ONCOIMMUNOLOGY
2025, VOL. 14, NO. 1, 2432726
https://doi.org/10.1080/2162402X.2024.2432726

Taylor & Francis
Taylor & Francis Group

Pushing the boundaries of radiotherapy-immunotherapy combinations: highlights from the 7th immunorad conference

Pierre-Antoine Laurent[a,b], Fabrice André[c,d,e], Alexandre Bobard[f], Desiree Deandreis[g], Sandra Demaria[h,i,j], Stephane Depil[k,l], Stefan B. Eichmüller[m], Cristian Fernandez-Palomo[n], Floris Foijer[o], Lorenzo Galluzzi[h,j,p], Jérôme Galon[q,r], Matthias Guckenberger[s], Kevin J. Harrington[t], Fernanda G. Herrera[u,v,w], Peter E. Huber[x,y], Antoine Italiano[z,aa,bb], Sana D. Karam[cc,dd], Guido Kroemer[ee,ff,gg,hh], Philippe Lambin[ii,jj], Carola Leuschner[kk], Alberto Mantovani[ll,mm], Etienne Meylan[nn,oo,pp], Michele Mondini[b], Mikael J. Pittet[w,qq,rr,ss,tt], Jean-Pierre Pouget[uu], Jordi Remon[c], Claus S. Sørensen[vv], Christos Sotiriou[ww], Claire Vanpouille-Box[h,j], Ralph R. Weichselbaum[xx], James W. Welsh[kk], Laurence Zitvogel[yy,zz,aaa,bbb], Silvia C. Formenti[h,j], and Eric Deutsch[a,b,bbb,ccc]

[a]Department of Radiation Oncology, Gustave Roussy, Villejuif, France; [b]INSERM, U1030 "Molecular Radiotherapy and Therapeutic Innovations", Gustave Roussy, Villejuif, France; [c]Department of Medical Oncology, Gustave Roussy, Villejuif, France; [d]INSERM U981 "Molecular predictors and new targets in oncology", Gustave Roussy, Villejuif, France; [e]IHU PRISM Precision Medicine Cancer Center, Gustave Roussy, Villejuif, France; [f]SIRIC EpiCURE, Gustave Roussy, Villejuif, France; [g]Division of Nuclear Medicine, Gustave Roussy, Villejuif, France; [h]Department of Radiation Oncology, Weill Cornell Medicine, New-York, NY, USA; [i]Department of Pathology and Laboratory Medicine, Weill Cornell Medicine, New-York, NY, USA; [j]Sandra and Edward Meyer Cancer Center, New York, NY, USA; [k]Cancer Research Center of Lyon, Centre Léon Bérard, Université Claude Bernard, Lyon, France; [l]ErVimmune, Lyon, France; [m]Research Group GMP & T-cell therapy, Deutsches Krebsforschungszentrum (DKFZ), Heidelberg, Germany; [n]Institute of Anatomy, University of Bern, Bern, Switzerland; [o]European Research Institute for the Biology of Ageing, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands; [p]Caryl and Israel Englander Institute for Precision Medicine, New York, NY, USA; [q]INSERM, Laboratory of Integrative Cancer Immunology; Sorbonne Université; Sorbonne Paris Cité, Université de Paris, Paris, France; [r]Centre de Recherche des Cordeliers, Paris, France; [s]Department of Radiation Oncology, University Hospital Zurich, Zurich, Switzerland; [t]The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, National Institute of Health Research Biomedical Research Centre, London, UK; [u]Radiation Oncology Service, Department of Oncology, Lausanne University Hospital, Lausanne, Switzerland; [v]Immuno-oncology Service, Department of Oncology, Lausanne University Hospital, Lausanne, Switzerland; [w]Ludwig Institute for Cancer Research, University of Lausanne, Lausanne, Switzerland; [x]Department of Radio-oncology and Radiotherapy, University Hospital Heidelberg; Heidelberg Institute for Radiation Oncology (HIRO), Heidelberg, Germany; [y]Department of Molecular and Radiation Oncology, German Cancer Research Center (DKFZ), Heidelberg, Germany; [z]Department of therapeutic innovations (DITEP), Gustave Roussy, Villejuif, France; [aa]Department of Medicine, Institut Bergonié, Bordeaux, France; [bb]Faculty of Medicine, University of Bordeaux, Bordeaux, France; [cc]Department of Radiation Oncology, University of Colorado Anschutz Medical Campus, Aurora, CO, USA; [dd]Department of Immunology and Microbiology, University of Colorado Anschutz Medical Campus, Aurora, CO, USA; [ee]Centre de Recherche des Cordeliers, Université de Paris Cité, Sorbonne Université, Paris, France; [ff]Metabolomics and Cell Biology Platforms, Gustave Roussy, Villejuif, France; [gg]Department of Biology, Hôpital Européen Georges Pompidou AP-HP, Paris, France; [hh]Institut du Cancer Paris CARPEM, Paris, France; [ii]Department of Precision Medicine, GROW - Research Institute for Oncology and Reproduction, Maastricht University, Maastricht, the Netherlands; [jj]Department of Radiology and Nuclear Medicine, GROW - Research Institute for Oncology and Reproduction, Maastricht University Medical Centre+, Maastricht, the Netherlands; [kk]Department of Radiation Oncology, University of Texas MD Anderson Cancer Center, Houston, TX, USA; [ll]IRCCS Humanitas Research Hospital, Rozzano, MI, Italy; [mm]William Harvey Research Institute, Queen Mary University, London, UK; [nn]Laboratory of Immunobiology, Department of Molecular Biology, Faculty of Sciences, Université Libre de Bruxelles, Bruxelles, Belgium; [oo]Lung Cancer and Immuno-Oncology laboratory, Bordet Cancer Research Laboratories, Institut Jules Bordet, Hôpital Universitaire de Bruxelles, Faculty of Medicine, Université libre de Bruxelles, Bruxelles, Belgium; [pp]ULB Cancer Research Center (U-CRC) and ULB Center for Research in Immunology (U-CRI), Bruxelles, Belgium; [qq]Department of Pathology and Immunology, University of Geneva, Geneva, Switzerland; [rr]AGORA Cancer Research Center, Lausanne, Switzerland. Swiss Cancer Center Leman, Lausanne, Switzerland; [ss]Translational Research Center in Onco-Haematology (CRTOH), University of Geneva, Geneva, Switzerland; [tt]Department of Oncology, Geneva University Hospitals (HUG), Geneva, Switzerland; [uu]Institut de Recherche en Cancérologie de Montpellier (IRCM)INSERM U1194, Université de Montpellier, Institut régional du Cancer de Montpellier (ICM), Montpellier, France; [vv]Biotech Research and Innovation Centre, University of Copenhagen, Copenhagen, Denmark; [ww]Breast Cancer Translational Research Laboratory, Institut Jules Bordet, Hôpital Universitaire de Bruxelles (H. U.B), Université Libre de Bruxelles (ULB), Brussels, Belgium; [xx]Department of Radiation and Cellular Oncology, Ludwig Center for Metastasis Research; University of Chicago, Chicago, IL, USA; [yy]ClinicObiome, Gustave Roussy, Villejuif, France; [zz]INSERM U1015 "Tumor Immunology and Anti-Cancer Immunotherapy Unit", Gustave Roussy, Villejuif, France; [aaa]Center of Clinical Investigations in Biotherapies of Cancer (BIOTHERIS), Villejuif, France;

CONTACT Eric Deutsch eric.deutsch@gustaveroussy.fr Department of Radiation Oncology, Gustave Roussy, Villejuif, France;
Silvia C. Formenti formenti@med.cornell.edu Department of Radiation Oncology, Weill Cornell Medicine, New-York, NY 10065, USA

[bbb]Division of Medicine, Paris-Saclay University, Ile-de-France, France; [ccc]RHU LySAIRI "Lymphocyte-Sparing Artificial Intelligence-guided Radio-Immunotherapy", Gustave Roussy, Villejuif, France

ABSTRACT

Over the last decade, the annual Immunorad Conference, held under the joint auspicies of Gustave Roussy (Villejuif, France) and the Weill Cornell Medical College (New-York, USA) has aimed at exploring the latest advancements in the fields of tumor immunology and radiotherapy-immunotherapy combinations for the treatment of cancer. Gathering medical oncologists, radiation oncologists, physicians and researchers with esteemed expertise in these fields, the Immunorad Conference bridges the gap between preclinical outcomes and clinical opportunities. Thus, it paves a promising way toward optimizing radiotherapy-immunotherapy combinations and, from a broader perspective, improving therapeutic strategies for patients with cancer. Herein, we report on the topics developed by key-opinion leaders during the 7th Immunorad Conference held in Paris-Les Cordeliers (France) from September 27th to 29th 2023, and set the stage for the 8th edition of Immunorad which will be held at Weill Cornell Medical College (New-York, USA) in October 2024.

ARTICLE HISTORY
Received 25 July 2024
Revised 12 November 2024
Accepted 18 November 2024

KEYWORDS
Cancer; FLASH radiotherapy; immune checkpoint; immunorad; immunotherapy; low-dose radiotherapy; lymph-node sparing; radiotherapy; T cells; tumor-associated macrophages

Introduction

Exploring the immunological properties of radiotherapy (RT) within tumors, as well as the synergy of radiotherapy-immunotherapy combinations for the treatment of cancer has become increasingly important over the last decade. Since its inaugural edition in 2016, the Immunorad Conference, which is held annually under the joint auspicies of Gustave Roussy (Villejuif, France) and the Weill Cornell Medical College (New-York, USA), aims at describing the latest advances in this field, with a particular focus on bridging the gap between preclinical findings and clinical opportunities.

The 7th Immunorad Conference took place from September 27th to 29th 2023 at the Research Center of Paris-Les Cordeliers, France. Similar to previous editions, hundreds of participants attending the conference were able to receive insightful and thought-provoking presentations delivered by talented junior researchers as well as key-opinion leaders in the field of radiation oncology and tumor immunology. The active and engaging participation of attendees to discussions during and after presentations was remarkable, and it contributed to fueling the debate about the most promising therapeutic combinations for cancer treatment.

In this synopsis article, we outline the significant findings discussed at Immunorad 2023. The exploration of established biological paradigms, alongside emerging opportunities, paves the way for a promising future in radiotherapy-immunotherapy combinations.

I/When established players in the preclinical setting share the spotlight with potential new partners: insights from the bench

The Immunorad conference uniquely emphasizes the coexistence of preclinical and clinical topics in presentations delivered by a diverse array of speakers, ranging from clinicians to fundamental researchers. This year again, the highly-valued "bench-to-bedside" approach facilitated the attendees in expanding their individual horizons, providing each participant with insightful perspectives to translate into their respective fields of interest. Notably, in the preclinical context, the presentations of the 7th edition significantly enhanced the existing knowledge of established biological patterns in radiation-induced anti-tumor immunity. Moreover, they shed light on potential newcomers in this field. Therefore, considering both the established biological patterns and the potential newcomers is likely to optimize radiotherapy-immunotherpy combinations (Figure 1).

1/The enduring significance of established biological paradigms: shaping past, present and future advances in radiation and anti-tumor immunity research

As in the previous editions since 2017, the 2023 Immunorad Conference included an educational session. This special segment aimed to bridge the gap for non-specialists by inviting key opinion leaders in the field of radiation-induced anti-tumor immunity to share their groundbreaking contributions in an accessible manner.

Prof. Alberto Mantovani (Istituto Clinico Humanitas, Milan, Italy) provided a comprehensive overview of the pivotal role of myeloid cells within the tumor microenvironment. He further discussed how understanding these specific features opens avenues for anti-cancer immunotherapy by exploiting myeloid cells.[1]

Prof. Mikael Pittet (University of Geneva, Switzerland) widened the perspective by giving an overview of the prognostic information provided by tumor-associated macrophages (TAMs). Notably, the polarity of these cells, which can be captured by measuring the expression of CXCL9 and SPP1, is strongly associated with the clinical outcome of patients; it is also tightly linked to a network of pro- or antitumor activities involving each tumor-associated cell type, revealing the existence of coordinated responses that control human cancers.[2]

Prof. Guido Kroemer (Cordeliers Research Center, Paris, France), who is a pioneer in elucidating the revolutionary concept of immunological cell death (ICD) in cancer,[3,4] provided an update on the field. This presentation was the occasion to expose the recent breakthrough advances for the induction of ICD in tumors, including anthracycline-based chemotherapy[5,6] as well as some cytotoxic molecules (lurbinectedin,[7] ruxotemitide[8] or antibody-drug conjugates (ADC) (belantamab mafodotin).[9] Concurrently, efforts are directed toward overcoming the challenges posed by the heterogeneity and plasticity of tumor cells in inducing ICD. A specific focus is on enhancing ICD through the activation of conventional dendritic cells type 1 (cDC1). One promising

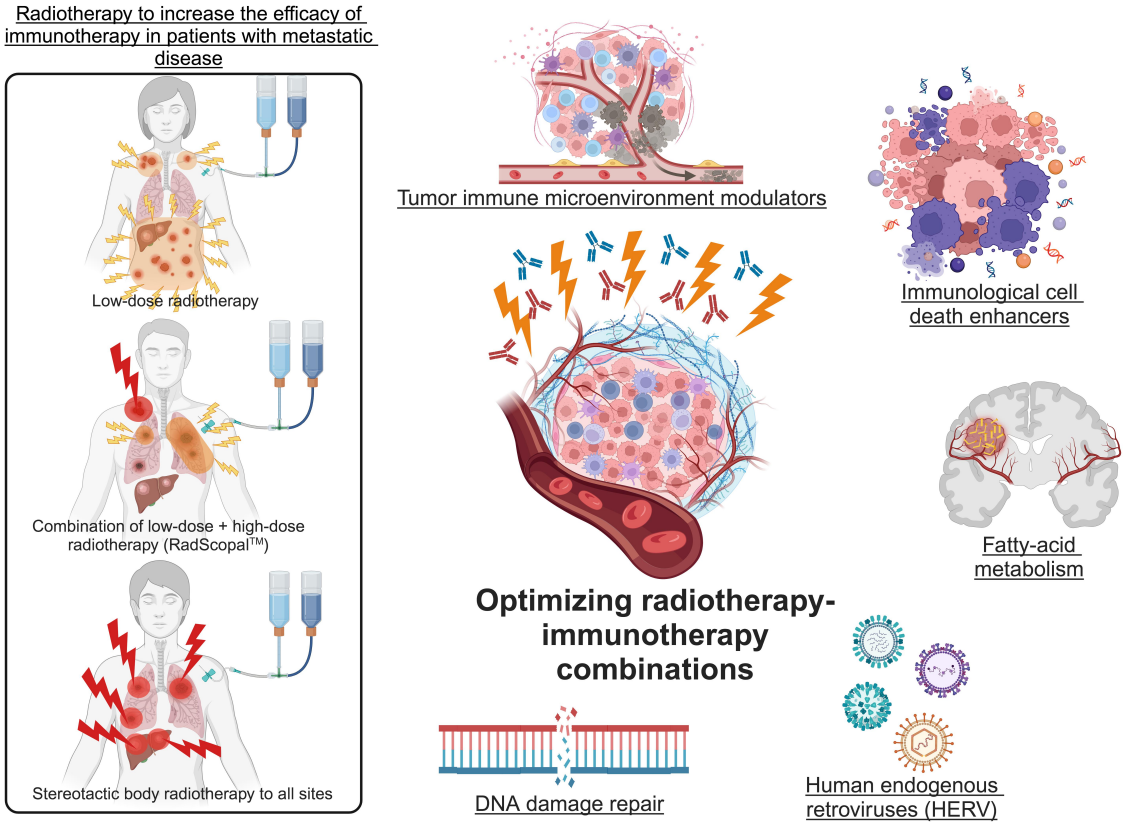

Figure 1. Overview of thematic discussions on optimizing radiotherapy-immunotherapy combination strategies at the immunorad Conference.

avenue involves the inhibition of the anti-apoptotic protein BCL2 (B-cell lymphoma 2). The BCL2 inhibitor Venetoclax has demonstrated its ability to sensitize tumors to anti-PD-1/PD-L1 based immunotherapies in diverse preclinical models and patients with acute myeloid leukemia (AML). Its effectiveness stems from the activation of dendritic cells type 1 (cDC1) resulting from the release of mitochondrial DNA (mtDNA) into the cytosol, the activation of the cGAS/STING/IRF3 pathway, and the engagement of the interferon type I (IFN-I) pathway.[10] These results constitute an interesting crossover opportunity given the impact of RT within the tumor immune microenvironment. From that point of view, ICD induced by RT was the focus of a presentation by Dr. Lorenzo Galluzzi (Weill Cornell Medical College, USA). Notably, the discovery and subsequent implementation of ICD inducers, enhancers or correctors in this field appear as critical for the optimization of new strategies of association using RT.[11]

Concluding this educational session, Dr. Silvia C. Formenti, Chair of Radiation Oncology at Weill Cornell Medicine (New-York, USA), presented the rationale behind combining RT and immunotherapy for the treatment of solid tumors, which inspired the name "Immunorad" for this conference. Dr. Formenti articulated her vision for the fields of RT and immune oncology. Over the past decades, she explored the capacity of focal RT to transform tumors into in-situ vaccines,[12] thereby eliciting a systemic anti-tumor immune response known as the abscopal effect. She introduced new considerations regarding the conditions necessary to induce such effect, notably highlighting findings from animal experiments that indicate higher doses of focal radiation may not always yield the most favorable outcomes when combined with immunotherapy.[13,14] Moreover, based on preclinical and clinical data, she fueled the debate on personalizing RT in the context of combinatorial treatments. Notably, she highlighted sparing draining lymph nodes (LN) to increase the efficacy of immunotherapy mediated by $CD8^+$ T cells,[15] and simultaneously targeting different compartments within the tumor immune microenvironment to decrease tumor resistance to immune-checkpoint blockades.[16] Finally, she discussed the potential benefits of delivering low-dose incidental irradiation to a significant volume of healthy lung tissue surrounding the tumor, that can mitigate the immune-suppressive effects of focal RT to lung cancer. This information can be harnessed to augment the pathological response in patients with non-small cell lung cancer (NSCLC) receiving SBRT and Durvalumab in the neoadjuvant setting.

2/Harmonizing established paradigms and disruptive innovations: redefining radiotherapy-immunotherapy combinations in oncology

In 2023 as in previous years, the Immunorad conference served as a platform to build bridges between the past, the present, and the future of tumor immunology and radiation. With combinations of RT and immunotherapy emerging as pivotal in the future of curative-intent oncology treatments, numerous thought-provoking presentations centered on innovations, both technological and biological in nature.

In the inaugural educational session, Prof. Antoine Italiano (Gustave Roussy, France) emphasized tertiary lymphoid structures (TLS) as crucial promoters of cellular and hormonal

responses in cancer. He showcased the added value of leveraging these structures in the current landscape of personalized immunotherapy. Notably, in soft-tissue sarcoma, where immunotherapy opportunities are limited and where B cell signatures outperform $CD8^+$ T cells or cytotoxic signatures as predictors for overall survival (OS),[17,18] the TLS PEMBROSARC cohort underscored the relevance of TLS as a predictive marker for the response of locally advanced/metastatic soft-tissue sarcomas to anti-PD-1/PD-L1 immunotherapy. The objective response rate to Pembrolizumab among these patients reached 30%, compared to a mere 2.3% in previous PEMBROSARC cohorts, resulting in significant improvements in median progression-free survival (PFS), overall survival (OS), and a 6-month non-progression rate soaring from 4.9% (TLS-negative patients) to 40% (TLS-positive patients).[19] These promising findings pave the way for widespread TLS utilization in guiding therapeutic decisions regarding immune-checkpoint blockade in soft-tissue sarcomas. However, it is important to note that not all TLS-positive tumors respond to immune checkpoint inhibition. Understanding the determinants of response to immunotherapy in these tumors is crucial. Other populations within the tumor microenvironment, such as regulatory T cells (Tregs) and fibroblasts, may play key roles in modulating the anti-tumor activity of TLS, influencing the overall effectiveness of immunotherapy.

Dr. Etienne Meylan (Université libre de Bruxelles, Belgium) provided insights into targeting a long-surviving subset of tumor-associated neutrophils (TANs). TANs have been given special focus due to their emerging role as a key player in the tumor immune microenvironment.[20] After discussing both the pro- and anti-tumor properties of TANs, Dr. Meylan presented a strategy to target the long-lived, tumor supportive TAN subset found within the immune microenvironment of human and murine lung tumors.[21] His laboratory identified the Bcl-xL anti-apoptotic protein as highly expressed in aging TANs, inhibition of which can be achieved using Navitoclax (AbbVie™) or the novel agent A-1331852, which selectively induces apoptosis in Bcl-xL dependent cells.[22] Oral administration of A-1331852 considerably reduces the number of old but not young TANs in the $Kras^{Frt\text{-}STOP\text{-}Frt\text{-}G12D/WT}$; $p53^{Frt/Frt}$ (KP) mouse model of lung adenocarcinoma, thereby inhibiting tumor growth. Intermittent administrations were particularly effective in maintaining selective depletion of tumor-supporting TANs.[23]

The Immunorad conference was the place to rediscover new actors in anti-tumor immunity and, in the light of the 2020s, evaluate the relevance of harnessing them for the treatment of refractory cancers and deleterious conditions. From this perspective, Dr. Vanpouille-Box (Weill Cornell Medicine, New-York, USA), presented her recent data dealing with the impact of fatty acid metabolism on the phenotype of irradiated tumors. Notably, this impact was explored in the particularly difficult indication of glioblastoma (GBM). In GBM, RT leads to an augmentation of the synthesis of fatty acids, which results in the downregulation of type I interferon pathway, a critical pathway for the induction of immune anti-tumor response.[24] Therefore, adding an inhibitor of FASN to the combination of RT and anti-PD-1 significantly improved the survival of mice bearing GL261 tumors.[25] This represents an interesting opportunity to improve the currently poor prognosis of patients with GBM. Another interesting perspective is represented by the use of human endogenous retroviruses (HERVs) for the development of T cell-based immunotherapies. Their ability to represent a reservoir of tumor epitopes shared across patients and tumors in the setting of cancer immunotherapy has been comprehensively explained by Prof. Stéphane Depil (Léon Bérard Cancer Center, Lyon). HERV-derived epitopes are presented on HLA molecules on the surface of tumor cells and induce high-avidity T cell clones that specifically recognize and kill tumor cells, with evidence of their expression in tumors with low mutational burden, such as triple negative breast cancer, ovarian cancer and acute-myeloid leukemia (AML).[26,27]

Prof. Sana Karam (University of Colorado, USA) elucidated new concepts of immune modulation within tumors, particularly revisiting the traditional use of IL-2 to counteract the immunosuppressive effects of SBRT in pancreatic cancer. This exploration yielded promising results, demonstrating synergy with a triple combination of RT, anti-PD-1/PD-L1, and IL-2 in murine models of pancreatic tumors.[28] Interestingly, the addition of anti-CD25 to this triple combination failed to provide additional benefits and had a detrimental effect on the activation of CD8+ T cells and the production of pro-inflammatory cytokines. Notably, the triple combination of RT, anti-PD-1, and IL-2 elicited durable responses in mice with KPC tumors who underwent adoptive T cell transfer before therapy. Furthermore, this combination induced robust immune memory capable of rejecting secondary tumors upon rechallenge in mice with complete responses.

During a special keynote presentation, attendees gained insights into the future evolution of radiotherapy-immunotherapy combinations from Prof. Ralph Weichselbaum (University of Chicago Medical Center, USA), a pioneering figure in the field. He emphasized the potential of targeting YTHDF2, a protein involved in the degradation of modified RNA coding for M6 methyladenosine (M6A) within myeloid cells. This targeting approach decreased the expression of NF-ΚB, hampering the migration and immunosuppressive function of myeloid-derived suppressor cells within tumors following irradiation. Consequently, YTHDF2 inhibition increased the efficacy of RT and checkpoint inhibitors in various murine models: MC38 (colorectal cancer), B16 (melanoma), and LLC (Lewis lung carcinoma).[29] First performed in genetically-engineered *Ythdf2*-cKO mice, these observations were reproduced by using the pharmacological inhibitor DC-Y13-27, and showed consistent results regarding the efficacy of the combination of RT and anti-PD-1 antibody, with an effect on both local tumor growth and distant metastasis occurrence. Therefore, YTHDF2 inhibition represents a potential paradigm shift in radiosensitization.

Dr. Sandra Demaria (Weill Cornell Medical College, USA) described new data showing that radiation induces the accumulation of cytosolic RNA-DNA hybrids in mouse and human breast cancer cells, which contribute to the cancer cell-intrinsic activation of interferon type I (IFN-I) pathway. Her lab is currently investigating if such RNA-DNA hybrids, which they also found within the cargo of small extracellular

vesicles (sEVs) produced by irradiated cancer cells, also contribute to the activation of dendritic cells that uptake sEVs.[30] Recent evidence that altered R-loop processing results in increased generation and export of RNA-DNA hybrids from the nucleus to the cytosol where they activate IFN-I via cGAS/STING and TLR3,[31] suggests that deregulation of R-loop dynamics occurs in irradiated cancer cells. These findings should be considered alongside the known ability of RT to activate cGAS-STING and type I interferon pathways in tumor cells through multiple processes including micronuclei generation.[32] Therefore, targeting the R-loop process could potentially enhance the radiation-induced activation of innate immune responses against cancer cells and amplify the efficacy of radiotherapy-immunotherapy combinations. From a larger perspective, DNA damage modulation may be harnessed to enhance radiotherapy-immunotherapy combinations, as explained by Prof. Kevin Harrington (The Institute of Cancer Research, London, UK), with a special focus on agents able to inhibit Ataxia Telangiectasia and RAD3 related (ATR) kinase that are capable of generating vulnerabilities to rationally selected immune checkpoint blockade (using anti-PD-L1 and anti-NKG2A antibodies).[33] Moreover, Prof. Claus Sørensen (University of Copenhagen, Denmark) explained how cancer cells use self-inflicted DNA breaks to promote their evasion,[34] and Prof. Floris Foijer (University of Groningen, the Netherlands) gave interesting insights in harnessing the inflammation caused by chromosomal instability to activate the tumor immune microenvironment.[35–37]

II/Stepwise implementation of advanced biological and technological tools toward personalized cancer medicine

Known as a 'bench-to-bedside' focused conference, Immunorad provided attendees with the opportunity to explore new visions and tools shaping personalized oncology of tomorrow. This year, advanced technological tools synergized notably with biological discoveries to offer a comprehensive view of what personalized treatments could represent in the near future (Figure 2).

1/Precision medicine, intestinal microbiota and immunoscore biopsy: fostering the future of precision oncology

Prof. Fabrice André (Gustave Roussy, France) shared his vision for the future of precision medicine in metastatic breast cancer. He emphasized the importance of leveraging tools and markers based on the individual biology of both the host and the cancer to stratify patients according to prognosis and thus personalize therapeutic approaches. This strategy aims for a significant shift in cancer classification, moving away from categorizing tumors based solely on their primary organ to a new classification grounded in molecular and biological characteristics at the individual level. This updated classification could incorporate traditional histologic markers, reinforced by the progressive integration of artificial intelligence, as demonstrated in previous experiences.[38] Furthermore, given the significance of molecular mechanisms in personalized medicine, this reclassification should utilize high-throughput sequencing in tissue

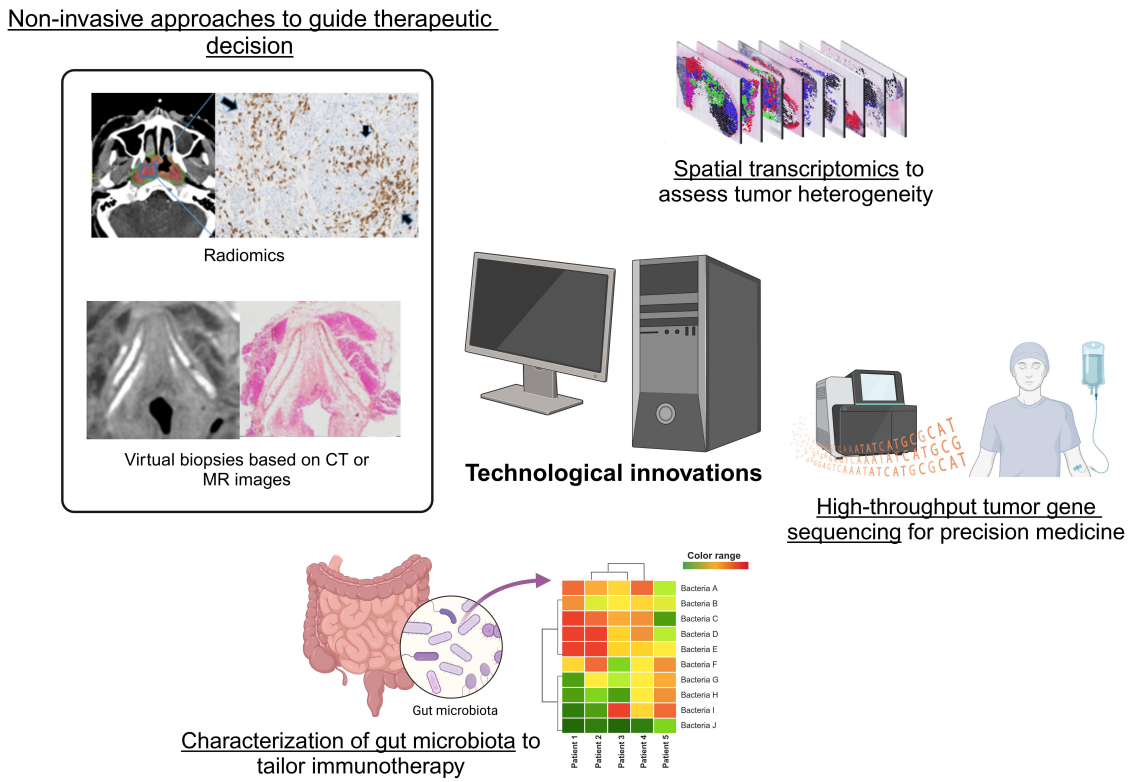

Figure 2. Overview of the technological innovations in the field of precision oncology and personalized medicine presented and discussed at immunorad Conference.

biopsy or circulating tumor DNA to identify targetable alterations in oncogenic drivers, illustrated by the example of Alpelisib in metastatic breast cancer with PI3K mutations.[39] Additionally, monitoring strategies could include iterative biopsies to determine on tumor specimens the mechanisms of each cancer's progression and propose the most suitable targeted therapy for each patient on an individual basis.[40] Personalized oncology could involve exploring circulating tumor cells (CTCs) for the early detection of tumor escape. Finally, Prof. André introduced the revolutionary ORGANOTREAT concept, in which tumor specimens from each patient are transformed into organoids. These organoids can then be cultured *in vitro* and serve as a tool for wide drug screening, thereby guiding the final therapeutic decision. This currently represents the largest clinical trial in functional precision medicine, including more than 1000 patients with a large variety of solid tumors[41] (*Clinicaltrials.gov* identifier: NCT05267912).

Prof. Laurence Zitvogel (Gustave Roussy, France) shared novel insights into personalized treatments based on individual scoring of dysbiosis of intestinal microbiota, in order to compensate resistance to immunotherapy by microbiota-centered interventions. She highlighted the promising opportunity of fecal microbial transplantation to enhance the efficacy of front-line anti-PD-1 therapy in metastatic melanoma patients, as demonstrated in recent publications.[42–44] Aligning perfectly with the theme of the Immunorad conference, she discussed recent research indicating that incidental exposure of the abdominal cavity to low-dose radiation, such as during stereotactic-body RT for liver lesions, leads to an abundance of beneficial commensals in patients' feces. This phenomenon resulted in long-term clinical benefits from anti-PD-1 based immunotherapy. These findings underscore the significance of the intestinal microbiota in assisting clinicians in distinguishing between patients likely to respond to front-line immunotherapy and those unlikely to do so, as well as the immunomodulatory properties of low-dose irradiation. Hence, it is crucial to optimize clinically relevant scoring systems that synthesize the prevalence of beneficial and harmful commensals in patients' stools. For instance, the TOPOSCORE, based on the prevalence of harmful and beneficial commensals including the specific relative abundance of *Akkermansia muciniphila* in stools at baseline, can be evaluated through metagenomics or polymerase-chain reaction (PCR), and may help to identify patients who are more likely to benefit from immunotherapy.[45–47]

Prof. Jérôme Galon (Cordeliers Research Center, Paris, France) described how the precise characterization of the tumor immune microenvironment could be used to stratify patients and personalize treatments. In colorectal cancer patients, this characterization may involve gene expression profiling and pre-defined immune signatures (IMMUNOSIGN), or immunohistochemistry combined with quantitative digital pathology (IMMUNOSCORE).[48] Interestingly, with the recent emergence of surgical de-escalation strategies in the treatment of rectal cancer, the use of Immunoscore biopsy is of interest for deciphering the patients able to benefit from a "watch-and-wait" strategy without excessive risk of relapse.[49] This finding constitutes a promising opportunity to tailor the indications of organ preservation in patients undergoing neoadjuvant chemoradiation for rectal carcinoma.

2/Technological advances: guiding decisions and enhancing radiotherapy delivery

As the leading conference on radiotherapy-immunotherapy combinations, Immunorad has also the mission to provide new technological insights and visions that aid the personalization of cancer treatments while reshaping the current paradigms of RT (Figure 3).

Prof. Désirée Deandreis (Gustave Roussy) discussed the future perspectives of using positron-emission tomography (PET) as a predictive and prognostic tool in cancer treatment. Advanced image analysis techniques, such as whole-body tumor volume quantification and radiomics, enable the extrapolation of biomarkers that are potentially representative of the tumor immune microenvironment. Additionally, she highlighted the potential of zirconium-89 (89Zr) immuno-PET radiotracers in identifying patients likely to respond to immune-checkpoint inhibitors, a promising strategy currently being tested in various clinical settings.[50]

Prof. Christos Sotiriou (Université Libre de Bruxelles, Belgium) elaborated on how spatial transcriptomics can be leveraged to address tumor heterogeneity and predict tumor responses to various treatments, with a particular focus on its impact on triple-negative breast cancer.[51] Moreover, the prevalence of tertiary lymphoid structures (TLS) previously described as a predictive factor of response to immunotherapy, can also be assessed by means of spatial transcriptomics, or by searching for TLS gene signatures within sequencing data.[52]

Dr. Cristian Fernandez-Palomo (Universität Bern, Switzerland) introduced the concept of spatially-fractionated RT (SFRT), an innovative approach involving the delivery of heterogeneous doses in RT. This method is characterized by alternating high (peaks) and low (valleys) radiation doses within the target volume. Microbeam Radiation Therapy (Microbeam RT), the most advanced type of preclinical SFRT, represents the cutting edge in this field by delivering high-dose (>100 Gy) ultra-narrow beams of 50 µm in width. Microbeam RT shows promise in improving the response to RT in tumors known for their intrinsic resistance, such as mouse B16-F10 melanoma[53,54] or rat F98 glioma tumors,[55] with overall good overall tolerability on the skin[56] and brain tissue,[57] also preventing late radiation effects such as lung fibrosis.[58,59] Furthermore, Microbeam RT has the potential to enhance key pathways involved in the anti-tumor immune response, including type I interferon, inflammatory cytokines, and immune-cell cytotoxicity (under review). Microbeam RT administered in a fractionated regimen triggered a regression of out-of-field locoregional metastasis.[60] Additionally, recent findings from their lab demonstrate that a single fraction of Microbeam RT enhances the infiltration of cytotoxic T cells into the tumor microenvironment. Importantly, depleting these T cells compromises tumor control, underscoring the

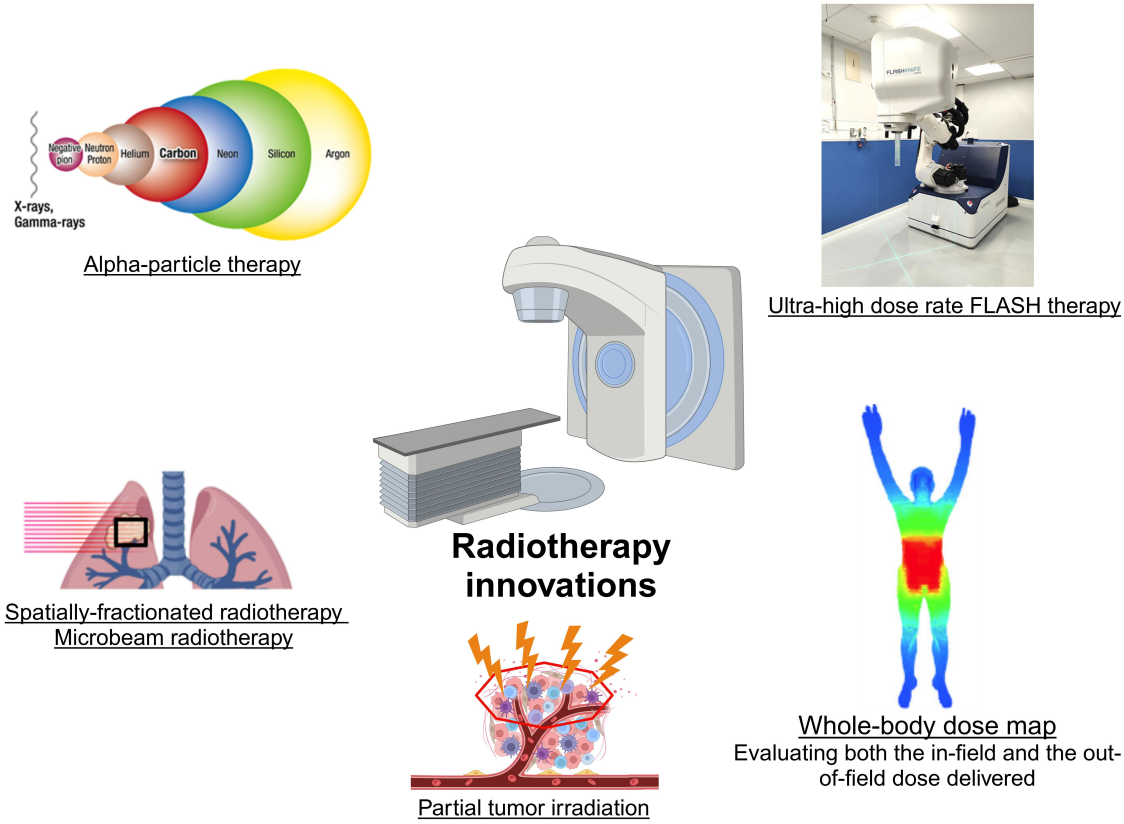

Figure 3. Summary of the advances presented at immunorad conference likely to change the paradigms of radiotherapy in the future.

critical role of the immune system in the efficacy of Microbeam RT.[61] This study, currently under review, further demonstrated a synergistic effect when a single fraction of Microbeam RT was combined with anti-CTLA-4 and anti-PD-1. Survival analysis revealed that 40% of mice treated with the combined Microbeam RT and anti-CTLA-4/anti-PD-1 therapy achieved long-term survival, compared to 0% for those that received Microbeam RT alone.

Dr. Michele Mondini (Gustave Roussy, France) highlighted recent advances pertaining to the use of low-dose RT, either alone in a whole-tumor irradiation or in combination with high-dose ablative RT delivered to a partial tumor volume. This innovative approach of heterogeneous delivery of RT holds great promise to modulate the tumor immune microenvironment and to restore the sensitivity of an irradiated tumor to immunotherapy. Notably, the non-homogenous irradiation of a tumor, with half of the tumor receiving low-dose RT and the other half receiving high-dose RT, enhances the efficacy of anti-PD-1 in different preclinical models, with an interesting synergy with CXCR2 antagonist SB225002.[62] These encouraging preclinical findings call for additional studies and translation to the clinic.

III/Building the clinical future of radiotherapy-immunotherapy combinations

The 7th Immunorad conference provided an opportunity to update existing data on the clinical implementation of significant preclinical advances in the field of radioimmunotherapy combinations. To illustrate this perspective, Dr. Jordi Remon (Gustave Roussy, France) presented recent improvements in the use of immunotherapy for patients with NSCLC.[63] The numerous evolutions in the standards of care for this type of cancer over the past years make NSCLC a model to create therapeutic combinations using chemo-radiation and immunotherapy. Regarding the treatment of small cell lung cancer (SCLC), a promising path was highlighted by Prof. Julien Sage (Stanford University, USA), with the use of CD47 inhibitors to increase the efficacy of RT in both irradiated and distant sites with a notable T-cell independent abscopal effect.[64]

In line with the previous talks, several impactful presentations highlighted the potential of new strategies discovered in experimental settings, paving the way for a promising future in clinical oncology.

1/RT in the particular setting of oligometastatic disease

Prof. Matthias Guckenberger (University of Zurich Hospital, Switzerland) provided a comprehensive view of the state-of-the-art in managing oligometastatic cancer. The prevailing approach emphasized multimodal treatment, incorporating both RT and systemic approaches. A key consideration is leveraging the substantial global investment in systemic cancer treatments to enhance the relevance and efficacy of therapeutic combinations with RT.[65] While the strategy of adding novel systemic drugs to curative intent RT has resulted in only few registered combinations, *e.g.* cetuximab added to RT in head and neck carcinomas and durvalumab added to RT in NSCLC, a potential alternative strategy lies in an approach where RT is added to standard-of-care systemic therapy to overcome heterogeneity and resistance development.[65] This approach could

prolong disease-free survival and address initial or acquired drug resistance. Moreover, it could yield significant financial benefits by delaying the initiation of expensive drugs and allowing treatment breaks until disease progression. With this purpose, Prof. Guckenberger outlined the ESTRO and EORTC OligoCARE cohort study, aiming at collecting real-world data about patients with oligometastatic cancer treated with locally ablative RT. The preliminary data inform about the different SBRT doses delivered to oligometastases, as well as the acute toxicities encountered in treated patients, especially those receiving concurrent systemic treatments.[66] To date, this cohort study has included more than 1600 patients, with an approximate recruitment rate of 80 patients/month. Moreover, Prof. Guckenberger discussed the ETOP CHESS trial, an innovative approach of combinatorial treatment for de novo oligometastatic NSCLC, using a combination of SBRT to all oligometastatic sites, concurrent and adjuvant Durvalumab, concurrent Tremelimumab and concurrent chemotherapy, all of these treatments administered in the induction phase. Beyond the setting of de novo oligometastatic cancer, using ablative SBRT is also of interest in oligoprogressive lesions while being under systemic therapy, as recently demonstrated in the CURB phase 2 trial.[67] A similar approach has been proposed in the HALT phase 2 trial, that enrolled patients with advanced, oncogene-addicted NSCLC (with EGFR mutation or ALK rearrangement) and oligoprogressive disease after one prior line of targeted therapy.[68]

2/Low-dose RT in the setting of combinatorial treatments in metastatic patients

Some interesting results emerged regarding the use of low-dose irradiation to reinvigorate anti-tumor immune responses in immune-deserted tumors or in patients with metastatic tumors progressing under immunotherapy.

Prof. Fernanda Herrera (Lausanne University Hospital, Switzerland) reported findings from the RACIN phase I clinical trial (ClinicalTrials.gov identifier: NCT03728179) investigating the efficacy of low-dose (≤1 Gy) bi-weekly RT to a large tumor volume to induce immune remodeling in patients with "cold" multimetastatic solid tumors. This treatment was combined with low-dose cyclophosphamide to deplete regulatory T cells (Tregs), anti-CTLA-4, and anti-PD-1 monoclonal antibodies to enhance the cytotoxicity of T cells, along with aspirin/COX-2 inhibitors to overcome vasculature barriers for T-cell homing within the tumor microenvironment. Mandatory paired biopsies from the same irradiated lesion before starting the combinatorial regimen demonstrated that low-dose RT increased the presence of $Ki67^+$ T cells with cytotoxic features, evidenced by high expression of granzyme B and perforin. This regimen overcame immunotherapy resistance in immune-deserted tumors, with one ovarian cancer patient notably achieving a long-term complete response. This innovative approach had previously shown promising results in a murine model of metastatic ovarian cancer where low-dose RT upregulated co-stimulatory (*e.i.* CD40, CD28) as well as co-inhibitory (*e.i.* CTLA-4, PD-1) molecules that could be targeted therapeutically, prompting the initiation of this confirmatory early-phase clinical trial.[69] Preliminary data shows that non-responder patients exhibited infiltration of myeloid suppressive cells, such as macrophages, within the tumor microenvironment, with consistent findings in both human and murine studies. As we await the full results of the Phase I RACIN trial, these preliminary data could pave the way for personalizing the use of low-dose RT to enhance the efficacy of immunotherapy in the common scenario of immune-deserted tumors.

Prof. James Welsh (MD Anderson Center, USA) presented another impactful example of using RT to sensitize resistant tumors to immunotherapy within the RADSCOPAL™ scheme. This regimen combines high-dose ablative stereotactic body RT (SBRT) with low-dose RT to overcome secondary resistance to immunotherapy.[70] Focal SBRT not only reduced tumor burden but also activated effector T cells within tumors. Simultaneously delivering low-dose radiation may enhance the attraction of activated T cells to immunotherapy-resistant tumors. This strategy is particularly relevant for PD-1/PD-L1 low-expressing tumors, where out-of-field lesions respond to pembrolizumab only in the presence of RT, compared to no response with pembrolizumab alone.[71] Similarly to the low-dose RT approach in the RACIN trial, using low-dose RT increased immune infiltration in irradiated tumors, as demonstrated for $CD8^+$, $CD4^+$ T cells, and NK cells. Concomitant use of low-dose RT with SBRT demonstrated clear benefits compared to SBRT alone. Future optimization of this approach in clinical radiotherapy-immunotherapy combinations may involve using nanoparticles (e.g., NBTXR3, Nanobiotix™)[72] or proton-beam irradiation to enhance the biological effectiveness of radiation and its immune benefits in tumors.[73] There is also a particular interest in combining high-dose and low-dose RT, according to the RADSCOPAL™ regimen, with anti-PD-1 and anti-TIGIT antibodies to promote the synergy existing between both these antibodies in the generation of a systemic anti-tumor immune response in low-dose irradiated but also un-irradiated tumors.[74]

3/Improving radiotherapy-immunotherapy combinations through carbon-ion irradiation

Prof. Stefan Eichmüller (DFKZ, Heidelberg, Germany) presented recent research about the differential impact of carbon-ion irradiation versus photon irradiation regarding the modulation of the tumor immune microenvironment, and explained the potential implications of these results on future strategies of radiotherapy-immunotherapy using carbon-ion irradiation. Indeed, comparing the therapeutic effects of conventional photon irradiation to recent carbon ion irradiation in a murine tumor model,[75] Prof. Stefan Eichmüller found that both irradiation modalities mediated tumor rejection with equal efficiency. However, when combined with checkpoint inhibitors, radioimmunotherapy comprising CTLA-4 blockade was clearly superior to anti-PD-L1 antibody, irrespective of the chosen radiation modality. Notably, single cell RNA-sequencing of tumor derived CD45+ cells revealed that carbon ion-based radioimmunotherapy changed the composition and gene expression pattern of TAMs. Moreover, as determined in a bilateral tumor setting, radioimmunotherapy with carbon ions plus anti-CTLA-4 treatment enhanced the number of

activated CD8+ T cells in non-irradiated tumors. This led to the notion that irradiation causing tissue damage could lead to TAMs scavenging dying tumor cells and priming tumor-specific CD8+ T cells in draining LNs. This process is supported by anti-CTLA-4 treatment and leads to activated T cells which eventually reach out to kill non-irradiated tumors, thereby causing so called abscopal effect.

4/The double-edged sword of RT: dealing with tumor heterogeneity and radiation-induced lymphopenia

Prof. Eric Deutsch (Gustave Roussy, France) concluded the conference by highlighting the essential role of functional lymphocytes in all radiotherapy-immunotherapy combinative approaches. He discussed current methods and future perspectives to efficiently spare lymphocytes from radiation, preserving these crucial soldiers of anti-cancer immunotherapy. Prof. Deutsch first addressed the duality of activating and immunosuppressive effects of RT, followed by an overview of current options for lymphocyte preservation and treatment personalization using imaging techniques. This includes the use of noninvasive radiomics approaches to characterize intra-tumor and inter-tumor heterogeneities, aiding in predicting overall survival in patients with metastatic disease treated with anti-PD-1/PD-L1 therapies.[76,77] Similarly, the role of noninvasive approaches based on standard imaging for the preservation of lymphocytes and the optimization of immunotherapy in patients was highlighted in the presentation of Prof. Philippe Lambin (University of Maastricht, the Netherlands). Additionally, Prof. Deutsch discussed the optimization of virtual biopsies, transforming computed tomography (CT) or magnetic resonance (MR) images into fixed histology slices for noninvasive characterization of tumor infiltration at the micron level.[78] Furthermore, he emphasized the importance of advanced software to accurately calculate incidental low-dose radiation received by patients, considering the high radiosensitivity of lymphocytes. Indeed, the currently available treatment planning software applications inadequately estimate these incidental low doses, necessitating the development of new tools to optimize "immunologically-tailored" RT.[79,80] Finally, Prof. Deutsch highlighted next-generation RT modalities likely to efficiently spare lymphocytes, such as ultra-high dose rate FLASH RT,[81] proton-beam or carbon-ion RT,[82,83] and spatial modulation of RT using boron-neutron capture therapy (BNCT).[84,85] With regards to FLASH RT, the main question is whether delivering RT with ultra-high dose rate is able to minimize subsequent lymphodepletion by limiting the irradiation of circulating lymphocytes. Moreover, regarding the use of alpha-radiotherapy in radiotherapy-immunotherapy combinations, this was the focus of the presentation from Prof. Peter Huber (DKFZ and University of Heidelberg, Germany), highlighting the interest of this modality in modulating the immune response within the tumor microenvironment.[86] Prof. Huber reported that photon RT orchestrates NK cell-dependent anti-tumor immune responses through CXCL8[87] and also introduced the terminology of an "immune response" relative biological efficiency (RBE) equivalent for particle RT involving proton, carbon, helium and oxygen ions. Moreover, the radiobiology of charged particle radiation was revisited and explained during the presentation of Dr. Jean-Pierre Pouget (Institute of Cancer Research of Montpellier, France) who highlighted the role of intercellular communications (bystander cytotoxicity and immunity) during this low dose rate and high linear energy transfer RT modality. Therefore, harnessing these innovations in the field of RT has the potential to personalize RT indications and delivery, refining treatment volumes beyond standard guidelines to better suit individual patients.

Conclusion: on the way to 8th immunorad conference

The journey through the 7th Immunorad Conference has illuminated transformative strides in the integration of RT and immunotherapy, heralding a new era in cancer treatment. Pioneering research presented by a group of speakers with multidisciplinary expertise has unveiled innovative strategies to harness the synergistic potential of these modalities, promising enhanced therapeutic outcomes and prolonged survival for patients affected by various malignancies. From novel approaches in managing oligometastatic cancer to the meticulous preservation of lymphocytes amid radiation exposure, each revelation underscores the intricate interplay between technology, biology, and clinical practice. As we eagerly await the report of the 8th Immunorad Conference, held October 3–5th, 2024, in New-York, the momentum gained from these groundbreaking endeavors propels us toward further advances in radiotherapy-immunotherapy combinations, with hope to translate encouraging preclinical opportunities into clinical benefits for patients.

Declaration of interest

F.A. reports travel/accommodation/expenses from AstraZeneca, GlaxoSmithKline, Novartis, Pfizer, and Roche, and his institution has received research funding from AstraZeneca, Daiichi Sankyo, Lilly, Novartis, Pfizer, and Roche. He received Consultant/Advisory fees from Amgen, Astellas, AstraZeneca, Bayer, BeiGene, BMS, Celgene, Debiopharm, Genentech, Ipsen, Janssen, Lilly, MedImmune, MSD, Novartis, Pfizer, Roche, Sanofi, Orion. S.D. is the founder and chairman of ErVimmune. L.G. is/ has been holding research contracts with Lytix Biopharma, Promontory and Onxeo, has received consulting/advisory honoraria from Boehringer Ingelheim, AstraZeneca, OmniSEQ, Onxeo, Longevity Labs, Inzen, Imvax, Sotio, Promontory, Noxopharm, EduCom, and the Luke Heller TECPR2 Foundation, and holds Promontory stock options. He is an Editorial Board Member for *OncoImmunology* and was not involved in the editorial review or the decision to publish this article. J. G. is a co-founder of HalioDx. K.H. reports Advisory Board/Steering Committee Membership: ALX Pharma; AstraZeneca; Bicara; BMS; Boehringer-Ingelheim; Exelixis; GSK; Merck-Serono; Merus; MSD; Replimune, and Research Grants: AstraZeneca; Boehringer-Ingelheim; Replimune. A.I. has received research grant from Bayer, Bristol Myers Squibb, Roche, Novartis, Chugai, Merck, AstraZeneca, Merck Sharp & Dohme and IPSEN and is an advisory board member for Bayer, Bristol Myers Squibb, Roche, Novartis, Chugai, Merck, AstraZeneca, Merck Sharp & Dohme, IPSEN and Parthenon. S.K. receives also receives preclinical research funding from Roche, which supported some of the work presented in this manuscript. G.K. is an Editorial Board Member for *OncoImmunology* and was not involved in the editorial review or the decision to publish this article. J.R. is an Editorial Board Member/ Editor-in-Chief/Associate Editor/Guest Editor for JCO, JTO, JTO, CCR, Lung Cancer and was not involved in the editorial review or the decision to publish this article. R.R.W. has stock and other ownership interests with Boost Therapeutics, Immvira LLC, Reflexion Pharmaceuticals,

Coordination Pharmaceuticals Inc., Magi Therapeutics, Oncosenescence, Aqualung Therapeutics Corporation, Cyntegron and PersonaDX. He has served in a consulting or advisory role for Aettis Inc., AstraZeneca, Coordination Pharmaceuticals, Genus, Merck Serono S.A., Nano Proteagen, NKGen Biotech, Shuttle Pharmaceuticals, Highlight Therapeutics, S.L., Aqualung Therapeutics Corporation. He has research grants with Varian and Regeneron. J.W.W. reports grant funding from Alkermes, Nanobiotix, Merck, GlaxoSmithKline, Checkmate Pharmaceuticals, Varian, Bristol Myers Squibb, Reflexion, Artidis, Takeda, Gilead, HotSpot Therapeutics, and Kiromic; travel grants from Ventana, Aileron, Nanobiotix, Varian, and Reflexion; advisory fees from Alpine Immune Sciences, Reflexion, Aileron, Molecular Match, OncoResponse, Checkmate Pharmaceuticals, and Marvu Pharmaceuticals; a consultant role for Alpine Immune Sciences, Reflexion, Merck, Molecular Match, OncoResponse, Checkmate Pharmaceuticals, Marvu Pharmaceuticals, Incyte, Nanobiotix, Aileron, GI Innovation, Legion Healthcare, Roche, and Ventana Medical Systems; and stock options in Alpine Immune Sciences, Reflexion, Legion Healthcare, Molecular Match, OncoResponse, and Nanorobotix. L.Z. has been an editor-in-chief of *Oncoimmunology* from 2011 to 2021 and has not been involved in the editorial review or the decision to publish this article. L.Z. is a founder of everIMMUNE, a biotech company involved in the development of live biotherapeutics including *Akkermansia spp*. in the arena of oncoimmunology. As such LZ is the SAB President of everIMMUNE and receives a financial compensation and is supported via a research contract. L.Z. is supported by Pileje to work on prebiotics in IO. S.C.F. has consultant: Bayer, Bristol Myers Squibb, Varian, ViewRay, Accuray, Elekta, Janssen, Regeneron, GlaxoSmithKline, Eisai, Astra Zeneca, MedImmune, Merck US, EMD Serono/Merck, Genentech/ROCHE, Boehringer Ingelheim, Nanobiotix and Grant/Research support from: Bristol Myers Squibb, Varian, Regeneron, Merck, Celldex. All other authors have no conflict of interest to declare. E.D. reports grants and personal fees from Roche Genentech; grants from Servier; grants from AstraZeneca; grants and personal fees from Merck-Serono; grants from BMS; and grants from MSD outside the submitted work. All other authors have no conflict of interest to declare.

Disclosures from the last 36 months within and outside the submitted work: PL: none related to the current manuscript; outside of current manuscript: grants/sponsored research agreements from Radiomics SA, Convert Pharmaceuticals SA and LivingMed Biotech srl. He received a presenter fee and/or reimbursement of travel costs/consultancy fee (in cash or in kind) from Astra Zeneca, BHV srl & Roche. PL has/had minority shares in the companies Radiomics SA, Convert pharmaceuticals SA, Comunicare SA, LivingMed Biotech srl and Bactam srl. PL is co-inventor of two issued patents with royalties on radiomics (PCT/NL2014/050248 and PCT/NL2014/050728), licensed to Radiomics SA; one issued patent on mtDNA (PCT/EP2014/059089), licensed to ptTheragnostic/DNAmito; one granted patent on LSRT (PCT/ P126537PC00, US patent No. 12,102,842), licensed to Varian; one issued patent on Radiomic signature of hypoxia (U.S. Patent 11,972,867), licensed to a commercial entity; one issued patent on Prodrugs (WO2019EP64112) without royalties; one non-issued, non-licensed patents on Deep Learning-Radiomics (N2024889) and three non-patented inventions (softwares) licensed to ptTheragnostic/DNAmito, Radiomics SA and Health Innovation Ventures). PL confirms that none of the above entities were involved in the preparation of this paper.

Funding

The author(s) reported there is no funding associated with the work featured in this article. Authors acknowledge financial support from ERC advanced grant (ERC-ADG-2015 n° 694812 – Hypoximmuno. Authors also acknowledge financial support from the European Union's Horizon research and innovation programme under grant agreement: ImmunoSABR n° 733008 (main contributor, CHAIMELEON n° 952172, EuCanImage n° 952103, IMI-OPTIMA n° 101034347, AIDAVA (HORIZON-HLTH-2021-TOOL-06) n°101057062, REALM (HORIZON-HLTH-2022-TOOL-11) n° 101095435, RADIOVAL (HORIZON-HLTH-2021-DISEASE-04-04) n° 101057699, EUCAIM (DIGITAL-2022-CLOUD-AI-02) n°101100633, GLIOMATCH n° 101136670 and KWF-Alpe d'HuZes n° 13058.

ORCID

Philippe Lambin http://orcid.org/0000-0001-7961-0191
Michele Mondini http://orcid.org/0000-0001-5803-0083
Eric Deutsch http://orcid.org/0000-0002-8223-3697

References

1. Mantovani A, Allavena P, Marchesi F, Garlanda C. Macrophages as tools and targets in cancer therapy. Nat Rev Drug Discov. 2022;21(11):799–820. doi:10.1038/s41573-022-00520-5.
2. Bill R, Wirapati P, Messemaker M, Roh W, Zitti B, Duval F, Kiss M, Park JC, Saal TM, Hoelzl J, et al. CXCL9: SPP1 macrophage polarity identifies a network of cellular programs that control human cancers. Science. 2023;381(6657):515–524. doi:10.1126/science.ade2292.
3. Zitvogel L, Casares N, Péquignot MO, Chaput N, Albert ML, Kroemer G. Immune response against dying tumor cells. Adv Immunol. 2004;84:131–179. doi:10.1016/S0065-2776(04)84004-5.
4. Kroemer G, Galluzzi L, Kepp O, Zitvogel L. Immunogenic cell death in cancer therapy. Annu Rev Immunol. 2013;31(1):51–72. doi:10.1146/annurev-immunol-032712-100008.
5. Galluzzi L, Vitale I, Warren S, Adjemian S, Agostinis P, Martinez AB, Chan TA, Coukos G, Demaria S, Deutsch E, et al. Consensus guidelines for the definition, detection and interpretation of immunogenic cell death. J Immunother Cancer. 2020;8(1):e000337. doi:10.1136/jitc-2019-000337.
6. Kroemer G, Galassi C, Zitvogel L, Galluzzi L. Immunogenic cell stress and death. Nat Immunol. 2022;23(4):487–500. doi:10.1038/s41590-022-01132-2.
7. Xie W, Forveille S, Iribarren K, Sauvat A, Senovilla L, Wang Y, Humeau J, Perez-Lanzon M, Zhou H, Martínez-Leal JF, et al. Lurbinectedin synergizes with immune checkpoint blockade to generate anticancer immunity. OncoImmunol. 2019;8(11):e1656502. doi:10.1080/2162402X.2019.1656502.
8. Zhou H, Forveille S, Sauvat A, Yamazaki T, Senovilla L, Ma Y, Liu P, Yang H, Bezu L, Müller K, et al. The oncolytic peptide LTX-315 triggers immunogenic cell death. Cell Death Dis. 2016;7(3):e2134–e2134. doi:10.1038/cddis.2016.47.
9. Montes De Oca R, Alavi AS, Vitali N, Bhattacharya S, Blackwell C, Patel K, Seestaller-Wehr L, Kaczynski H, Shi H, Dobrzynski E, et al. Belantamab mafodotin (GSK2857916) drives immunogenic cell death and immune-mediated antitumor responses in vivo. Mol Cancer Ther. 2021;20(10):1941–1955. doi:10.1158/1535-7163.MCT-21-0035.
10. Zhao L, Liu P, Mao M, Zhang S, Bigenwald C, Dutertre C-A, Lehmann CHK, Pan H, Paulhan N, Amon L, et al. BCL2 inhibition reveals a dendritic cell–specific immune checkpoint that controls tumor immunosurveillance. Cancer Discov. 2023;13(11):2448–2469. doi:10.1158/2159-8290.CD-22-1338.
11. Liu P, Zhao L, Zitvogel L, Kepp O, Kroemer G. Immunogenic cell death (ICD) enhancers—drugs that enhance the perception of ICD by dendritic cells. Immunol Rev. 2024;321(1):7–19. doi:10.1111/imr.13269.
12. Formenti SC, Demaria S. Radiation therapy to convert the tumor into an in situ vaccine. Int J Radiat Oncol. 2012;84(4):879–880. doi:10.1016/j.ijrobp.2012.06.020.
13. Vanpouille-Box C, Alard A, Aryankalayil MJ, Sarfraz Y, Diamond JM, Schneider RJ, Inghirami G, Coleman CN, Formenti SC, Demaria S. DNA exonuclease Trex1 regulates radiotherapy-induced tumour immunogenicity. Nat Commun. 2017;8(1):15618. doi:10.1038/ncomms15618.
14. Ban Y, Markowitz GJ, Zou Y, Ramchandani D, Kraynak J, Sheng J, Lee SB, Wong STC, Altorki NK, Gao D, et al. Radiation-activated secretory proteins of Scgb1a1+ club cells increase the efficacy of immune checkpoint blockade in lung cancer. Nat Cancer. 2021;2(9):919–931. doi:10.1038/s43018-021-00245-1.
15. Altorki NK, Walsh ZH, Melms JC, Port JL, Lee BE, Nasar A, Spinelli C, Caprio L, Rogava M, Ho P, et al. Neoadjuvant durvalumab plus radiation versus durvalumab alone in stages I–III non-

small cell lung cancer: survival outcomes and molecular correlates of a randomized phase II trial. Nat Commun. 2023;14(1):8435. doi:10.1038/s41467-023-44195-x.
16. Rudqvist N-P, Charpentier M, Lhuillier C, Wennerberg E, Spada S, Sheridan C, Zhou XK, Zhang T, Formenti SC, Sims JS. Immunotherapy targeting different immune compartments in combination with radiation therapy induces regression of resistant tumors. Nat Commun. 2023;14(1). doi:10.1038/s41467-023-40844-3.
17. Toulmonde M, Penel N, Adam J, Chevreau C, Blay J-Y, Le Cesne A, Bompas E, Piperno-Neumann S, Cousin S, Grellety T, et al. Use of PD-1 targeting, macrophage infiltration, and IDO pathway activation in sarcomas: a phase 2 clinical trial. JAMA Oncol. 2018;4(1):93. doi:10.1001/jamaoncol.2017.1617.
18. Petitprez F, De Reyniès A, Keung EZ, Chen T-W, Sun C-M, Calderaro J, Jeng Y-M, Hsiao L-P, Lacroix L, Bougoüin A, et al. B cells are associated with survival and immunotherapy response in sarcoma. Nature. 2020;577(7791):556–560. doi:10.1038/s41586-019-1906-8.
19. Italiano A, Bessede A, Pulido M, Bompas E, Piperno-Neumann S, Chevreau C, Penel N, Bertucci F, Toulmonde M, Bellera C, et al. Pembrolizumab in soft-tissue sarcomas with tertiary lymphoid structures: a phase 2 PEMBROSARC trial cohort. Nat Med. 2022;28(6):1199–1206. doi:10.1038/s41591-022-01821-3.
20. Que H, Fu Q, Lan T, Tian X, Wei X. Tumor-associated neutrophils and neutrophil-targeted cancer therapies. Biochim Biophys Acta BBA - Rev Cancer. 2022;1877(5):188762. doi:10.1016/j.bbcan.2022.188762.
21. Zilionis R, Engblom C, Pfirschke C, Savova V, Zemmour D, Saatcioglu HD, Krishnan I, Maroni G, Meyerovitz CV, Kerwin CM, et al. Single-cell transcriptomics of human and mouse lung cancers reveals conserved myeloid populations across individuals and species. Immunity. 2019;50(5):1317–1334.e10. doi:10.1016/j.immuni.2019.03.009.
22. Wang L, Doherty GA, Judd AS, Tao Z-F, Hansen TM, Frey RR, Song X, Bruncko M, Kunzer AR, Wang X, et al. Discovery of A-1331852, a first-in-class, potent, and orally-bioavailable BCL-X$_L$ inhibitor. ACS Med Chem Lett. 2020;11(10):1829–1836. doi:10.1021/acsmedchemlett.9b00568.
23. Bodac A, Mayet A, Rana S, Pascual J, Bowler AD, Roh V, Fournier N, Craciun L, Demetter P, Radtke F, et al. Bcl-xL targeting eliminates ageing tumor-promoting neutrophils and inhibits lung tumor growth. EMBO Mol Med. 2023;16(1):158–184. doi:10.1038/s44321-023-00013-x.
24. De Martino M, Daviaud C, Minns HE, Lazarian A, Wacker A, Costa AP, Attarwala N, Chen Q, Choi S-W, Rabadàn R, et al. Radiation therapy promotes unsaturated fatty acids to maintain survival of glioblastoma. Cancer Lett. 2023;570:216329. doi:10.1016/j.canlet.2023.216329.
25. Martino MD, Daviaud C, Vanpouille-Box C 2nd November In: London, UK: BMJ Publishing Group Ltd; 2023 Targeting FASN sensitizes irradiated glioblastoma to immune checkpoint blockade 2023 Annual meeting of the Society for Immunotherapy of Cancer (SITC) 1st to 5th November 2023 San Diego p. A508–A508 https://jitc.bmj.com/lookup/doi/10.1136/jitc-2023-SITC2023.0457 doi:10.1136/jitc-2023-SITC2023.0457.
26. Alcazer V, Bonaventura P, Tonon L, Michel E, Mutez V, Fabres C, Chuvin N, Boulos R, Estornes Y, Maguer-Satta V, et al. HERVs characterize normal and leukemia stem cells and represent a source of shared epitopes for cancer immunotherapy. Am J Hematol. 2022;97(9):1200–1214. doi:10.1002/ajh.26647.
27. Bonaventura P, Alcazer V, Mutez V, Tonon L, Martin J, Chuvin N, Michel E, Boulos RE, Estornes Y, Valladeau-Guilemond J, et al. Identification of shared tumor epitopes from endogenous retroviruses inducing high-avidity cytotoxic T cells for cancer immunotherapy. Sci Adv. 2022;8(4):eabj3671. doi:10.1126/sciadv.abj3671.
28. Piper M, Hoen M, Darragh LB, Knitz MW, Nguyen D, Gadwa J, Durini G, Karakoc I, Grier A, Neupert B, et al. Simultaneous targeting of PD-1 and IL-2Rβγ with radiation therapy inhibits pancreatic cancer growth and metastasis. Cancer Cell. 2023;41(5):950–969.e6. doi:10.1016/j.ccell.2023.04.001.
29. Wang L, Dou X, Chen S, Yu X, Huang X, Zhang L, Chen Y, Wang J, Yang K, Bugno J, et al. YTHDF2 inhibition potentiates radiotherapy antitumor efficacy. Cancer Cell. 2023 May. 41(7):S1294–1308.e8. doi:10.1016/j.ccell.2023.04.019.
30. Diamond JM, Vanpouille-Box C, Spada S, Rudqvist N-P, Chapman JR, Ueberheide BM, Pilones KA, Sarfraz Y, Formenti SC, Demaria S. Exosomes shuttle TREX1-sensitive IFN-Stimulatory dsDNA from irradiated cancer cells to DCs. Cancer Immunol Res. 2018;6(8):910–920. doi:10.1158/2326-6066.CIR-17-0581.
31. Crossley MP, Song C, Bocek MJ, Choi J-H, Kousouros JN, Sathirachinda A, Lin C, Brickner JR, Bai G, Lans H, et al. R-loop-derived cytoplasmic RNA–DNA hybrids activate an immune response. Nature. 2023;613(7942):187–194. doi:10.1038/s41586-022-05545-9.
32. Cimprich KA, Li G-M, Demaria S, Gekara NO, Zha S, Chen Q. The crosstalk between DNA repair and immune responses. Mol Cell. 2023;83(20):3582–3587. doi:10.1016/j.molcel.2023.09.022.
33. Patin EC, Dillon MT, Nenclares P, Grove L, Soliman H, Leslie I, Northcote D, Bozhanova G, Crespo-Rodriguez E, Baldock H, et al. Harnessing radiotherapy-induced nk-cell activity by combining DNA damage–response inhibition and immune checkpoint blockade. J Immunother Cancer. 2022;10(3):e004306. doi:10.1136/jitc-2021-004306.
34. Larsen BD, Benada J, Yung PYK, Bell RAV, Pappas G, Urban V, Ahlskog JK, Kuo TT, Janscak P, Megeney LA, et al. Cancer cells use self-inflicted DNA breaks to evade growth limits imposed by genotoxic stress. Science. 2022;376(6592):476–483. doi:10.1126/science.abi6378.
35. Van Den Brink A, Suárez Peredo Rodríguez MF, Foijer F. Chromosomal instability and inflammation: a catch-22 for cancer cells. Chromosome Res. 2023;31(3):19. doi:10.1007/s10577-023-09730-y.
36. Foijer F, Xie SZ, Simon JE, Bakker PL, Conte N, Davis SH, Kregel E, Jonkers J, Bradley A, Sorger PK. Chromosome instability induced by Mps1 and p53 mutation generates aggressive lymphomas exhibiting aneuploidy-induced stress. Proc Natl Acad Sci USA. 2014;111(37):13427–13432. doi:10.1073/pnas.1400892111.
37. Hong C, Schubert M, Tijhuis AE, Requesens M, Roorda M, Van Den Brink A, Ruiz LA, Bakker PL, Van Der Sluis T, Pieters W, et al. cGAS–sting drives the IL-6-dependent survival of chromosomally instable cancers. Nature. 2022;607(7918):366–373. doi:10.1038/s41586-022-04847-2.
38. Garberis IJ, Saillard C, Drubay D, Schmauch B, Aubert V, Jaeger A, Sapateiro M, De Lavergne A, Kamoun A, Courtiol P, et al. 1124O prediction of distant relapse in patients with invasive breast cancer from deep learning models applied to digital pathology slides. Ann Oncol. 2021;32:1 S921. doi:10.1016/j.annonc.2021.08.766.
39. André F, Ciruelos E, Rubovszky G, Campone M, Loibl S, Rugo HS, Iwata H, Conte P, Mayer IA, Kaufman B, et al. Alpelisib for PIK3CA -Mutated, hormone receptor–positive advanced breast cancer. N Engl J Med. 2019;380(20):1929–1940. doi:10.1056/NEJMoa1813904.
40. Arnedos M, Vicier C, Loi S, Lefebvre C, Michiels S, Bonnefoi H, Andre F. Precision medicine for metastatic breast cancer—limitations and solutions. Nat Rev Clin Oncol. 2015;12(12):693–704. doi:10.1038/nrclinonc.2015.123.
41. Cartry J, Bedja S, Boilève A, Mathieu JRR, Gontran E, Annereau M, Job B, Mouawia A, Mathias P, De Baère T, et al. Implementing patient derived organoids in functional precision medicine for patients with advanced colorectal cancer. J Exp Clin Cancer Res. 2023;42(1):281. doi:10.1186/s13046-023-02853-4.
42. Baruch EN, Youngster I, Ben-Betzalel G, Ortenberg R, Lahat A, Katz L, Adler K, Dick-Necula D, Raskin S, Bloch N, et al. Fecal microbiota transplant promotes response in immunotherapy-refractory melanoma patients. Science. 2021;371(6529):602–609. doi:10.1126/science.abb5920.
43. Davar D, Dzutsev AK, McCulloch JA, Rodrigues RR, Chauvin J-M, Morrison RM, Deblasio RN, Menna C, Ding Q, Pagliano O, et al. Fecal microbiota transplant overcomes resistance to anti–PD-1

therapy in melanoma patients. Science. 2021;371(6529):595–602. doi:10.1126/science.abf3363.
44. Routy B, Lenehan JG, Miller WH, Jamal R, Messaoudene M, Daisley BA, Hes C, Al KF, Martinez-Gili L, Punčochář M, et al. Fecal microbiota transplantation plus anti-PD-1 immunotherapy in advanced melanoma: a phase I trial. Nat Med. 2023;29 (8):2121–2132. doi:10.1038/s41591-023-02453-x.
45. Derosa L, Routy B, Thomas AM, Iebba V, Zalcman G, Friard S, Mazieres J, Audigier-Valette C, Moro-Sibilot D, Goldwasser F, et al. Intestinal akkermansia muciniphila predicts clinical response to PD-1 blockade in patients with advanced non-small-cell lung cancer. Nat Med. 2022;28(2):315–324. doi:10.1038/s41591-021-01655-5.
46. Derosa L, Alves Costa Silva C, Iebba V, Routy B, Reni A, Audigier-Valette C, Zalcman G, Mazieres J, Friard S, Goldwasser F, et al. Friendly-user score assessing gut dysbiosis and resistance to immune checkpoint inhibitors (ICI). J Clin Oncol. 2023;41 (16_suppl):103–103. doi:10.1200/JCO.2023.41.16_suppl.103.
47. Derosa L, Iebba V, Silva CAC, Piccinno G, Wu G, Lordello L, Routy B, Zhao N, Thelemaque C, Birebent R, et al. Custom scoring based on ecological topology of gut microbiota associated with cancer immunotherapy outcome. Cell. 2024;187(13):3373–3389. e16. doi:10.1016/j.cell.2024.05.029.
48. Galon J, Costes A, Sanchez-Cabo F, Kirilovsky A, Mlecnik B, Lagorce-Pagès C, Tosolini M, Camus M, Berger A, Wind P, et al. Type, density, and location of immune cells within human colorectal tumors predict clinical outcome. Science. 2006;313 (5795):1960–1964. doi:10.1126/science.1129139.
49. El Sissy C, Kirilovsky A, Lagorce Pagès C, Marliot F, Custers PA, Dizdarevic E, Sroussi M, Castillo-Martin M, Haicheur N, Dermani M, et al. International validation of the immunoscore biopsy in patients with rectal cancer managed by a watch-and-wait strategy. J Clin Oncol. 2024;42(1):70–80. doi:10.1200/JCO.23.00586.
50. Liberini V, Laudicella R, Capozza M, Huellner MW, Burger IA, Baldari S, Terreno E, Deandreis D. The future of cancer diagnosis, treatment and surveillance: a systemic review on immunotherapy and immuno-pet radiotracers. Molecules. 2021;26(8):2201. doi:10.3390/molecules26082201.
51. Bareche Y, Buisseret L, Gruosso T, Girard E, Venet D, Dupont F, Desmedt C, Larsimont D, Park M, Rothé F, et al. Unraveling triple-negative breast cancer tumor microenvironment heterogeneity: towards an optimized treatment approach. JNCI J Natl Cancer Inst. 2020;112(7):708–719. doi:10.1093/jnci/djz208.
52. Bareche Y, Kelly D, Abbas-Aghababazadeh F, Nakano M, Esfahani PN, Tkachuk D, Mohammad H, Samstein R, Lee C-H, Morris LGT, et al. Leveraging big data of immune checkpoint blockade response identifies novel potential targets. Ann Oncol. 2022;33(12):1304–1317. doi:10.1016/j.annonc.2022.08.084.
53. Potez M, Fernandez-Palomo C, Bouchet A, Trappetti V, Donzelli M, Krisch M, Laissue J, Volarevic V, Djonov V. Synchrotron microbeam radiation therapy as a new approach for the treatment of radioresistant melanoma: potential underlying mechanisms. Int J Radiat Oncol. 2019;105(5):1126–1136. doi:10.1016/j.ijrobp.2019.08.027.
54. Fernandez-Palomo C, Trappetti V, Potez M, Pellicioli P, Krisch M, Laissue J, Djonov V. Complete remission of mouse melanoma after temporally fractionated microbeam radiotherapy. Cancers. 2020;12 (9):2656. doi:10.3390/cancers12092656.
55. Potez M, Bouchet A, Flaender M, Rome C, Collomb N, Grotzer M, Krisch M, Djonov V, Balosso J, Brun E, et al. Synchrotron X-Ray boost delivered by microbeam radiation therapy after conventional X-Ray therapy fractionated in time improves F98 glioma control. Int J Radiat Oncol. 2020;107(2):360–369. doi:10.1016/j.ijrobp.2020.02.023.
56. Potez M, Bouchet A, Wagner J, Donzelli M, Bräuer-Krisch E, Hopewell JW, Laissue J, Djonov V. Effects of synchrotron X-Ray micro-beam irradiation on normal mouse ear pinnae. Int J Radiat Oncol. 2018;101(3):680–689. doi:10.1016/j.ijrobp.2018.02.007.
57. Laissue JA, Geiser G, Spanne PO, Dilmanian FA, Gebbers J-O, Geiser M, Wu X-Y, Makar MS, Micca PL, Nawrocky MM, et al. Neuropathology of ablation of rat gliosarcomas and contiguous brain tissues using a microplanar beam of synchrotron-wiggler-generated X rays. Int J Cancer. 1998;78(5):654–660.
58. Wright MD, Romanelli P, Bravin A, Le Duc G, Brauer-Krisch E, Requardt H, Bartzsch S, Hlushchuk R, Laissue J-A, Djonov V. Non-conventional ultra-high dose rate (FLASH) microbeam radiotherapy provides superior normal tissue sparing in rat lung compared to non-conventional ultra-high dose rate (FLASH) radiotherapy. Cureus. 2021;13(11):e19317. Nov 6. doi:10.7759/cureus.19317.
59. Trappetti V, Fernandez-Palomo C, Smyth L, Klein M, Haberthür D, Butler D, Barnes M, Shintani N, De Veer M, Laissue JA, et al. Synchrotron microbeam radiation therapy for the treatment of lung carcinoma: a preclinical study. Int J Radiat Oncol. 2021;111(5):1276–1288. doi:10.1016/j.ijrobp.2021.07.1717.
60. Trappetti V, Potez M, Fernandez-Palomo C, Volarevic V, Shintani N, Pellicioli P, Ernst A, Haberthür D, Fazzari JM, Krisch M, et al. Microbeam radiation therapy controls local growth of radioresistant melanoma and treats out-of-field locoregional metastasis. Int J Radiat Oncol. 2022;114(3):478–493. doi:10.1016/j.ijrobp.2022.06.090.
61. Trappetti V, Fernández-Palomo C, Arora P, Potez M, Pellicioli P, Fazzari J, Shintani N, Sanchez-Gonzalez I, Wu CT, de Breuyn Dietler B, et al. Towards melanoma in situ vaccination with multiple ultra-narrow X-ray beams. Cancer Lett. 2024; doi:10.1016/j.canlet.2024.217326.
62. Bergeron P, Dos Santos M, Sitterle L, Tarlet G, Lavigne J, Liu W, Gerbé De Thoré M, Clémenson C, Meziani L, Schott C, et al. Non-homogenous intratumor ionizing radiation doses synergize with PD1 and CXCR2 blockade. Nat Commun. 2024;15(1):8845. doi:10.1038/s41467-024-53015-9.
63. Reck M, Remon J, Hellmann MD. First-line immunotherapy for non–small-Cell lung cancer. J Clin Oncol. 2024;40(6):586–597. doi:10.1200/JCO.21.01497.
64. Nishiga Y, Drainas AP, Baron M, Bhattacharya D, Barkal AA, Ahrari Y, Mancusi R, Ross JB, Takahashi N, Thomas A, et al. Radiotherapy in combination with CD47 blockade elicits a macrophage-mediated abscopal effect. Nat Cancer. 2022;3 (11):1351–1366. doi:10.1038/s43018-022-00456-0.
65. McIntosh SA, Alam F, Adams L, Boon IS, Callaghan J, Conti I, Copson E, Carson V, Davidson M, Fitzgerald H, et al. Global funding for cancer research between 2016 and 2020: a content analysis of public and philanthropic investments. Lancet Oncol. 2023;24(6):636–645. doi:10.1016/S1470-2045(23)00182-1.
66. Christ SM, Alongi F, Ricardi U, Scorsetti M, Livi L, Balermpas P, Lievens Y, Braam P, Jereczek-Fossa BA, Stellamans K, et al. Cancer-specific dose and fractionation schedules in stereotactic body radiotherapy for oligometastatic disease: an interim analysis of the EORTC-ESTRO E2-RADIatE OligoCare study. Radiother Oncol. 2024;195:110235. doi:10.1016/j.radonc.2024.110235.
67. Tsai CJ, Yang JT, Shaverdian N, Patel J, Shepherd AF, Eng J, Guttmann D, Yeh R, Gelblum DY, Namakydoust A, et al. Standard-of-care systemic therapy with or without stereotactic body radiotherapy in patients with oligoprogressive breast cancer or non-small-cell lung cancer (consolidative use of radiotherapy to block [CURB] oligoprogression): an open-label, randomised, controlled, phase 2 study. Lancet. 2024;403(10422):171–182. doi:10.1016/S0140-6736(23)01857-3.
68. McDonald F, Guckenberger M, Popat S, Faivre-Finn C, Andratschke N, Riddell A, Hanna GG, Hiley C, Prakash V, Nair A, et al. EP08.03-005 hALT - Targeted therapy with or without dose-intensified radiotherapy in oligo-progressive disease in oncogene addicted lung tumours. J Thorac Oncol. 2022;17(9):S492. doi:10.1016/j.jtho.2022.07.861.
69. Herrera FG, Ronet C, Ochoa de Olza M, Barras D, Crespo I, Andreatta M, Corria-Osorio J, Spill A, Benedetti F, Genolet R, et al. Low-dose radiotherapy reverses tumor immune desertification and resistance to immunotherapy. Cancer Discov. 2021 Sep 3. 12(1):108–133. doi:10.1158/2159-8290.CD-21-0003.

70. Patel RR, He K, Barsoumian HB, Chang JY, Tang C, Verma V, Comeaux N, Chun SG, Gandhi S, Truong MT, et al. High-dose irradiation in combination with non-ablative low-dose radiation to treat metastatic disease after progression on immunotherapy: results of a phase II trial. Radiother Oncol. 2021;162:60–67. doi:10.1016/j.radonc.2021.06.037.
71. Theelen WSME, Chen D, Verma V, Hobbs BP, Peulen HMU, Aerts JGJV, Bahce I, Niemeijer ALN, Chang JY, de Groot PM, et al. Pembrolizumab with or without radiotherapy for metastatic non-small-cell lung cancer: a pooled analysis of two randomised trials. Lancet Respir Med. 2021;9(5):467–475. doi:10.1016/S2213-2600(20)30391-X.
72. Hu Y, Paris S, Barsoumian H, Abana CO, He K, Wasley M, Younes AI, Masrorpour F, Chen D, Yang L, et al. Radiation therapy enhanced by NBTXR3 nanoparticles overcomes anti-PD1 resistance and evokes abscopal effects. Int J Radiat Oncol. 2021;111(3):647–657. doi:10.1016/j.ijrobp.2021.06.041.
73. Hu Y, Paris S, Sahoo N, Bertolet G, Wang Q, Wang Q, Barsoumian HB, Da Silva J, Huang A, Doss DJ, et al. Nanoparticle-enhanced proton beam immunoradiotherapy drives immune activation and durable tumor rejection. JCI Insight. 2023;8(12):e167749. doi:10.1172/jci.insight.167749.
74. Barsoumian HB, Sezen D, Menon H, Younes AI, Hu Y, He K, Puebla-Osorio N, Wasley M, Hsu E, Patel RR, et al. High plus low dose radiation strategy in combination with TIGIT and PD1 blockade to promote systemic antitumor responses. Cancers. 2022;14(1):221. doi:10.3390/cancers14010221.
75. Hartmann L, Osen W, Eichmüller OL, Kordaß T, Furkel J, Dickes E, Reid C, Debus J, Brons S, Abdollahi A, et al. Carbon ion irradiation plus CTLA4 blockade elicits therapeutic immune responses in a murine tumor model. Cancer Lett. 2022;550:215928. doi:10.1016/j.canlet.2022.215928.
76. Sun R, Limkin EJ, Vakalopoulou M, Dercle L, Champiat S, Han SR, Verlingue L, Brandao D, Lancia A, Ammari S, et al. A radiomics approach to assess tumour-infiltrating CD8 cells and response to anti-PD-1 or anti-PD-L1 immunotherapy: an imaging biomarker, retrospective multicohort study. Lancet Oncol. 2018;19(9):1180–1191. doi:10.1016/S1470-2045(18)30413-3.
77. Sun R, Sundahl N, Hecht M, Putz F, Lancia A, Rouyar A, Milic M, Carré A, Battistella E, Alvarez Andres E, et al. Radiomics to predict outcomes and abscopal response of patients with cancer treated with immunotherapy combined with radiotherapy using a validated signature of CD8 cells. J Immunother Cancer. 2020;8(2):e001429. doi:10.1136/jitc-2020-001429.
78. Leroy A, Cafaro A, Lepetit V, Paragios N, Deutsch E, Grégoire V. OC-0448 bridging the gap between radiology and histology through ai-driven registration and reconstruction. Radiother Oncol. 2023;182:S350–S352. doi:10.1016/S0167-8140(23)08620-6.
79. Benzazon N, Carré A, De Kermenguy F, Niyoteka S, Maury P, Colnot J, M'hamdi M, Aichi ME, Veres C, Allodji R, et al. Deep-learning for rapid estimation of the out-of-field dose in external beam photon radiation therapy – a proof of concept. Int J Radiat Oncol. 2024 Mar. 120(1):S253–264. doi:10.1016/j.ijrobp.2024.03.007.
80. De Kermenguy F, Benzazon N, Maury P, Vauclin R, M'hamdi M, Cifliku V, Limkin E, Diallo I, Morel D, Milewski C, et al. LymphoDose: a lymphocyte dose estimation framework—application to brain radiotherapy. Phys Med Biol. 2024;69(10):105009. doi:10.1088/1361-6560/ad3c8d.
81. De Kermenguy F, Maury P, Nathan B, Deutsch E, Robert C. OC-0623 ultra-high dose rate irradiation spares a large quantity of circulating lymphocytes in brain tumours. Radiother Oncol. 2023;182:S512–S513. doi:10.1016/S0167-8140(23)08679-6.
82. Li Y, Fan X, Yu Q, Zhai H, Mo M, Sun J, Mi J, Lu R, Mao J, Chen J, et al. Proton and carbon ion radiation therapy decreased severe lymphopenia by reducing thoracic vertebra and aortic doses in non-small cell lung cancer versus intensity modulated radiation therapy. Int J Radiat Oncol. 2023;116(3):579–589. doi:10.1016/j.ijrobp.2022.12.030.
83. Wang X, Van Rossum PSN, Chu Y, Hobbs BP, Grassberger C, Hong TS, Liao Z, Yang J, Zhang X, Netherton T, et al. Severe lymphopenia during chemoradiation therapy for esophageal cancer: comprehensive analysis of randomized phase 2B trial of proton beam therapy versus intensity modulated radiation therapy. Int J Radiat Oncol. 2024;118(2):368–377. doi:10.1016/j.ijrobp.2023.08.058.
84. Hirose K, Sato M, Kato T, Takayama K, Suzuki M, Yamaguchi H, Seto I, Kikuchi Y, Murakami M, Takai Y. Profile analysis of adverse events after boron neutron capture therapy for head and neck cancer: a sub-analysis of the JHN002 study. J Radiat Res (Tokyo). 2022;63(3):393–401. doi:10.1093/jrr/rrac012.
85. Jin WH, Seldon C, Butkus M, Sauerwein W, Giap HB. A review of boron neutron capture therapy: its history and current challenges. Int J Part Ther. 2022;9(1):71–82. doi:10.14338/IJPT-22-00002.1.
86. König L, Hommertgen A, Orschiedt L, Hörner-Rieber J, Brons S, Huber PE, Debus J, Rieken S. Influence of photon, proton and carbon ion irradiation on differentiation, maturation and functionality of dendritic cells. Front Biosci-Sch. 2022;14(1):1. doi:10.31083/j.fbs1401002.
87. Walle T, Kraske JA, Liao B, Lenoir B, Timke C, Tran F, Halbach E, Tran F, Griebel P, Albrecht D, et al. Radiotherapy orchestrates natural killer cell dependent antitumor immune responses through CXCL8. Sci Adv. 2022;8(12):eabh4050. doi:10.1126/sciadv.abh4050.