in improved clinical outcomes (64-66).

VII. Data Sharing and Publication Bias

A current challenge in our biomedical research community is a tendency towards publication bias of positive results, documented decades ago wherein meta-analyses of published data would have overestimated the treatment benefit vs. results from registered clinical trials (67). This tendency continues today, wherein more than 20% of Phase III clinical trial abstracts presented at ASCO remain unpublished after 6.5 years, or took longer than 5 years to be published (68).
The requirement to reproduce published data is a fundamental tenet to achieving true medical advances. The lack of data reproducibility is a major problem for drug development, wherein two-thirds of these studies have significant inconsistencies (69, 70). One example relates to Motexafin Gadolinium that proceeded to Phase III testing (71), despite laboratory evidence documenting its lack of radiosensitization (72). The lack of reproducibility costs both patients, for participating in treatments which are unlikely to be beneficial, and society. Pharmaceutical companies lose time and money on pursuing academic discoveries that remain difficult to reproduce (73, 74), which can be further compounded by off-target effects with siRNAs (75, 76).

In the current era of genomic medicine, this situation becomes even more challenging (77); data from only 2 of 18 micro-array publications in *Nature Genetics* could be replicated. The major problem being inaccessibility to the original raw data files (78), with potentially dire consequences for patients (77). *Science* devoted its entire Dec 2nd, 2011 issue to this very topic (79), and recommended 6 steps: 1) analytical validity (different platforms); 2) repeatability (different scientists); 3) replication (meta-analyses of different data sets); 4) external validation (consistent large-scale datasets); 5) clinical validity (can predict clinical outcome); and 6) clinical utility (actually improves clinical outcome), before any –omic data be utilized in clinical medicine. Similar guidelines have been suggested for predictive or prognostic biomarkers based on 5 levels of evidence, ranging from under-powered observational reports to prospectively-designed clinical trials examining a specific biomarker (80).

These recommendations have been developed to temper human nature which prefers celebratory vs. sobering news, the competition in science and academia, and
the explosive quadrupling growth in the number of scientific Journals from 1970 to 2011. E-Journals such as *BMC Research Notes* encourage the publication of negative data and replication of previously-reported results. Recognizing the academic and societal value of well-conducted but null or negative publications would enhance the likelihood of such studies becoming publicly available.

**VIII. Consideration of an International Consortium**

The clinical development of radiation modifiers is frequently a secondary path, spin-off or occasional afterthought to drug development by industry, academia or government (Fig 1). Basic discovery defines a tumor molecular target, and if the developer considers this to be potentially useful in combination with RT, it will be included in the developmental plans (Fig 1). In this context, the formation of an International Consortium for the Evaluation of Radiation Modifiers could be considered with pooling of resources, developed in a collaborative manner, to expedite the discovery and translation of effective agents which will enhance the curative outcomes of RT for cancer patients.

As shown in Figure 1, there could be a step-wise progression of examining molecular targets combined with RT, prioritized through a Steering Committee, with assignation of specific assays to different groups with such expertise. This will result in a pipeline of potential therapeutic candidates advancing through *in vitro*, *in vivo*, PK/PD, and Phase 0/I to II, and even RCTs, if such targets fulfill the pre-defined criteria for progression. Furthermore, the prompt publication of null, negative or positive results can be of great benefit in avoiding patient toxicity as well as the needless expense in developing a less-than-adequate drug.
CONCLUSION

Several recently-conducted Radiation Oncology clinical trials were presented and discussed at an NCI-US sponsored Workshop. By nature, clinical trials, which are resource-intensive, can often lead to null observations; hence, it behooves us to capitalize upon each opportunity, in order to maximize the derived information. To that end, important themes emerged from this Workshop, including: a) deriving robust preclinical data; b) conducting companion translational studies; c) designing appropriately-powered clinical trials; and d) performing expeditious real-time QA of RT plans.

The resources available through the NCI-US Molecular Radiation Therapeutics Branch, the QIN, and the Frederick National Laboratory for Cancer Research should be harnessed by the Radiation Oncology biomedical research community before embarking on designing future RT clinical trials, particularly when combined with novel targeted agents. Exploring the establishment of an International Consortium for the Evaluation of Radiation Modifiers should be undertaken to pool resources in this important pursuit. Finally, we must remember that the focus of our research efforts is the patient; our obligations are first and foremost, to them.

ACKNOWLEDGEMENT

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FIGURE LEGEND

Figure 1. Pathway of in vitro to in vivo to Phase I/II/III clinical trials. Proposed model and activities of an International Consortium whereby potential drugs can be provided from academia, industry and government, and prioritized for evaluation through a ‘Steering Committee’.
Table 1
Radiation Oncology Phase III randomized clinical trials on central nervous system, head and neck, lung, gastrointestinal, and genitourinary malignancies presented and discussed by the Workshop participants.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Target Tumor Site</th>
<th>Primary Objective (&amp; Results)</th>
<th>Accrual Period</th>
<th>Patients Accrued (completed or randomized)</th>
<th>Notable Secondary Findings</th>
<th>Ref</th>
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<tr>
<td>RTOG 0525</td>
<td>GBM</td>
<td>Does dose-intensifying adjuvant TMZ improve OS? (No evidence for improvement)</td>
<td>01/2006 to 06/2008</td>
<td>1173 (833)</td>
<td>- MGMT validated as a prognostic marker.</td>
<td>(3)</td>
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<tr>
<td>EORTC 26052-22053</td>
<td></td>
<td>Phase I/II study of EGFR TK inhibition (Iressa™) with RT (No OS benefit for patients treated with gefitinib + RT vs. RT alone)</td>
<td>Phase I: 31 Phase II: 147 (119 successfully completed therapy)</td>
<td></td>
<td>- Correlative immunohistochemical analysis of tissue for prognostic markers of survival (src, IGF1R, PTEN, AKT), and predictive value of these markers for gefitinib response. - Some markers (elevated Src and PTEN) predicted for poorer response with gefitinib.</td>
<td>(4)</td>
</tr>
<tr>
<td>RTOG 0211</td>
<td>GBM</td>
<td>Does accelerated RT combined with cisplatin improve survival of patients with LA HNSCC? (No evidence for improvement)</td>
<td>07/2002 to 05/2005</td>
<td>743 patients</td>
<td>- Cisplatin offset tumor clonogen repopulation during the course of fractionated RT.</td>
<td>(7)</td>
</tr>
<tr>
<td>RTOG 0129</td>
<td>HNSCC</td>
<td>Does adding a hypoxic toxin (Tirapazamine) to RT-cisplatin regimen improve survival for patients with LA HNSCC? (No evidence for improvement)</td>
<td>09/2002 to 04/2005</td>
<td>861 patients</td>
<td>- RT QA critical. - Need for tumor hypoxia stratification.</td>
<td>(8)</td>
</tr>
<tr>
<td>TROG 02.02</td>
<td>HNSCC</td>
<td>Does higher RT dose (60 Gy vs. 74 Gy with CRT + Cetuximab) confer a treatment response benefit? (No evidence for improvement)</td>
<td>11/2005 to 03/2009</td>
<td>940 enrolled (895 evaluable)</td>
<td>- Mechanism of cetuximab and cisplatin radiosensitization may overlap. - The triplet regimen was associated with higher rates of mucositis and Cetuximab-induced skin reactions. - Effects of HPV status on response to be investigated.</td>
<td>(11)</td>
</tr>
<tr>
<td>RTOG 0617</td>
<td>NSCLC</td>
<td>Does dose-intensifying adjuvant TMZ improve OS? (No evidence for improvement)</td>
<td>11/2007 to 04/2011</td>
<td>423 enrolled</td>
<td>- Futility analysis resulted in closure of high-dose arms, and the standard dose of RT for Stage III NSCLC remains at 60 Gy. Surprisingly, no significant difference in treatment-related toxicity between high-dose vs. standard RT arms. - RTOG has issued a Request for Proposal to conduct translational research using materials obtained from this trial.</td>
<td>(12)</td>
</tr>
<tr>
<td>Study</td>
<td>Disease</td>
<td>Question</td>
<td>Design</td>
<td>Patients/Enrolled</td>
<td>Outcome(s)</td>
<td></td>
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<tr>
<td>RTOG 9811</td>
<td>Anal Canal</td>
<td>Is efficacy of cisplatin-based (experimental) therapy better than mitomycin-based (standard) therapy in treatment of anal canal carcinoma? 5FU/CDDP + RT vs. 5FU/MMC + RT</td>
<td>10/1998 to 06/2005</td>
<td>682 randomized (644 included in outcomes analysis)</td>
<td>- No difference in DFS between the 2 arms, but, cisplatin-based therapy resulted in a significantly worse colostomy rate. (14)</td>
<td></td>
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<tr>
<td>RTOG 0020</td>
<td>Pancreatic Cancer</td>
<td>Does addition of maintenance with a farnesyltransferase inhibitor (FTI) improve gemcitabine/Taxol chemoradiotherapy? Weekly Gemcitabine, Paclitaxel and External Irradiation (50.4 Gy) followed by the FTI R115777 (Addition of FTI demonstrated no improvement in clinical outcome, yet was associated with increased toxicities)</td>
<td>11/2001 to 09/2003</td>
<td>195 accrued (174 in analysis)</td>
<td>- Maintenance R115777 did not increase survival and was associated with increased toxicities. - Trial did not address potential for radiosensitization by FTI. - K-Ras was known not to be a target for FTI inhibition. (15)</td>
<td></td>
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<tr>
<td>RTOG 94-13</td>
<td>High-risk Prostate Cancer</td>
<td>Does pelvic RT improve progression-free survival compared with prostate-only RT among patients with a chance of lymph node involvement? (No evidence for improvement)</td>
<td>04/1995 to 06/1999</td>
<td>1323 patients accrued (1292 enrolled)</td>
<td>- Study underpowered for pair-wise comparisons. - Long-term follow-up results refuted short-term benefit reported. - Similar European trial, GETUG-01, showed no difference in progression-free survival between the pelvis and prostate-only arms. (16)</td>
<td></td>
</tr>
<tr>
<td>EORTC 22961</td>
<td>High-risk Prostate Cancer</td>
<td>6 months androgen-suppression followed by RT, then either observed or additional 2.5 years of androgen-suppression. (Marginal improvement in long-term outcome)</td>
<td>04/1997 to 11/2001</td>
<td>1113 patients</td>
<td>- Longer-term was marginally superior to short-term androgen-suppression. (18)</td>
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</tbody>
</table>
### Table 2
Summary of Recommendations from the Workshop.

<table>
<thead>
<tr>
<th>Emerging Themes</th>
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</thead>
<tbody>
<tr>
<td><strong>Preclinical Studies</strong></td>
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<tr>
<td>• Must conduct at least <em>in vitro</em> clonogenic assay</td>
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<tr>
<td>• Contact the Molecular Radiation Therapeutics Branch at NCI, which has generated data for multiple targeted agents combined with RT in panels of human cancer cells, before embarking on combinatorial therapies</td>
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<tr>
<td>• Generate <em>in vivo</em> data using different human cancer xenograft models</td>
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<tr>
<td><strong>Biomarkers</strong></td>
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<tr>
<td>• Develop and validate tumor microenvironment predictive biomarkers</td>
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<tr>
<td>• Develop and validate predictive biomarkers of sensitivity to molecular targeted therapies</td>
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<tr>
<td>• Utilize &quot;clinical-ready&quot; pharmacodynamic read-outs</td>
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<tr>
<td>• Need for robust imaging methods for tumor identification, segmentation and characterization, across institutions</td>
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<tr>
<td><strong>Clinical Trial Design</strong></td>
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<tr>
<td>• Simple</td>
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<tr>
<td>• Ensure study statistically powered (i.e. sufficient sample size)</td>
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<tr>
<td>• Consider utilization of adaptive trial design</td>
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<tr>
<td><strong>Quality Assurance</strong></td>
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<tr>
<td>• Perform expeditious real-time QA of RT plans</td>
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<tr>
<td><strong>Publication Bias</strong></td>
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<tr>
<td>• Publish results of trials regardless of the outcome</td>
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<tr>
<td>• Public sharing of raw data</td>
</tr>
<tr>
<td><strong>International Consortium</strong></td>
</tr>
<tr>
<td>• Establish a consortium for the evaluation of radiation modifiers to expedite the discovery and translation of effective agents which will enhance the curative outcomes of RT for cancer patients</td>
</tr>
</tbody>
</table>
APPENDIX 1

Workshop participants

- Abrams, Jeffrey - NIH, Bethesda, MD
- Ang, Kian - MD Anderson Cancer Center, Houston, TX
- Ataman, Ozlem - AstraZeneca Corporation, Manchester, U.K.
- Bailey, Paul - Pfizer Corporation, New York, NY
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- White, Julia - Medical College of Wisconsin, Milwaukee, WI
- Willett, Christopher - Duke University Medical Center, Durham, NC
- Williams, Jackie - Rochester Medical Center, Rochester, NY
- Winter, Kathryn - American College of Radiology, Reston, VA
- Zwiebel, James - NIH, Bethesda, MD
Figure 1:

Development and assessment of radiation modifiers - An International Consortium

Lab  →  In vitro  →  In vivo  →  Clinic

Basic science discovery

Simple HTP assays (generally 1 log)
Newer HTP assays (possibly larger range)
HTP clonogenic assays (multi-log)

Standard models
Tumor control
GEMMs–tumor, normal tissues
Tumor xenografts
Patient derived xenografts

PK and PD
Phase 0–I
Phase II
Phase III
Post-market

Mechanism of action during development and ‘bedside to bench’
Clinical Cancer Research

Lessons Learned from Radiation Oncology Clinical Trials
Fei-Fei Liu, Paul Okunieff, Eric J Bernhard, et al.

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