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

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A B S T R A C T

Over the past century, technologic advances have promoted the evolution of radiation therapy into a precise treatment modality allowing for the maximal administration of dose to tumors while sparing normal tissues. In parallel with this technological maturation, the rapid expansion in understanding the basic biology and heterogeneity of cancer has led to the development of several compounds that target specific pathways. Many of them are in advanced steps of clinical development for combination treatments with radiotherapy, and can be incorporated into radiation oncology practice for a personalized approach to maximize the therapeutic gain. This review describes the rationale for combining novel agents with radiation, and provides an overview of the current landscape focused on treatment efficacy.

1. Introduction

In many solid tumors, radiotherapy (RT) is combined with chemotherapeutic agents to improve treatment efficacy. This approach, initially described by Steel and Peckham in 1979 (Steel and Peckham, 1979), is based on the premise that such combinations have spatial cooperation as the former targets the primary tumor site, whereas the latters target tumor cells outside the tumor irradiation field (micrometastases). A further effect depends on the interactions between RT and chemotherapy (CT) that occur at multiple levels. The better understanding of the genetic framework of specific tumors, as well as contributions of tumor microenvironment to tumor growth and

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treatment response, molecular mechanisms of signaling transduction and the role of immune modulation on treatment outcomes, have improved strategies to target these distinctive tumors features through the development of new molecularly targeted drugs as well as immunotherapeutic agents. Coupled with biomarkers of response (clinical, molecular, or imaging), this breakthrough can drive the precision medicine process by incorporating agents that molecularly target drivers of radiation resistance into radiation oncology practice with the aim of maximize the therapeutic gain from chemoradiotherapy (CT-RT), while causing minimal collateral normal tissue damage. In this Review, we describe the rationale of the association of RT and novel systemic agents for multiple disease sites and summarize the updated results of clinical trials using this strategy. Additionally, we discuss potential opportunities for and challenges to the use of RT and new compounds, along with its introduction into routine clinical practice, and examine areas in which further research and clinical evidence is warranted. The first part is focused on the treatment efficacy, while safety issues are discussed in a parallel manuscript.

2. Monoclonal antibodies

2.1. EGFR inhibitors: Cetuximab and Panitumumab

The epidermal growth factor receptor (EGFR) is a receptor tyrosine kinase consisting of an extracellular domain, a single transmembrane region, and a cytoplasmic kinase domain (Gullick et al., 1985). Phosphorylation of the EGFR stimulates intracellular downstream pathways leading to cellular proliferation, arrest of apoptosis, neovascularization and activation of cancer invasion and metastasis. The mechanism of radiosensitization with EGFR inhibitors is complex: ionizing radiation induces the nuclear translocation of EGFR, where it associates with the catalytic subunit of DNA-dependent protein kinase (DNA-PKcs), stimulating the repair of double-strand breaks. The use of EGFR inhibitors hinders DNA repair by blocking the nuclear translocation of EGFR and hence increases the radiosensitivity (Liccardi et al., 2014). EGFR's role in the radiation response includes also the activation of prosurvival pathways and enhances cell proliferation (Huang and Harari, 2000; Nyati et al., 2006; Chen and Nirodi, 2007).

In squamous cell carcinoma of the head and neck (SCCHN) a first randomized trial demonstrated an improvement in the duration of control of locoregional disease (the primary endpoint of the study) and overall survival (OS) (secondary endpoint) adding Cetuximab to RT versus RT alone, especially in younger patients with oropharynx primary treated with accelerated RT (Bonner et al., 2006). This benefit was not so clear when Cetuximab was tested in combination with CT-RT: while Cetuximab plus Cisplatin-RT did not improve outcomes for patients with stage III/IV SCCHN compared to Cisplatin-RT in the phase III RTOG 0522 trial (Ang et al., 2014), the recently published GORTEC 2007-01 study (Tao et al., 2018) demonstrated the effect of adding concomitant CT to Cetux-RT, by increasing the 3-year progression-free survival (PFS) (primary endpoint) rate from 40.5% to 52.5% (P = 0.015), but no significant advantage in OS (HR, 0.80; P = .11) in patients with oral cavity, oro/hypopharynx and larynx cancers (mostly HPV-negative) with no or limited nodal spread (≤N2b). Lefebre et al. (Lefebvre et al., 2013) attempted to replace CT with Cetuximab as a radiosensitizer, and compared the efficacy and safety of induction CT followed by CT-RT or bioradiotherapy Cetuximab-RT in terms of larynx preservation (primary endpoint): no evidence that one treatment was superior to the other was found. A phase II trial (Magrini et al., 2016) compared RT with concomitant Cisplatin versus concomitant Cetuximab as first-line treatment of locally advanced (LA) SCCHN having compliance, toxicity, and efficacy as primary endpoints: similar patterns of locoregional control, failure and survivals were found between the treatment arms. The same authors in a subgroup analysis (Buglione et al., 2017) detected a lower efficacy of Cetuximab in patients with p16/Human Papilloma Virus (HPV+) oropharyngeal squamous cell carcinoma (OPSCC). This finding was confirmed in the NRG-RTOG 1016, a non-inferiority Phase III Trial comparing RT with Cetuximab to RT with Cisplatin in HPV + OPSCC, that revealed an inferior OS (primary endpoint) and PFS in the former group (Trotti et al., 2018).

(Argiris et al., 2010) incorporated Cetuximab into the induction therapy and subsequent CT-RT of head and neck cancer with promising 3-year PFS and OS (70% and 74%, respectively), both primary endpoints of the study. Conflicting data emerged when Cetuximab-RT was preceded by induction CT in a similar setting: the GORTEC 2007-02 phase III trial (Geoffrois et al., 2018); (Marur et al. (2016)) evaluated Cetuximab in induction and concomitant phase in the subset of p16/HPV + OPC: after median follow-up of 35.4 months, 2-year PFS (primary endpoint) and OS rates were 80% and 94%, respectively, for patients who achieved a primary site clinical complete response to induction CT treated with 54 Gy of RT, and 96% and 96%, respectively, for those (with < T4, < N2c) who were treated with RT dose reduction (≤ 54 Gy).

In locally advanced non small cell lung cancer (LA NSCLC) available data are based mainly on phase II and randomized controlled trials, where Cetuximab has been investigated in association with concurrent CT-RT without advantage in OS (Blumenschein et al., 2011; Govindan et al., 2011; van den Heuvel et al., 2014; Bradley et al., 2015; Walraven et al., 2016). As far as gastrointestinal cancers are concerned, preliminary phase I/II trial evaluated the addition of Cetuximab to CT-RT (Hofheinz et al., 2006; Machiels et al., 2007); (Dwedney et al. (2012)) evaluated 165 high-risk rectal cancer patients who randomly received 4 cycles of Capecitabine/Oxaliplatin (CAPOX) followed by Capecitabine CT-RT, surgery, and adjuvant CAPOX (4 cycles) versus the same regimen plus weekly Cetuximab (CAPOX + C), and found no advantage in the primary endpoints (CR or PFS), but a significant improvement of radiological response and OS.

In esophageal cancer, two phase II trials (Safran et al., 2008; Lledo et al., 2016) evaluated the safety and efficacy of concomitant Cetuximab added to CT-RT in locally advanced inoperable patients: Safran et al. (Safran et al., 2008)(Lledo et al. (2016))(Crosby et al. (2013)) observed a shorter (22.1 months vs 25.4 months; P = 0.035) median OS (primary endpoint) in patients who received CT-RT plus Cetuximab compared to those who received CT-RT. Similarly, a phase III trial (Suntharalingam et al., 2017) evaluated the benefit of Cetuximab added to concurrent CT-RT therapy and found that it did not improve OS (primary endpoint). In locally advanced, but still resectable, esophageal carcinoma, the SAKK 75/08 trial (Ruhstaller et al., 2018) compared CT-RT followed by surgery with or without neoadjuvant and adjuvant Cetuximab: median PFS (primary endpoint) was not significantly improved with the addition of Cetuximab (2.9 years versus 2 years, respectively) [P = 0.13], while median OS was 5.1 years versus 3.0 years for Cetuximab and control, respectively (P = 0.055). Other studies evaluated Cetuximab as induction treatment and its subsequent association with neoadjuvant or radical CT-RT, with wide rates of pCR (6–40%) (Tomblyn et al., 2012; Ruhstaller et al., 2011). The controversial findings of these trials point to little benefit to current EGFR-targeted agents in an unselected patient population, and highlight the need for predictive biomarkers in the treatment of esophageal cancer.

(Giralt et al. (2015)); (Siu et al. (2016)) compared PFS in patients with LA SCCHN treated with standard-fractionation RT plus high-dose Cisplatin vs accelerated-fractionation RT plus Panitumumab: with a median follow-up of 46 months, 2-year PFS of the experimental arm was not superior to Cisplatin plus standard-fractionation RT (73% [95% CI, 65%–79%] versus 76% [95% CI, 68%–82%], respectively (P = 0.83), and non-inferiority was not proven. Mesia et al. (Mesía et al., 2015) randomised patients with unresected LA SCCHN to receive CT—RT plus Panitumumab versus CT—RT alone: again, no significant difference between the two groups in terms of 2-year loco-regional control – the primary endpoint of the study – was found (61% [95% CI, 50–71] vs 68% [95% CI, 54–78], respectively).

In gastrointestinal cancers Panitumumab has been tested mainly in

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Table 1
Major studies for RT and Cetuximab/Panitumumab.

Author and year	Study type	N	Tumor site and stage (if available)	RT technique/dose/fractionation	Combination (concomit, other)	Primary Endpoint	Treatment outcome
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	LRC	Median LRC: 24.4 VS 14.9 months (P = 0.005) 5-yy OS: 45.6% vs 36.4% (P = 0.018)
Ang et al. (2014)	Phase III	940	LA-SCCHN	-ART 72 Gy/42 fx or -IMRT 70 Gy/35 fx	CT-RT (CDDP) +/- Ctx	PFS	3-yy PFS: 72.8% vs 49.2% (P < .001) 3-yy OS: 85.6% vs 60.1% (P < .001
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	PFS	3-yy PFS: 52.3% vs 40.5% (P = .015) 3-yy OS: 60.8% vs 54.9% (P = 0.11)
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	LP	3-months LP: 95% vs 93% (P = NS) 18-months OS: 92% vs 89% (P = NS)
Magrini et al. (2016)	Phase II R	35	LA-SCCHN	3DCRT/IMRT 70 Gy/35 fx	CT-RT (CDDP) +/- Ctx	LC	2-yy LC: 100% vs 72.9% (P = NS) 2-yy OS: 100% vs 77.8% (P = NS)
Trotti et al. (2018)	Phase III	805	OPSCC HPV+	IMRT 70 Gy/35 fx	RT + CDDP vs RT + Ctx	OS	5-yy OS: 84.6% vs 77.9% (HR 1.45; 95% CI 1.03-2.05) 5-yy PFS: 78.4% vs 67.3% (HR 1.72; 95% CI 1.29-2.29)
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)	PFS	3-yy PFS: 70% 3-yy OS: 74%
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)	PFS	Median PFS: 12.5 vs 11.5 months (P = 0.74) Median OS: 22.8 vs 24.6 months (P = 0.48)
Marur (2017)	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)	PFS	For 54 Gy −2-yy PFS: 80% −2-yy OS: 94%
Govinda et al.n (2011)	Phase II R	101	Stage III NSCLC	3DCRT 70 Gy/35 fx	CT- RT (Carboplatin + PEM) +/- Ctx	OS	18-month OS: 58% vs 54% (P = .667)
Van den Heuvel et al. (2014)	Phase II R	102	Stage III NSCLC	ART 66 Gy/24 fx	CT-RT (CDDP) +/- Ctx	LCR	LRC: 84% vs 92% (P = 0.36) 1 yy OS: 82% vs 71% (P = 0.99)
Bradley et al. (2015)	Phase III	544	Stage III NSCLC	60 Gy/30 fx vs 74 Gy/37 fx	CT- RT (Carboplatin + PAC) +/- Ctx	OS	Median OS: 25 vs 24 months (P = 0.29)
Walraven et al. (2016)	Phase II R	102	Stage II-III NSCLC	ART 66 Gy/24 fx	CT-RT (CDDP) +/- Ctx	OS	Median OS: 33 vs 30 months (P = 0.722) 2-yy OS: 60.8% vs 58.8% (P = 0.840) 5-yy OS: 37.3% vs 37.3% (P = 1.000)
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	CR	CR: 14% vs 18% (P = .574) pCR: 15% vs 18% (P = .453)
Safran et al. (2008)	Phase II	60	−57 esophageal cancer −3 gastric cancer	3DCRT 50.4 Gy/28 fx	CT- RT (Carboplatin + PAC) + Ctx	Safety/Efficacy	CCR: 70%

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Table 1 (*continued*)

Author and year	Study type	N	Tumor site and stage (if available)	RT technique/dose/fractionation	Combination (concomit, other)	Primary Endpoint	Treatment outcome
Lledo et al. (2016)	Phase II	79	Stage III EC or GEJC	3DCRT 50.4 Gy/30 fx	FOLFOX) + Ctx	ORR	ORR: 77% pCR: 40% Median OS: 21.6 months Median PFS: 11.3 months
Crosby et al. (2013)	Phase II -III	258	stage I-III EC	3DCRT 50 Gy/25 fx	CT-RT (CDDP + 5-FU) +/- Ctx	OS	Median OS: 25.4 vs 22 months (P = 0.035)
Suntharalingam et al. (2017)	Phase III	344	T3-4 and or N + EC	3DCRT 50.4 Gy/28 fx	CT-RT (CDDP + PAC) +/- Ctx	OS	2-yy OS: 44% vs 45% 3-yy OS: 28% vs 34% (P = .47)
Ruhstaller et al. (2011)	Phase III	300	cT3-4a (90% cN+) EC	3DCRT 45 Gy/25 fx	Induction CT→ CT-RT (CDDP + TXT) +/- Ctx → S	PFS	Median PFS: 2.9 vs 2 years (P = 0.13) Median OS: 5.1 vs 3 years (P = 0.055)
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)	LRC	2-yy LRC: 61% vs 51% (P = 0.06) 2-yy OS: 71% vs 63% (p = 010)
Siu et al. (2016)	Phase III	315	LA-SCCHN	3DCRT/IMRT 70 Gy/ 35 fx in 7 weeks vs 70 Gy/ 35 fx in 6 weeks	CT-RT (CDDP) vs CT-RT (PAN)	PFS	2-yy PFS: 73% vs 76% (P = .83) 2-yy OS: 85% vs 88% in arm B (P = .66)
Mesia et al. (2015)	Phase II R	150	LA-SCCHN	3DCRT/IMRT 70-72 Gy/ 30-32 fx	CT-RT (CDDP) +/- PAN	LRC	2-yy LRC: 68% vs 61% (HR = 0.66)
Helbling et al. (2013)	Phase II R	68	LARC	3DCRT/IMRT 45 Gy/25 fx	Neoadjuvant CT-RT (CAP) +/- PAN	pNC/CR	pNC/CR: 32% vs 53%

Abbreviations: ART = accelerated radiotherapy; CAP = Capecitabine; CAPOX = Capecitabine + Oxaliplatin; CDDP = Cisplatin; CR = complete response; CT = chemotherapy; CT-RT = chemoradiotherapy; Ctx = Cetuximab; IMRT = intensity modulated radiotherapy; DFS = disease-free survival; EC = esophageal carcinoma; fx = fractions; GEJC = gastro-esophageal junction carcinoma; IRI = Irinotecan; LARC = locally advanced rectal cancer; LC = local control; LRC = loco-regional control; LP = larynx preservation; LPFS = local progression-free survival; LR = local relapse; NSCLC = non small cell lung cancer; ORR = objective response rate; OPSCC = oropharingeal squamous cell carcinoma; OS = overall survival; PAC = Paclitaxel; PAN = Panitumumab; PEM = Pemetrexed; pCR = pathologic complete response; PFS = progression-free survival; pNC = pathologic near-complete response; R = randomized; RT = radiotherapy; 3DCRT = 3D conformal radiotherapy; RR = response rate; TPF = Docetaxel/Cisplatin/Fluorouracil, TXT = Taxotere.

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phase II trials for locally advanced esophageal cancer (LAEC) and LARC in neoadjuvant setting associated to CT-RT, with promising results: in the ACOSOG Z4051 trial (Lockhart et al., 2014) the rate of pathologic response (primary endpoint) and near pathologic response (secondary endpoint) was 53.7%, exceeding the prespecified thresholds, when Panitumumab was added to Docetaxel-Cisplatin based CT-RT; in the SAKK 41/07 trial the addition of Panitumumab to neoadjuvant CT-RT resulted in a high pNC/CR rate (primary endpoint), mostly grade 3 DC (Helbling et al., 2013).

Summary: currently Cetuximab is strongly recommended in LA SSCHN cancer patients unfit for standard CT, while the association of Cetuximab to CT-RT has been proven superior to CT-RT only in selected patients. In LAEC, the addition of Cetuximab to CT-RT cannot be recommended, as a trend toward improved outcomes was seen only in patients with locally advanced, but still resectable disease. Panitumumab should be not routinely administered in association with RT since the only randomized trial that demonstrated a clinical benefit evaluated only few patients with LARC. Table 1 summarizes major clinical trials of Cetuximab and RT for different tumor sites.

2.2. HER2 inhibitors: trastuzumab and Pertuzumab

Human epidermal growth receptor factor 2 (HER2) targeting immunotherapeutic agents, comprising of HER2 specific humanized monoclonal antibodies Trastuzumab and Pertuzumab have acquired a central position as targeted anticancer modalities and are currently being extensively studied (Moasser and Krop, 2015). Trastuzumab consists of two antigen-specific sites that bind to the juxta-membrane portion of the extracellular domain of the HER2 receptor and that prevent the activation of its intracellular tyrosine kinase (Hudis and Clifford., 2007). Several possible mechanisms by which Trastuzumab might decrease signaling include prevention of HER2-receptor dimerization, increased endocytotic destruction of the receptor, inhibition of shedding of the extracellular domain, and immune activation (Valabrega et al., 2007). Preclinical models suggested that Trastuzumab recruits immune effector cells that are responsible for antibody-dependent cytotoxicity (Weiner and Adams, 2000). Studies in animal models of breast cancer in which HER2 is overexpressed indicate that angiogenesis may be inhibited by Trastuzumab, which induces normalization and regression of the vasculature by modulating proangiogenic and antiangiogenic factors (Petit et al., 1997; Viloria-Petit et al., 2001). Pertuzumab, a newer antibody that binding HER2 near the center of domain II appears to be more efficient due to increased inhibition of hetero-dimerization (Badache and Hynes, 2004). Despite the widespread concomitant use of both Trastuzumab and RT in HER2-positive breast cancer, this combination underwent only limited investigation in the context of clinical trials (Belkacémi et al., 2008; Halyard et al., 2009; Perez et al., 2008; Meattini et al., 2014). In vitro studies showed that Trastuzumab enhances radiosensitivity (Azria et al., 2003; Pietras et al., 1999). Clinical data provided evidence for a radio-sensitizing effect in breast cancer and a good safety profile of combination with RT (Horton et al., 2010). Even if there is not a direct comparison between concomitant and sequential schedules, combined results of two trials (B-31 and N9831) that compared adjuvant CT with or without concurrent Trastuzumab in women with surgically removed HER2-positive breast cancer showed an absolute difference in disease-free survival (DFS) (primary endpoint) between the Trastuzumab group and the control group of 12 percent at three years, and a 33 percent reduction in the risk of death (P = 0.015) in the former group (Romond et al., 2005). Although relatively little follow-up information is available beyond three years, current data rule out a risk of distant recurrence among Trastuzumab-treated patients of greater than 27 per 1000 women per year, in contrast to a risk of 90 per 1000 women per year in the control group.

The Brown University Oncology Group (Safran et al., 2007) investigated the OS for patients with locally advanced, HER2 overexpressing, adenocarcinoma of the esophagus receiving Trastuzumab concurrently with Paclitaxel, Cisplatin, and RT on a Phase I-II pilot study: the median survival of all patients was 24 months and the 2-year survival was 50%, similar to prior studies without an increase in toxicity.

Recently, the Radiation Therapy Oncology Group (RTOG) 0524 study showed encouraging response rates (secondary endpoint) in patients with HER2-positive muscle-invasive bladder cancer unfit for surgery who were treated with RT and Paclitaxel + Trastuzumab as a bladder preservation therapy (Michaelson et al., 2017). No published data exists concerning concomitant Pertuzumab-Trastuzumab treatment.

Summary: Currently, Trastuzumab concurrent with RT could be safely administered in women with surgically removed HER2-positive breast cancer, provided that cardiac tissue sparing is warranted.

2.3. VEGF inhibitors: Bevacizumab

Several growth factors have been shown to contribute to angiogenesis, and among them, vascular endothelial growth factor (VEGF) is reputed as one of the most important ones involved (Folkman, 1971; Ferrara, 2002; Weis and Cheresh, 2011). Since the effects of RT on tumors are regarded as being dependent on the functional state of the vascular tumor bed and vascular-dependent supply of nutrients and oxygen (Ostergaard and Tietze, 2013), the development of antibodies and soluble receptors that inhibit the binding of VEGF to its receptors has the potential to act synergistically with irradiation.

Bevacizumab (BEV) is a humanized monoclonal antibody that inhibits VEGF. In combination with CT, BEV was associated with prolonged OS in phase III trials of metastatic colorectal cancer and NSCLC and with PFS in recurrent high grade glioma (HGG), metastatic breast and renal cancers (Polivka et al., 2017). BEV was extensively examined in clinical trials for treatment of recurrent as well as newly diagnosed HGG, as a single agent and in various combinations with CT and other targeted therapeutics (Fu et al., 2016). In addition, based on a well tolerated treatment with a high clinical response rates and prolonged PFS (Narayana et al., 2009), in 2009 BEV was approved by the US Food and Drug Administration (FDA) for the treatment of recurrent HGG. Combination of BEV with standard treatment for newly diagnosed HGG, including RT, was tested in one phase II and two large phase III clinical trials. An improved PFS (13.6 vs. 7.6 months) without improved OS (19.6 vs 21.1 months) – the primary endpoint of the study – was reported in 70 patients with HGG who were enrolled in the prospective, multicenter single-arm phase II study combining BEV with conventional temozolomide (TMZ)-based CT-RT (Lai et al., 2011). Likewise, in the phase III AVAglio trial (Chinot et al., 2014), that investigated the addition of BEV to RT + TMZ for the treatment of newly diagnosed glioblastoma, an improved PFS, but not OS – both coprimary endpoints – as well as maintenance of baseline quality of life and performance status were observed with BEV. A similar trend, with the addition of BEV to standard TMZ-based CT-RT was confirmed in the RTOG 0825 trial, designed to detect a 25% reduction in the risk of death and a 30% reduction in the risk of progression or death, the two coprimary end points: PFS was prolonged in the BEV group (10.7 months vs. 7.3 months; HR for progression or death, 0.79), but did not reach the prespecified improvement target, while no significant difference in the duration of OS was detected between the groups (Gilbert et al., 2014). The phase II, randomized, multicentric GENOM 009 study compared the efficacy and safety of treatment with TMZ or TMZ + BEV prior to and concomitant with RT in unresectable glioblastoma having as primary endpoint the response according to RANO criteria after the 2 pre-RT cycles: the primary endpoint was met, with a response rate significantly higher in the BEV arm. A tendency towards improved PFS, and OS was also observed in the BEV Arm, although the trial was not powered to detect statistical significance for these outcomes (Balana et al., 2014). Conversely, the efficacy outcomes and exploratory

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analyses of the randomized, multi-center phase II trial ARTE (Wirsching et al., 2018) evaluating the addition of BEV to hypofractionated RT (40 Gy in 15 fractions) in elderly (≥ 65 years) patients with newly diagnosed glioblastoma, do not support the hypothesis that the addition of BEV to RT generally prolongs survival in this setting.

Disappointing results were reported in phase II trials investigating BEV in combination with CT-RT for unresectable stage III NSCLC, due to life-threatening sequelae (details provided in a parallel manuscript), and at present BEV cannot be recommended for routine clinical use (Sandomenico et al., 2012). BEV has been tested with pre-operative RT or CT-RT in LARC in several phase II trials. Most of them had as primary endpoint the pCR, that seems to have an impact on local control, disease free survival (DFS) and OS, ranging between 15–25% with neoadjuvant CT-RT (Fornaro et al., 2014). A modest benefit by the BEV addition seems to be achieved in term of pCR (range = 14–32%) in a number of phase II trials, and conclusions about the impact on long-term outcome are difficult to draw due to the different trials design. An advantage in terms of pCR was also not observed (range = 8–21%) in additional phase II trials evaluating the addiction of BEV to neoadjuvant regimens integrated with Oxaliplatin, with the exception of the non-randomized phase II study by Avallone et al. (Avallone et al., 2015), reporting a pCR rate of 50%.

*Summary:*currently BEV should be not routinely administered in association with CT-RT since only one randomized trial showed an advantage in PFS, but not in OS, in HGG patients. In those with rectal cancer, a clear benefit from the addition of BEV in terms of pCR was not demonstrated. Table 2 summarizes major clinical trials of BEV and RT in preoperative CT-RT for rectal cancer.

3. Small molecules inhibitors

3.1. TKI (tinib):Erlotinib, Gefitinib, Afatinib

Anti-EGFR drugs reduce radiation-induced expression of DNA repair proteins (Chinnaiyan et al., 2005). When radiation reaches cell surface, it causes EGFR internalization. The receptor moves into the nucleus by binding proteins - Ku70/Ku80 and DNA-dependent protein kinase, catalytic subunit (DNA-PKcs) - and activates damage repair. If antibodies or tyrosine kinase inhibitors (TKIs) block EGFR, the complex does not enter into the nucleus, resulting in the inhibition of DNA repair (Baumann et al., 2007). Moreover, anti-EGFR drugs influence cancer cell clonogenic survival, with a modest but consistent reduction in clonogenic survival when the drug is administered before RT (Baumann et al., 2007; Palumbo et al., 2014).

A direct comparison in terms of oncological outcomes between TKI alone and TKI associated with RT is not available. Four randomized phase II trials (Martins et al., 2013; Martinez et al., 2016; Lee et al., 2014; Pesce et al., 2012) and a single randomized phase III trial (Hammel et al., 2016) compared RT with or without TKI. Martins et al. (Martins et al., 2013) evaluated the impact of Cisplatin-irradiation with or without Erlotinib in 204 LA SCCHN patients. At a median follow up of 26 months, the addition of Erlotinib to Cisplatin-RT failed to increase both the complete response rate (primary endpoint) (P = .08) and the PFS rate (secondary endpoint) (P = 0.71). In the multicenter randomized controlled open-label trial by Martinez et al. (Martinez et al., 2016), the concurrent addition of Erlotinib to RT in 90 L A NSCLC patients versus RT alone was analyzed. Compared to RT-alone, the association of Erlotinib/RT showed a scarce clinical benefit, limited to complete responses and longer cancer specific survival (CSS) rate. In

Table 2
Major clinical trials on RT and Bevacizumab in preoperative chemo-radiotherapy for rectal cancer.

Author and year	Study type	N	Tumor site	RT technique/dose/ fractionation	Combination (concomit, other)	Primary Endpoint	Treatment outcome
Avallone (2015)	Phase II	46	LARC	3DCRT 45 Gy/25 fx	CT-RT (OXATOM-FUFA) + BEV	TRG1	TRG1: 50% 5- yy PFS: 80% 5- yy OS: 85%
Willett (2009)	Phase I-II	32	LARC	3DCRT 50.4 Gy/28 fx	CT-RT (5-FU) + BEV	Safety/Efficacy	pCR: 16% 5-yy DFS: 75% 5-yy OS: 100%
Crane (2010)	Phase II	25	LARC	3DCRT 50.4 Gy/28 fx	CT-RT (CAP) + BEV	Safety/Efficacy	pCR: 32%, 2- yy DFS: 69% 2- yy OS 95%
Gasparini (2012)	Phase II	43	LARC	3DCRT 50.4 Gy/28 fx	CT-RT (CAP) + BEV	Safety/Efficacy	pCR: 14% 3- yy DFS: 75%
Spigel (2012)	Phase II	66	stage II/III rectal cancer	3DCRT 50.4 Gy/28 fx	CT-RT (5-FU) + BEV	DFS	2-yy (Preop) DFS: 97% 2-yy (adjuv) DFS: 89%
Salazar (2015)	Phase II R	90	LARC	3DCRT 45 Gy/25 fx	CT-RT (CAP) + /- BEV	pCR	pCR: 11% vs 16% (P = 0.54)
Kennecke (2012)	Phase II	42	high-risk rectal cancer	3DCRT 50.4 Gy/28 fx	CT-RT (CAPOX) + BEV	TRG1	TRG1: 18.4%
Dellas (2013)	Phase II	70	LARC	3DCRT 50.4 Gy/28 fx	CT-RT (CAPOX) + BEV	Safety/Efficacy	pCR: 17.4%
Landry (2013)	Phase II	57	LARC	3DCRT 50.4 Gy/28 fx	CT-RT (CAPOX) + BEV	Safety/Efficacy	pCR: 17%
Verstraete (2015)	Phase II R	82	LARC	3DCRT 45 Gy/25 fx	CT-RT (BEV + CAP) + /- OX	pCR	pCR: 8% vs 27% (P = 0.05)
Velenik (2011)	Phase II	61	LARC	3DCRT 50.4 Gy/28 fx	CT-RT (CAP) + BEV	pCR	pCR: 13%
Noguè (2011)	Phase II	47	LARC	3DCRT 50.4 Gy/28 fx	CT-RT (CAP) + BEV	pCR	pCR: 36%
Dipetrillo et al. (2012)	Phase II	26	LARC	3DCRT 50.4 Gy/28 fx	Induction FOLFOX + BEV →CT-RT (5-FU-OX) + BEV	pCR	pCR: 20% 3- yy OS: 95%
Vivaldi et al. (2016)	Phase II	48	LARC	3DCRT 50.4 Gy/28 fx	Induction FOLFOXIRI + BEV → CT-RT (CAP or 5-FU) + BEV	ORR	ORR: 89%

Abbreviations: BEV = Bevacizumab; CAP = Capecitabine; CT = chemotherapy; CT-RT = chemo-radiotherapy; DFS = disease-free survival; FOLFOX = fluorouracil/ Leucovorin/Oxaliplatin; 5-FU = 5 Fluorouracil; LARC = locally advanced rectal cancer; OX = Oxaliplatin; OXATOM-FUFA = Oxaliplatin/Raltitrexed/5-Fluorouracil modulated by folinic acid; ORR = overall response rate; OS = overall survival; pCR = pathologic complete response; PFS = progression-free survival; R = randomized; RT = radiotherapy; 3DCRT = 3D conformal radiotherapy; TRG1 = pathological complete tumor regression.

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the context of locally advanced pancreatic cancer, the LAP07 trial (Hammel et al., 2016) was designed as a two-steps randomized phase III trial. In the first step, patients were randomized to receive induction CT with Gemcitabine or Gemcitabine plus Erlotinib for 4 cycles. In the second step, patients with controlled tumor (stable disease or objective response) were randomly assigned to CT-RT versus CT alone. In both arms, Erlotinib maintenance therapy was administered. With a median follow-up of 36.7 months, there was no significant difference in OS (primary endpoint) with CT-RT compared with CT alone (HR 1.03; 95% CI, 0.79–1.34; P = .83), nor with Gemcitabine compared with Gemcitabine plus Erlotinib used as maintenance therapy (HR, 1.19; 95% CI, 0.97–1.45; P = .09). 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 irradiation combined with Gefitinib versus TMZ. A total of 59 patients were enrolled. At a median follow up of 34 months, median OS (primary endpoint) in the Gefitinib arm was 6.3 months (95% CI 2.1–14.6) versus 4.9 months (95% CI 2.3–5.6) in TMZ treated patients.

*Summary:*currently, no evidence supports the routinely concomitant integration of TKI and RT. No data are available on Afatinib and RT, thus, their combination in daily clinical practice is recommended only within clinical trials. Table 3 summarizes major clinical trials of TKI and RT for different tumor sites.

3.2. TKI (nib):Sunitinib and Sorafenib

Sunitinib is a TKI that targets multiple receptors such as VEGF receptor 1,2 and 3, Platelet-Derived Growth Factor (PDGF) receptor alpha and beta, tyrosine-protein kinase receptor (c-KIT), Fms-like tyrosine kinase 3 receptor (FLT-3), transmembrane tyrosine kinase receptor (RET), Colony-stimulating factor 1 receptor (CSF-1R), leading to deactivation of multiple signaling pathways involved in tumor growth and survival, angiogenesis and immune escape (Kleibeuker et al., 2015). At present time Sunitinib is approved, and currently adopted, for the treatment of metastatic renal cell carcinoma, pancreatic neuroendocrine tumors, while Imatinib for resistant gastro-intestinal stromal tumors (GIST). Acting on multiple targets, Sunitinib could enhance apoptosis and reduce clonogenic survival when given together with RT, both on tumor cells (Cuneo et al., 2008; Zwolak et al., 2008) and on endothelial cells (Schueneman et al., 2003; Zhang et al., 2011). Sunitinib is generally delivered at 50 mg/daily in a 6-week schedule (4 weeks on and 2 weeks off). A phase I (Kao et al., 2009) and II trials (Tong et al., 2012) have been published, where Sunitinib in a 6-week schedule was delivered with image-guided radiotherapy (IGRT). Taken together, these phase II trials (Kao et al., 2014), explored in 46 patients the combination of hypofractionated IGRT (50 Gy in 10 fractions) with reduced dose of concurrent Sunitinib (37.5 mg) in a 6-week schedule in very different tumors (head and neck, HCC, NSCLC, renal, prostate, colorectal, pancreatic and melanoma) mainly in patients with two metastatic sites (68%) in one organ (76%) mostly bone (40%), lung (28%) lymph node (14%) and liver (13%). Moreover, 39% of patients received maintenance Sunitinib. The analysis was conducted to determine the long-term survival and cancer control outcomes for this novel regimen. Four-years local control (LC), distant control (DC), PFS and OS were 75%, 40%, 34% and 29%, respectively. Staehler et al. (Staehler et al., 2012; Staehler et al., 2011) investigated the feasibility 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-week schedule. After this combination strategy, all but one patients experienced a response or stable disease for a median duration of disease stabilization of 14.7 months. Sorafenib is an inhibitor of multiple kinases that blocks tumor cell proliferation by targeting the serine/threonine-protein kinase (Raf)/ Mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) signaling pathway (Wilhelm et al., 2006; Liu et al., 2006), clinically approved for HCC (Cheng et al., 2009). It has also shown clinical activity against advanced renal cell carcinoma and is considered an option in second-line therapy in this setting (Escudier et al., 2007). The mechanism of Sorafenib with its ability to act against VEGF and VEGF receptor (Gorski et al., 1999; Liu et al., 2005) provides a strong rationale for its combination with RT. Two studies examined the combination of Sorafenib and concurrent stereotactic radiosurgery (SRS). The aforementioned authors (Staehler et al., 2011) analysed the efficacy of simultaneous standard anti-angiogenic therapy and (SRS) in patients with spinal and cerebral metastases from renal cell carcinoma, having local control as the primary endpoint: forty-five patients were treated with Sunitinb and 61 patients with Sorafenib. Local tumour control 15 months after SRS was 98% (95% CI, 89–99%). The high local tumor control rate after SRS adds a valuable palliative tool to the therapeutic approach of metastatic renal cell carcinoma. In a phase II study, aimed at evaluating the response rate after combined treatment and the tolerability and toxicity as primary objectives, Chen et al. (Chen et al., 2014) reported results on 40 patients with unresectable locally advanced HCC treated with conventionally fractionated RT (2–2.5 Gy per daily fraction; dose range 40–60 Gy) with concurrent and sequential Sorafenib. Twenty-two (55.0%) patients achieved complete or partial remission at the initial assessment, with 2-year in-field PFS of 39%, which does not appear to be particularly superior to the results from some retrospective studies investigating response rates with RT alone (Park et al., 2002; Kim et al., 2005; Kim et al., 2006). In a report by Kasibhatla et al. (Kasibhatla et al., 2007) three consecutive patients with renal cell carcinoma experienced disease progression on Sorafenib therapy and received palliative RT for painful metastatic or locally recurrent disease, while undergoing Sorafenib therapy. All patients record a complete pain relief.

Summary: currently the association of Sunitinib and RT holds potential in increasing tumor response, provided that the dose is reduced to 37.5 mg daily in a classical 6-week schedule, or to 25 mg daily if a continuous schedule is applied. Sorafenib combined with cranial SRS records high local control rate, while in association with liver RT showed some activity.

3.3. poli-ADP-ribose polymerase (PARP) inhibitors (parib)

The effectiveness of PARP inhibitors has shown to be able to selectively target Breast Cancer Type susceptibility protein (BRCA) mutant tumor cells in pre-clinical models. A possible explanation of PARP inhibitors inefficacy is related to mechanisms of resistance due to additional mutations in the either the BRCA1 or BRCA2 genes in BRCA mutant patients (Satoh et al., 1993). Regarding a possible interaction with RT, it is known that ionizing radiation exposure results in the rapid activation and recruitment of PARP1 to damaged DNA. In pre-clinical models, the association between PARP inhibitors and RT can elicit tumor inhibition with minimal effects on proliferating normal tissue, suggesting an actionable therapeutic window (Chalmers et al., 2004). To date, it remains to be determined whether a concurrent PARP inhibitors/RT combination versus a sequential approach will be more effective in a clinical setting. Additionally, efforts in identifying a biomarker for response to a combination PARP inhibitors/RT are needed to facilitate the application of this combination in clinical practice (Gani et al., 2015). Two phase I studies are available in literature exploring the combination of Velaparib and RT. In the trial by Reiss et al. (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 dose of 80–320 mg daily. Low dose RT consisted of 21.6 Gy in 36 fractions (0.6 Gy twice daily). No objective responses were observed. Disease stabilization longer than 24 weeks was observed in 33% of cases. Patients with ovarian and fallopian cancers had better quality of life (QoL) over time than those with other cancers. The phase I study by Mehta et al. (Mehta et al., 2015), evaluated the safety, and secondarily the

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Table 3
Major studies on RT and TKIs Oncologic outcomes.

Author and year	Study type	N	Tumor site	RT technique/dose/ fractionation	Combination (concomit, other.)	Primary Endpoint	Treatment outcome
Martins et al. (2013)	Phase II R	95	LA-SCCHN	IMRT 70 Gy/35 fx	CT-RT (CDDP) +/-E	CRR	CR: 40% vs 52% (P = 0.08)
Martinez et al. (2016)	Phase II R	90	NSCLC	3DCRT 66 Gy/33 fx	RT alone vs RT + E	Feasibility/ Tolerability	Median OS: 11.4 vs 8.9 months (P = 0.835)
Herchenhorn et al. (2010)	Phase I/II	31	LA-SCCHN	TCT 70.2 Gy/39 fx	CT-RT (CDDP) + E	Safety/Efficacy	3-yy PFS = 61% 3-yy OS: 72%
Yao et al. (2016)	Phase II	43	LA-SCCHN	IMRT 70 Gy/35 fx	CT-RT (weekly DOC) +E (daily,continued until 2-years)	DFS	3-yy DFS: 69.5% 3-yy OS: 81%
Hainsworth et al. (2009)	Phase II	60	LA-SCCHN	3DCRT 68.4 Gy/38 fx	Induction BEV/5-FU/Carbo/PAC → CT-RT (PAC + BEV) + E	PFS	3-yy PFS: 71% 3-yy OS: 82%
Lilenbaum et al. (2015)	Phase II	75	Unresectable NSCLC	3DCRT 66 Gy/33 fx	Induction Carbo/Paclitaxel → RT + E	OS	Median OS: 17 months 1-yy OS: 57%
Ramella et al. (2013)	Phase I-II	60	Unresectable NSCLC	3DCRT 59.4 Gy/33 fx	CT-RT + Erlotinib	Feasibility/ Tolerability	Median OS : 23.3 months Median PFS: 4.7 months
Herman et al. (2013)	Phase II	48	Resectable PA	IMRT 50.4 Gy/28 fx	CT-RT (CAP) + E → GEM + E	RFS	Median RFS: 15.6 months Median OS: 24.4 months
Hammel et al. (2016)	Phase III	133	Unresectable PA	3DCRT 54 Gy/30 fx	Induction GEM alone vs GEM + E → CT vs CT-RT	OS	Median OS: 13.6 vs 11.9 months (P = 0.09)
Nogueira-Rodrigues et al. (2014)	Phase II	36	LACC	3DCRT 45Gy/25 fx + BRT 24 Gy/4 fx	CT-RT (CDDP) +E	Safety/Efficacy	2-yy OS: 91.7% 2-yy PFS: 80.6%
Blaszkowsky et al. (2014)	Phase II	32	LARC	3DCRT 50.4 Gy/28	CT-RT (5-FU-BEV) + E	Safety/Efficacy	3-yy DFS: 75.5%
Zhao et al. (2016)	Phase II	21	Inoperable ESCC	IMRT 60Gy/30 fx	CT-RT (weekly PAC) + E	Safety/Efficacy	Median OS: 22.9 months
Iyengar et al. (2014)	Phase II	24	Stage IV NSCLC	SBRT 27-33 Gy/3 fx 35-40 Gy/ 5 fx 19-20/1 fx	SBRT + E (1 week before and during)	PFS	Median PFS: 14.7 months Median OS: 20.4 months
Welsh et al. (2013)	Phase II	40	BM	3DCRT 35 Gy/14 fx	WBRT + E (then maintained until neurological progression)	MST	MST: 11.8 months
Zhuang et al. (2013)	Phase II R	54	BM	3DCRT 30 Gy/10 fx	WBRT +/- E	LPFS	Median LPFS: 6.8 vs 10.6 months (P = 0.003) Median OS: 8.9 vs 10.7 months (P = 0.02)
Lee et al. (2013)	Phase II R	80	BM	3DCRT 20 Gy/5 fx	WBRT +/- E	nPFS	Median nPFS: 1.6 vs 1.6 months Median OS: 2.9 vs 3.4 months (P = .83)
Pesce et al. (2012)	Phase II R	59	BM	3DCRT 30 Gy/10 fx	WBRT + TMZ vs WBRT + G	OS	Median OS: 4.9 vs 6.3 months
Wang et al., (2014)	Phase II	14	Stage IV NSCLC	SBRT 48-60 Gy/3 fx	SBRT + G (1 week before and until progression)	Tolerability/ Efficacy	Median PFS: 7 months Median OS: 19 months
Valentini et al. (2008)	Phase I-II	41	LARC	3DCRT 50.4 Gy/28 fx	CT-RT (5-FU) + G	MTD/TRG	TRG1 30.3% TRG2: 21.2 %

Abbreviations: BEV = Bevacizumab; BM = brain metastases; BRT = brachytherapy; CAP = Capecitabine; CDDP = Cisplatin; CRR = complete response rate; CT = chemotherapy; CT-RT = chemoradiotherapy; DFS: disease free survival; DOC = Docetaxel; E = Erlotinib; ESCC = esophageal squamous cell carcinoma; fx = fractions; 5-FU = 5-Fluorouracil; G = Gefitinib; GEM = Gemcitabine; IMRT = intensity modulated radiotherapy; LACC = locally advanced cervical cancer; LA-SCCHN = locally advanced squamous cell carcinoma of head and neck; LC = local control; LRFS = local relapse free survival; LPFS = local progression free survival; MTD = maximum tolerated dose; MST = median survival time; NSCLC = non-small cell lung cancer; nPFS = neurological progression free survival; OR: objective response; ORR = overall response rate; OS = overall survival; PA = pancreatic adenocarcinoma; PAC = Paclitaxel; pCR = pathologic complete response; PFS = progression-free survival; R = randomized; RFS = relapse free survival; RR = response rate; RT = radiotherapy; 3DCRT = 3D conformal radiotherapy; SBRT = stereotactic body radiotherapy; TCT = telecobaltotherapy; TMZ = temozolomide; TRG = tumor-regression grade; WBRT = whole brain radiotherapy.

antitumor activity of Veliparib, administered at the dose of 10–300 mg orally, in combination with whole brain radiation therapy (WBRT) (30–37.5 Gy in 10–15 fractions), due to its ability to cross the blood-brain barrier. Eighty-one patients affected by brain metastases, mainly from NSCLC and breast cancer, were treated: the median survival time (MST) for the NSCLC subgroup was 10.0 months (3.9–13.5) and for the breast cancer subgroup was 7.7 months (2.8–15.0), far better than predicted by a nomogram-model hypothesized by the authors themselves. Preclinical evidence showed that Olaparib, a highly potent PARP inhibitor, may enhance radiation response in cholangiocarcinoma, a highly malignant tumor typically resitant to RT alone (Mao et al., 2018).

Summary:although the mechanisms of interaction between PARP inhibitors and RT is intriguing, available data are far to be applicable in clinical practice. Further studies are advocated.

3.4. PI3K/mTOR inhibitors: Everolimus

Everolimus is an oral inhibitor of mammalian target of rapamycin (mTOR) pathway (Yang and Guan, 2007). There is also a connection between the PI3K pathway and angiogenesis, and agents that can inhibit PI3K and/or mTOR signaling in tumor cells have effects on

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angiogenesis as well as on tumor cell proliferation and survival (Karar and Maity, 2011). Everolimus is approved for the treatment of patients with advanced renal cell carcinoma, whose disease has progressed on or after treatment with VEGF-targeted therapy (Motzer et al., 2008), for treatment of postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer in combination with Exemestane, after failure of treatment with Letrozole or Anastrozole (Beaver and Park, 2012). Synergistic effect of Everolimus and RT has been reported by several investigators and can be summarized in three points: perturbation of the proangiogenetic factors' release and also targeting tumor endothelial cells (Garcia-Barros et al., 2003; Paris et al., 2001; Carmeliet and Jain, 2000; Garcia-Barros et al., 2004), favors radiation induced autophagy of cancer cells (Lorin et al., 2008; Palumbo and Comincini, 2013), and finally blocks radiation-induced stress response of tumor cells and cycle progression and cell proliferation (Manegold et al., 2008). Phase I trials of concurrent RT and Everolimus have been published in lung (Deutsch et al., 2015), head and neck (Fury et al., 2013) cervical cancer (de Melo et al., 2016) and for salvage treatment of biochemical recurrence in prostate cancer (PC) patients following prostatectomy (Narayan et al., 2017) identifying maximum tolerated daily or weekly dose. The most significant experience investigating the association between Everolimus and RT consisted in a phase II trial (Chinnaiyan et al., 2018) evaluating the efficacy of Everolimus administered daily with conventional CT-RT in 171 patients with newly diagnosed glioblastoma: no significant difference in PFS (primary endpoint) was found between patients randomized to Everolimus compared with control (median PFS: 8.2 vs 10.2 months, respectively; $P = 0.79$), while OS for patients in the experimental arm was inferior to that for control patients (MST: 16.5 vs 21.2 months, respectively; $P = 0.008$).

Summary: the available clinical data of the association between Everolimus and RT are not sufficient to draw definitive conclusions on its applicability in the clinical practice.

3.5. BRAF inhibitor: Vemurafenib, Dabrafenib

BRAF is an integral part of the RAS-RAF-MEK-ERK (mitogen-activated protein kinase) signal transduction pathway, a protein kinase cascade which regulates cellular growth, proliferation, differentiation, and survival in response to extracellular signals, including growth factors, cytokines, and hormones Some mutations in the BRAF gene including V600E result in constitutively activated BRAF proteins, which can cause cell proliferation in the absence of growth factors that would normally be required for proliferation. BRAF gene mutations are found in about 60% of melanoma cells. The most common mutation in BRAF is caused by a single aminoacid substitution of valine for glutamine at codon 600, representing the majority of BRAF mutations found in human cancer (Wellbrock et al., 2004).

Vemurafenib was the first selective BRAF inhibitor approved in advanced melanoma with BRAF V600 mutation (Ceolin Foletto and Haas, 2014), followed by Dabrafenib, a potent and reversible ATP-competitive inhibitor that selectively inhibits the BRAF V600E kinase (Hauschild et al., 2012). Inhibition of BRAF has been associated with radiosensitization in vitro. Sambade et al. (Sambade et al., 2011) found that for V600E mutant melanoma cell lines, radiosensitization was due, in part, to alterations in the cell cycle distribution: Vemurafenib increased cell cycle arrest in G1 through inhibition of the MAPK/Erk signal transduction pathway. This suggests that PLX-4032 or other BRAF inhibitors in combination with RT could provide improved radiotherapeutic response in BRAF mutant melanomas. Interesting results have been reported in 6 patients with unresectable melanoma disease, treated with induction Vemurafenib and then receiving RT (median dose 57 Gy, conventional fractionation), with 3 patients receiving debulking interval surgery (Seeley et al., 2015). With 29 months' follow-up, LC was 100%. The 3 patients who experienced relapse received salvage therapy to become free of disease at latest follow-up. Lee et al. (Lee et al., 2013) reported a case report in which a patient with positive cerebral spinal fluid cytology developed after 4 months of Vemurafenib, underwent WBRT (30 Gy in 10 fr) with Vemurafenib held 7 days before and after RT. With a follow-up of 18 months after RT, the cerebral spinal fluid was still negative without skin or non-dermatitis skin toxicity. The authors hypothesized that RT could have altered the permeability of the blood brain barrier allowing greater absorption of the drug in the spinal fluid. Baroudjian et al. (Baroudjian et al., 2014) reported a complete metabolic response in a patient who had progression in the axilla, after RT (30 Gy in 6 fractions) with concomitant Vemurafenib.

Summary: The data are insufficient to make recommendations about the concomitant use of BRAFi and RT.

3.6. Hedgehog signalling pathway inhibitors: vismodegib, onidegib

The Hedgehog (HH) signaling pathway is involved in cell proliferation and differentiation during embryonic period and is largely suppressed in the adult. Recently, the HH pathway has been implicated in resistance to both CT and RT (Meng et al., 2015). In sporadic basal cell carcinoma (BCC), mutations induced by UV radiation can be found in the HH pathway (López Estebaranz, 2012). The effect of Vismodegib administration in BCC patients is a significant decrease in HH signaling. On the other hand, Sonidegib blocks Hedgehog signalling (Pan et al., 2010). In the 3 largest trials evaluating the efficacy and safety of Vismodegib in patients with advanced BCC (Sekulic et al., 2015; Chang et al., 2014; Basset-Seguin et al., 2015), was tested and proven, thus adding a novel therapeutic modality in this setting. Block et al. (Block et al., 2015) reported a case of locally advanced BCC (LA BCC) treated with trimodality therapy (Vismodegib, RT, and local excision), resulting in excellent outcome and facial cosmesis, without requiring extensive resection or reconstructive surgery; Jacobsen et al. (Jacobsen and Strasswimmer, 2016) has reported resolution with Vismodegib of relapsing BCC after 14 months from previous RT; finally, the cases reported by Amici et al. (Amici and Beylot-Barry, 2015) elicited the possible interest of RT in combination or after tumor debulking by Vismodegib. Pollom et al. (Pollom et al., 2015) reported 2 cases of recurrent BCC treated with concurrent RT and Vismodegib. Concurrent treatment was found to be efficacious and both patients had no evidence of progressive disease at last follow-up. Raleigh et al. (Raleigh et al., 2015) described the case of a patient affected by auricular LA BCC treated with induction Vismodegib and RT, reaching durable local control of disease. Schulze et al. (Schulze et al., 2016) studied four patients (3 with recurrent BCC and one with locoregional lymph node involvement) who received Vismodegib and RT (50.4–66 Gy) in combination. Three of the 4 patients experienced a complete response; one showed stable disease for 6 months and then experienced disease progression.

The approval of Sonidegib by the FDA was based on the demonstration of durable objective response rate from the phase II, multicenter, randomized and double-blinded Basal Cell Carcinoma Outcomes with LDE225 Treatment (BOLT) clinical trial, which investigated the treatment with two different doses of Sonidegib in patients with metastatic or LA BCC (Midgen et al., 2015). The primary endpoint was the proportion of patients who achieved an objective response. Overall, 230 patients were evaluated, 79 in the 200 mg Sonidegib group and 151 in the 800 mg Sonidegib group. In the primary efficacy analysis population, an objective response was detected in 20 (36%, 95% CI 24–50) of 55 patients receiving 200 mg Sonidegib and 39 (34%, 25–43) of 116 receiving 800 mg Sonidegib. Interestingly, Sonidegib was administered after RT in 19 patients of the 200 mg group and 49 of the 800 mg group. Sonidegib is currently evaluated not only in BCC patients, but also in clinical trials for management of myelofibrosis, leukaemia and solid tumors sharing mutations like in BCC.

*Summary:*A paucity of data supports the use of Vismodegib and Sonidegib concurrently with RT. Further prospective data are

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Table 4
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.)	Primary Endpoint	Treatment Outcome
Chang et al. (2014)	Open label, multicentre trial	119 (*)	laBCC (62) or mBCC (57)	N.R.	Vismodegib after RT	Safety/Efficacy	OR: 46.4% (laBCC) 30.8% (mBCC)
Basset-Seguin et al. (2015)	Open label, multicentre trial	499 (**)	laBCC	N.R.	Vismodegib after RT	Safety	OR: 66.7% (laBCC) 37.9% (mBCC)
Block et al. (2015)	Case report	1	Right cheek BCC	3DCRT 50Gy /20 fx	Vismodegib (4 months)→RT→ S	N.A.	PR
Jacobsen and Strasswimmer (2016)	Case report	1	Left eye BCC	N.R.	Vismodegib after RT	N.A.	CR
Amici and Beylot-Barry (2015)	Case report	2	laBCC	3DCRT 45Gy/15 fx Contact RT 40 Gy/10 fx (2 fx per week)	RT between Vismodegib cycles RT after Vismodegib	N.A.	PR PR
Pollom et al. (2015)	Case report	2	Left nasal tip BCC Lateral canthal BCC	VMAT 66 Gy/33 fx 6-MeV and 9-MeV electrons 51 Gy/17 fx	Vismodegib and concurrent RT Vismodegib and concurrent RT	N.A.	9 months SD, improvement in facial weakness, and pain free 12-months DFS
Raleigh et al. (2015)	Case report	1	Right ear BCC	IMRT/70 Gy/35 fx	Vismodegib and concurrent RT	N.A.	PR
Schulze et al. (2016)	Case series	4	Recurrent 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	N.A.	6-months: CR (3) and SD (1)
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	OR	OR: 36.3% (200 mg group) 33.6% (800 mg group)

Abbreviations: BCC = basal cell carcinoma; BRT = brachytherapy; CR = complete response; DFS = disease free survival; fx = fractions; 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; OR = objective response; PD = progressive disease; PR = partial response; R = randomized; RT = radiotherapy; 3DCRT = 3D conformal radiotherapy; S = surgery; SD = stable disease; VMAT = volumetric modulated arc radiotherapy.
(*) previous RT in 38 patients.
(**) previous RT in 134 patients.
(***) previous RT in 19 (200 mg group) and 49 (800 mg group) patients.

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warranted. Table 4 summarizes major clinical trials of Vismodegib/Sonidegib and RT for LA BCC.

4. Immune check point blockade

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

Cytotoxic T-lymphocyte–associated antigen (CTLA-4) is a master regulator of T-cell activation that plays a key role in maintaining tolerance to self-antigens, as demonstrated by the development of lymphoproliferative disease with massive T-cell infiltration of multiple organs in CTLA-4 knockout mice (Tivol and Borriello, 1995; Waterhouse and Penninger, 1995). However, in the immunosuppressive microenvironment of cancer, CTLA-4 becomes an obstacle to the activation and function of antitumor T cells. In a seminal study, antibody-mediated blockade of CTLA-4 was shown to induce effective antitumor immunity in mice (Leach and Krummel, 1996). The synergy of local RT with anti–CTLA-4 agents was seen in different tumor sites in the clinic. Two pivotal clinical reports showed how RT with Ipilimumab (Ipi), a monoclonal antibody targeting CTLA-4, might obtain better disease control by enhancing the abscopal effect on un-irradiated sites in advanced melanoma. (Postow et al., 2012; Hiniker et al., 2012). A retrospective series on 23 patients treated with palliative RT after Ipi reported abscopal responses in 11/23 (52%); median OS for patients obtaining an abscopal response was significantly higher than for non-responding patients (22.4 vs. 8.3 months) (Grimaldi et al., 2014). Similar results were reported by Chandra et al. (Chandra et al., 2015) in 47 consecutive metastatic melanoma patients treated with Ipi and RT: in 68% of cases, RT was associated with an improved rate of index lesion (outside radiation fields) response. Importantly, these studies demonstrated that oligofractionation of RT (3 fractions of 8 Gy each) was more effective at inducing an abscopal response than a single large fraction of 20 Gy or more fractionated treatment (5 fractions of 6 Gy each). Filippi et al. (Filippi et al., 2016) reviewed the possible combinations of immune checkpoints inhibitors and RT for advanced melanoma, highlighting the multiple options in terms of sequence and timing. The combination has been also explored for brain metastases. Trino et al. (Trino et al., 2017) revised the specific use of immune checkpoints inhibitors and SRS, summarizing the clinical results and toxicity of this approach in a non-systematic review. Researchers from the University of Michigan (US) analyzed the clinical and radiographic outcomes of 70 patients with melanoma brain metastases (MBM) who were treated with WBRT or SRS between 2005 and 2012 (Silk et al., 2013): those who received Ipi (33) had a censored median survival of 18.3 months (95% confidence interval 8.1–25.5), compared with 5.3 months (95% confidence interval 4.0–7.6) for patients who did not receive Ipi. Knisely et al. (Knisely and Yu, 2012) retrospectively reported on 77 patients with MBM treated with SRS: the median survival of patients managed with Ipi and definitive SRS was 21.3 months, as compared with 4.9 months in patients who did not receive Ipi. Conversely, in a similar study from New York University on 58 patients treated with SRS for MBM, the administration of Ipi did not result in improved intracerebral disease control, nor in increased OS (Mathew et al., 2013). Similar findings were replicated by Patel et al. (Patel et al., 2017), who compared the efficacy of Ipi and SRS to SRS alone for newly diagnosed MBM having OS as the primary endpoint: the Ipi cohort had no difference in 1-year OS (37.1% vs. 38.5%, p = 0.84), nor in 1 year local control (71.4% vs. 92.3%, p = 0.40) and intracranial control (12.7% vs. 29.1%, p = 0.59). Interestingly however, patients administered Ipi within 14 days of SRS had higher, although not statistically significant, 1-year and 2-year OS relative to Ipi delivered > 14 days and SRS alone.These latter findings were confirmed by Investigators at the Memorial Sloan Kettering Cancer Centre (MSKCC) who reported on 46 patients with MBM treated with Ipi and SRS: on multivariate analysis, prolonged survival was associated with the delivery of SRS during Ipi (Kiess et al., 2015). A single report (Golden et al., 2013) beared promising results, showing an abscopal response in a case of advanced heavily pretreated lung adenocarcinoma, receiving RT together with Ipi with palliative intent. Results are awaited from a prospective phase II study combining RT and Ipi in metastatic NSCLC (NCT02221739), and from a phase III randomized trial for patients with metastatic melanoma (NCT01689974).

An open-label phase I/II trial for men with metastatic castration resistant prostate cancer (mCRPC) tested escalated doses of Ipi from 3 mg/kg up to 10 mg/kg in 33 patients with or without a single 8 Gy dose directed at one to three osseous metastases. The highest dose of Ipi was well tolerated and an additional 34 patients were treated with concurrent RT with only 25% of patients demonstrating progressive disease (Slovin et al., 2013). To further test this treatment approach, a multicentre, randomized, double-blind, phase III trial was conducted in 799 men with at least one bone metastasis from mCRPC that had progressed after docetaxel, having OS as the primary endpoint: patients were randomly assigned to receive bone-directed RT (8 Gy in one fraction) followed by either Ipi 10 mg/kg or placebo every 3 weeks for up to four doses. No difference was detected in OS in the population as a whole (Kwon et al., 2014). However, in subset analysis there was an improvement in OS of patients with a limited burden of metastatic disease, demonstrated by alkaline phosphatase less than 1.5 the upper limit of normal, hemoglobin greater than 11 g/dL, and an absence of visceral metastases.

PD-1 is another inhibitory receptor expressed by T cells on activation that plays a critical role in manteining the peripheral tolerance. In contrast to CTLA-4, however, PD-1 has a more restricted role and is thought to be mainly involved in limiting damage to normal tissue during inflammatory responses (Topalian and Drake, 2012). Its expression is restricted largely to myeloid cells, while PD-L1 is broadly expressed on hematopoietic and non-hematopoietic cells. Upregulation of PD-L1 is common in tumors and has been correlated with progression and poor prognosis (Dong et al., 2002; Zhang et al., 2014; Thompson et al., 2006). Antibodies targeting PD-L1 or PD-1 have been shown to promote CTL expansion and tumor regression in many mouse tumor models (Pilon-Thomas et al., 2010; Goding et al., 2013). These findings have been successfully translated to patients with metastatic melanoma treated either with Nivolumab and Pembrolizumab and SRS, WBRT or extracranial RT (Liniker et al., 2016): response in irradiated extracranial/intracranial SRS lesions was 44% for sequential treatment and 64% for concurrent treatment (p = 0.448). Likewise, no significant difference between sequential or concurrent treatment in lesional response of non-irradiated lesions was observed. Ahmed et al. (Ahmed et al., 2016) retrospectively analyzed a series of 160 patients with both resected and unresectable MBM, of whom 26 patients received SRS, from two prospective Nivolumab protocols: although the primary endpoint was neurotoxicity, local brain metastases control and survival (secondary endpoints) were prolonged compared with standard current treatment. Antonia et al. (Antonia et al., 2017) showed a longer PFS (primary endpoint) with Durvalumab, an anti PD-L1 antibody, as consolidation therapy than with placebo in stage III NSCLC patients who did not have disease progression after two or more cycles of platinum-based CT-RT. Interestingly, PFS was better when Durvalumab was initiated ≤2 weeks of RT (HR 0.39) rather than > 2 weeks after RT (HR 0.63). Inhibition of the PD-1 axis is therefore expected to be most efficient when it attenuates the radiation-induced immune response in close temporal relation to the radiation course. In the updated analysis (Antonia et al., 2018), the PFS benefit has translated to a significant prolongation in OS (second primary endpoint), leading to a 24-month OS rate of 66.3% (95% CI, 61.7 to 70.4) in the treatment group, compared with 55.6% (95% CI, 48.9 to 61.8) in the placebo group (stratified HR for death, 0.68; 99.73% CI, 0.47 to 0.997; P = 0.0025). Based on these results, Durvalumab was approved for the treatment of patients with unresectable stage III NSCLC whose disease had not progressed after platinum-based CT-RT. Otherwise, due to the disappointing results of a phase I trial (Lin et al., 2017), criteria were met

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for advancement to part II of the study where Atezolizumab (another anti PD-L1 antibody) would be added to CT-RT followed by consolidation Atezolizumab, Carboplatin, and Paclitaxel in LA NSCLC patients.

Summary: the combination of Ipi and RT is partially effective, especially for MBM. A trend towards a positive synergistic effect has been shown in a trial on mCRPC patients with bone metastases. Results from a phase III trial suggest that Durvalumab may be an effective adjuvant therapy in patients with stage III disease after standard treatment.

5. Androgen receptor pathway

The androgen pathway represents a crucial therapeutic target in PC treatment. Several mechanisms are advocated in case of metastatic castration resistant disease: 1) mutations of androgen receptor (AR); 2) the intracrine and paracrine effects of in situ androgen synthesis or circulating adrenal derived steroid precursors that significantly contribute to PC growth; 3) abnormalities within the AR pathway, involving coactivators and corepressors that predispose to AR pathway activation (Niraula et al., 2012). To date, there are broadly two new classes of hormonally active drugs in development: more effective AR antagonists, such as MDV3100 (Enzalutamide), ARN-509 (Apalutamide), TOK-001 (Galeterone), and inhibitors of the androgen biosynthetic pathway, such as Abiraterone.

5.1. Abiraterone

So far, the combination of Abiraterone (+ Prednisone) and RT has been investigated only in few studies: in a secondary analysis of the COU-AA-301 randomised trial (Logothetis et al., 2012), palliative RT to bone in patients experiencing localized progression at a single site, allowed to continue Abiraterone in men who were gaining benefit from this agent. These findings were confirmed in a recent retrospective study (Detti et al., 2017) that evaluated treatment outcomes of ongoing Abiraterone therapy with the addition of RT for oligoprogression or with a palliative intent, showing that RT may prolong Abiraterone treatment in metastatic castration resistant patients.

The potential interactions between Abiraterone and RT may also enhance the therapeutic ratio in case of high-risk localized disease, as well as postpone the subsequent systemic schedules in case of oligoprogressive castration resistant PC (oligo-CRPC) by virtue of SBRT. In the former setting, a phase II study (Cho et al., 2015) has been published regarding the concomitant use of RT and Abiraterone in men with localized disease (86% with high-risk PC) having the safety of this combination as primary endpoint. The study intervention consisted of 6 months of neoadjuvant and concurrent Abiraterone with LHRH analogues and RT (dose range 77.4–81 Gy). At median follow-up of 21 months (range: 3–37 months), only 1 patient (who had discontinued Abiraterone at 3 months) had biochemical relapse. In the latter one, Triggiani et al. (Triggiani et al., 2017) evaluated the impact of metastases-directed SBRT in two groups of oligometastatic PC patients: oligorecurrent PC and (oligo-CRPC). The primary endpoint in oligo-CRPC patients was distant progression-free survival (DPFS). At a median follow-up of 23.4 months, 1-and 2-year DPFS were 43.2% and 21.6% in the target population. A single case report (Martínez-Fernández et al., 2016) confirmed the ability of SBRT to delay the emergence of castration resistance and the need for systemic therapy when used after androgen deprivation therapy (ADT) failure.

Summary:currently, little evidence supports the use of Abiraterone in combination with RT, which warrants further validation.

5.2. Enzalutamide (MDV 3100)

Enzalutamide (MDV 3100) is a non-steroidal, second-generation Androgen Receptor (AR) antagonist that binds the AR with a higher affinity than Bicalutamide. It belongs to the class of next generation anti-androgens that have been recently approved for the treatment of mCRPC, both in the pre- and post-CT setting (Beer et al., 2014; Scher et al., 2012). Enzalutamide acts at different levels of the AR signaling pathway, not only antagonizing the AR, but also preventing the nuclear translocation and coactivating the recruitment of the ligand–receptor complex, as well as inducing tumor cell apoptosis (Locke et al., 2015). The rationale behind the combination between RT and Enzalutamide arises from data suggesting that, following RT, androgen receptor enhances DNA damage repair and contributes to resistance of PC cells to RT itself. Enzalutamide as a potent AR inhibitor could be considered a potential radiosensitizer and its mechanism of action in castration resistant PC cells could be partially due to the inhibition of DNA damage repair. The results of a preclinical study demonstrated a significant enhancement of RT efficacy and confirmed the rationale for exploring this combination in ongoing clinical trials (Ghashghaei et al., 2017). Enzalutamide recently demonstrated an important clinical response also in non-castrate resistant disease, thus representing a promising drug in combination with RT also in the earlier stage of PC: Tombal et al. (Tombal et al., 2014) in a phase II trial assessed the efficacy and safety of 25-weeks (~6-months) of Enzalutamide alone in patients with PC (all risk groups for whom hormone therapy was indicated) who had never received hormone therapy, presenting with non-castrate testosterone levels (230 ng/dl). The primary outcome was the proportion of patients with an 80% or greater decline in PSA at week 25. Enzalutamide alone for 6-months achieved a high PSA response rate with efficacy similar to castration, but alike from castration, bone mineral density remained stable and metabolic balance was not substantially impacted. These findings suggest that Enzalutamide monotherapy in men with hormone-naive PC of varying severity provides a robust disease suppression. Preliminary studies have shown significant volume reductions of the primary prostate tumors according to ^{18}Fluoro-choline PET/CT evaluation. These findings could suggest the potential of Enzalutamide even in the setting of localized PC (Caffo et al., 2014).

*Summary:*no definitive data are currently available regarding the efficacy of the combination of RT and Enzalutamide. Table 5 summarizes on-going prospective trials evaluating the combination RT and Enzalutamide.

5.3. Newest compounds

5.3.1. Apalutamide (ARN-509)

Apalutamide acts on the same pathway of Enzalutamide, selectively and irreversibly binding itself to AR receptor. There are no published clinical data about the interaction between ARN-509 and RT. Preclinical data obtained in prostate cell cultures seem to point to a synergistic cell killing of Apalutamide and RT; this additivity seems mediated by the inhibition of DNA double strand breaks (DSB) repair mechanisms. LNCaP cells treated with Apalutamide showed decreased DSB repair pathway non-homologous end joining repair (NHEJ) (Bartek et al., 2013; Ferrarelli, 2013).

Two phase II trials confirmed the efficacy of Apalutamide in non-mCRPC and mCRPC (Rathkopf et al., 2017; Smith et al., 2016), and, based on the results of the phase III SPARTAN (Selective Prostate Androgen Receptor Targeting with ARN-509) trial, Apalutamide becomes the first drug that was approved by the FDA for the treatment of non-mCRPC on the basis of a primary end point of metastasis-free survival (MFS). In that study, Apalutamide plus ADT led to a 72% lower risk of metastasis or death and a 24-month delay in the development of metastases, as compared with placebo plus ADT (Smith and Saad, 2018). Two currently ongoing phase III trials [NCT02531516 and NCT03488810] aim to determine if the combination of Apalutamide with ADT by LHRH agonists in patients with intermediate and high-risk PC receiving primary RT result in an improvement of MFS and DFS, respectively. Another single arm phase II trial [NCT02772588] is running to seek whether anti-testosterone medications (Leuprolide,

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Table 5
On-going prospective trials evaluating the combination RT and Enzalutamide.

Author	Study type	Clinical trial.gov number	Tumor site	RT technique/dose/ fractionation	Combination (concomit, other.)	Primary Endpoint
Den, Thomas Jefferson University	Phase Ib	NCT02023463	Prostate	IMRT or VMAT daily five days a week for 8 weeks	RT + ENZ in Patients With Intermediate or High-Risk PCa	Safety
Courtney, UT Southwestern Medical Center	Phase II	NCT02064582	Prostate	EBRT standard protocol	ENZ + ADT Before, During, and After RT for High Risk Localized PCa	Safety and Tolerability
Bubley, Beth Israel Deaconess Medical Center	Phase II	NCT02028988	Prostate	EBRT 75.6-79.2 Gy/1.8 Gy fx	ENZ + EBRT in Intermediate Risk PCa	Biochemical Control
Lara, Hospital Universitario de Canarias	Phase II	NCT03196388	Prostate	HRT 70 Gy/28 fx	ENZ + HRT in Intermediate Risk PCa	Biochemical Control
Nguyen, University of California	Phase II	NCT02508636	Prostate + Pelvic nodes	N.R.	LEU-ENZ + RT in High Risk PCa	Toxicity and biochemical control
Nguyen, Dana Farber Cancer Institute and ANZUP	Phase III	NCT02446444	Prostate	EBRT 78 Gy/39 fx	ADT + RT +/- ENZ for High Risk, Clinically Localised, PCa	OS
Armstrong, Duke University	Phase II	NCT02057939	Prostate (BR)	Salvage EBRT 66 Gy/33 fx	Salvage RT + ENZ and ADT in Men With Recurrent PCa	PFS
Tran, Johns Hopkins	Phase II R	NCT02203695	Prostate (BR)	Salvage EBRT 66.6-70.2 Gy/37-39 fx	Salvage RT +/- ENZ for Biochemically Recurrent PCa	FFPP

Abbreviations: ADT = androgen deprivation therapy; BR = biochemical recurrence; EBRT = external beam radiotherapy; ENZ = Enzalutamide; FFPP = freedom-from-PSA-progression; fx = fractions; HRT = hypofractionated radiotherapy; IMRT = intensity modulated radiotherapy; LEU = Leuprolide; PCa = prostate cancer; RT = radiotherapy; 3D-CRT = 3D conformal radiotherapy; VMAT = volumetric modulated arc radiotherapy.

Abiraterone and Apalutamide) combined with prostate SBRT are effective in preventing biochemical failure.

Summary:Apalutamide has been approved for non-metastatic PC patients with rising PSA during ADT. Ongoing clinical trials are evaluating whether this benefit can be replicated in patients with localized disease receiving primary RT.

5.3.2. Darolutamide (ODM-201)

Darolutamide is a mixture (1:1) of two pharmacologically active diastereomers. ODM-201 (both diastereomers) and its major metabolite, ORM-15341, have a higher AR-binding affinity than bicalutamide, enzalutamide and ARN-509. Additionally, ODM-201 inhibits nuclear translocation of AR in AR-overexpressing cells and inhibits tumor growth in the murine model. (Leibowitz-Amit and Joshua, 2012; Fizazi et al., 2013; Moilanen et al., 2013). No published data are present regarding the possible interaction with RT.

5.3.3. Orteronel (TAK-700)

Orteronel is an inhibitor of CYP17. When circulating testosterone is at castrate-levels, prostate cells can yet convert the adrenal androgens such as Dehydroepiandrosterone (DHEA) and Androstenedione (AED) to dihydrotestosterone (DHT). Orteronel preferentially inhibits 17,20-lyase activity and this may reduce the need for corticosteroid supplementation. No clinical data are published about the use of TAK-700 with RT. Only one study is registered targeting the use of the drug in association with RT and hormonal treatment, but it is currently not recruiting patients [NCT01546987].

5.3.4. Galeterone (TOK-001)

Galeterone in vitro increases AR protein degradation in PC derived cells expressing a T878 A mutant AR. There are no data on the potential interactions of RT with Galeterone.

6. Perspectives and conclusions

Over the last decades, RT has been in the midst of new developments in technology. High-tech improvements have allowed for the maximal administration of dose to tumors while sparing normal tissues. In parallel, systemic therapies have been combined with radiation in an effort to improve tumor control. Conventional cytotoxic agents have improved survival in several tumor types but at the cost of increased toxicity due to effects on normal tissues. More recently, a better knowledge of the biological differences between tumor and normal cells as well as the differential responses of tumor and normal cells to radiation has prompted the investigation of molecularly targeted drugs and immunotherapeutic agents that may act synergistically with radiation. Despite intense work in this area, only two targeted drug classes are considered standard therapy with radiation: epidermal growth fac- tor receptor (EGFR) inhibition with Cetuximab in head and neck cancer, and androgen receptor targeting with testosterone deprivation in intermediate and high-risk PC, thus reflecting a scenario where few drugs targeting new pathways are in clinical practice, although many are in clinical trials. This discrepancy can be in part explained by limited regulatory rules for drug-RT combination, as well as perceived challenges in designing trials with drugs developed specifically for use with RT, which should rely on relevant preclinical models. Definitely, the optimal dosing and timing have to be explored. Furthermore, predictive biomarkers are mandatory to drive treatment selection but only few have already been validated in patients receiving RT with molecular targeted therapy. In conclusion, the combination of modern RT and novel systemic compounds has the potential to translate in long-term clinical benefits for patients. A better understanding of new drugs and RT combination will require a truly multidisciplinary translational approach starting already in the preclinical phase and continuing through the clinical phase I, II, and III trials as well as during the post marketing studies.

Conflict of interest declaration

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References

Ahmed, K.A., Stallworth, D.G., Kim, Y., et al., 2016. Clinical outcomes of melanoma brain

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metastases treated with stereotactic radiation and anti-PD-1 therapy. Ann. Oncol. 27, 434–441.
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 (September (27)), 2940–2950.
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 (December (36)), 5294–5300.
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 (October (30)), 30394–30407.
Azria, D., Larbouret, C., Robert, B., et al., 2003. Radiotherapy and inhibitors of epidermal growth factor receptor: preclinical findings and preliminary clinical trials. Bull. Cancer 90, S202–S212.
Badache, A., Hynes, N.E., 2004. A new therapeutic antibody masks ErbB2 to its partners. Cancer Cell 5, 299–301 27.
Balana, C., De Las Penas, R., Sepúlveda, J.M., et al., 2014. A multicenter randomized study comparing temozolomide (TMZ) versus TMZ-plus-bevacizumab (BEV) before standard treatment in unresectable glioblastoma (GBM) patients (p): the GENOM 009 study by the GEINO group. J. Clin. Oncol. 32 (5s) suppl; abstr 2028.
Baroudjian, B., Boussemart, L., Routier, E., et al., 2014. Dramatic response to radiotherapy combined with vemurafenib. Is vemurafenib a radiosensitizer? Eur. J. Dermatol. 24, 265–267.
Bartek, J., Mistrik, M., Bartkova, J., 2013. Androgen receptor signaling fuels DNA repair and radioresistance in prostate cancer. Cancer Discov. 3, 1222–1224.
Basset-Seguin, N., Hauschild, A., Grob, J., et al., 2015. Vismodegib in patients with advanced basal cell carcinoma (STEVIE): a pre-planned interim analysis of an international, open-label trial. Lancet Oncol. 16, 729–736.
Baumann, M., Krause, M., Dikomey, E., et al., 2007. EGFR-targeted anti-cancer drugs in radiotherapy: preclinical evaluation of mechanisms. Radiother. Oncol. 83, 238–248.
Beer, T.M., Armstrong, A.J., Rathkopf, D.E., et al., 2014. Enzalutamide in metastatic prostate cancer before chemotherapy. N. Engl. J. Med. 371, 424–433.
Beaver, J.A., Park, B.H., 2012. The BOLERO-2 trial: the addition of everolimus to exemestane in the treatment of postmenopausal hormone receptor-positive advanced breast cancer. Future Oncol. 8 (June (6)), 651–657.
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.
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 (June (17)), 2312–2318.
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 (January (1)), 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.
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 (February (6)), 567–578.
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 (February (2)), 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 (March (3)), 462–472.
Caffo, O., Maines, F., Donner, D., et al., 2014. Impact of enzalutamide administration on primary prostate cancer volume: a metabolic evaluation by choline positron emission tomography in castration-resistant prostate cancer patients. Clin. Genitourin. Cancer 12 (October (5)), 312–316.
Carmeliet, P., Jain, R.K., 2000. Angiogenesis in cancer and other diseases. Nature. 407 (September (6801)), 249–257.
Ceolin Foletto, M., Haas, S.E., 2014. Cutaneous melanoma: new advances in treatment. An. Bras. Dermatol. 89 (March-April (2)), 301–310.
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 (March (3)), 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 (June (7)), 627–637. https://doi.org/10.1016/S1470-2045(13)70136-0.
Chalmers, A., et al., 2004. PARP-1 PARP-2, and the cellular response to low doses of ionizing radiation. Int. J. Radiat. Oncol. Biol. Phys. 58 (2), 410–419.
Chandra, R.A., Wilhite, T.J., Balboni, T.A., et al., 2015. A systematic evaluation of abscopal responses following RT in metastatic melanoma patients treated with ipilimumab. Oncoimmunology 4 (11), e1046028.
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, 60–69.
Chen, D.J., Nirodi, C.S., 2007. The epidermal growth factor receptor: a role in repair of radiation-induced DNA damage. Clin. Cancer Res. 13, 6555–6560.
Chen, S.W., Lin, L.C., Kuo, Y.C., et al., 2014. Phase 2 study of combined sorafenib and radiation therapy in patients with advanced hepatocellular carcinoma. Int. J. Radiat. Oncol. Biol. Phys. 88 (5), 1041–1047.
Cheng, A.L., Kang, Y.K., Chen, Z., et al., 2009. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol. 10 (1), 25–34.
Chinnaiyan, P., Huang, S., Vallabhaneni, G., et al., 2005. Mechanisms ofenhanced radiation response following epidermal growth factorreceptor signaling inhibition by erlotinib (Tarceva). Cancer Res. 65 (8), 3328–3335.
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 (April (5)), 666–673.
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., et al., 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 (June (2)), 236–243.
Cuneo, K.C., Geng, L., Fu, A., et al., 2008. SU11248 (sunitinib) sensitizes pancreatic cancer to the cytotoxic effects of ionizing radiation. Int. J. Radiat. Oncol. Biol. Phys. 71, 873–879.
de Melo, A.C., Grazziotin-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.
Detti, B., D'Angelillo, R.M., Ingrosso, G., et al., 2017. Combining abiraterone and radiotherapy in prostate Cancer patients who progressed during abiraterone therapy. Anticancer Res. 37 (July (7)), 3717–3722.
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.
Dipetrillo, 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 (January (1)), 124–129.
Dong, H., Strome, S.E., Salomao, D.R., et al., 2002. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. Nat. Med. 8, 793–800.
Dwedney, A., Cunningham, D., Tabernero, 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 (May (14)), 1620–1627.
Escudier, B., Eisen, T., Stadler, W.M., et al., 2007. Sorafenib in advanced clear-cell renal-cell carcinoma. N. Engl. J. Med. 356 (2), 125–134.
Ferrara, N., 2002. VEGF and the quest for tumour angiogenesis factors. Nat. Rev. Cancer 2 (10), 795–803.
Ferrarelli, L.K., 2013. Hormones in repair and resistance. Sci. Signal. 6, 304. https://doi.org/10.1126/scisignal.2004956. pp.ec 293.
Filippi, A.R., Fava, P., Badellino, S., Astrua, C., Ricardi, U., Quaglino, P., 2016. Radiotherapy and immune checkpoints inhibitors for advanced melanoma. Radiother. Oncol. 120 (July (1)), 1–12.
Folkman, J., 1971. Tumor angiogenesis: therapeutic implications. N. Engl. J. Med. (21), 1182–1186.
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 (May (20)), 6081–6091.
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.
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 (May (5)), 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 (November (3)), 479–486.
Gani, C., Coackley, C., Kumareswaran, R., et al., 2015. In vivo studies of the PARP inhibitor, AZD-2281, in combination with fractionated radiotherapy: an exploration of the therapeutic ratio. Radiother. Oncol 2015 116 (September (3)), 486–494.
Garcia-Barros, M., Paris, F., Cordon-Cardo, C., 2003. Tumor response to radiotherapy regulated by endothelial cell apoptosis. Science. 300 (May (5622)), 1155–1159.
Garcia-Barros, M., Moeller, B.J., Cao, Y., et al., 2004. Radiation activates HIF-1 to regulate vascular radiosensitivity in tumors: role of reoxygenation, free radicals, and stress granules. Cancer Cell 5 (May (5)), 429–441.
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 (March (1)), 141–150.
Geoffrois, L., Martin, L., De Raucourt, D., et al., 2018. Induction chemotherapy followed

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by cetuximab radiotherapy is not superior to concurrent chemoradiotherapy for head and neck carcinomas. Results of the GORTEC-02 phase III randomized trial. J. Clin. Oncol.(July).
Ghashghaei, M., Muanza, T., Paliouras, M., Niazi, T., 2017. Effect of enzalutamide on sensitivity in prostate cancer cells to radiation by inhibition of DNA double strand break repair. J. Clin. Oncol. 35 (6_suppl) 208-208.
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 randomized controlled, open label phase 2 trial. Lancet Oncol. 16 (February (2)), 221–232.
Goding, S.R., Wilson, K.A., Xie, Y., et al., 2013. Restoring immune function of Tumor specific CD4 fl T cells during recurrence of melanoma. J. Immunol. 190, 4899–4909.
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.
Gorski, D.H., Beckett, M.A., Jaskowiak, N.T., et al., 1999. Blockage of the vascular endothelial growth factor stress response increases the antitumor effects of ionizing radiation. Cancer Res. 59 (14), 3374–3378.
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 (August (23)), 3120–3125.
Grimaldi, A.M., Simeone, E., Giannarelli, D., et al., 2014. Abscopal effects of RT on advanced melanoma patients who progressed after ipilimumab immunotherapy. Oncoimmunology e28780 1-8.
Gullick, W.J., Downward, J., Parker, P.J., et al., 1985. The structure and function of the epidermal growth factor receptor studied by using antisynthetic peptide antibodies. Proc. R. Soc. Lond., B, Biol. Sci. 226, 127–134.
Hainsworth, J.D., Spigel, D.R., Greco, F.A., et al., 2011. Combined modality treatment with chemotherapy, radiation therapy, bevacizumab, and erlotinib in patients with locally advanced squamous carcinoma of the head and neck: a phase II trial of the Sarah Cannon oncology research consortium. Cancer J. 17 (September-October (5)), 267–272.
Halyard, M.Y., Pisansky, T.M., Dueck, A.C., et al., 2009. Radiotherapy and adjuvant trastuzumab in operable breast cancer: tolerability and adverse event data from the NCCTG phase III trial N9831. J. Clin. Oncol. 27, 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 (May (17)), 1844–1853.
Hauschild, A.1, Grob, J.J., Demidov, L.V., 2012. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet. 380 (July (9839)), 358–365.
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, multicenter, phase II trial SAKK 41/07. Ann. Oncol. 24 (March (3)), 718–725.
Herchenhorn, D., Dias, F.L., Viegas, C.M., et al., 2010. Phase I/II study of erlotinib combined with cisplatin and radiotherapy in patients with locally advanced squamous cell carcinoma of the head and neck. Int. J. Radiat. Oncol. Biol. Phys. 78 (November (3)), 696–702.
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 (July (4)), 678–685.
Hiniker, S.M., Chen, D.S., Reddy, S., et al., 2012. A systemic complete response of metastatic melanoma to local radiation and immunotherapy. Transl. Oncol. 5 (6), 404–407.
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 (December (5)), 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 (March (4)), 998–1004.
Huang, S.M., Harari, P.M., 2000. Modulation of radiation response after epidermal growth factor receptor blockade in squamous cell carcinomas: inhibition of damage repair, cell cycle kinetics, and tumor angiogenesis. Clin. Cancer Res. 6, 2166–2174.
Clifford, A., Hudis, M.D., 2007. Trastuzumab—mechanism of action and use in clinical practice. NEJM 357 (1), 39–51.
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 (December (34)), 3824–3830.
Jacobsen, A.A., Strasswimmer, J., 2016. Spontaneous resolution of advanced basal cell carcinoma after short-pulse treatment with hedgehog pathway inhibitor. JAAD Case Rep. 30 (2), 360–361.
Kao, J., Packer, S., Vu, H.L., et al., 2009. Phase 1 study of concurrent sunitinib and image-guided radiotherapy followed by maintenance sunitinib for patients with oligometastases: acute toxicity and preliminary response. Cancer 115 (August (15)), 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 (June (2)), 145–153.
Karar, J., Maity, A., 2011. PI3K/AKT/mTOR pathway in angiogenesis. Front. Mol. Neurosci. 4 (December (51)).
Kasibhatla, M., Steinberg, P., Meyer, J., et al., 2007. Radiation therapy and sorafenib: clinical data and rationale for the combination in metastatic renal cell carcinoma. Clin. Genitourin. Cancer 5 (4), 291–294.
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 (January (1)), 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.
Kim, D.Y., Park, W., Lim, D.H., et al., 2005. Three-dimensional conformal radiotherapy for portal vein thrombosis of hepatocellular carcinoma. Cancer 103, 2419–2426.
Kim, T.H., Kim, D.Y., Park, J.W., et al., 2006. Thee-dimensional conformal radiotherapy of unresectable hepatocellular carcinoma patients for whom transcatheter arterial chemoembolization was ineffective or unsuitable. Am. J. Clin. Oncol. 29, 568–575.
Kleibeuker, E.A., 2015. Ten Hooven MA, Verheul HM et al. Combining radiotherapy with sunitinib: lessons (to be) learned. Angiogenesis 18 (October (4)), 385–395.
Knisely, J.P., Yu, J.B., Flanigan, J., et al., 2012. Radiosurgery for melanoma brain metastases in the ipilimumab era and the possibility of longer survival. J. Neurosurg. 117, 227–233.
Kwon, E.D., Drake, C.G., Scher, H.I., CA184-043 Investigators, 2014. Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184-043): a multicentre, randomised, double-blind, phase 3 trial. Lancet Oncol. 15 (June (7)), 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: ECOG 3204. Cancer. 119 (April (8)), 1521–1527.
Leach, D., Krummel, M., Allison, J.P., 1996. Enhancement of anti-tumor immunity by CTLA4- blockade. Science 271, 1734–1736.
Lee, J.M., Mehta, U.N., Dsouza, L.H., et al., 2013. Long-term stabilization of leptomeningeal disease with whole-brain radiation therapy in a patient with metastatic melanoma treated with vemurafenib: a case report. Melanoma Res. 23, 175–178.
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 (July (7)).
Lefebvre, J.L., Pointreau, Y., Rolland, F., et al., 2013. Induction chemotherapy followed by either chemoradiotherapy or bioradiotherapy for larynx preservation: the TREMPLIN randomized phase II study. J. Clin. Oncol. 31 (March (7)), 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–S31 18.
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.
Liccardi, G., Hartley, J.A., Hochhauser, D., 2014. Importance of EGFR/ERCC1 interaction following radiation-induced DNA damage. Clin. Cancer Res. 20, 3496–3506.
Lilenbaum, R., Samuels, M., Wang, X., et al., 2015. A phase II study of induction chemotherapy followed by thoracic radiotherapy and erlotinib in poor-risk stage III non-small-cell lung cancer: results of CALGB 30605 (Alliance)/RTOG 0972 (NRG). J. Thorac. Oncol. 10 (January (1)), 143–147.
Lin, S.H., Lin, Y., Price, J., et al., 2017. 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. OncoImmunol. 5 (9).
Liu, L., Cao, Y., Chen, C., Zhang, X., et al., 2006. Sorafenib blocks the RAF/MEK/ERK pathway, inhibits tumor angiogenesis, and induces tumor cell apoptosis in hepatocellular carcinoma model PLC/PRF/5. Cancer Res. 66 (24), 11851–11858.
Liu, Y., Poon, R.T., Li, Q., et al., 2005. Both antiangiogenesis- and angiogenesis-independent effects are responsible for hepatocellular carcinoma growth arrest by tyrosine kinase inhibitor PTK787/ZK222584. Cancer Res. 65 (May (9)), 3691–3699.
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 (May (5)), 1039–1044.
Locke, J.A., Dal Pra, A., Supiot, S., et al., 2015. Synergistic action of image-guided radiotherapy and androgen deprivation therapy. Nat. Rev. Urol. 12 (April (4)), 193–204.
Logothetis, C.J., Basch, E., Molina, et al., 2012. Effect of abiraterone acetate and prednisone compared with placebo and prednisone on pain control and skeletal-related events in patients with metastatic castration-resistant prostate cancer: exploratory analysis of data from the COU-AA-301 randomised trial. Lancet Oncol. 13 (12), 1210–1217.
Lorin, S., Codogno, P., Djavaheri-Mergny, M., 2008. Autophagy: a new concept in cancer research. Bull. Cancer 95 (January (1)), 43–50.
López Estebaranz, J.L., 2012. Tratamiento del carcinoma basocelular invasivo o la vía del erizo. Piel 27, 425–428.
Machiels, J.P., Sempoux, C., Scalliet, P., et al., 2007. Phase I/II study of preoperative

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cetuximab, capecitabine, and external beam radiotherapy in patients with rectal cancer. Ann. Oncol. 18 (April (4)), 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 (February (5)), 427–435.
Manegold, P.C., Paringer, C., Kulka, U., et al., 2008. Antiangiogenic therapy with mammalian target of rapamycin inhibitor RAD001 (Everolimus) increases radiosensitivity in solid cancer. Clin Cancer Res. 14 (3), 892–900.
Mao, Y., Huang, X., Shuang, Z., et al., 2018. PARP inhibitor olaparib sensitizes cholangiocarcinoma cells to radiation. Cancer Med. 7 (April (4)), 1285–1296.
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.
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 (April (11)), 1415–1421.
Martinez, E., Martinez, M., Rico, M., et al., 2016. Feasibility, tolerability and efficacy of the concurrent addition of erlotinib to thoracic radiotherapy in locally advanced unresectable NSCLC: a phase II trial. Onco. Ther. 9 (March), 1057–1066.
Martínez-Fernández, M.I., Pérez Gracia, J.L., Gil-Bazo, I., et al., 2016. Stereotactic body radiation therapy (SBRT) delays the emergence of castration resistance in patients with oligometastatic prostate cancer. Clin. Transl. Oncol. 18 (7), 743–747.
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.
Meattini, I., Cecchini, S., Muntoni, C., et al., 2014. Cutaneous and cardiac toxicity of concurrent trastuzumab and adjuvant breast radiotherapy: a single institution series. Med. Oncol. 31 (April (4)), 891.
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 (April (2)), 409–417.
Meng, E., Hanna, A., Samant, R.S., Shevde, L.A., 2015. The impact of hedgehog signaling pathway on DNA repair mechanisms in human cancer. CancersBasel (Basel) 7, 1333–1348.
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 (February (2)), 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 (April (5)), 995–1001.
Midgen, 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.
Moasser, M.M., Krop, I.E., 2015. The evolving landscape of HER2 targeting in breast Cancer. JAMA Oncol. 1 1154-116.
Moilanen, A., Riikonen, R., Oksala, R., et al., 2013. ODM-201—new generation antiandrogen with excellent antiandrogenic and antitumor activity in nonclinical models of CRPC. Eur. J. Cancer 49 (suppl 2) abstr 685.
Motzer, R.J., Escudier, B., Oudard, S., et al., 2008. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. Lancet 372 (August (9637)), 449–456.
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.
Narayana, A., Kelly, P., Golfinos, J., et al., 2009. Antiangiogenic therapy using bevacizumab in recurrent high-grade glioma: impact on local control and patient survival. J. Neurosurg. 110.
Niraula, S., Chi, K., Joshua, A.M., 2012. Beyond castration-defining future directions in the hormonal treatment of prostate cancer. Horm. Cancer 3 (1-2), 3–13.
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.
Nogueira-Rodrigues, A., Moralez, G., Grazziotin, R., et al., 2014. Phase 2 trial of erlotinib combined with cisplatin and radiotherapy in patients with locally advanced cervical cancer. Cancer 120 (April (8)), 1187–1193.
Nyati, M.K., Morgan, M.A., Feng, F.Y., Lawrence, T.S., 2006. Integration of EGFR inhibitors with radiochemotherapy. Nat. Rev. Cancer 6, 876–885.
Ostergaard, L., Tietze, A., Nielsen, T., et al., 2013. The relationship between tumor blood flow, angiogenesis, tumor hypoxia, and aerobic glycolysis. Cancer Res. https://doi.org/10.1158/0008-. .CAN-13-0964.
Palumbo, S., Comincini, S., 2013. Autophagy and ionizing radiation in tumors: the "survive or not survive" dilemma. J. Cell. Physiol. 228 (January (1)), 1–8.
Palumbo, I., Piattoni, S., Valentini, V., et al., 2014. Gefitinib enhances the effects of combined radiotherapy and 5-fluorouracil in a colorectal cancer cell line. Int. J. Colorectal Dis. 29 (1), 31–41.
Pan, S., Wu, X., Jiang, J., et al., 2010. Discovery of NVP-LDE225, a potent and selective smoothened antagonist. ACS Med. Chem. Lett. 1, 130–134.
Park, H.C., Seong, J., Han, K.H., et al., 2002. Dose-response relationship in local radiotherapy for hepatocellular carcinoma. Int. J. Radiat. Oncol. Biol. Phys. 54, 150–155.
Paris, F., Fuks, Z., Kang, A., et al., 2001. Endothelial apoptosis as the primary lesion initiating intestinal radiation damage in mice. Science. 293 (July (5528)), 293–297.
Patel, K.R., Shoukat, S., Oliver, D.E., et al., 2017. Ipilimumab and stereotactic radiosurgery versus stereotactic radiosurgery alone for newly diagnosed melanoma brain metastases. Am. J. Clin. Oncol. 40 (October (5)), 444–450.
Perez, E.A., Suman, V.J., Davidson, N.E., et al., 2008. Cardiac safety analysis of doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab in the North Central Cancer treatment Group N9831 adjuvant breast cancer trial. J. Clin. Oncol. 26, 1231–1238.
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 (February (3)), 377–384.
Petit, A.M., Rak, J., Hung, M.C., et al., 1997. Neutralizing antibodies against epidermal growth factor and ErbB-2/neu receptor tyrosine kinases down-regulate vascular endothelial growth factor production by tumor cells in vitro and in vivo: angiogenic implications for signal transduction therapy of solid tumors. Am. J. Pathol. 151, 1523–1530.
Pietras, R.J., Poen, J.C., Gallardo, D., et al., 1999. Monoclonal antibody to HER-2/neureceptor modulates repair of radiation-induced DNA damage and enhances radiosensitivity of human breast cancer cells overexpressing this oncogene. Cancer Res. 59 (6), 1347–1355.
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.
Polivka Jr, J., Polivka, J., Holubec, L., et al., 2017. Advances in experimental targeted therapy and immunotherapy for patients with glioblastoma multiforme. Anticancer Res. 37 (January (1)), 21–33.
Postow, M.A., Callahan, M.K., Barker, C.A., et al., 2012. Immunologic correlates of the abscopal effect in a patient with melanoma. N. Engl. J. Med. 366 (10), 925–931.
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.
Rathkopf, D.E., Antonarakis, E.S., Shore, N.D., et al., 2017. Safety and antitumor activity of apalutamide (ARN-509) in metastatic castration-resistant prostate Cancer with and without prior abiraterone acetate and prednisone. Clin. Cancer Res.(February).
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 (January (1)), 68–76.
Romond, E.H., Perez, E.A., Bryant, J., et al., 2005. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N. Engl. J. Med. 353 (16), 1673–1684.
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 (February (6)), 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 (June (6)), 1386–1393.
Safran, H., Dipetrillo, 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 RadiatOncolBiol Phys 67, 405–409.
Safran, H., Suntharalingam, M., Dipetrillo, T., et al., 2008. Cetuximab with concurrent chemoradiation for esophagogastric cancer: assessment of toxicity. Int. J. Radiat. Oncol. Biol. Phys. 70 (February (2)), 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.
Sambade, M.J., Peters, E.C., Thomas, N.E., et al., 2011. Melanoma cells show a heterogeneous range of sensitivity to ionizing radiation and are radiosensitized by inhibition of B- RAF with PLX-4032. Radiother Oncol. 98 (Mar. (3)), 394–399.
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.
Satoh, M.S., Poirier, G.G., Lindahl, T., 1993. NAD(+)-dependent repair of Damaged DNA by human cell extracts. J. Biol. Chem. 268 (8), 5480–5487.
Scher, H.I., Fizazi, K., Saad, F., et al., 2012. Increased survival with enzalutamide in prostate cancer after chemotherapy. N. Engl. J. Med. 367 (13), 1187–1197.
Schueneman, A.J., Himmelfarb, E., Geng, L., et al., 2003. SU11248 maintenance therapy prevents tumor regrowth after fractionated irradiation of murine tumor models. Cancer Res. 63, 4009–4016.
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 : first clinical experience with vismodegib for locally advanced disease. Strahlenther. Onkol. 192, 25–31.
Seeley, A.R., De Los Santos, J.F., Conry, R.M., 2015. Induction vemurafenib followed by consolidative radiation therapy for surgically incurable melanoma. Melanoma Res. 25, 246–251.
Sekulic, A., Migden, M.R., Lewis, K., et al., 2015. ERIVANCE BCC investigators. Pivotal ERIVANCE basal cell carcinoma (BCC) study: 12-month update of efficacy and s safety of vismodegib in advanced BCC. J. Am. Acad. Dermatol. 72, 1021–1026 e8.
Silk, A.W., Bassetti, M.F., West, B.T., et al., 2013. Ipilimumab and radiation therapy for melanoma brain metastases. Cancer Med. 2, 899–906.

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Siu, L.L., Waldron, J.N., Chen, B.E., et al., 2016. Effect of standard radiotherapy with cisplatin vs accelerated radiotherapy with Panitumumab in locoregionally advanced squamous cell head and neck carcinoma: a randomized clinical trial. JAMA Oncol. (December).
Slovin, S.F., Higano, C.S., Hamid, O., et al., 2013. Ipilimumab alone or in combination with radiotherapy in metastatic castration resistant prostate cancer: results from an open- label, multicenter phase I/II study. Ann. Oncol. 24, 1813–1821.
Smith, M.R., Antonarakis, E.S., Ryan, C.J., et al., 2016. Phase 2 study of the safety and antitumor activity of apalutamide (ARN-509), a potent androgen receptor antagonist, in the high-risk nonmetastatic castration-resistant prostate Cancer cohort. Eur. Urol. 70, 963–970.
Smith, M.R., Saad, F., 2018. Chowdhury S. Apalutamide treatment and metastasis-free survival in prostate Cancer. N. Engl. J. Med. 378 (April (15)), 1408–1418.
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 (March (1)), 45–52.
Staehler, 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 (May-June (3)), 290–293.
Staehler, 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 (September (5)), 673–678.
Steel, G.G., Peckham, M.J., 1979. Exploitable mechanisms in combined radiotherapy-chemotherapy: the concept of additivity. Int. J. Radiat. Oncol. Biol. Phys. 5 (1), 85–91.
Suntharalingam, M., Winter, K., Ilson, 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 (November (11)), 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.
Thompson, R.H., Kuntz, S.M., Leibovich, B.C., et al., 2006. Tumor B7-H1 is associated with poor prognosis in renal cell carcinoma patients with long-term follow-up. Cancer Res. 66, 3381–3385.
Tivol, E.A., Borriello, F., Schweitzer, A.N., et al., 1995. Loss of CTLA-4 leads to massive lymphoproliferation and fatal multiorgan tissue destruction, revealing a critical negative regulatory role of CTLA-4. Immunity 3, 541–547.
Tombal, B., Borre, M., Rathenborg, P., et al., 2014. Enzalutamide monotherapy in hormone- naive prostate cancer: primary analysis of an open-label, single-arm, phase 2 study. Lancet Oncol. 15 (May (6)), 592–600.
Tomblyn, 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 (May (5)), 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.
Topalian, S.L., Drake, C.G., 2012. Pardoll DM: targeting the PD-1/B7-H1(PD-L1) pathway to activate anti-tumor immunity. Curr. Opin. Immunol. 24, 207–212.
Triggiani, L., Alongi, F., Buglione, M., et al., 2017. Efficacy of stereotactic body radiotherapy in oligorecurrent and in oligoprogressive prostate cancer: new evidence from a multicentric study. Br. J. Cancer 116 (12), 1520–1525.
Trino, E., Mantovani, C., Badellino, S., et al., 2017. Radiosurgery/stereotactic radiotherapy in combination with immunotherapy and targeted agents for melanoma brain metastases. Expert Rev. Anticancer Ther. 17 (April (4)), 347–356.
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.
Valabrega, G., Montemurro, F., Aglietta, M., 2007. Trastuzumab: mechanism of action, resistance and future perspectives in HER2- overexpressing breast cancer. Ann. Oncol. 1, 17.
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 BiolPhys. 72 (November (3)), 644–649.
van den Heuvel, M.M., Uyterlinde, 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 (January (1)), 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.
Verstraete, M., Debucquoy, A., Dekervel, J., et al., 2015. Combining bevacizumab and chemoradiation in rectal cancer. Translational results of the AXEBeam trial. Br. J. Cancer 112 (April (8)), 1314–1325.
Viloria-Petit, A., Crombet, T., Jothy, S., et al., 2001. Acquired resistance to the antitumor effect of epidermal growth factor receptor blocking antibodies in vivo: a role for altered tumor angiogenesis. Cancer Res. 61, 5090–5101.
Vivaldi, C., Buccianti, 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 (October (Suppl_6)).
Walraven, I., van den Heuvel, M., van Diessen, J., et al., 2016. Long-term follow-up of patients with locally advanced non-small cell lung cancer receiving concurrent hypofractionated chemoradiotherapy with or without cetuximab. Radiother. Oncol. 118 (March (3)), 442–446.
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 (April (2)), 148–153.
Waterhouse, P., Penninger, J.M., Timms, E., et al., 1995. Lymphoproliferative disorders with early lethality in mice deficient in Ctla-4. Science 270, 985–988.
Weiner, L.M., Adams, G.P., 2000. New approaches to antibody therapy. Oncogene 19, 6144–6151.
Weis, S.M., Cheresh, D.A., 2011. Tumor angiogenesis: molecular pathways and therapeutic targets. Nat. Med. 17 (11), 1359–1370.
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 (March (7)), 895–902.
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 (June (6)), 1423–1430.
Wilhelm, S., Carter, C., Lynch, M., et al., 2006. Discovery and development of sorafenib: a multikinase inhibitor for treating cancer. Nat. Rev. Drug Discov. 5 (10), 835–844.
Wellbrock, C., Karasarides, M., Marais, R., 2004. The RAF proteins take centre stage. Nat. Rev. Mol. Cell Biol. 5, 875–885.
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 (June (18)), 3020–3026.
Yang, Q., Guan, K.-L., 2007. Expanding mTOR signaling. Cell Res. 17, 666–681.
Yao, M., Woods, C., Lavertu, P., et al., 2016. Phase II study of erlotinib and docetaxel with concurrent intensity-modulated radiotherapy in locally advanced head and neck squamous cell carcinoma. Head Neck 38 (April (Suppl 1)), E1770–E1776.
Zhang, H.P., Takayama, K., Su, B., et al., 2011. Effect of sunitinib combined with ionizing radiation on endothelial cells. J. Radiat. Res. 52, 1–8.
Zhang, Y., Wang, L., Li, Y., et al., 2014. Protein expression of programmed death 1 ligand1 and ligand2 independently predict poor prognosis in surgically resected lung adenocarcinoma. Onco. Ther. 7, 567–573.
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 (August (35)), 57310–57316.
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.
Zwolak, P., Jasinski, P., Terai, K., et al., 2008. Addition of receptor tyrosine kinase inhibitor to radiation increases tumour control in an orthotopic murine model of breast cancer metastasis in bone. Eur. J. Cancer 44, 2506–2517.

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