

Clinical Development of Novel Drug-Radiotherapy Combinations

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Translational Relevance

More than half of patients receive radiotherapy as part of their cancer treatment. Significant technical advances have been made in radiotherapy delivery, but little progress has been made in combining new cancer drugs with radiotherapy to improve the efficacy of combination treatment. In view of this lack of progress, the FDA-AACR-ASTRO Clinical Development of Drug-Radiotherapy Combinations Workshop was held in February 2018 to bring together stakeholders and opinion leaders from academia, clinical radiation oncology, industry, patient advocacy groups and the FDA in order to discuss challenges to introducing new drug-radiotherapy combinations to the clinic. This article summarises the themes and action points that were discussed to increase the number of novel drugs being successfully registered in combination with radiotherapy to improve clinical outcomes for patients with cancer.

Abstract

Radiotherapy is a fundamental component of treatment for the majority of patients with cancer. In recent decades, technological advances have enabled patients to receive more targeted doses of radiation to the tumour, with sparing of adjacent normal tissues. There had been hope that the era of precision medicine would enhance the combination of radiotherapy with targeted anticancer drugs, however this ambition remains to be realised. In view of this lack of progress, the FDA-AACR-ASTRO Clinical Development of Drug-Radiotherapy Combinations Workshop was held in February 2018 to bring together stakeholders and opinion leaders from academia, clinical radiation oncology, industry, patient advocacy groups and the FDA in order to discuss challenges to introducing new drug-radiotherapy combinations to the clinic. This *Perspectives in Regulatory Science and Policy* article summarises the themes and action points that were discussed. Intelligent trial design is required to increase the number of studies which efficiently meet their primary outcomes; endpoints to be considered include local control, organ preservation and patient-reported outcomes. Novel approaches including immune-oncology or DNA repair inhibitor agents combined with radiotherapy should be prioritised. In this article, we focus on how the regulatory challenges associated with defining a new drug-radiotherapy combination can be overcome in order to improve clinical outcomes for patients with cancer.

Introduction

The FDA-AACR-ASTRO Clinical Development of Drug-Radiotherapy Combinations Workshop took place on February 22-23 2018 in Bethesda, Maryland in response to a consensus paper published on this topic led by the UK National Cancer Research Institute (NCRI) (1). The Workshop's principal aim was to bring together over 400 stakeholders and key opinion leaders from academia, clinical radiation oncology, industry, patient advocacy groups and the FDA to provide a forum to discuss real and perceived challenges to introducing new drug-radiotherapy combinations to the clinic. The primary outputs of this Workshop are summarized here (Textbox 1). In this article, we discuss the current landscape of drug-radiotherapy combinations, challenges associated with the development and approval of drug-radiotherapy combinations, and strategies that may be adopted by stakeholders to help overcome them.

The unrealised potential of drug-radiotherapy combinations

Radiotherapy is a key component in the management of 40% of cancer patients cured of their disease (2). Moreover it provides a highly effective treatment strategy for the palliation of symptoms in individuals suffering with advanced disease. There have been major advances in radiation technology over recent years. Radiotherapy is a cost-effective treatment modality (3).

In the radical treatment of cancer when the treatment intent is cure, radiotherapy is often combined with conventional cytotoxic drugs such as cisplatin or 5-fluorouracil. This radiosensitization approach is supported by robust Level 1 evidence (4). Within recent decades, the advent of precision medicine has shifted the focus of cancer drug discovery towards targeting specific proteins and pathways for therapeutic gain. This, along with advances in immuno-oncology (IO), has been associated with dramatic improvements in clinical outcomes (5-7). These observations have led researchers to hypothesize that similar benefits may be realised through combining novel targeted drugs with radiation.

The scientific rationale for combining radiotherapy with novel targeted agents has been appraised in previous reviews (1,4). The aim of any treatment combination is to improve the therapeutic ratio such that the anti-cancer effect is enhanced over and above any corresponding increase in normal tissue toxicity.

The FDA granted approval to a combination of radiotherapy with a targeted agent in March 2006. However in the 12 years that have followed, no new drug-radiotherapy combinations have been approved (8). The combinatory drug approved at that time was cetuximab – an anti-epidermal growth factor receptor (EGFR) monoclonal antibody – for use in head and neck cancers. It had been widely perceived that, as more novel targeted agents entered the clinic, the number of clinically effective drug-radiotherapy combinations would also significantly increase.

While no new drug-radiotherapy combinations have passed regulatory approval during this period, the FDA has approved more than 130 novel drug indications in oncology. Moreover a Pubmed database search for entries from 2006 onwards using

the keyword ‘radiosensitization’ identifies 1713 articles published, suggesting that pre-clinical and clinical research in this area remains highly active. So what is driving this stark disparity? It was with this question in mind that the FDA-AACR-ASTRO Workshop was developed.

What Guidance is Required to Make Progress?

A number of factors were identified that implied that the pathway to approval of a novel drug-radiotherapy combination is hindered from Day Zero. To date, the FDA has not published a regulatory guidance document specifically detailing the approval pathway for a drug-radiotherapy combination. Pharmaceutical industry representatives cited the lack of regulatory guidance as a significant hurdle. Without regulatory guidelines to support drug development, strategic decisions on investment into drug-radiotherapy combinations cannot be de-risked against specific criteria pertaining to approval. This may result in combination strategies being de-prioritised. However, there is no published evidence that the publication of a specific regulatory guidance document increases industry-led drug development within that area. Some of the existing regulatory guidance on drug-drug combinations may in fact be applied to drug-radiotherapy combinations (see below) (9).

There is evidence of a significant lag time in testing drugs in combination with radiotherapy during the clinical development of a novel agent (10,11). One study demonstrated the median interval between the opening of phase 1 trials without radiotherapy, and those with, was 6 years. Further, phase 1 trials with radiotherapy were typically published after 9 years of the drug patent had lapsed (11). With drug patents limited to 20 years, a lag of this magnitude would significantly diminish the potential profitability of a drug-radiotherapy combination. In light of this, there are few incentives for pharmaceutical companies to take promising phase 1 data through to a costly phase 3 registration study with radiation. This is particularly true given the high attrition rates seen from phase 1 to phase 3.

Pharmaceutical companies are further discouraged from investigating drug-radiotherapy combinations due to misconceptions and uncertainty around the pre-clinical data required for regulatory approval, particularly regarding safety. Moreover, generating appropriate pre-clinical data in the context of radiation requires special assays and know-how to which pharmaceutical companies may not have access. At the Workshop, FDA representatives provided detailed clarification on this matter and a summary is provided in Textbox 2.

Regulators highlighted the challenge of providing a comprehensive guidance document due to the many possible development scenarios for drug-radiotherapy approaches. As with many development programs, each case is unique and the most detailed advice to sponsors can be offered when the FDA performs clinical trial reviews for investigational new drug applications. It was suggested that industry representatives arrange formal meetings with the FDA at an early stage to help define a clear line of sight to registration for each individual drug-radiotherapy combination (12). For broader advice, much of the guidance relating to drug-drug combinations may be applicable to combinations with radiation (9).

Toxicity data for new treatment combinations may not be required, depending on the extent of toxicity data available for each individual agent (13). A strong rationale for combining the drug with radiation should be presented with consideration given to potential organs at risk of toxicity. If this is based on clear and robust science further pre-clinical experiments to support the hypothesis are not always necessary. Again, case-by-case discussions with regulators should be sought.

In the case of investigational compounds at early stages of development (i.e. human toxicity data remains uncharacterised), pre-clinical data with a particular focus on safety, are necessary. A pharmacology study supporting the rationale for the combination should be provided. Such a study should demonstrate increased activity in the absence of a substantial increase in toxicity on the basis of limited safety endpoints, such as mortality, clinical signs and body weight.

The role of pre-clinical data within the regulatory approval process represents a relatively ‘easy-win’ for industry. For drugs already approved in most circumstances, there may be no need to generate further pre-clinical data. In drugs at earlier stages of development, there are significant incentives in performing the pre-clinical experiments outlined in Textbox 2 as the drug may subsequently be approved in combination with radiation for a longer duration during the compound’s patent. These experiments may be performed in collaboration with partners in academia. Indeed, throughout the Workshop there were calls to improve communication between industry and academia/radiation oncology.

An increasing number of assays and model systems have been studied that examine radiation-related toxicity (14). Murine models can be utilised to study the effects of thoracic radiation with and without a novel targeted agent. Early access to these model systems during the drug discovery process would enable the prioritisation of agents as clinical radiosensitizers (15). However, the development of model systems predicting radiation-related toxicity remains at an early stage and consequently data generated from these models should not be over-interpreted.

Finally, discussions between radiation oncologists and industry will ensure industry-led studies are designed to collect data on long-term toxicity. This area is often neglected in drug-only studies but is critical to radiotherapy as it is late toxicities that are dose-limiting.

How to Improve the Design of Future Clinical Trials?

A large number of clinical trials investigating novel drug-radiotherapy combinations have been negative studies. Historically studies have not enriched for, or sub-stratified patients based on, genotypic or phenotypic information to increase the likelihood of a positive outcome. For instance, there are compelling non-clinical data to suggest that hypoxia-modifying agents may improve radiotherapy outcomes (16). However, clinical trial data have been underwhelming, and a potential reason for this is that patients were not selected on the basis of their tumor’s hypoxic status (17).

Further, the outcome data from radiotherapy-based clinical studies may be confounded by variability in radiotherapy technique across participating centers (18).

Data from the RTOG 0617 study investigating radiotherapy dose escalation in the treatment of non-small cell lung cancer demonstrated improved overall survival (OS) in patients treated at institutions with higher clinical trial accrual volumes (19).

Apart from radiotherapy technique, dose-fractionation and drug scheduling are also likely to be of significance, particularly in the context of IO agents in combination with radiotherapy. For instance, pre-clinical data have shown that PD-L1 blockade can overcome resistance to fractionated low-dose radiotherapy but not high-dose radiotherapy (20). This observation is by no means generalizable and our understanding of the interaction of radiation with the host immune system remains only partly understood (21).

A number of potential solutions may help to improve the design of clinical drug-radiotherapy trials. Biomarker-driven studies should allow more evidence-based patient selection ensuring that the efficacy of a novel agent is more accurately evaluated. To bolster the development of biomarkers, window-of-opportunity studies in the neoadjuvant setting may be of more value as they allow access to tumor tissue to assess for pharmacodynamic (PD) studies. Furthermore, since phase 1 toxicity studies are often limited to specific anatomic sites and may not be generalizable to other cancers with a different spectrum of normal tissue toxicities, umbrella studies (one cancer – multiple mutations - multiple drugs) and basket studies (multiple cancers – one mutation – one drug) run using adaptive trial designs should be considered to allow more efficient use of resources and enable multiple hypotheses to be tested within one clinical trial.

The role of radiotherapy quality assurance (RTQA) within all clinical studies cannot be overstated and efforts to harmonize international RTQA standards are essential. Within the US, the Imaging and Radiation Oncology Core (IROC) run out of the MD Anderson Cancer Center has developed many important resources enabling robust RTQA. Within the UK, this role is taken by the RTTQA group (22). However the challenges associated with RTQA must also be acknowledged and addressed. Providing real-time QA such that plans are appraised prior to the patient starting treatment is significantly resource-intensive. Investments in human and computing resources will partly address this problem however more imaginative solutions such as artificial intelligence-based QA strategies may also be of value.

Uncertainties around RT scheduling and fractionation in combination with IO and other novel agents must be informed by preclinical evidence. However these efforts should not significantly delay clinical studies which should be designed so that tissue samples can be used to back-translate into the laboratory to better understand the biology behind the responses seen *in vivo*.

Classically recognized regulatory endpoints for clinical trials of systemic treatment such as disease-free survival (DFS) and OS may be impractical for some clinical trials of new drug-radiotherapy combinations in the context of a local treatment used with curative intent. OS endpoints may take many years to be reached in patients with good prognosis diseases. Established endpoints such as DFS or OS can still be evaluated as secondary endpoints during longer-term follow-up to confirm clinical benefit in a study that meets an earlier, primary endpoint.

Common early endpoints such as local control can provide evidence of anti-tumor activity and could be supported by clinically relevant endpoints such as organ preservation rates and assessment of symptoms and function using clinical outcome assessments (Table 1 and Textbox 3). Regulatory approval could potentially be granted based on earlier endpoints. There is a clear need to develop early and intermediate endpoints of the efficacy, and toxicity, of the new combination. Appropriate early endpoints are likely to be sub-site specific and therefore a consensus should be reached in partnership with the FDA potentially through organ-specific workshops. There are valid concerns that endpoints such as organ-preservation may be influenced by bias, thus trial protocols should seek to define prospective criteria for surgical intervention.

Dialogue between Key Stakeholders

At the Workshop, it was acknowledged that the lack of clinical trial activity investigating novel drug-radiotherapy combinations has contributed to the lack of successful regulatory approvals. The incentives underlying academic interest in combining radiation with novel drugs is likely to differ significantly from those within industry. Within the US, perceived tensions between medical and radiation oncologists may also exist due to historically low levels of research collaboration. Moreover, the FDA as a regulatory body weighs the balance between safety and efficacy from a different perspective for a patient with early-stage disease compared to a patient with terminal cancer with no treatment options available. Consequently, dialogue and collaboration between the stakeholders involved in the clinical development of drug-radiotherapy combinations is critical to enable a better understanding and alignment of interests.

Initiatives should be prioritized to improve collaboration, and this includes engagement with patient advocacy groups (Textbox 4). An example of this is the RaDCom program in the UK (23) which is a formal collaboration across multiple disciplines with the primary aim of improving the development of drug-radiotherapy combinations. Multi-center trials will be necessary to investigate many of the potential combinations, and one barrier that was identified is the perception that academic clinical investigators are not sufficiently rewarded for their participation in these trials by research funding bodies such as the National Cancer Institute. Finally the academic community should reach a consensus as to which areas to prioritise, for instance IO with radiotherapy, to generate a sufficient critical mass of personnel and resources to perform large-scale practice-changing research.

Conclusions

We have witnessed the recent approval of many systemic therapies with varied mechanisms of action leading to an unprecedented opportunity to investigate new drug-radiotherapy combinations. Perceived challenges associated with generating pre-clinical data and establishing trial endpoints for registration should be readily tractable. Insufficient novel drug-radiotherapy combinations have reached the clinic, and the attendees of this Workshop identified several opportunities to foster

development in this important cancer therapeutic space. Workshop participants felt energized to take forward the solutions proposed in this summary article to transform the landscape of translational radiation biology and significantly improve clinical outcomes for cancer patients.

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References

1. Sharma RA, Plummer R, Stock JK, Greenhalgh TA, Ataman O, Kelly S, *et al.* Clinical development of new drug-radiotherapy combinations. *Nature reviews Clinical oncology* **2016**;13(10):627-42
2. Ringborg U, Bergqvist D, Brorsson B, Cavallin-Stahl E, Ceberg J, Einhorn N, *et al.* The Swedish Council on Technology Assessment in Health Care (SBU) systematic overview of radiotherapy for cancer including a prospective survey of radiotherapy practice in Sweden 2001--summary and conclusions. *Acta oncologica* **2003**;42(5-6):357-65.
3. Atun R, Jaffray DA, Barton MB, Bray F, Baumann M, Vikram B, *et al.* Expanding global access to radiotherapy. *The Lancet Oncology* **2015**;16(10):1153-86
4. Lawrence YR, Vikram B, Dignam JJ, Chakravarti A, Machtay M, Freidlin B, *et al.* NCI-RTOG translational program strategic guidelines for the early-stage development of radiosensitizers. *Journal of the National Cancer Institute* **2013**;105(1):11-24
5. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, *et al.* Improved survival with ipilimumab in patients with metastatic melanoma. *The New England journal of medicine* **2010**;363(8):711-23
6. Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, *et al.* Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *The New England journal of medicine* **2001**;344(11):783-92
7. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, *et al.* Durvalumab after Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. *The New England journal of medicine* **2017**;377(20):1919-29
8. Bonner JA, Harari PM, Giralt J, Azarnia N, Shin DM, Cohen RB, *et al.* Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *The New England journal of medicine* **2006**;354(6):567-78
9. FDA. 2010 12 June 2018. Guidance for Industry. S9 Nonclinical evaluation for Anticancer Pharmaceuticals.
<<https://www.fda.gov/downloads/Drugs/Guidances/ucm085389.pdf>>3E. Accessed 2018 12 June 2018.
10. Ataman OU, Sambrook SJ, Wilks C, Lloyd A, Taylor AE, Wedge SR. The clinical development of molecularly targeted agents in combination with radiation therapy: a pharmaceutical perspective. *International journal of radiation oncology, biology, physics* **2012**;84(4):e447-54
11. Blumenfeld P, Pfeffer RM, Symon Z, Den RB, Dicker AP, Raben D, *et al.* The lag time in initiating clinical testing of new drugs in combination with radiation therapy, a significant barrier to progress? *British journal of cancer* **2014**;111(7):1305-9
12. FDA. Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products Guidance for Industry **2017**.
13. Walker AJ, Kim H, Saber H, Kluetz PG, Kim G, Pazdur R. Clinical Development of Cancer Drugs in Combination With External Beam Radiation Therapy: US Food and Drug Administration Perspective. *International journal of radiation oncology, biology, physics* **2017**;98(1):5-7

14. Bristow RG, Alexander B, Baumann M, Bratman SV, Brown JM, Camphausen K, *et al.* Combining precision radiotherapy with molecular targeting and immunomodulatory agents: a guideline by the American Society for Radiation Oncology. *The Lancet Oncology* **2018**;19(5):e240-e51
15. Lourenco LM, Jiang Y, Drobnitzky N, Green M, Cahill F, Patel A, *et al.* PARP Inhibition Combined With Thoracic Irradiation Exacerbates Esophageal and Skin Toxicity in C57BL6 Mice. *International journal of radiation oncology, biology, physics* **2018**;100(3):767-75
16. Overgaard J. Hypoxic radiosensitization: adored and ignored. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **2007**;25(26):4066-74
17. Hammond EM, Asselin MC, Forster D, O'Connor JP, Senra JM, Williams KJ. The meaning, measurement and modification of hypoxia in the laboratory and the clinic. *Clinical oncology* **2014**;26(5):277-88
18. Peters LJ, O'Sullivan B, Giralt J, Fitzgerald TJ, Trotti A, Bernier J, *et al.* Critical impact of radiotherapy protocol compliance and quality in the treatment of advanced head and neck cancer: results from TROG 02.02. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **2010**;28(18):2996-3001
19. Eaton BR, Pugh SL, Bradley JD, Masters G, Kavadi VS, Narayan S, *et al.* Institutional Enrollment and Survival Among NSCLC Patients Receiving Chemoradiation: NRG Oncology Radiation Therapy Oncology Group (RTOG) 0617. *Journal of the National Cancer Institute* **2016**;108(9)
20. Dovedi SJ, Adlard AL, Lipowska-Bhalla G, McKenna C, Jones S, Cheadle EJ, *et al.* Acquired resistance to fractionated radiotherapy can be overcome by concurrent PD-L1 blockade. *Cancer research* **2014**;74(19):5458-68
21. Weichselbaum RR, Liang H, Deng L, Fu YX. Radiotherapy and immunotherapy: a beneficial liaison? *Nature reviews Clinical oncology* **2017**;14(6):365-79
22. Radiotherapy Trials Quality Assurance. 31st July. RTTQA website. RTTQA <<http://www.rtttrialsqa.org.uk/rttqa/%3E>. Accessed 2018 31st July.
23. CTRad. 31st July. Radiotherapy-Drug Combinations Consortium (RaDCom). <<http://ctrad.ncri.org.uk/research-support/radiation-drug-combinations-radcom%3E>. Accessed 2018 31st July.
24. FDA. 2010 12 June 2018. Guidance for Industry. S9 Nonclinical evaluation for Anticancer Pharmaceuticals. <<https://http://www.fda.gov/downloads/Drugs/Guidances/ucm085389.pdf%3E>. Accessed 2018 12 June 2018.
25. Verstovsek S, Mesa RA, Gotlib J, Levy RS, Gupta V, DiPersio JF, *et al.* A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. *The New England journal of medicine* **2012**;366(9):799-807 doi 10.1056/NEJMoa1110557.

Table 1: Summary of clinical trial endpoints to be considered in testing new drug-radiotherapy combinations

Endpoint	Advantages	Disadvantages
Overall survival	<ul style="list-style-type: none"> - Universally accepted measure of direct benefit - Easily and precisely measurable - Blinding not needed 	<ul style="list-style-type: none"> - Trials in radical setting will generally be of a long duration - May require larger trials - May be affected by crossover and subsequent therapies - Includes non-cancer deaths
Symptom endpoints/ patient reported outcomes	<ul style="list-style-type: none"> - Patient perspective of direct clinical benefit - Data acquisition ideal for incorporation into digital health technologies 	<ul style="list-style-type: none"> - Blinding often difficult - Data frequently missing or incomplete - Clinical significance of small changes unknown - Lack of validated instruments - Bias from multiple-testing may occur
Organ-preservation	<ul style="list-style-type: none"> - Important endpoint for patients - Ideal in head and neck cancer (tracheostomy-free) and bladder cancer (bladder-preservation) trials - Easily measurable 	<ul style="list-style-type: none"> - Without blinding and clear protocols, surgical timing may be subject to bias - Limited to certain disease sites
Loco-regional control	<ul style="list-style-type: none"> - Applicable to most cancers treated with RT - Smaller sample size and follow-up duration compared to survival studies - Unaffected by crossover and subsequent therapies - Generally based on objective quantitative assessment - May be more reflective of RT effect than disease-free survival 	<ul style="list-style-type: none"> - Also influenced by surgery and/or chemotherapy therefore may not be a direct measure of RT effect - Definitions may vary based on trials - May not be of clinical significance in all settings - Not precisely measured and may be subject to assessment bias - Radiological or other assessments must be frequent and balanced across treatment arms
Disease-free survival	<ul style="list-style-type: none"> - In some scenarios, may correlate better with overall survival than local control - May capture abscopal effects of IO-RT better than local control 	<ul style="list-style-type: none"> - As per loco-regional control above
Complete or objective response rates	<ul style="list-style-type: none"> - Suitable for neoadjuvant studies - Assessed earlier and in smaller studies compared to survival studies 	<ul style="list-style-type: none"> - Not a direct measure of benefit in all cases - Only a subset of patients who benefit
Progression-free survival (includes all deaths) or time to progression (deaths before progression censored)*	<ul style="list-style-type: none"> - May be suitable in IO-RT studies within metastatic setting - Assessed earlier and in smaller studies compared to survival studies - Stable disease included - Unaffected by crossover and subsequent therapies 	<ul style="list-style-type: none"> - Not valid surrogate for survival in all settings - Not precisely measured and may be subject to assessment bias - Frequent radiological or other assessments required - Less relevant for drug-RT trials

Abbreviations used: IO – immuno-oncology, RT - radiotherapy

*Landmark analyses associated with these endpoints may be particularly suitable for IO-RT trials. In landmark analyses, a fixed-time after the initiation of therapy is selected and only patients alive at that time are included in the analysis, separated into 2 response categories according to whether they have responded up to that time.