ONCOIMMUNOLOGY
2016, VOL. 5, NO. 9, e1214790 (14 pages)
http://dx.doi.org/10.1080/2162402X.2016.1214790

Taylor & Francis
Taylor & Francis Group

REVIEW

Trial Watch: Immunotherapy plus radiation therapy for oncological indications

Erika Vacchelli[a,b,c,d,e,*], Norma Bloy[a,b,c,d,e,*], Fernando Aranda[f], Aitziber Buqué[a,b,c,d,e], Isabelle Cremer[a,b,c,g], Sandra Demaria[h], Alexander Eggermont[e], Silvia Chiara Formenti[h], Wolf Hervé Fridman[a,b,c,g], Jitka Fucikova[i,j], Jérôme Galon[a,b,c,k], Radek Spisek[i,j], Eric Tartour[b,l,m,n], Laurence Zitvogel[e,o], Guido Kroemer[a,b,c,d,p,q,r,**], and Lorenzo Galluzzi[a,b,c,d,e,h,**]

[a]INSERM, U1138, Paris, France; [b]Université Paris Descartes/Paris V, Sorbonne Paris Cité, Paris, France; [c]Université Pierre et Marie Curie/Paris VI, Paris, France; [d]Equipe 11 labellisée par la Ligue Nationale contre le Cancer, Center de Recherche des Cordeliers, Paris, France; [e]Gustave Roussy Cancer Campus, Villejuif, France; [f]Group of Immune receptors of the Innate and Adaptive System, Institut d'Investigacions Biomédiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain; [g]Equipe 13, Center de Recherche des Cordeliers, Paris, France; [h]Department of Radiation Oncology, Weill Cornell Medical College, New York, NY, USA; [i]Sotio, Prague, Czech Republic; [j]Department of Immunology, 2nd Faculty of Medicine and University Hospital Motol, Charles University, Prague, Czech Republic; [k]Laboratory of Integrative Cancer Immunology, Center de Recherche des Cordeliers, Paris, France; [l]INSERM, U970, Paris, France; [m]Paris-Cardiovascular Research Center (PARCC), Paris, France; [n]Service d'Immunologie Biologique, Hôpital Européen Georges Pompidou (HEGP), AP-HP, Paris, France; [o]INSERM, U1015, CICBT1428, Villejuif, France; [p]Pôle de Biologie, Hôpital Européen Georges Pompidou, AP-HP, Paris, France; [q]Metabolomics and Cell Biology Platforms, Gustave Roussy Cancer Campus, Villejuif, France; [r]Department of Women's and Children's Health, Karolinska University Hospital, Stockholm, Sweden

ABSTRACT

Malignant cells succumbing to some forms of radiation therapy are particularly immunogenic and hence can initiate a therapeutically relevant adaptive immune response. This reflects the intrinsic antigenicity of malignant cells (which often synthesize a high number of potentially reactive neo-antigens) coupled with the ability of radiation therapy to boost the adjuvanticity of cell death as it stimulates the release of endogenous adjuvants from dying cells. Thus, radiation therapy has been intensively investigated for its capacity to improve the therapeutic profile of several anticancer immunotherapies, including (but not limited to) checkpoint blockers, anticancer vaccines, oncolytic viruses, Toll-like receptor (TLR) agonists, cytokines, and several small molecules with immunostimulatory effects. Here, we summarize recent preclinical and clinical advances in this field of investigation.

Abbreviations: CTL, cytotoxic T lymphocyte; CTLA4, cytotoxic T lymphocyte associated protein 4; DC, dendritic cell; EBRT, external beam radiation therapy; FDA, Food and Drug Administration; GM-CSF, granulocyte macrophage colony-stimulating factor; HNSCC, head and neck squamous cell carcinoma; ICD, immunogenic cell death; IDH, isocitrate dehydrogenase ($NADP^+$) 1, cytosolic; IDO1, indoleamine 2,3-dioxygenase 1; IL, interleukin; mAb, monoclonal antibody; NK, natural killer; NSCLC, non-small cell lung carcinoma; TAA, tumor-associated antigen; TAM, tumor-associated macrophage; TGFβ1, transforming growth factor β1; TNF, tumor necrosis factor; TLR, Toll-like receptor

ARTICLE HISTORY
Received 15 July 2016
Accepted 15 July 2016

KEYWORDS
Danger-associated molecular patterns; immunogenic cell death; ipilimumab; nivolumab; pembrolizumab; TGFβ1

Introduction

Ionizing irradiation constitutes one of the pillars of modern cancer therapy.[1-4] According to current estimates, indeed, at least 50% of subjects with cancer (all confounded) have received or will receive radiation therapy in the course of their disease.[5,6] For a long time, radiation therapy was believed to operate in a merely cell-intrinsic manner, i.e., by promoting the death or permanent proliferative arrest of malignant cells upon the establishment of oxidative damage to macromolecules including DNA.[7-12] More recently, however, it has become clear that the antineoplastic effects of ionizing irradiation also involve a considerable cell-extrinsic component. Irradiated cancer cells release a wide panel of biologically active mediators that act locally to promote the death of bystander cells.[13-15] These factors include not only reactive oxygen and nitrogen species,[16-18] but also various potentially cytotoxic (and immunomodulatory) cytokines such as interleukin (IL)-6,[19] IL-8,[20] transforming growth factor β1 (TGFβ1),[21-24] and tumor necrosis factor (TNF).[25] Moreover, radiation therapy can promote a particularly immunogenic form of cell death that eventually stimulates the activation of a tumor-targeting immune response with systemic therapeutic potential.[26-32] The capacity of ionizing irradiation to stimulate anticancer immunity upon the induction of immunogenic cell death (ICD) explains the so-called abscopal or out-of-field effect, i.e., the relatively rare but sometimes very pronounced clinical response to radiation therapy that can manifest in distant, non-irradiated lesions.[33-38] Finally, some forms of radiation therapy promote the normalization of the tumor vasculature, hence improving the access of

CONTACT Guido Kroemer kroemer@orange.fr; Lorenzo Galluzzi deadoc@vodafone.it Center de Recherche des Cordeliers Equipe 11 (Kroemer) 15, rue de l'Ecole de Médecine, F-75006 Paris, France.
*These authors contributed equally to this work.
**These authors share senior co-authorship.

© 2016 Taylor & Francis Group, LLC

chemotherapeutic agents and immune effector cells to malignant lesions.[39-41]

For the purpose of this Trial Watch, radiation therapy can be broadly subdivided into two major therapeutic paradigms: external-beam radiotherapy (EBRT) and internal radiotherapy.[3,4] In the former setting, malignant lesions are treated across the intact skin, according to collimation procedures that can concentrate the irradiation energy on very specific areas of the tumor.[42,43] In the latter setting, radionuclides are brought in direct contact with transformed cells, either as pellets that are deposited within the tumor mass (a strategy that is known as brachytherapy), or upon conjugation with (or encapsulation within) tumor-targeting agents, including monoclonal antibodies (mAbs).[44-46] Both types of radiation therapy are associated with acute and chronic side effects.[47-50] Acute side effects stem from the unavoidable (but ever more limited, thanks to the technological advances in modern irradiators for clinical use) damage temporarily imposed by irradiation on particularly radiosensitive healthy tissues (like the skin) and often resolve in a few days/weeks after interruption.[44,51] On the contrary, the chronic toxicity of radiation therapy originates from the permanent damage possibly imposed by considerable radiation doses to stem cell compartments like intestinal crypts,[44,51] coupled to the establishment of dysregulated chronic inflammatory processes.[52] Moreover, radiation therapy has been linked to a small but non-negligible increase in incidence of secondary, treatment-related malignancies later in life.[53-55]

Throughout the past five decades, several strategies have been conceived to improve the therapeutic index of radiation therapy by either improving efficacy (radiosensitization) and/or by selectively limiting toxicity to normal tissues (radioprotection).[2,56-58] Multiple molecules have been shown to mediate consistent radiosensitization or radioprotection in rodent models of radiation therapy.[42] However, the antioxidant amifostine (also known as Ethyol®) remains the only agent that is licensed by the US Food and Drug Administration (FDA) for use as a radioprotector in humans.[59-63] One of the most common practices in radiation oncology is dose fractionation, i.e., the delivery of the total irradiation dose in multiple fractions (therapy sessions spaced by at least 6 h) over several days or weeks.[64,65] Fractionation exploits the improved capacity of normal over malignant tissues to repair the damage imposed by irradiation, hence maximizing its therapeutic window.[64,65] Importantly, total dose and delivery schedule have a prominent impact on the ability of radiation therapy to promote ICD and hence drive the establishment of a therapeutically relevant anticancer immune response.[28,64,66,67]

Classically, radiation therapy has been employed in the context of combinatorial treatment regimens (involving surgery and chemotherapy), either with a curative objective (i.e., with the aim to eradicate primary neoplasms or prevent recurrence) or with a palliative intent (i.e., to limit the pain/discomfort caused by malignancies at specific anatomical locations).[5,6] Along with the recognition that radiation therapy can mediate potent immunostimulatory effects, considerable interest has been attracted by combinatorial regimens involving EBRT plus one (or more) immunotherapeutic agent(s),[68-71] including checkpoint blockers,[72-75] immunostimulatory antibodies,[72,76] recombinant cytokines,[77-79] anticancer vaccines,[80-84] indoleamine 2,3-dioxygenase 1 (IDO1) inhibitors,[85,86] adoptively transferred cells,[87-89] oncolytic viruses,[90-93] Toll-like receptor (TLR) agonists,[94,95] and various small molecules that operate on the immunological tumor microenvironment. In this Trial Watch, we summarize recent preclinical and clinical advances in the development of combinatorial anticancer regimens based on EBRT plus immunotherapy.

Published literature—highlights

On 2016 May 1st, querying PubMed with the string "cancer AND radiation therapy AND (2014 OR 2015 OR 2016)" returned more than 23,000 entries, which gives a good indication on the continuous interest of scientists and clinicians in radiation oncology (source http://www.ncbi.nlm.nih.gov/pubmed). Obviously, a considerable fraction of such an extremely abundant literature deals with the cancer cell-intrinsic effects of radiation therapy.

Among these reports, we found of particular interest (and at least partially related to immunotherapy) the works of: (1) Boelens and collaborators (from the University of Pennsylvania, Philadelphia, PA, US), who identified an exosome-dependent mechanism linked to antiviral signaling[96] whereby stromal cells improve the resistance of breast cancer cells to radiation therapy;[97] (2) Leder and colleagues (from the University of Minnesota, Minneapolis, MN, US), who developed a mathematical model of platelet-derived growth factor (PDGF)-driven glioblastoma that allowed for the identification of optimal radiation dosing schedules;[98] (3) Tavora *et al.* (from the Queen Mary University, London, UK), who identified protein tyrosine kinase 2 (PTK2; best known as FAK)[99] within the endothelial (not malignant) tumor compartment as a prominent player in the resistance of neoplasms of DNA-damaging agents including radiation therapy;[100] (4) Tollini and co-workers (from the University of North Carolina at Chapel Hill, Chapel Hill, NC, US), who demonstrated that the capacity of MDM2 to tag tumor protein p53 (TP53; best p53)[101-103] for proteasomal degradation is dispensable during embryogenesis and development, but essential for normal cellular responses to DNA damage;[104] (5) Ceccaldi and collaborators (from the Harvard Medical School, Boston, MA, US), who identified in polymerase (DNA) theta (POLQ)[105] a key regulator or DNA repair in homologous recombination (HR)-deficient tumors;[106] (6) Moding and colleagues (from the Duke University Medical Center, Durham, NC, US), who showed that ATM (a kinase with a key role in the DNA damage response)[107] in malignant cells, but not in endothelial cells, is required for the eradication of experimental sarcomas by stereotactic body radiation therapy;[108] (7) Osswal *et al.* (from the University Hospital Heidelberg, Heidelberg, Germany), who identified cellular networks involving malignant astrocytes that underlie (at least in part) the pronounced radio- and chemoresistance of astrocytomas;[109] (8) Reid and coworkers (University of California at San Diego, La Jolla, CA, US), who demonstrated that the radiosensitizer RRx-001 (a hypoxia-inducible agent)[110] is well tolerated by patients with advanced solid tumors and appears to mediate clinical activity (at least to some extent);[111] (9) Tarish and collaborators (Karolinska Institute, Stockholm, Sweden), who demonstrated that the response of prostate cancer patients to radiation therapy is

exacerbated by chemical castration[112] (at least in part) as a consequence of deficient DNA repair in malignant cells;[113] and (10) Zhang and colleagues (University of Michigan, Ann Arbor, MI, US), who reported that the haploinsufficient tumor suppressor F-box and WD repeat domain containing 7 (FBXW7)[114-116] may constitute a promising target for radiosensitization owing to its role in non-homologous end-joining[117] DNA repair.[118]

Moreover, approximately 600 PubMed entries of those mentioned above contained the keyword "immunotherapy," dealing (from an experimental or theoretical perspective) with the possibility to combine radiation therapy with anticancer immunotherapy *in vitro, in vivo* or in patients (source http://www.ncbi.nlm.nih.gov/pubmed). Of these studies, we found of special interest the work of: (1) Deng and colleagues (from the University of Chicago, Chicago, Illinois, US), who not only demonstrated that radiation therapy and checkpoint blockade with antibodies specific for CD274 (best known as PD-L1)[119] synergize to promote antitumor immunity in mice, but also reported that transmembrane protein 173 (TMEM173; best known as STING)[120-122] signaling in dendritic cells (DCs) is essential for the elicitation of antitumor immune responses by radiation therapy;[123,124] (2) Denham and collaborators (from the University of Newcastle, Newcastle, Australia), who showed that zoledronic acid, an immunostimulatory agent that targets immunosuppressive tumor-associated macrophages (TAMs),[125-129] synergizes with radiation therapy and intermediate-term androgen deprivation in the treatment of patients with locally advanced prostate carcinoma;[130] (3) Vantourout *et al.* (from the King's College, London, UK), who confirmed that irradiation increases the immunological visibility of tumors also by promoting the upregulation of killer cell lectin-like receptor K1 (KLRK1; best known as NKG2D)[131-134] ligands in epithelial cells, hence favoring natural killer (NK) cell activation;[135,136] (4) Surave and colleagues (from the University of Zurich, Zurich, Switzerland), who involved the complement system in radiation therapy-driven anticancer immune responses;[137] and (5) Twyman-Saint Victor and collaborators (University of Pennsylvania, Philadelphia, PA, US), who identified in the upregulation of PD-L1 a common mechanism whereby human and murine tumors become resistant to radiation therapy plus checkpoint blockers specific for cytotoxic T lymphocyte-associated protein 4 (CTLA), and demonstrated that anti-PD-L1 antibodies can be efficiently employed to revert resistance (at least in mice).[138] Moreover, one of our laboratories provided proof-of-principle clinical evidence in support of the possibility to combine local radiation therapy with recombinant granulocyte macrophage colony-stimulating factor (GM-CSF) to increase the incidence of therapeutically relevant abscopal effects in patients with advanced solid tumors.[139] Finally, we demonstrated that the so-called immunoscore (a multiparametric biomarker conveying quantitative and spatial information on the immunological tumor infiltrate)[140] not only conveys prognostic information for patients with rectal carcinoma treated by primary surgery, but also predicts clinical response to preoperative chemoradiation.[141]

Besides unveiling parts of the mechanism whereby cancer cells may become resistant to the cytostatic and cytotoxic effects of irradiation, these findings lend additional support to the notion that radiation therapy and immunotherapy may be conveniently combined to improve disease outcome in cancer patients.

Ongoing studies

In the period of time elapsing since the publication of the latest Trial Watch dealing with topic (2014 July 1st)[42] through 2016 May 1st, no less than 620 clinical studies testing the safety and efficacy of anticancer therapeutic regimens based on (or at least involving) EBRT have been initiated (source: https://clinicaltrials.gov/). Nearly one-third of these studies (210 trials) investigates the clinical profile of EBRT as a standalone therapeutic intervention, in particular among patients affected by breast carcinoma (34 studies), prostate cancer (44 studies), non-small cell lung carcinoma (NSCLC; 15 studies), and hepatocellular carcinoma (14 studies). Some additional 220 trials initiated between 2014 July 1st and 2016 May 1st assess the safety and efficacy EBRT in combination with various chemotherapeutic regimens, for the most part among individuals with head and neck cancer (34 studies), esophageal cancer (32 studies), pancreatic carcinoma (25 studies), and NSCLC (19 studies). Finally, approximately 70 of these trials evaluate the therapeutic profile of EBRT combined with targeted anticancer agents, including tumor-targeting mAbs such as the epidermal growth factor receptor (EGFR)-specific molecule cetuximab,[142-145] or with various alternative non-immunotherapeutic interventions, like hyperthermia or nanoparticles. Since all these studies do not involve *bona fide* immunotherapeutic agents, we will not discuss them in further detail here. Rather, we will focus on 95 clinical trials initiated between 2014 July 1st and 2016 May 1st that aim to evaluate the safety and efficacy of EBRT combined with immunomodulatory mAbs including checkpoint blockers (66 studies), adoptive cell transfer (4 studies), TLR agonists (4 studies), DC-based vaccination (5 studies), recombinant cytokines (4 studies), peptide-based vaccines (3 studies), oncolytic virotherapy (2 studies), or other immunostimulatory agents (10 studies) (source: https://clinicaltrials.gov/).

The safety and efficacy of EBRT combined with the FDA-approved CTLA4-targeting checkpoint blocker ipilimumab[36,146,147] alone or with ipilimumab plus the experimental TLR9 agonist SD-101[94,148-150] is being assessed in cohorts of melanoma patients (NCT02406183, NCT02662725), NSCLC patients (NCT02221739),[151] lymphoma patients (NCT02254772),[152] and individuals with advanced solid tumors (NCT0223 9900). EBRT is being tested together with nivolumab, an FDA-approved checkpoint blocker targeting programmed cell death 1 (PDCD1; best known as PD-1),[153-155] alone or in combination with cytotoxic chemotherapy or targeted anticancer agents, in patients with breast carcinoma (NCT02499367), glioblastoma (NCT02617589, NCT02667587), head and neck squamous cell carcinoma (HNSCC) (NCT02684253, NCT02764593), melanoma (NCT02716948), and NSCLC (NCT02768558). In addition, EBRT plus a combined immunotherapeutic regimen involving both ipilimumab and nivolumab is being assessed for safety and efficacy in individuals affected by melanoma (NCT02659540) or intracranial metastases originated from NSCLC (NCT02696993). The clinical profile of EBRT given in combination with yet another FDA-approved PD-1-targeting checkpoint blocker, i.e.,

Table 1. Clinical trials recently started to investigate the safety and efficacy of EBRT plus immunostimulatory antibodies in cancer patients*.

Antibody	Indication(s)	Phase	Status	Type of RT	Notes	Ref.
Adalimumab	Thyroid cancers	I	Recruiting	EBRT	Combined with chemotherapy	NCT02516774
AMP-224**	Colorectal carcinoma	I	Active, not recruiting	SBRT	Combined with cyclophosphamide	NCT02298946
Atezolizumab	NSCLC	0	Recruiting	HIGRT	None	NCT02463994
		I	Not yet recruiting	SBRT	None	NCT02400814
		I	Not yet recruiting	SBRT	None	NCT02599454
		II	Not yet recruiting	EBRT	Combined with carboplatin and paclitaxel	NCT02525757
Avelumab	Merkel cell carcinoma	I/II	Recruiting	EBRT	Combined with recombinant IFN-β and polyclonal autologous $CD8^+$ CTLs	NCT02584829
Combo	Melanoma	I	Not yet recruiting	EBRT	Ipilimumab and/or nivolumab	NCT02659540
	Pancreatic cancer	I	Recruiting	SBRT	Tremelimumab and/or MEDI4736	NCT02311361
	SCLC	II	Recruiting	HRT, SBRT	Durvalumab and/or tremelimumab	NCT02701400
	Solid tumors	I	Recruiting	HRT	Durvalumab and/or tremelimumab	NCT02639026
		I/II	Not yet recruiting	SRS, WBRT	Ipilimumab and/or nivolumab	NCT02696993
Durvalumab	Esophageal carcinoma	I/II	Not yet recruiting	EBRT	Combined with CAPOX	NCT02735239
	Glioblastoma	II	Recruiting	EBRT	None	NCT02336165
Fresolimumab	NSCLC	I/II	Not yet recruiting	SABR, SBRT	None	NCT02581787
IPH2201	HNSCC	I/II	Recruiting	EBRT	None	NCT02331875
Ipilimumab	Lymphoma	I/II	Recruiting	EBRT	Combined with SD-101 (TLR9 agonist)	NCT02254772
	Melanoma	I	Recruiting	SBRT	None	NCT02406183
		II	Completed	SRS	None	NCT02662725
	NSCLC	II	Active, not recruiting	3D-EBRT, IMRT	None	NCT02221739
	Solid tumors	I/II	Recruiting	SBRT	None	NCT02239900
Nivolumab	Breast carcinoma	II	Recruiting	EBRT	None	NCT02499367
	Glioblastoma	II	Recruiting	EBRT	Combined with temozolomide	NCT02667587
		III	Not yet recruiting	EBRT	Combined with temozolomide	NCT02617589
	HNSCC	I	Not yet recruiting	IMRT	Combined with cetuximab and/or cisplatin	NCT02764593
		II	Recruiting	SBRT	None	NCT02684253
	Melanoma	I	Recruiting	SBRT	None	NCT02716948
	NSCLC	III	Not yet recruiting	3D-EBRT, IMRT	Combined with cisplatin and etoposide	NCT02768558
Pembrolizumab	Bladder carcinoma	I	Not yet recruiting	EBRT	None	NCT02560636
		II	Not yet recruiting	EBRT	Combined with gemcitabine	NCT02621151
		II	Not yet recruiting	EBRT	Combined with cisplatin	NCT02662062
	Breast carcinoma	I	Recruiting	SABR	None	NCT02303366
		II	Not yet recruiting	EBRT	None	NCT02730130
	Colorectal carcinoma	II	Not yet recruiting	EBRT	Combined with capecitabine	NCT02586610
		II	Recruiting	EBRT	None	NCT02437071
	Endometrial carcinoma	0	Not yet recruiting	EBRT	Combined with carboplatin and paclitaxel	NCT02630823
	Gastroesophageal carcinoma	0	Not yet recruiting	HDRB	None	NCT02642809
		I/II	Not yet recruiting	EBRT	Combined with carboplatin and paclitaxel	NCT02730546
	Glioblastoma	I/II	Recruiting	Focal RT	Combined with temozolomide	NCT02530502
	Glioma	I	Recruiting	HSBRT	Combined with bevacizumab	NCT02313272
	HNSCC	I	Not yet recruiting	IMRT	Combined with cisplatin	NCT02775812
		I	Recruiting	EBRT	Combined with cisplatin	NCT02586207
		I/II	Recruiting	EBRT	Combined with cisplatin	NCT02759575
		II	Not yet recruiting	IMRT	None	NCT02609503
		II	Not yet recruiting	EBRT	Combined with cetuximab	NCT02707588
		II	Not yet recruiting	IMRT	Combined with cisplatin	NCT02777385
		II	Recruiting	EBRT	None	NCT02289209
		II	Recruiting	IGRT, IMRT	Combined with cisplatin	NCT02296684
		II	Recruiting	EBRT	Combined with cisplatin	NCT02641093
	Lymphoma	II	Recruiting	EBRT	Combined with autologous DCs	NCT02677155
	Melanoma	II	Not yet recruiting	EBRT	None	NCT02562625
	NSCLC	I	Not yet recruiting	3D-EBRT, IMRT	Combined with carboplatin and paclitaxel	NCT02621398
		I/II	Recruiting	SBRT, WFRT	None	NCT02444741
		II	Not yet recruiting	SFRT	None	NCT02658097
		II	Recruiting	SBRT	None	NCT02492568
	Pancreatic carcinoma	I/II	Recruiting	EBRT	Combined with capecitabine	NCT02305186
		II	Not yet recruiting	SBRT	Combined with a genetically-modified allogenic cancer cell-based vaccine and cyclophosphamide	NCT02648282
	Renal cell carcinoma	II	Not yet recruiting	SBRT	None	NCT02599779
	SCLC	I	Recruiting	EBRT	Combined with multimodal chemotherapy	NCT02402920
	Solid tumors	I	Not yet recruiting	SBRT	None	NCT02608385
		I	Recruiting	HRT	None	NCT02303990
		I	Recruiting	EBRT	None	NCT02318771
		I/II	Recruiting	SBRT	None	NCT02407171
	Thoracic tumors	I	Not yet recruiting	Palliative RT	None	NCT02587455
REGN2810	Solid tumors	I	Recruiting	HRT	Combined with cyclophosphamide	NCT02383212
Tremelimumab	Breast carcinoma	EBRT	Recruiting	SRS WBRT	None	NCT02563925
Varlilumab	Prostate cancer	I	Recruiting	SBRT	None	NCT02284971

Abbreviations: 3D-CRT, 3D conformal radiotherapy; CAPOX, capecitabine plus oxaliplatin; CTL, cytotoxic T lymphocyte; DC, dendritic cell; EBRT, external beam radiation therapy; HIGRT, hypofractionated image-guided radiotherapy; HNSCC, head and neck squamous cell carcinoma; HRT, hypofractionated radiation therapy; HSRT, hypofractionated stereotactic radiation therapy; IFN-β, interferon β; IMRT, intensity-modulated radiation therapy; NSCLC, non-small cell lung carcinoma; SART, stereotactic ablation radiation therapy; SBRT, stereotactic body radiation therapy; SCLC, small cell lung carcinoma; SRS, stereotactic radiosurgery; WBRT, whole brain radiation therapy; WFRT, wide-field radiation therapy. *initiated between 2014, July 1st and 2016, May 1st; **anti-PD-1 fusion protein.

pembrolizumab,[156-160] generally alone or in the context of conventional chemotherapeutic regimens, is being investigated among patients with HNSCC (NCT02289209, NCT02296684, NCT02402920, NCT02586207, NCT02609503, NCT02641093, NCT02707588, NCT02759575, NCT02775812, NCT02777385), lung carcinoma (NCT02444741, NCT02492568, NCT02621398, NCT02658097), bladder carcinoma (NCT02560636, NCT02621151, NCT02662062), brain tumors (NCT02530502, NCT02313272), colorectal carcinoma (NCT02437071, NCT02586610),[161] gastroesophageal cancer (NCT02730546), breast carcinoma (NCT02303366, NCT02730130), endometrial cancer (NCT02630823), melanoma (NCT02562625), pancreatic carcinoma (NCT02305186), renal cell carcinoma (NCT02599779), thoracic tumors (NCT02587455), or advanced solid tumors of multiple derivation (NCT02303990, NCT02318771, NCT02407171, NCT02608385). In addition, EBRT plus pembrolizumab-based immunotherapy is being tested in combination with a genetically modified allogenic cancer cell-based vaccine (GVAX)[162-164] in subjects with pancreatic cancer (NCT02648282), or together with intratumoral autologous DCs[165-171] in patients with lymphoma (NCT02677155) (Table 1).

Additional (hitherto experimental) checkpoint blockers that are being investigated for their capacity to synergize with EBRT include: (1) atezolizumab, a mAb specific for PD-L1,[119,172-175] which is administered together with EBRT alone or with EBRT plus conventional chemotherapy to NSCLC patients (NCT02400814, NCT02463994, NCT02525757, NCT02599454); (2) avelumab, another PD-L1-targeting mAb,[175-177] which is given to Merkel cell carcinoma patients in combination with EBRT (as a measure to upregulate MHC Class I expression by cancer cells) and optionally autologous T lymphocytes genetically redirected against tumor-associated antigens (TAAs) (NCT02584829); (4) the PD-L1-specific mAbs durvalumab,[178] which is tested in combination with EBRT alone, EBRT plus chemotherapy, or EBRT plus the CTLA4-targeting agent tremelimumab[179,180] in patients with esophageal cancer (NCT02735239), glioblastoma (NCT02336165) small cell lung carcinoma (NCT02701400), and advanced solid tumors (NCT02639026), and MEDI4736,[181-184] which is studied in combination with EBRT plus tremelimumab in subjects with unresectable pancreatic cancer (NCT02311361); (5) a new mAb specific for PD-1, namely, REGN2810, whose safety and efficacy in combination with EBRT plus cyclophosphamide-based chemotherapy and recombinant GM-CSF are assessed in patients with advanced solid neoplasms (NCT02383212);[185] (6) a novel fusion protein-targeting PD-1 (called AMP-224; source http://www.cancer.gov/publications/dictionaries/cancer-drug?cdrid=700595), which is tested together with EBRT in colorectal carcinoma patients (NCT02298946); (7) tremelimumab, whose clinical profile in combination with EBRT is investigated in breast carcinoma patients (NCT02563925); and IPH2201, a mAb specific for killer cell lectin-like receptor C1 (KLRC1; an inhibitory NK-cell receptor best known as NKG2A),[186-188] which is studied together with EBRT in HNSCC patients (NCT02331875) (Table 1).

The following immunostimulatory antibodies that do not operate as checkpoint blockers are also being evaluated for their safety and efficacy when administered in combination with EBRT: (1) the FDA-approved mAb adalimumab, an inhibitor of TNF and hence of immunosuppressive TAMs,[189-193] which is tested together with EBRT in patients with anaplastic thyroid tumors (NCT02516774); (2) fresolimumab, a mAb that neutralizes TGFβ1,[22,66,194-197] which is studied in combination with EBRT in individuals with NSCLC (NCT02581787); and (3) varlilumab, an immunostimulatory mAb specific for CD27,[198-201] which is assessed for its capacity to improve the efficacy of EBRT in subjects with prostate carcinoma (NCT02284971) (Table 1).

As for immunotherapies not based on checkpoint blockers and other immunostimulatory antibodies, EBRT is being evaluated in combination with: (1) autologous DCs expanded *ex vivo* in the presence of tumor cell lysates[202,203] in children with advanced solid tumors (NCT02496520) or in Grade IV glioma patients (NCT02772094); (2) unmodified autologous DCs re-infused upon expansion *ex vivo*, in subjects with NSCLC concurrently receiving standard-of-care platinum-based chemotherapy[204,205] (NCT02662634); (3) an autologous DC-based vaccine specific for mutant isocitrate dehydrogenase (NADP$^+$) 1, cytosolic (IDH1)[206-208] in glioma patients bearing IDH1^{R132H} (NCT02771301); and (4) vaccines based on TAA-derived peptides or heat-shock protein (HSP)-enriched preparations of tumor lysates[209] in glioma patients (NCT02287428, NCT02722512) or women with cervical carcinoma concurrently receiving cisplatin-based chemotherapy (NCT02722512); (5) FDA-approved[90,210] or experimental[211] oncolytic viruses in individuals with soft tissue sarcoma (NCT02453191) or children with brain malignancies (NCT02457845) (Table 2).

In addition, the safety and efficacy of EBRT combined with immunotherapy is being assessed in the context of (1) adoptive cell transfer,[87,212] in colorectal cancer patients receiving autologous DCs plus cytokine induced killer (CIK) cells along with FOLFOX (folinic acid plus 5-fluoruracil plus oxaliplatin) chemotherapy (NCT02202928), sarcoma patients treated with autologous CD8$^+$ cytotoxic T lymphocytes (CTLs) genetically modified to recognize the TAA NY-ESO-1 (NCT02319824), and hepatocellular carcinoma patients receiving highly purified autologous CD8$^+$ CTLs (NCT02678013); (2) TLR stimulation,[94] in soft tissue sarcoma patients receiving the experimental TLR4 agonist glucopyranosyl lipid adjuvant in stable emulsion (GLA-SE)[213,214] (NCT02180698), lymphoma patients concurrently administered with the experimental TLR9 agonist SD-101[215,216] (NCT02266147), and melanoma patients co-treated with the FDA-approved TLR7 agonist imiquimod[217-221] (NCT02394132); and (3) relatively unspecific immunostimulation with recombinant IL-2 or GM-CSF in patients with renal cell carcinoma (NCT02306954), glioblastoma (NCT02663440), and NSCLC (NCT02735850), with thymalfasin (a recombinant version of the human T$_H$1-skewing peptide thymosin α1)[222] in colorectal cancer patients (NCT02535988), lung cancer patients (NCT02542137, NCT02542930), and esophageal cancer patients (NCT02545751), with TAM-targeting agents like trabectedin[223-225] or zoledronic acid[128,226] in subjects with soft tissue sarcoma (NCT02275286) or metastatic NSCLC (NCT02480634), with a chemical inhibitor of IDO1 (i.e., indoximod)[196,227] in children with brain tumors concurrently receiving temozolomide-based chemotherapy (NCT02502708), with chemical inhibitors of the TGFβ1 receptor[228-230] in breast carcinoma patients (NCT02538471) and rectal carcinoma patients concurrently treated with standard-of-care chemotherapy (NCT026887129), and with

Table 2. Clinical trials recently started to investigate the safety and efficacy of EBRT plus other forms of immunotherapy in cancer patients*.

Immunotherapy	Indication(s)	Phase	Status	Type of RT	Notes	Ref.
ACT	Colorectal carcinoma	II	Active, not recruiting	EBRT	DC-CIK cells combined with FOLFOX regimen	NCT02202928
	Hepatocellular carcinoma	III	Active, not recruiting	RFA	Highly-purified autologous $CD8^+$ CTLs	NCT02678013
	Merkel cell carcinoma	I/II	Recruiting	EBRT	Polyclonal autologous $CD8^+$ CTLs combined with recombinant IFN-β and an anti-PD-L1 mAb	NCT02584829
	Sarcoma	I	Recruiting	Palliative EBRT	Autologous NY-ESO-1-specific $CD8^+$ CTLs	NCT02319824
Celecoxib	HNSCC	II	Recruiting	EBRT	COX2 inhibitor	NCT02739204
Cytokines	Glioblastoma	II	Recruiting	HIMRT	GM-CSF combined with temozolomide	NCT02663440
	Merkel cell carcinoma	I/II	Recruiting	EBRT	Recombinant IFN-β combined with polyclonal autologous $CD8^+$ CTLs and an anti-PD-L1 mAb	NCT02584829
	NSCLC	II	Not yet recruiting	SBRT	L19-IL2 immunocytokine	NCT02735850
	Renal cell carcinoma	II	Recruiting	SBRT	High-dose IL-2	NCT02306954
DC-based interventions	Glioma	n.a.	Recruiting	EBRT	Combined with chemotherapy	NCT02771301
	Glioma	II	Active, not recruiting	EBRT	Combined with temozolomide	NCT02772094
	Lymphoma	II	Recruiting	EBRT	Combined with pembrolizumab	NCT02677155
	NSCLC	I/II	Recruiting	EBRT	Combined with chemotherapy	NCT02662634
	Solid tumors	I/II	Recruiting	EBRT	Combined with chemotherapy	NCT02496520
Indoximod	Brain tumors	I	Recruiting	CRT	IDO1 inhibitor, combined with temozolomide	NCT02502708
LY2157299	Breast carcinoma	II	Recruiting	EBRT	TGFBR1 inhibitor	NCT02538471
	Rectal carcinoma	II	Not yet recruiting	EBRT	TGFBR1 inhibitor, combined with chemotherapy	NCT02688712
Oncolytic virotherapy	Brain tumors	I	Not yet recruiting	EBRT	Oncolytic HSV-1 (G207)	NCT02457845
	Soft tissue sarcoma	I/II	Recruiting	EBRT	Talimogene laherparepvec	NCT02453191
Thymalfasin	Colorectal carcinoma	II	Not yet recruiting	EBRT	Unspecific immunostimulatory agent, aimed at improving abscopal effects	NCT02535988
	Esophageal carcinoma	II	Not yet recruiting	SBRT	Unspecific immunostimulatory agent, aimed at improving abscopal effects	NCT02545751
	NSCLC	II	Not yet recruiting	EBRT	Unspecific immunostimulatory agent, aimed at improving abscopal effects	NCT02542930
	SCLC	II	Not yet recruiting	EBRT	Unspecific immunostimulatory agent, aimed at improving abscopal effects	NCT02542137
TLR agonists	Lymphoma	I/II	Recruiting	EBRT	SD-101 (TLR9 agonist), combined with ipilimumab	NCT02254772
		I/II	Recruiting	EBRT	SD-101 (TLR9 agonist)	NCT02266147
	Melanoma	III	Not yet recruiting	EBRT	Imiquimod (TLR7 agonist)	NCT02394132
	Soft tissue sarcoma	I	Recruiting	EBRT	GLA-SE (TLR4 agonist)	NCT02180698
Trabectedin	Soft tissue sarcoma	I/II	Recruiting	3D-CRT	TAM-targeting agent	NCT02275286
Vaccination	Cervical cancer	II	Not yet recruiting	EBRT	Peptide-based vaccine, combined with cisplatin	NCT02501278
	Glioblastoma	I	Recruiting	EBRT	Peptide-based vaccine	NCT02287428
	Glioma	I	Not yet recruiting	Focal RT	HSP-based vaccine	NCT02722512
	Pancreatic carcinoma	II	Not yet recruiting	SBRT	Allogenic cancer cell-based vaccine, combined with cyclophosphamide and pembrolizumab	NCT02648282
Zoledronic acid	NSCLC	IV	Not yet recruiting	EBRT	TAM-targeting agent	NCT02480634

Abbreviations: 3D-CRT, 3D conformal radiotherapy; ACT, adoptive cell transfer; CIK, cytokine induced killer; CRT, conformal radiotherapy; CTL, cytotoxic T lymphocyte; DC, dendritic cell; EBRT, external beam radiation therapy; FOLFOX, folinic acid plus 5-fluoruracil plus oxaliplatin; GLA-SE, glucopyranosyl lipid adjuvant in stable emulsion; GM-CSF, granulocyte macrophage colony-stimulating factor; HIMRT, hypofractionated intensity-modulated radiation therapy; HNSCC, head and neck squamous cell carcinoma; HSP, heat-shock protein; HSV-1, herpes simplex virus type 1; IDO1, indoleamine 2,3-dioxygenase 1; IFN-β, interferon β; IL-2, interleukin-2; mAb, monoclonal antibody; NSCLC, non-small cell lung carcinoma; RFA, radiofrequency ablation; RT, radiation therapy; SBRT, stereotactic body radiation therapy; SCLC, small cell lung carcinoma; TAM, tumor-associated macrophage; TGFBR1, transforming growth factor β receptor 1; TLR, toll-like receptor. *initiated between 2014, July 1st and 2016, May 1st.

celecoxib, an inhibitor of the immunosuppressive enzyme prostaglandin-endoperoxide synthase 2 (PTGS2; best known as COX2),[231,232] in HNSCC patients (NCT02739204) (Table 2).

With a single exception, all these studies are ongoing (i.e., they are listed as "Active, not recruiting," "Not yet recruiting" or "Recruiting" by official sources). NCT02662725, a Phase II clinical trial testing stereotactic radiosurgery plus ipilimumab-based immunotherapy in melanoma patients with brain metastases, appears as "Completed." To the best of our knowledge, however, he results of this study have not yet been disseminated (sources: https://clinicaltrials.gov/; http://www.ncbi.nlm.nih.gov/pubmed; and http://meetinglibrary.asco.org/abstracts;).

Concluding remarks

Total-body irradiation has been extensively employed in the clinic as a myelo- and lymphoablating measure to pre-condition hematopoietic stem cell transplantation recipients.[233] Nonetheless, it is now well established that the localized, targeted irradiation of malignant lesions in the context of dose

fractionation within the standard therapeutic range promotes direct antineoplastic effects while eliciting a therapeutically relevant anticancer immune response.[234] Thus, radiation therapy currently stands out as an accessible and promising tool for improving the efficacy of immunotherapeutic agents as diverse as checkpoint blockers, immunostimulatory antibodies, anticancer vaccines, oncolytic viruses, recombinant cytokines, TLR agonists, and small molecules that repolarize the tumor microenvironment. The clinical activity of all these immunotherapeutic interventions (and presumably that of many chemotherapeutic agents as well)[29] relies indeed on the activation of a robust and polyclonal tumor-specific immune response, and radiation therapy has been convincingly demonstrated to promote such a response by favoring the release of immunostimulatory signals by dying cancer and stromal cells, hence improving their adjuvanticity.[31,235] Intriguingly, fractionated radiation appears to be superior to single-dose radiation therapy in its capacity to trigger anticancer immune responses *in vivo*.[64,236] This has been linked to improved capacity of fractionated radiation (as compared to single-dose radiation therapy) to induce the release of damage-associated molecular patterns (DAMPs) by the tumor.[237,238] In addition, it may reflect (at least in part) the capacity of fractionated (but not single-dose) radiation to temporarily allow for the survival of malignant cells accumulating genetic and genomic defects that result in exacerbated antigenicity.[239-241] This intriguing hypothesis has not yet been formally addressed. Irrespectively, by virtue of its well-established efficacy and safety profile, radiation therapy lies together with chemotherapy and immunotherapy at the core of a multimodal therapeutic regimen that holds great promise for the future of clinical tumor immunology.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

Funding

FA is supported by Sara Borrell fellowship CD15/00016 from Instituto de Salud Carlos III. GK is supported by the French Ligue contre le Cancer (équipe labellisée); Agence National de la Recherche (ANR) – Projets blancs; ANR under the frame of E-Rare-2, the ERA-Net for Research on Rare Diseases; Association pour la recherche sur le cancer (ARC); Cancéropôle Ile-de-France; Institut National du Cancer (INCa); Institut Universitaire de France; Fondation pour la Recherche Médicale (FRM); the European Commission (ArtForce); the European Research Council (ERC); the LeDucq Foundation; the LabEx Immuno-Oncology; the SIRIC Stratified Oncology Cell DNA Repair and Tumor Immune Elimination (SOCRATE); the SIRIC Cancer Research and Personalized Medicine (CARPEM); and the Paris Alliance of Cancer Research Institutes (PACRI). SD is supported by the National Institutes of Health R01 CA201246 and R01 CA198533, the Breast Cancer Research Foundation, and the Chemotherapy Foundation. SCF is supported by the National Institutes of Health R01 CA161891, the USA Department of Defense Breast Cancer Research Program (W81XWH-11-1-0530); and the Breast Cancer Research Foundation.

References

1. Bernier J, Hall EJ, Giaccia A. Radiation oncology: a century of achievements. Nat Rev Cancer 2004; 4:737-47; PMID:15343280; http://dx.doi.org/10.1038/nrc1451
2. Thariat J, Hannoun-Levi JM, Sun Myint A, Vuong T, Gerard JP. Past, present, and future of radiotherapy for the benefit of patients. Nat Rev Clin Oncol 2013; 10:52-60; PMID:23183635; http://dx.doi.org/10.1038/nrclinonc.2012.203
3. Baumann M, Krause M, Overgaard J, Debus J, Bentzen SM, Daartz J, Richter C, Zips D, Bortfeld T. Radiation oncology in the era of precision medicine. Nat Rev Cancer 2016; 16:234-49; PMID:27009394; http://dx.doi.org/10.1038/nrc.2016.18
4. Schaue D, McBride WH. Opportunities and challenges of radiotherapy for treating cancer. Nat Rev Clin Oncol 2015; 12:527-40; PMID:26122185; http://dx.doi.org/10.1038/nrclinonc.2015.120
5. Delaney G, Jacob S, Featherstone C, Barton M. The role of radiotherapy in cancer treatment: estimating optimal utilization from a review of evidence-based clinical guidelines. Cancer 2005; 104:1129-37; PMID:16080176; http://dx.doi.org/10.1002/cncr.21324
6. Siegel R, DeSantis C, Virgo K, Stein K, Mariotto A, Smith T, Cooper D, Gansler T, Lerro C, Fedewa S et al. Cancer treatment and survivorship statistics, 2012. CA Cancer J Clin 2012; 62:220-41; PMID:22700443; http://dx.doi.org/10.3322/caac.21149
7. Roos WP, Thomas AD, Kaina B. DNA damage and the balance between survival and death in cancer biology. Nat Rev Cancer 2016; 16:20-33; PMID:26678314; http://dx.doi.org/10.1038/nrc.2015.2
8. Perez-Mancera PA, Young AR, Narita M. Inside and out: the activities of senescence in cancer. Nat Rev Cancer 2014; 14:547-58; PMID:25030953; http://dx.doi.org/10.1038/nrc3773
9. Bolanos-Garcia VM. Formation of multiprotein assemblies in the nucleus: the spindle assembly checkpoint. Int Rev Cell Mol Biol 2014; 307:151-74; PMID:24380595; http://dx.doi.org/10.1016/B978-0-12-800046-5.00006-0
10. Vitale I, Galluzzi L, Castedo M, Kroemer G. Mitotic catastrophe: a mechanism for avoiding genomic instability. Nat Rev Mol Cell Biol 2011; 12:385-92; PMID:21527953; http://dx.doi.org/10.1038/nrm3115
11. Galluzzi L, Bravo-San Pedro JM, Kroemer G. Organelle-specific initiation of cell death. Nat Cell Biol 2014; 16:728-36; PMID:25082195; http://dx.doi.org/10.1038/ncb3005
12. Campisi J, d'Adda di Fagagna F. Cellular senescence: when bad things happen to good cells. Nat Rev Mol Cell Biol 2007; 8:729-40; PMID:17667954; http://dx.doi.org/10.1038/nrm2233
13. Mothersill C, Seymour CB. Radiation-induced bystander effects–implications for cancer. Nat Rev Cancer 2004; 4:158-64; PMID:14964312; http://dx.doi.org/10.1038/nrc1277
14. Prise KM, O'Sullivan JM. Radiation-induced bystander signalling in cancer therapy. Nat Rev Cancer 2009; 9:351-60; PMID:19377507; http://dx.doi.org/10.1038/nrc2603
15. Golden EB, Formenti SC. Is tumor (R)ejection by the immune system the "5th R" of radiobiology? Oncoimmunology 2014; 3:e28133; PMID:24800177; http://dx.doi.org/10.4161/onci.28133
16. Lehnert BE, Goodwin EH, Deshpande A. Extracellular factor(s) following exposure to alpha particles can cause sister chromatid exchanges in normal human cells. Cancer Res 1997; 57:2164-71; PMID:9187116
17. Shao C, Furusawa Y, Aoki M, Matsumoto H, Ando K. Nitric oxide-mediated bystander effect induced by heavy-ions in human salivary gland tumour cells. Int J Radiat Biol 2002; 78:837-44; PMID:12428924; http://dx.doi.org/10.1080/09553000210149786
18. Shao C, Stewart V, Folkard M, Michael BD, Prise KM. Nitric oxide-mediated signaling in the bystander response of individually targeted glioma cells. Cancer Res 2003; 63:8437-42; PMID:14679007
19. Chou CH, Chen PJ, Lee PH, Cheng AL, Hsu HC, Cheng JC. Radiation-induced hepatitis B virus reactivation in liver mediated by the bystander effect from irradiated endothelial cells. Clin Cancer Res 2007; 13:851-7; PMID:17289877; http://dx.doi.org/10.1158/1078-0432.CCR-06-2459
20. Narayanan PK, LaRue KE, Goodwin EH, Lehnert BE. Alpha particles induce the production of interleukin-8 by human cells. Radiat Res 1999; 152:57-63; PMID:10381841; http://dx.doi.org/10.2307/3580049
21. Iyer R, Lehnert BE, Svensson R. Factors underlying the cell growth-related bystander responses to alpha particles. Cancer Res 2000; 60:1290-8; PMID:10728689

22. Vanpouille-Box C, Diamond JM, Pilones KA, Zavadil J, Babb JS, Formenti SC, Barcellos-Hoff MH, Demaria S. TGFbeta is a master regulator of radiation therapy-induced antitumor immunity. Cancer Res 2015; 75:2232-42; PMID:25858148; http://dx.doi.org/10.1158/0008-5472.CAN-14-3511
23. Bouquet F, Pal A, Pilones KA, Demaria S, Hann B, Akhurst RJ, Babb JS, Lonning SM, DeWyngaert JK, Formenti SC et al. TGFbeta1 inhibition increases the radiosensitivity of breast cancer cells in vitro and promotes tumor control by radiation in vivo. Clin Cancer Res 2011; 17:6754-65; PMID:22028490; http://dx.doi.org/10.1158/1078-0432.CCR-11-0544
24. Young KH, Gough MJ, Crittenden M. Tumor immune remodeling by TGFbeta inhibition improves the efficacy of radiation therapy. Oncoimmunology 2015; 4:e955696; PMID:25949887; http://dx.doi.org/10.4161/21624011.2014.955696
25. Zhou H, Ivanov VN, Gillespie J, Geard CR, Amundson SA, Brenner DJ, Yu Z, Lieberman HB, Hei TK. Mechanism of radiation-induced bystander effect: role of the cyclooxygenase-2 signaling pathway. Proc Natl Acad Sci U S A 2005; 102:14641-6; PMID:16203985; http://dx.doi.org/10.1073/pnas.0505473102
26. Galluzzi L, Bravo-San Pedro JM, Vitale I, Aaronson SA, Abrams JM, Adam D, Alnemri ES, Altucci L, Andrews D, Annicchiarico-Petruzzelli M et al. Essential versus accessory aspects of cell death: recommendations of the NCCD 2015. Cell Death Differ 2015; 22:58-73; PMID:25236395; http://dx.doi.org/10.1038/cdd.2014.137
27. Golden EB, Pellicciotta I, Demaria S, Barcellos-Hoff MH, Formenti SC. The convergence of radiation and immunogenic cell death signaling pathways. Front Oncol 2012; 2:88; PMID:22891162; http://dx.doi.org/10.3389/fonc.2012.00088
28. Golden EB, Frances D, Pellicciotta I, Demaria S, Helen Barcellos-Hoff M, Formenti SC. Radiation fosters dose-dependent and chemotherapy-induced immunogenic cell death. Oncoimmunology 2014; 3:e28518; PMID:25071979; http://dx.doi.org/10.4161/onci.28518
29. Galluzzi L, Buque A, Kepp O, Zitvogel L, Kroemer G. Immunological effects of conventional chemotherapy and targeted anticancer agents. Cancer Cell 2015; 28:690-714; PMID:26678337; http://dx.doi.org/10.1016/j.ccell.2015.10.012
30. Kroemer G, Galluzzi L, Kepp O, Zitvogel L. Immunogenic cell death in cancer therapy. Annu Rev Immunol 2013; 31:51-72; PMID:23157435; http://dx.doi.org/10.1146/annurev-immunol-032712-100008
31. Krysko DV, Garg AD, Kaczmarek A, Krysko O, Agostinis P, Vandenabeele P. Immunogenic cell death and DAMPs in cancer therapy. Nat Rev Cancer 2012; 12:860-75; PMID:23151605; http://dx.doi.org/10.1038/nrc3380
32. Formenti SC, Demaria S. Radiation therapy to convert the tumor into an in situ vaccine. Int J Radiat Oncol Biol Phys 2012; 84:879-80; PMID:23078897; http://dx.doi.org/10.1016/j.ijrobp.2012.06.020
33. Kaminski JM, Shinohara E, Summers JB, Niermann KJ, Morimoto A, Brousal J. The controversial abscopal effect. Cancer Treat Rev 2005; 31:159-72; PMID:15923088; http://dx.doi.org/10.1016/j.ctrv.2005.03.004
34. Demaria S, Ng B, Devitt ML, Babb JS, Kawashima N, Liebes L, Formenti SC. Ionizing radiation inhibition of distant untreated tumors (abscopal effect) is immune mediated. Int J Radiat Oncol Biol Phys 2004; 58:862-70; PMID:14967443; http://dx.doi.org/10.1016/j.ijrobp.2003.09.012
35. Dewan MZ, Galloway AE, Kawashima N, Dewyngaert JK, Babb JS, Formenti SC, Demaria S. Fractionated but not single-dose radiotherapy induces an immune-mediated abscopal effect when combined with anti-CTLA-4 antibody. Clin Cancer Res 2009; 15:5379-88; PMID:19706802; http://dx.doi.org/10.1158/1078-0432.CCR-09-0265
36. Golden EB, Demaria S, Schiff PB, Chachoua A, Formenti SC. An abscopal response to radiation and ipilimumab in a patient with metastatic non-small cell lung cancer. Cancer Immunol Res 2013; 1:365-72; PMID:24563870; http://dx.doi.org/10.1158/2326-6066.CIR-13-0115
37. Hiniker SM, Chen DS, Knox SJ. Abscopal effect in a patient with melanoma. N Engl J Med 2012; 366:2035; author reply -6; PMID:22621637; http://dx.doi.org/10.1056/NEJMc1203984
38. Siva S, Macmanus MP, Martin RF, Martin OA. Abscopal effects of radiation therapy: a clinical review for the radiobiologist. Cancer Lett 2015; 356(1):82-90; PMID:24125863; http://dx.doi.org/10.1016/j.canlet.2013.09.018
39. Goel S, Duda DG, Xu L, Munn LL, Boucher Y, Fukumura D, Jain RK. Normalization of the vasculature for treatment of cancer and other diseases. Physiol Rev 2011; 91:1071-121; PMID:21742796; http://dx.doi.org/10.1152/physrev.00038.2010
40. Jain RK. Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy. Science 2005; 307:58-62; PMID:15637262; http://dx.doi.org/10.1126/science.1104819
41. Tartour E, Pere H, Maillere B, Terme M, Merillon N, Taieb J, Sandoval F, Quintin-Colonna F, Lacerda K, Karadimou A et al. Angiogenesis and immunity: a bidirectional link potentially relevant for the monitoring of antiangiogenic therapy and the development of novel therapeutic combination with immunotherapy. Cancer Metastasis Rev 2011; 30:83-95; PMID:21249423; http://dx.doi.org/10.1007/s10555-011-9281-4
42. Bloy N, Pol J, Manic G, Vitale I, Eggermont A, Galon J, Tartour E, Zitvogel L, Kroemer G, Galluzzi L. Trial Watch: radioimmunotherapy for oncological indications. Oncoimmunology 2014; 3:e954929; PMID:25941606; http://dx.doi.org/10.4161/21624011.2014.954929
43. Vacchelli E, Vitale I, Tartour E, Eggermont A, Sautes-Fridman C, Galon J, Zitvogel L, Kroemer G, Galluzzi L. Trial Watch: anticancer radioimmunotherapy. Oncoimmunology 2013; 2:e25595; PMID:24319634; http://dx.doi.org/10.4161/onci.25595
44. Ahmad SS, Duke S, Jena R, Williams MV, Burnet NG. Advances in radiotherapy. BMJ 2012; 345:e7765; PMID:23212681; http://dx.doi.org/10.1136/bmj.e7765
45. DeVita Jr. VT, Lawrence TS, Rosenberg SA. Cancer: Principles & Practice of Oncology. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins, 2008.
46. Smaglo BG, Aldeghaither D, Weiner LM. The development of immunoconjugates for targeted cancer therapy. Nat Rev Clin Oncol 2014; 11:637-48; PMID:25265912; http://dx.doi.org/10.1038/nrclinonc.2014.159
47. Milano MT, Constine LS, Okunieff P. Normal tissue tolerance dose metrics for radiation therapy of major organs. Semin Radiat Oncol 2007; 17:131-40; PMID:17395043; http://dx.doi.org/10.1016/j.semradonc.2006.11.009
48. Stone HB, Coleman CN, Anscher MS, McBride WH. Effects of radiation on normal tissue: consequences and mechanisms. Lancet Oncol 2003; 4:529-36; PMID:12965273; http://dx.doi.org/10.1016/S1470-2045(03)01191-4
49. Trotti A, Colevas AD, Setser A, Rusch V, Jaques D, Budach V, Langer C, Murphy B, Cumberlin R, Coleman CN et al. CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. Semin Radiat Oncol 2003; 13:176-81; PMID:12903007; http://dx.doi.org/10.1016/S1053-4296(03)00031-6
50. Emami B, Lyman J, Brown A, Coia L, Goitein M, Munzenrider JE, Shank B, Solin LJ, Wesson M. Tolerance of normal tissue to therapeutic irradiation. Int J Radiat Oncol Biol Phys 1991; 21:109-22; PMID:2032882; http://dx.doi.org/10.1016/0360-3016(91)90171-Y
51. Jereczek-Fossa BA, Marsiglia HR, Orecchia R. Radiotherapy-related fatigue. Crit Rev Oncol Hematol 2002; 41:317-25; PMID:11880207; http://dx.doi.org/10.1016/S1040-8428(01)00143-3
52. Schaue D, Micewicz ED, Ratikan JA, Xie MW, Cheng G, McBride WH. Radiation and inflammation. Semin Radiat Oncol 2015; 25:4-10; PMID:25481260; http://dx.doi.org/10.1016/j.semradonc.2014.07.007
53. Travis LB, Ng AK, Allan JM, Pui CH, Kennedy AR, Xu XG, Purdy JA, Applegate K, Yahalom J, Constine LS et al. Second malignant neoplasms and cardiovascular disease following radiotherapy. J Natl Cancer Inst 2012; 104:357-70; PMID:22312134; http://dx.doi.org/10.1093/jnci/djr533
54. Berrington de Gonzalez A, Curtis RE, Kry SF, Gilbert E, Lamart S, Berg CD, Stovall M, Ron E. Proportion of second cancers attributable to radiotherapy treatment in adults: a cohort study in the US SEER cancer registries. Lancet Oncol 2011; 12:353-60; PMID:21454129; http://dx.doi.org/10.1016/S1470-2045(11)70061-4
55. Tubiana M. Can we reduce the incidence of second primary malignancies occurring after radiotherapy? A critical review. Radiother Oncol 2009; 91:4-15; discussion 1-3; PMID:19201045; http://dx.doi.org/10.1016/j.radonc.2008.12.016

56. Movsas B, Vikram B, Hauer-Jensen M, Moulder JE, Basch E, Brown SL, Kachnic LA, Dicker AP, Coleman CN, Okunieff P. Decreasing the adverse effects of cancer therapy: National Cancer Institute guidance for the clinical development of radiation injury mitigators. Clin Cancer Res 2011; 17:222-8; PMID:21047979; http://dx.doi.org/10.1158/1078-0432.CCR-10-1402
57. Marks LB, Yorke ED, Jackson A, Ten Haken RK, Constine LS, Eisbruch A, Bentzen SM, Nam J, Deasy JO. Use of normal tissue complication probability models in the clinic. Int J Radiat Oncol Biol Phys 2010; 76:S10-9; PMID:20171502; http://dx.doi.org/10.1016/j.ijrobp.2009.07.1754
58. Barnett GC, West CM, Dunning AM, Elliott RM, Coles CE, Pharoah PD, Burnet NG. Normal tissue reactions to radiotherapy: towards tailoring treatment dose by genotype. Nat Rev Cancer 2009; 9:134-42; PMID:19148183; http://dx.doi.org/10.1038/nrc2587
59. Hensley ML, Hagerty KL, Kewalramani T, Green DM, Meropol NJ, Wasserman TH, Cohen GI, Emami B, Gradishar WJ, Mitchell RB et al. American Society of Clinical Oncology 2008 clinical practice guideline update: use of chemotherapy and radiation therapy protectants. J Clin Oncol 2009; 27:127-45; PMID:19018081; http://dx.doi.org/10.1200/JCO.2008.17.2627
60. Schuchter LM, Hensley ML, Meropol NJ, Winer EP. 2002 update of recommendations for the use of chemotherapy and radiotherapy protectants: clinical practice guidelines of the American Society of Clinical Oncology. J Clin Oncol 2002; 20:2895-903; PMID:12065567; http://dx.doi.org/10.1200/JCO.2002.04.178
61. Brizel DM, Wasserman TH, Henke M, Strnad V, Rudat V, Monnier A, Eschwege F, Zhang J, Russell L, Oster W et al. Phase III randomized trial of amifostine as a radioprotector in head and neck cancer. J Clin Oncol 2000; 18:3339-45; PMID:11013273
62. Pouget JP, Navarro-Teulon I, Bardies M, Chouin N, Cartron G, Pelegrin A, Azria D. Clinical radioimmunotherapy–the role of radiobiology. Nat Rev Clin Oncol 2011; 8:720-34; PMID:22064461; http://dx.doi.org/10.1038/nrclinonc.2011.160
63. Huang EY, Wang FS, Chen YM, Chen YF, Wang CC, Lin IH, Huang YJ, Yang KD. Amifostine alleviates radiation-induced lethal small bowel damage via promotion of 14-3-3sigma-mediated nuclear p53 accumulation. Oncotarget 2014; 5:9756-69; PMID:25230151; http://dx.doi.org/10.18632/oncotarget.2386
64. Demaria S, Formenti SC. Radiation as an immunological adjuvant: current evidence on dose and fractionation. Front Oncol 2012; 2:153; PMID:23112958; http://dx.doi.org/10.3389/fonc.2012.00153
65. Fenton-Kerimian M, Maisonet O, Formenti SC. Changes in breast radiotherapy: prone positioning and hypofractionation. Clin J Oncol Nurs 2013; 17:550-3; PMID:24080055; http://dx.doi.org/10.1188/13.CJON.550-553
66. Demaria S, Pilones KA, Vanpouille-Box C, Golden EB, Formenti SC. The optimal partnership of radiation and immunotherapy: from preclinical studies to clinical translation. Radiat Res 2014; 182:170-81; PMID:24937779; http://dx.doi.org/10.1667/RR13500.1
67. Kepp O, Senovilla L, Vitale I, Vacchelli E, Adjemian S, Agostinis P, Apetoh L, Aranda F, Barnaba V, Bloy N et al. Consensus guidelines for the detection of immunogenic cell death. Oncoimmunology 2014; 3:e955691; PMID:25941621; http://dx.doi.org/10.4161/21624011.2014.955691
68. Formenti SC, Demaria S. Combining radiotherapy and cancer immunotherapy: a paradigm shift. J Natl Cancer Inst 2013; 105:256-65; PMID:23291374; http://dx.doi.org/10.1093/jnci/djs629
69. Crittenden M, Kohrt H, Levy R, Jones J, Camphausen K, Dicker A, Demaria S, Formenti S. Current clinical trials testing combinations of immunotherapy and radiation. Semin Radiat Oncol 2015; 25:54-64; PMID:25481267; http://dx.doi.org/10.1016/j.semradonc.2014.07.003
70. Formenti SC. Immunological aspects of local radiotherapy: clinical relevance. Discov Med 2010; 9:119-24; PMID:20193637
71. Bernstein MB, Krishnan S, Hodge JW, Chang JY. Immunotherapy and stereotactic ablative radiotherapy (ISABR): a curative approach? Nat Rev Clin Oncol 2016; 13(8):516-24; PMID:26951040; http://dx.doi.org/10.1038/nrclinonc.2016.30
72. Buque A, Bloy N, Aranda F, Castoldi F, Eggermont A, Cremer I, Fridman WH, Fucikova J, Galon J, Marabelle A et al. Trial Watch: Immunomodulatory monoclonal antibodies for oncological indications. Oncoimmunology 2015; 4:e1008814; PMID:26137403; http://dx.doi.org/10.1080/2162402X.2015.1008814
73. Mayor S. Radiation in combination with immune-checkpoint inhibitors. Lancet Oncol 2015; 16:e162; PMID:25773169; http://dx.doi.org/10.1016/S1470-2045(15)70118-X
74. Sharabi AB, Lim M, DeWeese TL, Drake CG. Radiation and checkpoint blockade immunotherapy: radiosensitisation and potential mechanisms of synergy. Lancet Oncol 2015; 16:e498-509; PMID:26433823; http://dx.doi.org/10.1016/S1470-2045(15)00007-8
75. Vanpouille-Box C, Pilones KA, Wennerberg E, Formenti SC, Demaria S. In situ vaccination by radiotherapy to improve responses to anti-CTLA-4 treatment. Vaccine 2015; 33:7415-22; PMID:26148880; http://dx.doi.org/10.1016/j.vaccine.2015.05.105
76. Newcomb EW, Lukyanov Y, Kawashima N, Alonso-Basanta M, Wang SC, Liu M, Jure-Kunkel M, Zagzag D, Demaria S, Formenti SC. Radiotherapy enhances antitumor effect of anti-CD137 therapy in a mouse Glioma model. Radiat Res 2010; 173:426-32; PMID:20334514; http://dx.doi.org/10.1667/RR1904.1
77. Vacchelli E, Aranda F, Obrist F, Eggermont A, Galon J, Cremer I, Zitvogel L, Kroemer G, Galluzzi L. Trial watch: Immunostimulatory cytokines in cancer therapy. Oncoimmunology 2014; 3:e29030; PMID:25083328; http://dx.doi.org/10.4161/onci.29030
78. Seung SK, Curti BD, Crittenden M, Walker E, Coffey T, Siebert JC, Miller W, Payne R, Glenn L, Bageac A et al. Phase 1 study of stereotactic body radiotherapy and interleukin-2–tumor and immunological responses. Sci Transl Med 2012; 4:137ra74; PMID:22674552; http://dx.doi.org/10.1126/scitranslmed.3003649
79. Yasuda K, Nirei T, Tsuno NH, Nagawa H, Kitayama J. Intratumoral injection of interleukin-2 augments the local and abscopal effects of radiotherapy in murine rectal cancer. Cancer Sci 2011; 102:1257-63; PMID:21443690; http://dx.doi.org/10.1111/j.1349-7006.2011.01940.x
80. Pol J, Bloy N, Obrist F, Eggermont A, Galon J, Herve Fridman W, Cremer I, Zitvogel L, Kroemer G, Galluzzi L. Trial Watch: DNA vaccines for cancer therapy. Oncoimmunology 2014; 3:e28185; PMID:24800178; http://dx.doi.org/10.4161/onci.28185
81. Pol J, Bloy N, Buque A, Eggermont A, Cremer I, Sautes-Fridman C, Galon J, Tartour E, Zitvogel L, Kroemer G et al. Trial Watch: peptide-based anticancer vaccines. Oncoimmunology 2015; 4:e974411; PMID:26137405; http://dx.doi.org/10.4161/2162402X.2014.974411
82. Buckel L, Advani SJ, Frentzen A, Zhang Q, Yu YA, Chen NG, Ehrig K, Stritzker J, Mundt AJ, Szalay AA. Combination of fractionated irradiation with anti-VEGF expressing vaccinia virus therapy enhances tumor control by simultaneous radiosensitization of tumor associated endothelium. Int J Cancer 2013; 133:2989-99; PMID:23729266; http://dx.doi.org/10.1002/ijc.28296
83. Iinuma H, Fukushima R, Inaba T, Tamura J, Inoue T, Ogawa E, Horikawa M, Ikeda Y, Matsutani N, Takeda K et al. Phase I clinical study of multiple epitope peptide vaccine combined with chemoradiation therapy in esophageal cancer patients. J Transl Med 2014; 12:84; PMID:24708624; http://dx.doi.org/10.1186/1479-5876-12-84
84. Mondini M, Nizard M, Tran T, Mauge L, Loi M, Clemenson C, Dugue D, Maroun P, Louvet E, Adam J et al. Synergy of Radiotherapy and a Cancer Vaccine for the Treatment of HPV-Associated Head and Neck Cancer. Mol Cancer Ther 2015; 14:1336-45; PMID:25833837; http://dx.doi.org/10.1158/1535-7163.MCT-14-1015
85. Vacchelli E, Aranda F, Eggermont A, Sautes-Fridman C, Tartour E, Kennedy EP, Platten M, Zitvogel L, Kroemer G, Galluzzi L. Trial watch: IDO inhibitors in cancer therapy. Oncoimmunology 2014; 3:e957994; PMID:25941578; http://dx.doi.org/10.4161/21624011.2014.957994
86. Zamarin D, Postow MA. Immune checkpoint modulation: rational design of combination strategies. Pharmacol Ther 2015; 150:23-32; PMID:25583297; http://dx.doi.org/10.1016/j.pharmthera.2015.01.003
87. Aranda F, Buque A, Bloy N, Castoldi F, Eggermont A, Cremer I, Fridman WH, Fucikova J, Galon J, Spisek R et al. Trial Watch: adoptive cell transfer for oncological indications. Oncoimmunology 2015; 4:e1046673; PMID:26451319; http://dx.doi.org/10.1080/2162402X.2015.1046673
88. Wei S, Egenti MU, Teitz-Tennenbaum S, Zou W, Chang AE. Effects of tumor irradiation on host T-regulatory cells and systemic immunity in the context of adoptive T-cell therapy in mice. J Immunother

2013; 36:124-32; PMID:23377667; http://dx.doi.org/10.1097/CJI.0b013e31828298e6

89. Klug F, Prakash H, Huber PE, Seibel T, Bender N, Halama N, Pfirschke C, Voss RH, Timke C, Umansky L et al. Low-dose irradiation programs macrophage differentiation to an iNOS(+)/M1 phenotype that orchestrates effective T cell immunotherapy. Cancer Cell 2013; 24:589-602; PMID:24209604; http://dx.doi.org/10.1016/j.ccr.2013.09.014
90. Pol J, Bloy N, Obrist F, Eggermont A, Galon J, Cremer I, Erbs P, Limacher JM, Preville X, Zitvogel L et al. Trial Watch: oncolytic viruses for cancer therapy. Oncoimmunology 2014; 3:e28694; PMID:25097804; http://dx.doi.org/10.4161/onci.28694
91. Kyula JN, Khan AA, Mansfield D, Karapanagiotou EM, McLaughlin M, Roulstone V, Zaidi S, Pencavel T, Touchefeu Y, Seth R et al. Synergistic cytotoxicity of radiation and oncolytic Lister strain vaccinia in (V600D/E)BRAF mutant melanoma depends on JNK and TNF-alpha signaling. Oncogene 2014; 33:1700-12; PMID:23624923; http://dx.doi.org/10.1038/onc.2013.112
92. Chen RF, Li YY, Li LT, Cheng Q, Jiang G, Zheng JN. Novel oncolytic adenovirus sensitizes renal cell carcinoma cells to radiotherapy via mitochondrial apoptotic cell death. Mol Med Rep 2015; 11:2141-6; PMID:25411768; http://dx.doi.org/10.3892/mmr.2014.2987
93. Wang W, Chen MN, Cheng K, Zhan LL, Zhang J. Cytotoxic effect of a combination of bluetongue virus and radiation on prostate cancer. Exp Ther Med 2014; 8:635-41; PMID:25009632; http://dx.doi.org/10.3892/etm.2014.1751
94. Aranda F, Vacchelli E, Obrist F, Eggermont A, Galon J, Sautes-Fridman C, Cremer I, Henrik Ter Meulen J, Zitvogel L, Kroemer G et al. Trial Watch: Toll-like receptor agonists in oncological indications. Oncoimmunology 2014; 3:e29179; PMID:25083332; http://dx.doi.org/10.4161/onci.29179
95. Dovedi SJ, Melis MH, Wilkinson RW, Adlard AL, Stratford IJ, Honeychurch J, Illidge TM. Systemic delivery of a TLR7 agonist in combination with radiation primes durable antitumor immune responses in mouse models of lymphoma. Blood 2013; 121:251-9; PMID:23086756; http://dx.doi.org/10.1182/blood-2012-05-432393
96. Ye SB, Li ZL, Luo DH, Huang BJ, Chen YS, Zhang XS, Cui J, Zeng YX, Li J. Tumor-derived exosomes promote tumor progression and T-cell dysfunction through the regulation of enriched exosomal microRNAs in human nasopharyngeal carcinoma. Oncotarget 2014; 5:5439-52; PMID:24978137; http://dx.doi.org/10.18632/oncotarget.2118
97. Boelens MC, Wu TJ, Nabet BY, Xu B, Qiu Y, Yoon T, Azzam DJ, Twyman-Saint Victor C, Wiemann BZ, Ishwaran H et al. Exosome transfer from stromal to breast cancer cells regulates therapy resistance pathways. Cell 2014; 159:499-513; PMID:25417103; http://dx.doi.org/10.1016/j.cell.2014.09.051
98. Leder K, Pitter K, Laplant Q, Hambardzumyan D, Ross BD, Chan TA, Holland EC, Michor F. Mathematical modeling of PDGF-driven glioblastoma reveals optimized radiation dosing schedules. Cell 2014; 156:603-16; PMID:24485463; http://dx.doi.org/10.1016/j.cell.2013.12.029
99. O'Brien S, Golubovskaya VM, Conroy J, Liu S, Wang D, Liu B, Cance WG. FAK inhibition with small molecule inhibitor Y15 decreases viability, clonogenicity, and cell attachment in thyroid cancer cell lines and synergizes with targeted therapeutics. Oncotarget 2014; 5:7945-59; PMID:25277206; http://dx.doi.org/10.18632/oncotarget.2381
100. Tavora B, Reynolds LE, Batista S, Demircioglu F, Fernandez I, Lechertier T, Lees DM, Wong PP, Alexopoulou A, Elia G et al. Endothelial-cell FAK targeting sensitizes tumours to DNA-damaging therapy. Nature 2014; 514:112-6; PMID:25079333; http://dx.doi.org/10.1038/nature13541
101. Vousden KH, Lane DP. p53 in health and disease. Nat Rev Mol Cell Biol 2007; 8:275-83; PMID:17380161; http://dx.doi.org/10.1038/nrm2147
102. Kubbutat MH, Jones SN, Vousden KH. Regulation of p53 stability by Mdm2. Nature 1997; 387:299-303; PMID:9153396; http://dx.doi.org/10.1038/387299a0
103. Pant V, Lozano G. Dissecting the p53-Mdm2 feedback loop in vivo: uncoupling the role in p53 stability and activity. Oncotarget 2014; 5:1149-56; PMID:24658419; http://dx.doi.org/10.18632/oncotarget.1797
104. Tollini LA, Jin A, Park J, Zhang Y. Regulation of p53 by Mdm2 E3 ligase function is dispensable in embryogenesis and development, but essential in response to DNA damage. Cancer Cell 2014; 26:235-47; PMID:25117711; http://dx.doi.org/10.1016/j.ccr.2014.06.006
105. Osipov AN, Grekhova A, Pustovalova M, Ozerov IV, Eremin P, Vorobyeva N, Lazareva N, Pulin A, Zhavoronkov A, Roumiantsev S et al. Activation of homologous recombination DNA repair in human skin fibroblasts continuously exposed to X-ray radiation. Oncotarget 2015; 6:26876-85; PMID:26337087; http://dx.doi.org/10.18632/oncotarget.4946
106. Ceccaldi R, Liu JC, Amunugama R, Hajdu I, Primack B, Petalcorin MI, O'Connor KW, Konstantinopoulos PA, Elledge SJ, Boulton SJ et al. Homologous-recombination-deficient tumours are dependent on Poltheta-mediated repair. Nature 2015; 518:258-62; PMID:25642963; http://dx.doi.org/10.1038/nature14184
107. Vendetti FP, Lau A, Schamus S, Conrads TP, O'Connor MJ, Bakkenist CJ. The orally active and bioavailable ATR kinase inhibitor AZD6738 potentiates the anti-tumor effects of cisplatin to resolve ATM-deficient non-small cell lung cancer in vivo. Oncotarget 2015; 6:44289-305; PMID:26517239; http://dx.doi.org/10.18632/oncotarget.6247
108. Moding EJ, Castle KD, Perez BA, Oh P, Min HD, Norris H, Ma Y, Cardona DM, Lee CL, Kirsch DG. Tumor cells, but not endothelial cells, mediate eradication of primary sarcomas by stereotactic body radiation therapy. Sci Transl Med 2015; 7:278ra34; PMID:25761890; http://dx.doi.org/10.1126/scitranslmed.aaa4214
109. Osswald M, Jung E, Sahm F, Solecki G, Venkataramani V, Blaes J, Weil S, Horstmann H, Wiestler B, Syed M et al. Brain tumour cells interconnect to a functional and resistant network. Nature 2015; 528:93-8; PMID:26536111; http://dx.doi.org/10.1038/nature16071
110. Overgaard J. Hypoxic radiosensitization: adored and ignored. J Clin Oncol 2007; 25:4066-74; PMID:17827455; http://dx.doi.org/10.1200/JCO.2007.12.7878
111. Reid T, Oronsky B, Scicinski J, Scribner CL, Knox SJ, Ning S, Peehl DM, Korn R, Stirn M, Carter CA et al. Safety and activity of RRx-001 in patients with advanced cancer: a first-in-human, open-label, dose-escalation phase 1 study. Lancet Oncol 2015; 16:1133-42; PMID:26296952; http://dx.doi.org/10.1016/S1470-2045(15)00089-3
112. Tombal B, Borre M, Rathenborg P, Werbrouck P, Van Poppel H, Heidenreich A, Iversen P, Braeckman J, Heracek J, Baskin-Bey E et al. Enzalutamide monotherapy in hormone-naive prostate cancer: primary analysis of an open-label, single-arm, phase 2 study. Lancet Oncol 2014; 15:592-600; PMID:24739897; http://dx.doi.org/10.1016/S1470-2045(14)70129-9
113. Tarish FL, Schultz N, Tanoglidi A, Hamberg H, Letocha H, Karaszi K, Hamdy FC, Granfors T, Helleday T. Castration radiosensitizes prostate cancer tissue by impairing DNA double-strand break repair. Sci Transl Med 2015; 7:312re11; PMID:26537259; http://dx.doi.org/10.1126/scitranslmed.aac5671
114. Yumimoto K, Nakayama KI. Fbxw7 suppresses cancer metastasis by inhibiting niche formation. Oncoimmunology 2015; 4:e1022308; PMID:26405580; http://dx.doi.org/10.1080/2162402X.2015.1022308
115. Sakai K, Kazama S, Nagai Y, Murono K, Tanaka T, Ishihara S, Sunami E, Tomida S, Nishio K, Watanabe T. Chemoradiation provides a physiological selective pressure that increases the expansion of aberrant TP53 tumor variants in residual rectal cancerous regions. Oncotarget 2014; 5:9641-9; PMID:25275295; http://dx.doi.org/10.18632/oncotarget.2438
116. Wang L, Ye X, Liu Y, Wei W, Wang Z. Aberrant regulation of FBW7 in cancer. Oncotarget 2014; 5:2000-15; PMID:24899581; http://dx.doi.org/10.18632/oncotarget.1859
117. Beckta JM, Dever SM, Gnawali N, Khalil A, Sule A, Golding SE, Rosenberg E, Narayanan A, Kehn-Hall K, Xu B et al. Mutation of the BRCA1 SQ-cluster results in aberrant mitosis, reduced homologous recombination, and a compensatory increase in non-homologous end joining. Oncotarget 2015; 6:27674-87; PMID:26320175; http://dx.doi.org/10.18632/oncotarget.4876
118. Zhang Q, Karnak D, Tan M, Lawrence TS, Morgan MA, Sun Y. FBXW7 facilitates nonhomologous end-joining via K63-linked

polyubiquitylation of XRCC4. Mol Cell 2016; 61:419-33; PMID:26774286; http://dx.doi.org/10.1016/j.molcel.2015.12.010
119. Dovedi SJ, Illidge TM. The antitumor immune response generated by fractionated radiation therapy may be limited by tumor cell adaptive resistance and can be circumvented by PD-L1 blockade. Oncoimmunology 2015; 4:e1016709; PMID:26140246; http://dx.doi.org/10.1080/2162402X.2015.1016709
120. Huang L, Li L, Lemos H, Chandler PR, Pacholczyk G, Baban B, Barber GN, Hayakawa Y, McGaha TL, Ravishankar B et al. Cutting edge: DNA sensing via the STING adaptor in myeloid dendritic cells induces potent tolerogenic responses. J Immunol 2013; 191:3509-13; PMID:23986532; http://dx.doi.org/10.4049/jimmunol.1301419
121. Liu S, Cai X, Wu J, Cong Q, Chen X, Li T, Du F, Ren J, Wu YT, Grishin NV et al. Phosphorylation of innate immune adaptor proteins MAVS, STING, and TRIF induces IRF3 activation. Science 2015; 347:aaa2630; PMID:25636800; http://dx.doi.org/10.1126/science.aaa2630
122. Zitvogel L, Galluzzi L, Kepp O, Smyth MJ, Kroemer G. Type I interferons in anticancer immunity. Nat Rev Immunol 2015; 15:405-14; PMID:26027717; http://dx.doi.org/10.1038/nri3845
123. Deng L, Liang H, Burnette B, Beckett M, Darga T, Weichselbaum RR, Fu YX. Irradiation and anti-PD-L1 treatment synergistically promote antitumor immunity in mice. J Clin Invest 2014; 124:687-95; PMID:24382348; http://dx.doi.org/10.1172/JCI67313
124. Deng L, Liang H, Xu M, Yang X, Burnette B, Arina A, Li XD, Mauceri H, Beckett M, Darga T et al. STING-dependent cytosolic DNA Sensing promotes radiation-induced Type I interferon-dependent antitumor immunity in immunogenic tumors. Immunity 2014; 41:843-52; PMID:25517616; http://dx.doi.org/10.1016/j.immuni.2014.10.019
125. Salaroglio IC, Campia I, Kopecka J, Gazzano E, Orecchia S, Ghigo D, Riganti C. Zoledronic acid overcomes chemoresistance and immunosuppression of malignant mesothelioma. Oncotarget 2015; 6:1128-42; PMID:25544757; http://dx.doi.org/10.18632/oncotarget.2731
126. Bowman RL, Joyce JA. Therapeutic targeting of tumor-associated macrophages and microglia in glioblastoma. Immunotherapy 2014; 6:663-6; PMID:25041027; http://dx.doi.org/10.2217/imt.14.48
127. Comito G, Segura CP, Taddei ML, Lanciotti M, Serni S, Morandi A, Chiarugi P, Giannoni E. Zoledronic acid impairs stromal reactivity by inhibiting M2-macrophages polarization and prostate cancer-associated fibroblasts. Oncotarget 2016; PMID:27223431; http://dx.doi.org/10.18632/oncotarget.9497
128. Hattori Y, Shibuya K, Kojima K, Miatmoko A, Kawano K, Ozaki K, Yonemochi E. Zoledronic acid enhances antitumor efficacy of liposomal doxorubicin. Int J Oncol 2015; 47:211-9; PMID:25955490; http://dx.doi.org/10.3892/ijo.2015.2991
129. Riganti C, Castella B, Kopecka J, Campia I, Coscia M, Pescarmona G, Bosia A, Ghigo D, Massaia M. Zoledronic acid restores doxorubicin chemosensitivity and immunogenic cell death in multidrug-resistant human cancer cells. PLoS One 2013; 8:e60975; PMID:23593363; http://dx.doi.org/10.1371/journal.pone.0060975
130. Denham JW, Joseph D, Lamb DS, Spry NA, Duchesne G, Matthews J, Atkinson C, Tai KH, Christie D, Kenny L et al. Short-term androgen suppression and radiotherapy versus intermediate-term androgen suppression and radiotherapy, with or without zoledronic acid, in men with locally advanced prostate cancer (TROG 03.04 RADAR): an open-label, randomised, phase 3 factorial trial. Lancet Oncol 2014; 15:1076-89; PMID:25130995; http://dx.doi.org/10.1016/S1470-2045(14)70328-6
131. Hervieu A, Rebe C, Vegran F, Chalmin F, Bruchard M, Vabres P, Apetoh L, Ghiringhelli F, Mignot G. Dacarbazine-mediated upregulation of NKG2D ligands on tumor cells activates NK and CD8 T cells and restrains melanoma growth. J Invest Dermatol 2013; 133:499-508; PMID:22951720; http://dx.doi.org/10.1038/jid.2012.273
132. Iannello A, Raulet DH. Immunosurveillance of senescent cancer cells by natural killer cells. Oncoimmunology 2014; 3:e27616; PMID:24800169; http://dx.doi.org/10.4161/onci.27616
133. Joncker NT, Raulet DH. Regulation of NK cell responsiveness to achieve self-tolerance and maximal responses to diseased target cells. Immunol Rev 2008; 224:85-97; PMID:18759922; http://dx.doi.org/10.1111/j.1600-065X.2008.00658.x
134. Raulet DH, Guerra N. Oncogenic stress sensed by the immune system: role of natural killer cell receptors. Nat Rev Immunol 2009; 9:568-80; PMID:19629084; http://dx.doi.org/10.1038/nri2604
135. Ruocco MG, Pilones KA, Kawashima N, Cammer M, Huang J, Babb JS, Liu M, Formenti SC, Dustin ML, Demaria S. Suppressing T cell motility induced by anti-CTLA-4 monotherapy improves antitumor effects. J Clin Invest 2012; 122:3718-30; PMID:22945631; http://dx.doi.org/10.1172/JCI61931
136. Vantourout P, Willcox C, Turner A, Swanson CM, Haque Y, Sobolev O, Grigoriadis A, Tutt A, Hayday A. Immunological visibility: post-transcriptional regulation of human NKG2D ligands by the EGF receptor pathway. Sci Transl Med 2014; 6:231ra49; PMID:24718859; http://dx.doi.org/10.1126/scitranslmed.3007579
137. Surace L, Lysenko V, Fontana AO, Cecconi V, Janssen H, Bicvic A, Okoniewski M, Pruschy M, Dummer R, Neefjes J et al. Complement is a central mediator of radiotherapy-induced tumor-specific immunity and clinical response. Immunity 2015; 42:767-77; PMID:25888260; http://dx.doi.org/10.1016/j.immuni.2015.03.009
138. Twyman-Saint Victor C, Rech AJ, Maity A, Rengan R, Pauken KE, Stelekati E, Benci JL, Xu B, Dada H, Odorizzi PM et al. Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer. Nature 2015; 520:373-7; PMID:25754329; http://dx.doi.org/10.1038/nature14292
139. Golden EB, Chhabra A, Chachoua A, Adams S, Donach M, Fenton-Kerimian M, Friedman K, Ponzo F, Babb JS, Goldberg J et al. Local radiotherapy and granulocyte-macrophage colony-stimulating factor to generate abscopal responses in patients with metastatic solid tumours: a proof-of-principle trial. Lancet Oncol 2015; 16:795-803; PMID:26095785; http://dx.doi.org/10.1016/S1470-2045(15)00054-6
140. Galon J, Mlecnik B, Bindea G, Angell HK, Berger A, Lagorce C, Lugli A, Zlobec I, Hartmann A, Bifulco C et al. Towards the introduction of the 'Immunoscore' in the classification of malignant tumours. J Pathol 2014; 232:199-209; PMID:24122236; http://dx.doi.org/10.1002/path.4287
141. Anitei MG, Zeitoun G, Mlecnik B, Marliot F, Haicheur N, Todosi AM, Kirilovsky A, Lagorce C, Bindea G, Ferariu D et al. Prognostic and predictive values of the immunoscore in patients with rectal cancer. Clin Cancer Res 2014; 20:1891-9; PMID:24691640; http://dx.doi.org/10.1158/1078-0432.CCR-13-2830
142. Ceresa BP, Peterson JL. Cell and molecular biology of epidermal growth factor receptor. Int Rev Cell Mol Biol 2014; 313:145-78; PMID:25376492; http://dx.doi.org/10.1016/B978-0-12-800177-6.00005-0
143. Vacchelli E, Pol J, Bloy N, Eggermont A, Cremer I, Fridman WH, Galon J, Marabelle A, Kohrt H, Zitvogel L et al. Trial Watch: Tumor-targeting monoclonal antibodies for oncological indications. Oncoimmunology 2015; 4:e985940; PMID:25949870; http://dx.doi.org/10.4161/2162402X.2014.985940
144. Cunningham D, Humblet Y, Siena S, Khayat D, Bleiberg H, Santoro A, Bets D, Mueser M, Harstrick A, Verslype C et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. N Engl J Med 2004; 351:337-45; PMID:15269313; http://dx.doi.org/10.1056/NEJMoa033025
145. de La Motte Rouge T, Galluzzi L, Olaussen KA, Zermati Y, Tasdemir E, Robert T, Ripoche H, Lazar V, Dessen P, Harper F et al. A novel epidermal growth factor receptor inhibitor promotes apoptosis in non-small cell lung cancer cells resistant to erlotinib. Cancer Res 2007; 67:6253-62; PMID:17616683; http://dx.doi.org/10.1158/0008-5472.CAN-07-0538
146. Aranda F, Vacchelli E, Eggermont A, Galon J, Fridman WH, Zitvogel L, Kroemer G, Galluzzi L. Trial Watch: immunostimulatory monoclonal antibodies in cancer therapy. Oncoimmunology 2014; 3:e27297; PMID:24701370; http://dx.doi.org/10.4161/onci.27297
147. Luke JJ, Ott PA. PD-1 pathway inhibitors: the next generation of immunotherapy for advanced melanoma. Oncotarget 2015; 6:3479-92; PMID:25682878; http://dx.doi.org/10.18632/oncotarget.2980
148. Kortylewski M, Swiderski P, Herrmann A, Wang L, Kowolik C, Kujawski M, Lee H, Scuto A, Liu Y, Yang C et al. In vivo delivery of siRNA to immune cells by conjugation to a TLR9 agonist enhances antitumor immune responses. Nat Biotechnol 2009; 27:925-32; PMID:19749770; http://dx.doi.org/10.1038/nbt.1564

149. Kortylewski M, Kuo YH. Push and release: TLR9 activation plus STAT3 blockade for systemic antitumor immunity. Oncoimmunology 2014; 3: e27441; PMID:24800162; http://dx.doi.org/10.4161/onci.27441
150. Moreira D, Zhang Q, Hossain DM, Nechaev S, Li H, Kowolik CM, D'Apuzzo M, Forman S, Jones J, Pal SK et al. TLR9 signaling through NF-kappaB/RELA and STAT3 promotes tumor-propagating potential of prostate cancer cells. Oncotarget 2015; 6:17302-13; PMID:26046794; http://dx.doi.org/10.18632/oncotarget.4029
151. Golden EB, Chachoua A, Fenton-Kerimian M, Demaria S, Formenti SC. Abscopal responses in patients with refractory metastatic NSCLC treated with concurrent radiotherapy and CTLA-4 immune checkpoint blockade: evidence for the in situ vaccination hypothesis of radiotherapy. Cancer Research 2015; 75:S244; http://dx.doi.org/10.1158/1538-7445.AM2015-244
152. Khodadoust MS, Chu MP, Czerwinski D, McDonald K, Long S, Kohrt HE, Hoppe RT, Advani RH, Lowsky R, Levy R. Phase I/II study of intratumoral injection of SD-101, an immunostimulatory CpG, and intratumoral injection of ipillumumab, an anti-CTLA-4 monoclonal antibody, in combination with local radiation in low-grade B-cell lymphomas. ASCO Annual Meeting, 2015
153. Wei H, Zhao L, Hellstrom I, Hellstrom KE, Guo Y. Dual targeting of CD137 co-stimulatory and PD-1 co-inhibitory molecules for ovarian cancer immunotherapy. Oncoimmunology 2014; 3:e28248; PMID:25050196; http://dx.doi.org/10.4161/onci.28248
154. Robert C, Long GV, Brady B, Dutriaux C, Maio M, Mortier L, Hassel JC, Rutkowski P, McNeil C, Kalinka-Warzocha E et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med 2015; 372(4):2006-17; PMID:25399552; http://dx.doi.org/10.1056/NEJMoa1412082
155. Ansell SM, Lesokhin AM, Borrello I, Halwani A, Scott EC, Gutierrez M, Schuster SJ, Millenson MM, Cattry D, Freeman GJ et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. N Engl J Med 2015; 372(4):311-9; PMID:25482239; http://dx.doi.org/10.1056/NEJMoa1411087
156. Robert C, Ribas A, Wolchok JD, Hodi FS, Hamid O, Kefford R, Weber JS, Joshua AM, Hwu WJ, Gangadhar TC et al. Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial. Lancet 2014; 384:1109-17; PMID:25034862; http://dx.doi.org/10.1016/S0140-6736(14)60958-2
157. Tumeh PC, Harview CL, Yearley JH, Shintaku IP, Taylor EJ, Robert L, Chmielowski B, Spasic M, Henry G, Ciobanu V et al. PD-1 blockade induces responses by inhibiting adaptive immune resistance. Nature 2014; 515:568-71; PMID:25428505; http://dx.doi.org/10.1038/nature13954
158. Garon EB, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, Eder JP, Patnaik A, Aggarwal C, Gubens M, Horn L et al. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med 2015; 372:2018-28; PMID:25891174; http://dx.doi.org/10.1056/NEJMoa1501824
159. Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, Daud A, Carlino MS, McNeil C, Lotem M et al. Pembrolizumab versus ipilimumab in advanced melanoma. N Engl J Med 2015; 372:2521-32; PMID:25891173; http://dx.doi.org/10.1056/NEJMoa1503093
160. Kroemer G, Galluzzi L. Combinatorial immunotherapy with checkpoint blockers solves the problem of metastatic melanoma-An exclamation sign with a question mark. Oncoimmunology 2015; 4:e1058037; PMID:26140249; http://dx.doi.org/10.1080/2162402X.2015.1058037
161. Segal NH, Kemeny NE, Cercek A, Reidy DL, Raasch PJ, Warren P, Hrabovsky AE, Campbell N, Shia J, Goodman KA et al. Non-randomized phase II study to assess the efficacy of pembrolizumab (Pem) plus radiotherapy (RT) or ablation in mismatch repair proficient (pMMR) metastatic colorectal cancer (mCRC) patients. ASCO Annual Meeting, 2016
162. Le DT, Wang-Gillam A, Picozzi V, Greten TF, Crocenzi T, Springett G, Morse M, Zeh H, Cohen D, Fine RL et al. Safety and survival with GVAX pancreas prime and *Listeria monocytogenes*-expressing mesothelin (CRS-207) boost vaccines for metastatic pancreatic cancer. J Clin Oncol 2015; 33:1325-33; PMID:25584002; http://dx.doi.org/10.1200/JCO.2014.57.4244
163. Brower V. New approaches tackle rising pancreatic cancer rates. J Natl Cancer Inst 2014; 106; PMID:25535299; http://dx.doi.org/10.1093/jnci/dju417
164. Soares KC, Rucki AA, Wu AA, Olino K, Xiao Q, Chai Y, Wamwea A, Bigelow E, Lutz E, Liu L et al. PD-1/PD-L1 blockade together with vaccine therapy facilitates effector T-cell infiltration into pancreatic tumors. J Immunother 2015; 38:1-11; PMID:25415283; http://dx.doi.org/10.1097/CJI.0000000000000062
165. Kroemer G, Galluzzi L. Immunotherapy of hematological cancers: PD-1 blockade for the treatment of Hodgkin's lymphoma. Oncoimmunology 2015; 4:e1008853; PMID:26155425; http://dx.doi.org/10.1080/2162402X.2015.1008853
166. Palucka K, Banchereau J. SnapShot: cancer vaccines. Cell 2014; 157:516-e1; PMID:24725415; http://dx.doi.org/10.1016/j.cell.2014.03.044
167. Palucka K, Banchereau J. Cancer immunotherapy via dendritic cells. Nat Rev Cancer 2012; 12:265-77; PMID:22437871; http://dx.doi.org/10.1038/nrc3258
168. Kolstad A, Olweus J. "In situ" vaccination for systemic effects in follicular lymphoma. Oncoimmunology 2015; 4:e1014773; PMID:26140239; http://dx.doi.org/10.1080/2162402X.2015.1014773
169. Bol KF, Figdor CG, Aarntzen EH, Welzen ME, van Rossum MM, Blokx WA, van de Rakt MW, Scharenborg NM, de Boer AJ, Pots JM et al. Intranodal vaccination with mRNA-optimized dendritic cells in metastatic melanoma patients. Oncoimmunology 2015; 4:e1019197; PMID:26405571; http://dx.doi.org/10.1080/2162402X.2015.1019197
170. Ueno H, Palucka AK, Banchereau J. The expanding family of dendritic cell subsets. Nat Biotechnol 2010; 28:813-5; PMID:20697407; http://dx.doi.org/10.1038/nbt0810-813
171. Ueno H, Klechevsky E, Schmitt N, Ni L, Flamar AL, Zurawski S, Zurawski G, Palucka K, Banchereau J, Oh S. Targeting human dendritic cell subsets for improved vaccines. Semin Immunol 2011; 23:21-7; PMID:21277223; http://dx.doi.org/10.1016/j.smim.2011.01.004
172. Deng L, Liang H, Burnette B, Weicheslbaum RR, Fu YX. Radiation and anti-PD-L1 antibody combinatorial therapy induces T cell-mediated depletion of myeloid-derived suppressor cells and tumor regression. Oncoimmunology 2014; 3:e28499; PMID:25050217; http://dx.doi.org/10.4161/onci.28499
173. More Benefits for Checkpoint Inhibitors in NSCLC. Cancer Discov 2015; 5:OF2; PMID:26511141; http://dx.doi.org/10.1158/2159-8290.CD-NB2015-148
174. Chawla A, Philips AV, Alatrash G, Mittendorf E. Immune checkpoints: a therapeutic target in triple negative breast cancer. Oncoimmunology 2014; 3:e28325; PMID:24843833; http://dx.doi.org/10.4161/onci.28325
175. Garon EB. Current perspectives in immunotherapy for non-small cell lung cancer. Semin Oncol 2015; 42 Suppl 2:S11-8; PMID:26477470; http://dx.doi.org/10.1053/j.seminoncol.2015.09.019
176. Scarpace SL. Metastatic squamous cell non-small-cell lung cancer (NSCLC): disrupting the drug treatment paradigm with immunotherapies. Drugs Context 2015; 4:212289; PMID:26576187; http://dx.doi.org/10.7573/dic.212289
177. Boyerinas B, Jochems C, Fantini M, Heery CR, Gulley JL, Tsang KY, Schlom J. Antibody-dependent cellular cytotoxicity activity of a novel anti-PD-L1 antibody avelumab (MSB0010718C) on human tumor cells. Cancer Immunol Res 2015; 3:1148-57; PMID:26014098; http://dx.doi.org/10.1158/2326-6066.CIR-15-0059
178. Reichert JM. Antibodies to watch in 2016. MAbs 2016; 8:197-204; PMID:26651519; http://dx.doi.org/10.1080/19420862.2015.1125583
179. Robert L, Harview C, Emerson R, Wang X, Mok S, Homet B, Comin-Anduix B, Koya RC, Robins H, Tumeh PC et al. Distinct immunological mechanisms of CTLA-4 and PD-1 blockade revealed by analyzing TCR usage in blood lymphocytes. Oncoimmunology 2014; 3:e29244; PMID:25083336; http://dx.doi.org/10.4161/onci.29244
180. Calabro L, Maio M. Immune checkpoint blockade in malignant mesothelioma: a novel therapeutic strategy against a deadly disease? Oncoimmunology 2014; 3:e27482; PMID:24734215; http://dx.doi.org/10.4161/onci.27482
181. Zielinski CC. A phase I study of MEDI4736, NNT-PD-L1 antibody in patients with advanced solid tumors. Transl Lung Cancer Res

2014; 3:406-7; PMID:25806335; http://dx.doi.org/10.3978/j.issn.2218-6751.2014.08.07
182. Ibrahim R, Stewart R, Shalabi A. PD-L1 blockade for cancer treatment: MEDI4736. Semin Oncol 2015; 42:474-83; PMID:25965366; http://dx.doi.org/10.1053/j.seminoncol.2015.02.007
183. Lee SM, Chow LQ. A new addition to the PD-1 checkpoint inhibitors for non-small cell lung cancer-the anti-PDL1 antibody-MEDI4736. Transl Lung Cancer Res 2014; 3:408-10; PMID:25806336; http://dx.doi.org/10.3978/j.issn.2218-6751.2014.11.10
184. Creelan BC. Update on immune checkpoint inhibitors in lung cancer. Cancer Control 2014; 21:80-9; PMID:24357746
185. Papadopoulos KP, Crittenden MR, Johnson ML, Lockhart AC, Moore KN, Falchook GS, Formenti S, Carvajal RD, Leidner RS, Naing A et al. A first-in-human study of REGN2810, a monoclonal, fully human antibody to programmed death-1 (PD-1), in combination with immunomodulators including hypofractionated radiotherapy (hfRT). ASCO Annual Meeting, 2016
186. Ruggeri L, Urbani E, Andre P, Mancusi A, Tosti A, Topini F, Blery M, Animobono L, Romagne F, Wagtmann N et al. Effects of anti-NKG2A antibody administration on leukemia and normal hematopoietic cells. Haematologica 2016; 101:626-33; PMID:26721894; http://dx.doi.org/10.3324/haematol.2015.135301
187. Zhang Y, Lv G, Lou X, Peng D, Qu X, Yang X, Ayana DA, Guo H, Jiang Y. NKG2A expression and impaired function of NK cells in patients with new onset of Graves' disease. Int Immunopharmacol 2015; 24:133-9; PMID:25281394; http://dx.doi.org/10.1016/j.intimp.2014.09.020
188. Demaria S, Pilones KA, Formenti SC, Dustin ML. Exploiting the stress response to radiation to sensitize poorly immunogenic tumors to anti-CTLA-4 treatment. Oncoimmunology 2013; 2:e23127; PMID:23802063; http://dx.doi.org/10.4161/onci.23127
189. Prica A, Buckstein R. Myelodysplastic syndrome successfully treated with adalimumab. J Clin Oncol 2015; 33:e4-6; PMID:24567429; http://dx.doi.org/10.1200/JCO.2013.49.4948
190. Senovilla L, Vacchelli E, Galon J, Adjemian S, Eggermont A, Fridman WH, Sautes-Fridman C, Ma Y, Tartour E, Zitvogel L et al. Trial Watch: prognostic and predictive value of the immune infiltrate in cancer. Oncoimmunology 2012; 1:1323-43; PMID:23243596; http://dx.doi.org/10.4161/onci.22009
191. Senovilla L, Aranda F, Galluzzi L, Kroemer G. Impact of myeloid cells on the efficacy of anticancer chemotherapy. Curr Opin Immunol 2014; 30C:24-31; PMID:24950501; http://dx.doi.org/10.1016/j.coi.2014.05.009
192. Banerjee S, Halder K, Ghosh S, Bose A, Majumdar S. The combination of a novel immunomodulator with a regulatory T cell suppressing antibody (DTA-1) regress advanced stage B16F10 solid tumor by repolarizing tumor associated macrophages in situ. Oncoimmunology 2015; 4:e995559; PMID:25949923; http://dx.doi.org/10.1080/2162402X.2014.995559
193. Cannarile MA, Ries CH, Hoves S, Ruttinger D. Targeting tumor-associated macrophages in cancer therapy and understanding their complexity. Oncoimmunology 2014; 3:e955356; PMID:25941615; http://dx.doi.org/10.4161/21624011.2014.955356
194. Trachtman H, Fervenza FC, Gipson DS, Heering P, Jayne DR, Peters H, Rota S, Remuzzi G, Rump LC, Sellin LK et al. A phase 1, single-dose study of fresolimumab, an anti-TGF-beta antibody, in treatment-resistant primary focal segmental glomerulosclerosis. Kidney Int 2011; 79:1236-43; PMID:21368745; http://dx.doi.org/10.1038/ki.2011.33
195. Morris JC, Tan AR, Olencki TE, Shapiro GI, Dezube BJ, Reiss M, Hsu FJ, Berzofsky JA, Lawrence DP. Phase I study of GC1008 (fresolimumab): a human anti-transforming growth factor-beta (TGFbeta) monoclonal antibody in patients with advanced malignant melanoma or renal cell carcinoma. PLoS One 2014; 9:e90353; PMID:24618589; http://dx.doi.org/10.1371/journal.pone.0090353
196. Wu AA, Drake V, Huang HS, Chiu S, Zheng L. Reprogramming the tumor microenvironment: tumor-induced immunosuppressive factors paralyze T cells. Oncoimmunology 2015; 4:e1016700; PMID:26140242; http://dx.doi.org/10.1080/2162402X.2015.1016700
197. Chen X, Wakefield LM, Oppenheim JJ. Synergistic antitumor effects of a TGFbeta inhibitor and cyclophosphamide. Oncoimmunology 2014; 3:e28247; PMID:25050195; http://dx.doi.org/10.4161/onci.28247
198. He LZ, Prostak N, Thomas LJ, Vitale L, Weidlick J, Crocker A, Pilsmaker CD, Round SM, Tutt A, Glennie MJ et al. Agonist anti-human CD27 monoclonal antibody induces T cell activation and tumor immunity in human CD27-transgenic mice. J Immunol 2013; 191:4174-83; PMID:24026078; http://dx.doi.org/10.4049/jimmunol.1300409
199. Thomas LJ, He LZ, Marsh H, Keler T. Targeting human CD27 with an agonist antibody stimulates T-cell activation and antitumor immunity. Oncoimmunology 2014; 3:e27255; PMID:24605266; http://dx.doi.org/10.4161/onci.27255
200. Ruf M, Moch H, Schraml P. Interaction of tumor cells with infiltrating lymphocytes via CD70 and CD27 in clear cell renal cell carcinoma. Oncoimmunology 2015; 4:e1049805; PMID:26587319; http://dx.doi.org/10.1080/2162402X.2015.1049805
201. Ramakrishna V, Sundarapandiyan K, Zhao B, Bylesjo M, Marsh HC, Keler T. Characterization of the human T cell response to in vitro CD27 costimulation with varlilumab. J Immunother Cancer 2015; 3:37; PMID:26500773; http://dx.doi.org/10.1186/s40425-015-0080-2
202. Cho HI, Jung SH, Sohn HJ, Celis E, Kim TG. An optimized peptide vaccine strategy capable of inducing multivalent CD8+ T cell responses with potent antitumor effects. Oncoimmunology 2015; 4:e1043504; PMID:26451316; http://dx.doi.org/10.1080/2162402X.2015.1043504
203. Rainone V, Martelli C, Ottobrini L, Biasin M, Borelli M, Lucignani G, Trabattoni D, Clerici M. Immunological characterization of whole tumour lysate-loaded dendritic cells for cancer immunotherapy. PLoS One 2016; 11:e0146622; PMID:26795765; http://dx.doi.org/10.1371/journal.pone.0146622
204. Galluzzi L, Vitale I, Michels J, Brenner C, Szabadkai G, Harel-Bellan A, Castedo M, Kroemer G. Systems biology of cisplatin resistance: past, present and future. Cell Death Dis 2014; 5:e1257; PMID:24874729; http://dx.doi.org/10.1038/cddis.2013.428
205. Galluzzi L, Senovilla L, Vitale I, Michels J, Martins I, Kepp O, Castedo M, Kroemer G. Molecular mechanisms of cisplatin resistance. Oncogene 2012; 31:1869-83; PMID:21892204; http://dx.doi.org/10.1038/onc.2011.384
206. Galluzzi L, Kepp O, Vander Heiden MG, Kroemer G. Metabolic targets for cancer therapy. Nat Rev Drug Discov 2013; 12:829-46; PMID:24113830; http://dx.doi.org/10.1038/nrd4145
207. Yan H, Parsons DW, Jin G, McLendon R, Rasheed BA, Yuan W, Kos I, Batinic-Haberle I, Jones S, Riggins GJ et al. IDH1 and IDH2 mutations in gliomas. N Engl J Med 2009; 360:765-73; PMID:19228619; http://dx.doi.org/10.1056/NEJMoa0808710
208. Zhao S, Lin Y, Xu W, Jiang W, Zha Z, Wang P, Yu W, Li Z, Gong L, Peng Y et al. Glioma-derived mutations in IDH1 dominantly inhibit IDH1 catalytic activity and induce HIF-1alpha. Science 2009; 324:261-5; PMID:19359588; http://dx.doi.org/10.1126/science.1170944
209. Galluzzi L, Vacchelli E, Bravo-San Pedro JM, Buque A, Senovilla L, Baracco EE, Bloy N, Castoldi F, Abastado JP, Agostinis P et al. Classification of current anticancer immunotherapies. Oncotarget 2014; 5:12472-508; PMID:25537519; http://dx.doi.org/10.18632/oncotarget.2998
210. Andtbacka RH, Kaufman HL, Collichio F, Amatruda T, Senzer N, Chesney J, Delman KA, Spitler LE, Puzanov I, Agarwala SS et al. Talimogene laherparepvec improves durable response rate in patients with advanced melanoma. J Clin Oncol 2015; 33:2780-8; PMID:26014293; http://dx.doi.org/10.1200/JCO.2014.58.3377
211. Markert JM, Razdan SN, Kuo HC, Cantor A, Knoll A, Karrasch M, Nabors LB, Markiewicz M, Agee BS, Coleman JM et al. A phase 1 trial of oncolytic HSV-1, G207, given in combination with radiation for recurrent GBM demonstrates safety and radiographic responses. Mol Ther 2014; 22:1048-55; PMID:24572293; http://dx.doi.org/10.1038/mt.2014.22
212. Aranda F, Vacchelli E, Obrist F, Eggermont A, Galon J, Herve Fridman W, Cremer I, Tartour E, Zitvogel L, Kroemer G et al. Trial Watch: adoptive cell transfer for anticancer immunotherapy. Oncoimmunology 2014; 3:e28344; PMID:25050207; http://dx.doi.org/10.4161/onci.28344
213. Matzner P, Sorski L, Shaashua L, Elbaz E, Lavon H, Melamed R, Rosenne E, Gotlieb N, Benbenishty A, Reed SG et al. Perioperative treatment with the new synthetic TLR-4 agonist GLA-SE reduces

cancer metastasis without adverse effects. Int J Cancer 2016; 138:1754-64; PMID:26453448; http://dx.doi.org/10.1002/ijc.29885
214. Orr MT, Duthie MS, Windish HP, Lucas EA, Guderian JA, Hudson TE, Shaverdian N, O'Donnell J, Desbien AL, Reed SG et al. MyD88 and TRIF synergistic interaction is required for TH1-cell polarization with a synthetic TLR4 agonist adjuvant. Eur J Immunol 2013; 43:2398-408; PMID:23716300; http://dx.doi.org/10.1002/eji.201243124
215. Krieg AM. Toll-like receptor 9 (TLR9) agonists in the treatment of cancer. Oncogene 2008; 27:161-7; PMID:18176597; http://dx.doi.org/10.1038/sj.onc.1210911
216. Mella M, Kauppila JH, Karihtala P, Lehenkari P, Jukkola-Vuorinen A, Soini Y, Auvinen P, Vaarala MH, Ronkainen H, Kauppila S et al. Tumor infiltrating CD8+ T lymphocyte count is independent of tumor TLR9 status in treatment naive triple negative breast cancer and renal cell carcinoma. Oncoimmunology 2015; 4:e1002726; PMID:26155410; http://dx.doi.org/10.1080/2162402X.2014.1002726
217. van Seters M, van Beurden M, ten Kate FJ, Beckmann I, Ewing PC, Eijkemans MJ, Kagie MJ, Meijer CJ, Aaronson NK, Kleinjan A et al. Treatment of vulvar intraepithelial neoplasia with topical imiquimod. N Engl J Med 2008; 358:1465-73; PMID:18385498; http://dx.doi.org/10.1056/NEJMoa072685
218. Henriques L, Palumbo M, Guay MP, Bahoric B, Basik M, Kavan P, Batist G. Imiquimod in the treatment of breast cancer skin metastasis. J Clin Oncol 2014; 32:e22-5; PMID:24419128; http://dx.doi.org/10.1200/JCO.2012.46.4883
219. Smyth EC, Flavin M, Pulitzer MP, Gardner GJ, Costantino PD, Chi DS, Bogatch K, Chapman PB, Wolchok JD, Schwartz GK et al. Treatment of locally recurrent mucosal melanoma with topical imiquimod. J Clin Oncol 2011; 29:e809-11; PMID:22010009; http://dx.doi.org/10.1200/JCO.2011.36.8829
220. Dewan MZ, Vanpouille-Box C, Kawashima N, DiNapoli S, Babb JS, Formenti SC, Adams S, Demaria S. Synergy of topical toll-like receptor 7 agonist with radiation and low-dose cyclophosphamide in a mouse model of cutaneous breast cancer. Clin Cancer Res 2012; 18:6668-78; PMID:23048078; http://dx.doi.org/10.1158/1078-0432.CCR-12-0984
221. Demaria S, Vanpouille-Box C, Formenti SC, Adams S. The TLR7 agonist imiquimod as an adjuvant for radiotherapy-elicited in situ vaccination against breast cancer. Oncoimmunology 2013; 2:e25997; PMID:24404422; http://dx.doi.org/10.4161/onci.25997
222. Garaci E, Pica F, Matteucci C, Gaziano R, D'Agostini C, Miele MT, Camerini R, Palamara AT, Favalli C, Mastino A et al. Historical review on thymosin alpha1 in oncology: preclinical and clinical experiences. Expert Opin Biol Ther 2015; 15 Suppl 1:S31-9; PMID:26096345; http://dx.doi.org/10.1517/14712598.2015.1017466
223. De Sanctis R, Marrari A, Santoro A. Trabectedin for the treatment of soft tissue sarcomas. Expert Opin Pharmacother 2016; 17(11):1569-77; PMID:27328277; http://dx.doi.org/10.1080/14656566.2016.1204295
224. Gordon EM, Sankhala KK, Chawla N, Chawla SP. Trabectedin for soft tissue sarcoma: current status and future perspectives. Adv Ther 2016; 33(7):1055-71; PMID:27234989; http://dx.doi.org/10.1007/s12325-016-0344-3
225. Kawai A, Araki N, Sugiura H, Ueda T, Yonemoto T, Takahashi M, Morioka H, Hiraga H, Hiruma T, Kunisada T et al. Trabectedin monotherapy after standard chemotherapy versus best supportive care in patients with advanced, translocation-related sarcoma: a randomised, open-label, phase 2 study. Lancet Oncol 2015; 16:406-16; PMID:25795406; http://dx.doi.org/10.1016/S1470-2045(15)70098-7
226. Jia XH, Du Y, Mao D, Wang ZL, He ZQ, Qiu JD, Ma XB, Shang WT, Ding D, Tian J. Zoledronic acid prevents the tumor-promoting effects of mesenchymal stem cells via MCP-1 dependent recruitment of macrophages. Oncotarget 2015; 6:26018-28; PMID:26305552; http://dx.doi.org/10.18632/oncotarget.4658
227. Andersen MH, Svane IM. Indoleamine 2,3-dioxygenase vaccination. Oncoimmunology 2015; 4:e983770; PMID:25949864; http://dx.doi.org/10.4161/2162402X.2014.983770
228. Park SY, Kim MJ, Park SA, Kim JS, Min KN, Kim DK, Lim W, Nam JS, Sheen YY. Combinatorial TGF-beta attenuation with paclitaxel inhibits the epithelial-to-mesenchymal transition and breast cancer stem-like cells. Oncotarget 2015; 6:37526-43; PMID:26462028; http://dx.doi.org/10.18632/oncotarget.6063
229. Park CY, Min KN, Son JY, Park SY, Nam JS, Kim DK, Sheen YY. An novel inhibitor of TGF-beta type I receptor, IN-1130, blocks breast cancer lung metastasis through inhibition of epithelial-mesenchymal transition. Cancer Lett 2014; 351:72-80; PMID:24887560; http://dx.doi.org/10.1016/j.canlet.2014.05.006
230. Adams JL, Smothers J, Srinivasan R, Hoos A. Big opportunities for small molecules in immuno-oncology. Nat Rev Drug Discov 2015; 14:603-22; PMID:26228631; http://dx.doi.org/10.1038/nrd4596
231. Li ZL, Ye SB, OuYang LY, Zhang H, Chen YS, He J, Chen QY, Qian CN, Zhang XS, Cui J et al. COX-2 promotes metastasis in nasopharyngeal carcinoma by mediating interactions between cancer cells and myeloid-derived suppressor cells. Oncoimmunology 2015; 4:e1044712; PMID:26451317; http://dx.doi.org/10.1080/2162402X.2015.1044712
232. Buque A, Bloy N, Aranda F, Cremer I, Eggermont A, Fridman WH, Fucikova J, Galon J, Spisek R, Tartour E et al. Trial Watch: small molecules targeting the immunological tumor microenvironment for cancer therapy. Oncoimmunology 2016; 5(6):e1149674; PMID:27471617; http://dx.doi.org/10.1080/2162402X.2016.1149674
233. Bieri S, Helg C, Chapuis B, Miralbell R. Total body irradiation before allogeneic bone marrow transplantation: is more dose better? Int J Radiat Oncol Biol Phys 2001; 49:1071-7; PMID:11240249; http://dx.doi.org/10.1016/S0360-3016(00)01491-7
234. Derer A, Frey B, Fietkau R, Gaipl US. Immune-modulating properties of ionizing radiation: rationale for the treatment of cancer by combination radiotherapy and immune checkpoint inhibitors. Cancer Immunol Immunother 2016; 65:779-86; PMID:26590829; http://dx.doi.org/10.1007/s00262-015-1771-8
235. Krysko DV, Agostinis P, Krysko O, Garg AD, Bachert C, Lambrecht BN, Vandenabeele P. Emerging role of damage-associated molecular patterns derived from mitochondria in inflammation. Trends Immunol 2011; 32:157-64; PMID:21334975; http://dx.doi.org/10.1016/j.it.2011.01.005
236. Vatner RE, Cooper BT, Vanpouille-Box C, Demaria S, Formenti SC. Combinations of immunotherapy and radiation in cancer therapy. Front Oncol 2014; 4:325; PMID:25506582; http://dx.doi.org/10.3389/fonc.2014.00325
237. Demaria S, Golden EB, Formenti SC. Role of local radiation therapy in cancer immunotherapy. JAMA Oncol 2015; 1:1325-32; PMID:26270858; http://dx.doi.org/10.1001/jamaoncol.2015.2756
238. Vanpouille-Box CI, Aryankalayil M, Pilones KA, Formenti SC, Coleman N, Demaria S. Fractionated but not single dose radiation is an optimal adjuvant for in situ tumor vaccination. Cancer Res 2015; 75:S2493; http://dx.doi.org/10.1158/1538-7445.AM2015-2493
239. Gay S, Foiani M. Nuclear envelope and chromatin, lock and key of genome integrity. Int Rev Cell Mol Biol 2015; 317:267-330; PMID:26008788; http://dx.doi.org/10.1016/bs.ircmb.2015.03.001
240. Nicholson JM, Cimini D. Link between aneuploidy and chromosome instability. Int Rev Cell Mol Biol 2015; 315:299-317; PMID:25708466; http://dx.doi.org/10.1016/bs.ircmb.2014.11.002
241. Zitvogel L, Galluzzi L, Smyth MJ, Kroemer G. Mechanism of action of conventional and targeted anticancer therapies: reinstating immunosurveillance. Immunity 2013; 39:74-88; PMID:23890065; http://dx.doi.org/10.1016/j.immuni.2013.06.014