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Review

Design and conduct of early-phase radiotherapy trials with targeted therapeutics: Lessons from the PRAVO experience

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ABSTRACT

New strategies to facilitate the improvement of physical and integrated biological optimization of high-precision treatment protocols are an important priority for modern radiation oncology. From a clinical perspective, as knowledge accumulates from molecular radiobiology, there is a complex and exciting opportunity to investigate novel approaches to rational patient treatment stratification based on actionable tumor targets, together with the appropriate design of next-generation early-phase radiotherapy trials utilizing targeted therapeutics, to formally evaluate relevant clinical and biomarker endpoints. A unique aspect in the development pathway of systemic agents with presumed radiosensitizing activity will also be the need for special attention on patient eligibility and the rigorous definition of radiation dose–volume relationships and potential dose-limiting toxicities. Based on recent experience from systematically investigating histone deacetylase inhibitors as radiosensitizing agents, from initial studies in preclinical tumor models through the conduct of a phase I clinical study to evaluate tumor activity of the targeted agent as well as patient safety and tumor response to the combined treatment modality, this communication will summarize principles relating to early clinical evaluation of combining radiotherapy and targeted therapeutics.

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With current advances in molecular radiobiology, strategies for improving the efficacy of clinical radiotherapy are increasingly focused on exploiting actionable tumor-specific molecular targets (Table 1). Conceptually, it is likely, given the mechanism of action, that a number of currently available targeted therapeutics may be expected to modulate one or more of the phenomena described by 'the 5Rs' of classic radiobiology and thereby have the potential to enhance tumor radiosensitivity [97]. On review of almost 100 recent early-phase trials that have examined radiotherapy combined with targeted therapeutics, a number of actionable tumor signaling pathways involved in tumor proliferation, angiogenesis, and hypoxia were found to have been modulated, with tolerability, safety, and efficacy as study endpoints. Of note, in these trials, treatment outcome was diverse, ranging from tolerable to significant toxicities, and from lack of additional via significant responses to unexpected early disease progression (Table 1).

In the context of 'the 5Rs', an important hallmark of many malignancies is tumor hypoxia, recognized as one of the determinants contributing to clinical radiation resistance, that could potentially be counteracted by therapeutic targeting of hypoxia-dependent perturbations [98]. One rational and appealing strategy for improving radiation efficacy is via the inhibition of hypoxia-driven tumor signaling by histone deacetylase (HDAC) inhibitors [99,100]. Treatment with HDAC inhibitors leads to acetylation of histone and non-histone proteins, and the resultant changes in gene transcription cause alterations in key molecules that orchestrate a wide range of cellular functions, including cell cycle progression, DNA damage signaling and repair, and cell death by apoptosis and autophagy [101–104]. Specifically, HDAC inhibition has been shown to suppress hypoxia-induced activation of the transcription factor hypoxia-inducible factor type 1α, thereby counteracting angiogenesis and other tumor processes directly stimulated by a hypoxic microenvironment [99,100]. In the clinical context, investigations using HDAC inhibitors as single-agent treatment have reported low toxicity and favorable safety profiles, suggesting that these drugs can be combined with standard cytotoxic therapies [105,106].

Following the initial demonstration that HDAC inhibitors enhanced radiation-induced clonogenic suppression of experimental *in vitro* and *in vivo* colorectal carcinoma models [107–109], the phase I Pelvic Radiation and Vorinostat (PRAVO) study (ClinicalTrials NCT00455351) was conducted [66,67]. This trial, undertaken in

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[1] *In memoriam* Prof. Donal Hollywood, President-Elect of the European Society for Radiotherapy & Oncology 2011–2013, to which this work is dedicated.

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Table 1
Early-phase clinical trials combining radiotherapy and targeted therapeutics.

Anatomical site	Tumor type	Molecular drug target(s)	Other concomitant systemic agent(s)	Radiation dose fractionation schedule	Therapeutic intent	Study endpoint(s)	Study outcome	Conclusion	Clinical phase design	Publication year(s)	Reference(s)
Central nervous system											
	GBM	VEGF	Temozolomide	2.0 Gy once daily/30 days	Postoperative	Safety and efficacy	Toxicity and response determined	Unclear whether any additional response	II	2008, 2011	[1,2]
	GBM	VEGF	Temozolomide	1.8 Gy once daily/33 days	Postoperative	Safety	Toxicity determined	Safe combination	II	2011, 2012	[3,4]
	GBM	VEGF	Temozolomide	1.8 Gy once daily/33 days	Postoperative	Safety and efficacy	Toxicity and response determined	Active and generally well tolerated combination	II	2012	[5]
	GBM	VEGF	Temozolomide	Not specified	Postoperative	Efficacy	Response determined	Active combination	II	2012	[6]
	GBM	VEGFR + PDGFR (multitargeted agent)	Temozolomide	Not specified	Postoperative	Tolerability	MTD not determined	Safe combination	I	2011	[7]
	GBM	VEGFR + EGFR + MET (multitargeted agent)	Temozolomide	1.8–2.0 Gy once daily/30–33 days	Postoperative	Safety and tolerability	DLT and MTD determined	Safe combination	I	2010	[8]
	GBM	Thalidomide targets	Temozolomide	2.0 Gy once daily/30 days	Postoperative	Safety and efficacy	Toxicity and response determined	Unclear whether any additional response	II	2004	[9]
	Childhood glioma	Thalidomide targets	None	1.8 Gy once daily/31 days	Local disease control	Efficacy	Response determined	No additional response	II	2007	[10]
	Childhood glioma	EGFR	None	1.8 Gy once daily/31 days	Local disease control	Tolerability	MTD determined	Phase II dose of systemic agent achieved	I	2010	[11]
	Childhood glioma	EGFR	None	1.8 Gy once daily/31 days	Local disease control	Safety and efficacy	Toxicity and response determined	Significant response	II	2011	[12]
	Childhood glioma	RAS	None	1.8 Gy once daily/31 days	Local disease control	Safety and tolerability	DLT and MTD determined	None	I	2008	[13]
	Childhood glioma	RAS	None	1.8 Gy once daily/31 days	Local disease control	Safety and efficacy	Toxicity and response determined	No additional response	II	2011	[14]
	GBM	EGFR	Temozolomide	2.0 Gy once daily/30 days	Postoperative	Efficacy	Response determined	No additional response	I/II	2008	[15]
	GBM	EGFR	Temozolomide	1.8–2.0 Gy once daily/30–33 days	Postoperative	Efficacy	Response determined	Significant response	II	2009	[16]
	GBM	EGFR	Temozolomide	2.0 Gy once daily/30 days	Postoperative	Safety and efficacy	Excessive DLT incidence, trial terminated	Significant toxicity and unexpected early disease progression	II	2010	[17]
	GBM	RAS	Temozolomide or none	2.0 Gy once daily/30 days	Postoperative	Tolerability	MTD determined	Well tolerated combination	I	2011	[18]
	GBM	mTOR	Temozolomide	2.0 Gy once daily/30 days	Postoperative	Safety and tolerability	DLT and MTD determined	Significant toxicity	I	2010	[19]
	GBM	mTOR	Temozolomide	2.0 Gy once daily/30 days	Postoperative	Safety and tolerability	DLT and MTD determined	Reasonably well tolerated combination	I	2011	[20]
	Brain metastases	EGFR	None	2.0 Gy once daily/20 days/4 days weekly	Local disease control	Safety and efficacy	Toxicity and response determined	Active and generally well tolerated combination	II	2009	[21]
	Mainly brain metastases	VEGFR + PDGFR (multitargeted agent)	None	Various	Symptomatic relief	Safety and efficacy	Toxicity and response determined	Active and generally well tolerated combination	I	2011	[22]

Head/neck											
	SCC	EGFR	None	2.2 Gy once daily/28–30 days	Local disease control	Safety and tolerability	Acute grade 3 toxicities in 11 of 13 patients	Significant toxicity	I	2010	[23]
	SCC	EGFR	None	2.0 Gy once daily/35 days or 1.2 Gy twice daily/32 days	Local disease control	Safety and efficacy	Toxicity and response determined	Phase II dose of systemic agent determined	I	2001	[24]
	SCC	EGFR	None	Not specified	Definitive/local disease control	Safety, tolerability, and efficacy	DLT, MTD, and response determined	No additional response	I/II	2008	[25]
	SCC	EGFR	None or cisplatin	2.0 Gy once daily/35–36 days	Definitive	Safety and tolerability	DLT determined	Well tolerated combination	I	2007	[26]
	SCC	EGFR	Cisplatin	2.0 Gy once daily/33–35 days	Definitive/local disease control	Tolerability and efficacy	MTD not determined, response determined	Active and generally well tolerated combination	I	2012	[27]
	SCC	EGFR	Cisplatin	2.0 Gy once daily/15 days, followed by 1.4 Gy twice daily/15 days	Definitive	Safety and tolerability	Toxicity and response determined	Active and well tolerated combination	I	2010	[28]
	SCC	EGFR	Docetaxel	1.8 Gy once daily/38 days	Local disease control	Safety and efficacy	Toxicity and response determined	Unclear whether any additional response	II	2009	[29]
	SCC	EGFR	Paclitaxel	1.8 Gy once daily/37–42 days	Local disease control	Safety, tolerability, and efficacy	DLT, MTD, and response determined	No additional response	I	2010	[30]
	SCC	EGFR	Carboplatin and paclitaxel	1.8 Gy once daily/39 days	Definitive	Safety and efficacy	Toxicity and response determined	Active and well tolerated combination	II	2011	[31]
	SCC	EGFR	5-FU and hydroxyurea	1.5 Gy twice daily/24 days, split course	Local disease control	Tolerability and efficacy	Toxicity and response determined	Active and reasonably well tolerated combination	II	2011	[32]
	SCC	EGFR + ERBB2 (multitargeted agent)	Cisplatin	2.0 Gy once daily/33–35 days	Definitive	Safety, tolerability, and efficacy	DLT, MTD, and response determined	Phase II dose of systemic agent determined	I	2009	[33]
	SCC	EGFR and VEGF (two agents)	Cisplatin	1.25 Gy twice daily/28 days, split course	Definitive	Safety and efficacy	Toxicity and response determined	Significant response with 9 late DLTs in 28 patients	I/II	2012	[34]
	SCC	EGFR and VEGF (two agents)	Paclitaxel	1.8 Gy once daily/38 days	Local disease control	Safety and efficacy	Toxicity and response determined	Significant response without additional toxicity	II	2011	[35]
	SCC	EGFR and proteasome (two agents)	None	2.0 Gy once daily/35–37 days	Local disease control	Safety and efficacy	Toxicity and response determined, trial terminated	Unexpected early disease progression	I	2011	[36]
	SCC	EGFR and COX-2 (two agents)	None	2.2 Gy once daily/32 days	Local disease control	Tolerability and efficacy	MTD and response determined	Active combination with 3 late DLTs in 14 patients	I	2011	[37]
	SCC	VEGF	5-FU and hydroxyurea	1.8–2.0 Gy once daily/28–35 days, split course	Local disease control	Safety and tolerability	DLT and MTD determined	9 late DLTs in 43 patients	I	2008	[38]
Thorax/mediastinum											
	NSCLC	EGFR	None	2.0. Gy once daily/30 days	Local disease control	Safety and efficacy	Toxicity and response determined	Additional toxicity and additional response	II	2010	[39]
	NSCLC	EGFR	None	2.0. Gy once daily/32 days	Local disease control	Safety	Toxicity determined	Acceptable toxicity	I	2008	[40]
	NSCLC	EGFR	None	2.0. Gy once daily/33 days	Local disease control	Safety and efficacy	Toxicity and response determined	Well tolerated combination	II	2011	[41]

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Table 1 (*continued*)

Anatomical site	Tumor type	Molecular drug target(s)	Other concomitant systemic agent(s)	Radiation dose fractionation schedule	Therapeutic intent	Study endpoint(s)	Study outcome	Conclusion	Clinical phase design	Publication year(s)	Reference(s)
	NSCLC	EGFR	None	2.5 Gy once daily/16–20 days, hypofractionated	Local disease control	Safety and efficacy	Toxicity and response determined	Active and generally well tolerated combination	II	2011	[42]
	NSCLC	EGFR	None	3 Gy once daily/10–12 days	Symptomatic relief	Safety and efficacy	Toxicity and response determined	Well tolerated combination	I	2011	[43]
	NSCLC	EGFR	None or paclitaxel	2.0. Gy once daily/33 days	Local disease control	Safety and efficacy	Toxicity and response determined	No or significant response without additional toxicity	II	2010	[44]
	NSCLC	EGFR	Docetaxel	2.0. Gy once daily/35 days	Local disease control	Safety and tolerability	DLT and MTD determined	Acceptable toxicity	I	2010	[45]
	NSCLC	EGFR	Cisplatin	1.8 Gy once daily/25 days, followed by 2.0 Gy once daily/9 days	Local disease control	Safety	DLT determined	Additional toxicity	I	2011	[46]
	NSCLC	EGFR	Carboplatin and paclitaxel	1.8 Gy once daily/35 days	Local disease control	Safety and efficacy	Toxicity and response determined	Large radiation volumes correlated with DLT, active combination	II	2011	[47]
	NSCLC	EGFR	Carboplatin and paclitaxel	2.0. Gy once daily/37 days	Local disease control	Safety and efficacy	Toxicity and response determined	Acceptable toxicity without additional response	II	2008	[48]
	NSCLC	VEGF	None	2.0. Gy once daily/33 days	Local disease control	Safety and tolerability	DLT in 2 of 6 patients, trial terminated	Significant toxicity	I	2012	[49]
	NSCLC	VEGF	Carboplatin and pemetrexed	1.8 Gy once daily/34 days	Local disease control	Safety and efficacy	Trial termination for safety concerns	Significant toxicity	II	2010	[50]
	NSCLC	EGFR and VEGF (two agents)	Carboplatin and paclitaxel	2.0. Gy once daily/37 days	Local disease control	Safety and efficacy	Toxicity and response determined	Significant toxicity	I/II	2012	[51]
	Small cell lung carcinoma	VEGF	Carboplatin and irinotecan	1.8 Gy once daily/34 days	Definitive	Safety and efficacy	Excessive DLT incidence, trial terminated	Significant toxicity	II	2010	[50]
	NSCLC	mTOR	Cisplatin	2.0. Gy once daily/30 days	Local disease control	Safety	DLT determined	Safe combination	I	2007	[52]
	Breast AC	ERBB2	None	2.0. Gy once daily/25 days	Preoperative	Safety and efficacy	Toxicity and response determined	Safe and active combination	II	2010	[53]
	Esophageal AC	ERBB2	Paclitaxel and cisplatin	1.8 Gy once daily/28 days	Local disease control	Safety	Toxicity determined	No additional toxicity	I	2004	[54]
	Esophageal AC	ERBB2	Paclitaxel and cisplatin	1.8 Gy once daily/28 days	Local disease control	Efficacy	Response determined	No additional response	I/II	2007	[55]
	Esophageal AC or SCC	EGFR	Tegafur and oxaliplatin	1.8 Gy once daily/33 days	Local disease control	Safety, tolerability, and efficacy	DLT, MTD, and response determined	Safe combination with significant response	I	2012	[56]
	Esophageal AC or SCC	EGFR	Irinotecan and cisplatin	1.8 Gy once daily/28 days	Local disease control	Safety and efficacy	Toxicity and response determined, trial terminated	Significant toxicity	II	2012	[57]
	Esophageal AC	EGFR and VEGF (two agents)	5-FU, paclitaxel, and carboplatin	1.8 Gy once daily/25 days	Preoperative	Safety and efficacy	Toxicity and response determined	No additional response	II	2012	[58]

Abdomen											
	Pancreatic AC	EGFR	Gemcitabine	1.8 Gy once daily/28 days	Local disease control	Safety	Toxicity determined	Acceptable toxicity	I	2011	[59]
	Pancreatic AC	EGFR	Gemcitabine	1.8 Gy once daily/28 days	Local disease control	Safety, tolerability, and efficacy	DLT, MTD, and response determined	Active and reasonably well tolerated combination	I	2008	[60]
	Pancreatic AC	EGFR	Gemcitabine	2.0. Gy once daily/15–19 days	Local disease control	Safety and tolerability	DLT and MTD determined	Phase 2 radiation dose determined	I	2012	[61]
	Pancreatic AC	EGFR	Capecitabine	1.8 Gy once daily/28 days	Preoperative	Safety	DLT in 6 of 10 patients, trial terminated	Significant toxicity	I	2006	[62]
	Pancreatic AC	EGFR	Paclitaxel	1.8 Gy once daily/28 days	Local disease control	Safety and tolerability	Toxicity determined	Acceptable toxicity	I	2009	[63]
	Pancreatic AC	VEGF	Capecitabine	1.8 Gy once daily/28 days	Local disease control	Safety and efficacy	Toxicity and response determined	Large radiation volumes correlated with DLT, no additional response	II	2009	[64]
	Hepatocellular carcinoma	Thalidomide targets	None	2.0. Gy once daily/25 days	Local disease control	Safety and efficacy	Toxicity and response determined	Acceptable toxicity without additional response	II	2012	[65]
Pelvis											
	Gastrointestinal AC	HDAC	None	3 Gy once daily/10 days	Symptomatic relief	Safety and tolerability	DLT and MTD determined	Safe combination, high radiation dose-volume effects contributed to DLT	I	2010,2011	[66,67]
	Prostate AC	EGFR	None	1.8 Gy once daily/28 days, then 2.0 Gy daily/11 days	Definitive	Safety and efficacy	DLT in 16 of 42 patients, response determined	Active combination with significant toxicity	I/II	2010	[68]
	Rectal AC	EGFR	5-FU	1.8 Gy once daily/28 days	Preoperative	Safety and efficacy	Toxicity and response determined	Significant toxicity and additional response	I/II	2008	[69]
	Rectal AC	EGFR	5-FU	1.8–2.0 Gy once daily/25–28 days	Preoperative	Safety and efficacy	Toxicity and response determined	No additional response	II	2009	[70]
	Rectal AC	EGFR	Capecitabine	1.8 Gy once daily/28 days	Preoperative	Safety	DLT in 2 of 6 patients, trial terminated	Significant toxicity	I	2006	[62]
	Rectal AC	EGFR	Capecitabine	1.8 Gy once daily/25 days	Preoperative	Safety and efficacy	Toxicity and response determined	No additional response	I/II	2007	[71]
	Rectal AC	EGFR	Capecitabine	1.8 Gy once daily/25 days	Preoperative	Safety and efficacy	Toxicity and response determined	No additional response	II	2010	[72]
	Rectal AC	EGFR	5-FU and oxaliplatin	1.8 Gy once daily/28 days	Preoperative	Safety and efficacy	Toxicity and response determined	Significant toxicity without additional response	II	2011	[73]
	Rectal AC	EGFR	Capecitabine and oxaliplatin	1.8 Gy once daily/28 days	Preoperative	Safety and efficacy	Toxicity and response determined	No additional response	I/II	2008	[74]
	Rectal AC	EGFR	Capecitabine and irinotecan	1.8 Gy once daily/28 days	Preoperative	Safety	DLT determined	Safe combination	I	2006	[75]
	Rectal AC	EGFR	Capecitabine and irinotecan	1.8 Gy once daily/28 days	Preoperative	Safety and efficacy	Toxicity and response determined	No additional response	II	2009	[76]
	Rectal AC	EGFR	Capecitabine and irinotecan	1.8 Gy once daily/28 days	Preoperative	Safety and efficacy	Toxicity and response determined	No additional response	II	2011	[77]
	Rectal AC	VEGF	5-FU	1.8 Gy once daily/28 days	Preoperative	Safety and efficacy	Toxicity and response determined	Safe and active combination	I/II	2009	[78]

(*continued on next page*)

Table 1 (*continued*)

Anatomical site	Tumor type	Molecular drug target(s)	Other concomitant systemic agent(s)	Radiation dose fractionation schedule	Therapeutic intent	Study endpoint(s)	Study outcome	Conclusion	Clinical phase design	Publication year(s)	Reference(s)
	Rectal AC	VEGF	Capecitabine	3.4 Gy once daily/15 days, split-course, hypofractionated accelerated	Local disease control	Safety and efficacy	Toxicity and response determined	Significant response	I/II	2009	[79]
	Rectal AC	VEGF	Capecitabine	1.8 Gy once daily/28 days	Preoperative	Safety and efficacy	Toxicity and response determined	Safe and active combination	II	2010	[80]
	Rectal AC	VEGF	Capecitabine	1.8 Gy once daily/28 days	Preoperative	Safety and efficacy	Toxicity and response determined	No additional response	II	2011	[81]
	Rectal AC	VEGF	Capecitabine	3.4 Gy once daily/10 days, hypofractionated accelerated	Preoperative	Safety and efficacy	Toxicity and response determined	Additional toxicity and additional response	II	2011	[82]
	Rectal AC	VEGF	Capecitabine	1.8 Gy once daily/28 days	Preoperative	Safety and efficacy	Toxicity and response determined	Safe and active combination	II	2012	[83]
	Rectal AC	VEGF	Capecitabine	1.8 Gy once daily/28 days	Preoperative	Safety and efficacy	Toxicity and response determined	Active combination with acceptable toxicity	II	2012	[84]
	Rectal AC	VEGF	Capecitabine	1.8 Gy once daily/28 days	Preoperative	Safety and efficacy	Toxicity and response determined	Additional response and additional surgical complications	II	2011	[85]
	Rectal AC	VEGF	Capecitabine	1.8 Gy once daily/25 days	Preoperative	Safety and efficacy	DLT in 4 of 8 patients, trial terminated	Significant toxicity	II	2012	[86]
	Rectal AC	VEGF	5-FU and oxaliplatin	1.8 Gy once daily/28 days	Preoperative	Safety and efficacy	DLT in 19 of 25 patients, trial terminated	Significant toxicity without additional response	II	2012	[87]
	Rectal AC	VEGF	Capecitabine and oxaliplatin	1.8 Gy once daily/28 days	Preoperative	Safety and efficacy	DLT in 5 of 11 patients, response determined	Active combination with significant toxicity	I	2007	[88]
	Rectal AC	VEGF	Capecitabine and oxaliplatin	1.8 Gy once daily/28 days	Preoperative	Safety and efficacy	Toxicity and response determined	Active combination with acceptable toxicity	II	2012	[89]
	Prostate AC	VEGF	Androgen deprivation	77.9 Gy in 38 fractions	Local disease control	Safety	Toxicity determined	10 late DLTs in 18 patients	II	2012	[90]
	Prostate AC	COX-2	None	2.0 Gy once daily/35–37 days	Definitive	Safety	Toxicity determined	No additional toxicity	I	2006	[91]
Skin											
	T-cell lymphoma	HDAC	None	Various	Symptomatic relief	Feasibility	Measurements of response	Significant response without additional toxicity	Case reports	2012	[92]
	SCC	EGFR	None	Not specified	Definitive	Safety and efficacy	Toxicity and response determined	Active and well tolerated combination	II	2012	[93]

Multiple											
	Soft-tissue sarcoma	VEGF	None	1.8 Gy once daily/28 days	Preoperative	Safety and efficacy	Toxicity and response determined	Significant response	II	2011	[94]
	Oligometastasis	VEGFR + PDGFR (multitargeted agent)	None	4.0–6.0 Gy once daily/ 10 days	Local disease control	Safety and efficacy	DLT, MTD, and response determined	Phase II dose of systemic agent determined	I	2009	[95]
	Multiple	PI3K/AKT	None	Various	Symptomatic relief	Safety and tolerability	DLT and MTD determined	Safe combination	I	2006	[96]

Data were retrieved from PubMed (http://www.ncbi.nlm.nih.gov/pubmed?db=pubmed) as of January 25, 2013, following searches combining the term "radiation OR radiotherapy" with the term "targeted AND therapy" or with each of the terms "EGFR", "cetuximab", "panitumumab", "gefitinib", "erlotinib", "angiogenesis", "bevacizumab", "trastuzumab", "lapatinib", "sunitinib", "sorafenib", "mTOR", "imatinib", "dasatinib", "pazopanib", and "histone deacetylase" separately. The search was limited to Clinical Trial as article type, and the retrieved data were curated to include trials with a design no more advanced than non-randomized phase 2 and to exclude trials using stereotactic radiation techniques or particle therapy.

Abbreviations: GBM, glioblastoma multiforme; SCC, squamous cell carcinoma; NSCLC, non-small cell lung carcinoma; AC, adenocarcinoma; VEGF, vascular endothelial growth factor; PDGFR, platelet-derived growth factor receptor; MET, met oncoprotein; EGFR, epidermal growth factor receptor; RAS, Ras-kinase; mTOR, mechanistic target of rapamycin; ERBB2, HER-2/neu oncoprotein; COX-2, cyclooxygenase-2; HDAC, histone deacetylase; PI3K/AKT, phosphatidylinositol-3-kinase/Akt-kinase; 5-FU, 5-fluorouracil; MTD, maximum-tolerated dose; DLT, dose-limiting toxicity.

sequential patient cohorts exposed to escalating dose levels of the HDAC inhibitor vorinostat combined with pelvic palliative radiotherapy for advanced gastrointestinal malignancy, was the first to report on the therapeutic use of an HDAC inhibitor in clinical radiotherapy. It was designed to demonstrate a number of key questions; firstly, whether the investigational agent reached the specific target (detection of tumor histone acetylation), secondly, the applicability of non-invasive tumor response assessment (using functional imaging), and importantly, that the combination of using an HDAC inhibitor together with radiation was safe and tolerable.

In general, phase I studies are first-in-human explorations of new therapeutic principles, typically a single-agent systemic compound with the determination of safety being the primary study objective. By convention, treatment tolerability is defined by dose-limiting toxicity (DLT) and maximum-tolerated dose (MTD) [110]. A DLT is a toxic effect related to the treatment and that is considered unacceptable because of its severity or irreversibility, or both, and is typically specified using standardized grading criteria. The assessment of MTD is based on dose escalation and is often defined as the highest dose level at which no more than one-third of patients experience DLT. The ultimate goal of a phase I trial is therefore to establish a recommended dose, which ideally is both a safe and efficacious dose, that can be subsequently used in follow-up expanded phase II efficacy trials.

In contrast to studies that examine the use of a single compound, the combination of a new systemic agent with radiation is a more complex trial setting that demands special consideration of study design and endpoints that reflect both radiation effect and potential independent and overlapping toxicities. Integrating targeted drugs into early-phase radiotherapy trials will also need particular attention on more stringent definition of patient eligibility, including the issue of restricting the study population to an anatomically defined, advanced stage of disease that is treatable with radiotherapy, the definition of radiation dose–volume relationships, and the evaluation of normal tissue toxicities. Based on our recent translational study experiences, this communication will summarize a number of principles relating to early clinical evaluations of radiotherapy with targeted therapeutics.

Preclinical proof-of-concept

Experimental radiosensitization

A thorough preclinical evaluation is an absolute prerequisite for the subsequent development of early-phase protocols combining radiotherapy with targeted therapeutics. The candidate substance should be evaluated, using appropriate assays in relevant experimental tumor models, to establish evidence of enhancement of *in vitro* and *in vivo* radiation-induced inhibition of clonogenicity, while at the same time recognizing that preclinical assessment of radiosensitizing ability is no guarantee that a drug will work in the clinical situation. Importantly, the final decision of further clinical implementation should also take into account that study endpoint deficiencies in preclinical models may be specific for the species or experimental design and hence, may not necessarily translate into lack of clinical efficacy.

Experimental tumor models

Locally advanced rectal cancer is an example of an ideal model system to explore the possible role of tumor hypoxia in a defined clinical context. Whilst randomized studies have highlighted the central role of neoadjuvant radiotherapy/chemoradiotherapy in conjunction with surgical resection to eradicate tumor within the pelvic cavity and improve long-term outcome [111], inherent tumor resistance to the neoadjuvant treatment is seen in a subgroup

of patients. In regard to the PRAVO study, our systematic investigation of HDAC inhibitors as radiosensitizing agents was initiated in experimental *in vitro* and *in vivo* human colorectal carcinoma models, and demonstrated that vorinostat and other HDAC inhibitors significantly enhanced radiation-induced clonogenic suppression [107–109]. Recently, using the same tumor models, we also demonstrated experimental radiosensitization by vorinostat under hypoxic conditions [112]. In addition, a range of experimental studies performed by other investigators have shown that HDAC inhibitors reduce the capacity of the tumor cells to repair radiation-induced DNA damage, both at the level of damage signaling and by affecting the major DNA repair pathways [104].

Patient eligibility

Non-curative radiotherapy

In the context of combining a systemic targeted agent with radiotherapy, it is acknowledged that the delivered radiation dose may on occasion be close to normal tissue tolerance. Any DLT that causes an interruption in the radiation delivery is likely to have a negative impact on the probability of tumor control. For that reason, in a trial setting of evaluating tolerability by defining treatment toxicity of a first-in-human combination of radiation with a targeted therapeutic, only patients that are not candidates for any curative radiotherapy protocol should be regarded as eligible. In Norway, for example, where the PRAVO study was conducted, committees for medical and health research ethics as a general principle will waive approval of first-in-human experimental therapeutic approaches in patients with curative intention of standard treatment; we believe that this will be an approach adopted in many European and other countries.

To enable correct interpretation of the study data, patients should be required to have recovered from acute toxicities of any prior therapy regardless of duration of the preceding period off active treatment. On the other hand, cancer patients that are not candidates for curative radiotherapy are often in an advanced disease stage and commonly in need of further treatment, usually palliative systemic therapy. Therefore, in order to prevent unnecessary restriction in patient eligibility, study patients should be allowed to commence treatment they otherwise would have been offered after completion of the study's radiotherapy course. However, any toxicity appearing before the end-of-study evaluation should be recorded, even if considered to be unrelated to the study treatment, and evaluated for possible interrelations to this, as was done in the PRAVO study.

Curative radiotherapy

Importantly, treatment toxicity from combined-modality targeted therapeutics and radiotherapy will commonly be different in a palliative regimen compared with an intensified curative radiation schedule, as further discussed below. Hence, in considering the clinical implementation of a systemic agent with radiosensitizing activity following a first-in-human testing of safety in a palliative setting, the combination will require new evaluation in patients that are candidates for curative protocols. The challenge of radiotherapy encountering toxicity at the limits of normal tissue tolerance, particularly when being used as curative modality, must be specifically addressed with regard to patient eligibility. In this setting, it has been suggested to conduct trials in patient groups with historically poor treatment outcomes, for example locally advanced lung cancer or pancreatic cancer [113]. Of note in this regard, one-third of early-phase studies that were identified with definitive or preoperative therapeutic intent reported significant toxicity (Table 1).

Tumor location

A standard phase I study conducted to evaluate a single-agent systemic compound will typically allow a wide range of tumor types in end-stage disease. In contrast to early-phase safety studies with systemic therapies, where disease location is less critical for the evaluation of treatment tolerability, in radiotherapy trials the anatomical site of the target lesions determines the adjacent organs at risk. To enable full interpretation of the outcome toxicity data of early-phase radiotherapy and targeted therapeutics studies, both the tumor type and the potential anatomical disease site being irradiated will need to be clearly specified within the study's eligibility criteria. Additionally, as shown in the PRAVO study and discussed below, this will ultimately allow the assessment of treatment efficacy and the application of pharmacodynamic biomarkers.

Radiotherapy technique and administration

Target volumes and dose–volume constraints

In some studies, it is likely that acute radiation-induced toxicities may comprise a major contribution to the total toxicity profile; hence, the radiation technique should be reported in detail. As a minimum, the description should include precise definitions of specific target volumes (gross tumor volume and clinical and planning target volumes), tumor dose and dose fractionation, overall treatment time, and dose variations within all relevant organs at risk. Data defining the relevant dose–volume constraint and dose–volume histograms should also be made available either in graphical format or as supplemental information. The study protocol may also specify a more sophisticated description of dose–volume constraints, according to the recent QUANTEC recommendations [114].

Ultimately, the descriptions of detailed radiation dose–volume dependencies within the treatment protocol may facilitate identification of adverse radiation effects that are separate from toxic effects of the investigational systemic agent, and also adhere to the requirement for radiation dose–volume effects to be reported in a standardized manner. For example, in our experience of the PRAVO study, when protocols employ simple or multifield techniques that result in unavoidable irradiation of the bowel, moderate to severe acute gastrointestinal toxicity, primarily diarrhea, is observed in a number of patients. Furthermore, the probability and severity of such effects increase with the size of the therapeutic target volume and the dose per fraction [115]. Within the PRAVO study, the predominant DLTs reported by the study patients were gastrointestinal adverse events, representing a toxicity profile of either vorinostat [105] or indeed radiotherapy to pelvic target volumes. In this setting, it was difficult to decide whether or not a toxic event occurring during treatment was greater than might be expected for either of the therapeutic components, and specifically whether the event should be considered a DLT of the systemic agent [66]. In a reanalysis of the study data, quantification of radiation dose–volume effects enabled us to consider a more precise interpretation of the contribution of vorinostat to the overall toxicity profile [67]. Similar considerations have also been noted by other investigators (Table 1; [47,64]).

Treatment administration

The timing of administration of the systemic drug with regard to radiation exposure should also be given. This will be important in examining the utility of any pharmacodynamic biomarker demonstrating the presence of the investigational agent in the radiotherapy target tissue, and ideally also reflecting the general mechanism of drug action. Within the PRAVO study, tumor histone

acetylation was considered a biomarker of vorinostat activity [116]. Importantly, in prior preclinical *in vivo* studies, we had also observed that tumor histone acetylation reached a maximum three hours after intraperitoneal vorinostat injection into experimental animals [109]. Hence, within the PRAVO study, one patient at each vorinostat dose level had both a baseline and a repeat tumor biopsy two-and-a-half hours after the daily oral administration of vorinostat (on day 3 of the treatment protocol). Of note, histone acetylation was observed in all on-treatment biopsy samples, confirming that biological drug activity was achieved at the time of the daily radiation exposure, and supporting the temporal relationship of delivering the radiotherapy three hours after vorinostat administration.

Endpoints

Dose and toxicity parameters

The ultimate goal of a first-in-human therapy trial is to conclude with a recommended treatment dose for follow-up expanded efficacy trials, and in achieving this, a phase I study typically is designed to determine treatment toxicity and tolerability (in terms of DLT and MTD, respectively) [110,117], as detailed below. For molecularly targeted agents, the dose that results in a relevant level of target modulation may differ greatly from the MTD, and generally, we do not have a good understanding of the relationship between the MTD and the dose required to achieve the desired therapeutic effect. An optimum biological dose may be the dose that meets a predefined level of inhibitory activity on a key target in the tumor or a surrogate tissue; that is the dose that is associated with a preselected pharmacodynamic biomarker reflecting the mechanism of drug action. This implies that proof of biological activity of the investigational agent that is relevant for the radiosensitizing ability should be regarded as a main objective in early-phase radiotherapy trials with targeted therapeutics.

As mentioned above, within the PRAVO study, tumor histone acetylation was considered to be the mechanism of action conferred by the investigational systemic drug. This was observed in therapy targets at all dose levels of vorinostat, highlighting that biological activity was achieved at the lowest examined dose, and in addition, suggesting that the optimum biological dose on concomitant use with radiotherapy may be lower than the determined MTD (second highest dose level).

Pharmacodynamic and surrogate response parameters

In general, early-phase therapy studies accrue a limited number of patients, inevitably with some heterogeneity in cancer types and disease sites, and any study endpoints beyond treatment safety and tolerability may therefore lack strength. Nevertheless, in any experimentation using humans, inclusion of additional endpoints should be encouraged, and patients eligible for and willing to participate in a biomarker substudy should be requested to sign a separate consent regarding the additional procedures.

Pharmacodynamic and surrogate response data may be collected by functional imaging as an alternative to tissue biopsy sampling. This is particularly relevant where biopsies from deep-seated tumors in patients with advanced disease are hazardous and, if associated with complications, will place additional suffering onto the patient or delay the commencement of the therapy. In addition to ethical concerns pertaining to the requirement for the inclusion of biopsies in clinical trials, practical issues may relate to the availability and quantity of the tissue retrieved, and whether the obtained tissue samples are high-quality research material. Moreover, the clinical study design as such may be incompatible with high-standard procedures for biomarker identification. If an objective is to determine mechanisms of action, as opposed to biological activity, of the investigational agent in the radiotherapy target, tumor specimens for this particular purpose cannot be sampled after the patient has commenced the radiation treatment. Any regulatory activity in on-treatment samples would reflect the combined effect of radiation and the systemic drug, and the contribution of the latter would probably be indiscernible from the effect of the actual accumulated radiation dose. Instead, studies can be designed such that patients receive the study drug for a period before starting the radiotherapy course, for example during the treatment planning period. In that setting, it is also possible to randomize the patients between the investigational drug and placebo [113].

Traditionally, in phase I studies testing single-agent systemic compounds, response measurements have commonly been forgone as such evaluations may not be seen as meaningful in patient populations comprising a wide range of tumor types in end-stage disease. However, if the study eligibility criteria of an early-phase radiotherapy trial with a targeted drug employ the recommended principle that tumor type and anatomical locations of the radiotherapy target lesions should be restricted, the more homogeneous patient population that possibly results from this strategy may be more like a traditional phase II study population and may therefore enable treatment response evaluation by either conventional methods or novel investigational approaches. Within the PRAVO study, comprising a relatively homogenous patient population with advanced gastrointestinal malignancy manifested adjacent to or within the pelvic cavity, serial diffusion-weighted magnetic resonance imaging allowed correlation of the individual patient's change in tumor apparent diffusion coefficient with tumor volume measurements, to evaluate the use of the former modality as a surrogate biomarker of treatment response.

Pharmacokinetic parameters

Detailed recording of pharmacokinetic variables is a major objective in first-in-human testing of therapies. Presumably, in the setting of an early-phase study combining radiotherapy and a systemic drug, the molecularly targeted compound of interest has already been thoroughly investigated as single-agent therapeutic. If this is the case, pharmacokinetic characteristics are well known and further analysis may be omitted. On the contrary, there may be a need to verify the single-agent data when used with radiotherapy. Conceptually, pharmacokinetic variables might be affected by organ-based changes following irradiation as any change in treatment response or adverse effects may be non-linear. For example, in the early gene therapy work, radiation was found to increase vector transfection efficiency [118]. Moreover, there is currently a deficiency in the knowledge about biological effects of radiation within low-dose volumes that are inevitably irradiated when applying advanced technologies. Most systemic compounds are eliminated by hepatic or renal metabolism, and in a recent experimental model, it was demonstrated that the off-target radiation dose to the liver significantly reduced the bioavailability of the radiosensitizing drug [119].

Design

Dose escalation protocols

The conventional 3 + 3 expansion cohort design remains the prevailing method for conducting first-in-human trials in cancer therapy [110,120]. The rationale for the design is pragmatic with regard to documenting adverse events associated with the administration of new therapies, as it requires no modeling of the dose-toxicity curve beyond the classic assumption for cytotoxic agents, including radiotherapy, that toxicity increases with dose. This design, em-

ployed in the PRAVO study, involves treating cohorts of patients with gradually increasing doses of the investigational agent. Typically, patients are enrolled onto sequential dose levels of the drug from a starting dose and with a defined dose escalation. Often, one patient is entered at each dose level until moderate symptoms related to the therapy appear. From a dose level with moderate symptoms, dose escalation take place for every third evaluable patient that has completed the preceding level. An individual patient cohort is expanded up to six if one of the three initial patients experiences a DLT. If two patients at a given dose level experience a DLT, the MTD is determined as the preceding dose level, provided an observed incidence of DLT in no more than one of the six patients.

In combination with a prescribed radiotherapy schedule, either the dose in itself or the duration of the investigational systemic compound may be escalated. With the latter, the objective is to escalate the number of radiation fractions that are potentially sensitized by the drug with the ultimate goal to combine the two modalities for the entire radiation course [113]. Hence, a single drug dose is administered throughout the study, but successive patients cohorts receive the drug combined with radiotherapy concomitantly for progressively longer periods.

Alternatively, dose escalation of the systemic agent may follow a modified Fibonacci sequence, in which the dose increments become smaller as the dose increases. A disadvantage of this design, however, is that it often may involve an excessive number of escalation steps. The application of accelerated titration designs may compensate for a lengthy trial period and make the study conduct more efficient. Various types of accelerated dose titration methods have been described in recent reviews [110,117]. All the methods are based on an initial rapid increment in doses involving one or two patients or intrapatient dose escalation, until a DLT or alternatively two moderate toxicities in accordance with a predefined stopping rule are observed, at which point the dose adjustment method is converted to a more conservative one and with the possibility to do dose deescalation during the course of patient enrollment. Alternatively, when the single-agent MTD is already known and the delivered radiation dose is close to the limits of normal tissue tolerance, which may often be the case, as few as two or three dose levels of the investigational drug can be used to perform an efficient and safe phase I trial.

Traditional phase I trial methods are convenient to employ as they are both simple to implement and safe. A review of dose escalation methods used in clinical practice showed that the vast majority of phase I trials published have used the 3 + 3 design or variations [110].

Adaptive protocols

An alternative dose finding method for early-phase trials is to use statistical models that actively seek a dose level that produces a prespecified probability of the chosen endpoint on the basis of the outcome data from all patients previously treated in the trial. In this way, adaptive designs check data during the course of the trial and incorporate this existing information as it accrues, to decide how to treat the next study patient. However, despite the initial enthusiasm for novel dose-finding methodologies, such trial designs are uncommon in clinical trial practice, mainly because of computational complexity and unfamiliarity with practical implementation [120]. Recognizing this experience in the trial community, it remains uncertain to what extent statistical model-based designs will be applicable to early-phase radiotherapy trials with targeted therapeutics.

In a trial employing a potential radiosensitizing agent, the demonstration of its presence in the radiotherapy target tissue at achievable drug concentrations by a biomarker reflecting its biological activity may be used to support the selected schedule of the combination treatment. As mentioned above, within the PRAVO study, histone acetylation was observed in the therapy target at the lowest dose level of vorinostat, which was far below the determined MTD. Hence, if an adaptive trial design based on this biomarker had been applied, information on treatment tolerability would not have been revealed. Moreover, many biomarkers for novel agents are minimally validated at the time of early-phase clinical trials; thus, a tight adaptation of the trial design to biomarker examination may be counterproductive.

Statistical analysis

Generally, for early-phase trials, the size of the study population is limited. Thus, the resulting data will usually be solely descriptive. If statistical adaptation is required, the use of standard statistical methods may probably be sufficient.

Toxicity recording

Toxicity assessments

In radiotherapy, toxic complications are both common and acceptable, and late adverse events may be significant. Adhering to the principle that only patients in a non-curative disease setting should be eligible for initial (first-in-human) radiotherapy trials with targeted therapeutics, the issue of late toxicity may be a less essential endpoint. However, a systemic agent with radiosensitizing activity will ultimately need to be evaluated as a component of a curative treatment regimen, and in this context, late toxicity is likely to be the major safety consideration dictating the feasibility of the new combination, as discussed below. Currently, there is no consensus as to how to balance the risk of late toxicity against the benefit of developing a new therapeutic concept that may ultimately improve local disease control and survival, other than careful implementation of the new treatment based on interpretation of outcome data from already conducted studies of radiotherapy combined with targeted therapeutics in the palliative setting. To date, late adverse events have been reported in a few trials where local control was the therapeutic intent (Table 1; [34,37,38,90]).

The Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 was established as a system for recording acute and late toxic effects with all types of cancer therapy and to uniform severity scaling. Close attention was paid to the boundary between grade 2 and grade 3, demarcating a clearly higher level of severity [121]. CTCAE grade 3 toxicity reflects severe injury and implicates events that commonly trigger dose reduction or other therapy adjustments in addition to intensified supportive care intervention. In radiotherapy, a dose reduction is often manifested as interruption or premature cessation of the treatment and is likely to have a negative impact on outcome [122].

In the early-phase trial setting of testing a targeted drug in patients receiving radiotherapy, any acute CTCAE grade $\geqslant 3$ toxicity related to radiation exposure of normal tissues should be considered a DLT, as should a treatment delay longer than a predefined period. Treatment-related adverse events will represent cumulative toxicities, as they generally appear on completion of the treatment course or in the immediate follow-up period, which is typically associated with radiotherapy. Hence, as was implemented in the PRAVO study, toxicity should be recorded continuously during the duration of the treatment and reexamined for example two and six weeks after treatment completion to observe the full course of appearance of the toxicity profile. In line with this, subsequent patient cohorts should not be treated until the defined evaluation window is closed, and additionally, patients discontinuing the investigational drug should be regarded as non-

evaluable for DLTs and therefore replaced within the study protocol.

Toxicity issues in follow-up expanded efficacy trials

The PRAVO study also illustrated a central issue with regard to possible transition to a phase II efficacy study, as one might question whether the MTD that was determined for vorinostat in combination with pelvic palliative radiotherapy might be tolerable in an intensified curative radiation schedule, for example vorinostat as an additional component of neoadjuvant chemoradiotherapy for locally advanced rectal cancer. We believe that the design of a trial to investigate vorinostat as a possible radiosensitizing agent with long-term curative pelvic radiotherapy should take into account both intensity and duration of the phase I toxicity profiles and ideally, to diminish the hazard of treatment interruption caused by acute toxicity, would have a phase I/II design with a starting vorinostat dose below the MTD obtained in the PRAVO study. We equally believe it is important to determine a new MTD for a long-term schedule, even though the PRAVO study clearly demonstrated the presence of vorinostat in the radiotherapy target tissue at dose levels far below the phase I MTD. At the current stage, it is obviously unknown whether there may exist linearity in terms of drug doses between tumor histone acetylation and yet uncharacterized biomarkers of the radiosensitizing action of the HDAC inhibitor. As long as minimal validation of a mechanistic rationale for using a molecularly targeted compound remains, a traditional dose escalation study design should prevail.

Conclusions

The following summarizes our recommendations on principles for the design and conduct of early-phase radiotherapy trials with targeted therapeutics.

Preclinical proof-of-concept

The investigational drug should have been proven to facilitate biological mechanisms of radiosensitization in relevant preclinical tumor models.

Patient eligibility

Study patients should have tumor manifestations within a restricted anatomical location, to provide a relatively homogeneous patient population that enables the evaluation of relevant treatment toxicity, pharmacodynamic biomarkers, and therapy response. For a first-in-human evaluation of radiation combined with a targeted therapeutic, only patients that are not candidates for any curative radiotherapy protocol should be regarded as eligible, to avoid compromising the probability of tumor control in curative treatment should any DLT cause interruption in radiation delivery.

Radiotherapy technique and administration

Description of the target volume and in particular, dose variations within the organs at risk will be required. In addition, the temporal relationship of the administered systemic agent and the radiation course should be given.

Endpoints

Types of endpoints should include toxicity (DLT) and tolerability (MTD), as well as a suggested optimum biological dose defined by a pharmacodynamic biomarker reflecting the mechanism of drug action.

Design

Either the dose in itself or the duration of the investigational drug may be escalated, and deescalated, if required, in successive patient cohorts. The escalation schedule may be adapted to a biomarker of the proposed mechanism of drug action.

Toxicity recording

The CTCAE version 3.0 or higher is recommended as the toxicity scoring system, and any grade $\geqslant 3$ toxicity should be considered a DLT, as should a treatment delay beyond a predefined length of period. Treatment-related adverse events in radiotherapy typically represent cumulative toxicities; hence, toxicity should be recorded continuously during the duration of treatment and reexamined after treatment completion and a prolonged follow-up period, when expedient, to observe the full course of appearance of the toxicity profile.

Conflict of interest statement

The PRAVO study received support from Merck & Co., Inc. directed at supporting recruitment and overheads associated with the study; however, this funding source had no role in the study design or collection, analysis, and interpretation of data.

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