



Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Combination of novel systemic agents and radiotherapy for solid tumors – Part II: An AIRO (Italian association of radiotherapy and clinical oncology) overview focused on treatment toxicity

Stefano Arcangeli^{a,*}, Barbara Alicia Jerezek-Fossa^b, Filippo Alongi^c, Cynthia Aristei^d, Carlotta Becherini^e, Liliana Belgioia^f, Michela Buglione^g, Luciana Caravatta^h, Rolando Maria D'Angelilloⁱ, Andrea Riccardo Filippi^j, Michele Fioreⁱ, Domenico Genovesi^h, Carlo Grecoⁱ, Lorenzo Livi^e, Stefano Maria Magrini^g, Giulia Marvaso^b, Rosario Mazzola^c, Icro Meattini^e, Anna Merlotti^k, Isabella Palumbo^d, Stefano Pergolizzi^l, Sara Ramellaⁱ, Umberto Ricardi^m, Elvio Russi^k, Marco Trovòⁿ, Alessandro Sindoni^p, Vincenzo Valentini^o, Renzo Corvò^f

^a Department of Radiation Oncology, Policlinico S. Gerardo and University of Milan “Bicocca”, Milan, Italy

^b Department of Radiation Oncology of IEO European Institute of Oncology IRCCS, Milan, Italy

^c Department of Radiation Oncology, Sacro Cuore Don Calabria Cancer Care Center, Negrar-Verona, University of Brescia, Brescia, Italy

^d Radiation Oncology Section, Department of Surgical and Biomedical Science, University of Perugia, Perugia General Hospital, Perugia, Italy

^e Radiotherapy Unit, Department of Experimental and Clinical Biomedical Sciences, University of Florence, Firenze, Italy

^f Department of Radiation Oncology, Ospedale Policlinico San Martino and University of Genoa, Genoa, Italy

^g Department of Radiation Oncology, University and Spedali Civili Hospital, Brescia, Italy

^h Department of Radiation Oncology, SS. Annunziata Hospital, G. D'Annunzio University of Chieti, Chieti, Italy

ⁱ Radiotherapy Unit, Campus Bio-Medico University, Rome, Italy

^j Department of Radiation Oncology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

^k Department of Radiation Oncology, S. Croce and Carle Teaching Hospital, Cuneo, Italy

^l Department of Biomedical Sciences and Morphological and Functional Images, University of Messina, Italy

^m Department of Oncology, University of Turin, Torino, Italy

ⁿ Department of Radiation Oncology, Azienda Sanitaria Universitaria Integrata of Udine, Udine, Italy

^o Gemelli Advanced Radiation Therapy Center, Fondazione Policlinico Universitario “A. Gemelli”, Catholic University of Sacred Heart, Rome, Italy

^p Department of Public Health and Infectious Diseases, Sapienza University of Rome, Rome, Italy

ARTICLE INFO

Keywords:

Radiotherapy

Systemic compounds

Toxicity

ABSTRACT

Clinical development and use of novel systemic agents in combination with radiotherapy (RT) is at nowadays most advanced in the field of treatment of solid tumors. Although for many of these substances preclinical studies provide sufficient evidences on their principal capability to enhance radiation effects, the majority of them have not been investigated in even phase I clinical trials for safety in the context of RT. In clinical practice, unexpected acute and late side effects may emerge especially in combination with RT. As a matter of fact, despite combined modality treatment holds potential for enhancing the therapeutic ratio, some concerns are raised from the lack of high-quality clinical data to guide the care of patients who are treated with novel compounds in conjunction with RT. The aim of this review is to provide, from a radio-oncological point of view, an overview of the most advanced combined treatment concepts for solid tumors focusing on treatment toxicity.

1. Introduction

Chemo-radiotherapy (CT-RT) for many solid tumors is a well established approach to potentially improve treatment efficacy. This

combination is driven by molecular mechanisms that may result in synergistic or supra-additive interactions. In the last two decades targeted cancer therapies that act on specific drivers of oncogenesis have entered clinical use, based on robust preclinical evidence that they may act as

* Corresponding author at: Department of Radiation Oncology, Policlinico S. Gerardo and University of Milan “Bicocca”, Milan, Italy.

E-mail addresses: stefano.arcangeli@yahoo.it, stefano.arcangeli@unimib.it (S. Arcangeli).

<https://doi.org/10.1016/j.critrevonc.2018.11.006>

Received 8 December 2017; Received in revised form 13 November 2018; Accepted 20 November 2018

1040-8428/ © 2018 Elsevier B.V. All rights reserved.

radiosensitizers, with the potential to improve cure rates when utilized in combination treatment regimens. Recently, the interaction of RT and the immune response has become another key approach to the clinical use of radiation and systemic therapy. However this synergy, which under optimal conditions should be restricted to the tumor tissue and spare normal cells, may be difficult to achieve in clinical practice. Since most of the treatment schedules are relatively novel, unexpected acute and late side effects may emerge especially when coupled with RT. Particularly, the introduction of radiation treatment techniques, such as intensity modulated radiation therapy (IMRT), which are associated with larger irradiated volumes (usually to low doses) as well as with altered fractionated schedules compared with older conventional irradiation techniques, may lead to side effects in an unpredictable manner. On the other hand, image-guided techniques and availability of stereotactic RT (high doses given to small volumes) allowed for ablative RT that most probably acts through different biological mechanisms. As a matter of fact, the discrepancy between the huge number of compounds being investigated and the low number of final approvals reflects the risks and uncertainties that are inherently associated with the drug development process. In a parallel manuscript we have already addressed the rationale of the association of RT and novel systemic agents for multiple disease sites focusing on treatment efficacy. The present review aims to examine the adverse effects of such combination.

2. Monoclonal antibodies

2.1. EGFR inhibitors: cetuximab and panitumumab

In locally advanced squamous cell carcinoma of head and neck (LA SCCHN), the randomized trial by [Bonner et al. \(2006\)](#) compared RT alone versus RT + Cetuximab and found improved local control and survival in the experimental arm, with \geq G3 toxicity (secondary endpoint), not significantly different between the two groups, with the exception of acneiform rash; the other two relevant data that emerged from this study were that younger patients with oropharynx tumor, and those who developed severe acneiform rash, had better outcomes than patients not having these features. Thereafter data regarding Cetuximab in head and neck cancer have increased, and several studies have been performed to test Cetuximab and RT versus standard CT–RT or in association with CT–RT. In this frame, phase II and phase III trials have showed increased toxicity: [Ang et al. \(2014\)](#) tested the hypothesis that adding Cetuximab to the RT–Cisplatin platform improves progression-free survival (PFS): the study failed to meet the primary endpoint, while showed more frequent interruptions in RT (26.9% vs 15.1%, respectively) and more G3–G4 radiation mucositis (43.2% vs 33.3%, respectively), rash, fatigue, anorexia, and hypokalemia – but not more late toxicity – in the experimental arm. Likewise, a phase II trial ([Xu et al., 2015](#)) evaluating Cisplatin-based CT–RT versus Cetuximab-RT in locally advanced nasopharyngeal carcinoma was closed ahead of schedule because of the unexpectedly high rates of G3–G4 mucositis observed in the experimental arm. In 406 patients with LA SCCHN randomly assigned to either concomitant Cetuximab + CT–RT or Cetuximab-RT PFS favored the former regimen, but the intensified combination resulted in a higher incidence of G3 or G4 mucositis (73% vs 61%, respectively, $P = 0.014$), and of hospitalizations for toxicity (42% vs 22%, respectively, $P < 0.001$). Although this is the first evidence of a clinical benefit for treatment intensification using Cetux + CT–RT, acute and consequential toxicities remained statistically increased over standard Cetux- RT ([Tao et al., 2018](#)). Unlike these findings, [Lefebvre et al. \(2013\)](#) registered a better treatment compliance in patients who underwent concomitant Cetuximab compared to those who received concomitant CT–RT following induction CT, although the trial was not powered to test difference in toxicity. The use of Cetuximab as a radiation sensitizer instead of CT, has been investigated by [Magrini et al. \(2016\)](#); [Buglione et al. \(2017\)](#): they found that Cetuximab concomitant to RT lowered treatment compliance and increased acute toxicity rates,

especially in the subgroup of patients with oropharyngeal carcinoma, who developed more infective complications.

In the recent non-inferiority phase III NRG-RT0G 1016 trial ([Trotti et al., 2018](#)) comparing RT and Cetuximab to RT and Cisplatin in HPV-related oropharyngeal squamous cell carcinoma (OPSCC), acute G3–G4 adverse events were 81.7% and 77.4% with Cisplatin and Cetuximab, respectively ($P < 0.001$); the distribution of G3–G4 adverse events varied by treatment with skin rash more common with Cetuximab. Overall, late G3–G4 toxicity did not significantly differ between the two arms (20% with Cisplatin and 17% with Cetuximab, respectively). Long-term severe dysphagia was 4% in the Cisplatin arm and 6% in the Cetuximab arm.

Cetuximab as inductive therapy has been evaluated by [Argiris et al. \(2010\)](#), who incorporated Cetuximab into the induction therapy and subsequent CT–RT of LA SCCHN in a phase II trial: acute toxicities included G3–4 oral mucositis (54%) and hypomagnesemia (39%) in the experimental arm, which were consistent with quality of life (QoL) scores showing a significant decrement at 3 months. Conflicting data emerged when induction CT was followed by Cetuximab-RT in a similar setting: in the recently published phase III GORTEC 2007-02 trial ([Geoffrois et al., 2018](#)), Cetuximab-RT preceded by 3 cycles of induction CT (TPF) was tested against standard CT–RT (5-FU/Carboplatin) in 380 patients with \geq cN2b inoperable LA-SCCHN: after a median follow up of 2.8 years, a significantly higher rate of G3–G4 hematologic toxicity and treatment related deaths was possibly due to the use of induction CT, which also did not improve outcomes. Conversely, an improved swallowing and nutritional status was detected in stage III–IV HPV-related OPSCC who received reduced-dose IMRT with concurrent Cetuximab following 3 cycles of induction CT with Cisplatin, Paclitaxel, and Cetuximab ([Marur et al., 2016](#)).

In locally advanced non small cell lung cancer (NSCLC) data on toxicity profile of Cetuximab are based mainly on prospective trials where the association with CT–RT has been investigated: [Blumenschein et al. \(2011\)](#) in a phase II trial tested the combination of Cetuximab with concomitant Carboplatin and Paclitaxel based CT–RT in unresectable NSCLC, whose primary endpoints included safety and compliance of the novel schedule: fifty-two patients (60%) experienced treatment-related \geq G3 non-hematologic toxicity (thus confirming the hypothesis that the true rate was no more than 60%). Likewise [Govindan et al. \(2011\)](#) investigated in a phase II trial the addition of Cetuximab to standard Carboplatin and Pemetrexed based CT–RT in a similar setting: although the study was powered to estimate the OS as primary objective, no difference in G3 and G4 non-hematologic toxicity was detected (46% and 6%, respectively, in the control arm versus 53% and 9%, in the experimental arm). Conversely, [Van De Heuvel et al. \(2014\)](#) reported on the safety and efficacy of the combination of daily dose Cisplatin and concurrent RT with or without weekly Cetuximab: disease control compared equally between both groups, but \geq G3 acute toxicity was increased with the addition of Cetuximab. In a randomized trial by [Bradley et al. \(2015\)](#), patients were offered RT (high or standard dose) and concurrent Carboplatin and Paclitaxel with or without Cetuximab: the use of Cetuximab was associated with a higher rate of \geq G3 toxicity (secondary endpoint) (86% vs 70%; $P < 0.0001$), and there were more treatment-related deaths in the high-dose CT–RT and Cetuximab groups.

In locally advanced rectal cancer, some phase I trials evaluated the addition of Cetuximab to preoperative CT–RT ([Hofheinz et al., 2006](#); [Machiels et al., 2007](#)) used Capecitabine, Irinotecan and Cetuximab, while [Machiels et al. \(2007\)](#) Capecitabine and Cetuximab. Both these regimens were shown to be tolerable and safe with no unexpected toxicities but no improvements in pathologic complete response (pCR). Confirmatory data were provided by subsequent prospective trials in the same setting ([Sun et al., 2012](#); [Dwedney et al., 2012](#)).

In esophageal cancer two phase II trials ([Safran et al., 2008](#); [Lledo et al., 2016](#)) evaluated the feasibility and toxicity of concomitant Cetuximab and CT–RT in locally advanced inoperable patients: ([Safran et al., 2008](#)) found no increase in esophagitis (G3 and G4 esophagitis

rates of 12% and 3%, respectively) or other radiation-enhanced toxicity adding Cetuximab to Paclitaxel and Carboplatin against a 70% rate of clinical complete response, while Lledo et al. (2016) added Cetuximab to CT (FOLFOX) and RT reported G3-G4 oesophagitis rates of 12%, with one treatment related death due to esophagitis with gastrointestinal bleeding. Unfortunately, these results were not confirmed in two recent phase III studies: in a phase II-III trial by Crosby et al. (2013) a worse toxicity and decreased survival was reported when Cetuximab was added to CT-RT (Cisplatin and 5-FU). A phase III trial (Suntharalingam et al., 2017) failed to document an OS improvement (primary endpoint) associated with Cetuximab and Paclitaxel-Cisplatin based CT-RT in patients with inoperable esophageal cancer, while more G5 adverse effects were possibly attributed to the experimental treatment (6 vs 2). Conversely, the trial SAKK 75/08 (Ruhstaller et al., 2018) investigated the addition of Cetuximab in locally advanced, but still resectable esophageal carcinoma: a statistically not-significant, but clinically meaningful improvement of OS was observed, without increasing relevant toxicity or postoperative morbidity.

Panitumumab has been tested in LA SCCHN instead of CT with no significant differences in the rate of major toxicities (Giralt et al., 2015), and associated to CT-RT with higher toxicity in the experimental arm (Mesía et al., 2015).

In gastrointestinal cancers it has been tested mainly in phase II trials for locally advanced esophageal cancer and rectal cancer in neoadjuvant setting associated to CT-RT, with promising results but also increased toxicity: in the ACOSOG Z4051 trial (Lockhart et al., 2014) 48.5% of patients had \geq G4 toxicity, while in the SAKK 41/07 trial (Helbling et al., 2013) \geq G3 diarrhoea and anastomotic leakage rates of 10% and 15% respectively, were documented in the experimental arm (6% and 4% in the control arm).

2.1.1. Summary

Currently further trials are needed to identify specific subgroup of patients in whom the benefits of anti-EGFR antibodies balance the possible adverse events. Table 1 summarizes major clinical trials of Cetuximab and RT for different tumor sites.

2.2. HER2 inhibitors: trastuzumab and pertuzumab

Although there is emerging evidence regarding the radio-sensitizing effects of Trastuzumab, little information exists on the clinical complications seen in some patients receiving concurrent anti-HER2 therapy and RT. Katz et al. (2015) reported two cases of patients with HER2-positive metastatic breast cancer who developed radiation-related complications likely caused by the radio-sensitizing effects of anti-HER2 therapy. These two cases suggest that the gastrointestinal tract may be more vulnerable when exposed to concurrent RT and anti-HER2 therapy. Despite the widespread use of both Trastuzumab and RT in HER2-positive breast cancer, the combination of both has undergone only limited investigation in the context of clinical trials. Early phase II data from a multicenter French study (Belkacémi et al., 2008) suggested the potential for cardiac toxicity with concurrent administration of Trastuzumab and RT (10% and 6% of the patients had a \geq G2 of left ventricular ejection fraction decrease after RT), although a subsequent phase II trial (Horton et al., 2010) in patients with HER2-positive, CT-refractory, locally advanced or locoregionally recurrent breast cancer did not reproduce such toxicity and indicated potential for radio-sensitization.

Concurrent Trastuzumab with CT-RT in the adjuvant setting has been tested by investigators from the Brown University Oncology Group (Halyard et al., 2009), who showed a good safety profile in patients with locally advanced adenocarcinoma of the esophagus.

The Radiation Therapy Oncology Group (RTOG) 0524 trial demonstrated a comparable treatment-related toxicity (the primary endpoint of the study) when weekly Trastuzumab was added to standard Paclitaxel-based CT-RT for inoperable muscle-invasive urothelial

carcinoma. Specifically, the majority of adverse events were gastrointestinal, including one treatment-related death (Safran et al., 2007), (Michaelson et al., 2017).

2.2.1. Summary

Initial data seem to show a good safety profile for Trastuzumab combined with RT, while no sufficient data allow to draw conclusions on the combination between Pertuzumab and RT. Table 2 summarizes major clinical trials of Trastuzumab and RT for different tumor sites.

2.3. VEGF inhibitors: bevacizumab

Bevacizumab (BEV) was the first antiangiogenic therapy used in patients with cancer. The safety of the association with RT have been investigated in different clinical trials in brain, lung and gastrointestinal tumors (Fu et al., 2016). The intense and aberrant vascularization and the high resistance of high grade gliomas (HGG) to RT and CT have made these tumors suitable candidates for efficacy studies of BEV. Seventy patients with newly diagnosed HGG were enrolled in the prospective, multicenter single-arm phase II study (Lai et al., 2011) that combined BEV to the standard Temozolomide (TMZ) based CT-RT. Although the study was not powered to assess differences in toxicity, toxicity was similar to that found in historical trials, with the most common non-hematologic G3-G4 adverse events being fatigue (20%). The AVAglio (Chinot et al., 2014) and RTOG 0825 (Gilbert et al., 2014) phase III trials evaluated BEV-containing schedules compared to standard regimen alone (RT plus TMZ) in patients with newly diagnosed glioblastoma. In the former trial, in the BEV group the baseline health-related quality of life (QoL) and performance status were maintained longer with a lower requirement of glucocorticoids, but more patients had \geq G3 toxicity in the BEV than in the placebo group (66.8% vs. 51.3%).

Likewise, in the RTOG 0825 study (Gilbert et al., 2014), \geq G3 hematological toxicity – namely lymphopenia – occurred in approximately 10% of patients in both arms, while neutropenia (7.3% vs. 3.7%) and thrombocytopenia (10.2% vs. 7.7%) were more common in the BEV group. Unlike the AVAglio trial, however, a greater deterioration in neurocognitive function, as well as in perceived cognitive function was recorded in patients receiving BEV, suggesting either unrecognized tumor progression or BEV-related neurotoxicity. The TEMAVIR randomized phase II trial (Chauffert et al., 2014) evaluated BEV and Irinotecan as neo-adjuvant and adjuvant treatment combined with TMZ-based CT-RT for unresectable glioblastoma: the primary endpoint (PFS) was not met and a significant toxicity occurred in the BEV plus Irinotecan arm (three fatal intracranial bleedings, three bile duct or digestive perforations/infections, and six thrombotic episodes). The authors concluded that neo-adjuvant and adjuvant BEV plus Irinotecan, combined with TMZ-based CT-RT, is not recommended. In the phase II ARTE trial (Wirsching et al., 2018) aimed at exploring the efficacy of BEV in combination with hypofractionated RT in elderly patients with newly diagnosed glioblastoma, more severe and life-threatening thromboembolic events occurred in the experimental arm (16% versus 8%).

Antiangiogenic agents, including both monoclonal antibodies (BEV) have been investigated also in the management of NSCLC (Sandomenico et al., 2012). Disappointing results were reported in a phase II trial investigating BEV in combination with CT-RT for unresectable stage III NSCLC, due to the occurrence of life-threatening adverse effects (trachea-oesophageal fistulae). The enrollment was stopped early when 2 of the 5 patients who underwent RT plus BEV and Pemetrexed/Carboplatin-based concomitant and adjuvant CT, followed by maintenance BEV, developed trachea-oesophageal fistulae (Spigel et al., 2010). Similar results have been reported in a subsequently phase I-II trial (Socinski et al., 2012) evaluating induction and concurrent Carboplatin/Paclitaxel CT plus BEV and thoracic conformal RT to 74 Gy. G3 or G4 esophagitis was reported in 29% of patients, with one patient with a G3 trachea-oesophageal fistula. Consolidation therapy

Table 1
Major studies for RT and Cetuximab/Panitumumab.

| Author and year | Study type | N | Tumor site/stage | RT technique/ dose/ fractionation | Combination (concomit, other) | G3-4 Non-HEM AEs | Treatment related deaths | Incomplete RT |
|----------------------------------|---------------|-----|--|---|---|--|-----------------------------|---------------------------------|
| (Bonner et al., 2006) | Phase III | 211 | LA-SCCHN | –70 Gy/35 fx or –72-76.8 Gy/ 60-64 fx (twice daily) or –72 Gy/42 fx | CT-RT (CDDP) +/- Ctx | acneiform rash: 1%vs 17% (P < 0.001) infusion reaction: 0 vs 3% (P = 0.01) | 0 | 4% vs 6% |
| (Ang et al., 2014) | Phase III | 940 | LA-SCCHN | -ART 72 Gy/42 fx or -IMRT 70 Gy/35 fx | CT-RT (CDDP) +/- Ctx | mucositis 33.3% vs 43.2% (P = 0.02) skin reactions: 15 % vs 25% (P < 0.001) | 1.8% vs 2% (P = .81) | 15.1% vs 26.9% (P = .001) |
| (Xu et al., 2015) | Phase II R | 44 | LANPC | IMRT 66 Gy-70.4/ 30-32 fx | Induction CT→ CT-RT (CDDP) +/- Ctx | oral mucositis: 47.8%vs 80.9% (P = 0.023) acneiform rash: 0 vs 33.3% (P = 0.009) dysphagia: 13% vs 47.6% (P = 0.012) | 0 | 0 |
| (Tao et al., 2018) | Phase III | 406 | LA-SCCHN (non- palpable N0-N2b) | 3DCRT/IMRT 70 Gy/35 fx | Ctx + CT-RT vs Ctx-RT | oral mucositis: 73% vs 61% (P = .014) hospitalizations: 42% vs 22% (P < .001) | 4.9% vs 1.5% | 15% vs 14% |
| (Lefebvre et al., 2013) | Phase II R | 116 | stage III - IV larynx/ hypopharynx SCC | 3DCRT 70 Gy/ 35 fx | Induction CT→ CT-RT (CDDP) +/- Ctx | mucositis: 45% vs 45% skin toxicity: 26% vs 57% | 2.5% after Induction CT | 57% vs 34% |
| (Magrini et al., 2016) | Phase II R | 35 | LA-SCCHN | 3DCRT/IMRT 70 Gy/35 fx | CT-RT (CDDP) +/- Ctx | skin toxicity: 21% vs 44% (P = .039) mucositis: 4% vs 4% Dysphagia: 4% vs 6% | 3% vs 19% (P = .044) | 0 vs 12% (P = .05) |
| (Blumenschein et al., 2011) | Phase III | 805 | OPSCC HPV + | IMRT 70 Gy/35 fx | RT + CDDP vs RT + Ctx | oral mucositis: 54% | 0 | N.R. |
| (Argiris et al., 2010) | Phase II | 39 | LA-SCCHN | IMRT 70 Gy/35 fx | Induction - TPE (3 cycles q21) Concomitant - RT + CDDP + Ctx (weekly) Maintenance - Ctx (6 months) | in-field dermatitis: 27% dysphagia: 48% | 2.5% | 5% |
| (Geoffrois et al., 2018) | Phase III | 370 | LA-SCCHN (≥N2b) | RT 70 Gy/35 fx | Induction TPF → RT + Ctx vs CT-RT (Carbo + 5-FU) | oral mucositis: 48% vs 50% (P = .7) in-field dermatitis: 53% vs 29% (P = .001) | 6.6% vs 0.6% (P = .0016) | 18% vs 13% |
| (Marur et al., 2016) | Phase II | 90 | OPSCC HPV + | IMRT 69.3 Gy/33 fx or 54 Gy/27 fx (if CR to induction) | Induction CDDP + PAC + Ctx Concomitant RT + Ctx (weekly) | –69.3 Gy group: mucositis: 47% dysphagia: 29% acneiform rash: 24% radiation dermatitis :12% | N.R. | 34.7% 22.5% |
| (Blumenschein et al., 2011) | Phase II | 93 | Stage III NSCLC | 3DCRT 63 Gy/35 fx | CT- RT (Carboplatin + PAC) + Ctx | esophagitis: 8% pneumonitis: 7% | 5% | 3% |
| (Govindan et al., 2011) | Phase II R | 101 | Stage III NCLC | 3DCRT 70 Gy/35 fx | CT- RT (Carboplatin + PEM) +/- Ctx | 52% vs 62% | 4% vs 5.5% | 14% |
| (Van den Heuvel et al., 2014) | Phase II R | 102 | Stage III NSCLC | ART 66 Gy/24 fx | CT-RT (CDDP) +/- Ctx | 45% vs 65% (P = 0.03) | 0% vs 4% | 16% vs 12% (P = 0.77) |
| (Bradley et al., 2015) | Phase III | 544 | Stage III NSCLC | 60 Gy/30 fx vs 74 Gy/37 fx | CT- RT (Carboplatin + PAC) +/- Ctx | 70% vs 86% (P < 0.0001) | 1.8% vs 3.6% | 17% vs 26% (P = 0.02) |
| (Hofheinz et al., 2006) | Phase I | 20 | LARC | 3DCRT 50.4 Gy/28 fx | CT-RT (CAP + weekly IRI) + Ctx | diarrhoea: 20% | 0 | 0 |
| (Machiels et al., 2007) | Phase I/II | 40 | LARC | 3DCRT 45 Gy/25 fx | CT-RT (CAP) + Ctx | diarrhoea: 15% infection: 5% thrombo-embolism: 2.5% | 0 | 5% |
| (Sun et al., 2012) | Phase II | 63 | LARC | 3DCRT 45 Gy/25 fx | CT-RT (CAP) + Ctx | radiodermatitis: 16% diarrhoea: 6% acneiform rash: 6% | 0 | 0 |
| (Dwedney et al., 2012) | Phase II R | 165 | High risk rectal cancer | 3DCRT 45 Gy/25 fx + boost 16.2 Gy/3 fx | CT-RT (CAPOX) +/- Ctx | diarrhoea: 10% | 0 | N.R. |
| (Safran et al., 2008) | Phase II | 60 | | | | | 0 | 0 |

(continued on next page)

Table 1 (continued)

| Author and year | Study type | N | Tumor site/stage | RT technique/ dose/ fractionation | Combination (concomit, other) | G3-4 Non-HEM AEs | Treatment related deaths | Incomplete RT |
|-------------------------------|------------------|-----|--|--|--|--|-----------------------------|---------------|
| (Lledo et al., 2016) | Phase II | 79 | –57 EC –3 gastric cancer stage III EC or GEJC | 3DCRT 50.4 Gy/28 fx 3DCRT 50.4 Gy/30 fx | CT- RT (Carboplatin + PAC) + Ctx CT- RT (FOLFOX) + Ctx | cutaneous rash: 25% esophagitis: 15% esophagitis: 12% rash: 11% allergy: 9% | 0 | N.R. |
| (Crosby et al., 2013) | Phase II -III | 258 | stage I-III EC | 3DCRT 50 Gy/25 fx | CT-RT (CDDP +5-FU) +/- Ctx | 63% vs 79% (P = 0.004) | 6% vs 13% | 10% vs 22% |
| (Suntharalingam et al., 2017) | Phase III | 344 | T3-4 and or N + EC | 3DCRT 50.4 Gy/28 fx | CT-RT (CDDP + PAC) +/- Ctx | acneiform rash: 1% vs 6% diarrhoea: 36% vs 46% | 1% vs 4% | 12% vs 13% |
| (Helbling et al., 2013) | Phase III | 300 | cT3-4a (90% cN+) EC | 3DCRT 45 Gy/25 fx | Induction CT→ CT-RT (CDDP + TXT) +/- Ctx → S | esophagitis: 9% vs 14% dysphagia: 13% vs 26% hypomagnesemia: 6% vs 3% | 7% vs 7% | 11% vs 14% |
| (Tomblyn et al., 2012) | Phase II | 21 | Stage III non- cervical EC | 3DCRT 50.4 Gy/28 fx | Preoperative CT-RT (CDDP + IRI) + Ctx | 85.7% (G3) 38.1% (G4) | 9.5% | N.R. |
| (Ruhstaller et al., 2011) | Phase IB/II | 28 | LA- resectable EC | 3DCRT 45 Gy/25 fx | Preoperative Induction CT (CDDP + DOC + Ctx)→ CT-RT (CDDP + Ctx) | esophagitis: 26% rash: 11% anorexia: 11% thrombosis: 7% | 0% | 14% |
| (Giralt et al., 2015) | Phase II R | 151 | LA-SCCHN | 3DCRT/IMRT 70-72 Gy/ 30-32 fx | CT-RT (CDDP) vs CT-RT (PAN) | mucositis 40% vs 42% dysphagia: 32% vs 40% radiation dermatitis: 11% vs 24% | | |
| (Mesia et al., 2015) | Phase II R | 150 | LA-SCCHN | 3DCRT/IMRT 70-72 Gy/ 30-32 fx | CT-RT (CDDP) +/- PAN | dysphagia: 27% vs 40% mucositis: 24% vs 55% radiation dermatitis: 13% vs 31% | | |
| (Helbling et al., 2013) | Phase II R | 68 | LARC | 3DCRT/IMRT 45 Gy/25 fx | Neoadjuvant CT-RT (CAP) +/- PAN | diarrhoea: 4% vs 10% anastomotic leakage: 4% vs 15% rash: 0 vs 2% | 0 vs 3% | 3% vs 14.7% |

Abbreviations: AEs = adverse effects; ART = accelerated radiotherapy; CDDP = Cisplatin; CAP = Capecitabine; CAPOX = Capecitabine + Oxaliplatin; CR = complete response; CT = chemotherapy; CT-RT = chemoradiotherapy; Ctx = Cetuximab; EC = esophageal carcinoma; FOLFOX = Folfiri + Oxaliplatin; fx = fractions; GEJC = gastro-esophageal junction carcinoma; HEM = hematologic; IMRT = intensity modulated radiotherapy; IRI = Irinotecan; LANPC = locally advanced nasopharyngeal carcinoma; LARC = locally advanced rectal cancer; LA-SCCHN = locally advanced squamous cell carcinoma of head and neck; NSCLC = non small cell lung cancer; OPSCC = oropharyngeal squamous cell carcinoma; PAC = Paclitaxel; PAN = Panitumumab; PEM = Pemetrexed; R = randomized; RT = radiotherapy; 3DCRT = 3D conformal radiotherapy; TPF = Docetaxel/Cisplatin/Fluorouracil, TXT = Taxotere.

with Erlotinib and BEV was also programmed, but not administered due to the high toxicity rates. BEV has been tested with pre-operative RT or CT-RT in locally advanced rectal cancer (LARC) in several phase II trials (Fornaro et al., 2014). The safety profile of BEV concomitantly with fluoropyrimidine based CT-RT (45–50.4 Gy in 25–28 fractions) showed promising results, in terms of acceptable grade toxicity (G3 or G4 diarrhoea range 0–22%), although a moderate rate of major post-operative sequelae, in terms of wound complications, delayed wound healing, and infection or abscess, requiring surgical intervention, was reported. Additional phase II trials evaluating the advantage of adding BEV to neoadjuvant regimens integrated with Oxaliplatin showed similar toxicities to those reported in previous CT-RT Oxaliplatin studies without BEV. Diarrhoea (4–24%) was the most common G3 or G4 toxicity during the treatment with an acceptable rate of major post-operative complications (6–10%) (Fornaro et al., 2014).

2.3.1. Summary

In patients with newly diagnosed glioblastoma, the use of BEV concomitant to RT is not endorsed due to higher rates of neurocognitive decline, increased symptom severity, and decline in health-related QoL.

For NSCLC, preliminary phase I-II trials showed that, due to major complications, BEV should not be administered concurrently with RT. For rectal cancer, the addition of BEV to RT resulted in acceptable rates of late toxicity although not showing clear benefits in terms of efficacy, and therefore cannot be recommended outside a clinical trial. Table 3 summarizes major clinical trials on RT and BEV in preoperative CT-RT for rectal cancer.

3. Small molecules inhibitors

3.1. TKI (tinib): erlotinib, gefitinib, afatinib

In the studies here analyzed, a total of 931 patients were treated with RT in combination with tyrosin-kinase inhibitors (TKI). In detail, 253 patients were affected by head and neck cancer, 158 by NSCLC, 216 by pancreatic cancer, 50 by rectal cancer, 36 by cervical cancer and 21 by esophageal cancer. In all these cases, Erlotinib was the TKI combined with RT. In addition, most of patients presented a locally advanced disease. In the metastatic setting, a total of 197 cases are reported in the herein selected studies. Of these, 143 patients affected by brain

Table 2
Major studies on RT and Trastuzumab.

| Author and year | Study type | N | Tumor site | RT technique/dose/fractionation | Combination (concomit, other) | G3-4 Non-HEM AEs or \geq G2 CE | Treatment related deaths | Incomplete RT |
|---------------------------|------------|------------|------------|--|-------------------------------------|---|--------------------------|--|
| (Belkacémi et al., 2008) | Phase II | 146 | BC | 3DCRT 50 Gy/25 fx (71% IMC-RT) | 46% TAM + IHRH Analogues 54% AI | dermatitis: 6% esophagitis: 1% decrease in LVEF: 10% | 0 | 2% |
| (Halyard et al., 2009) | Phase III | 2148 (*) | BC | 3DCRT 45.0 to 50.4 Gy/ 25 to 28 fx | AC→PAC vs AC→PAC→T vs AC→PAC/T→T | dermatitis: 5.6% vs 5.9% vs 4.3% (P = .51) cardiac events: 0.2% vs 2.7% (P = .04) vs 1.7% | 0 | (All causes) 24.2% vs 24.6% vs 26.3% (Skin toxicity) 2.8% vs 0.6% vs 1.4% |
| (Michaelson et al., 2017) | Phase I/II | 68 (**) | UC | 3DCRT 64.8 Gy/36 fx | weekly PAC + T | diarrhoea: 20% myocardial ischemia: 5% bleeding: 10% infection: 5% | 5% | 40% |

Abbreviations: A = doxorubicin; AEs = adverse events; AI: aromatase-inhibitors; BC = breast carcinoma; C = cyclofosamide; CDDP = Cisplatin; CE = cardiac events; fx = fractions; HEM = hematologic; IMC-RT: internal mammary chain-radiation therapy; LVEF: left ventricular ejection fraction; OT = hormonal therapy; PAC = Paclitaxel; RT = radiotherapy; 3DCRT = 3D conformal radiotherapy; T = Trastuzumab; TAM = Tamoxifen; UC urothelial carcinoma.

(*) RT report available in 1503 patients.

(**) 20 patients received Trastuzumab.

metastases from NSCLC were treated with RT/Erlotinib whereas in 30 cases Gefitinib was combined with RT. Iyengar et al (Iyengar et al., 2014) explored the feasibility and tolerability of stereotactic body RT (SBRT) and Erlotinib in the oligometastatic setting by NSCLC, whereas Wang et al. (2014) evaluated a similar approach using a combination of Stereotactic Body Radiation Therapy (SBRT)/Gefitinib in previously treated patients with advanced NSCLC. No studies of RT in combination with Afatinib were found. Regarding the modality of adopted RT, all head and neck patients were treated with radical intent. IMRT with conventional fractionation was performed in 149 cases; a 3-dimensional conformal RT (3D-CRT) was used in the remaining 104. In case of NSCLC patients, RT with definitive intent was delivered with conventional fractionation by means of 3D-CRT technique. For pancreatic cancer, in patients who were candidates for a neoadjuvant approach conventional fractionation was used, while in a single-phase II study (Herman et al., 2013) the impact of IMRT in the postoperative setting was analyzed in 48 patients. Gefitinib can be associated with 5-FU–based preoperative chemoradiation at the dose of 500 mg without any life-threatening toxicity and with a high pCR (30.3%). Valentini et al. (2008) evaluated the combination of Gefitinib, infusional 5-FU, and preoperative RT in resectable LARC in a phase I-II study: they found that Gefitinib can be associated with 5-FU–based preoperative CT-RT at the dose of 500 mg without any life-threatening toxicity and with a high pCR (30.3%). However, owing the relevant rate of Grade 3 gastrointestinal toxicity, they suggest that 250 mg would be more tolerable dose in a neoadjuvant approach with RT and infusional 5-FU. Available data regarding brain metastases seem quite heterogeneous in terms of TKI using (Erlotinib or Gefitinib) and RT adopted schedules, with three fractionations mostly used (i.e. 30 Gy/10, 20 Gy/5, 35 Gy/14) (Lee et al., 2014; Welsh et al., 2013; Zhuang et al., 2013; Pesce et al., 2012). Erlotinib and Gefitinib in combination with SBRT were evaluated in two reports Iyengar et al., 2014; Wang et al. (2014) in the setting of oligometastatic NSCLC. A direct comparison in terms of safety profile when TKI is associated with RT comparing to TKI alone is not available. Four randomized phase II studies (Lee et al., 2014; Pesce et al., 2012; Martins et al., 2013; Martinez et al., 2008) and a single randomized phase III trial (Hammel et al., 2016) compared RT with or without TKI. Martins et al. (2013) evaluated the impact of Cisplatin-irradiation

with or without Erlotinib in 204 LA SSSCHN patients. At a median follow-up of 26 months, the addition of Erlotinib to Cisplatin-RT did not increase the toxicity. In the multicenter randomized controlled open-label trial by Martinez et al. (2008), the concurrent addition of Erlotinib to RT in 90 LA NSCLC patients versus RT alone was analyzed. Compared to RT alone, no increased toxicity was observed when Erlotinib was added to RT. In the context of locally advanced pancreatic cancer, the LAP07 trial (Hammel et al., 2016) was a two-step randomized phase III trial that randomized patients to receive induction CT with Gemcitabine or Gemcitabine plus Erlotinib for 4 cycles (1st step). Those with controlled tumor (stable or objective response) were randomly assigned to CT-RT versus CT alone (2nd step). In both arms, Erlotinib maintenance therapy was administered. No increase in severe toxicity was recorded. Finally, in the SAKK 70/03 randomized phase II trial (Pesce et al., 2012), patients with brain metastases from NSCLC were randomly assigned to receive whole brain RT (WBRT) combined with Gefitinib versus TMZ. A total of 59 patients were enrolled. At a median follow-up of 34 months, no relevant toxicities, nor increased survival (primary endpoint) were observed.

3.1.1. Summary

Tolerability profile of the association between TKI and RT seems to be acceptable. Table 4 summarizes the tolerability data regarding the major studies evaluating the association of RT and TKI.

3.2. TKI (nib): sunitinib and sorafenib

Sunitinib has been tested in a 6 week schedule in combination with hypofractionated IGRT in a phase I (Kao et al., 2009) and II trials (Tong et al., 2012). Taken together these phase I and II trials (Kao et al., 2014) enrolled 46 patients with very different tumors (head and neck, hepatocellular, NSCLC, renal, prostate, colorectal, pancreatic and melanoma). Sixty-eight percent of patients had two metastatic sites, mostly bone (40%), lung (28%) lymph node (14%) liver (13%). The dose of concurrent Sunitinib was reduced to 37.5 mg. Thirty-three per cent of patients experienced a \geq G3 toxicity, and two fatal hemorrhages were recorded. Surprisingly, compared to Sunitinib alone, the combination

Table 3
Major clinical trials on RT and Bevacizumab in preoperative CT-RT for LARC.

| Author and year | Study type | N | RT technique/dose/ fractionation | Combination (concomit, other) | G3-4 Non-HEM AEs, or major postop complications | Treatment related deaths | Incomplete RT |
|---------------------------|---------------|--------|-------------------------------------|--|---|-----------------------------|---------------|
| (Avallone et al., 2015) | Phase II | 62 | 3DCRT 45 Gy/25 fx | CT-RT (OXATOM-FUFA) + BEV | diarrhoea: 6% hypertension: 6% anastomotic deishences: 18% | 0 | 2% |
| (Willett et al., 2009) | Phase I-II | 32 | 3DCRT 50.4 Gy/28 fx | CT-RT (5-FU) + BEV | diarrhoea: 22 % hypertension: 9% major post-operative complications: 4% | 0 | 0 |
| (Crane et al., 2010) | Phase II | 25 | 3DCRT 50.4 Gy/28 fx | CT-RT (CAP) + BEV | GI: 0% perineal wound dehiscences: 12% | 0 | 0 |
| (Gasparini et al., 2012) | Phase II | 43 | 3DCRT 50.4 Gy/28 fx | CT-RT (CAP) + BEV | diarrhoea: 7 % major post-operative complications: 7% | 0 | 9.5% |
| (Spigel et al., 2012) | Phase II | 66 (*) | 3DCRT 50.4 Gy/28 fx | CT-RT (5-FU) + BEV | diarrhoea: 14% mucositis: 23% fatigue: 6% major post-operative complications: 3% | 0 | 11% |
| (Salazar et al., 2015) | Phase II | 90 | 3DCRT 45 Gy/25 fx | CT-RT (CAP) +/- BEV | 13% vs 16% (P=0.70) | 0 | 7% vs 7% |
| (Kennecke et al., 2012) | R Phase II | 42 | 3DCRT 50.4 Gy/28 fx | CT-RT (CAPOX) + BEV | diarrhoea: 24% pelvic pain: 10% fatigue: 10% anastomotic leakage: 5% delayed healing: 8% | 0 | 16.5% |
| (Dellas et al., 2013) | Phase II | 70 | 3DCRT 50.4 Gy/28 fx | CT-RT (CAPOX) + BEV | diarrhoea: 4% delayed healing: 1% ileus: 1% | 0 | 16% |
| (Landry et al., 2013) | Phase II | 57 | 3DCRT 50.4 Gy/28 fx | CT-RT (CAPOX) + BEV | diarrhoea:13% fatigue: 15% rectal pain: 16% major post-operative complications: 6% | 3.6% | 9% |
| (Velenik et al., 2011) | Phase II | 61 | 3DCRT 50.4 Gy/28 fx | CT-RT (CAP) + BEV | dermatitis: 9.8% proteinuria: 6.5% diarrhoea: 1.6% delayed healing: 30.0% infection/abscess: 20.0%) anastomotic leakage: 11.7% | 0 | 9% |
| (Nogu e et al., 2011) | Phase II | 47 | 3DCRT 50.4 Gy/28 fx | CT-RT (CAP) + BEV | diarrhoea: 11% fatigue: 4% rectal tenesmus: 2.5% major post-operative complications: 24% | 0 | 15% |
| (Dipetrillo et al., 2012) | Phase II | 26 | 3DCRT 50.4 Gy/28 fx | Induction FOLFOX + BEV à CT-RT (5-FU- OX) + BEV | diarrhoea: 44% pain: 16% nausea: 12% dermatitis: 8% bleeding: 4% major post-operative complications: 7.5% | 3.8% | 0 |
| (Vivaldi et al., 2016) | Phase II | 45 | 3DCRT 50.4 Gy/28 fx | Induction FOLFOXIRI + BEV à CT-RT (CAP or 5-FU) + BEV | hand-foot syndrome: 23% proctitis: 23% anastomotic dehiscence: 18% | 2.2% | 29% |

Abbreviations: AEs = adverse events; BEV = Bevacizumab; CAP = Capecitabine; CT = chemotherapy; CT-RT = chemo-radiotherapy; HEM = hematologic; 5-FU = 5 Fluorouracil; FOLFOX = Fluorouracil/Leucovorin/Oxaliplatin; FOLFOXIRI = fluorouracil/Leucovorin/Oxaliplatin/Irinotecan; OX = Oxaliplatin; OXATOM-FUFA = Oxaliplatin/Raltitrexed/5-Fluorouracil modulated by folinic acid; R = randomized; RT = radiotherapy; 3DCRT = 3D conformal radiotherapy. (*) 35 patients received CT-RT + BEV with neoadjuvant intent.

with RT resulted in a further reduction of haemopoiesis, although the methods employed to evaluate this end-point were quite doubtful (Kao et al., 2016). Staehler et al. (2012) explored the adoption of high dose hypo-fractionated RT concurrently with Sunitinib in progressive metastatic renal cell carcinoma. RT was delivered in median 12 fractions with 3.5 Gy daily fraction up to 40 Gy in 22 patients during standard 50 mg Sunitinib on a 6 weeks schedule. One G4 heart toxicity was encountered (cardiac failure due to arterial hypertension). The difference between the RT intended dose (40 Gy in 5 Gy daily fractions) and the actually delivered dose (40 Gy in 3.5 Gy fractions) points out as RT should be optimized according to organ at risk from an expert point of view, thus unlikely reproducible. Similarly, the same authors (Staehler

et al., 2011) published a case series of 106 patients with cerebral or spinal metastases treated with radiosurgery (SRS) concurrently to Sunitinib or Sorafenib. In 51 patients with brain metastases, SRS was delivered at 20 Gy in single fraction. Five patients (9.8%) experienced an adverse event within 6-weeks, 3 convulsions and 2 bleeding into the treated cranial lesion. Moreover, no radiation-related necrosis was recorded but one patient, receiving Sunitinib, experienced a fatal cerebral bleeding 3 months after SRS. Fifty-five patients received a single 20 Gy SRS to spinal lesions concurrently with Sunitinib and Sorafenib. One patient developed temporary abdominal pain within 6 weeks. Ahluwalia et al. (2015) explored the adoption of Sunitinib after SRS for 1–3 brain metastases in 14 patients enrolled in a phase II trial having

Table 4
Major studies on RT and TKIs.

| Author and year | Study type | N | Tumor site | RT technique/ dose/fractionation | Combination (concomit, other.) | G3-4 Non-HEM AEs | Treatment related deaths | Incomplete RT |
|---------------------------------|-------------|-----------|---------------------------------|---|---|--|-----------------------------|------------------------------|
| (Iyengar et al., 2014) | Phase II | 24 | Oligometastatic NSCLC | SBRT 27-33 Gy/3 fx 35-40 Gy/ 5 fx 19-20/1 fx | E 1 week before and during SBRT | 28% | 13% | 0 |
| (Wang et al., 2014) | Phase II | 14 | Advanced (pre-treated) NSCLC | SBRT 48-60 Gy/3 fx | G during SBRT and continued as maintenance | 29% (G3) 0 (G4) | 0 | N.R. |
| (Herman et al., 2013) | Phase II | 48 | Resectable PA | IMRT 50.4 Gy/28 fx | CT-RT (CAP) + E | 44% | N.R. | 17% |
| (Valentini et al., 2008) | Phase I-II | 41 | LARC | 3DCRT 50.4 Gy/28 fx | CT-RT (5-FU) + G | 41% | 0 | 12.8% |
| (Lee et al., 2014) | Phase II R | 80 | BM | 3DCRT 20 Gy/5 fx | WBRT +/- E | rash: 5% vs 20% fatigue: 35% vs 17.5% | 0 | 15% vs 15% |
| (Welsh et al., 2013) | Phase II | 40 | BM | 3DCRT 35 Gy/14 fx | WBRT + E (u.p.) | rash: 15% fatigue: 12.5% diarrhoea: 10% | 0 | N.R. |
| (Zhuang et al., 2013) | Phase II R | 54 | BM | 3DCRT 30 Gy/10 fx | WBRT +/- E | anorexia: 0 vs 8.6% (P < 0.05) dizziness: 3.2% vs 4.3% | 0 | N.R. |
| (Pesce et al., 2012) | Phase II R | 59 | BM | 3DCRT 30 Gy/10 fx | WBRT + TMZ (u.p.) vs WBRT + G (u.p.) | 18.6% vs 37.5% | 7% vs 6.2% | 0 |
| (Martins et al., 2013) | Phase II R | 95 | LA-SCCHN | IMRT 70 Gy/35 fx | CT-RT (CDDP) +/- E | rash: 2% vs 13% (P = .005) GI: 43% vs 48% (P = .43) | 0 (both arms) | 10% vs 6% (P = .31) |
| (Martinez et al., 2008) | Phase II R | 90 (*) | LA-NSCLC | 3DCRT 66Gy/33 fx | RT +/- E | 37.9% vs 65% (P = 0.016) | 0 vs 1.6% | 30% vs 60% |
| (Hammel et al., 2016) | Phase III R | 133 | Unresectable PA | 3DCRT 54Gy/30 fx | Induction GEM alone vs GEM + E à CT vs CT-RT | nausea: 0 vs 5.9% (P = .008) | 0 | 18% (CT-RT) group N.R. |
| (Arias de la Vega et al., 2012) | Phase I | 13 | LA-SCCHN | 3DCRT 63Gy/35 fx | CT-RT (CDDP) + E | mucositis: 53% (all dose levels) skin toxicity: 23% (levels II/III) diarrhea: 15% (level III) | 0 | |
| (Ahn et al., 2016) | Phase I | 13 | LA-SCCHN | IMRT 70 Gy/35 fx | Induction TPF-Eà CT-RT (CDDP + BEV) + E | GI bleeding/ perforation 15.5% diarrhea: 7.5% | 0 | 15.3% |
| (Ramella et al., 2013) | Phase I-II | 60 | LA or metastatic NSCLC | 3DCRT 59.4Gy/33 fx | Standard CT-RT + E | esophagitis: 2% pneumonitis: 8% rash: 7% diarrhea: 5% | 3.3% | N.R. |
| (Chadha et al., 2016) | Phase I | 17 | Unresectable PA | 3DCRT 50.4Gy/28 fx | CT-RT (CAP + BEV) + E | 17.6% (level V) | 0 | 0 |
| (Jiang et al., 2014) | Phase I | 18 | Unresectable PA | 3DCRT 50.4Gy/ 28 fx | CT-RT (CAP) + E | 0 | 0 | N.R. |
| (Blaszkwosky et al., 2014) | Phase I/II | 32 | LARC | 3DCRT 50.4Gy/28 | CT-RT (5-FU + BEV) + E | Overall 28% diarrhoea 18.8% rash 6.3% | 0 | 21.8% |
| (Das et al., 2014) | Phase I | 18 | LARC | 3DCRT 50.4Gy/28 fx | CT-RT (5-FU + BEV) + E | hypertension 5% | 0 | 0 |
| (Zhao et al., 2016) | Phase II | 21 | Inoperable ESCC | IMRT 60Gy/30 fx | CT-RT (weekly PAC) + E | esophagitis: 9% pneumonitis: 5% | 0 | N.R. |

Abbreviations: AEs = adverse effects; BEV = Bevacizumab; BM = brain metastases; BRT = brachytherapy; CAP = Capecitabine; CDDP = Cisplatin; CT = chemotherapy; CT-RT = chemoradiotherapy; DLT = dose-limiting toxicity; DOC = Docetaxel; E = Erlotinib; ESCC = esophageal squamous cell carcinoma; fx = fractions; 5-FU = 5-Fluorouracil; G = Gefitinib; GEM = Gemcitabine; IMRT = intensity modulated radiotherapy; LARC = locally advanced rectal cancer; LA-SSCHN = locally advanced squamous cell carcinoma of head and neck; NSCLC = non small cell lung cancer; PA = pancreatic adenocarcinoma; PAC = Paclitaxel; R = randomized; RT = radiotherapy; 3DCRT = 3D conformal radiotherapy; SBRT = stereotactic body radiotherapy; TMZ = temozolomide; TKIs = tyrosine kinase inhibitors; u.p. = until progression; WBRT = whole brain radiotherapy.

(*) not eligible to standard CT.

the rate of CNS progression at 6 months as the primary endpoint: toxicity included grade 3 or higher fatigue in five patients and neutropenia in two patients. Finally, there are several case reports that describe radiation recall toxicity such as pneumonitis (Yuasa et al., 2013) and dermatitis (Chung et al., 2010).

3.2.1. Summary

Some concerns remained according to rare but severe side effects such as perforations of gastrointestinal (GI) tract and hemorrhages. Particular attention should be paid to dose-constraints for organs at risk, especially when GI or airways are included or are next to treated lesions (Barney et al., 2013).

3.3. *Poli-ADP-Ribose polymerase (PARP) inhibitors (parib)*

Two phase I trials are available in literature exploring the combination of Velaparib and RT. In the trial by Reiss et al. (2015), low dose fractionated RT was associated to Velaparib in 22 patients affected by peritoneal carcinomatosis from advanced solid tumor malignancies. Patients were treated with Velaparib at the dosage of 80–320 mg daily. Low dose RT consisted of 21.6 Gy in 36 fractions (0.6 Gy twice daily). Non-hematological treatment related Grade 3–4 toxicities was 4%. In the phase I trial by Mehta et al. (2015), Velaparib was administered at the dose of 10–300 mg orally in association with WBRT (30–37.5 Gy in 10–15 fractions) in 81 patients affected by brain metastases: the addition of Velaparib to WBRT did not result in enhanced toxicity when compared to WBRT alone.

3.3.1. Summary

Although the mechanisms of interaction between PARP inhibitors and RT is intriguing, available data are far to be applicable in clinical practice.

3.4. - *PI3K/mTOR inhibitors: everolimus*

Bourgier et al. (2011) reported three cases highly suggestive of radiation recall syndrome occurred after exposure to mammalian target of rapamycin (mTOR) kinase inhibitors within pre-irradiated areas. In particular, it should be noted that the toxic effects were always in the gastroenteric tract. A similar effect was reported in 2013 by Miura et al. (2013) in a patient who received RT from T6 to T10 because of back pain and experienced an erosive esophagitis corresponding to the irradiation field having started Everolimus thereafter. A radiation-recall dermatitis with the Everolimus/Exemestane combination has also been reported in a caucasian 58-year-old female 10 years after adjuvant whole-breast RT (Ioannidis et al., 2014).

Two initial phase I trials (Sarkaria et al., 2011; Chinnaiyan et al., 2013) investigated the safety and tolerability of Everolimus in combination with RT and TMZ in two different schedules: weekly in the NCCTG trial (Sarkaria et al., 2011) and daily in the RTOG trial (Chinnaiyan et al., 2013). They reported a recommended dose for the weekly and the daily administration of 70 mg and 10 mg, respectively. The activity of the association was then tested in two phase II trial (Ma et al., 2015; Chinnaiyan et al., 2018): in the former one, weekly Everolimus was associated with 57% of patients having at least one \geq G3 adverse event and 23% having a G4 adverse event; in the RTOG trial, combining Everolimus with conventional CT-RT led to increased treatment-related toxicities, namely lymphopenia and thrombocytopenia, and treatment-related deaths. One of the initial applications for mTOR inhibitors was in trasplanted patients because of their effective immunosuppressive potential. The risk of infectious during cancer therapy is a clear concern as demonstrated by Sakaria et al. (Sarkaria et al., 2010), investigating the role of Temserolimus in glioblastoma patients. However, the risk of infectious did not seemed to be increased with Everolimus in both weekly and daily administration trials although this difference may be attributed to prophylaxis against

pneumocystis jiroveci/carinii pneumonitis.

Fury et al. (2013) reported a phase I trial of Everolimus plus weekly Cisplatin and IMRT in head and neck cancer patients. The most common \geq G3 treatment-related adverse event was lymphopenia (92%), mucositis (functional 62%, clinical 31%), pain in the oral cavity (31%) and dysphagia (23%). The maximum tolerated dose recommended for phase II studies was 5 mg/day.

Thoracic RT for NSCLC patients in combination with mTOR inhibitors may be challenging, since pneumonitis is a known side effect of mTOR inhibitors and may occur in the absence of RT (Iacovelli et al., 2012). This combination has been investigated only in a dose escalation trial (Deutsch et al., 2015) in twenty-six patients, who were offered Everolimus at incremental steps and administered weekly (10, 20 or 50 mg) or daily (2.5, 5 or 10 mg) one week before, during RT, and 3.5 weeks thereafter. In the weekly group, Everolimus could be administered safely up to the maximum planned weekly dose of 50 mg while in the daily group there were five patients with G3–4 treatment-related interstitial pneumonitis.

Everolimus in association with Cisplatin and RT was also tested in a phase I trial on locally advanced cervix cancer (de Melo et al., 2016) aimed at using three dose levels of daily doses (2.5, 5 and 10 mg/day), from day 7 up to the last day of brachytherapy. The maximum tolerated dose (MTD) in this combination has been defined as 5 mg/day. The dose limiting toxicities reported were G4 acute renal failure, G3 rash and G4 neutropenia. Among 13 patients, 10 experienced diarrhoea and nausea as the most frequent adverse events, even if G3 toxicity was reported in only one patient. Recently, a phase I trial of Everolimus and RT for salvage treatment of biochemical recurrence in prostate cancer patients following prostatectomy has been published (Narayan et al., 2017). The safety and tolerability of the concurrent treatment after a two weeks period of Everolimus have been reported. Common acute toxicities included G1-G2 mucositis (56%), G1-2 fatigue (39%), G1-2 rash (61%) and G1 urinary symptoms (61%). Acute G3 toxicities occurred in 22% of cases (rash and hematological toxicities) and no patients had \geq G3 chronic toxicity. Therefore at daily doses \leq 10 mg Everolimus does not appear to increase salvage radiation-related normal tissue toxicity.

3.4.1. Summary

No sufficient clinical data allow to adequately evaluate the risks and potential benefits of a combined use of mTOR-inhibitors with RT. Caution should be given when RT involves GI tracts and when PI3K/mTOR inhibitors are administered after RT.

3.5. *BRAF inhibitors: vemurafenib, dabrafenib*

Radiosensitization by combined treatment with Serine/Threonine-protein kinase B (BRAF) inhibitors (BRAFi) and RT has been described as an increase in the occurrence and severity of skin disorders, which was restricted to the irradiated areas in the vast majority of cases. In addition, enhanced radiation toxicity within the irradiated target areas has also been reported. The radiosensitizing effect of BRAFi probably also sensitizes melanoma cells, maybe even to a greater extent than keratinocytes. In a multicenter study conducted by Hecht et al. (2015) a total of 161 melanoma patients from 11 European skin cancer centers were evaluated for acute and late toxicity, of whom 70 received RT with concomitant BRAFi treatment by Vemurafenib or Dabrafenib, or sequential application of these agents. Any grade acute or late toxicity appeared in 57% of patients treated with RT and concomitant BRAFi. Skin toxicity appeared frequently whereas other toxicities were rare. With RT and concomitant BRAFi the rate of acute radiodermatitis \geq G2 was 36% and follicular cystic proliferation was observed in 13%.

The correlation between the dermatitis and the type of BRAFi was also evaluated. Concomitant treatment with Vemurafenib induced acute radiodermatitis \geq G2 more frequently than treatment with Dabrafenib (40% versus 26%, $P = 0.07$), but G3 toxicities were similar. Notably, radiodermatitis \geq G2 following WBRT was 44% and 8%

($p < 0.001$) for patients with and without BRAFi, respectively. No toxicities were reported after SRS. Severe non-cutaneous (visceral) radiosensitizing effects with Vemurafenib have been described too: [Peuvrel et al. \(2013\)](#) reported on a patient with ongoing Vemurafenib for metastatic melanoma treated with palliative RT for a primary rectal cancer: the patient developed a G3 ano-rectitis and diarrhoea, with severe pain refractory to morphine and corticosteroids and finally colostomy was required 10 months after RT. [Merten et al. \(2014\)](#) reported a case of G3 esophagitis that required hospitalization for parenteral nutrition following RT for spine metastases concurrently with Vemurafenib.

[Patel et al. \(2016\)](#) retrospectively compared the outcomes and toxicities of melanoma brain metastases (MBM) patients treated with Vemurafenib/Dabrafenib and SRS (15 patients) or with SRS alone (87 patients). They included patients treated with Vemurafenib 12 days before SRS or Dabrafenib 2 days before SRS: radiation necrosis was higher in the SRS + BRAFi cohort (22.2% vs. 11% at 1 year, $P < 0.001$). Symptomatic radionecrosis was higher in patients receiving BRAFi (28.2% vs. 11.1%, at 1 year $P < 0.001$), without difference in the rate of local recurrence.

[Ly et al. \(2015\)](#), in a report of 52 patients with known BRAF mutation status, identified 17 patients treated with BRAFi with a washout period initiated before and after SRS (median, 7 days; range, 1–20 days). At a median follow-up of 10.5 months, no patient had radionecrosis, but BRAFi treatment for patients with BRAF mutant melanoma was associated with a decreased rate of freedom from hemorrhage (77.0% vs 39.3% at 1 year, $P = .0003$).

A prospective study was conducted by [Wolf et al. \(2016\)](#) who evaluated the impact of BRAFi on OS in patients receiving SRS for MBM. They collected treatment parameters and outcomes for 80 patients with MBM who underwent SRS with 18 Gy in 1 fraction. Of 80 patients analysed, 35 patients harbored the BRAF mutation and 45 patients did not. No significant difference in hemorrhage (16% after BRAF and SRT vs. 8% after SRT alone, ns) was detected.

[Ejlsmark et al. \(2017\)](#) described recall radiation-induced myelitis in the thoracic spine caused by RT followed radiosensitization by Dabrafenib 8 months after SRS to a large central left sided pulmonary lung metastasis; treatment was given with 56 Gy in 8 fraction. The dose to the spinal cord did not exceed 33.5 Gy. In contrast [Stefan et al. \(2016\)](#) described the case of a patient treated with SRS for a L3 metastases using the Cyberknife platform at 10 Gy in one fraction, started 1 month after Vemurafenib. The patient received steroids on several weeks, showing a partial response without neurological, skin or mucosal toxicity, 8 months after completion of this combination.

[Baroudjian et al. \(2014\)](#) described a case of a hemo-pneumothorax after RT of the right axillary area, which ultimately led to the death of the patient 1 month after RT with a prior Vemurafenib therapy. Radiation recall pneumonitis may occur from RT and BRAFi association. [Forschner et al. \(2014\)](#) described radiation pneumonitis in a patients receiving adjuvant RT of right axilla and right supraclavicular, infraclavicular and pectoral regions (50 Gy at 2 Gy per fraction) and a symptomatic paramediastinal radiation pneumonitis in a patient treated for an obstruction of the left main bronchus. Both patients received Vemurafenib after treatment end.

Vemurafenib alone could cause hepatic toxicity involving transaminase increase. A case of exceptional fatal liver toxicity after RT of the lumbar vertebra was reported by [Anker et al. \(2013\)](#) after 20 Gy of RT administered in five fractions to the painful bone metastases with 2D-technique to T10 to L1, and Vemurafenib stopped for 4 days before and 2 days after RT. Other experiences reported on patients treated with RT with concurrent Vemurafenib and Dabrafenib to the same region, but

without severe hepatotoxicity ([Churilla et al., 2013](#); [Satzger et al., 2013](#); [Ducassou et al., 2013](#)).

3.5.1. Summary

Until more prospective data are available, the consensus recommendations of the Eastern Cooperative Oncology Group (ECOG) include the following for all patients receiving a BRAFi, MEKi, or both BRAFi and MEKi (eg, Vemurafenib/Dabrafenib and Trametinib/Cobimetinib) ([Anker et al., 2016](#)).

For drug

- hold ≥ 3 days before and after fractionated RT;
- hold ≥ 1 day before and after SRS.

For RT:

- consider dose per fraction < 4 Gy unless using a stereotactic approach or the patient has very poor prognosis/performance status;
- for adjuvant nodal pelvic RT, consider a dose ≤ 48 to 50 Gy in 20 fractions;
- for spine metastases, consider posterior oblique RT fields when feasible and safe to minimize exit dose through visceral organs.

3.6. Hedgehog signalling pathway inhibitors: vismodegib, sonidegib

The two Hedgehog (HH) inhibitors Vismodegib and Sonidegib were approved by the U.S. Food and Drug Administration (FDA) for the treatment of patients with locally advanced basal cell carcinoma (LA BCC), either locally recurrent after surgery or not suitable for surgery or RT. Vismodegib was also approved for patients with metastatic BCC (mBCC). The availability of these agents as highly targeted therapy represents a success in translational medicine. The SafeTyEvents in Vismodegib (STEVIE) study is an international multicentre open-label study, containing important data regarding safety (primary endpoint) of Vismodegib for laBCC or mBCC ([Basset-Séguin et al., 2017](#)). Most patients (98%) had ≥ 1 treatment-emergent adverse events. Severe (G3-G4) toxicity occurred in 289 of 1215 patients (23.8%). Exposure ≥ 12 months did not lead to increased incidence or severity of new treatment-emergent adverse events. The phase II BOLT trial ([Midgen et al., 2015](#)) (primary endpoint: objective response rate) randomized 230 patients with laBCC or mBCC to receive 200 mg or 800 mg oral Sonidegib daily. Notably, in a relevant proportion of patients (19 in the 200 mg group and 49 in the 800 mg group), Sonidegib was administered after RT: after a median follow up of 13.9 months, serious adverse events occurred in 11 (14%) of 79 patients in the 200 mg group and 45 (30%) of 150 patients in the 800 mg group. The most common G3-G4 toxicities were raised creatine kinase (6% in the 200 mg group vs 13% in the 800 mg group) and lipase concentration (5% vs 5%). Long-term follow-up ([Dummer et al., 2016](#)) confirmed that G3-G4 toxicities and those leading to discontinuation were less frequent with Sonidegib 200 versus 800 mg. Considering sequential schemes of treatment, a number of case series ([Block et al., 2015](#); [Pollom et al., 2015](#); [Raleigh et al., 2015](#); [Rodon et al., 2014](#)) reported no relevant adverse effects due to drug-radiation interaction.

3.6.1. Summary

Available data support the safety of the combination of both Sonidegib and Vismodegib concurrently with RT in laBCC and mBCC. Further data testing this combination are needed. [Table 5](#) summarizes major clinical trials of Vismodegib/ Sonidegib and RT for laBCC.

Table 5
Major clinical trials of Vismodegib/ Sonidegib and RT for laBCC.

| Author and year | Study type | N | Tumour site | RT technique/dose/fractionation | Combination (concomit, other.) | G3-4 Non-HEM AEs | Treatment related deaths | Incomplete RT |
|------------------------------|-------------------------------|---|--------------------------|---|---|--|---|---------------|
| (Basset-Séguin et al., 2017) | Open label, multicentre trial | 499 (*) | laBCC | N.R. | Vismodegib after RT | 39% | 4% | N.A. |
| (Midgen et al., 2015) | Phase II R | 230 (79 in the 200 mg and 151 in the 800 mg group) (**) | laBCC (194) or mBCC (36) | N.R. | Sonidegib after RT | 31% (200 mg group) vs 56% (800 mg group) | 1.4% (200 mg group) vs 30% (800 mg group) | N.A. |
| (Block et al., 2015) | Case report | 1 | Right cheek BCC | 3DCRT 50 Gy/20 fx | Vismodegib (4 months)→RT→S | 0 | 0 | 0 |
| (Pollom et al., 2015) | Case report | 2 | Left nasal tip BCC | VMAT 66 Gy/33 fx | Vismodegib and concurrent RT | 0 | 0 | 0 |
| (Raleigh et al., 2015) | Case report | 1 | Lateral canthus BCC | 6-MeV and 9-MeV electrons 51 Gy/17 fx | Vismodegib and concurrent RT | 0 | 0 | 0 |
| (Schulze, 2016) | Case series | 4 | Right ear BCC | IMRT 70 Gy/35 fx | Vismodegib and concurrent RT | 0 | 0 | 0 |
| | | | Facial BCC | Case 1: 3DCRT 54.0 Gy/27 fx + interstitial HDR BRT boost of 12 Gy/2 fx Case 2: 3DCRT 66 Gy/33 fx Case 3: HRT 55 Gy/20 fx Case 4: HRT 55 Gy/20 fx | Vismodegib and concurrent RT | 0 | 0 | 0 |
| (Anici et al., 2015) | Case report | 2 | laBCC | 3DCRT 45 Gy/15 fx Contact RT 40 Gy/10 fx (2 fx per week) | RT between Vismodegib cycles RT after Vismodegib | 0 | 0 | 0 |
| (Chang, 2014) | Open label, multicentre trial | 119 (***) | laBCC (62) or mBCC (57) | N.R. | Vismodegib after RT | muscle spasms, diarrhoea, fatigue: 27.7% | 1.68% | N.A. |

Abbreviations: AEs = adverse effects; BCC = basal cell carcinoma; BRT = brachytherapy; fx = fractions; HEM = hematologic; HDR = high dose rate; HRT = hypofractionated radiotherapy; laBCC = locally advanced basal cell carcinoma; mBCC = metastatic basal cell carcinoma; N.A = not applicable; N.R = not reported; R = randomized; RT = radiotherapy; 3DCRT = 3D conformal radiotherapy; S = surgery; VMAT = volumetric modulated arc radiotherapy.

(*) previous RT in 134 patients.

(**) previous RT in 19 (200 mg group) and 49 (800 mg group) patients.

(***) previous RT in 38 patients.

4. Immune check Point blockade

4.1. CTLA-4, PD-1 and PD-L1 antagonists

The effects of radiation on tumor microenvironment and its interaction with the immune system appear as a complex balance of activating and suppressing signals (Formenti and Demaria, 2013). Investigators at the MSKCC performed a retrospective analysis of 29 patients with metastatic melanoma who received extra-cranial RT in combination with Ipilimumab (Ipi): no significant increase in adverse effects was observed (Barker et al., 2013). The results in terms of toxicity of the combination of Ipi with RT for brain metastases from melanoma (MBM) are extremely controversial; while Gerber et al. (Tazi et al., 2015) demonstrated new or increased intracranial bleeding, a study from the New York University (Mathew et al., 2013) on 58 patients treated with brain SRS, reported no difference in frequency of intracranial hemorrhage in patients who did or did not receive Ipi. (Kiess et al. (2015)) documented an increase in brain metastasis size > 150% in 40% of the treated lesions with SRS before or during Ipi, and in 10% of the metastases treated with SRS after Ipi. Hemorrhage was observed after SRS during Ipi in 42% of brain metastases. Recently, a phase I trial (William et al., 2017) was performed to determine the maximum tolerable dose and safety of Ipi with SRS or WBRT in patients with MBM. Concurrent Ipi 10 mg/kg with SRS was safe. The WBRT arm was closed early because of slow accrual but demonstrated safety with Ipi 3 mg/kg.

Ipi combined with RT has been tested against advanced NSCLC in few trials. A single report (Golden et al., 2013) showed promising results and abscopal effect in a case of advanced lung adenocarcinoma heavily pretreated with CT and receiving RT together with Ipi. Results are awaited from a prospective phase II study combining RT and Ipi in metastatic lung cancer (NCT02221739). Ipi was also used in combination with RT in the setting of metastatic prostate cancer (PC): a randomised, phase 3 trial (Kwon et al., 2014) randomized 799 men with at least one bone metastasis from castration-resistant PC who had progressed after Docetaxel to receive bone-directed RT (8 Gy in one fraction) followed by either Ipi or placebo every 3 weeks for up to four doses. The most common G3-G4 toxicities were immune-related, and occurred in 101 (26%) patients in the Ipi group versus 11 (3%) of patients in the placebo group. Four (1%) deaths occurred, all in the Ipi group.

Liniker et al. (2016) reported on 53 patients with metastatic melanoma treated either with Nivolumab and Pembrolizumab and SRS, WBRT or extracranial RT without excess in toxicity. Out of 6 patients receiving SRS, one developed a G3 radiation necrosis. Among 21 patients receiving WBRT, one developed Stevens–Johnson syndrome, one acute neurocognitive decline, and one significant cerebral edema in the site of the disease. Ahmed et al. (2016) retrospectively analyzed a series of patients with both resected and unresectable MBM from two prospective Nivolumab protocols. Neurotoxicity was mild and regressed with steroids. Clinical data on the combination of anti PD-1 and RT in non-melanoma patients are even smaller. Preliminary reports on the safety of Pembrolizumab plus RT seem to favor this approach, as no severe or enhanced toxicity was observed. A small study of 10 NSCLC patients with brain metastasis treated with sequential RT and Pembrolizumab showed no > G3 toxicity (Goldberg et al., 2015).

In two prospective trials (Segal et al., 2016; Lin et al., 2017a) only mild drug-related toxicities was reported in patients affected by metastatic colo-rectal cancer and renal cell carcinoma, both treated with Pembrolizumab and ablative or palliative RT. In a phase II trial (Ho et al., 2017) including 9 patients with triple-negative metastatic breast cancer treated with RT and Pembrolizumab, only mild toxicities were preliminarily reported. Preliminary results from a phase I dose-finding trial (Duffy et al., 2017) showed no DLTs when SBRT (8 Gy x 1 or 5 Gy x 5) and the anti-PD-L1 Durvalumab or the CTLA-4 inhibitor Tremelimumab (or combination of all 3) was administered as second-line

therapy to 24 patients with metastatic pancreatic adenocarcinoma. A unique clinical scenario is represented by thoracic RT given concomitantly with immunotherapy. Anti-PD-1/PD-L1 related pneumonitis is a known complication, and its incidence varies from 2.7% to 6.6% (Nishino et al., 2016). RT could possibly enhance the PD-1/PD-L1 expression also in non-irradiated regions and therefore increase the risk of side effects by combinative therapy with RT and anti-PD-1 treatment, even if this phenomenon is still unclear (Lu and Liu, 2017), and potential beneficial effects of the combination could be possibly shown in future trials.

Reassuringly, the PD-L1 inhibitor Durvalumab was granted FDA approval based on superior PFS (Antonia et al., 2017) and OS (Antonia et al., 2018) but similar safety compared to placebo following platinum-based CT–RT in unresectable LA NSCLC: major (\geq G3-G4) adverse events of any cause occurred in 30.5% in the Durvalumab group and in 26.1% in the placebo group, and the most frequent adverse events leading to the discontinuation of the treatment were pneumonitis (4.8% in the Durvalumab group and in 2.6% in the placebo group, respectively). Despite the promising results of the PACIFIC trial (Antonia et al., 2017, 2018), the potential mechanisms driving the interaction between immunotherapy and CT–RT are still under debate, as conflicting results came from a phase I trial (Lin et al., 2017b) involving patients in a similar stage of disease, receiving Atezolizumab (a new anti PD-L1 antibody) as consolidation treatment with Carboplatin and Paclitaxel following standard CT-RT: based on safety and tolerability of patients in part I, criteria were met for advancement to part II of the study.

4.1.1. Summary

The combination of Ipi and RT is safe and partially effective, particularly for MBM. A trend towards a positive synergistic effect has been shown in a trial on metastatic prostate cancer patients with bone metastases. Still few data are available on the combination of anti-PD-1 agents and RT, and preliminary evidence suggests the absence of toxicity for brain RT. Data from a phase III trial show that Durvalumab has manageable side effects after CT-RT for LA NSCLC.

5. Androgen pathway therapy

5.1. Abiraterone

A single experience (Cho et al., 2015) has been published in literature regarding the concomitant use of RT and Abiraterone in men with localized disease. The study intervention consisted of 12 weeks of neoadjuvant LHRH analogue and Abiraterone followed by definitive RT. Twenty-two patients were enrolled. Most of them (86%) had high-risk PC. At a median follow up of 21 months (range, 3–37 months), Abiraterone was discontinued early in 6 patients for fatigue or atrial fibrillation or hypertension. No increased toxicity was observed when RT was concomitantly delivered with Abiraterone, and there were no delays in RT duration attributable to concomitant Abiraterone administration.

In the setting of metastatic PC, a post hoc exploratory analysis of the COU-AA-301 randomised trial (Saad et al., 2012) revealed that palliative RT to bone was safely administered with Abiraterone in patients experiencing localized progression at a single site, supporting the maintenance of Abiraterone in men receiving palliative RT who were gaining benefit from this agent.

5.1.1. Summary

Despite the limited existing data, experiences herein reported extrapolated from large series, such as the COU-AA-301 trial, confirmed the feasibility of the combination Abiraterone/RT in PC.

5.2. Enzalutamide (MDV3100)

No data are currently available regarding the toxicity and the efficacy of a combination of RT and Enzalutamide. In two large studies (AFFIRM, PREVAIL) (Scher et al., 2012; Beer et al., 2017) on Enzalutamide administered in monotherapy in castration-resistant prostate cancer, the treatment was stopped in case of skeletal events (including events that required RT), so no direct data on the potential toxicity of a combination Enzalutamide and RT are available.

6. Summary

No data on the safety of RT and Enzalutamide are available. Noteworthy, some of the adverse events associated with the use of Enzalutamide as monotherapy may overlap with RT-induced toxicity (fatigue, nausea etc.), thus patients receiving Enzalutamide and RT should be carefully monitored for these symptoms.

7. Newest compounds

7.1. Apalutamide (ARN-509)

ARN-509 (Apalutamide) acts selectively and irreversibly binding itself to AR receptor with a higher therapeutic index in comparison with Enzalutamide. Based on the results of the phase III SPARTAN (Selective Prostate Androgen Receptor Targeting with ARN-509) trial (Smith et al., 2018), Apalutamide has been approved for non-metastatic PC patients with rising PSA during androgen deprivation therapy (ADT). So far, no clinical data on the interaction between Apalutamide and RT are available. Two phase III trials [NCT02531516 and NCT03488810] are running to seek at the combination of Apalutamide with ADT by LHRH agonists in patients with intermediate and high-risk PC receiving primary RT. Another ongoing single arm phase II trial [NCT02772588] aims to determine if anti-testosterone medications (Leuprolide, Abiraterone and Apalutamide) combined with prostate SBRT are effective in preventing biochemical failure.

7.2. Darolutamide (ODM-201)

ODM-201 (Darolutamide) is an AR antagonist. ODM-201 and its major metabolite, ORM-15341, have a very high AR-binding affinity. Preclinical data suggest low-risk of seizures in relation with low intake in the brain (Leibowitz-Amit and Joshua, 2012; Fizazi et al., 2013; Moilanen et al., 2013). No data are published regarding interaction with radiation and no studies are ongoing.

7.3. Orteronel (TAK-700)

Orteronel (TAK-700) preferentially inhibits cytochrome P450 17,20-lyase (CYP17) (in respect to 17 α -hydroxylase) and it can reduce the need for corticosteroid supplementation and could lead to an improved toxicity profile (Zhu et al., 2010) No clinical data are published about the use of TAK-700 with RT and one, not recruiting, study is registered on the ClinicalTrials registry about the use of the drug in association with RT [NCT01546987].

7.4. Galeterone (TOK-001)

Galeterone (TOK-001), in vitro, increases AR protein degradation in prostate cancer derived cells expressing a T878 A mutant AR. There are no data on the potential interactions of RT with Galeterone.

7.5. Seviteronel (VT-464)

Seviteronel (VT-464) is a non-steroidal CYP17A1 inhibitor, mainly directed at 17,20-lyase blockade having the theoretical advantage of a reduced need for glucocorticoid supplementation (Anon, 2018). No study has evaluated the combination of Seviteronel (VT-464) and RT.

7.5.1. Summary

A paucity of prospective data are available on the optimal AR antagonist administered in combination with RT.

8. Perspectives and conclusions

The published clinical trials investigating the combination between novel systemic agents and RT have provided mixed data, with some suggesting safety and others suggesting unexpected toxicities. While many of these agents have been demonstrated in the preclinical setting to enhance the radiation effect, the majority have not been tested in even phase I clinical trials for safety in the context of RT. Despite the common use of RT in cancer treatment, there is a difficulty in incorporating RT in clinical trials investigating novel compounds, due to limited regulatory landmarks in the development of drugs specifically designed for RT combination. Under these circumstances, there is a lack of high-quality clinical data to guide the decision making process of patients who are treated with these drugs, and are eligible for RT. There is a significant unmet need to define the therapeutic index of combining two treatment modalities (RT and systemic therapy) that have experienced significant recent advances. While awaiting the results of the available ongoing prospective trials, caution should be paid in order not to cause toxicity and compromise quality of life. Careful patient selection and risk-adapted radiation dose fractionation regimens will be critical in this regard.

References

- Ahluwalia, M.S., Chao, S.T., Parsons, M.W., et al., 2015. Phase II trial of sunitinib as adjuvant therapy after stereotactic radiosurgery in patients with 1-3 newly diagnosed brain metastases. *J. Neurooncol.* 124 (3) Spetember), 485–491.
- Ahmed, K.A., Stallworth, D.G., Kim, Y., et al., 2016. Clinical outcomes of melanoma brain metastases treated with stereotactic radiation and anti-PD-1 therapy. *Ann. Oncol.* 27, 434–441.
- Ahn, P.H., Machtay, M., Anne, P.R., et al., 2016. Phase I trial using induction cisplatin, docetaxel, 5-FU and erlotinib followed by cisplatin, bevacizumab and erlotinib with concurrent radiotherapy for advanced head and neck cancer. *Am J. Clin. Oncol.* (July).
- Amici, J.M., Beylot-Barry, M., 2015. Locally advanced basal-cell carcinoma: Combined alternative treatments beyond surgery. *Ann. Chir. Plast. Esthet.* 60, 321–325.
- Ang, K.K., Zhang, Q., Rosenthal, D.I., et al., 2014. Randomized phase III trial of concurrent accelerated radiation plus cisplatin with or without cetuximab for stage III to IV head and neck carcinoma: RTOG 0522. *J. Clin. Oncol.* 32 (27)September), 2940–2950.
- Anker, A., Ribas, A.H., Grossmann, X., et al., 2013. Severe liver and skin toxicity after radiation and vemurafenib in metastatic melanoma. *J. Clin. Oncol.* 31 (17)June), e283.
- Anker, C.J., Grossmann, K.F., Atkins, M.B., et al., 2016. Avoiding severe toxicity from combined BRAF inhibitor and radiation treatment: consensus guidelines from the Eastern cooperative oncology group (ECOG). *Int. J. Radiat. Oncol. Biol. Phys.* 95 (2) June), 632–646.
<http://www.pharmaceutical-technology.com/news/newsfda-grants-fast-track-status-innocrins->
- Antonia, S.J., Villegas, A., Daniel, D., et al., 2017. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *N Engl. J. Med.* 377, 1919–1929.
- Antonia, S.J., Villegas, A., Daniel, D., et al., 2018. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. *N Engl. J. Med.* <https://doi.org/10.1056/NEJMoa1809697>.
- Argiris, A., Heron, D.E., Smith, R.P., et al., 2010. Induction docetaxel, cisplatin, and cetuximab followed by concurrent radiotherapy, cisplatin, and cetuximab and maintenance cetuximab in patients with locally advanced head and neck cancer. *J. Clin.*

- Oncol. 28 (36)December), 5294–5300.
- Arias de la Vega, F., Contreras, J., de Las Heras, M., et al., 2012. Erlotinib and chemoradiation in patients with surgically resected locally advanced squamous cell carcinoma of the head and neck: a GICOR phase I trial. *Ann. Oncol.* 23 (4) April), 1005–1009.
- Avallone, A., Pecori, B., Bianco, F., et al., 2015. Critical role of bevacizumab scheduling in combination with pre-surgical chemo-radiotherapy in MRI-defined high-risk locally advanced rectal cancer: results of the BRANCH trial. *Oncotarget* 6 (30) October), 30394–30407.
- Barker, C.A., Postow, M.A., Khan, S.A., et al., 2013. Concurrent RT and ipilimumab immunotherapy for patients with melanoma. *Cancer Immunol. Res.* 1, 92–98.
- Barney, B.M., Markovic, S.N., Laack, N.N., et al., 2013. Increased bowel toxicity in patients treated with a vascular endothelial growth factor inhibitor (VEGFI) after stereotactic body radiation therapy (SBRT). *Int. J. Radiat. Oncol. Biol. Phys.* 87 (1) September), 73–80.
- Baroudjian, B., Boussebart, L., Routier, E., et al., 2014. Dramatic response to radiotherapy combined with vemurafenib. Is Vemurafenib Radiosensitizing? *Eur. J. Dermatol.* 24, 265–267.
- Basset-Séguin, N., Hauschild, A., Kunstfeld, R., et al., 2017. Vismodegib in patients with advanced basal cell carcinoma: primary analysis of STEVIE, an international, open-label trial. *Eur. J. Cancer.* 86 (November), 334–348.
- Beer, T.M., Armstrong, A.J., Rathkopf, D., et al., 2017. Enzalutamide in men with chemotherapy-naïve metastatic castration-resistant prostate cancer: extended analysis of the phase 3 PREVAIL study. *Eur. Urol.* 71 (2) February), 151–154.
- Belkacémi, Y., Gligorov, J., Ozsahin, M., et al., 2008. Concurrent trastuzumab with adjuvant radiotherapy in HER2-positive breast cancer patients: acute toxicity analyses from the French multicentric study. *Ann. Oncol.* 19, 1110–1116.
- Blaszkowsky, L.S., Ryan, D.P., Szymonifka, J., et al., 2014. Phase I/II study of neoadjuvant bevacizumab, erlotinib and 5-fluorouracil with concurrent external beam radiation therapy in locally advanced rectal cancer. *Ann. Oncol.* 25 (1) January), 121–126.
- Block, A.M., Alite, F., Diaz, A.Z., et al., 2015. Combination trimodality therapy using vismodegib for basal cell carcinoma of the face. *Case Rep. Oncol. Med.* 2015 827608.
- Blumenschein Jr, G.R., Paulus, R., Curran, W.J., et al., 2011. Phase II study of cetuximab in combination with chemoradiation in patients with stage IIIA/B non-small-cell lung cancer: RTOG 0324. *J. Clin. Oncol.* 29 (17) June), 2312–2318.
- Bonner, J.A., Harari, P.M., Giralt, J., et al., 2006. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl. J. Med.* 354 (6)February), 567–578.
- Bourgier, C., Massard, C., Moldovan, C., 2011. Total recall of radiotherapy with mTOR inhibitors: a novel and potentially frequent side-effect? *Ann. Oncol.* 2, 485–486.
- Bradley, J.D., Paulus, R., Komaki, R., et al., 2015. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. *Lancet Oncol.* 16 (2) February), 187–199.
- Buglione, M., Maddalo, M., Corvò, R., et al., 2017. Subgroup analysis according to human papillomavirus Status and tumor site of a randomized phase II trial comparing cetuximab and cisplatin combined with radiation therapy for locally advanced head and neck cancer. *Int. J. Radiat. Oncol. Biol. Phys.* 97 (3) March), 462–472.
- Chadha, A.S., Skinner, H.D., Gunther, J.R., et al., 2016. Phase I trial of consolidative radiotherapy with concurrent bevacizumab, erlotinib and capecitabine for unresectable pancreatic cancer. *PLoS One.* 11 (6) June) e0156910.
- Chang, A.L., Solomon, J.A., Hainsworth, J.D., et al., 2014. Expanded access study of patients with advanced basal cell carcinoma treated with the Hedgehog pathway inhibitor, vismodegib. *J. Am. Acad. Dermatol.* 70 (Jan (1)), 60–69.
- Chauffert, B., Feuvret, L., Bonnetain, F., et al., 2014. Randomized phase II trial of irinotecan and bevacizumab as neo-adjuvant and adjuvant to temozolomide-based chemoradiation compared with temozolomide-chemoradiation for unresectable glioblastoma: final results of the TEMAVIR study from ANOCEF. *Ann. Oncol.*
- Chinnaiyan, P., Won, M., Wen, P.Y., et al., 2018. A randomized phase II study of everolimus in combination with chemoradiation in newly diagnosed glioblastoma: results of NRG oncology RTOG 0913. *Neuro Oncol.* 20 (5) April), 666–673.
- Chinnaiyan, P., Won, M., Wen, P.Y., et al., 2013. RTOG 0913: a phase I study of daily everolimus (RAD001) in combination with radiation therapy and temozolomide in patients with newly diagnosed glioblastoma. *Int. J. Radiat. Oncol. Biol. Phys.* 86 (5) August), 880–884.
- Chinot, O.L., Wick, W., Mason, W., et al., 2014. Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma. *N Engl. J. Med.* 370, 709–722.
- Cho, E., Mostaghel, E.A., Russell, K.J., Liao, J.J., Konodi, M.A., Kurland, B.F., Marck, B.T., Matsumoto, A.M., Dalkin, B.L., Montgomery, R.B., 2015. External beam radiation therapy and abiraterone in men with localized prostate cancer: safety and effect on tissue androgens. *Int. J. Radiat. Oncol. Biol. Phys.* 92 (2)June), 236–243.
- Chung, C., Dawson, L.A., Joshua, A.M., Brade, A.M., 2010. Radiation recall dermatitis triggered by multi-targeted tyrosine kinase inhibitors: sunitinib and sorafenib. *Anticancer Drugs.* 21 (2) February), 206–209.
- Churilla, T.M., Chowdhry, V.K., Pan, D., et al., 2013. Radiation-induced dermatitis with vemurafenib therapy. *Pract. Radiat. Oncol.* 3, e195–e198.
- Crane, C.H., Eng, C., Feig, B.W., et al., 2010. Phase II trial of neoadjuvant bevacizumab, capecitabine, and radiotherapy for locally advanced rectal cancer. *Int. J. Radiat. Oncol. Biol. Phys.* 76 (3)March), 824–830.
- Crosby, T., Hurt, C.N., Falk, S., et al., 2013. Chemoradiotherapy with or without cetuximab in patients with oesophageal cancer (SCOPE1): a multicentre, phase 2/3 randomised trial. *Lancet Oncol.* 14 (7) June), 627–637.
- Das, P., Eng, C., Rodriguez-Bigas, M.A., et al., 2014. Preoperative radiation therapy with concurrent capecitabine, bevacizumab, and erlotinib for rectal cancer: a phase I trial. *Int. J. Radiat. Oncol. Biol. Phys.* 88 (2) February), 301–305.
- de Melo, A.C., Grazzotin-Reisner, R., Erlich, F., et al., 2016. A phase I study of mTOR inhibitor everolimus in association with cisplatin and radiotherapy for the treatment of locally advanced cervix cancer: PHOENIX I. *Cancer Chemother. Pharmacol.* 78 (1), 101–109.
- Dellas, K., Höhler, T., Reese, T., et al., 2013. Phase II trial of preoperative radiochemotherapy with concurrent bevacizumab, capecitabine and oxaliplatin in patients with locally advanced rectal cancer. *Radiat. Oncol.* 8 (April), 90.
- Deutsch, E., Le Péchoux, C., Faivre, L., et al., 2015. Phase I trial of everolimus in combination with thoracic radiotherapy in non-small-cell lung cancer. *Ann. Oncol.* 26, 1223–1229.
- Dipertillo, T., Pricolo, V., Lagares-Garcia, J., et al., 2012. Neoadjuvant bevacizumab, oxaliplatin, 5-fluorouracil, and radiation for rectal cancer. *Int. J. Radiat. Oncol. Biol. Phys.* 82 (1) January), 124–129.
- Ducassou, A., David, I., Delannes, M., et al., 2013. Radiosensitization induced by vemurafenib. *Cancer Radiother.* 17, 304–307.
- Duffy, A.G., Makarova-Rusher, O.V., Kleiner, D.E., et al., 2017. A pilot study of immune checkpoint inhibition in combination with radiation therapy in patients with metastatic pancreatic cancer [abstract]. *J. Clin. Oncol.* 35 (Abstr nr e15786).
- Dummer, R., Guminski, A., Gutzmer, R., et al., 2016. The 12-month analysis from basal cell carcinoma outcomes with LDE225 treatment (BOLT): a phase II, randomized, double blind study of sonidegib in patients with advanced basal cell carcinoma. *J. Am. Acad. Dermatol.* 75 113-125.e5.
- Dwivedy, A., Cunningham, D., Taberero, J., et al., 2012. Multicenter randomized phase II clinical trial comparing neoadjuvant oxaliplatin, capecitabine, and preoperative radiotherapy with or without cetuximab followed by total mesorectal excision in patients with high-risk rectal cancer (EXPERT-c). *J. Clin. Oncol.* 30 (14) May), 1620–1627.
- Ejlsmark, M.W., Kristiansen, C., Eriksen, J.C., et al., 2017. Recall radiation myelitis after stereotactic radiation and dabrafenib in metastatic melanoma. *Acta Oncol.* 56 (1) January), 109–110.
- Fizazi, K., Massard, C., James, N.D., et al., 2013. ODM-201, a new generation androgen receptor inhibitor for castration-resistant prostate cancer: preclinical and phase I data. *Proc. Am. Soc. Clin. Oncol.* 31 (suppl 6) abstr 65. 19.
- Formenti, S.C., Demaria, S., 2013. Combining RT and cancer immunotherapy: a paradigm shift. *J. Natl. Canc. Inst.* 105, 256–265.
- Fornaro, L., Caparello, C., Vivaldi, C., et al., 2014. Bevacizumab in the pre-operative treatment of locally advanced rectal cancer: a systematic review. *World J. Gastroenterol.* 20 (20)May), 6081–6091.
- Forschner, A., Zips, D., Schraml, C., et al., 2014. Radiation recall dermatitis and radiation pneumonitis during treatment with vemurafenib. *Melanoma Res.* 24, 512–516.
- Fu, P., He, Y.S., Huang, Q., et al., 2016. Bevacizumab treatment for newly diagnosed glioblastoma: systematic review and meta-analysis of clinical trials. *Mol. Clin. Oncol.* 4 (5) May), 833–838.
- Fury, M.G., Lee, N.Y., Sherman, E., et al., 2013. A phase I study of everolimus + weekly cisplatin + intensity modulated radiation therapy in head-and-neck cancer. *Int. J. Radiat. Oncol. Biol. Phys.* 87 (3) November), 479–486.
- Gasparini, G., Torino, F., Ueno, T., et al., 2012. A phase II study of neoadjuvant bevacizumab plus capecitabine and concomitant radiotherapy in patients with locally advanced rectal cancer. *Angiogenesis.* 15 (1) March), 141–150.
- Geoffrois, L., Martin, L., De Raucourt, D., et al., 2018. Induction chemotherapy followed by cetuximab radiotherapy Is not superior to concurrent chemoradiotherapy for head and neck carcinomas. Results of the GORTE-02 phase III randomized trial. *J. Clin. Oncol.*(July).
- Gilbert, M.R., Dignam, J.J., Armstrong, T.S., et al., 2014. A randomized trial of bevacizumab for newly diagnosed glioblastoma. *N Engl. J. Med.* 370, 699–708.
- Giralt, J., Trigo, J., Nuyts, S., et al., 2015. Panitumumab plus radiotherapy versus chemoradiotherapy in patients with unresected, locally advanced squamous-cell carcinoma of the head and neck (CONCERT-2): a randomised, controlled, open-label phase 2 trial. *Lancet Oncol.* 16 (2) February), 221–232.
- Goldberg, S.B., Gettinger, S.N., Mahajan, A., et al., 2015. Activity and safety of pembrolizumab in patients with metastatic Non-small cell lung cancer with untreated brain metastases. *J. Clin. Oncol.* 33 (Suppl; Abstr 8035).
- Golden, E.B., Demaria, S., Schiff, P.B., et al., 2013. An abscopal response to radiation and ipilimumab in a patient with metastatic non-small cell lung cancer. *Cancer Immunol. Res.* 1, 365–372.
- Govindan, R., Bogart, J., Stinchcombe, T., et al., 2011. Randomized phase II study of pemetrexed, carboplatin, and thoracic radiation with or without cetuximab in patients with locally advanced unresectable non-small-cell lung cancer: cancer and leukemia group B trial 30407. *J. Clin. Oncol.* 29 (23) August), 3120–3125.
- Halyard, M.Y., Pisansky, T., Dueck, A.C., et al., 2009. Radiotherapy and adjuvant trastuzumab in operable breast cancer: tolerability and adverse event data from the NCCCTG phase II trial N9831. *J. Clin. Oncol.* 27 (16) June), 2638–2644.
- Hammel, P., Huguet, F., van Laethem, J.L., et al., 2016. Effect of chemoradiotherapy vs chemotherapy on survival in patients with locally advanced pancreatic cancer controlled after 4 months of gemcitabine with or without erlotinib: the LAP07 randomized clinical trial. *JAMA.* 315 (17) May), 1844–1853.
- Hecht, M., Zimmer, L., Loquai, C., et al., 2015. Radiosensitization by BRAF inhibitor therapy-mechanism and frequency of toxicity in melanoma patients. *Ann. Oncol.* 26 (6), 1238–1244.
- Helbling, D., Bodoky, G., Gautschi, O., et al., 2013. Neoadjuvant chemoradiotherapy with or without panitumumab in patients with wild-type KRAS, locally advanced rectal cancer (LARC): a randomized, multicentre, phase II trial SAKK 41/07. *Ann. Oncol.* 24 (3) March), 718–725.
- Herman, J.M., Fan, K.Y., Wild, A.T., et al., 2013. Phase 2 study of erlotinib combined with adjuvant chemoradiation and chemotherapy in patients with resectable pancreatic

- cancer. *Int. J. Radiat. Oncol. Biol. Phys.* 86 (4 July), 678–685.
- Ho, A., Barker, C.A., Gucaip, A., et al., 2017. Preliminary results from a single-Arm, phase II study assessing the efficacy of pembrolizumab plus radiotherapy in metastatic triple negative breast cancer. *J. Clin. Oncol.* 35 (Suppl 7S) Abstract 95.
- Hofheinz, R.D., Horisberger, K., Woernle, C., et al., 2006. Phase I trial of cetuximab in combination with capecitabine, weekly irinotecan, and radiotherapy as neoadjuvant therapy for rectal cancer. *Int. J. Radiat. Oncol. Biol. Phys.* 66 (5 December), 1384–1390.
- Horton, J.K., Halle, J., Ferraro, M., et al., 2010. Radiosensitization of chemotherapy-refractory, locally advanced or locally recurrent breast cancer with trastuzumab: a phase II trial. *Int. J. Radiat. Oncol. Biol. Phys.* 76, 998–1004.
- Iacovelli, R., Palazzo, A., Mezi, S., et al., 2012. Incidence and risk of pulmonary toxicity in patients treated with mTOR inhibitors for malignancy. A meta-analysis of published trials. *Acta Oncol.* 51 (7 September), 873–879.
- Ioannidis, G., Gkogkou, P., Charalampous, P., et al., 2014. Radiation-recall dermatitis with the everolimus/exemestane combination ten years after adjuvant whole-breast radiotherapy. *Radiat. Oncol.* 112, 449–450.
- Iyengar, P., Kavanagh, B.D., Wardak, Z., et al., 2014. Phase II trial of stereotactic body radiation therapy combined with erlotinib for patients with limited but progressive metastatic non-small-cell lung cancer. *J. Clin. Oncol.* 32 (34 December), 3824–3830.
- Jiang, Y., Mackley, H.B., Kimchi, E.T., et al., 2014. Phase I dose escalation study of capecitabine and erlotinib concurrent with radiation in locally advanced pancreatic cancer. *Cancer Chemother. Pharmacol.* 74 (1 July), 205–210.
- Kao, J., Packer, S., Vu, H.L., et al., 2009. Phase I study of concurrent sunitinib and image-guided radiotherapy followed by maintenance sunitinib for patients with oligometastases: acute toxicity and preliminary response. *Cancer* 115 (15 August), 3571–3580.
- Kao, J., Chen, C.T., Tong, C.C., et al., 2014. Concurrent sunitinib and stereotactic body radiotherapy for patients with oligometastases: final report of a prospective clinical trial. *Target. Oncol.* 9 (2 June), 145–153.
- Kao, J., Timmins, J., Ozao-Choy, J., Packer, S., 2016. Effects of combined sunitinib and extracranial stereotactic radiotherapy on bone marrow hematopoiesis. *Oncol. Lett.* 12 (3 September), 2139–2144.
- Katz, D.A., Abrams, R.A., Schlamb, J.S., et al., 2015. Radiosensitizing effect of anti-HER2/neu agents: report of 2 cases and review of the literature. *Prac. Radiat. Oncol.* 5, e61–e65.
- Kennecke, H., Berry, S., Wong, R., et al., 2012. Pre-operative bevacizumab, capecitabine, oxaliplatin and radiation among patients with locally advanced or low rectal cancer: a phase II trial. *Eur. J. Cancer.* 48 (1 January), 37–45.
- Kiess, A.P., Wolchok, J.D., Barker, C.A., et al., 2015. Stereotactic radiosurgery for melanoma brain metastases in patients receiving ipilimumab: safety profile and efficacy of combined treatment. *Int. J. Radiat. Oncol. Biol. Phys.* 92, 368–375.
- Kwon, E.D., Drake, C.G., Scher, H.I., 2014. CA184043 investigators. Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184043): a multicentre, randomised, double-blind, phase 3 trial. *Lancet Oncol.* 15 (7 June), 700–712.
- Lai, A., Tran, A., Nghiemphu, P.L., et al., 2011. Phase II study of bevacizumab plus temozolomide during and after radiation therapy for patients with newly diagnosed glioblastoma multiforme. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* 29, 142–148.
- Landry, J.C., Feng, Y., Cohen, S.J., et al., 2013. Phase 2 study of preoperative radiation with concurrent capecitabine, oxaliplatin, and bevacizumab followed by surgery and postoperative 5-fluorouracil, leucovorin, oxaliplatin (FOLFOX), and bevacizumab in patients with locally advanced rectal cancer: EOCG 3204. *Cancer.* 119 (8 April), 1521–1527.
- Lee, S.M., Lewanski, C.R., Counsell, N., et al., 2014. Randomized trial of erlotinib plus whole-brain radiotherapy for NSCLC patients with multiple brain metastases. *J. Natl. Cancer Inst.* 106 (7 July).
- Lefebvre, J.L., Pointreau, Y., Rolland, F., et al., 2013. Induction chemotherapy followed by either chemoradiotherapy or bioradiotherapy for larynx preservation: the TREMPILIN randomized phase II study. *J. Clin. Oncol.* 31 (7 March), 853–859. <https://doi.org/10.1200/JCO.2012.42.3988>. Epub 2013 Jan 22. Erratum in: *J Clin Oncol.* 2013 May 1;31(13):1702.
- Leibowitz-Amit, R., Joshua, A.M., 2012. Targeting the androgen receptor in the management of castration-resistant prostate cancer: rationale, progress, and future directions. *Curr. Oncol.* 19 (suppl 3), S22–31.
- Lin, J., Hoffman-Censits, J.H., Kelly, W.K., et al., 2017a. An exploratory study to investigate the immunomodulatory activity of radiation therapy in combination with pembrolizumab in patients with renal cell cancer. *J. Clin. Oncol.* 35 (suppl 6S) abstract 518.
- Lin, S.H., Lin, Y., Price, J., et al., 2017b. DETERRED: PD-L1 blockade to evaluate the safety of lung cancer therapy using carboplatin, paclitaxel, and radiation combined with MPDL3280A (atezolizumab) [abstract]. *J. Clin. Oncol.* 35 (Abstr nr 3064).
- Liniker, E., et al., 2016. Activity and safety of radiotherapy with anti-PD-1 drug therapy in patients with metastatic melanoma. *Oncology* 5 (9).
- Lledo, G., Huguet, F., Chibaudel, B., et al., 2016. Chemoradiotherapy with FOLFOX plus cetuximab in locally advanced oesophageal cancer: the GERCOR phase II trial ERAFOX. *Eur. J. Cancer.* 56 (March), 115–121.
- Lockhart, A.C., Reed, C.E., Decker, P.A., et al., 2014. Phase II study of neoadjuvant therapy with docetaxel, cisplatin, panitumumab, and radiation therapy followed by surgery in patients with locally advanced adenocarcinoma of the distal esophagus (ACOSOG Z4051). *Ann. Oncol.* 25 (5 May), 1039–1044.
- Lu, C.S., Liu, J.H., 2017. Pneumonitis in cancer patients receiving anti-PD-1 and radiotherapies: Three case reports. *Med. (Baltim.)* (96), e5747.
- Ly, D., Bagshaw, H.P., Anker, C.J., et al., 2015. Local control after stereotactic radiosurgery for brain metastases in patients with melanoma with and without BRAF mutation and treatment. *J. Neurosurg.* 123, 395–401.
- Ma, D.J., Galanis, E., Anderson, S.K., et al., 2015. A phase II trial of everolimus, temozolomide, and radiotherapy in patients with newly diagnosed glioblastoma: NCCTG N057K. *Neuro Oncol.* 17 (9 September), 1261–1269.
- Machiels, J.P., Sempoux, C., Scalliet, P., et al., 2007. Phase I/II study of preoperative cetuximab, capecitabine, and external beam radiotherapy in patients with rectal cancer. *Ann. Oncol.* 18 (4 April), 738–744.
- Magrini, S.M., Buglione, M., Corvò, R., et al., 2016. Cetuximab and radiotherapy versus cisplatin and radiotherapy for locally advanced head and neck cancer: a randomized phase II trial. *J. Clin. Oncol.* 34 (5 February), 427–435.
- Martinez, E., Martinez, M., Vinolas, N., et al., 2008. Feasibility and tolerability of the addition of erlotinib to 3D thoracic radiotherapy (RT) in patients with unresectable NSCLC: a prospective randomized phase II study. *J. Clin. Oncol.* 26 abstr. 7563.
- Martins, R.G., Parvathaneni, U., Bauman, J.E., et al., 2013. Cisplatin and radiotherapy with or without erlotinib in locally advanced squamous cell carcinoma of the head and neck: a randomized phase II trial. *J. Clin. Oncol.* 31 (11 April), 1415–1421.
- Marur, S., Li, S., Cmelak, A.J., et al., 2016. Phase II trial of induction chemotherapy followed by reduced-dose radiation and weekly cetuximab in patients with HPV-associated resectable squamous cell carcinoma of the oropharynx- ECOG-ACRIN cancer research group. *J. Clin. Oncol.* (December) JCO2016683300.
- Mathew, M., Tam, M., Ott, P.A., et al., 2013. Ipilimumab in melanoma with limited brain metastases treated with stereotactic radiosurgery. *Melanoma Res.* 23, 191–195.
- Mehta, M.P., Wang, D., Wang, F., et al., 2015. Veliparib in combination with whole brain radiation therapy in patients with brain metastases: results of a phase 1 study. *J. Neurooncol.* 122 (2 April), 409–417.
- Merten, R., Hecht, M., Haderlein, M., et al., 2014. Increased skin and mucosal toxicity in the combination of vemurafenib with radiation therapy. *Strahlenther. Onkol.* 190 (12), 1169–1172.
- Mesía, R., Henke, M., Fortin, A., et al., 2015. Chemoradiotherapy with or without panitumumab in patients with unresected, locally advanced squamous-cell carcinoma of the head and neck (CONCERT-1): a randomised, controlled, open-label phase 2 trial. *Lancet Oncol.* 16 (2 February), 208–220.
- Michaelson, M.D., Hu, C., Pham, H.T., et al., 2017. Phase I/II trial of a combination of paclitaxel and trastuzumab with daily irradiation or paclitaxel alone with daily irradiation following transurethral surgery for non cystectomy candidates with muscle invasive bladder cancer (trial NRG oncology RTOG 0524). *Int. J. Radiat. Oncol. Biol. Phys.* 97 (5:April), 995–1001.
- Midge, M.R., Guminski, A., Gutzmer, R., et al., 2015. Treatment with two different doses of sonidegib in patients with locally advanced or metastatic basal cell carcinoma (BOLT): a multicentre, randomised, doubleblind phase 2 trial. *Lancet Oncol.* 16, 716–728.
- Miura, Y., Suyama, K., Shimomura, A., et al., 2013. Radiation-induced esophagitis exacerbated by everolimus. *Case Rep. Oncol.* 6, 320–324.
- Moilanen, A., Riikonen, R., Oksala, R., et al., 2013. ODM-201—new generation anti-androgen with excellent antiandrogenic and antitumor activity in nonclinical models of CRPC. *Eur. J. Cancer* 49 (suppl 2) abstr 685.
- Narayan, V., Vapiwala, N., Mick, R., et al., 2017. Phase 1 trial of everolimus and radiation therapy for salvage treatment of biochemical recurrence in prostate cancer patients following prostatectomy. *Int. J. Radiat. Oncol. Biol. Phys.* 97 (2), 355–361.
- Nishino, M., Giobbie-Hurder, A., Hatabu, H., et al., 2016. Incidence of programmed cell death 1 Inhibitor-Related pneumonitis in patients with advanced cancer: a systematic review and meta-analysis. *JAMA Oncol.* 2 (12), 1607–1616. <https://doi.org/10.1001/jamaoncol.2016.2453>.
- Nogué, M., Salud, A., Vicente, P., et al., 2011. Addition of bevacizumab to XELOX induction therapy plus concomitant capecitabine-based chemoradiotherapy in magnetic resonance imaging-defined poor-prognosis locally advanced rectal cancer: the AVACROSS study. *Oncologist* 16 (5), 614–620.
- Patel, K.R., Chowdhary, M., Switchenko, J.M., et al., 2016. BRAF inhibitor and stereotactic radiosurgery is associated with an increased risk of radiation necrosis. *Melanoma Res.* 26 (4 August), 387–394.
- Pesce, G.A., Klingbiel, D., Ribi, K., et al., 2012. Outcome, quality of life and cognitive function of patients with brain metastases from non-small cell lung cancer treated with whole brain radiotherapy combined with gefitinib or temozolomide. A randomised phase II trial of the swiss group for clinical cancer research (SAKK 70/03). *Eur. J. Cancer* 48 (3 February), 377–384.
- Peuvrel, L., Ruellan, A.L., Thillays, F., et al., 2013. Severe radiotherapy-induced extra-cutaneous toxicity under vemurafenib. *Eur. J. Dermatol.* 23 (6), 879–881.
- Pollom, E.L., Bui, T.T., Chang, A.L., et al., 2015. Concurrent vismodegib and radiotherapy for recurrent, advanced basal cell carcinoma. *JAMA Dermatol.* 151, 998–1001.
- Raleigh, D.R., Algazi, A., Arron, S.T., et al., 2015. Induction hedgehog pathway inhibition followed by combined-modality radiotherapy for basal cell carcinoma. *Br. J. Dermatol.* 173, 544–546.
- Ramella, S., Alberti, A.M., Cammilluzzi, E., et al., 2013. Erlotinib and concurrent chemoradiation in pretreated NSCLC patients: radiobiological basis and clinical results. *Biomed. Res. Int.* 2013 403869.
- Reiss, K.A., Herman, J.M., Zahurak, M., et al., 2015. A phase I study of veliparib (ABT-888) in combination with low-dose fractionated whole abdominal radiation therapy in patients with advanced solid malignancies and peritoneal carcinomatosis. *Clin. Cancer Res.* 21 (1 January), 68–76.
- Rodon, J., Tawbi, H.A., Thomas, A.L., et al., 2014. A phase I, multicenter, open-label, first-inhuman, dose-escalation study of the oral smoothed inhibitor sonidegib (LDE225) in patients with advanced solid tumors. *Clin. Cancer Res.* 20, 1900–1909.
- Ruhstaller, T., Pless, M., Dietrich, D., et al., 2011. Cetuximab in combination with chemoradiotherapy before surgery in patients with resectable, locally advanced esophageal carcinoma: a prospective, multicenter phase IB/II trial (SAKK 75/06). *J. Clin. Oncol.* 29 (6 February), 626–631.
- Ruhstaller, T., Thuss-Patience, P., Hayoz, S., et al., 2018. Neoadjuvant chemotherapy

- followed by chemoradiation and surgery with and without cetuximab in patients with resectable esophageal cancer: a randomized, open-label, phase III trial (SAKK 75/08). *Ann. Oncol.* 29 (6), June, 1386–1393.
- Saad, et al., 2012. American Urology Association Conference. Abstract 682 (Oral presentation).
- Safra, H., Dipertillo, T., Akerman, P., et al., 2007. Phase I/II study of trastuzumab, paclitaxel, cisplatin and radiation for locally advanced, HER2 overexpressing, esophageal adenocarcinoma. *Int. J. Radiat. Oncol. Biol. Phys.* 67, 405–409.
- Safra, H., Suntharalingam, M., Dipertillo, T., et al., 2008. Cetuximab with concurrent chemoradiation for esophagogastric cancer: assessment of toxicity. *Int. J. Radiat. Oncol. Biol. Phys.* 70 (2) February, 391–395.
- Salazar, R., Capdevila, J., Laquente, B., et al., 2015. A randomized phase II study of capecitabine-based chemoradiation with or without bevacizumab in resectable locally advanced rectal cancer: clinical and biological features. *BMC Cancer* 15 (February), 60.
- Sandomenico, C., Costanzo, R., Carillio, G., et al., 2012. Bevacizumab in non small cell lung cancer: development, current status and issues. *Curr. Med. Chem.* 19, 961–971.
- Sarkaria, J.N., Galanis, E., Wu, W., et al., 2010. Combination of temsirolimus (CCI-779) with chemoradiation in newly diagnosed glioblastoma multiforme (GBM) (NCCTG trial N027D) is associated with increased infectious risks. *Clin. Cancer Res.* 16 (22) November, 5573–5580.
- Sarkaria, J.N., Galanis, E., Wu, W., et al., 2011. North Central cancer treatment group phase I trial N057K of everolimus (RAD001) and temozolomide in combination with radiation therapy in patients with newly diagnosed glioblastoma multiforme. *Int. J. Radiat. Oncol. Biol. Phys.* 81 (2) October, 468–475.
- Satzger, I., Degen, A., Asper, H., et al., 2013. Serious skin toxicity with the combination of BRAF inhibitors and radiotherapy. *J. Clin. Oncol.* 31, e220–e222.
- Scher, H.I., Fizazi, K., Saad, F., et al., 2012. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl. J. Med.* 367, 1187–1197.
- Schulze, B., Meissner, M., Ghanaati, S., et al., 2016. Hedgehog pathway inhibitor in combination with radiation therapy for basal cell carcinomas of the head and neck. *Strahlenther. Onkol.* 192 (Jan. (1)), 25–31.
- Segal, N.H., Kemeny, N.E., Cercek, A., et al., 2016. 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. *J. Clin. Oncol.* 34 (suppl; abstr 3539).
- Smith, M.R., Saad, F., Chowdhury, S., 2018. Apalutamide treatment and metastasis-free survival in prostate cancer. *N Engl. J. Med.* 378 (15) April, 1408–1418.
- Socinski, M.A., Stinchcombe, T.E., Moore, D.T., et al., 2012. Incorporating bevacizumab and erlotinib in the combined-modality treatment of stage III non-small-cell lung cancer: results of a phase I/II trial. *J. Clin. Oncol.* 30, 3953–3959.
- Spigel, D.R., Hainsworth, J.D., Yardley, D.A., et al., 2010. Tracheoesophageal fistula formation in patients with lung cancer treated with chemoradiation and bevacizumab. *J. Clin. Oncol.* 28, 43–48.
- Spigel, D.R., Bendell, J.C., McCleod, M., et al., 2012. Phase II study of bevacizumab and chemoradiation in the preoperative or adjuvant treatment of patients with stage II/III rectal cancer. *Clin. Colorectal Cancer* 11 (1) March, 45–52.
- Staeher, M., Haseke, N., Nuhn, P., et al., 2011. Simultaneous anti-angiogenic therapy and single-fraction radiosurgery in clinically relevant metastases from renal cell carcinoma. *BJU Int.* 108 (5) September, 673–678.
- Staeher, M., Haseke, N., Stadler, T., et al., 2012. Feasibility and effects of high-dose hypofractionated radiation therapy and simultaneous multi-kinase inhibition with sunitinib in progressive metastatic renal cell cancer. *Urol Oncol.* 30 (3) May–June, 290–293.
- Stefan, D., Popotte, H., Stefan, A., et al., 2016. Vemurafenib and concomitant stereotactic radiation for the treatment of melanoma with spinal metastases: a case report. *Reports Prac. Oncol. Radiother.* 21, 76–80.
- Sun, P.L., Li, B., YE, Q.F., 2012. Effect of neoadjuvant cetuximab, capecitabine and radiotherapy for locally advanced rectal cancer: results of a phase II study. *Int. J. Colorectal Dis.* 27 (10) October, 1325–1332.
- Suntharalingam, M., Winter, K., Ison, D., et al., 2017. Effect of the addition of cetuximab to paclitaxel, cisplatin, and radiation therapy for patients with esophageal cancer: the NRG oncology RTOG 0436 phase 3 randomized clinical trial. *JAMA Oncol.* 3 (11) November, 1520–1528.
- Tao, Y., Auperin, A., Sire, C., et al., 2018. Improved outcome by adding concurrent chemotherapy to cetuximab and radiotherapy for locally advanced head and neck carcinomas: results of the GORTEC 2007-01 phase III randomized trial. *J. Clin. Oncol.* (June). <https://doi.org/10.1200/JCO.2017.76.2518>. JCO2017762518.
- Tazi, K., Hataway, A., Chiuzan, C., Shirai, K., 2015. Survival of melanoma patients with brain metastases treated with ipilimumab and stereotactic radiosurgery. *Cancer Med.* 4, 1–6.
- Tomblin, M.B., Goldman, B.H., Thomas Jr, C.R., et al., 2012. Cetuximab plus cisplatin, irinotecan, and thoracic radiotherapy as definitive treatment for locally advanced, unresectable esophageal cancer: a phase-II study of the SWOG (S0414). *J. Thorac. Oncol.* 7 (5) May, 906–912.
- Tong, C.C., Ko, E.C., Sung, M.W., et al., 2012. Phase II trial of concurrent sunitinib and image-guided radiotherapy for oligometastases. *PLoS One* 7 (6), e36979.
- Trotti, A., Harris, J., Gillison, M., et al., 2018. NRG-RTOG 1016: phase III trial comparing Radiation/Cetuximab to Radiation/Cisplatin in HPV-related cancer of the oropharynx. *Int. J. Radiat. Oncol. Biol. Phys. Supplement*.
- Valentini, V., De Paoli, A., Gambacorta, M.A., et al., 2008. Infusional 5-fluorouracil and ZD1839 (gefitinib-iressa) in combination with preoperative radiotherapy in patients with locally advanced rectal cancer: a phase I and II trial (1839IL/0092). *Int. J. Radiat. Oncol. Biol. Phys.* 72 (3) November, 644–649.
- Van den Heuvel, M.M., Uytendinck, W., Vincent, A.D., et al., 2014. Additional weekly cetuximab to concurrent chemoradiotherapy in locally advanced non-small cell lung carcinoma: efficacy and safety outcomes of a randomized, multi-center phase II study investigating. *Radiother. Oncol.* 110 (1) January, 126–131.
- Velenik, V., Ocvirk, J., Music, M., et al., 2011. Neoadjuvant capecitabine, radiotherapy, and bevacizumab (CRAB) in locally advanced rectal cancer: results of an open-label phase II study. *Radiat. Oncol.* 6 (August), 105.
- Vivaldi, C., Bucciati, G., Musettini, F., et al., 2016. TRUST: phase II trial of induction chemotherapy with FOLFOXIRI + bevacizumab followed by chemo-radiotherapy + bevacizumab and surgery in locally advanced rectal carcinoma. *Ann. Oncol.* 27 (suppl 6, October).
- Wang, Z., Zhu, X.X., Wu, X.H., et al., 2014. Gefitinib combined with stereotactic radiosurgery in previously treated patients with advanced non-small cell lung cancer. *Am. J. Clin. Oncol.* 37 (2) April, 148–153.
- Welsh, J.W., Komaki, R., Amini, A., et al., 2013. Phase II trial of erlotinib plus concurrent whole-brain radiation therapy for patients with brain metastases from non-small-cell lung cancer. *J. Clin. Oncol.* 31 (7) March, 895–902.
- Willett, C.G., Duda, D.G., di Tomaso, E., et al., 2009. Efficacy, safety, and biomarkers of neoadjuvant bevacizumab, radiation therapy, and fluorouracil in rectal cancer: a multidisciplinary phase II study. *J. Clin. Oncol.* 27 (18) June, 3020–3026.
- William, N.L., Wuthrick, E.J., Kim, H., et al., 2017. Phase I study of ipilimumab combine with whole brain radiation therapy Or radiosurgery for melanoma patients with brain metastases. *Int. J. Radiat. Oncol. Biol. Phys.* 99 (1) September, 22–30.
- Wirsching, H.G., Tabatabai, G., Roelcke, U., et al., 2018. Bevacizumab plus hypofractionated radiotherapy versus radiotherapy alone in elderly patients with glioblastoma: the randomized, open-label, phase II ARTE trial. *Ann. Oncol.* 29 (6) June, 1423–1430.
- Wolf, A., Zia, S., Verma, R., Pavlick, A., 2016. Impact on overall survival of the combination of BRAF inhibitors and stereotactic radiosurgery in patients with melanoma brain metastases. *J. Neurooncol.* 127 (3) May, 607–615.
- Xu, T., Liu, Y., Dou, S., et al., 2015. Weekly cetuximab concurrent with IMRT aggravated radiation-induced oral mucositis in locally advanced nasopharyngeal carcinoma: results of a randomized phase II study. *Oral Oncol.* 51 (9) September, 875–879.
- Yuasa, T., Kitsukawa, S., Sukegawa, G., et al., 2013. Early onset recall pneumonitis during targeted therapy with sunitinib. *BMC Cancer* 2 (13) January, 3.
- Zhao, C., Lin, L., Liu, J., et al., 2016. A phase II study of concurrent chemoradiotherapy and erlotinib for inoperable esophageal squamous cell carcinoma. *Oncotarget.* 7 (35) August, 57310–57316.
- Zhu, M.L., Horbinski, C.M., Garzotto, M., et al., 2010. Tubulin-targeting chemotherapy impairs androgen receptor activity in prostate cancer. *Cancer Res.* 70, 7992–8002.
- Zhuang, H., Yuan, Z., Wang, J., et al., 2013. Phase II study of whole brain radiotherapy with or without erlotinib in patients with multiple brain metastases from lung adenocarcinoma. *Drug. Des. Devel. Ther.* 7 (October), 1179–1186.