Proceedings of the National Cancer Institute Workshop on combining immunotherapy with radiotherapy: challenges and opportunities for clinical translation

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Radiotherapy both promotes and antagonises tumour immune recognition. Some clinical studies show improved patient outcomes when immunotherapies are integrated with radiotherapy. Safe, greater than additive, clinical response to the combination is limited to a subset of patients, however, and how radiotherapy can best be combined with immunotherapies remains unclear. The National Cancer Institute–Immuno-Oncology Translational Network–Society for Immunotherapy of Cancer–American Association of Immunology Workshop on Combining Immunotherapy with Radiotherapy was convened to identify and prioritise opportunities and challenges for radiotherapy and immunotherapy combinations. Sessions examined the immune effects of radiation, barriers to anti-tumour immune response, previous clinical trial data, immunological and computational assessment of response, and next-generation radiotherapy–immunotherapy combinations. Panel recommendations included: developing and implementing patient selection and biomarker-guided approaches; applying mechanistic understanding to optimise delivery of radiotherapy and selection of immunotherapies; using rigorous preclinical models including companion animal studies; embracing data sharing and standardisation, advanced modelling, and multidisciplinary cross-institution collaboration; interrogating clinical data, including negative trials; and incorporating novel clinical endpoints and trial designs.

Lancet Oncol 2025; 26: e152–70

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Introduction

The concept that host immune fitness is a determinant of tumour response to focal radiotherapy was first introduced in 1979.[1] These experiments, which compared tumour response to radiation in mice proficient or deficient in T cells, also suggested a systemic impact of local radiation and offered an explanation for an abscopal effect, in which local radiotherapy leads to regression of an unirradiated tumour. However, the concept remained on the sidelines of radiation sciences and medicine until the early 2000s, when advances in tumour immunology provided the means to test the effects of radiation on the anti-tumour immune response.

Foundational work on the dynamic interactions between cancer cells and the immune system led to the concept of cancer immunoediting,[2] which was pivotal in understanding that tumours can escape immune control in several ways. Additionally, the field evolved to focus on the tumour-immune microenvironment (TIME),[3] which ranges between the two extremes of cold (poorly immunogenic and with few tumour-infiltrating T cells) and hot (immunogenic and highly T-cell infiltrated). Seminal studies on the mechanisms that regulate T-cell activation and function identified cytotoxic T-lymphocyte associated protein (CTLA-4) and programmed cell death-1 (PD-1) as key immune checkpoints on T cells that have a key role in the escape of hot tumours from immune control, paving the way to clinical development of immune checkpoint inhibitor (ICI) therapy.[4–6] In the past decade, ICIs have shown activity across various histologies, but only in a subset of patients, prompting efforts to identify additional features of the TIME that shape the immune response either favourably or detrimentally.[7,8]

The hypothesis that radiation could serve as an in-situ tumour vaccine and sensitise cold tumours to ICI was tested first in a mouse model of metastatic and poorly immunogenic breast cancer. Results showed a synergistic interaction of radiation with CTLA-4 blockade, achieving improved control of the primary irradiated tumour and of spontaneous lung metastases outside of the radiation field that was mediated by CD8 T cells.[9] After the US Food and Drug Administration approval of the anti-CTLA-4 antibody ipilimumab in 2017 for melanoma, this combination of therapies was tested in patients with melanoma[10] and later lung cancer,[11] yielding proof-of-principle evidence that radiotherapy plus ICI could induce tumour-specific T cells and abscopal responses in some patients. Other studies showed efficacy of combinations of radiation with anti-PD-1 and anti-programmed death ligand-1 (PD-L1) antibodies in preclinical tumour models,[12,13] potentially counteracting the transient upregulation of PD-L1 in response to radiation-induced DNA damage.[14]

Mechanistically, additional work showed that radiation has the potential to promote anti-tumour immunity by acting at each step of the cancer immunity cycle, from priming of T cells by antigen-presenting cells in the

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draining lymph nodes, to their recruitment to the tumour and recognition of cancer cells.[15,16] Cyclic GMP-AMP synthase (cGAS) is a cytosolic DNA sensor that induces the type I interferon (IFN-I) cytokine in response to viruses.[17] Its discovery fostered studies linking radiation-induced DNA damage to the induction of IFN-1, a cytokine essential for anti-tumour immunity,[18] possibly via activation of cGAS–stimulator of interferon genes (STING).[19–24]

Importantly, radiotherapy also induces immunosuppression,[20,23–25] but whether these immunosuppressive mechanisms are uniquely affected by radiation dose and tumour histologies has not yet been fully elucidated. Therefore, a major goal is to identify an optimal dose or fractionation that reliably promotes tumour rejection.[26] Although most of the work combining radiotherapy with immunotherapy done to date has used external-beam radiotherapy (EBRT), many new approaches are currently under investigation, including stereotactic ablative radiotherapy (SABR; also called stereotactic body radiation or SBRT), radiopharmaceutical therapy, FLASH, and spatially fractionated radiotherapies, which can be produced by brachytherapy, GRID, or LATTICE. Work is in progress to improve combination therapies through innovative uses of radiotherapy, such as SABR or radiopharmaceutical therapy, to improve responses to ICI therapy by reducing tumour burden through treatment of all disease sites.[27,28] As most work has involved EBRT, throughout this Policy Review, radiotherapy will refer to EBRT, unless otherwise specified. As will be discussed in the following sections, there is a growing consensus that the choice of radiation dose, fractionation, and target volume should be guided by an improved understanding of radiation's potentially dichotomous outcomes in promoting or suppressing the immune response.

Recognising the challenges and the importance of carefully selecting radiation approaches and strategically applying combined pharmacological therapy, the National Cancer Institute (NCI), together with the Immuno-Oncology Translational Network (IOTN), Society for Immunotherapy of Cancer (SITC), and American Association of Immunology (AAI) organised the Workshop on Combining Immunotherapy with Radiotherapy on Jan 16–17, 2024, in Bethesda (MD, USA) and online.[29] The workshop had more than 790 registrants from 36 different countries, including Pakistan (n=17), India (n=15), Germany (n=12), Canada (n=10), the UK (n=6), Belgium (n=5), France (n=4), Switzerland (n=3), and South Korea (n=3). The workshop attendees (638 virtual; in-person attendees were not tracked) were from various institutions including universities, national laboratories, research centres, and industry (panel 1), representing all career stages, including 111 trainees (69 students or doctoral candidates, 42 postdoctoral fellows), 189 early career professors, 21 department chairs, 39 programme officers, 81 scientists, five clinicians, and five industry chief executive officers. The ensuing discussions delved into strategies to implement radiotherapy to generate in-situ vaccination, eradicate systemic therapy-resistant disease sites by ablation, or to modulate tumour cells and the TIME to promote anti-tumour immunity. These distinct mechanistic effects of radiation are optimised by different dosing and targeting approaches. Therefore, careful targeting and dosing of radiotherapy in a manner that is appropriate to achieve the intended effect in patient cohorts where such an effect is anticipated to confer clinically meaningful benefit is crucial. Key topics at the workshop included the use of multiple forms of radiation, preservation of lymphoid reservoirs, and the adaptation of radiotherapy approaches to diverse immunotherapeutic modalities beyond immune checkpoint blockade.

Panel 1: Fostering academic–corporate partnerships at the interface of radiotherapy and immunotherapies

Interest within the pharmaceutical industry to optimise pairing of radiotherapy with immunotherapy has been growing. Representatives from both large (eg, Johnson & Johnson) and small (eg, Telix Pharmaceuticals) companies presented guidance at the National Cancer Institute workshop on leveraging academic–industry partnerships to propose novel research studies and drive clinical development. The structure of these collaborations ranges from investigator-initiated trials with primary academic oversight to clinical trial agreements with primary industry oversight, and can involve data and material exchanges, preclinical experiments, or clinical trials. Smaller companies are often looking for partnerships that provide expertise of deep domain knowledge and infrastructure. In return, the industry partner can provide visibility, funding, access to emerging opportunities, and networks for clinical translation. Industry partners look for agreements that generate robust intellectual property by use of the partnering company's agents.

Challenges to developing clinical trials of radiotherapy with novel drugs include a lack of formal US Food and Drug Administration guidance on the preclinical data needed for regulatory approval. However, some inferences can be made from other guidance on drug–drug combinations. Toxicology studies would not be required for radiotherapy alone because it is well documented, but preclinical evidence would be needed for a recommended starting dose. Appropriate endpoint selection (eg, survival *vs* quality of life *vs* organ preservation) is paramount, as is long-term follow-up on late-event, dose-limiting toxicities for radiotherapy.

Audience responders felt that the best way for industry to work with academic groups was through direct grant programmes for preclinical studies (56%) and by setting up a dedicated website through which investigators can request drugs or funding for clinical trials (23%).

The radiated tumour microenvironment: challenges, opportunities, and appropriate model systems and their limitations

The TIME represses immunity through immunosuppressive cytokines, suppression of major histocompatibility complex presentation, and immunosuppressive cells such as myeloid-derived suppressor cells (MDSCs) and tumour-associated macrophages, cancer-associated fibroblasts, and T-regulatory cells. Furthermore, an aberrant vasculature and extracellular matrix prevents immune cell infiltration. The response of the TIME to radiotherapy could attenuate or amplify these mechanisms, probably depending on a range of factors including differing duration, dose, and type of radiation and differences in sequencing of therapies. Location provides an additional variable, with responses depending on the site of delivery and the spatial dose distribution. Patient heterogeneity presents a final challenge complicating each of these variables. This session discussed these many challenges.

Several factors are responsible for therapeutic interactions between radiotherapy and immunotherapies. First, radiotherapy can alter the TIME stroma and vasculature and release chemokines and cytokines that increase homing of immune cells into the TIME.[30,31] Second, radiotherapy induces immunogenic cell death by releasing tumour antigens and damage-associated molecular patterns.[32] Double-stranded DNA released into the cytosol after radiotherapy is sensed by the cGAS–STING pathway, leading to IFN-I production.[19] Interferon signalling, in addition to signalling via other damage-associated molecular patterns including high mobility group box 1, calreticulin, ATP, and others,[33,34] increases the maturation and activation of dendritic cells and increases their ability to take up and cross-present tumour antigens to the adaptive immune system. Furthermore, these activated dendritic cells upregulate co-stimulatory molecules such as CD80 and CD86 and inflammatory cytokines such IL-1β, IL-6, and TNF-α. Finally, radiotherapy alters the phenotype of surviving tumour cells by upregulating major histocompatibility complex class I to promote the recognition and killing of cancer cells by cytotoxic CD8+ T cells[35] and upregulating stress ligands that activate natural killer cells.[36] These processes are likely to be crucial to successful integration of radiotherapy and ICIs.[37]

Although the acute inflammatory response to radiotherapy can induce tumour immunity, this acute inflammatory response develops into chronic inflammation over time and becomes immunosuppressive. The immune system evolved to maintain immunological homoeostasis to respond to infection and injury but prevent uncontrolled inflammation. Therefore, the natural response to inflammation is to turn on immunosuppressive mechanisms designed to limit the acute inflammatory response and restore homoeostasis.[38,39]

The immunomodulatory effects of radiotherapy are diverse and highly dependent on the characteristics of radiotherapy delivery. In terms of dose, some preclinical studies suggest that 3×8 Gray (Gy) is more effective than a single dose of 20 Gy for inducing abscopal responses, as in murine models of breast and colon cancer where fractionated radiotherapy with anti-CTLA-4 produced a greater abscopal response than a similar dose delivered in a single fraction.[40] This systemic anti-tumour response is due, in part, to a negative feedback mechanism involving the induction of the exonuclease TREX1 resulting in reduced cGAS–STING–IFN-α pathway activation.[20] Other models and immunotherapy combinations have produced different results.[41] Thus, although potentially unique to each model, the concept that different radiotherapy doses and fractionation patterns can have different biological effects is a key consideration when designing clinical trials. The irradiated tissues are also likely to dictate the immunomodulatory effects of radiotherapy based on the resident immune cells in organs in the irradiated volume and direct and bystander effects on those resident immune cells.[42] Consistently, the systemic immune response after SABR differs depending on the site that was irradiated.[42] In possible support of these site-specific radiation responses, a post-hoc analysis of patients treated in a phase 1 trial with SABR and anti-CTLA-4 found that patients who received lung metastasis-targeted radiotherapy had significantly longer progression-free survival and overall survival than patients who received liver metastasis-targeted radiotherapy.[43]

The temporal sequencing of radiotherapy is also of fundamental importance, in part due to induction of homoeostatic immunosuppressive mechanisms at later timepoints and toxicity to immune cells. The optimal sequencing of radiotherapy and immunotherapy depends on the mechanism of the immunotherapy tested, as shown by the finding that anti-CTLA-4 is most effective when given before radiotherapy, due to regulatory T-cell depletion, whereas anti-OX40 agonist is most effective when delivered 1 day after radiotherapy to enhance T-cell activation during a period of increased antigen presentation.[44] Data are conflicting for sequencing radiotherapy and anti-PD-L1 therapies, with some studies suggesting initiation of checkpoint inhibition before radiotherapy[45] whereas others suggest this should be done after radiotherapy.[46] Again, consideration of how radiotherapy is being used is important. Large field radiotherapy with multiple fractions (particularly in combination with chemotherapy) can be lymphocyte-depleting and immunosuppressive;[47] thus, immunotherapy after radiotherapy might be preferred. Ablative radiotherapy approaches, with small field sizes and few fractions, might be used concurrently with, or even after, an initial period of immunotherapy. Given that circulating T cells are particularly sensitive to radiation at doses greater than 0·5 Gy,[48] the number of

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fractions delivered is likely to be more important than the dose per fraction, and short courses of SABR are likely to reduce T-cell death. The importance of sequencing is illustrated in clinical practice by comparing the PACIFIC[49] and PACIFIC-2 trials.[50] Both trials treated patients with stage III non-small-cell lung cancer (NSCLC) with chemoradiation and durvalumab. However, the original PACIFIC trial treated patients with adjuvant durvalumab, whereas the PACIFIC-2 trial treated with concurrent durvalumab during chemoradiation. The PACIFIC trial showed an impressive improvement in progression-free survival and overall survival at 5 years.[49,51] However, the PACIFIC-2 trial did not meet its primary endpoint of improvement in progression-free survival. Although sequencing was not the only difference between these trials, given negative results of many other clinical trials that also delivered anti-PD-L1 therapies concurrently with chemoradiation, the sequencing of treatments is a plausible contributing factor.

Several other variables can also influence the immunomodulatory effects of radiotherapy, including particle versus photon, dose rate, and amount of tumour treated.[52–67] In traditional radiotherapy approaches, leaving a portion of the tumour untreated would be expected to drastically reduce clinical benefit. However, approaches such as spatially fractionated radiotherapy produce intentional dose heterogeneity across the tumour. This type of radiotherapy can be delivered in the form of brachytherapy, which can deliver a single dose gradient across the entire tumour, or in forms which produce multiple regions of high and low doses. Multiple regions across a single tumour can be reached with GRID or LATTICE therapy, which can have spatial resolutions of cm to mm in two dimension (GRID) or three dimension (LATTICE), and with minibeam or microbeam radiation that generate regions with mm to μm spatial resolution, with minibeam generally producing wider regions. Heterogeneous radiation dose from brachytherapy has been shown to prime anti-tumour immunity more effectively than any single homogeneous radiation dose when combined with ICIs by activating multiple immunogenic effects in a single TIME.[52] Alternatively, tumours can be partly exposed to SABR. Preclinical studies suggest reduced side-effects from minibeam radiation in a rat model of glioma[53] and microbeam radiation in bones and teeth of healthy rabbits,[54] normal mouse ears,[55] normal murine liver, lung, and skin, and murine lung and melanoma tumours,[56,57] with potential for improved tumour control in murine melanoma[58] compared with homogeneous doses. This improved tumour control might be partly due to an improved immune response, which makes for promising partnership with ICIs.[59–61] Data also suggest that some forms of particle radiotherapy, namely carbon ions, might have improved immunomodulatory effects.[62–64] Several preclinical studies show improved synergy with immunotherapy and increased immune modulation when carbon ion radiotherapy is used as compared with photons in murine models of breast cancer[62] and melanoma.[63,64] In terms of dose rate, early studies have suggested an immune-sparing effect of FLASH radiotherapy, which is also notably effective in preclinical murine models, even under hypoxic conditions.[65] Preclinical data suggest increased recruitment of CD8+ T cells in murine NSCLC tumours treated with proton-FLASH radiotherapy compared with conventional protons,[66] and in a murine model of diffuse midline glioma, FLASH yielded distinct temporal immune responses compared with conventional radiotherapy, despite equivalent tumour control and survival outcomes.[67] These findings underscore the need for further research into how these mechanisms affect tumour control and long-term outcomes and potential synergy with immunotherapies.[63]

Because each individual patient's immune system mediates their immune response after radiation, baseline patient characteristics such as age,[68] sex,[69] co-morbidities,[70–72] and metabolic status[73] are also likely to strongly influence the immunomodulating effects of radiotherapy. Modelling this complexity is a limitation among preclinical models, yet is essential to rational clinical trial design and advancing the clinical success of radiotherapy in combination with immunotherapy. Age is one of the strongest risk factors for cancer overall, with fewer than 25 cases per 100 000 people younger than 20 years, increasing to 350 per 100 000 for people aged between 45 years and 49 years, and rising to more than 1000 per 100 000 in people aged over 60 years and older, and more than half of all cancers occurring in people aged over 65 years and older;[74,75] however, most murine models use young mice. Age can play an important part in immune response. Aged mice had higher toxicity in response to immunostimulatory agents as compared with young mice,[76] and ageing is also commonly accompanied by immunosenescence, which might impair immune response.[68] Thus, aged mice might better reflect the clinical scenario seen in many patients with cancer.[76] Moreover, research from the past 5 years suggests that senescence is a fundamental reaction to radiation exposure and that it might be responsible for radiotherapy's immunogenic effects—making the age of preclinical models a potential important confounding variable when assessing radiotherapy and immunotherapy combinations.[77–80] In mouse models and humans, obesity can also alter the function of the immune system and the efficacy of immunotherapy.[73,81] Use of aged or obese models that more closely reflect our patient population might provide more robust preclinical data upon which to base clinical trials. Furthermore, companion canine patients are excellent models for testing radiotherapy with immunotherapy.[38,82] Companion canines more closely reflect human cancer biology, with greater similarities in

their biological age, immune function, housing and environmental exposures, tumour heterogeneity, patterns of growth and spread, and the spontaneous development and growth of tumours over time under selective pressure from immune surveillance.

Figure 1 summarises the major challenges involved in combining immunotherapy and radiotherapy. Among audience members, most favoured expanding our approaches to encompass multiple types of immunotherapies, novel radiation approaches, and

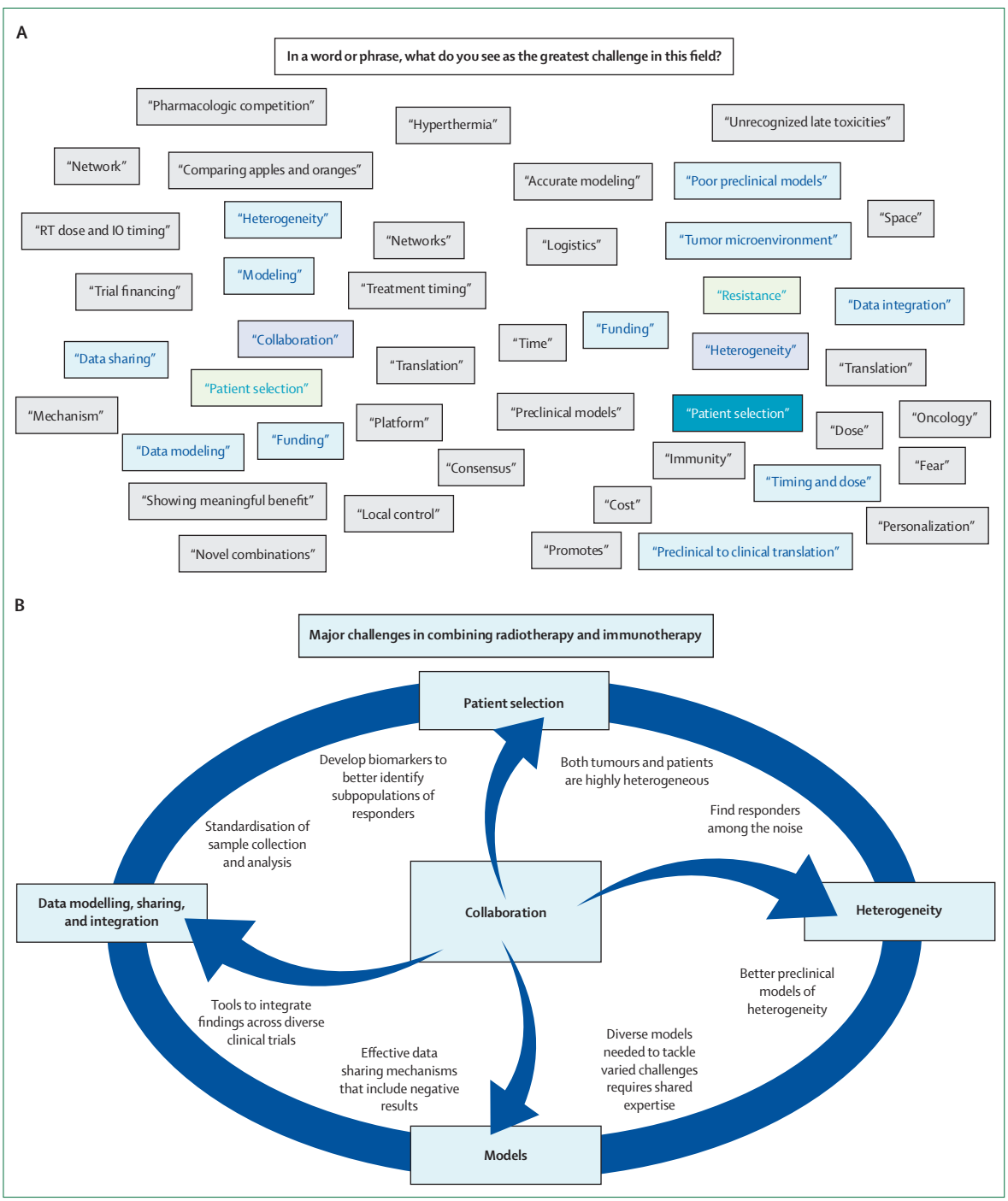

Figure 1: **Challenges in the field of combined radiotherapy and immunotherapy**
(A) Word cloud generated by audience replies when responding in real time to Slido poll questions addressing what the greatest challenges are in the field of combining radiotherapy with immunotherapy. (B) Collaboration is needed to address the interconnected challenges identified in this field. IO=immuno-oncology. RT=radiotherapy.

various sequencing strategies while also incorporating biomarkers. Generally, radiotherapy delivered just before immunotherapy was favoured by 62%. Questions arose regarding chemoradiation and previous exposure to chemotherapy, highlighting the need to better understand interactions between chemotherapy and radiotherapy. Recent landmark trials underscore the transformative potential of combining immunotherapy with neoadjuvant and adjuvant treatments in oncology. The phase 3 NIAGARA trial showed that adding durvalumab to neoadjuvant chemotherapy before radical cystectomy, followed by durvalumab monotherapy, significantly improved event-free survival and overall survival OS in patients with muscle-invasive bladder cancer compared with neoadjuvant chemotherapy alone.[83] Similarly, the phase 3 KEYNOTE-522 trial confirmed the benefit of pembrolizumab with standard chemotherapy in early-stage triple-negative breast cancer, showing improved pathological complete response and event-free survival at long-term follow-up.[84] The CheckMate 816 trial also highlighted the efficacy of neoadjuvant nivolumab plus chemotherapy in resectable NSCLC,[85] whereas the NICHE-2 study in mismatch repair-deficient populations of colon cancer revealed remarkable tumour regression with combined nivolumab and ipilimumab before surgery.[86] These findings prompt crucial questions about optimising neoadjuvant immunotherapy. Key considerations include whether treatment duration is sufficient for maximal response and whether immunoablation with organ preservation offers immunological advantages that could enhance long-term outcomes. Additionally, the management of patients not reaching pathological complete response remains an open area for exploration, potentially involving combinations of immunoradiotherapy or chemoradiotherapy. This pivotal moment in oncology not only presents opportunities to refine therapeutic strategies but also deepens our understanding of the molecular mechanisms driving these remarkable responses.

Limitations in reproducibility and translation of preclinical models were noted. Therefore, additional robust preclinical and translational data are required to guide future clinical trials in this field, demanding tumour models with reproducible results predictive for clinical trials (figure 2). Understanding how the complex variables discussed influence radiation-induced immune modulation and how best to model these complexities will facilitate the design of clinical trials with higher likelihood of success.

In summary, the TIME is a complex biological system that is perturbed by radiation in ways that can promote or hinder anti-tumour immunity. Greater understanding of these effects will create opportunities to more effectively combine different forms of radiotherapy and immunotherapy.

Barriers that hinder immune response in the irradiated tumour: an insurmountable challenge or opportunity for innovation?

Although radiotherapy activates many immune-stimulatory pathways, it can also elicit several immunosuppressive mechanisms, hindering the productive interaction between radiotherapy and immunotherapy and thus requiring strategies to block these immunosuppressive pathways. Radiotherapy can affect the vasculature, lymph nodes, and stroma including increased fibrosis[87,88] and lead to immuno-suppressive effects mediated by the various cell types found in the TIME. Tumour and non-tumour cells can undergo quiescent cell death such as apoptosis or ferroptosis, and apoptotic caspase activation has been shown to inhibit IFN-1 secretion by irradiated cancer cells.[89] Radiotherapy drives immunosuppressive autophagic responses, and inhibiting autophagy improves distant tumour control.[23] Endothelial cells, which are crucial for tumour immune cell infiltration, undergo apoptosis in response to ablative radiation[90] but irradiation at low doses can have effects on immune cell adhesion to and invasion through the endothelium.[91,92] Cancer-associated fibroblasts can have immuno-suppressive and tumour-promoting functions that are enhanced by radiation.[93,94] IL1-driven inflammatory cancer-associated fibroblasts promote radioresistance of colorectal cancer, whereas the addition of the IL1RA inhibitor anakinra can reduce tumour size, invasiveness, and metastases in mice when combined with 2×5 Gy radiotherapy. These effects correspond with increased $CD8^+$ T-cell infiltration and reduced collagen deposition.[95]

Dendritic cells are key antigen-presenting cells capable of cross-presentation and activation of $CD8^+$ T cells.[96] Dendritic cell maturation is required for $CD8^+$ T cells to respond to radiotherapy; when radiotherapy does not induce maturation, there is no CD8-dependent effect of radiotherapy.[97,98] Dendritic cells can be activated with polyinosinic-polycytidylic acid to enable a $CD8^+$ T-cell response.[97] The TYRO3–AXL–MERTK (TAM) family of receptors can be activated to suppress antigen-presenting cells.[99] Chronic antigen exposure from fractionated radiotherapy can promote T-cell exhaustion and T-regulatory cell infiltration. Compared with effector T cells, T-regulatory cells are less sensitive to radiation,[100] and T-regulatory cell depletion improves radiotherapy efficacy in mice.[101] Thus, drugs that preferentially promote proliferation of effector T cells over T-regulatory cells, such as bempegaldesleukin (NKTR-214; Nektar Therapeutics, San Francisco, CA, USA),[102] might be useful in moderating one of the potential negative effects of radiotherapy, the ratio of effector T cells to T-regulatory cells. Like cancer-associated fibroblasts, macrophages exhibit a range of functions that can change in response to radiation. Taking this range of functions into account, Akkari and colleagues[103] showed that the colony stimulating factor-1 receptor (CSF-1R) inhibitor sotuletinib (BLZ945; Novartis, Basel, Switzerland) can shift

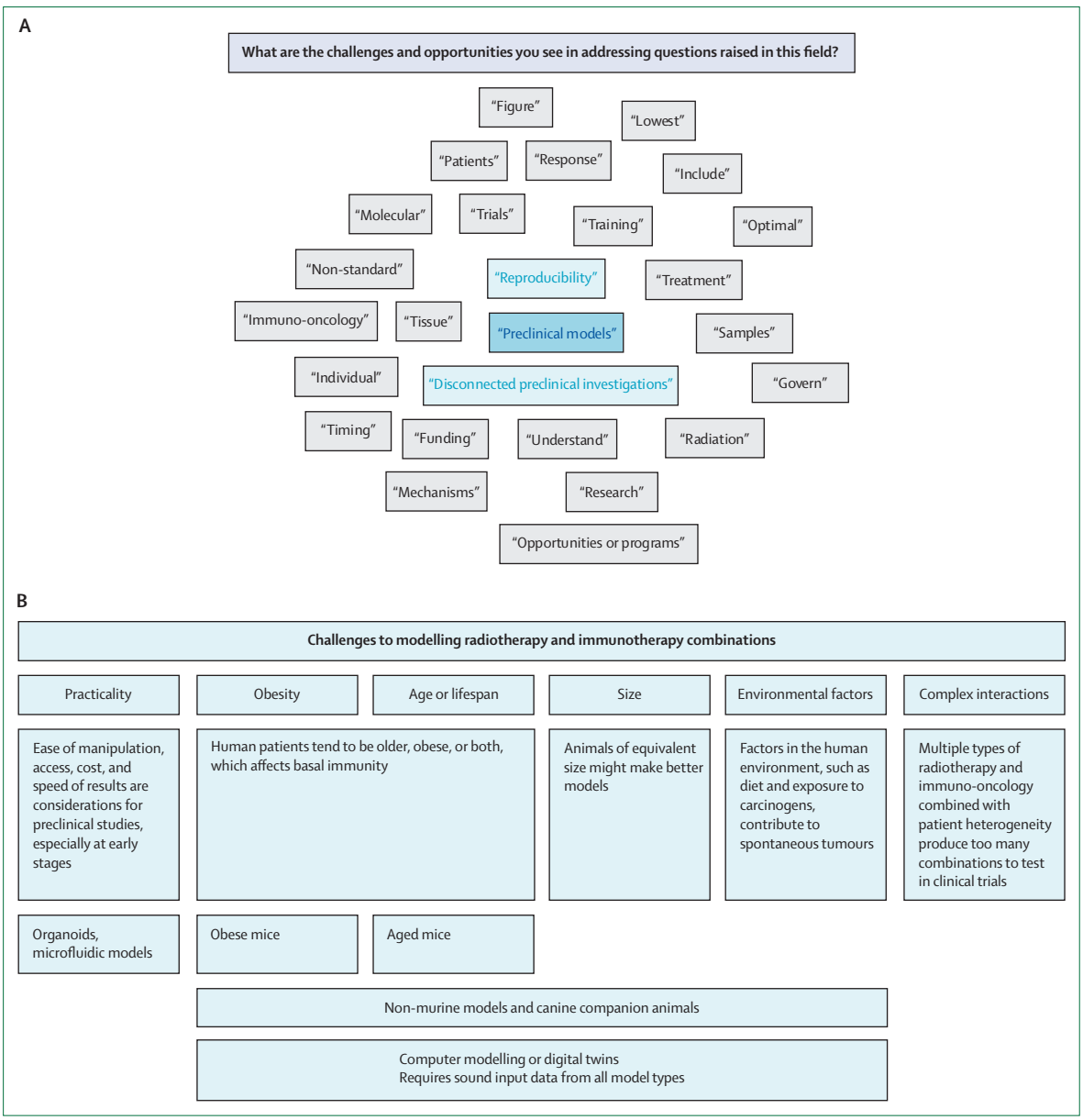

Figure 2: **Modelling radiotherapy and immunotherapy combinations**
(A) Word cloud highlighting audience replies when responding in real time to Slido poll questions focused on improving models. (B) Different models bring different strengths to preclinical research.

macrophage polarisation from the pro-tumourigenic M2 to the anti-tumourigenic M1 phenotype. When combined with radiation in mouse models of glioma, CSF-1R inhibition improves survival.[103] Finally, the immune-suppressive MDSCs can limit radiosensitivity, which can be restored by MDSC depletion or limiting MDSC suppressor functions and infiltration.[104,105]

Combining radiotherapy and immunotherapy requires balancing the risks of local, systemic, and regional recurrence. This need for balancing risks is seen when elective nodal irradiation, commonly used in head and neck squamous cell carcinoma (HNSCC) where there is a chance of occult nodal involvement, eradicates T-cell priming that occurs in the tumour-draining lymph node, hindering in-situ vaccination by radiotherapy and immunotherapy.[106] Preclinical murine models of melanoma suggest that delayed irradiation of tumour-draining lymph nodes could preserve the effects of ICIs that might normally be lost when combined with radiotherapy.[107]

The discussion which followed asked whether there was a synergistic interaction between radiotherapy and immunotherapy, namely a combined effect greater than either therapy's effect alone. Although 89% of respondents felt that there was a synergistic effect, 40%

	Short trial name	Phase	Cancer	Treatment	Major questions or observations
Theelen et al (2019)[109]	PEMBRO-RT	Phase 2	NSCLC	SABR (3 × 8 Gy) before pembrolizumab *vs* pembrolizumab alone	Is it more effective to add radiotherapy before immunotherapy? Can larger studies or improved patient selection detect effects on objective response rate in subpopulations?
Chang et al (2023)[110]	I-SABR	Phase 2	NSCLC	SABR with or without nivolumab within 30 min before or after first radiotherapy fraction	Concurrent ICI improves event-free survival when added to SABR
Spigel et al (2022)[49]	PACIFIC	Phase 3	NSCLC	Durvalumab following concurrent chemoradiation	Adjuvant ICI with chemoradiotherapy yielded significantly improved patient survival versus chemoradiation
Bradley et al (2019)[50]	PACIFIC-2	Phase 3	NSCLC	Concurrent durvalumab plus platinum-based chemotherapy and radiation	Concurrent plus adjuvant ICI with chemoradiation did not improve patient response, in contrast to the PACIFIC trial
NCT05401786	RAD-IO	Phase 2	NSCLC	Ipilimumab preceding SABR preceding cemiplimab	Can anti-PD1-refractory NSCLC be resensitised with anti-CTLA-4 and radiotherapy?
Palma et al (2020),[111] Palma et al (2019)[112]	SABR-COMET	Phase 2	Oligometastatic disease	Standard of care palliative radiotherapy *vs* standard of care plus SABR	Can SABR be safely used to treat oligometastatic disease? Found durable improvement of overall survival
Tsai et al (2024)[113]	CURB	Phase 2	Oligo-progressive metastatic breast cancer or NSCLC	Standard of care systemic therapy *vs* standard of care plus SABR	SABR improved response in lung cancer in treating oligometastatic disease but not breast cancer
Mattes et al (2021)[114]	NRG LU002	Phase2/3	Stage IV NSCLC	Standard of care systemic therapy that includes ICI *vs* standard of care plus SABR	Potential modest improvement with SABR but requiring further testing
Chmura et al (2022)[115]	NRG BR002	Phase 2/3	Metastatic breast cancer	Standard of care systemic therapy *vs* standard of care plus SABR	No improvement with SABR, but can that be changed with the addition of ICI?
NCT05846659	NA	Phase 2	Oligo-progressive solid tumours	IMSA101 (STING Agonist), ICI (pembrolizumab or nivolumab), PULSAR radiation	Novel combinations of ICI with new radiation techniques and other immunotherapy drugs (terminated early)
Fong et al (2021)[116]	NA	Phase 1	mCRPC	Atezolizumab (anti-PD-L1) + radium-223; varied sequencing	Can sequencing influence effectiveness of ICI plus radium-223? Does radium-223 alone stimulate immune response?
Marshall et al (2021)[117]	NA	Phase 2	mCRCP	Sipuleucel-T alone or with radium-223	Does combination of a radiopharmaceutical therapy with a novel immunotherapy agent improve efficacy?
Aggarwal et al (2023)[118]	NA	Phase 1b	mCRPC	^{177}Lu-PSMA-617 with maintenance ICI (pembrolizumab) either before, concurrent with, or after therapy	Can mild initial stimulation of immunity with a RPT (^{177}Lu-PSMA-617) improve immune response to ICI?
Lorusso et al (2024)[119]	KEYNOTE A-18	Phase 3	Advanced cervical cancer	Concurrent ICI (pembrolizumab) or placebo plus platinum-based chemoradiation	Concurrent ICI plus chemoradiation plus adjuvant ICI improved progression-free survival; contrasts with the PACIFIC-2 study
Tang et al (2017),[120] Welsh et al (2019)[121]	NA	Phase 1	Advanced solid tumours	SABR with ipilimumab	Progression-free survival differed based on which tissue site of metastasis was irradiated; followed up with immune correlates
Herrera et al (2022)[122]	RACIN	Phase 1	Advanced solid tumours	Nivolumab, ipilimumab, cyclophosphamide, low-dose radiation, and aspirin in patients with TIL-negative solid tumours	Low-dose radiation increased T-cell infiltration in responder patients
Bestvina et al (2022)[123]	COSINR	Phase 1	Stage IV NSCLC	Dual ICI (nivolumab and ipilimumab) plus sequential or concurrent multisite SABR	Identify safety and efficacy of different sequencing of SABR or ICI
Phillips et al (2020)[124]	ORIOLE	Phase 2	Oligometastatic prostate cancer	SABR to oligometastatic disease	Treatment of oligometastatic disease with SABR improves outcome and induces systemic immune response
Ost et al (2018)[125]	NA	Phase 2	mCSPC	Active surveillance *vs* surgery or SABR	Metastasis-directed therapy improves response
Iyengar et al (2018)[126]	NA	Phase 2	Stage IV NSCLC	Maintenance chemotherapy *vs* maintenance chemotherapy plus metastasis-directed SABR	Metastasis-directed therapy improves response
Tang et al (2020)[127]	NA	Phase 2	NSCLC	Metastasis-directed SABR *vs* maintenance therapy or observation	Liquid biomarker study to identify baseline or on-treatment predictors of response identified interleukin 1α
Tang et al (2021)[128]	NA	Phase 2	Oligometastatic renal cell carcinoma	SABR	Can SABR be used to defer systemic therapy?
Bauml et al (2019)[129]	NA	Phase 2	NSCLC	Pembrolizumab after locally ablative therapy	Longer progression-free survival, which was not associated with PD-L1 expression or CD8 T-cell tumour infiltration
Chen et al (2020)[130]	NA	NA	Metastatic NSCLC	Retrospective analysis of combined radiotherapy plus anti-CTLA-4 *vs* anti-PD-1	Both therapies provided improvement in outcomes, but anti-PD-1 had significantly better progression-free survival; retrospective analysis of combined radiotherapy plus anti-CTLA-4 *vs* anti-PD-1
Luke et al (2020)[25]	NA	Phase 1	Advanced solid tumours	SABR followed by pembrolizumab	Retrospective analysis of SABR-induced tumour gene expression as biomarker for tumour response to combined therapy
Parikh et al (2021)[131]	NA	Phase 1	MSS and MSI high colorectal and pancreatic cancer	Nivolumab and ipilimumab plus radiotherapy	Proof of concept for addition of radiotherapy to ICI in immunotherapy-resistant tumours

(Table continues on next page)

	Short trial name	Phase	Cancer	Treatment	Major questions or observations
(Continued from previous page)					
Shaverdian et al (2017)[132]	KEYNOTE-001	Phase 1	Solid tumours	Pembrolizumab	Secondary analysis in NSCLC identifying longer PFS and OS when patients received previous radiotherapy before pembrolizumab
Sundahl et al (2019)[133]	NA	Phase 2	Melanoma	Nivolumab plus SABR	Serial ctDNA analyses as follow-up, suggesting some patients only responded to nivolumab after SABR
McBride et al (2021)[134]	NA	Phase 2	HNSCC	Nivolumab *vs* SABR plus nivolumab	No benefit with addition of SABR; notably, nivolumab was started 14 days before SABR
Masini et al (2022)[135]	NIVES	Phase 2	Renal cell carcinoma	Nivolumab *vs* nivolumab plus SABR	No benefit with addition of SABR with few highly heterogenous patients
Segal et al (2021)[136]	NA	Phase 2	NSCLC and MSS colorectal cancer	Durvalumab and tremelimumab + 8 Gy × 3 or 0·5 Gy × 4	No benefit with the addition of hypofractionated or low-dose radiotherapy
Spaas et al (2023)[137]	CHEERS	Phase 2	Locally advanced or metastatic cancers	Standard of care ICI (nivolumab, pembrolizumab, or atezolizumab) with multisite stereotactic body radiation therapy (8 Gy × 3) *vs* ICI alone	No improvement in OS or PFS with addition of radiotherapy
Powles et al (2024)[83]	NIAGRA	Phase 3	MICB	Durvalumab and gemcitabine plus cisplatin *vs* gemcitabine plus cisplatin	Improved event-free survival and overall survival
Schmid et al (2024)[84]	KEYNOTE 522	Phase 3	Early-stage TNBC	Pembrolizumab plus chemotherapy *vs* chemotherapy (both neoadjuvant and adjuvant)	Improved pCR and event-free survival at long-term follow-up
Forde et al (2022)[85]	CHECKMATE 816	Phase 3	NSCLC	Nivolumab plus chemotherapy *vs* chemotherapy (neoadjuvant)	Neoadjuvant nivolumab plus chemotherapy improves event-free survival and pCR compared with chemotherapy alone
Chalabi et al (2024)[86]	NICHE-2	Phase 2	dMMR colon cancer	Neoadjuvant nivolumab plus ipilimumab	High proportion of pathological responses including pCR

dMMR=mismatch repair deficient. HNSCC=head and neck squamous cell carcinoma. ICI=immune checkpoint inhibition. mCRPC=metastatic castrate-resistant prostate cancer. mCSPC=metastatic castrate-sensitive prostate cancer. MICB=muscle-invasive bladder cancer. MSI=microsatellite instable. MSS=microsatellite stable. NA=not available. NSCLC=non-small-cell lung cancer. OS=overall survival. pCR=pathological complete response. PFS=progression-free survival. SABR=stereotactic ablative radiotherapy. TIL=tumour-infiltrating lymphocytes. TNBC=triple-negative breast cancer.

Table: **Clinical trials**

felt that evidence in humans was still lacking, and that this evidence was complicated by overgeneralising between different types of radiotherapy and immunotherapy. Nevertheless, most respondents felt that the preponderance of evidence suggests there was a positive effect to be exploited.

In summary, to optimise combinations of radiotherapy and immunotherapy, immunosuppressive effects of responses to radiation in the host and in the TIME must be managed.

The state of clinical translation

Despite abundant preclinical evidence of radiotherapy-induced immunogenicity, clinical translation is lagging,[87] in part due to difficulties in extrapolating findings regarding dose, timing, and fractionation from animal models to human patients who differ in many key aspects such as size, lifespan, environment, immune systems, diversity, and age. Additionally, no standardised guidelines exist for the irradiation of tumours in small animals. The use of different radiation protocols, fields, and equipment might increase discrepancies between studies and introduce potential artifacts. Most preclinical studies have used subcutaneous models, but the organ environment is emerging as important in shaping the response to ICIs.[108] Clinical research to dissect the immunological effects of radiotherapy as a standalone modality or in combination with immunotherapy is required to generate the fundamental human data necessary to interpret the effects of adding immunotherapy on irradiated tumours, normal tissue, and microbiome. This session addressed this challenge with three presentations from different clinical settings summarising results from completed trials and ongoing studies (table), highlighting the importance of treatment sequencing and potential of systemic effects, particularly in oligometastatic disease.

Secondary analyses of phase 1 trials investigating the safety of the combination of immunotherapies with radiotherapy done in advanced melanoma[138] and other tumour types[132,138] have shown higher response rates than for expectations based on historical data, suggesting a need for further study. Single-arm and randomised phase 2 trials, however, showed conflicting results regarding efficacy in multiple solid tumours.[109,133–137,139] The way these results conflict, however, has been enlightening. For example, the randomised PEMBRO-RT trial examining the addition of SBRT (3×8 Gy) to pembrolizumab in advanced NSCLC showed an increase in overall survival only in the PD-L1 negative subgroup with addition of radiotherapy, while showing only a non-significant trend towards improved objective response rates in the unselected group.[109] This trial delivered radiotherapy before the first course of immunotherapy, whereas, in a similar trial in patients with head and neck squamous cell carcinoma that did not replicate the

finding in the PD-L1-negative subgroup, radiotherapy was started after at least one course of immunotherapy,[134] suggesting sequencing, anatomical location, or disease histology could have a key role.

The importance of treatment sequencing in clinical trials has become increasingly evident. With sequencing in mind, efficacy of retreatment with anti-PD-1 (cemiplimab) therapy preceded by a single course of anti-CTLA-4 (ipilimumab) and SABR (3×8 Gy) is currently being investigated in anti-PD-1-refractory or anti-PD-1-resistant advanced NSCLC (NCT05401786). The phase 2 randomised I-SABR study showed that adding four doses of concurrent and adjuvant nivolumab to definitive SABR improved the event-free survival over SABR alone.[110]

Although ICIs with radiotherapy seem to yield outstanding clinical outcomes in early-stage and locally advanced NSCLC,[49,110] this strategy requires validation in other disease settings. Discussion identified an obvious barrier of reliable assessment of abscopal effects in single-arm studies of combined systemic immunotherapy and focal radiotherapy, without control groups of immunotherapy and radiotherapy only. To this end, in addition to reporting an objective in-field and out-of-field response, selection of clinically relevant endpoints, like time to progression and survival, is crucial.[140]

Workshop breakout session: define the opportunities and challenges for clinical translation of radiation–immunotherapy combinations

This virtual breakout session focused on defining opportunities and challenges for clinical translation of radiation–immunotherapy combinations. Online attendees identified converting tumours from immunologically cold to hot, biomarker identification and selection, dosing, timing, and addressing big data integration as essential questions. Challenges encompassed accessibility and affordability of treatments, reproducibility, optimal trial design and patient selection, funding sources, and the heterogeneity of response. Translating preclinical results to inform disease-specific trial designs has proven to be complex and prone to failure, and clinical trial design requires improved efficiency and accessibility for candidate patients. However, insufficient funding, prioritisation of practical considerations over immunological principles, and obstacles to data sharing hinder progress. To address these issues, the session proposed forming collaborative networks, rapid implementation of clinical trials, international collaborations, use of better animal models such as partnering with the canine veterinary oncology community, defining uniform standards for radiation studies including dosimetry, using real-world data, adapting to newer technologies, and enhancing public access to clinical trial data and data sharing. Additionally, clear definitions are lacking, particularly in terms of host immune fitness and response evaluation or endpoints, necessitating investment in biomarkers and imaging technologies.

Workshop attendees generally suggested a multifaceted approach. Sophisticated model systems such as organoids, patient-specific microfluidics models, paired tumour biopsies, and non-murine models can enhance our understanding and help to more accurately inform future clinical trial design. Harmonising data from ongoing and completed trials, including negative trials, and identification of more achievable endpoints is crucial. Biomarkers should test specific hypotheses regarding impacts on anti-tumour immunity. Future studies should validate and determine whether new biomarkers correlate with other tumour characteristics such as the amount of immune cell infiltration, tumour mutational burden, or homologous recombination status. Collaboration is key to building momentum around incremental progress, necessitating the creation of data warehouses and the use of federated learning and multi-institution networks. New opportunities exist for multidisciplinary collaboration to leverage artificial intelligence, multimodal data including spatial or single-cell multiomics, and standardised radiation oncology treatment planning software and dosimetry. Engaging experts from diverse fields will foster innovative solutions, helping to navigate the complexities of this evolving landscape and advance the field through future clinical investigations. Figure 3 illustrates the opportunities and future goals of combining radiotherapy and immunotherapy.

In summary, clinical translation from preclinical models and progress from phase 1 to successful phase 2 and phase 3 trials has produced mixed results for combinations of radiotherapy and immunotherapy, but much has been learned from these studies to guide future trial design.

Next-generation radiotherapy and immunotherapy combinations: new approaches and novel agents

This session addressed the many limitations of clinical trials in the context of developing radiotherapy and immunotherapy combinations. Most testing has been in combinations of SABR with either anti-PD-1, anti-PD-L1, or anti-CTLA-4. Novel approaches that require additional testing include cell-based therapies and different forms of checkpoint blockade or different modes of radiotherapy, such as radiotherapy to multiple sites, heterogeneous dose radiation, or radiopharmaceuticals. The main challenges include designing clinical trials with these combinations that identify the best sequence of therapies and provide a parallel information stream by examining potential biomarkers that can inform subsequent trials.

Improvement of patient outcomes requires standards of biological evidence and biomarkers that can show and

predict benefit from new combinations to optimise potential interaction between local radiotherapy and the immune system. These trials must consider dose, fractionation, timing, and target organs. These considerations are exemplified in an NSCLC randomised clinical trial that combined ICIs (nivolumab plus ipilimumab) with multisite SABR, collecting matched biopsies for before and after treatment.[141] ICIs were given either concurrently with SABR or 1 week after. An important highlight of the results was the finding that concurrent therapy particularly benefited a subset of patients with high, immunosuppressive aneuploidy, thus emphasising the value of thoughtful clinical trial designs, parameters for patient selection, and post-trial analyses.

Among other approaches to radiotherapy are radiopharmaceuticals, designed to deliver radiation directly to all tumour sites. An as-yet unanswered question in the field is the extent to which radiopharmaceutical therapy can initiate an immune response such as that seen with other forms of radiotherapy and how that varies based on type, timing, and tissue target. Addressing these questions were a set of clinical trials using radium-223 or ^{177}Lu-PSMA-617. Radium-223 was paired with PD-1 blockade in metastatic castration-resistant prostate cancer, which is refractory to PD-1 inhibition. Notably, with higher toxicity than either drug alone and no objective clinical response detected, this treatment was not recommended.[116] There were only minimal changes in immune markers post-treatment, and radium-223 alone did not substantially change immunomodulation. Adjustments to the treatment schedule provided little further improvement. However, pairing radium-223 with a different type of immunotherapy, the cellular vaccine sipuleucel-T, produced longer progression-free survival than sipuleucel-T alone.[117] Another combination of radiopharmaceutical therapy with immunotherapy paired a single priming dose of ^{177}Lu-PSMA-617 with maintenance ICI (pembrolizumab) either preceding, concurrent with, or after therapy, yielding an objective response rate of 56%, with responders characterised by higher frequencies of CD8$^+$ effector T cells, γδT cells, and natural killer cells after therapy.[118] This result highlights a major point of discussion, namely that testing of combination therapies must examine a variety of potential variables and that, although ICIs are an approved and commonly used treatment, they are not always the best choice, and additional types of immunotherapy must be considered to push clinical results further.

This session and the discussions that followed also provided emphasis on paradigms that included careful comparison of immunotherapies, such as blockade of PD-1, PD-L1, and CTLA-4,[130] and the new classes of immunotherapy such as the anti-TIGIT, LAG3, and TIM3 checkpoints; GITR agonists; CCR8 inhibition; and others. Cell-based immunotherapies, although less well studied in combination with radiotherapy, will also require future investigation, since preclinical models have suggested benefit in their combination with radiotherapy. A mouse model of pancreatic cancer suggests that radiation can enhance chimeric antigen receptor (CAR)-T cell-mediated killing,[142] whereas another study suggested combining natural killer-cell-enhancing C3a agonists with radiotherapy might improve survival.[143] A preclinical mouse model of melanoma and neuroblastoma showed improved CAR-T-cell activation against tumour cells when combined with

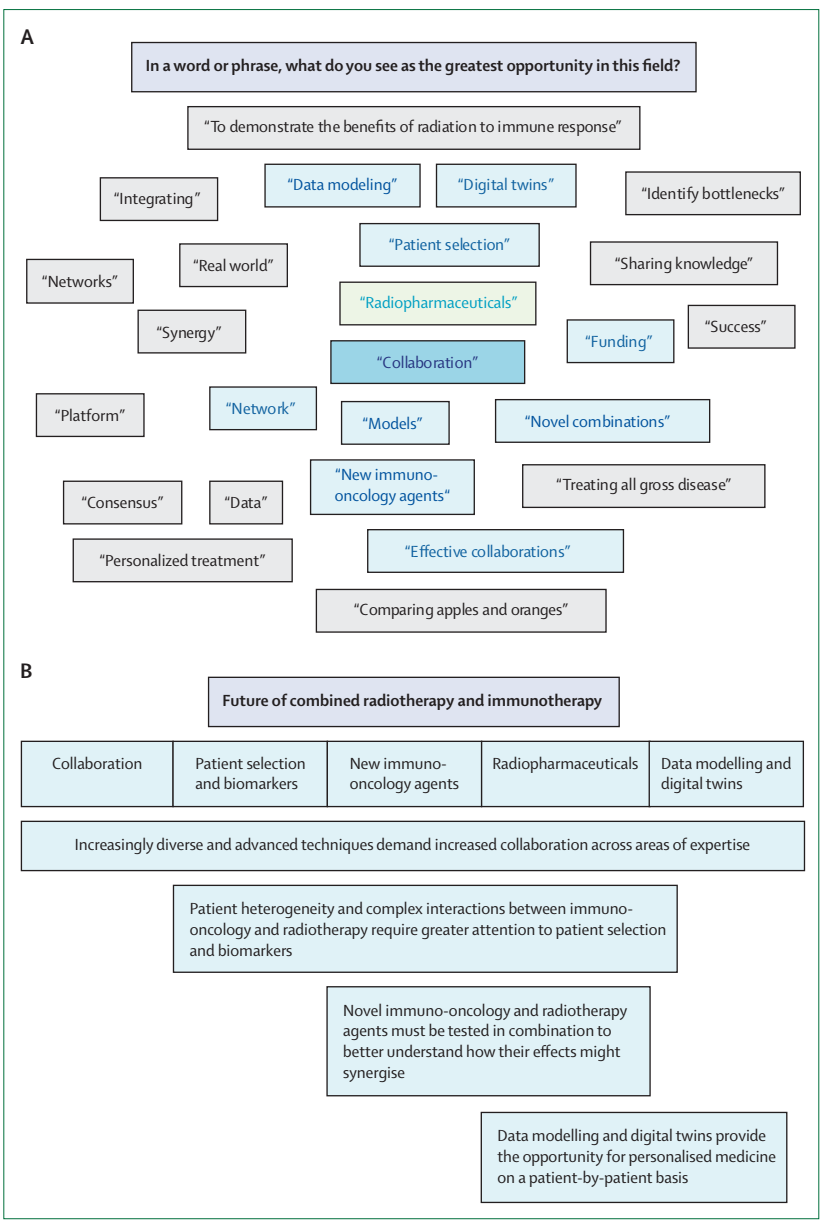

Figure 3: **The opportunities and future for combined radiotherapy and immunotherapy**
(A) Word cloud depicting most used words and phrases used by attendees responding in real time to Slido poll questions regarding the greatest opportunities in the field. (B) Many opportunities are available to explore the future of combined radiotherapy and immunotherapy, with collaboration an essential component required to access diverse tools necessary to implement new paradigms.

^{177}Lu- or ^{225}Ac-based radiopharmaceutical therapy.[144] Furthermore, engineered T cells can be used to deliver a deadly radioactive payload to the tumour with the goal of improving the anti-tumour efficacy of CAR T cells and T-cell receptor (TCR)-T-cell therapy. A preclinical study using CD19 CAR T cells expressing a DOTA antibody reporter suitable for labelling with imaging or therapeutic radionuclides showed that these engineered T cells preferentially accumulated α-emitting radionuclides (^{225}Ac) at tumour sites, thus increasing therapeutic potency.[145] In the clinic, bridge therapies that include radiotherapy for large B-cell lymphoma before CAR T-cell therapy improve overall survival and are equally effective at a low dose,[146] but further work is required to establish to what extent this improvement is the result of synergistic effects of radiotherapy combined with cell therapy. Exploration of therapies combining radiotherapy and immunotherapy with new additional mechanisms, such as DNA damage response inactivation and senolytics, should not be ignored. Patient characteristics were also deemed an important consideration. Given that cancer is age-related, and the immune system's

***Panel 2:* Studies proposed by multidisciplinary teams of conference attendees**

When asked to describe the study they would design (preclinical or clinical) to address the most important opportunity or challenge in the clinical translation of radiation-immunotherapy combinations, attendees to the National Cancer Institute conference answered:

(1) Colorectal liver metastases and primary liver cancer where SBRT is standard of care, but the tumour immune microenvironment typically blunts response to immunotherapy

- Ablative stereotactic body radiation therapy (SBRT) avoiding nodal irradiation with or without anti-PD-1
- Obtain enough patients to generate meaningful data through a consortium trial accruing more than 150 patients and collection of sufficient tissue to identify correlates to design future trials

(2) HPV-negative head and neck cancer

- Examine multiple immunotherapies on an evolving basis (like the STAMPEDE trial [NCT00268476])
- Neoadjuvant immunotherapy in age-stratified patients, with adaptive trial groups in which those groups not performing well against the control can be dropped and new ones added
- Collection of sufficient blood, tissue, and imaging samples before and after radiotherapy, with detailed protocols for sample collection for future standardisation
- Parallel canine group and a database of results accessible to all researchers

(3) Design a trial optimised for biomarkers that are predictive of outcome

- Requires higher proportions of responders
- To generate higher responder numbers, use a three-group study providing either a large ablative dose or a smaller, side-by-side non-ablative dose in a basket trial of all cancer types
- Comprehensive evaluation of samples at baseline and after radiotherapy to define the immune effects of these different radiotherapy regimens to drive biomarker discovery on which to base future clinical trials

(4) Oligoprogressive non-small-cell lung cancer, which already receives immunotherapy as standard of care

- Trial groups would include SBRT (10 × 5 Gy) or personalised ultrafractionated stereotactic adaptive radiotherapy (known as PULSAR; 12 Gy × 3 pulses, 3 weeks apart) with or without a STING or TLR7/8 agonist
- Patients stratified by anatomic site (nodal *vs* bone metastases); progression-free survival as the primary endpoint
- Understand response in the context of pre-existing immune fitness, measured through influenza or COVID-19 vaccination (among non-vaccinated patients)
- Understand lesion-specific response by deriving correlatives such as aneuploidy score, PD-L1 expression, and a systemic immune inflammation index

(5) Localised rectal cancer

- Low-risk, localised rectal cancer would be treated with surgery alone as the control group, whereas locally advanced tumours would receive SBRT alone or SBRT with the anti-CTLA4 (botensilimab), with MRI-guided radiotherapy and endpoints of progression-free survival and organ preservation
- This study would collect extensive baseline and on-trial data that includes peripheral blood mononuclear cells, stool collection, and tumour biopsy, and has an advantage of a wide range of ages in which this cancer presents (20–70 years); thus, extensive data would be available to identify factors that influence response

(6) Bladder cancer, which is highly metastatic

- Model trial design of the study by James and colleagues, which examined addition of chemotherapy to the standard of care, radiotherapy[159]
- This adaptable trial would treat with the standard of care or chemoradiation, with the ability to modify the volume of irradiation (whole bladder or partial) and choose whether or not to treat lymph nodes
- As transurethral resection is standard of care, patients can be stratified by the results of this resection
- Biological correlates from serum samples and biopsies would be assessed before and after radiotherapy and after immunotherapy, and a separate canine group would be included

function declines with age, an understanding of the dynamics of T cell to tumour cell proportions and interactions is vital to fulfil combination therapy's potential.

In summary, the investigation of combination therapies should move beyond SBRT and ICIs to fully embrace the potential for synergy between varied forms of radiotherapy and immunotherapy.

Immunological and computational assessment of radiotherapy and immunotherapy interactions: state of the art in treatment effect assessment in digital twins

With many potential combinations of types of radiotherapy, timing, sequence, fractionation, dose, immunotherapies, and patient heterogeneity, to exhaustively evaluate all combinations in every cancer is beyond the practical capacity of clinical trials. Additionally, although biomarkers and multidimensional analyses are a necessity to make full use of trial data, clinical trials are largely designed to address patients whose results are in the average range. Addressing this dilemma are computational tools that model and simulate radiotherapy, immunotherapy, and patient variables, which might eventually power computational models capable of making treatment predictions for an individual patient. Modelling and simulation are promising paths for the design of clinical trials to narrow the dimensions that require testing. If clinical trial data can be used to generate a model, that model can then be used to guide further testing,[147] a process described by Bekker and colleagues in examining the influence of the balance of tumour cell number to immune cell number for predicting tumour escape.[148] These and other models depend heavily on the quality of data input and our ability to understand the underlying physical processes. These are major challenges, since data complexity and heterogeneity in how the data are collected complicate models, and standardisation in the medical field can be difficult.

To understand and quantify the impact of radiotherapy on the immune system, Clemens Grassberger and colleagues presented the most recent methods for simulating the dose to circulating lymphocytes, revealing dose rate as an important factor that could enable us to better understand dynamic changes in lymphocytes compared with point measurements to minimise depletion of circulating lymphocytes.[149–152] However, although the dose to circulating lymphocytes is a main factor, the dose to lymphocytes residing in lymphatics is emerging as possibly being more important for radiotherapy and immunotherapy combinations.[153–155] These types of models and understanding the underlying processes are essential to developing what could be a key future tool in oncology: digital twins.

Digital twins are "a set of virtual information constructs",[156] which are unique from a typical model system or simulation in that they are connected to a physical system—in this case, a patient. Input is dynamically updated in a bidirectional manner between the virtual construct and the patient. Predictive capability of the digital twin provides feedback to guide best treatment practices for individual patients.[156,157] Although radiation oncology is well positioned to build digital twins with its wealth of imaging, standardising data collection for collaboration is a major difficulty. Many other factors must be considered, including tolerance for error, acceptance by patients and the medical industry, practical burdens on patients for data generation, privacy and ethics questions, and quality and quantifiability of data. These must be addressed and translated into clinical trials that are actionable for individual patients, rather than an average of patients, producing a quantitative measure of response.[158]

In summary, mathematical and computational modelling techniques can help to address the wide variability among patients in the form of digital twins, and these approaches will be optimised if data quality and understanding of underlying physical processes are advanced.

Workshop session: describe the study you would design (preclinical or clinical) to address the most important opportunity or challenge in the clinical translation of radiation–immunotherapy combinations

The final workshop session asked seven teams to design a clinical trial to address the most important challenge in the clinical translation of combined radiotherapy and immunotherapy. Clinical trial design that addresses the varied needs outlined at the workshop was essential. Innovative trial designs were discussed, including basket trials, which enrol patients based on the presence of a specific biomarker to test a cancer therapy across multiple cancer types, or platform trials, which use a

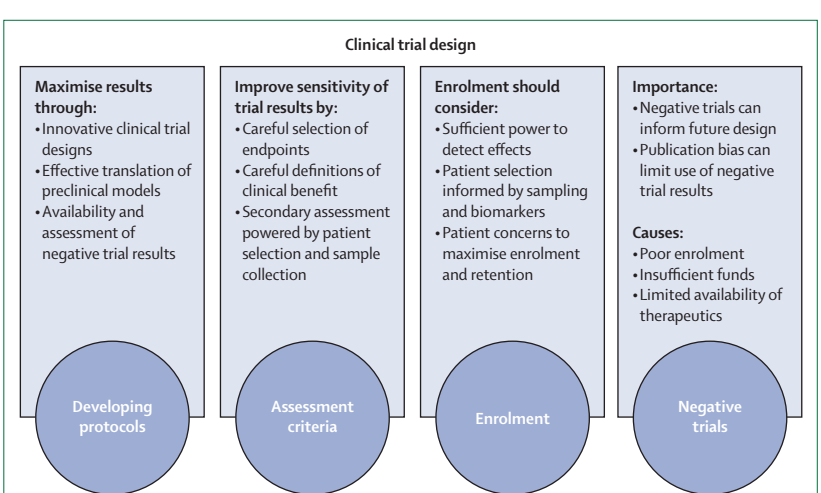

Figure 4: **Important considerations in clinical trial design**

Panel 3: Training, funding, and clinical research opportunities in the USA for investigators with a focus on the interface of radiotherapy and immunotherapies

Basic biology and preclinical studies by single or multiple investigators can be funded through investigator-initiated National Institutes of Health (NIH) R01 grants.[160] For cancer-related R01 applications that contain early-phase clinical trials, the National Cancer Institute's (NCI's) investigator-initiated early phase clinical trials for cancer treatment and diagnosis notice of funding opportunity should be used.[161] R01 grants are generally limited to a budget of US$500 000 direct costs per year. For the conduct of phase 3 clinical trials (and large phase 2 trials in which the sample size exceeds about 100 patients), the NCI funds the National Clinical Trials Network[162] and the NCI Clinical Oncology Research Program. Investigators from academic institutions and community practices are encouraged to join these networks and propose their research ideas to them. These networks offer a robust infrastructure that obviates the need for investigators to duplicate efforts across trials. Additional radiation-specific funding information can be found at the Radiation Research Program[163] and through the Radiation Oncology-Biology Integration Network (ROBIN) U54,[164] which focuses on radiotherapy and combined modality research concepts.

More specific or focused NIH funding opportunities can be found in the NIH guide for grants and contracts[165] and announcements for smaller grants such as R21 and R03 grants. There are also grants that are larger than R01s and contain multiple R01-sized projects and supporting cores. NCI's Program Project (or P01)[166] grants have a minimum of three research projects, an administrative core, and research support cores as needed. The research projects should be integrated such that the results from individual projects can influence and synergise with each other. Specialized Program of Research Excellence (or P50, SPORE) grants[167] have a minimum of three translational research projects with a human endpoint. A clinical trial is required. Projects can centre around a particular organ system or a biological mechanism. Budgets for P01 grants typically do not exceed $2 million total costs per year and SPORE grants do not exceed $1·4 million direct costs per year.

For more on the **NCI Clinical Oncology Research Program** see https://ncorp.cancer.gov/

Search strategy and selection criteria

The findings of this report were derived from presentations and discussion at the National Cancer Institute Workshop on combining immunotherapy with radiotherapy. Search and selection criteria were based on data presented therein. Literature searches were performed on PubMed and clinical trial records were accessed at ClinicalTrials.gov. Results in English were included from Nov 1, 1979, to June 29, 2024. PubMed search terms included, but were not limited to, combinations of radiotherapy-based terms such as "radiation", "radiotherapy", "radiation therapy", "EBRT", "SBRT", "SABR", "FLASH", "GRID", "LATTICE", "radiopharmaceutical therapy", "microbeam", and "minibeam", with search terms related to immuno-oncology including "immuno-oncology", "immunotherapy", "immune checkpoint inhibitor", "PD-1", "PD-L1", "CTLA-4", "sipuleucel-T", "CAR-T", and "tumor microenvironment", and any search terms required to confirm content of literature or findings cited by speakers at the workshop. The complete reference list was compiled based on originality, critical explanations for basic understanding of the foundation of the field, and relevance to the scope of the review.

single control group to test multiple interventions simultaneously with an adaptive trial design. Six in-person teams generated proposals (panel 2). The seventh group comprised virtual attendees who generated a ranked list of clinical trial ideas, with the most popular suggesting that a trial should include novel immunotherapy agents chosen based on radiotherapy and TIME markers. The second ranked study would involve a retrospective analysis of all patients from previous studies by a consortium of experts. Also receiving keen interest was the idea of studies involving the addition of dendritic cell activators, canine models, and radiopharmaceuticals. The proposed trials covered several cancers, and although addressed in different ways, each had common threads that emphasised monitoring of biomarkers with baseline, on-therapy, and post-therapy sample collection, and adaptability in treatment regimens as they expand on standard of care. Figure 4 summarises important considerations in clinical trial design.

The consensus was that clinical trials are needed that could more quickly move the field forward. Such trial designs require extensive biomarker data to guide future trials. Given this, trial proposal one (SBRT for colorectal liver metastases) and proposal three (basket trial) were highly favoured by the conference attendees.

Conclusions

The experts gathered at this meeting all shared a common goal: to bring the great potential of radiotherapy and immunotherapy as complementary therapies to fruition. A variety of novel approaches were proposed to overcome challenges presented by inadequate model systems, immunologically cold tumours, radiation-induced immunosuppression, and effective clinical trial design. The attendees clearly agreed that collaboration through multidisciplinary teams will be needed to address the many questions that remain with combining these treatment modalities, and a session was held to discussion opportunities for industry collaboration and funding (panels 1, 3). The consensus was that radiotherapy should be viewed as a set of diverse drugs with different efficacies and toxicities,[168] depending on radiotherapy dose regimens, tumour biology,[113] immune

status, disease stage, previous systemic therapy regimens, number of irradiated sites,[28] and individual patient immunological circumstances. The multidisciplinary approach enabled by conferences such as this *NCI–IOTN–SITC–AAI Workshop on Combining Immunotherapy with Radiotherapy* and related working groups will help address the diverse challenges surrounding radiotherapy and immunotherapy combinations to bring their potential benefits to patients.

Contributors

This Policy Review was conceived by ZSM, JDS, HE, SD, AMM, SCF, RRW, JW, AGS, SKh, MM, JDB, LF, JYC, HM, and AH. SCF, JDS, ATN, TAA, FH, RBP, CV-B, DS, SKh, HM, TJB, ZSM, MSK, LF, AMM, EHB, JD, and KHY wrote the original draft. TJB created the figures and tables. All authors reviewed and edited the Policy Review.

Declaration of interests

ZSM has served as a member of the scientific advisory board for Seneca Therapeutics, Archeus Technologies, NorthStar Medical Radioisotopes, and Cali Biomedical, as a consultant for Johnson & Johnson and Telix Pharmaceuticals, and has sponsored research agreements with Point Biopharmaceuticals and Telix Pharmaceuticals. He has received material support for research (drug reagents) from Bayer Pharmaceuticals, Bristol Myers Squibb (BMS), XRD Therapeutics, Seneca Therapeutics, AstraZeneca, HiberCell, Apeiron, Nektar Therapeutics, and Invenra. He is an inventor on patents held by the University of Wisconsin Alumni Research Foundation (Madison, WI, USA) related to select radiopharmaceutical therapies and related to combinations of radiotherapies with immunotherapies. AMM receives research support from Merck, Genentech, BMS, Transgene, Incyte, and the National Institutes of Health (NIH) via the National Cancer Institute (NCI) P30CA093373 and NCI (NIH) R01 CA240751; honoraria from the ANCO Association of Northern California Oncologists and MOASC *Medical Oncology Association of Southern California*; payment for expert testimony from Lewis-Brisbos and Bennett Bigelow & Leedom P S Law; and research materials from Incyte. MAH reports research support from Immune-Sensor and Novartis. LF reports research support in the institution from AbbVie, Bavarian Nordic, BMS, Dendreon, Janssen, Merck, Genentech (Roche); support as a consultant to Abbvie, Actym, Amgen, AstraZeneca, Atreca, Bioatla, Bolt, BMS, Crescendo, Daiichi Sankyo, Immunogenesis, Innovent, Merck, NGMBio, Nutcracker, RAPT Therapeutics, Senti, Sutro, and Genentech (Roche); and ownership interests in Actym, Atreca, Bioatla, Bolt, Immunogenesis, Nutcracker, RAPT, and Senti, unrelated to this Policy Review. HMM reports grants from NCI (NIH) and American Association for Cancer Research (AACR), and travel support from the Society for Immunotherapy of Cancer (SITC) to speak at this NCI–Immuno-Oncology Translational Network (IOTN)–SITC–American Association of Immunology (AAI) workshop. KHY reports grants from NCI (NIH); research support from BMS, Bicara Therapeutics, and Corbus Pharmaceuticals; and support as a consultant for Corbus Pharmaceuticals and Synthis Therapeutics. TAA receives research support from NCI (NIH; 5R01CA283953), Galera Therapeutic, Apexigen, and Canopy Cancer Collective; and licenses royalties and stock from Avelas Biosciences and AKSO Biopharmaceutical Biosciences. SKr has consulted for Telix Pharmaceuticals and acknowledges support for investigator services from RayzeBio; has patents PCT/US2021/039418 (THOR cell [tumour homing radioemitting cell]) and PCT/US2021/039420; and is supported by NIH R37 CA262557; Mr William H Goodwin, Mrs Alice Goodwin, the Commonwealth Foundation for Cancer Research, and The Center for Experimental Therapeutics of Memorial Sloan Kettering Cancer Center; and flexTDF Award. JYC reports research support from BMS, AstraZeneca, and Siemens; and serves as a clinical scientific committee member for Ion Beam Applications and consultant for AstraZeneca Global Oncology. MM declares research support from AstraZeneca, Merck Serono, BMS, Boehringer Ingelheim, Eli Lilly, and MSD, outside the submitted work. CK reports fellowship support from NCI (NIH) F30CA268780, NIH T32GM140935, a UW-Madison Radiology MD-PhD Graduate Student Fellowship, and travel support from the NCI (NIH) to speak at this NCI–IOTN–SITC–AAI workshop. CG reports research support from NCI (NIH; R21 CA248118 and P01 CA261669). JDS declares research support paid to their institution from Merck, BMS, Regeneron, Debiopharm, Seimens, and EMD Serono; consulting or participation on a scientific advisory board; travel fees and payments for lectures from Castle Biosciences, Genentech, Immunitas, Intragel, LEK, ACI Clinical, SIRPant, Merck KGA, and EMD Serono; expert witness fees from Burns and White; stock options from Immunitas and IntraGel; equity in Doximity; and has patent applications pending: Magea1 immunogenic peptides; binding proteins recognising Magea1 immunogenic peptides, and uses thereof; and nanobody bioconjugation for immune receptor targeting. JW served on the scientific advisory board for Novocure; scientific advisory board and consulting fees from Accuray, Boehringer Ingelheim, China Medical Tribune, Genentech, GI Innovation, Kezar Life Sciences, Legion Healthcare Partners, Life Science Dynamic, McKesson, Nanorobotix, Roche, and Roche Molecular Systems; SAB, consulting, and equity from Alpine Immune Science and Checkmate Pharmaceuticals; equity from Molecular Match; is a founder of OligoImmune; research grant, travel expenses, and scientific advisory board from Nanobiotix; research grants from BMS, Merck, Hotspot Therapeutics, Gilead, Bayer Healthcare, Kiromic, Artidis, Sciclone, Takeda, and Pebble Life Science; research grant, travel expenses, and clinical sponsored research from Varian; research grant, travel expenses, stock options, and scientific advisory board from Reflexion; scientific advisory board and stock options from Oncoresponse; has a research grant and is a consultant for AstraZeneca; and a research grant and scientific advisory board from Alkermes. RBP is funded by an NIH R01 and K08 grant related to radiation immunotherapy combination, has had travel reimbursed for invited talks on radiation immunotherapy combination, and has two patents with the Wisconsin Alumni Research Foundation related to this topic. SD declares consulting fees and serving on the scientific advisory board for Johnson & Johnson; institutional grants from Boheringer-Ingelheim, NCI, STARR Foundation, Breast Cancer Research Foundation, and Department of Defense; was on the data safety monitoring board for Le Centre hospitalier universitaire Vaudois (CHUV) and Department of Oncology Center for Experimental Therapeutics, University of Lausanne, Switzerland for trial CHUV-DO-0009-CyberImmunoBreast-2017; is on the scientific advisory board for Lytix Biopharma; and is the chair of the AACR Cancer Immunology Working Group. HE declares grant support from NCI (NIH) U01CA244100 and U01CA280849; holds US patents (10/301,793, 17642758 [provisional], and 63/010,327 [provisional]); and was Vice President and President for the Society for Mathematical Biology. LV received a National Institute of Health (NIH) grant (3R01CA240751-01A1S1). EHB received a grant from the NIH. RRW received grants or contracts from Varian and Regeneron; participated on a data safety monitoring board or advisory board for Aettis, AstraZeneca, Coordination Pharmaceuticals, Genus, Merck Serono SA, Nano Proteagen, NKGen Biotech, Shuttle Pharmaceuticals, Highlight Therapeutics SL, and Aqualung Therapeutics); and has stock or stock options for Boost Therapeutics, Immvira, Reflexion Pharmaceuticals, Coordination Pharm, Magi Therapeutics, Oncosenescence, Aqualung Therapeutics, Cyntegron, and PersonaDX. SKh received laboratory funding from NCI. JD received a one-time consulting fee from ViewRay. AGS received grants from the NIH and a sponsored research agreement from Celcuity. SCF received grants or contracts from BMS, Varian, Regeneron, Merck, and Eli Lilly; consulting fees and payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from BMS, Varian, ViewRay, Elekta, Regeneron, Eisai, AstraZeneca, Merck US, EMD Serono, Genentech (Roche), Accuray, Nanobiotix, EmBioSys, and Boehringer Ingelheim; has a leadership or fiduciary role in other boards, societies, committees, or advocacy groups, paid or unpaid for the American Association for Cancer Research, American Italian Cancer Foundation, and Society for Immunotherapy of Cancer. IMO received NIH travel support to attend meetings and workshops at the NIH. All other authors declare no competing interests.

Acknowledgments

We thank the NCI, IOTN, SITC, and AAI for generously funding the workshop. We acknowledge funding support from IOTN grants to AGS

(U01DE028233), ZSM (U01CA233102), LF (U01CA244452 and U01CA233100), and AH (U24CA232979). We thank Connie Sommers and Bhadrasain Vikram from the NCI for input on NCI funding opportunities and helpful discussions. We thank Charles Drake (Janssen, Johnson & Johnson Innovative Medicine), Kiran Devisetty (Interventional Oncology, Johnson & Johnson, New Brunswick, NJ, USA), and Kwame Twumasi-Boateng (Telix Pharmaceuticals, North Melbourne, VIC Australia) for their valuable insights on industry partnerships in panel 1.

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