The State of Preclinical Modeling for Early Phase Cancer Trials Using Molecularly Targeted Agents with Radiation

Authors: Hong, Julie A., Vikram, Bhadrasian, Buchsbaum, Jeffrey, Capala, Jacek, Livinski, Alicia, et al.

Source: Radiation Research, 198(6) : 625-631

Published By: Radiation Research Society

URL: https://doi.org/10.1667/RADE-22-00077.1

RADIATION RESEARCH **198**, 625–631 (2022)
0033-7587/22 $15.00

DOI: 10.1667/RADE-22-00077.1

SHORT COMMUNICATION

The State of Preclinical Modeling for Early Phase Cancer Trials Using Molecularly Targeted Agents with Radiation

Julie A. Hong,[a] Bhadrasian Vikram,[a] Jeffrey Buchsbaum,[a] Jacek Capala,[1] Alicia Livinski,[b] Beverly Teicher,[c] Pataje Prasanna,[a] Mansoor M. Ahmed,[a] Ceferino Obcemea,[a] C. Norman Coleman,[a] Michael Graham Espey[a,1]

[a]*Radiation Research Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, Rockville, Maryland 20892;* [b]*National Institutes of Health Library, Office of Research Services, Office of the Director, National Institutes of Health, Bethesda, Maryland 20892;* [c]*Molecular Pharmacology Branch, Division of Cancer Treatment and Diagnosis, National Cancer Institute, Rockville, Maryland 20892*

Hong JA, Vikram B, Buchsbaum J, Capala J, Livinski A, Teicher B, Prasanna P, Ahmed MM, Obcemea C, Coleman CN, Espey MG. The State of Preclinical Modeling for Early Phase Cancer Trials Using Molecularly Targeted Agents with Radiation. Radiat Res. 198, 625–631 (2022).

Preclinical studies inform and guide the development of novel treatment combination strategies that bridge the laboratory with the clinic. We aimed to evaluate approaches cancer researchers used to justify advancing new combinations of molecularly targeted agents and radiation treatment into early-phase human clinical trials. Unsolicited early phase clinical trial proposals submitted to the National Cancer Institute's Cancer Therapy Evaluation Program between January 2016 and July 2020 were curated to quantify key characteristics and proportion of preclinical data provided by trialists seeking to conduct molecularly targeted agent-radiation combination studies in cancer patients. These data elucidate the current landscape for how the rationale for a molecularly targeted agent-radiation combination therapy is supported by preclinical research and illustrate unique challenges faced in translation at the intersection of precision medicine and radiation oncology.

INTRODUCTION

Chemoradiation is a mainstay for treatment across a broad spectrum of cancers. Decades of empirical clinical experience have led to conventions for drug-radiation combination treatments in distinct cancer types (*1, 2*); however, many of the factors that govern an effective response at the individual patient level remain largely unknown. The radiation oncology field has witnessed a steady line of improvements in technologies that add both precision and accuracy to the physical delivery of radiation doses from external beam sources, notably in the last two decades. The basis for much of our understanding mechanistically about radiation-drug combinations from a biological perspective was built upon research from the latter half of the 20th century using two-dimensional mono-culture studies that are now often considered to be relatively antiquated in terms of representing the heterogeneity and dynamics of human tumors (*3*). Ideally the decision to advance new targeted agent candidates into clinical trials to evaluate the safety and potential efficacy of interaction with radiotherapy should be based on sound preclinical and/or clinical data that support the rationale for the combination (*4, 5*). In 2016, Stone et al. examined the quality, reproducibility, and utility of preclinical testing for radiation-drug combinations and detailed the need for improvements in the design, interpretation, and reporting of experiments (*6*). The current study was undertaken to survey recent trends in molecularly targeted agent-radiation combination studies submitted to the National Cancer Institute (NCI) as potential clinical trials and assess approaches used to justify human clinical trial proposals.

METHODS

Unsolicited ''Letter of Intent'' (LOI) proposals submitted to the NCI's Cancer Therapy Evaluation Program (CTEP) in the period between January 2016 and July 2020 for human clinical trials with a lead molecularly targeted agent were collected for curation and analysis ($N = 575$). To determine the subset of LOI records with a proposed study design that incorporated a radiation treatment modality, the following search terms were used: brachytherapy, chemoradiation, chemoradiotherapy, irradiation, IMRT (intensity modulated radiotherapy), radiation, reirradiation, radioembolization, radioimmunotherapy, RPT (radiopharmaceutical therapy), radiosurgery, radiotherapy, SBRT (stereotactic body radiotherapy), trimodality, WBRT (whole brain radiotherapy), and XBRT (external beam radiotherapy). Seventy-five LOI records (13% of those submitted) met the search criteria collectively for a radiation treatment and molecularly targeted agent combination trial proposal, which was

[1] Corresponding author: National Cancer Institute, 9609 Medical Center Dr, 3W232-Shady Grove, Rockville, MD 20850; email, SP@nih.gov.

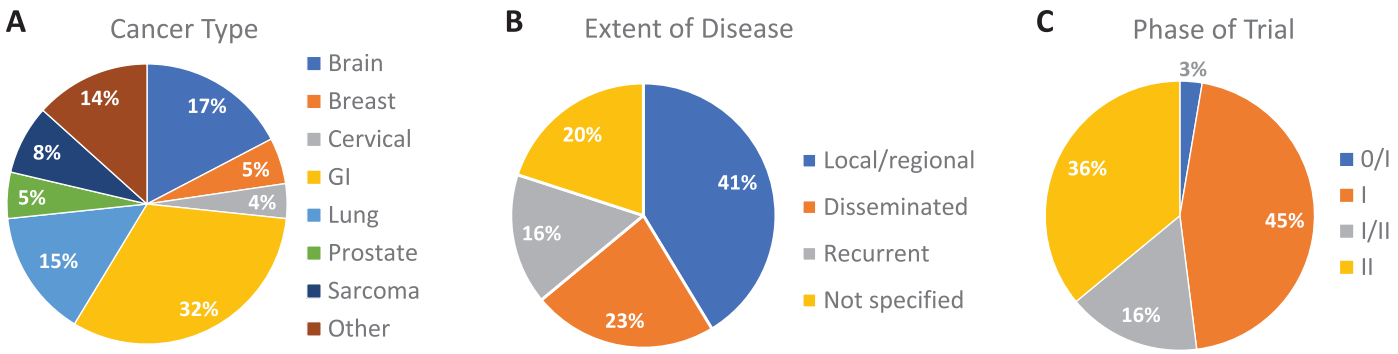


FIG. 1. Characteristics of proposed clinical trials and study eligibility criteria. Panel A: Cancer type. Panel B: Extent of disease. Panel C: Phase of trial. Data drawn from 75 radiation-molecularly targeted agent combination clinical trial proposals of the 575 total submitted LOIs to NCI CTEP between January 2016 and July 2020.

hand-curated and tabulated for categorical information. In addition to the combination of a molecularly targeted agent and radiation, 28% of these LOI proposals included additional standard of care chemotherapeutic study agents (e.g., capecitabine, cisplatin, doxorubicin, 5-fluorouracil, gemcitabine, paclitaxel, temozolomide).

RESULTS

Characteristics of clinical trial proposals that met our criteria for a radiation-molecularly targeted agent combination study ($N = 75$ of 575 CTEP LOI proposals submitted in the survey period) are shown in Figure 1. These data show a range of cancer types were chosen for study, with gastrointestinal (GI, 32%), brain (17%), and lung (15%) cancers as the top three primary anatomical sites (Fig. 1A). The extent of disease in subjects and clinical trial phase was relatively evenly distributed across study proposals, with either a Phase I or Phase II design comprising 81% of the LOIs (Fig. 1B and C).

The lead molecularly targeted agent proposed to be combined with radiation in the prospective clinical trials were categorized by the processes they are intended to target, as shown in Fig. 2A (*4*). Three-quarters of the molecularly targeted agent proposed for combination with radiation target either immunomodulation (45%) or DNA damage-repair pathways (30%). External beam radiation was the most common (81%) type of radiation treatment proposed to be combined with molecular targeted agents in the prospective clinical trial, with the remainder (19%) being radiopharmaceutical therapeutics (Fig. 2B). External beam radiation was also the most common (56%) type of radiation modality tested in preclinical experiments, while radiopharmaceutical therapeutics were examined in only 6% of proposals (Fig. 2C). In 37% of the clinical trials proposals, there was an absence of radiation tested either alone or in combination with the molecularly targeted agent in preclinical experiments (Fig. 2C.), and 19% presented no preclinical data (Fig. 3A). In the subset of proposals for which preclinical experiments involving radiation in combination with a molecularly targeted agent were performed, 64% used a fractionated radiation treatment schedule (Fig. 2D). The remainder (36%) examined responses from exposure to radiation delivered as a single (non-fractionated) dose, which typically included testing of one to two radiation dose points ranging between 2 and 12 Gy. For fractionation studies, radiation fraction size ranged from 0.83 to 10 Gy, with total doses ranged between 2.49 and 20 Gy.

Approaches to preclinical testing used to justify human radiation-drug combination clinical trials in the LOI proposals were tabulated. Approximately half of the proposals exclusively drew upon previously published preclinical data via citation to support the rationale for a new clinical trial, whereas only 7% presented solely unpublished primary preclinical data, while 25% utilized a mixture of both published and unpublished data (Fig. 3A). The remainder, approximately one-fifth (19%) of these proposals, neither cited prior preclinical studies nor contained new primary experimental data. An analysis of preclinical models utilized in proposals that tested a drug-radiation combination showed that the majority (64%) of experiments were conducted with cell lines, and overwhelmingly utilized xenograft or syngeneic mouse models (88%), while testing in patient derived xenograft (PDX) models or genetically engineered mouse models (GEMM) was seldomly observed (7% and 4%, respectively; Fig. 3B). Tumor growth assays (of any type), biomarker, and clonogenic assays were the most common experimental approaches (87%, 43% and 36%, respectively; Fig. 3C). Immunological assays (of any type) in preclinical models were used in only 11% of the clinical trial proposals. Discordance between the type of cancer either cited or modeled in preclinical experiments and the type of cancer the combination was proposed to treat in the clinical trial was observed in one-fourth of the proposals (Fig. 3D).

At present, there are no specific minimal data requirements for radiation-drug combination clinical trial proposals submitted to NCI CTEP (*4*). Thirty-seven percent ($N = 28$ of 75) of the radiation-molecularly targeted agent combination trial proposals submitted during the study period were approved by NCI CTEP. A discernable pattern relating the characteristics examined (shown in Figs. 1–3) to either

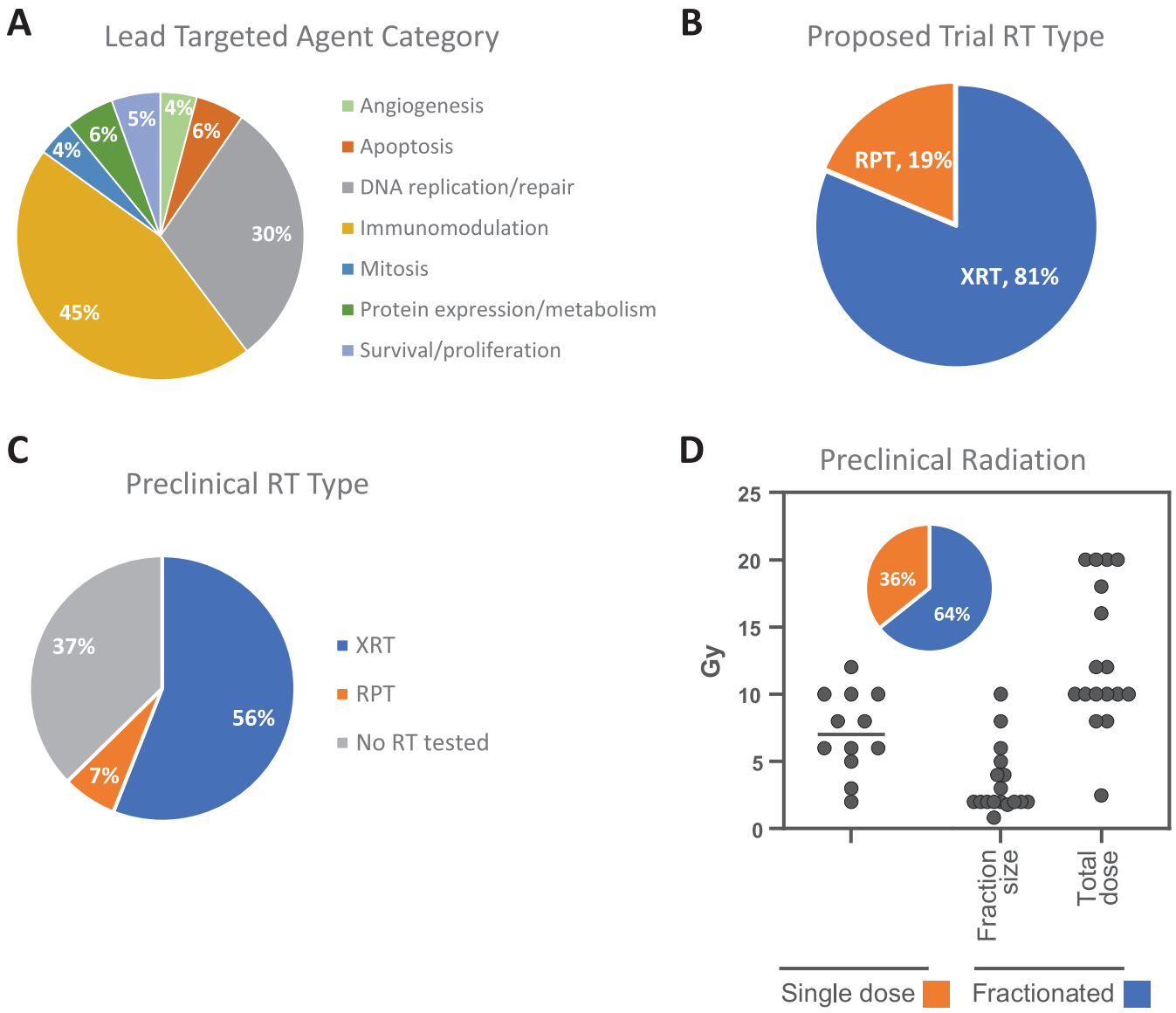


FIG. 2. Characteristics of the lead molecularly targeted agent and radiation therapy (RT) tested in preclinical and proposed clinical studies. Panel A: Category of the lead molecularly targeted agent tested in combination with radiation. Panel B: Type of radiation proposed for the clinical trials (RPT: radiopharmaceutical therapy; XRT: external beam radiation therapy). Panel C: Type of radiation tested in preclinical studies. Panel D: Treatment schedule, faction size, and total dose of radiation tested in preclinical studies (Insert: proportion of single vs fractionated dose tested). Categories in panel A are derived from Takebe et al. (*4*).

approval or disapproval was not evident, consistent with numerous factors outside of preclinical data have influence on this decision. Query of ClinicalTrials.gov indicated registration of these 28 NCI CTEP approved clinical trial proposals with 24 of these trials currently either recruiting or active. None of the approved and registered clinical trials examined in the study set have reported trial results, therefore further analysis relating preclinical data to radiation-drug combination clinical trial outcome or other measures was not possible.

How the rationale for combining radiation with a molecularly targeted agent was approached in the curated LOI proposals was divided into four non-mutually exclusive scenarios (Fig. 4). Approximately half (51%) of the proposals extrapolated the rationale from prior clinical data, in which the proposed trial testing of the treatment combination was based on a level of activity observed with radiation and/or the specific molecular targeted agent in human subjects having another type(s) of cancer. Slightly less than half (45%) of trial proposals deduced that clinical activity of either radiation or the specific agent as a monotherapy in a cancer type supported advancing testing of the combination in subjects with that same cancer type. Far less common (13%) was to build the rationale for combining a new molecularly targeted agent with radiation from prior preclinical and/or clinical data demonstrating activity with a drug or drugs with a similar mechanism of action. Very rarely (4%) the rationale for the proposed

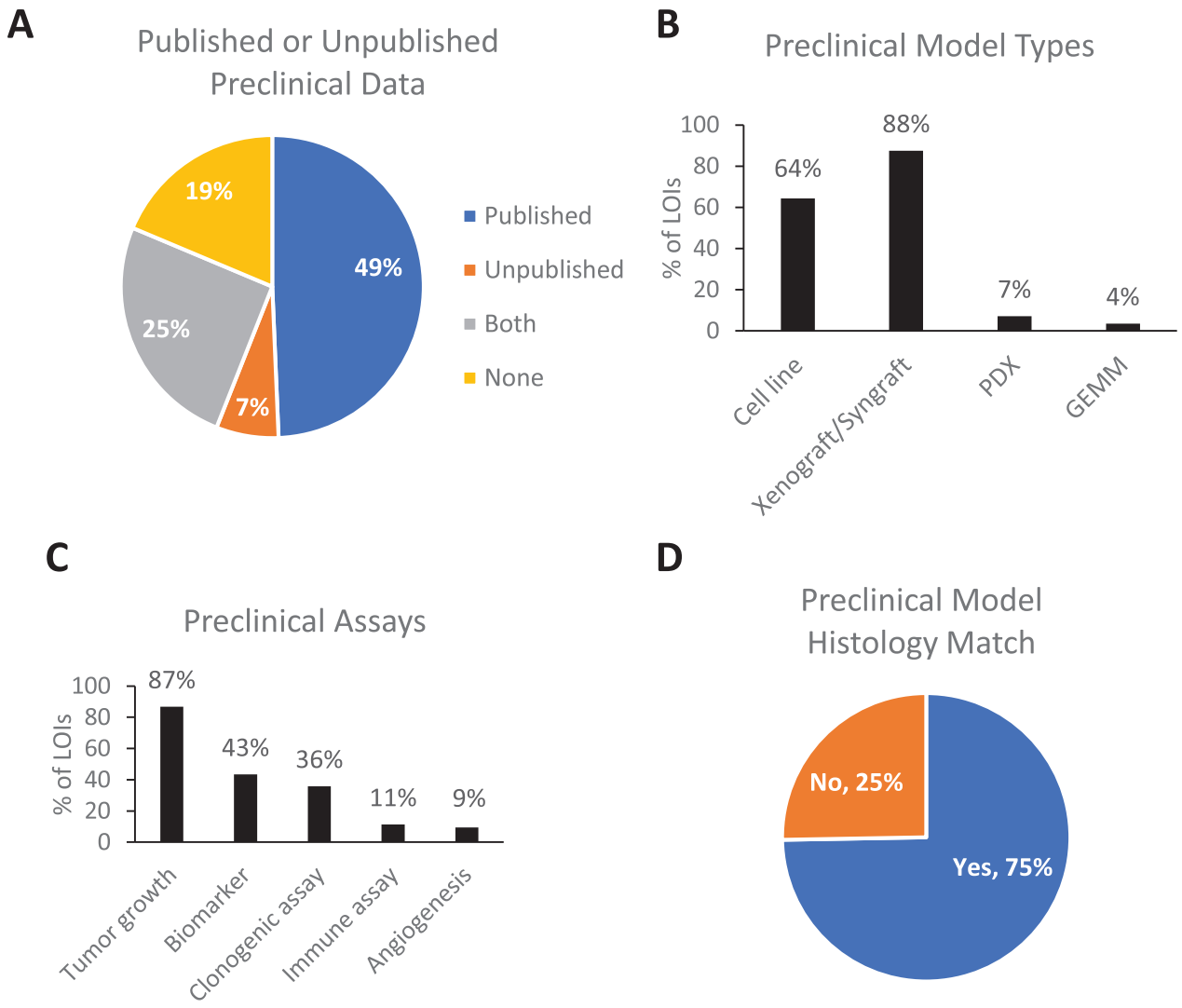


FIG. 3. Approaches to preclinical studies in the LOI proposals. Panel A: Publication status of preclinical data shown. Published: cites previously published work; unpublished: contains primary experimental data; both; none. Panel B: Preclinical model types. Panel C: Type of preclinical assays. Panel D: Proportion of the type of cancer tested in preclinical models matching the type of the cancer proposed in the LOI.

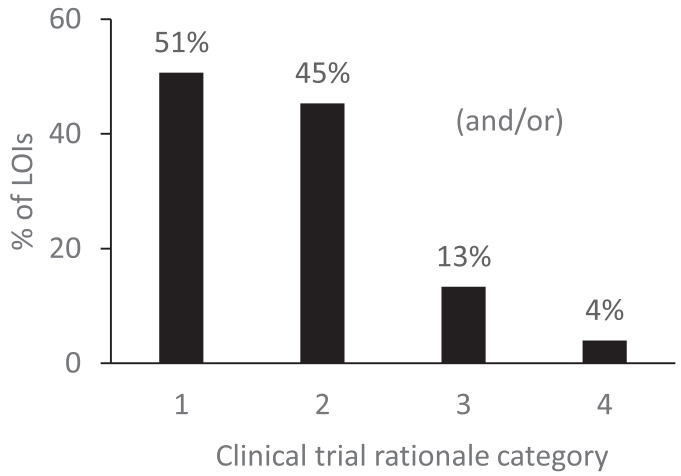
clinical trial was based on preclinical screening studies (e.g., high-throughput cancer cell line screening or testing a panel of patient-derived models) of specific drug-radiation combinations.

DISCUSSION

Most cancer patients receive radiation therapies during their treatment (*7*), which in recent years increasingly involves advanced imaging and treatment planning systems designed to deliver radiation doses in a precisely defined target volume of tissue where cancer cells reside. Radiation combined with systemic neoadjuvant and adjuvant therapies is typically administered to address distant recurrence from microscopic disease that may be disseminated outside the radiation treatment field. The advent of molecular profiling technologies designed to define genomic aberrations has led to an effort to identify and target alterations specific to an individual patient's tumors with drugs (*8*). We sought to examine the state of preclinical research that underpins the rationale to advance strategies that aim to combine molecularly targeted agents with radiation treatment into clinical oncology practice through analysis of clinical trial proposals (LOIs) submitted to NCI's Cancer Therapy Evaluation Program within the last five years.

The LOI proposals examined were exclusively early phase (e.g., I, I/II, II; Fig. 1D) experimental therapeutic clinical trials. Proposals that sought to combine radiation with a molecularly targeted agent comprised only 13% of those submitted ($N = 575$) over this period (2016– 2020), suggesting that trends continue for limited drug development in the context of radiation oncology (*9*). Given the preponderance of research pointing to DNA as a main target for the biological effects of radiation treatment (*10, 11*), it was not unexpected that 30% of clinical trial proposals in the set sought to examine the combination of radiation with

A



B

Description of clinical trial rationale categories –

1. Prior clinical evidence for drug and/or RT activity in one or more cancer types used to justify drug-RT combination in a new clinical trial of an unrelated cancer type;
2. Prior clinical evidence for activity of either a drug or RT as monotherapies in a specific cancer type used to justify drug-RT combination in that cancer type;
3. Prior pre-clinical or clinical data showing activity for a drug in similar class used to justify trial for a new drug in combination with RT;
4. Hit from preclinical screen of drug-RT combinations used to justify drug-RT combination in a new clinical trial.

FIG. 4. Four most common non-mutually exclusive categories (1–4) on how preclinical studies were used as rationale for the proposed clinical trial. Panel A: Clinical trial rationale categories. Panel B: Description of each clinical trial rationale category.

a molecularly targeted agent that inhibits or alters DNA replication and repair (Fig. 2A). Curation of the LOI set as a whole, however, revealed that interest in proposing radiation-immunomodulatory agent trial combinations nearly eclipsed all other categories combined (45%, Fig. 2A), consistent with the principle of connecting radiation-elicited DNA damage signaling with agents that promote tumor cell eradication by the immune system (*12*). It was noteworthy that despite the dominance of immunomodulators in radiation-molecularly targeted agent combination trial designs, preclinical assessments of immune response endpoints were included in only 11% of trial proposal submissions (Fig. 3C). Testing cancer cell autonomous responses as mono-cultures *in vitro* was frequently performed (64%; Fig. 3B); however, clonogenic assay data, a ''gold standard'' in radiobiology to quantify replicative cell death (*13*), was provided in only one-third of the radiation-molecular targeted agent combination proposals (Fig. 3C).

For any combination experiment matrix, pragmatic choices tied to expense are often made that limit permutations in dose and timing. Radiation from external beam sources differs from molecularly targeted agents in how physical dose is delivered, which can be clinically scheduled with different dose and fractionation schemes into precise volumes, thereby providing flexibility in radiotherapy suited to various treatment needs (*14*). Conventional radiotherapy fractionation schemes seek to balance tumor control while minimizing normal tissue injuries based on the 4 Rs' axiom: repair of DNA, cell cycle redistribution, repopulation, and reoxygenation; which partly encompasses radiobiological complexity (*15*). Figure

2D illustrates the range of preclinical radiation approaches tested with molecular targeted agents in the LOI proposals, as either single doses or fractionated. The dose and fractionation schedule tested in preclinical experiments was not correlated ($r^2 = 0.285$, data not shown) with that proposed for human trials. Equivalence in scaling irradiation fraction size and total dose in the volume of mouse xenografts to human tumors can pose technological challenges. The use of dosimetry standards and quality assurance to ensure that the experimental radiation dose was equivalent to those being administered clinically was typically absent.

Taken together, these observations highlight challenges in designing preclinical combinatorial experiments with radiation that scale to clinical practice. Methodologies used to model scheduling and dosing of radiation and drugs are typically treated independently, and frameworks developed to test their interaction as combinations are rarely used (*16, 17*). Radiation-drug combination testing adds complexities beyond drug-drug combination experiments (*18*), among which are inherent to fundamental modality differences in pharmacokinetic-pharmacodynamic profiles, an incomplete mechanistic understanding of molecular pathways affected by interactions over time, differential impact of the physical microenvironment [e.g., hypoxia (*19, 20*)], and shortcomings in biostatistical models that can computationally describe combinatorial responses in terms that predict desired clinical outcomes (*21–23*).

NCI's Molecular Analysis for Therapy Choice (MATCH) program exemplifies the precision medicine model where preclinical *in vivo* evidence from cell line xenografts and PDX are used to build the rationale for combination therapies targeted to patients identified through genomic sequencing and other biomarker tests (*24*). From the radiation-molecularly targeted agent trial proposals examined, it was common to describe growth inhibition responses to treatment combinations with both standard cell lines *in vitro* and as mouse xenograft models, whereas very few conducted tests using either patient-derived models (e.g., organoids, PDX) or GEMMs (7% or 4%, respectively; Fig. 3B). A surprising finding was that nearly 40% of submissions proposing to conduct an early phase clinical trial in humans for a radiation-molecular targeted agent combination wholly lacked preclinical data that included testing with radiation (Fig. 2C).

Several explanations may underlie the frequent omission of radiation in experimental work as the premise for combination trials with human subjects are being developed. Necessary specialized equipment, expertise, and licensure in the domain of radiobiologist and radiation oncologists may present a barrier to drug development laboratories for collaboration. Clinical experience with the radiation component as the standard of care may often be considered sufficient relative to investigating characteristics of the new molecular targeted agent in preclinical experiments, albeit as a monotherapy (*25*). It was evident from our analysis that extrapolation from either activity or a tolerable margin of safety from prior clinical data for the treatment combination (or similar combination) in other cancer types and/or in different anatomical locations was often proposed as a reasonable justification by trialists to forego specifically testing radiation in combinatorial preclinical experimental models (Fig. 4). This logic minimizes both organ-specific toxicities associated with radiation (*26*) and identification of potential tolerability issues from the radiation-drug combination prior to phase I testing in human subjects.

The frequent absence of preclinical testing (Fig. 3A) and discordance between the type of cancer either cited or modeled in preclinical experiments and that afflicting patients in the proposed clinical trial (Fig. 3D), suggests precision medicine principles are not consistently applied to radiation-molecularly targeted agent combination approaches (*23, 26–29*). These data contrast with a broader adoption in medical oncology to incorporate genomic-radiomic features, biomarkers, or tumor functional profiling in drug-drug combination workflows, such as those incorporated into the NCI MATCH program (*24*). Rarely (4%; Fig. 4A) in the examined proposal set was a stepwise ''bottom-up'' approach used to initially screen to identify potentially clinically actionable radiation-molecular targeted agent combinations followed by validation using *in vivo* preclinical models (*27, 30*). Significant investment has been made in cancer systems biology approaches for screening interactions, target identification, and predicting combinatorial responses (*31, 32*), which has potential to inform synthetic combination strategies for moving radiation-molecularly targeted agent combinations from discovery into preclinical testing and early-stage clinical trials (*33-35*). To address momentum for investigators poised at this intersection, the NCI has recently established the Precision Approaches in Radiation Synthetic Combinations [PAIRS, PAR-22-198, -199; (*36*)] program to foster development and adoption of radiation-treatment-based synthetic combination strategies into precision medicine approaches. Our survey of unsolicited early phase cancer trial proposals submitted to the NCI CTEP for using molecularly targeted agents with radiation suggests minimum standards for preclinical modeling are needed to advance these combinations toward clinical benefit for patients with cancer, consistent with recent guidance (*25, 30*).

ACKNOWLEDGMENTS

The authors thank Timothy Schulz for his assistance in making available clinical trial proposals from the NCI CTEP database. This article represents the opinion of the authors. It does not represent the opinion or policy of the U.S. National Cancer Institute of the National Institutes of Health.

Received: May 2, 2022; accepted: July 18, 2022; published online: August 17, 2022

REFERENCES

1. Connell PP, Hellman S. Advances in radiotherapy and implications for the next century: a historical perspective. Cancer Res. 2009; 69(2):383-92.
2. Harrington KJ, Billingham LJ, Brunner TB, Burnet NG, Chan CS, Hoskin P, et al. Guidelines for preclinical and early phase clinical assessment of novel radiosensitisers. Br J Cancer. 2011; 105(5):628-39.
3. Nagle PW, Coppes RP. Current and future perspectives of the use of organoids in radiobiology. Cells. 2020; 9(12):2649.
4. Takebe N, Ahmed MM, Vikram B, Bernhard EJ, Zwiebel J, Norman Coleman C, et al. Radiation—therapeutic agent clinical trials: Leveraging Advantages of a national cancer institute programmatic collaboration. Semin Radiat Oncol. 2016; 26(4):271-80.
5. Coleman CN, Eke I, Makinde AY, Chopra S, Demaria S, Formenti SC, et al. Radiation-induced adaptive response: New potential for cancer treatment. Clin Cancer Res. 2020; 26(22):5781-90.
6. Stone HB, Bernhard EJ, Coleman CN, Deye J, Capala J, Mitchell JB, et al. Preclinical data on efficacy of 10 Drug-radiation combinations: evaluations, concerns, and recommendations. Transl Oncol. 2016; 9(1):46-56.
7. Jaffray DA, Knaul FM, Atun R, Adams C, Barton MB, Baumann M, et al. Global task force on radiotherapy for cancer control. Lancet Oncol. 2015; 16(10):1144-6.
8. Garraway LA, Verweij J, Ballman KV. Precision oncology: An overview. J Clin Oncol. 2013; 31(15):1803-5.
9. 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. J Natl Cancer Inst. 2013; 105(1):11-24.
10. Lomax ME, Folkes LK, O'Neill P. Biological Consequences of radiation-induced DNA damage: Relevance to dadiotherapy. Clin Oncol. 2013; 25(10):578-85.
11. Morgan MA, Lawrence TS. Molecular Pathways: Overcoming Radiation resistance by targeting DNA damage response pathways. Clin Cancer Res. 2015; 21(13):2898-904.
12. Petroni G, Cantley LC, Santambrogio L, Formenti SC, Galluzzi L. Radiotherapy as a tool to elicit clinically actionable signalling pathways in cancer. Nat Rev Clin Oncol. 2022; 19(2):114-31.
13. Puck TT, Marcus PI. Action of x-rays on mammalian cells. J Exp Med. 1956; 103(5):653-66.
14. Brown JM, Carlson DJ, Brenner DJ. The tumor radiobiology of SRS and SBRT: are more than the 5 Rs involved? Int J Radiat Oncol Biol Phys. 2014; 88(2):254-62.
15. Pajonk F, Vlashi E, McBride WH. Radiation resistance of cancer stem cells: the 4 R's of radiobiology revisited. Stem Cells. 2010; 28(4):639-48.
16. Steel GG. Terminology in the description of drug-radiation interactions. Int J Radiat Oncol Biol Phys. 1979; 5(8):1145-50.
17. Grassberger C, Paganetti H. Methodologies in the modeling of combined chemo-radiation treatments. Phys Med Biol. 2016; 61(21):R344-R67.
18. Morris ZS, Harari PM. Interaction of radiation therapy with molecular targeted agents. J Clin Oncol. 2014; 32(26):2886-93.
19. Coleman CN. Hypoxia in Tumors: A Paradigm for the Approach to Biochemical and Physiologic Heterogeneity. J Natl Cancer Inst. 1988; 80(5):310-7.
20. Rickard AG, Palmer GM, Dewhirst MW. Clinical and Pre-clinical methods for quantifying tumor hypoxia. Adv Exp Med Biol. 2019; 1136:19-41.
21. Bodgi L, Canet A, Pujo-Menjouet L, Lesne A, Victor J-M, Foray N. Mathematical models of radiation action on living cells: From the target theory to the modern approaches. A historical and critical review. J Theor Biol. 2016; 394:93-101.
22. Grassberger C, Scott JG, Paganetti H. Biomathematical optimization of radiation therapy in the era of targeted agents. Int J Radiat Oncol Biol Phys. 2017; 97(1):13-7.
23. Enderling H, Alfonso JCL, Moros E, Caudell JJ, Harrison LB. Integrating mathematical modeling into the roadmap for personalized adaptive radiation therapy. Trends Cancer. 2019; 5(8):467-74.
24. Flaherty KT, Gray R, Chen A, Li S, Patton D, Hamilton SR, et al. The molecular analysis for therapy choice (NCI-MATCH) trial: Lessons for genomic trial design. J Natl Cancer Inst. 2020; 112(10):1021-9.
25. Walker AJ. Regulatory considerations in the development of radiation-drug combinations. Int J Radiat Oncol Biol Phys. 2021; 111(5):1140-4.
26. Quon H, McNutt T, Lee J, Bowers M, Jiang W, Lakshminarayanan P, et al. Needs and challenges for radiation oncology in the era of precision medicine. Int J Radiat Oncol Biol Phys. 2019; 103(4):809-17.
27. Baumann M, Krause M, Overgaard J, Debus J, Bentzen SM, Daartz J, et al. Radiation oncology in the era of precision medicine. Nat Rev Cancer. 2016; 16(4):234-49.
28. Kamran SC, Mouw KW. Applying precision oncology principles in radiation oncology. JCO Precis Oncol. 2018; 2:PO.18.00034.
29. Pilié PG, Tang C, Mills GB, Yap TA. State-of-the-art strategies for targeting the DNA damage response in cancer. Nat Rev Clin Oncol. 2019; 16(2):81-104.
30. Lin SH, Willers H, Krishnan S, Sarkaria JN, Baumann M, Lawrence TS. Moving beyond the standard of care: accelerate testing of radiation-drug combinations. Int J Radiat Oncol Biol Phys. 2021; 111(5):1131-9.
31. Haley B, Roudnicky F. Functional genomics for cancer drug target discovery. Cancer Cell. 2020; 38(1):31-43.
32. Ma J, Fong SH, Luo Y, Bakkenist CJ, Shen JP, Mourragui S, et al. Few-shot learning creates predictive models of drug response that translate from high-throughput screens to individual patients. Nat Cancer. 2021; 2(2):233-44.
33. Chan DA, Giaccia AJ. Harnessing synthetic lethal interactions in anticancer drug discovery. Nat Rev Drug Discov. 2011; 10(5):351-64.
34. Yard BD, Adams DJ, Chie EK, Tamayo P, Battaglia JS, Gopal P, et al. A genetic basis for the variation in the vulnerability of cancer to DNA damage. Nat Commun. 2016; 7:11428-.
35. Setton J, Zinda M, Riaz N, Durocher D, Zimmermann M, Koehler M, et al. Synthetic lethality in cancer therapeutics: The next generation. Cancer Discov. 2021; 11(7):1626-35.
36. Department of Health and Human Services. Part 1. Overview Information. (available online: https://grants.nih.gov/grants/guide/pa-files/PAR-22-198.html; https://grants.nih.gov/grants/guide/pa-files/PAR-22-199.html)