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Updates on radiotherapy-immunotherapy combinations: Proceedings of 8th Annual ImmunoRad Conference

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ABSTRACT

The annual ImmunoRad Conference has established itself as a recurrent occasion to explore the possibility of combining radiation therapy (RT) and immunotherapy (IT) for clinical cancer management. Bringing together a number of preclinical and clinical leaders in the fields of radiation oncology, immuno-oncology and IT, this annual event fosters indeed essential conversations and fruitful exchanges on how to address existing challenges to expand the therapeutic value of RT-IT combinations. The 8th edition of the ImmunoRad Conference, which has been held in October 2024 at the Weill Cornell Medical College of New York City, highlighted exciting preclinical and clinical advances at the interface between RT and IT, setting the stage for extra progress toward extended benefits for patients with an increasing variety of tumor types. Here, we critically summarize the lines of investigation that have been discussed at the occasion of the 8th Annual ImmunoRad Conference.

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Introduction

Over the past decade, considerable efforts have been dedicated to the development of safe and effective combinatorial regimens involving radiation therapy (RT) and immunotherapy (IT) for clinical cancer management, building on the notion that – at least when employed according to specific dose and fractionation schedules, and when delivered focally to limited target volumes that do not involve tumor-draining lymph nodes (TDLNs) and/or considerable amounts of circulating lymphocytes – RT can mediate robust immunostimulatory effects.[1–4] Importantly, while a few randomized clinical trials demonstrated that RT indeed can be safely and effectively combined with IT in specific oncological settings, *e.g.*, patients with stage III, unresectable non-small-cell lung carcinoma

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(NSCLC) receiving an immune checkpoint inhibitor (ICI) specific for CD274 (best known as PD-L1) after chemoradiotherapy,[5] many others failed to document any clinical benefit from the addition of ICIs to RT employed according to standard-of-care (SOC),[6–8] pointing to the existence of numerous obstacles against the widespread applicability of RT-IT combinations in the clinic.[1,9,10]

The ImmunoRad conference has been jointly established by Dr. Silvia Formenti from the Weill Cornell Medical College (New York, US) and Dr. Eric Deutsch from Gustave Roussy (Paris, France) in 2016, with the specific aim to understand the nature of – and hence ultimately circumvent – such obstacles, de facto fostering progress at the interface between RT and IT to achieve superior clinical outcome for an ever increasing number of patients with cancer. Since then, with the only exception of year 2020 as imposed by the COVID-19 pandemic,[11,12] the conference has been held annually, alternating between New York and Paris, attracting an ever wider and more diverse group of attendants.[13,14]

The 8th Annual ImmunoRad Conference has been held on October 3rd to 5th, 2024, at the Weill Cornell Medical College in New York City, continuing such a tradition of excellence. This year, the conference welcomed no less than 430 participants from over 19 different countries worldwide and featured more than 30 thought-provoking presentations from established and emergent scientists working on RT-IT combinations, encompassing an opening Keynote lecture from Dr. Laurence Zitvogel (Gustave Roussy), 4 lectures delivered as part of a CME-accredited primer on the ability of RT to alter the immunological tumor microenvironment (TME) plus 21 main talks, 4 short talks selected from abstracts, as well as a closing panel discussion with 4 panelists from industry. Alongside, the event hosted more than 25 poster presentations by trainees and young researchers cultivating an interest in the possibility to achieve superior therapeutic outcomes by combining RT and IT. Following up on previous editions of the event, outstanding contributions from young investigators in the fields were recognized with travel awards and poster prizes. The conference program incorporated discussions on tumor–host interactions, predictive biomarkers for patient stratification, and innovative clinical trial design, overall providing an interactive platform for sharing new knowledge and fostering promising research and clinical collaborations. For how the ImmunoRad Conference is built, all attendees enjoyed the chance to directly engage with key opinion leaders, facilitating in-depth discussions on the most pressing challenges and opportunities in RT-IT combinations.

Here, we report on the main topics that have been discussed at the occasion of the 8th Annual ImmunoRad Conference in New York City as we set the stage for the 9th installment of this exciting event, which will be held in Paris, on September 17th to 19th, 2025.

The dirty secrets of radiation oncology

As part of the opening Keynote lecture, Prof. Laurence Zitvogel (Gustave Roussy) provided critical insights into the influence of the gut microbiota – i.e., the bacterial, viral and fungal communities populating the intestinal tract[15] – on RT and IT outcomes in patients with cancer.[16–18] Over the past decade, pivotal work from Dr. Zitvogel and others underscored indeed the critical impact of the gut microbiome on the systemic immune set point, affecting the sensitivity of various tumor types to various therapeutic interventions.[19–22] In this context, microbiota-targeting strategies such as fecal microbiota transplantation (FMT) and probiotics were highlighted as effective approaches to overcome treatment resistance and improve disease outcome.[23–26] Moreover, Dr. Zitvogel presented compelling evidence supporting the value of intestinal low-dose radiotherapy (ILDR) as a combinatorial partner for stereotactic body radiotherapy (SBRT) and ICIs in metastatic pancreatic ductal adenocarcinoma (PDAC).[27] Mechanistically, ILDR appears indeed to elicit immunogenic changes in the gut microbiome that result in a reduced development of gut-derived regulatory T (T_{REG}) cells and improved tumor infiltration by non-exhausted $CD8^+$ T cells.[27] These findings point to ILDR as to safe and effective strategy to modulate the gut microbiome in support of superior disease outcome in patients with cancer receiving RT-IT combinations.

Radiation therapy-induced modulation of the tumor immune microenvironment

The first main session of the 8th annual Immunorad Conference was CME-accredited Primer on the capacity of RT to influence the TME.

Dr. James W. Welsh (MD Anderson Cancer Center) discussed strategies to overcome resistance to IT in patients with cancer through the so-called "radscopal effect", i.e., the ability of low-dose RT (LDRT) to reprogram the TME in favor of tumor-targeting immune responses.[28,29] In this context, Dr. Welsh emphasized the importance of optimizing radiation doses to activate specific immune cell populations, notable natural killer (NK) cells with low-dose radiation and $CD8^+$ cytotoxic T lymphocytes (CTLs) with high-dose RT (HDRT). Moreover, he presented data supporting the notion that a beneficial increase in the intratumoral CTL/T_{REG} cell ratio requires the early administration of pembrolizumab, an ICI specific for programmed cell death 1 (PDCD1, best known as PD-1), coupled with stereotactic body radiotherapy (SBRT) optionally along with functionalized hafnium oxide nanoparticles or C-C motif chemokine receptor 8 (CCR8)-targeting strategies.[30,31]

Dr. Fernanda G. Herrera (University of Lausanne) followed up on Dr. Welsh presentation by providing additional data on the promise of using LDRT as a strategy to recruit immune effector cells, notably $CD8^+$ CTLs, to the TME in support of superior therapeutic responses to ICIs.[32,33] Her team found that such an beneficial effect can be elicited by RT doses as low as one fraction of 1 Gy in preclinical models of ovarian cancer, resulting in improved intratumoral CTL/T_{REG} cell ratio and the local expression of pro-inflammatory cytokines and costimulatory molecules.[34] Alongside, Dr. Herrera presented results from the RACIM trial, which tested a combination of LDRT plus ICIs, cyclophosphamide and prostaglandin E synthase 2 (PTGES2, best known as COX2) inhibitors in patients with solid tumors exhibiting poor lymphocytic infiltration. In this clinical study, responders experienced an

increase in intratumoral $CD8^+$ CTLs, whereas the TME of non-responders appeared to promote the accumulation of macrophages, which are generally associated with local immunosuppression.[35] These findings highlight the clinical potential of LDRT as a strategy to optimize IT outcomes.

Dr. Eric Deutsch (Gustave Roussy) further explored the importance of RT dose in the context of RT-IT combinations. Indeed, while SBRT can effectively control tumor growth in a variety of settings, and (at least in some cases) elicit immunological alterations that can be harnessed with ICIs,[36] it cannot always be employed in a safe manner (for instance when target volumes are in the close proximity to an organ at risk). In the case of metastatic disease, LDRT may hence offer a complementary strategy to HDRT for lesions that are ineligible to the latter, resulting in superior systemic disease control in the context of IT with ICIs. Dr. Deutsch also emphasized the notion that spatially varied RT doses create considerable degrees of immune heterogeneity in the TME, with areas enriched in $CD8^+$ CTLs alongside regions abundantly infiltrated by with monocytes and neutrophils.[37] Importantly, targeting these immunosuppressive myeloid cell populations was shown to improve tumor control in preclinical models of colorectal and breast cancer, *de facto* compensating for the regional detrimental effects of heterogeneous RT doses.[37] In conclusion, the presentation by Dr. Deutsch reinstated the need for further research into optimal dosing, treatment intervals, and irradiation areas for improved therapeutic outcomes in patients receiving RT plus IT.[38]

Dr. Lorenzo Galluzzi (Weill Cornell Medical College) summarized an abundant preclinical and clinical literature demonstrating that – depending on a number of RT-related, cancer-related and host-related variables – RT can have both beneficial and detrimental effects on lymphocytes and their interactions with malignant cells, which has major implications for the development of effective RT-IT combination. To exemplify this concept, Dr. Galluzzi alluded to the fact that while circulating lymphocytes including T and B cells are highly sensitive to the cytotoxic effects of RT, intratumoral $CD8^+$ CTLs, especially tissue-resident $CD8^+$ T cells, persist upon RT in support of tumor-targeting immunity.[39] Moreover, he commented on the ability of low-dose total body irradiation (TBI) delivered before CAR T cell infusion to improve the therapeutic effects of the latter in preclinical models of leukemia and pancreatic cancer,[40,41] and presented unpublished results from his team demonstrating that hypofractionated RT in 3 doses of 10 Gy each prevents CDK4/6 inhibitors from eliciting the secretion of C-C motif chemokine ligand 2 (CCL2) in a uniquely translational model of HR^+ breast cancer,[42–45] thus impeding the recruitment of immunosuppressive γδ T cells to the TME. These data exemplify the highly context-dependent effects of RT on lymphocytes.

Radiation therapy and antigen presentation

Dr. Laura Santambrogio (Weill Cornell Medical College) discussed the critical role of the brain lymphatic system in maintaining homeostasis through meningeal lymphatics and deep cervical lymph nodes.[46,47] More specifically, she presented unpublished data demonstrating that disruptions in this drainage, whether through lymphatic ligation, cauterization, or ablation, result in metabolic stress and oxidative damage. Using state-of-the-art metabolomic approaches,[48] her team identified a shift from the NAD^+ salvage pathway to *de novo* synthesis, coupled with an increased flux through the pentose phosphate pathway and consequent glutathione neosynthesis, as major consequences of disruptions in the brain lymphatic system, culminating with markers of neurodegeneration including synaptic loss, disrupted neurogenesis, and protein aggregation. As emphasized by Dr. Santambrogio, these findings are highly relevant for patients with head and neck squamous cell carcinoma (HNSCC) receiving RT as the potential of the latter to impair lymphatic clearance may contribute to the development of neurodegenerative conditions like Alzheimer's disease. This research underscores the critical importance of preserving brain lymphatic function during cancer therapy to limit long-term neurological side effects.

Dr. Dörthe Schaue (David Geffen School of Medicine) discussed the connection between RT and antigen processing and presentation. RT is indeed known to promote antigen presentation by malignant cells via a number of mechanisms, including the upregulation of multiple components of the antigen presentation machinery (APM), generally culminating in increased cancer cell immunogenicity and visibility to $CD8^+$ CTLs.[49,50] However, malignant cells often acquire APM defects, most likely as a strategy to evade anticancer immunity,[51–53] which also prevents RT from stimulating $CD8^+$ CTL responses. Dr. Schaue noted that increased expression levels of APM components such as proteasome 20S subunit beta 8 (PSMB8, best known as LMP7) is critical for immunological tumor control, correlating with improved tumor infiltration by immune cells and superior overall survival across various cancer types,[54–57] pointing to LMP7 and the associated APM as potential therapeutic targets for the development of more effective RT-IT combinations.

Dr. Andrew Godkin (Cardiff University) went on to first discuss the ability of cyclophosphamide to modulate the immune response of solid tumors, based on findings from animal models of colorectal carcinoma (CRC) as well as human CRC samples, proposing cyclophosphamide as a potential combinatorial partner for RT. Specifically, he highlighted that low-dose cyclophosphamide effectively depletes intratumoral T_{REG} cells, as demonstrated in preclinical tumors models,[58,59] as well as in a clinical trial testing cyclophosphamide optionally in combination with a cancer vaccine in patients with metastatic CRC.[58] Previous findings support the notion that cyclophosphamide may also improve the interaction between RT and IT by depleting.[60] He also showed that cyclophosphamide can modulate the gut microbiome, resulting in further neoantigen recognition.[58]

Finally, he noted that high biologically effective doses (BEDs >100 Gy) of RT have been associated with immunosuppressive effects as illustrated by an elevated neutrophil-to-lymphocyte ratio (NLR) as a biomarker of worsened progression-free survival (PFS), and concluded by commenting on how RT can alter the nature of peptides presented by MHC molecules.

Immune inhibitory effects of radiation therapy

In the last session of Day 1, Dr. Nir Ben Chetrit (Weill Cornell Medical College) discussed the potential of reprogramming tumor-associated macrophages (TAMs) in combination with RT to improve disease outcome in cancer patients.[61] Using single-cell RNA sequencing (scRNAseq), he demonstrated that TAMs commonly found in breast cancer can either support immune effector cells (tumor-niche macrophages, TNMs) or suppress anticancer immunity (stromal-associated macrophages, SAMs), the latter contributing to poor disease outcomes and hence representing promising targets for novel immunotherapeutic interventions.[62] Dr. Ben Chetrit also presented results from macrophage reprogramming CRISPR screens in TAMs suggesting that inhibiting notch receptor 4 (NOTCH4) may constitute a valid approach to reprogram SAMs toward an immunostimulatory TNM-like phenotype, at least in preclinical models of breast and ovarian cancer.

Dr. Taha Merghoub (Weill Cornell Medical College) discussed the critical impact of intratumoral neutrophils on the efficacy of multiple (immuno)therapeutic anticancer agents, including RT. He explained that co-stimulatory molecules and ICIs not only promote the recruitment of neutrophils to the TME, but also activate effector mechanisms including the release of so-called "neutrophil extracellular traps" (NETs) and nitric oxide synthase 2 (NOS2)-dependent cytotoxicity.[63] This may be particularly relevant for tumors that evade immune recognition by adoptively transferred T cells by losing the expression of the antigenic target of the latter.[63] Dr. Merghoub also highlighted the considerable therapeutic challenges posed by tumor heterogeneity, which characterizes most (if not all) solid tumors,[64] and local immunosuppression,[65] calling for the development of combinatorial strategies targeting both malignant and immune TME components. Finally, he explored the potential of combining RT with immunostimulatory antibodies and ICIs, which (at least in some settings) rely on neutrophil function to maximize T cell responses. Such an approach stands out as a promising strategy to eradicate highly heterogeneous tumors that are resistant to conventional (immuno)therapeutics.

Dr. Dmitry I. Gabrilovich (AstraZeneca) closed Day 1 by discussing the dual role of myeloid cells in cancer sensitivity to RT and IT, emphasizing their two main functional states: classical (pro-inflammatory) and pathological (immunosuppressive).[61,66] He commented on the mechanisms through which TAMs and MDSCs contribute to tumor progression, metastasis, and resistance to (immuno)therapy, including the activation of transforming growth factor beta (TGF-β) and vascular endothelial growth factor (VEGF) signaling, the release of immunosuppressive factors such as interleukin 10 (IL10), as well as the remodeling of the tumor stroma via matrix metalloproteases (MMPs). Dr. Gabrilovich also discussed on the possibility of activating ferroptosis, a regulated form of cell death driven by oxidative stress and consequence lipid peroxidation, as a therapeutic strategy against cancer.[67,68] RT has been shown to elicit ferroptosis in malignant cells,[69] but whether ferroptosis potentiates or suppresses anticancer immunity remains a matter of debate.[70–72] Moreover, the ferroptotic death of intratumoral MDSCs and neutrophils potently suppresses anticancer immunity by $CD8^+$ CTLs,[73] suggesting that caution should be employed when developing ferroptosis-promoting strategies for cancer (immuno)therapy.

Oral presentations (day 2)

Day 2 started with two oral presentations that were selected from the pool of abstracts submitted to this edition of ImmunoRad.

Following up on a first oral communication by Anne-Gaëlle Goubet (University of Geneva), Donna Li (University of Wisconsin) presented her research on the role of NF-κB activation by RT-elicited DNA damage on anticancer immune responses.[74–76] Her unpublished results – originating from mice lacking a critical component of the canonical machinery for NF-κB signaling,[77] which results in impaired NF-κB responses to genotoxic stress – demonstrate that RT-driven NF-κB activation supports tumor infiltration by $CD8^+$ CTLs. Interestingly, such a beneficial reconfiguration of the TME was accompanied by the repolarization of TAMs toward an immunostimulatory state, as demonstrated by reduced colony stimulating factor 1 receptor (CSF1R) expression. These findings suggest that targeting the immunosuppressive receptor CSF1R may improve the susceptibility of some tumors to RT.

Rectal cancer as a model for studying RT-induced immune modulation

Dr. Encouse Golden (Weill Cornell Medical College) presented adenosine signaling as a significant obstacles to RT-driven anticancer immune responses.[78–81] RT favors indeed the accumulation of adenosine in TME, which mediates considerable immunosuppressive effects on both myeloid and lymphoid cells.[82] In line with this notion, blocking the extracellular enzyme that converts AMP into adenosine, namely 5'-nucleotidase ecto (NT5E, best known as CD73), has been shown to improve both local and distant tumor control by RT in preclinical models of various cancer types including CRC, alongside markers of response indicating improved tumor-targeting immunity.[82,83] These observations led to the initiation of clinical studies including PANTHER and ARC-9 testing potent dual adenosine receptor inhibitors (*e.g.*, etrumadenant) in combination with RT and/or ICIs and chemotherapy in patients with rectal cancer or metastatic CRC, respectively.[84,85] Preliminary results from these studies are promising. Two patients with rectal cancer who experienced a complete response to treatment were indeed presented by Dr. Golden, highlighting the potential of this specific RT-IT combination.

Dr. Alan A. Melcher (Institute of Cancer Research) next presented on the capacity of neoadjuvant RT for rectal cancer triggers immunological changes that resemble those elicited by viral infection, a beneficial situation commonly known as viral mimicry,[86,87] specifically in patients with pronounced responses to therapy.[88] He also highlighted the promise of using oncolytic virotherapy with T-Vec, a genetically engineered variant of herpes simplex virus (HSV-1),[89,90] as a strategy to kill malignant cells through immunogenic cell death (ICD),[91] resulting in a reshaped intratumoral TCR

repertoire in favor of highly active $CD8^+$ CTLs over their dysfunctional counterparts.[92,93] Finally, Dr. Melcher reported on yet another HSV-1-derived oncolytic virus, i.e., RP1. Similar to T-vec, RP1 could be favorably combined with PD-1 blockers in preclinical models of thyroid carcinoma and melanoma, resulting in superior tumor control along with a reconfiguration of the intratumoral T cell compartment toward the enrichment of ICI-sensitive pre-exhausted $CD8^+$ T cells.[94,95] Globally, these observations suggest that oncolytic viruses may inform strategies to improve the sensitivity of patients with cancer exhibiting limiting infiltration by $CD8^+$ CTLs to RT-IT combinations.

Dr. Kristina H. Young (Providence Cancer Institute) dissected the dual role of TGF-β signaling in rectal cancer development and sensitivity to treatment. Indeed, while TGF-β acts as a prominent oncosuppressive factor at early stage of rectal carcinogenesis,[96–98] it potently promotes immunoevasion and tumor progression at later stages of the disease.[98–100] Adding an extra layer of complexity, a number of nonmalignant components of the TME, notably cancer-associated fibroblasts (CAFs) can produce high levels of TGF-β, hence compensating for potential defects in TGF-β production by neoplastic cells.[101,102] A number of preclinical studies demonstrated that blocking TGF-β considerably improves local and distant tumor control by RT-IT combinations, alongside eliciting signs of superior anticancer immunity including a favorable increase in the intratumoral CTL/T_{REG} cell ratio.[103–107] In this context, Dr. Young highlighted the results of a Phase 2 trial testing neoadjuvant galunisertib (a small molecule inhibiting TGF-β signaling) with chemotherapy and RT to improve pathological complete response (pCR) rates in patients with locally advanced rectal cancer, demonstrating good tolerability and an overall response rate (ORR) of 32%.[108,109] That said, gene expression studies suggest that specific CRC subtypes including CMS3 and CMS4 might respond differently to RT plus TGF-β, raising the need for the development of personalized approaches to implement this specific RT-IT combination in patients with CRC.

Radiation therapy and immunotherapy in the management of solid tumors

Dr. Gaorav P. Gupta (University of North Carolina) discussed the potential of combining RT with ICIs for the treatment of early stage breast cancer. He emphasized that while RT can elicit immunostimulatory mechanisms including ICD activation and $CD8^+$ CTL recruitment, it can also promote immunosuppressive pathways including PD-L1 upregulation on the surface of malignant cells and T_{REG} recruitment to the TME.[1] Clinical trials enrolling women with triple-negative breast cancer (TNBC), such as PEARL and P-RAD, have shown that combining PD-L1 or PD-1 blockers with appropriate RT doses improves pCR rates, with cancer-related factors like MHC Class I expression levels influencing disease outcome.[110,111] The analysis of post-treatment samples from these clinical studies indicated that combining RT in 3 fractions of 8 Gy each with a PD-1 blocker stimulates immune responses in primary tumors and (at least in some patients) causes the regression of non-irradiated lymph nodes bearing metastatic disease. Dr. Gupta also noted that tumor biology, especially "cancer ecotypes" as defined by transcriptional profiles of the TME, may play a significant role in treatment response. In this context, optimizing RT dosing and delivery schedule with respect to ICIs stands out as a promising avenue to enhance efficacy in the context of acceptable toxicity.[112] Advances in digital pathology and spatial immune phenotyping are expected to assist the identification of biomarkers of response, ultimately leading to improved disease outcome in a number of oncological settings amenable to receive RT-IT combinations.[113]

Dr. Julien Sage (Stanford University) presented existing challenges for the treatment of small cell lung carcinoma (SCLC), a highly aggressive cancer associated with poor survival rates owing to its intrinsically metastatic and treatment-resistant nature.[114,115] Indeed, as most SCLCs are poorly infiltrated by $CD8^+$ CTLs and express reduced MHC Class I levels, ICIs targeting PD-1 or PD-L1 have provided only modest survival benefits to a limited number of patients with SCLC.[116] In this context, tarlatamab – a bispecific T-cell engager (BiTE) targeting delta-like canonical Notch ligand 3 (DLL3) – appears to holds some promise for improved treatment outcomes.[117] Dr. Sage also presented results from his team demonstrating that combining RT, a cornerstone in SCLC treatment, with inhibitors of the antiphagocytic ligand CD47 results in improved local and distant disease control along with improved macrophage-dependent anticancer immunity in preclinical models of SCLC.[118–120] Ongoing research focuses on optimizing RT dosing, exploring combinations with DLL3-targeting BiTEs, and identifying predictive biomarkers to overcome IT resistance and improve disease outcomes in patients with SCLC.

In continuation, Dr. Anna Wilkins (Institute of Cancer Research) discussed strategies to target the bladder TME to enhance RT sensitivity. More specifically, an association between an intratumoral enrichment of specific CAF populations and poor disease outcomes after RT, outlining that the most common CAF subpopulations found in bladder cancer that express high levels of podoplanin (PDPN), presumably independent of TGF-β signaling and immune exclusion.[121–123] Dr. Wilkins reinstated the promise of combining TGF-β inhibitors with RT to improve disease outcome across multiple cancer types, especially neoplasms characterized by an intense fibrotic response, by highlighting an abundant preclinical, preclinical[103–106] and clinical[108,109,124] literature. Moreover, she presented unpublished results demonstrating that RT-induced fibrosis can arise rapidly and independently of TGF-β via a lymphocyte-dependent mechanism that ultimately affects tumor infiltration by immune cells. In this setting, targeting PDPN may constitute an effective strategy to enhance therapeutic responses to RT in bladder cancer and other tumor types.

Role of radiotherapy and immunotherapy combinations in metastatic disease

Dr. Arta M. Monjazeb (UC Davis School of Medicine) reported on strategies combining RT with immunotherapeutic agents that extend beyond ICIs. First, he discussed

novel approaches focused on enhancing the immunostimulatory effects of RT as an *in situ* vaccine, including the intralesional delivery of recombinant IL2 to irradiated tumors, as currently investigated in preclinical settings as well as in the context of a clinical trial enrolling patients with metastatic NSCLC (NCT03224871). Strategies employing dendritic cell (DC)-activating immunotherapeutics were also discussed.[125] While RT *per se* may act indeed as *in situ* vaccine, exposing tumor-associated antigens and delivering potent immunostimulatory signals including type I interferon (IFN) via ICD induction,[126–128] the RT-driven activation of adaptive anticancer immunity strictly depends on DCs,[129,130] implying that boosting DC functions may enhance the immunostimulatory effects of RT. Such DC stimulators include CpG, a Toll-like receptor (TLR9) agonist that can be directly delivered to the tumor,[131–133] as well as epacadostat, an oral inhibitor of the immunosuppressive enzyme indoleamine 2,3-dioxygenase 1 (IDO1).[134,135] Dr. Monjazeb highlighted the ability of both CpG and epacadostat to increase the local and distant tumor control in preclinical tumor models, correlating with reduced levels of intratumoral T_{REG} cells and immunosuppressive MDSCs.[131,134,135] Results from a canine clinical trial lend further support to the validity of this approach to safely exacerbate the therapeutic activity of RT.[134] While these findings have already been translated into early-stage clinical trials with promising results, additional work is needed to fully elucidate the efficacy of DC-activating agents as combinatorial partners for RT.

Dr. Julie Constanzo (University of Montpellier) reported unpublished data on the ability of extracellular vesicles (EVs) released by cancer cells exposed to targeted radionuclide therapy (TRT) to promote beneficial immunological alterations of the TME that may be harnessed with ICIs.[136–138] Recent data suggest indeed that TRT may represent a powerful inducer of ICD, hence representing an optimal therapeutic partner for ICIs.[136,139,140] Her research demonstrates that mouse melanoma cells exposed to TRT *in vitro* release large EVs that can be used to elicit therapeutically relevant anticancer immune responses *in vivo* downstream of DC activation upon intratumoral administration. Dr. Constanzo went on to show that blocking EV release limits the anticancer activity of TRT, suggesting that EVs are crucial mediators of its immunostimulatory activity, hence representing potential targeting for the development of novel combinatorial partners thereof.

Dr. Sean Pitroda (University of Chicago) discussed the benefits of combining SBRT with dual PD-1 and cytotoxic T lymphocyte-associated protein 4 (CTLA4) blockade in patients with metastatic non-small cell lung carcinoma (NSCLC).[141] Such an approach resulted in improved T cell activation, increased TCR diversity and superior local and distant tumor control, *de facto* outperforming SBRT alone.[142] Of note, SBRT combined with dual PD-1 and CTLA4 blockade appeared particularly beneficial for patients bearing NSCLC with elevated degrees of aneuploidy, which typically correlates with immunosuppression and weaker responses to ICIs employed as standalone immunotherapeutics.[141,143] Ongoing research is focusing on understanding the mechanisms through which aneuploid cells evade anticancer immunosurveillance and refining strategies for best combining RT and ICIs in patients with NSCLC and other tumor types.

Cancer immunogenomics and RT

Dr. Timothy A. Chan (Cleveland Clinic) discussed the impact of genetic alterations and DNA repair defects on the efficacy of RT and IT in cancer. He explained that ICI sensitivity varies considerably across cancer types – for instance being high in melanoma and NSCLC, but limited in sarcoma and CRC – correlating with tumor mutation burden (TMB), neoantigen expression, and immunological features of the TME.[144–148] In this context, RT may enhance the sensitivity of some tumors to ICIs by reprogramming the TME toward an ICI-responsive status, although optimal biomarkers for combining RT and IT remain to be identified.[149] Importantly, clinical trials like NICHE-2 demonstrate the efficacy of neoadjuvant ICIs in patients with locally advanced CRC bearing defective mismatch repair (dMMR),[150] not only emphasizing the need for personalized treatment approaches to improve disease outcomes in response to IT, but also adding to an expanding literature revealing superior effects from neoadjuvant ICI administration.[151] Such a change in treatment paradigm may have profound implications for the development of effective RT-IT combinations.

Dr. Anguraj Sadanandam (Institute of Cancer Research) highlighted the critical importance of dissecting tumor heterogeneity for the development of effective cancer regimens, not only intratumorally, but also across distinct neoplastic lesions from the same patient, in both the spatial and temporal dimension.[64,152,153] Progress in this respect can only be achieved by state-of-the-art technologies that provide (spatial) single-cell resolution coupled with modern artificial intelligence/machine learning tools, ultimately enabling the integration of complex genomic, epigenomic, transcriptomic and proteomic spatial datasets from (whenever possible longitudinal) tissue samples.[154–156] Such a highly integrated approach may indeed offer critical insights toward the development of personalized treatment strategies. Dr. Sadanandam presented examples of molecular stratifications in CRCs and pancreatic neuroendocrine tumors, illustrating their profound therapeutic implications.[153,157,158] Ongoing research in this field aims at improving precision medicine through global collaborations and the development of public platforms with the goal of enhancing survival outcomes using biomarker-driven combination therapies.

Dr. Brian D. Brown (Icahn School of Medicine at Mount Sinai) concluded Day 2 by discussing the importance of the genetic factors that affect the TME in shaping tumor behavior and responses to therapy.[159] More specifically, he introduced Perturb-Map, a new technology that combines CRISPR screening with spatial proteomics and transcriptomics to study gene function in tissues, including the TME.[160,161] This method enabled Dr. Brown's team to identify genes including suppressor of cytokine signaling 1 (*Socs1*) and transforming growth factor beta receptor 2 (*Tgfbr2*) as critical determinants of tumor infiltration by $CD8^+$ CTLs in preclinical models of lung cancer,[160] as well as tumor-derived IL4 as a major driver

of resistance to PD-1 blockers in preclinical models of ovarian carcinoma.[162] This novel technology stands out as a powerful tool to identify novel determinants of resistance to RT-IT combinations.

Oral presentations (day 3)

Day 3 started with two oral presentations that were selected from the pool of abstracts submitted to this edition of ImmunoRad.

Dr. Sierra McDonald (University of North Carolina) presented the P-RAD clinical trial, a randomized phase II study testing neoadjuvant pembrolizumab with RT in patients with early-stage node-involved TNBC.[111] Preliminary results suggest that combining pembrolizumab with 3 RT fractions of 3 Gy or 9 Gy each not only causes a dose-dependent enrichment in transcriptional signatures associated with $CD8^+$ CTL functions, macrophage activation and inflammation, but also improves pCR rates compared to pembrolizumab alone. Unpublished data from a genetically engineered mouse model of TNBC mimicking the P-RAD study appear to recapitulate these effects and hence may assist the identification of determinants of response and resistance. Dr. McDonald concluded that combining RT with pembrolizumab as a neoadjuvant intervention holds potential for improving disease outcome in patients with early-stage TNBC eligible to surgery.

Dr. Erik Wennerberg (Institute of Cancer Research) discussed the role of ADP-ribosyltransferase 1 (ART1) in cancer immune evasion. Signaling via purinergic receptor P2× 7(P2RX7) as driven by extracellular ATP and NAD is indeed critical for optimal T cell fitness in the tumor microenvironment,[163,164] and ART1 expression by malignant cells actively interfere with such an immunostimulatory mechanism by promoting P2RX7 mono-ADP-ribosylation, a detrimental effect that is exacerbated when ADP-ribosyl cyclase CD38 is inhibited.[165] This is particularly relevant for RT-IT combinations – as demonstrated in NSCLC patients receiving SBRT plus a PD-L1 inhibitor[166] – because RT promotes ART1 upregulation in malignant cells. These findings point to ART1, CD38 and P2RX7 as potential targets to promote the efficacy of RT-IT combinations.

Novel approaches

Dr. Chandan Guha (Albert Einstein College of Medicine) presented the immunological consequences of carbon ion RT (CIRT).[167,168] Specifically, he provided unpublished evidence suggesting that CIRT productively jumpstarts the cancer-immunity cycle,[169] resulting in effective release of tumor-associated antigens, delivery of immunostimulatory cues to DCs and ultimately cross-priming of a therapeutically relevant tumor-targeting immune response. By scRNAseq, Dr. Guha's team demonstrated that while conventional RT promotes the expansion of immunosuppressive component 1, q subcomponent, and alpha polypeptide (C1QA)-expressing TAMs infiltrating mouse KPC pancreatic tumors, CIRT limits the abundance of $C1QA^+$ TAMs while increasing the expression of pro-inflammatory cytokines like C-X-C motif chemokine ligand 10 (CXCL10). Thus, CXCL10 secretion and the consequent reduction of $C1QA^+$ TAMs appear to underlie the immunostimulatory effects of CIRT, at least in preclinical models of pancreatic cancer.

Drs. Aisha Hasan (Johnson & Johnson, USA) discussed the evolving role of RT in the era of IT, particularly for the clinical management of NSCLC. She reinstated the ability of RT to act as an *in situ* vaccine, especially when combined with IT,[170] highlighting promising clinical results as obtained by combining SBRT with ICIs targeting CTLA4, PD-1 or PD-L1 in patients with NSCLC.[5,166,171,172] Finally, she commented on the potential for interventional oncology to promote the efficacy of RT in the context of reduced systemic toxicityfor instance, upon the intratumoral delivery of immunotherapeutics.[89,90]

Dr. Jalal Ahmed (Icahn School of Medicine at Mount Sinai) focused on the impact of DCs on CAR T cell therapy.[173,174] Successfully employing CAR T cells and other adoptively transferred lymphocytes for the management of solid neoplasms faces indeed considerable challenges, largely reflecting the harsh metabolic conditions that most characterize their TME.[80,173,175] At least in mouse tumor models, combining CAR T cell infusion with low-dose TBI has been shown promote disease control alongside improved CAR T cell expansion and (at least some degree of) cytotoxicity against antigen-loss cancer cell variants.[40,41] Moreover, recent preclinical data suggest that focal LDRT can support the therapeutic activity of CAR T cells by engaging endogenous $CD8^+$ CTLs upon DC-dependent crosspriming.[176] Ongoing research is focusing at the development of safe and effective strategies to combine RT with CAR T cells in eligible patients toward the rapid implementation of innovative clinical studies.

Panel discussion

Day 3 concluded with a panel discussion with four panelists from industry that was moderated by the conference Chairs Dr. Silvia Formenti (Weill Cornell Medical College) and Dr. Eric Deutsch (Gustave Roussy).

Dr. Philippe Szapary (Johnson & Johnson) highlighted the value of interventional oncology as a novel approach to achieve superior therapeutic efficacy in the context of limited systemic toxicity via the rational combination of intratumorally administered therapeutics such as oncolytic viruses or chemotherapy depots combined with systemic IT with ICIs. Specifically, he emphasized the promising potential of combining RT with investigational radioenhancing agents like JNJ-1900 (a functionalized hafnium oxide nanoparticles also known as NBTXR3) for the management of HNSCC and NSCLC.[30,31,177]

Dr. Howard Kaufman (Ankyra Therapeutics) introduced ANK-101, an aluminum hydroxide-anchored IL12 variant that exhibit superior retention within the TME upon intratumoral delivery, resulting not only in single agent activity across a variety of preclinical tumor models, but also in the activation of systemic immune responses effectively targeting distant tumors, especially in combination with otherwise inactive ICIs delivered systemically, pointing to ANK-101 as a promising agent for clinical development.[178]

Dr. Sébastien Paris (Nanobiotix) further commented on JNJ-1900, which – while initially conceived as a radioenhancer[179] – has turned out to considerably enhance the ability of focal RT to elicit anticancer immune responses with systemic outreach, at least in preclinical tumor models, prompting clinical development in patients with a variety of cancer eligible to irradiation.[180,181]

Dr. Dhan Chand (Agenus) discussed the promise of novel agents like botensilimab, a second generation CTLA4 inhibitor,[182,183] AGEN1423, a dual inhibitor of CD73 and TGF-β,[184] AGEN2373, an agonist of the immunostimulatory receptor TNF receptor superfamily member 9 (TNFRSF9, best known as CD137),[185–187] and AgenT-797, an allogenic cell therapy showing promising results in combination with RT.[188,189]

Concluding remarks

Dr. Formenti and Dr. Deutsch closed the meeting by emphasizing the importance of additional preclinical and clinical investigation for RT-IT combinations to be safely and successfully implemented into the clinical management of an increasing number of malignancies, as they recognized the progress that has been achieved over the past decade by the crosspollination between radiation oncology and clinical immunotherapy. The ImmunoRad Conference has considerably fostered such an advantageous interaction and will continue to do so at the Cordeliers Research Center in Paris, on September 17th to 19th 2025. You are all welcome to participate!

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BDB sits in the scientific advisory board (SAB) of Noetik. DC is a full-time employee of Agenus Inc. and holds equity in the company. DG is a full-time employee of AstraZeneca. EG declares research funding from Arcus Biosciences. CG sits in the data safety monitoring board (DSMB) for the Focused Ultrasound Foundation, is a co-founder of Bioconvergent Health and holds equity in the company. GPG declares funding from Merck, Breakpoint Therapeutics, the V Foundation, as well as ownership, intellectual property rights and royalties from Naveris Inc. AH is a full-time employee of Johnson & Johnson, hold stocks in the company, and declares royalties from Atara Biotherapeutics. FGH declares research funding from Accuray, Bioprotect, Bristol-Myers Squibb, Roche-ImFlame/ImCore, Nanobiotix, AstraZeneca, Eisai, MSD, Seagen, RaySearch Laboratories, as well as consultation fees, and travel expenses from Johnson & Johnson, Boehringer Ingelheim, Bristol-Myers Squibb, AstraZeneca, Eisai and Telix. 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