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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

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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

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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 ≥ 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-RTOG 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% wih 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 consistant 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 ≥ 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 ≥ 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. (Van den 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 ≥ 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 ≥ 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 ≥ G4 toxicity, while in the SAKK 41/07 trial (Helbling et al., 2013) ≥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 informations exist 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 ≥ 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 ≥ 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), ≥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-esophageal 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%	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	Dysphagia: 4% vs 6%	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) Manteinance – Ctx (6 months)	oral mucositis: 54% 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% −54 Gy group: mucositis: 30% dysphagia: 15% acneiform rash: 12% radiation dermatitis: 7%	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
			−57 EC −3 gastric cancer	3DCRT 50.4 Gy/28 fx	CT- RT (Carboplatin + PAC) + Ctx	cutaneous rash: 25% esophagitis: 15%		
(Lledo et al., 2016)	Phase II	79	stage III EC or GEJC	3DCRT 50.4 Gy/30 fx	CT- RT (FOLFOX) + Ctx	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%		
(Mesía 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 nasopharingeal 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 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 ≥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 + lHRH 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	diarrohea: 20% myocardial ischemia: 5% bleeding: 10% infection: 5%	5%	40%

Abbreviations: A = doxorubicin; AEs = adverse events; AI: aromatase-inhibitors; BC = breast carcinoma; C = cyclofosfamide; 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 neaoadjuvant 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 L A SSCHN 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 L A 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 ≥ 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 R	90	3DCRT 45 Gy/25 fx	CT-RT (CAP) + /- BEV	13% vs 16% (P = 0.70)	0	7% vs 7%
(Kennecke et al., 2012)	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%
(Nogué 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 àCT-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 neoadjuvat 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
(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	N.R
(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 metastaticNSCLC	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.
(Blaszkowsky 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 = brian 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 ehanced 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 ≥ G3 adverse event and 23% having a G4 adverse event; in the RTOG trial, combining Everolimus with conventional CT-RT leaded 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 immunosoppressive 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. Hovewer, 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 ≥ G3 treatment-related adverse event was lymphopenia (92%), mucositis (functional 62%, clinical 31%), pain in the oral cavity (31%) and disphagia (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 ≥ G3 cronic toxicity. Therefore at daily doses ≤ 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 ≥ 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 ≥ G2 more frequently than treatment with Dabrafenib (40% versus 26%, P = 0.07), but G3 toxicities were similar. Notably, radiodermatitis ≥ 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.

Eilsmark et al. (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. Forshner et al. (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 hepatoxicity (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)	14% (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
			Lateral canthus BCC	6-MeV and 9-MeV electrons 51 Gy/17 fx	Vismodegib and concurrent RT	0	0	0
(Raleigh et al., 2015)	Case report	1	Right ear BCC	IMRT 70 Gy/35 fx	Vismodegib and concurrent RT	0	0	0
(Schulze, 2016)	Case series	4	Facial BCC	Case 1: 3DCRT 54.0 Gy/27 fx + interstitial HDR BRT boost of 12 Gy/2 fx	Vismodegib and concurrent RT	0	0	0
				Case 2: 3DCRT 66 Gy/33 fx		0	0	0
				Case 3: HRT 55 Gy/20 fx		0	0	0
				Case 4: HRT 55 Gy/20 fx		0	0	0
(Amici et al., 2015)	Case report	2	laBCC	3DCRT 45 Gy/15 fx	RT between Vismodegib cycles	0	0	0
				Contact RT 40 Gy/10 fx (2 fx per week)	RT after Vismodegib	0	0	N.A.
(Chang, 2014)	Open label, multicentre trial	119 (***)	laBCC (62) or mBCC (57)	N.R.	Vismodegib after RT	muscle spams, 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 intralesional 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 (≥ 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, receving Azetolizumab (a new anti PD-L1 antibody) as consolidation treatment with Carboplatin and Paclitaxel following stadard 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 administrated 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 17α-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.

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