Trial Watch

Radioimmunotherapy for oncological indications

Norma Bloy1,2,3,4,1, Jonathan Pol1,2,3,1, Gwenola Manic5, Ilio Vitale5, Alexander Eggemont1, Jérôme Galon2,6,7,8, Eric Tartour6,9,10, Laurence Zitvogel1,11, Guido Kroemer2,3,6,10,12,*,1 and Lorenzo Galluzzi1,3,6,,*

1 Gustave Roussy Cancer Campus; Villejuif, France; 2 INSERM, U1138; Paris, France; 3 Equipe 11 labellisée par la Ligue Nationale contre le Cancer; Centre de Recherche des Cordeliers; Paris, France; 4 Université Paris-Sud/Paris XI; Paris, France; 5 Regina Elena National Cancer Institute; Rome, Italy; 6 Université Paris Descartes/Paris V; Sorbonne Paris Cité; Paris, France; 7 Université Pierre et Marie Curie/Paris VI; Paris, France; 8 Laboratory of Integrative Cancer Immunology, Centre de Recherche des Cordeliers; Paris, France; 9 INSERM, U970; Paris, France; 10 Poêle de Biologie, Hôpital Européen Georges Pompidou, AP-HP; Paris, France; 11 INSERM, U1015; CICBT507; Villejuif, France; 12 Metabolomics and Cell Biology Platforms; Gustave Roussy Cancer Campus; Villejuif, France

These authors equally contributed to this work.

Keywords: CTLA4, dendritic cells, ibritumomab tiuxetan, immunostimulatory cytokines, peptide-based anticancer vaccine, Toll-like receptor agonists

Abbreviations: DC, dendritic cell; EBRT, external-beam radiation therapy; EGFR, epidermal growth factor receptor; FDA, Food and Drug Administration; ICD, immunogenic cell death; IL, interleukin; mAb, monoclonal antibody; NHL, non-Hodgkin’s lymphoma; TLR, Toll-like receptor.

During the past two decades, it has become increasingly clear that the antineoplastic effects of radiation therapy do not simply reflect the ability of X-, β- and γ-rays to damage transformed cells and directly cause their permanent proliferative arrest or demise, but also involve cancer cell-extrinsic mechanisms. Indeed, among other activities, radiotherapy has been shown to favor the establishment of tumor-specific immune responses that operate systemically, underpinning the so-called ‘out-of-field’ or ‘abscopal’ effect. Thus, ionizing rays appear to elicit immunogenic cell death, a functionally peculiar variant of apoptosis associated with the emission of a particularly immunostimulatory combination of damage-associated molecular patterns. In line with this notion, radiation therapy fosters, and thus exacerbates, the antineoplastic effects of various treatment modalities, including surgery, chemotherapy and various immunotherapeutic agents. Here, we summarize recent advances in the use of ionizing rays as a means to induce or potentiate therapeutically relevant anticancer immune responses. In addition, we present clinical trials initiated during the past 12 months to test the actual benefit of radioimmunotherapy in cancer patients.

Introduction

Radiation therapy perhaps constitutes the most widely employed antineoplastic intervention of all time.¹,² Current estimates indicate that more than 50% of cancer patients will undergo radiotherapy at some point in the course of their disease.³,⁴ Originally conceived in the early 1900s following the groundbreaking discovery of Wilhelm Conrad Röntgen,¹ the possibility of treating malignant lesions with ionizing rays has transformed into a robust clinical paradigm coincident with the huge technological advances achieved throughout the 20th century.¹,² Nowadays, ionizing irradiation is frequently administered in combination with other treatment modalities (including surgery and chemotherapy), either with a curative intent (i.e., to eradicate primary tumors or prevent disease recurrence) or as a palliative approach (i.e., to relieve the pain/discomfort provoked by tumors at particular anatomical locations).³,⁴ Depending on the specific case, irradiation can be administered as a neo-adjuvant intervention (to limit the esthetic/anatomical impact of the procedure and minimize the risk of recurrence), intra-operatively (granting access to neoplastic lesions with a particularly complicated anatomical localization), or as an adjuvant treatment (constituting an efficient means to prevent disease relapse).⁵,⁷

For the purpose of this discussion, radiation therapy can be broadly subdivided into 2 large categories: external-beam radiation therapy (EBRT) and internal radiotherapy.²,⁸ EBRT generally relies on an external source of collimated X- or γ-rays targeting neoplastic lesions across the intact skin. We have previously discussed in detail the types of EBRT most commonly employed for oncological indications.¹ Internal radiotherapy can be further subdivided into 2 variants: (1) brachytherapy, which involves the seeding of small radioactive pellets within the tumor mass (interstitial brachytherapy) or in an adjacent cavity (intracavitary brachytherapy); and (2) systemic radiation therapy, consisting in the oral or intravenous administration of a radionuclide, often (but not always) coupled to a tumor-targeting monoclonal antibody (mAb).⁸,⁹ EBRT, brachytherapy and systemic radiation therapy are associated with specific advantages
and drawbacks that render them particularly conducive to the treatment of specific tumors. A detailed discussion of these aspects goes beyond the scope of this Trial Watch and can be found in Refs. 2, 7 and 8.

For a long time, the therapeutic potential of ionizing rays has been exclusively ascribed to their ability to mediate robust anti-proliferative and cytotoxic effects as they directly damage various macromolecules (including lipids and DNA) and favor the establishment of oxidative stress (which also promotes DNA damage).10-12 The molecular damage inflicted by radiation therapy can cause: (1) a permanent proliferative arrest known as cellular senescence; 13-16 (2) mitochondrial outer membrane permeabilization, which can cause: (1) a permanent proliferative arrest known as cellular senescence; 13-16 (2) mitochondrial outer membrane permeabilization, de facto committing cells to die along with the massive activation of caspases;37,7-21 or (3) various forms of regulated necrosis, including a receptor-interacting protein kinase 3 (RIPK3)- and mixed lineage kinase domain-like (MLKL)-dependent variant commonly referred to as necroptosis, 22-25 as well as poly(ADP-ribose) polymerase 1 (PARP1)- and apoptosis-inducing factor, mitochonrdion-associated, 1 (AIFM1)-dependent subroutine known as parthanatos.26,27 The induction of regulated cell death by irradiation often, but not always, involves tumor protein p53 (TP53, best known as p53), 28-30 and results from the activation of mitotic catastrophe, an oncopsuppressive mechanism for the elimination of cells unable to complete mitosis.31,32

During the past 2 decades, it has become clear that the clinical activity of radiation therapy also involves various cell-extrinsic mechanisms. First, malignant cells exposed to ionizing irradiation die while releasing a wide panel of cytotoxic mediators, including reactive oxygen and nitrogen species, 33-35 as well as several cytokines like interleukin (IL)-6,36 IL-8,37 transforming growth factor β1 (TGFβ1)38 and tumor necrosis factor α (TNFα).39 These biologically active molecules de facto promote the demise of non-irradiated neighboring cells, underpinning the ability of radiation therapy to mediate local bystander effects. 10,40,41 Second, cancer cells are thought to succumb to radiation therapy by undergoing an immunogenic variant of apoptosis commonly known as immunogenic cell death (ICD).12,17,42,43 ICD is intimately linked to the emission of various damage-associated molecular patterns in a manner that is spatiotemporally compatible with the recruitment of antigen-presenting cells and the elicitation of adaptive immunity.42,44-46 Thus, irradiated cancer cells can, at least under some circumstances, prime a tumor-specific immune response that operates systemically, underpinning the long-range bystander effects of radiation therapy commonly known as “out-of-field” or “abscopal” reactions.47-52 Finally, several types of radiotherapy favor the normalization of the tumor vasculature, a process that inhibits tumor growth while facilitating the access of neoplastic lesions by chemotherapeutic agents and immune effector cells.53,55

Radiation therapy causes both acute and chronic side effects.56-59 The former, which generally resolves in a few days/ weeks after interruption, generally reflect the temporary damage inflicted to highly proliferative normal tissues inevitably irradiated along with neoplastic lesions (e.g., the skin in the case of EBRT). 60 Conversely, the latter result from the permanent damage of highly proliferating cell compartments, such as the intestinal mucosa. In addition, radiation therapy is associated with a small but quantifiable increase in the risk of developing a secondary, treatment-induced neoplasm later in life.61-63 Several strategies have been developed throughout the past 50 years to increase the therapeutic index of radiation therapy, that is, to maximize its anti-neoplastic activity (“radiosensitization”) while limiting its cytotoxic effects on non-transformed tissues (“radioprotection”).1,2,64-66 Fractionation, i.e., the delivery of radiotherapy in multiple sessions (spaced by at least 6 hours) over several weeks, is by far the most common approach to simultaneously achieve this goal.1 Moreover, several molecules have been shown to mediate bona fide “radiosensitizing” or “radioprotective” effects in preclinical models.67-82 Nonetheless, the radical scavenger amifostine (also known as Ethyol®) is the only chemical currently approved by the US Food and Drug Administration (FDA) for use as a radioprotector in cancer patients.83-85

One year ago, in the September issue of OncoImmunology, we discussed in detail the scientific grounds for the use of ionizing irradiation as a means to elicit or boost tumor-targeting immune responses in cancer patients and presented recent clinical trials investigating the actual therapeutic profile of this approach.1 In this Trial Watch, we summarize the latest developments in this promising area of clinical investigation, focusing on clinical and preclinical paradigms of radioimmunotherapy, i.e., the combinatorial administration of radiation therapy and one or more immunostimulatory interventions.

**Literature Update**

Since the submission of our latest Trial Watch dealing with the topic (June 2013),7 the results of some 130 clinical studies evaluating the therapeutic profile of anticancer radioimmunotherapy have been published in the peer-reviewed scientific literature (source http://www.ncbi.nlm.nih.gov/pubmed). The largest fraction of these studies investigated the safety and efficacy of potentially immunogenic chemoradiotherapy, i.e., combinatorial regimens involving EBRT or internal radiotherapy plus immunostimulatory chemotherapeutics86-90 including (but not limited to) 5-fluorouracil (a pyrimidine analog generally utilized for the therapy of head and neck carcinoma and colorectal neoplasms) and its precursors (capecitabine and S-1, both of which are currently approved by the US FDA for use in colorectal cancer patients),91-131 etoposide (a topoisomerase inhibitor currently employed against testicular tumors and small cell lung cancer), 132-136 docetaxel and paclitaxel (two microtubular inhibitors of the taxane family routinely harnessed for the treatment of several carcinomas),96,97,111,113,127,134,136-153 ifosfamide and cyclophosphamide (two alkylating agents licensed by the US FDA for the therapy of various solid malignancies), 154,155 gemcitabine (a nucleoside analog currently employed in patients affected by various carcinomas),109,131,150,156,157 bortezomib (a proteasomal inhibitor most commonly utilized in multiple myeloma patients), 158 and various platinum derivatives (i.e., cisplatin, carboplatin and oxaliplatin, which are employed for the treatment of various carcinomas).91,92,95-104,106-108,111-
In addition, several research groups worldwide assessed the clinical profile of EBRT in combination with naked tumor-targeting mAbs, immunostimulatory mAbs, dendritic cell (DC)-based or peptide-based anticancer vaccines, or multiple immunogenic interventions (most often a tumor-targeting mAbs plus immunostimulatory chemotherapy). Finally, a few studies evaluated the therapeutic potential of mAb-based internal radiotherapy, either employed as a stand alone intervention or combined with additional immunotherapeutic agents, most often naked tumor-targeting mAbs.

Most clinical studies on the therapeutic activity of radioimmunotherapy published during the last 13 months enrolled patients bearing solid tumors, including subjects with glioma or glioblastoma, breast carcinoma, head and neck cancer, gastric or gastroesophageal carcinoma, endometrial carcinoma, colorectal or anal carcinoma, bladder carcinoma, cervical carcinoma, prostate carcinoma, and others. In addition, a few groups assessed the safety and efficacy of radiation therapy (most often internal radiotherapy) combined with immunostimulatory interventions in patients affected by various forms of lymphoma, colorectal or anal carcinoma, bladder carcinoma, cervical carcinoma, prostate carcinoma, and others. Taken together, these studies corroborate the notion that both EBRT and internal radiotherapy can be combined with a wide panel of immunostimulatory agents in the absence of accrued toxicity. As exceptions to this trend, Vakalov and colleagues found that the combination of 90Y-ibritumomab tiuxetan, a radiolabelled CD20-targeting mAb approved by the US FDA for use against non-Hodgkin lymphoma (NHL), and rituximab, a naked CD20-specific mAb currently employed for the treatment of chronic lymphocytic leukemia and NHL, correlates with an increased rate of Grade 3-4 adverse events relative to 90Y-ibritumomab tiuxetan monotherapy among NHL patients.

Among recent translational studies focusing on radioimmunotherapy in general, we found of particular interest the work of (1) Deng and collaborators (The Ludwig Center for Metastasis Research; Chicago, IL, US), who demonstrated that the immunosuppressive receptor programmed cell death 1 (PD-L1) is upregulated in the tumor microenvironment in response to EBRT, and that the administration of a mAb targeting the PD-1 ligand CD274 (best known as PD-L1) synergize with irradiation to provoke a therapeutically relevant antitumor immune response; (2) Klug and colleagues (German Cancer Research Center; Heidelberg, Germany), who proved that low-dose γ-rays administered in a neoadjuvant setting stimulate the differentiation of M1 macrophages hence promoting the normalization of the tumor vasculature and orchestrating an efficient tumor-targeting immune response; (3) Nam and coworkers (University of Ulsan College of Medicine; Seoul, Korea), who reported that the mechanistic target of rapamycin (MTOR) inhibitor rapamycin (which is currently approved by the US FDA for use as an immunosuppressive agent to prevent the rejection of solid organ transplants and coronary stents) can be employed to promote cellular senescence among radioresistant cancer cells, in spite of its ability to potently stimulate autophagy; (4) Bos et al. (Memorial Sloan-Kettering Cancer Center; New York, NY, US), who proved that the short-term ablation of CD4+CD25+FOXP3+ regulatory T cells (Tregs) significantly ameliorates the therapeutic efficacy of EBRT in a genetically-driven, autochthonous model of tumorigenesis; (5) Liu and collaborators (Chang Gung University; Taoyuan, Taiwan), who demonstrated that leukemia inhibitory factor (LIF), a cytokine of the IL-6 family, plays a significant role in the acquisition of radioresistance by nasopharyngeal carcinoma; (6) Zhou and colleagues (University of Michigan School of Dentistry; Ann Arbor, MI, US), who proved that the administration of the recombiant WNT agonist R-spondin 1 (RSPO1) combined with the transgene-driven overexpression of slit homolog 2 (SLIT2) mitigates the lethal effects of high-dose irradiation to the intestine but does not compromise its antineoplastic activity; (7) Sharma and collaborators (University Hospital Zurich; Zurich, Switzerland) and Gerber et al. (University of Rochester Medical Center; Rochester, NY, US), who independently showed that radiation therapy induces an intratumoral immune response (characterized by the recruitment of T lymphocytes and the secretion of Th1 cytokines), whose magnitude correlates with disease outcome; (8) Spary and colleagues (Cardiff University; Cardiff, UK), who demonstrated that low-dose irradiation significantly boosts the effector functions of T lymphocytes upon antigenic stimulation; and (9) Eke and co-workers (Dresden University of Technology; Dresden, Germany).
the overexpression of fibronectin and the resultant increase in cell-fibronectin interactions as a possible means by which cetuximab promotes radioresistance. It remains to be determined whether this mechanism is also responsible for the accrued toxicity of cetuximab-based radioimmunotherapy observed in recent clinical trials.

**Update On Ongoing Clinical Trials**

When this Trial Watch was being redacted (June 2014), official sources listed no less than 98 clinical trials launched after June 1st, 2013 aiming to evaluate the efficacy and safety of radioimmunotherapy in cancer patients (source http://www.clinicaltrials.gov). Of these studies, (1) 2 trials involve tumor-targeting mAbs, such as cetuximab or the vascular endothelial growth factor (VEGF)-targeting mAb bevacizumab (which is currently approved by the US FDA for use in patients affected by colorectal, lung and renal carcinoma); (2) 4 studies involve immunostimulatory mAbs, such as the cytotoxic T lymphocyte-associated protein 4 (CTLA4)-specific mAb ipilimumab (which is currently licensed for use in melanoma patients); (3) 62 immunostimulatory chemotherapeutics, including ICD-inducing agents as well as compounds that stimulate anticancer immune responses in an ICD-unrelated manner; (4) 3 recombinant cytokines, including IL-2; (5) 1 experimental Toll-like receptor (TLR) agonist; and (6) 1 experimental RNA-based anticancer vaccine. Reflecting currently approved therapeutic protocols, many of these clinical trials enroll patients with head and neck cancer (15 trials), gastric or gastroesophageal carcinoma (8 trials), colorectal carcinoma (14 trials), pancreatic cancer (11 trials) or non-small cell lung carcinoma (7 trials). In these settings, a variant of EBRT is generally combined with an immunostimulatory chemotherapeutic regimen, most often based on oxaliplatin in the case of individuals with colorectal carcinoma, gemcitabine in the case of pancreatic cancer patients, and a platinum derivative plus a taxane in the case of subjects bearing head and neck, gastric, gastroesophageal or pulmonary neoplasms. Along similar lines, 5 studies have recently been initiated to investigate the safety and efficacy of radiation therapy combined with ipilimumab or high-dose IL-2 in melanoma patients. These observations suggest that most of the recent clinical trials involving EBRT and one or more immunostimulatory agents rely on radiochemotherapeutic protocols developed prior to the recognition of the immunomodulatory potential of some chemotherapeutics (Table 1). In line with this notion, only a few such studies are being performed in the context of

**Table 1. Current trends in anticancer radioimmunotherapy**

| Cancer type                              | Phase | N  | Notes                                                                 |
|------------------------------------------|-------|----|----------------------------------------------------------------------|
| Brain tumors                             | I-III | 5  | The panel of radioimmunotherapeutic paradigms tested for these oncological indications is relatively heterogeneous |
| Breast carcinoma                         | 0-III | 4  | In a majority of cases, EBRT is administered together with immunostimulatory chemotherapy plus a tumor-targeting mAb |
| Colorectal carcinoma                     | I-III | 14 | EBRT is generally employed in combination with oxaliplatin-based chemotherapy |
| Gastroesophageal carcinoma                | I-III | 8  | Most often, EBRT is administered in combination with one or more immunostimulatory chemotherapeutic agents, including paclitaxel and capetabine |
| Head and neck cancer                     | I-III | 15 | In the majority of indications, EBRT is combined with paclitaxel, cisplatin and/or an EGFR-targeting mAb |
| Hematological neoplasms                  | I-III | 8  | Internal radiotherapy based on a tumor-targeting mAb is given alone or together with another immunostimulatory agent |
| Hepatic neoplasms                        | II-III| 2  | Radiation therapy is coupled to TACE based on immunostimulatory chemotherapeutics |
| Melanoma                                 | I-II  | 6  | EBRT is generally given in combination with ipilimumab |
| Neuroectodermal tumors and sarcomas      | II    | 2  | EBRT is combined with immunostimulatory chemotherapy, alone or together with the VEGF-neutralizing mAb bevacizumab |
| Pancreatic cancer                        | 0-III | 11 | Most frequently, EBRT in one of its variants is administered in the context of gemcitabine-based chemotherapeutic regimens |
| Pulmonary carcinomas                     | I-III | 8  | EBRT is generally combined with immunostimulatory chemotherapy based on and a platinum derivative plus a taxane |
| Renal cell carcinoma                     | I-II  | 3  | SBRT is combined either with high-dose IL-2 or with the adoptive transfer of autologous lymphocytes |
| Reproductive tract neoplasms             | II-III| 7  | EBRT is often given in combination with immunostimulatory chemotherapeutics including taxanes a platinum derivatives |
| Others                                   | I-III | 5  | The radioimmunotherapeutic regimens in these oncological indications are relatively heterogeneous |

**Abbreviations:** EBRT, external body radiation therapy; EGFR, epidermal growth factor receptor; IL-2, interleukin-2; mAb, monoclonal antibody; SBRT, stereotactic body radiation therapy; TACE, transarterial chemoembolization; VEGF, vascular endothelial growth factor.

*Based on clinical trials started after 2013 June 1st and not withdrawn, terminated or suspended by the day of manuscript submission (source www.clinicaltrials.gov).
appropriate immunomonitoring procedures, allowing investigators to assess not only toxicity and efficacy, but also the actual involvement of the immune system in disease outcome.

As for the clinical trials listed in our previous Trial Watch dealing with this topic, the following studies have changed status during the past 12 months: (1) NCT01730157 and NCT01769222, which have been “suspended”; (2) NCT01326293 and NCT01790516, which have been “terminated”; (3) NCT01634880, NCT01652261 and NCT01728480, which have been “withdrawn”; (4) NCT01290120, NCT01468740, NCT01567202, NCT01569984, NCT01612247, and NCT01653301, whose status is now “unknown”; (5) NCT01760811, which is listed as “not yet recruiting”; (6) NCT01362127, which appears to be “enrolling by invitation”; (7) NCT01347034, NCT01440270, NCT01497275, NCT01507103, NCT01539824, NCT01566435, and NCT01740258, which are indicated as “active, not recruiting”; (8) NCT01557114, NCT01749956, NCT01765908, NCT01795430, NCT01798004, NCT01807065, NCT01818996, NCT01821729, NCT01833208, NCT01843829, NCT01850888, NCT01857934, which are now “recruiting” participants; and (9) NCT01249352, NCT01271439, NCT01298401, NCT01322929, NCT01434147 and NCT01523847, which are listed as “completed” (source http://www.clinicaltrials.gov). NCT01730157, testing radioembolization plus ipilimumab in patients with metastatic uveal melanoma, has been suspended owing to administrative issues, whereas NCT01769222, investigating the clinical profile of radiation therapy plus ipilimumab in patients with melanoma, colorectal carcinoma or NHL, has been suspended following the decision of the local Data and Safety Monitoring Committee. NCT01326923 and NCT01790516, both assessing the therapeutic profile of cisplatin-based chemoradiation plus cetuximab in patients with locally advanced head and neck squamous cell carcinoma, have been terminated either because the principal investigator left the institution or owing to an excessively low accrual rate, respectively. Along similar lines, NCT01634880, testing adjuvant irradiation plus an experimental EGFR-targeting mAb in subjects with high-risk salivary gland malignancies, and NCT01652261, investigating the clinical profile of radiation therapy plus multimodal immunostimulatory chemotherapy in Hodgkin’s lymphoma patients, have been withdrawn prior to enrollment for lack of accrual. Conversely, NCT01728480, which aimed at assessing the safety and efficacy of cisplatin-based chemoradiation plus a recombinant TLR5 agonist (i.e., entolimod), has been withdrawn as per the request of the sponsoring agency. Finally, to the best of our knowledge, the results of NCT01249352 (testing chemoradiation plus an EGFR-specific mAb in subjects with locally advanced esophageal carcinoma), NCT01271439 (assessing the clinical profile chemoradiation plus cetuximab in nasopharyngeal carcinoma patients), NCT01298401 (investigating the safety and efficacy of EBRT plus immunostimulatory chemotherapy and/or a mAb targeting the insulin-like growth factor receptor in individuals with pancreatic cancer), NCT01332929 (testing radiation therapy in combination with bevacizumab for the treatment of brain metastases), NCT01434147 (evaluating whether immunostimulatory chemotherapy, bevacizumab and EBRT can be safely and effectively combined for use in colorectal cancer patients) and NCT01523847 (assessing the clinical profile of an immunostimulatory chemotherapeutic regimen optionally administered together with EBRT in cardiopathic subjects with Hodgkin’s lymphoma) have not yet been released (source: http://www.clinicaltrials.gov).

Concluding Remarks

Similar to the action of some chemotherapeutic agents, such as the nucleoside analog gemcitabine and the DNA alkylating agent cyclophosphamide, radiotherapy per se mediates direct antineoplastic effects while stimulating the insurgence of a tumor-specific adaptive immune response. Besides accounting for the so-called abscopal effect, i.e., the ability of ionizing irradiation to induce the regression of distant, non-irradiated lesions, such a dual activity may explain the relative success of this widely employed therapeutic option. If this were the case, X- or γ-rays would improve the clinical profile of immunotherapeutic agents including DNA-based, peptide-based or DC-based vaccines, immunomodulatory cytokines, TLR agonists, and immunostimulatory antibodies. One of the major impediments against the development of radioimmunotherapeutic paradigms of this type is the identification of the doses and administration schedules that maximize the immunostimulatory potential of ionizing irradiation while preserving its ability to directly inhibit tumor growth. The results of large, randomized and properly monitored trials are urgently awaited to facilitate the design of novel radioimmunotherapeutic regimens with improved clinical activity.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Funding

Authors are supported by Associazione Italiana per la Ricerca sul Cancro (AIRC), Ligue contre le Cancer (équipe labelisée); Agence National de la Recherche (ANR); Association pour la recherche sur le cancer (ARC); Cancéropolle Ile-de-France; AXA Chair for Longevity Research; Institut National du Cancer (INCa); Fondation Bettencourt-Schueller; Fondation de France; Fondation pour la Recherche Médicale (FRM); the European Commission (ArtForce); the European Research Council (ERC); 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).
equilibrium between the proliferation and T lymphocyte-mediated death of malignant cells. Oncoimmunology 2013; 2:e25668; PMID:24319637; http://dx.doi.org/10.1080/20015468080350924

53. Gottfried L, Mann LL, Boucher Y, Fukushima D, Jain RK. Normalization of the vasculature: a emerging concept in antiangiogenic therapy. Science 2005; 307:58-62; PMID:15637262; http://dx.doi.org/10.1126/science.1104819

54. Tartour E, Peer H, Maillere B, Termes M, Mezlin N, Taib J, Sandolé 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:21424923; http://dx.doi.org/10.1007/s10555-011-9281-4

55. Emami B, Lyman J, Brown A, Coia L, Goitein M, Tartour E, Pere H, Maillere B, Terme M, Merillon N, Goel S, Duda DG, Xu L, Munn LL, Boucher Y, 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; 76:510-9; PMID:20171502; http://dx.doi.org/10.1016/j.ijrobp.2009.07.1754

56. Barnier BJ, Paganelli G, Dunning AM, Elliott RM, Coles CE, Pharoah PD, Burnett NG. Normal tissue reactions to radiotherapy: towards tailoring treatment dose by genotype. Nat Rev Cancer 2009; 9:134-42; PMID:19418818; http://dx.doi.org/10.1038/nrcc28787

57. Mahmoud J, Kewalramani T, Zaidi A, Doctorow SR, Hill RP. Mitigation of radiation-induced lung injury by genistein and EUK-207. Int J Radiat Biol 2011; 87:889-901; PMID:21675818; http://dx.doi.org/10.3109/00207662.2011.595592

58. Zhao J, Stoyanov L, Duda DG. A mitochondria-targeted triphenylphosphonium-conjugated nitrogas function as a radiotherapeutic/mitigator. Radiat Res 2009; 172:706-17; PMID:19992417; http://dx.doi.org/10.1664/R729.1

59. Empey RB, Grau C, Lindegaard JC. Chemical radioprotection: a critical review of amifostine as a cytoprotective agent. Semin Radiat Oncol 2005; 15:62-72; PMID:12520447; http://dx.doi.org/10.1016/j.semradonc.2005.04.006

60. Xavier S, Yamada K, Samuni AM, Samuni A, DeGraff W, Krishna MC, et al. Differential protection by nitrosothiols and cyanoguanidine against radiation-induced and metal ion-catalyzed oxidative damage. Biochem Biophys Acta 2002; 1573:109-20; PMID:12399020; http://dx.doi.org/10.1016/S0006-291X(02)00339-9

61. Ackerman J, Kapralov AA, Yamasu T, Yurino Y, Aomata AA, Peritoneal, Jiang Z, Huang Z, Miniz AH, Greenberg JS, et al. A mitochondria-targeted inhibitor of cytochrome c peroxidase mitigates radiation-induced death. Nat Commun 2011; 2:407; PMID:21899813; http://dx.doi.org/10.1038/ncomms1495

62. Meyn RB, Henk AL, Gers D. The role of apoposis in radiation oncology. Int J Radiat Biol 2009; 85:87-15; PMID:19288463; http://dx.doi.org/10.1080/09553008082652259

63. Bella C, Budach W. Anti-apoptotic Bcl-2 proteins: structure, function and relevance for radiation biology. Int J Radiat Biol 2002; 78:643-58; PMID:12065567; http://dx.doi.org/10.1080/09553000210003715

64. Rezzell ED, Lee SJ, Res KE, Chen JN, DiPalma CR, Whitsell OM, Yin S, Hill DC, Wiemann B, Starnes CO, et al. Keratinocyte growth factor protects mice from chemotherapy and radiation-induced gastrointestinal injury and mortality. Cancer Res 1998; 58:93-4; PMID:9500453; http://dx.doi.org/10.1158/0008-5472.CAN-97-1190

65. Le QT, Kim HE, Schneider CJ, Murakoya G, Sla- dowski K, Reinisch S, Chen Y, Hickey M, Mo M, Chen MG, et al. Palifermin reduces severe mucositis in advanced head and neck cancer: a randomized, placebo-con- trolled study. J Clin Oncol 2011; 29:2808-14; PMID:21670453; http://dx.doi.org/10.1200/JCO.2010.32.4095

66. Spiegelberger R, Stiff P, Bentzke W, Gentile PA, Wein- dorf D, Kewalramani T, Shea T, Yavinich S, Hansch N, Koga S, et al. Palifermin for oral mucositis after radiotherapy. J Natl Cancer Inst 2002; 94:1286-96; PMID:11054386; http://dx.doi.org/10.1093/jnci/dmg012

67. Zheng H, Wang J, Koteliansky VE, Gotwals PJ, Colombo CM, Li X, Liu HJ, Chen Y. Toll-like receptor 5 agonism promotes chemotaxis and immunity. J Immunol 2008; 180:2880-5; PMID:18523294; http://dx.doi.org/10.1049/jimunol.2008.12280

68. Hasselt OA, Bogen C, Corrahy A. A model for cancer-suppressive inflammation. Oncoimmunology 2012; 1:1146-55; PMID:23170261; http://dx.doi.org/10.1080/20015468080350924

69. Hensley ML, Hagerty KL, Kewalramani T, Green DM, Merton NJ, Wasserman TH, Cohen GI, Emami B, Gladisah WJ, Mitchell RB, et al. Ameri- can Society of Clinical Oncology 2008 clinical prac- tice 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.2008.20.17627

70. Schuchter LM, Hensley ML, Merton NJ, Winer EP. 2002 update of recommendations for the use of chemothera- peutic and radiotherapy protectants: clinical prac- tice guidelines of the American Society of Clinical Oncology. J Clin Oncol 2002; 20:2895-903; PMID:12065567; http://dx.doi.org/10.1200/JCO.2002.15.04.178

71. Britel DM, Wasserman TH, Henke M, Strnad V, Radiat V, Montier A, Eschwege F, Zhang J, Russell L, Oster W, et al. Phase III randomized trial of amifos- tine as a radioprotector in head and neck cancer. J Clin Oncol 2000; 18:339-45; PMID:11013273

72. Bracci L, Schiavoni G, Sintignis A, Belardelli F. Immune-based mechanisms of cytotopic chemother- apy: implications for the design of novel and rationally-based combined treatments against cancer. Cell Death Differ 2014; 21:333-43; PMID:24778994; http://dx.doi.org/10.1038/cdd.2013.67

73. Dudek AM, Garg AD, Krysko DV, De Ruyscher G, Agostinis P. Inducers of immunogenic cancer cell death. Cytokine Growth Factor Rev 2013; 24:319- 33; PMID:23901812; http://dx.doi.org/10.1016/j.cyto.2013.01.005

74. Zitvogel L, Galluzzi L, Smyth MJ, Kroemer G. Mech- anisms of action of conventional and targeted anticancer therapies: reinstating immunosurveillance. Immunology 2013; 139:74-88; PMID:23809005; http://dx.doi.org/10.1111/imm.12016

75. Galluzzi L, Senovilla L, Zitvogel L, Kroemer G. The secret ally: immunostimulation by anticancer drugs. Oncoimmunology 2012; 1:227-38; PMID:22880905; http://dx.doi.org/10.1080/20015468080350924

76. Sunar S, Bapardekar M, Manderscheid-Kern P, Bell- man D, Kirovskaya SV, Jansen E, Gradov AV. Toll-like receptor 5 agonist protects mice from derma- tritis and oral mucositis caused by local radiation: implications for head-and-neck cancer radiotherapy. Int J Radiat Oncol Biol Phys 2012; 82:228-34; PMID:22009579; http://dx.doi.org/10.1016/j.ijrobp.2011.05.055

77. Jang H, Chun M, Cho O, Heo JS, Ryu HS, Chang SJ. Prognostic factors and treatment outcome after radiotherapy in cervical cancer patients with isolated para-aortic lymph node metastases. J Gynecol Oncol...
of capcitabine and oxaliplatin administered prior to and then concomitant to radiotherapy in high risk locally advanced rectal cancer. J Surg Oncol 2014; 109:478-82; PMID:24828803

11. Lu JY, Xiao Y, Canghp L, Long DP, Lin GL, Xu L, Zhang GN, Hu K. Clinical outcome of neoadjuvant chemoradiation therapy with capcitabine and oxaliplatin or 5-fluorouracil for locally advanced rectal cancer. J Surg Oncol 2013; 108:213-9; PMID:23917597; http://dx.doi.org/10.1002/jsco.23106.

12. Nilsson PJ, van Etten B, Hoppers GA, Pahlman L, van de Velde CJ, Beets-Tan RG, Blomqvist I, Beukema JC, Kapiteijn E, Marini CN, et al. Short-course radiotherapy followed by neo-adjuvant chemotherapy in locally advanced rectal cancer—the RAPIDO trial. BMC Cancer 2013; 13:279; PMID:23742033; http://dx.doi.org/10.1186/1471-2407-13-279.

13. Funahashi K, Koike J, Shikohwa K, Ushigome M, Shimada H, Kaneko H, Terahata A. Phase 1 trial of preoperative chemoradiation therapy with S-1 for low rectal cancer. Hepatogastroenterology 2014; 61:99-104; PMID:24895802.

14. Baruskov YA, Gordersey SS, Tkachev SI, Fedyanin MY, Petchkovsky JS, et al. Paclitaxel combined with concurrent chemoradiotherapy with local hyperthermia and meta- ronidazole for locally advanced fixed rectal cancer. Colorectal Dis 2013; 15:1107-14; PMID:23668626.

15. Calvo SA, Cove S, Jannuzzi T, Del Valle G, Rodriguez M, Munoz-Calero A, et al. Randomized trial of preoperative chemotherapy with taxane and oxaliplatin versus induction chemotherapy plus radiation in patients with locally advanced squamous cancer of the neck and head. Jpn J Clin Oncol 2014; 44:416-21; PMID:24668804; http://dx.doi.org/10.1111/jco.12196.

16. Balermpas P, Bauer C, Fraunholz I, Ottinger A, Komatsu M, Shiono O, Taguchi T, Sakuma Y, Nishimura T, et al. Concurrent chemoradiotherapy with local hyperthermia and metronidazole for exceptionally advanced rectal cancer. Blood 2013; 121:125-33; PMID:24940093; http://dx.doi.org/10.3747/blood-2013-03-53033.

17. Hennings JM, Fan KY, Wild AT, Hacker-Prietz R, Wood LD, Blackford AL, Ellsworth S, Zheng L, De Jesus-Acosta A, et al. Phase 2 study of erlotinib combined with adjuvant chemotherapy and chemoradiation in patients with stage III colon cancer. Int J Radiat Oncol Biol Phys 2013; 85:768-85; PMID:23773391; http://dx.doi.org/10.1016/j.ijrobp.2013.02.016.

18. Passoni P, Reni M, Cartano GM, Simi C, Seregni E, Balzano G, Licciatore B, Bianchini V, Mignolli L, et al. Hypofractionated image-guided IMRT in advanced pancreatic cancer: a prospective randomized phase II study. Eur J Cancer 2013; 49:4117-22; PMID:23943843; http://dx.doi.org/10.1016/j.ejca.2013.02.009.

19. Chen SS, Yang XC, Chi F, Yu WZ, Wang Z, Ning FL, Yu ZS, Hao YL, Li ML, Wang F, et al. Phase II study of preoperative chemotherapy with modified FOLFOX6 followed by surgery and postoperative chemotherapy in patients with locally advanced gastric adenocarcinoma. Oncol Res 2013; 21:327-32; PMID:23879173; http://dx.doi.org/10.4088/orn.v33n06.d109.

20. Michel P, Breyninger G, Monnex F, Seitz JP, Perneger T, Merle-Laplant S, Fernandez A, et al. Definitive chemoradiotherapy versus surgery plus concomitant chemoradiotherapy in patients with newly diagnosed brainstem gliomas and high-grade gliomas. Neuro Oncol 2013; 15:759-66; PMID:23592571; http://dx.doi.org/10.1093/neuonc/no335.

21. Kilburn LB, Kocak M, Schaeckl Stark F, Meneses Lorente G, Brownstein C, Hussain S, Chintapudumba M, Thompson PA, Gururangan S, Banerjee A, et al. Phase I trial of capcitabine rapidly disintegrating tablets and concomitant chemoradiation in patients with resectable pancreatic carcinoma. Br J Cancer 2013; 109:478-82; PMID:24243088; http://dx.doi.org/10.1038/bjc.2013.100.
irradiation for Stage II-III esophageal carcinoma. Jpn J Clin Oncol 2013; 43:608-15; PMID:23585687; http://dx.doi.org/10.1093/jjco/hyt048

124. Nakamura K, Kato K, Igalgi H, Ito Y, Mizusawa J, Ando N, Udagawa H, Tsouhara Y, Daiko H, Hiraozaka S, et al. Three-arm phase III trial comparing cisplatin plus 5-FU (CF) versus docetaxel, cisplatin plus 5-FU (DCF) versus radiotherapy with CF (CF-RT) as preoperative therapy for locally advanced esophageal cancer: the NEST study. Jpn J Clin Oncol 2013; 43:752-5; PMID:23265203; http://dx.doi.org/10.1093/jjco/hyt061

125. Chira C, Kirova YM, Liem X, Campana F, Peurien D, Chira C, Kirova YM, Liem X, Campana F, Peurien D, et al. Alpha emitter radium-223 and survival of patients with advanced hormone-refractory castration-resistant prostate cancer: results of a randomized phase II trial of Radium-223 therapy. Br J Cancer 2013; 109:109-14; http://dx.doi.org/10.1038/bjc.2013.230

126. Wu CE, Lin YC, Hong JH, Chuang CK, Pang ST, et al. Helical tomotherapy for inoperable breast cancer patients: increase in local failure and survival. Cancer Radiother 2013; 17:593-8; http://dx.doi.org/10.1016/j.crad.2012.12.776

127. Kollmannsberger P, Kuhns WM, Kaufman DS, Uzo R, Wu CI, Buyyounouski MK, Sandler H, Zietman AL. Transurethral surgery and twice-daily radiation plus paclitaxel-cisplatin or fluorouracil-cisplatin with selective bladder preservation and adjuvant chemotherapy for men with muscle-invasive bladder cancer: a new promising tool. Biomed Res Int 2013; 2013:639876; http://dx.doi.org/10.1155/2013/639876

128. Gunderston LH, Mosquag A, Jajja AJ, Pedersen JE, Winter KA, Benson AB, 3rd, Thomas CR Jr, Mayer RJ, Haddock MG, Rich TA, et al. Anal carcinoma: A phase I study of concurrent weekly carboplatin and paclitaxel combined with intensity-modulated pelvic radiotherapy as an adjuvant treatment for early-stage cervical cancer patients with positive pelvic lymph nodes. Int J Radiat Oncol Biol Phys 2013; 87:1597-605; http://dx.doi.org/10.1016/j.ijrobp.2013.07.035

129. Chirapatanan I, Tharavichitkul E, Kamerndusopph P, Pukanapin N, Yongtaa R. Randomized phase III trial comparing chemoradiotherapy versus accelerated hyperfractionation radiotherapy in locally advanced head and neck cancer. J Radiat Res 2013; 54:110-5; PMID:23740894; http://dx.doi.org/10.1093/jrr/sss054

130. Kondel Y, Nasser NJ, Purim O, Yerushalmi R, Fenig P, et al. Randomized phase III trial comparing cisplatin and paclitaxel followed by concurrent chemotherapy and radiation vs paclitaxel or docetaxel or gemcitabine in unresectable non-small cell lung cancer: long-term follow-up of Radiation Therapy Oncology Group (RTOG) randomized trial 9801. Lung Cancer 2013; 80:298-305; PMID:23747790; http://dx.doi.org/10.1016/j.lungcan.2013.06.007

131. Oh JJ, Kim KS, Kim YC, Ban HJ, Kwon Y, Kim YI, Lim SC, Chung WK, Nam TK, Song JY. A phase III trial of concurrent chemoradiotherapy plus concomitant accelerated boost technique and chemotherapy in locally advanced non-small cell lung cancer: results of a prospective, multicenter phase-II study of the NOGGO (North-Eastern German Society of Gynaecological Oncology). Cancer Chemother Pharmacol 2013; 72:135-9; PMID:23740894; http://dx.doi.org/10.1007/s00280-013-2157-2

132. Schneider BJ, Lee JS, Hayman JA, Chang AC, Oshima T, Kawasaki M, Imanaga T, Kubo M, Takagi J, Waetjen W, Sonoda Y, Barakat RR, Alektiar KM. Pre-operative external beam radiation therapy and concurrent cisplatin induced by CD8+ CD103+ CD4+ T cells in stage III (FIGO 2009) endometrial cancer. Gynecol Oncol 2013; 130:436-40; PMID:23535505; http://dx.doi.org/10.1016/j.ygyno.2013.11.005

133. Garrido P, Rosell R, Arellano A, Andreu F, Domenech D, Bamberg M, Markmann JA, et al. A phase II study of weekly neoadjuvant paclitaxel to carboplatin based chemotherapy plus concomitant chemoradiation therapy in stage IIIC endometrial cancer: a new promising tool. Oncotarget 2013; 4:899-910; PMID:23995698; http://dx.doi.org/10.18632/oncotarget.2235-2

134. Eckert F, Gan C, Kuhn T, Mayer F, Kopp HG, Zips D, Bamborg M, Müller AC. Effect of concurrent irradiation for Stage II-III esophageal carcinoma. Jpn J Clin Oncol 2013; 43:608-15; PMID:23585687; http://dx.doi.org/10.1093/jjco/hyt048

135. Nakamura K, Kato K, Igalgi H, Ito Y, Mizusawa J, Ando N, Udagawa H, Tsouhara Y, Daiko H, Hiraozaka S, et al. Three-arm phase III trial comparing cisplatin plus 5-FU (CF) versus docetaxel, cisplatin plus 5-FU (DCF) versus radiotherapy with CF (CF-RT) as preoperative therapy for locally advanced esophageal cancer: the NEST study. Jpn J Clin Oncol 2013; 43:752-5; PMID:23265203; http://dx.doi.org/10.1093/jjco/hyt061

136. Chira C, Kirova YM, Liem X, Campana F, Peurien D, Amessis M, Fourtis-Bidon N, Picpere YJ, Dendale R, Bey P, et al. HeliCa tomotherapy: a new promising tool. Biomed Res Int 2013; 2013:643006; PMID:24078909; http://dx.doi.org/10.1155/2013/643006

137. Wu CE, Lin YC, Hong JH, Chuang CK, Pang ST, Liw CC. Prognostic value of complete response to patients with muscle-invasive bladder cancer undergoing concurrent chemoradiotherapy. Anticancer Res 2013; 33:2605-10; PMID:23749195

138. Schepitko EY, Kaufman DS, Uzo R, Wu CI, Buyyounouski MK, Sandler H, Zietman AL. Transurethral surgery and twice-daily radiation plus paclitaxel-cisplatin or fluorouracil-cisplatin with selective bladder preservation and adjuvant chemotherapy for men with muscle-invasive bladder cancer (RTOG 0235): a randomised multicentre phase 2 trial. Lancet Oncol 2013; 14:863-72; PMID:23823157; http://dx.doi.org/10.1016/S1470-2045(13)70255-9

139. Gunderson LH, Mosquag A, Jajja AJ, Pedersen JE, Winter KA, Benson AB, 3rd, Thomas CR Jr, Mayer RJ, Haddock MG, Rich TA, et al. Anal carcinoma: impact of TN category of disease on survival, disease relapse, and colostomy failure in US Gastrointestinal Intestinal tract Cancer Study Group. Int J Radiat Oncol Biol Phys 2013; 87:638-45; PMID:23420537; http://dx.doi.org/10.1016/j.ijrobp.2013.07.035

140. Chirapatanan I, Tharavichitkul E, Kamerndusopph P, Pukanapin N, Yongtaa R. Randomized phase III trial comparing chemoradiotherapy versus accelerated hyperfractionation radiotherapy in locally advanced head and neck cancer. J Radiat Res 2013; 54:1110-7; PMID:23740894; http://dx.doi.org/10.1093/jrr/sss054

141. Kondel Y, Nasser NJ, Purim O, Yerushalmi R, Fenig P, et al. Phase II study of concurrent capetitane and external beam radiotherapy for pain control of hormone-refractory prostate cancer patients with localized recurrent of primary rectal cancer. Oncotarget 2013; 4:8689-916; PMID:23765188

142. Nakamura A, Iitaka S, Takako K, Kawaguchi Y, Shiibuya K, Yoshimura M, Matsuo Y, Mizotaki T, Uemoto S, Hiraksa M. Radiotherapy for patients with isolated local recurrence of primary rectal cancer. Prolonged disease-free interval associated with favorable prognosis. Strahlenther Onkol 2014; 190:490-5; PMID:24593944; http://dx.doi.org/10.1007/s00061-014-0610-9

143. Wagner S, Schwarz K, Schreiber S, Schmidt B, Wexter H, Schwaiger M, Pesch C, von Schilling C, Scheidauer K, Keller U. Myeloablative anti-CD20 radioimmunotherapy +/- high-dose chemotherapy followed by autologous stem cell support for relapsed/refractory B-cell lymphoma resulting in excellent long-term survival. Oncotarget 2013; 4:899-916; PMID:23765188

144. Kruger PC, Cosney JP, Turner JH. Lodiein-131 rituximab radioimmunotherapy with BEAM conditioning and autologous stem cell transplant cell salvage therapy for relapsed/refractory aggressive non-Hodgkin lymphoma. Cancer Biother Radiopharm 2012; 27:552-60; PMID:2356821353; http://dx.doi.org/10.1089/cbr.2012.1275
Klug F, Prakas H, Huber PE, Seibel T, Bender N, Halama N, Fiehlsche C, Voss RH, Timcke C, Umskali L, et al. Low-dose irradiation programs macrophage differentiation toward an iNOS+/M1 phenotype that orchestrates effects on tumor growth. J Immunother Cancer 2013; 2:2458-60; PMID:24260906; http://dx.doi.org/10.1002/jctc.2013.09.014

Blagosklonny MV. Immunosuppressants in cancer prevention and therapy. Oncoimmunology 2013; 2:e23849; PMID:23762809; http://dx.doi.org/10.4161/onci.23849

Raymackers E, Demaerela P, Van Cutsem E, Van Dael JC, Smet MJ, Van Cutsem E, et al. Tumor-associated immunosuppressive regulatory T cells in colorectal cancer. J Clin Oncol 2014; 32:3919-26; PMID:25083328; http://dx.doi.org/10.1200/JCO.2013.51.6178; http://dx.doi.org/10.1002/ijc.28558

Kronke G, Uderhardt S, Kim KA, Stock M, Scholtyseck S, et al. Exploiting the stress response to radiation to sensitize tumors and radiation-resistant tumors to cancer therapy. J Clin Invest 2013; 123:5269-83; PMID:24270418; http://dx.doi.org/10.1172/JCI65428

Deng L, Liang H, Burnette B, Beckett M, Harrick A, Verhey C, et al. Cetuximab monotherapy and cetuximab plus vemurafenib without mutational changes in EGFR. N Engl J Med 2009; 360:1408-17; PMID:19393720; http://dx.doi.org/10.1056/NEJMoa0805019

Tsuchida Z, Khamaba-Foro S, Hanna N, Janne PA. Anti-PD-1 antibodies for the treatment of re- treated indolent lymphoma: half of patients respond. J Clin Oncol 2014; 32:1985-33; PMID:24885449; http://dx.doi.org/10.1200/JCO.2013.51.5635

Cunningham D, Humblet Y, Siena S, Khayat D, Bleiberg P, et al. Phase III, randomized study of mTOR inhibitors and cetuximab in metastatic colorectal cancer. J Clin Oncol 2014; 32:1985-33; PMID:24885449; http://dx.doi.org/10.1200/JCO.2013.51.5635

Ming Lim C, Stephenson R, Salazar AM, Ferris RL. Immunostimulatory cytokines. Oncoimmunology 2012; 1:1445-7; PMID:23243431; http://dx.doi.org/10.4161/onci.23849

Thomas-Schoeman A, Batteux F, Alexandre J. A new strategy to target regulatory T cells in solid tumors. Oncoimmunology 2013; 2:e23538; PMID:23802078

Boos PD, Pitas G, Rudra D, Lee SY, Rudensky AY. Autophagy-dependent anticancer immune responses: a new frontier. Cell 2013; 153:211-27; PMID:23973220; http://dx.doi.org/10.4161/onci.29030

Chen CR, Makhson A, D’Haens G, Pinto L, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. J Clin Oncol 2014; 32:1985-33; PMID:24885449; http://dx.doi.org/10.1200/JCO.2013.51.5635

Ferrara N, Hillan KJ, Gerber HP, Novotny W. Disruption of the vascular endothelial growth factor/VEGF receptor-2 signaling pathway: a new therapeutic target for cancer? Cancer Res 2004; 64:3951-8; PMID:15335389; http://dx.doi.org/10.1158/0008-5472.CAN-03-0834

Goldberg RM. Cetuximab. Nat Rev Drug Discov 2005; 4:91-100; PMID:15696254; http://dx.doi.org/10.1038/nrd1728

Brueckler I, White CA, Cabanillas F, et al. Rituximab augments chemoradioprotection. Nature 2013; 501:107-11; PMID:23936657; http://dx.doi.org/10.1038/nature12416

Dannenmann SR, Thielicke J, Stockli M, Matter C, von Boehmer L, van den Broek M. Radiotherapy of human sarcoma promotes an intratumoral immunogenic effector signature. Clin Cancer Res 2013; 19:4843-53; PMID:23861514; http://dx.doi.org/10.1158/1078-0432.CCR-12-3116

Spary LK, Al-Taci S, Salimu J, Cook AD, Ager A, Watson HA, Clayton A, Staffurth J, Mason MD, Tabi Z. Enhancement of T cell responses as a result of synergy between lower doses of radiation and T cell stimulatory ligands. Oncoimmunology 2014; 3:e29030; PMID:25083328; http://dx.doi.org/10.4161/onci.29030

Eike I, Storch K, Krause M, Cordes N. Cetuximab attenuates cytotoxicity and cytokine production by inducing immunosuppression. Cancer Res 2013; 73:5869-79; PMID:23722550; http://dx.doi.org/10.1158/1078-0432.CCR-13-0544
