

Radiotherapy and new drugs for solid tumors: what is known and what is not?

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RAO

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POSITION PAPER INDEX

1		Introduction	Authors	Page 5			
2		Materials and methods		8			
3		Results		10			
	3a	First explored Monoclonal Antibodies					
		anti EGFR (cetuximab, panitumumab)	LB, RC	10			
		anti HER 2 (trastuzumab – pertuzumab)	IM, CB, LL	49			
		anti VEGF (bevacizumab)	DG, LC	58			
	3b	Small molecules					
		TKI (tinib)	FA, RM	78			
		TKI (nib)	SR, RDA, MF,CG	93			
		cyclin dependant kinase(CDK) inhibitors (ciclib)	FA, RM	117			
		poli-ADP-ribose polymerase (PARP) inhibitor (parib)	FA, RM 120				
		PI3K/mTOR dual inhibitors	SR, RDA, MF, CG 12				
		BRAF inhibitors	SR, RDA, MF, CG	139			
		Hedgehog signalling pathway inhibitor (erivedge, sonidegib	SP, AS	156			
	3c	Immune Check Point Blockade	AF, AM, MT, LB, FM	174			
	3d	Androgen Pathway Therapy					
		Abiraterone	FA, RM	189			
		Enzalutamide	GM, BJ	192			
		Other new androgen pathway drugs	MB, SM	200			
4		Take Home Messages	CA, IP	232			
5	5.1	Key Messages		243			
	5.2	Summary Table with Quality of Evidence and Strenght of		250			
		Recommendation					
6		Conclusions		251			



1. Introduction

Just a decade ago, only a limited range of therapeutic strategies was available with emerging evidences of new targeted molecules responsible for disease development and progression of both malignant and non-malignant diseases. For the treatment of malignant diseases, a number of conventional genotoxic and/or cytotoxic anticancer agents were generally utilized as a single agent but mostly in combination with Radiation Therapy. Recently, innovative therapeutics were envisaged which would aim at specific molecules responsible for disease pathogenesis for improved therapeutic outcomes. The outcomes obtained with innovative biological agents have been excellent for the control of some locally advanced cancers (i.e. GIST, melanoma, myeloid leukemia) but for others the efficacy has been surprisingly limited when compared with preclinical experimental data.

In the last years Radiation Oncologist has been daily facing the challenge to associate these new biological agents with radiotherapy: the best strategy has been to explore the Radiotherapy/Targeted Therapy/Immunotherapy strategy within a controlled clinical trial in order to assess new toxicity and test efficacy in cancer control. In other clinical settings, outside of clinical trial, Radiation Oncologist remained and still remains puzzled on the potential clinical effects of these new associations due to the potential risk to add toxicity to the patients without a true clinical benefit. The main reason of this critical issue is related to the lacking data emerging from translational research on the biological effects in vitro or in vivo by combining radiation with a new agent. The classic multi-step process consisting of design and enrollment of patients in Phase I-II and III trials generally does not include the associations of the new explored agent with radiotherapy or versus radiotherapy alone.

Of consequence, in clinical practice many concerns remain regards as:

- the indications or the contraindications to associate radiotherapy concomitantly with a new targeted therapy or immunotherapy



- the knowledge of the best timing of the association of two modalities (radiotherapy and innovative drug)
- the potential risk of inducing unexpected acute or late reactions with new association modalities
- the potential risk to reduce the dose of radiotherapy when associated with a new agent consequentially by increasing the risk of a lower control rate of tumor otherwise well controlled with full radiation dose.

These daily questions, often debated in multidisciplinary settings, are correlated to the unknown radiobiological mechanisms of interaction of new agents with radiotherapy: if spatial cooperation may offer safe combinations of radiation with drugs, addictive or supraddictive effects of new drug with radiations could improve the clinical outcome but inducing potential severe side effects.

In November 2016 the Board of the Italian Association of Radiation Oncology (AIRO) decided to give to the own Member the opportunity to browse a Position Paper entitled "*Radiotherapy and new drugs for solid tumor: what is known and what is not*" in order to increase the actual status of emerging agents which may currently be associated with Radiotherapy. A group of Italian Radiation Oncologists was chosen on the basis of their expertise documented on their recent paper publication on this topic. The main task of the Experts was, as specified the Materials and Methods Section, to focus the literature research on innovative drugs associated with radiotherapy in experimental approaches or in controlled clinical trial.

The present Position Paper aims also to give Key Messages to the AIRO Members about the Risks and/or Benefits of combinations of radiotherapy with new drugs listed in the following **Table I**.

 Table I – Novel Drugs recently introduced in clinical practice and potentially associated with Radiotherapy.

First explored Monoclonal Antibodies - anti EGFR (cetuximab, panitumumab) - anti HER2 trastuzumab – pertuzumab



- anti VEGF (bevacizumab)

Small molecules

- TKI (tinib)
- TKI (nib)
- cyclin dependant kinase(CDK) inhibitors (ciclib)
- poli-ADP-ribose polymerase (PARP) inhibitor (parib)
- PI3K/mTOR dual inhibitors
- BRAF inhibitors
- Hedgehog signalling pathway inhibitor (erivedge, sonidegib)

Recent Monoclonal Antibodies: Immune Check Point Blockade

Androgen pathway therapy

- Abiraterone
- Enzalutamide
- Other new androgen pathway drugs

A big effort to indicate the Therapeutic Index (Increased /stable/decreased) of RT/TT/Immunotherapy new associations has been made from the Expert Panel, trying also to evidence a Grade of Recommendations of the delivery of a novel biological drug associated in clinics with radiotherapy. Radiotherapy is considered administered "concurrently" with Systemic Therapy when administered in a period less than five half-lives of the drug. The half-live of some of novel biological drugs used in the cure of solid tumors are listed in Appendix 1 at page 231.



The final impact of the Position Paper is to drive Radiation Oncologist to a better clinical decision in oncological treatment by learning better the recent literature data and well adapting the emerging data on the individual patient.

2. Materials and Methods

Search strategy

For every group of innovative drug potentially delivered with radiotherapy to patients with solid cancer the Authors were invited to describe:

Background of novel drug

- Mechanisms of actions (free research)
- Potential interaction with radiotherapy (free research)
- Preclinical <u>data</u> (free research)

Foreground Questions

- Clinical data on efficacy and toxicity (research according PICO Criteria see Table II)
- Summary

TABLE II PICO RESEARCH (questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design-->

 pico search Medline/pubmed NIH):

P: Population - Cancer patients treated with innovative drug or new class of innovative drug

I: Intervention- Innovative Drug plus Radiotherapy (with indication of body cancer site and, if available of fractionation and timing of irradiation)

C: Comparison- innovative drug plus radiotherapy versus drug alone or radiotherapy alone (if available) (optional)



0: Outcome → Cancer control efficacy and Patient Tolerability/Toxicity (Therapeutic Index or Balance)

The key issue was formulated in one final question: "Is the association of the novel drug with radiotherapy recommended in the clinical practice"?

The issues to collect in order to answer to the Key question are listed see **Table III**. The literature search was performed in the following databases and online trial registry from January 2005 to May 2017: MEDLINE, EMBASE, Cochrane Database of Systematic Reviews and Cochrane Controlled Trials Register. Reference lists of retrieved studies were also searched. Titles and abstracts were screened independently by twelve teams of Authors to determine relevant references to include for full-text reviews.

TABLE III: DATA TO COLLECT FROM RECENT LITERATURE DATA for EVERY INNOVATIVE DRUG

Drug (dose)	Author and year	Study type	Number pts	Tumor site	RT technique/dose /fractionation	Combination (concomitant, other.)	Toxicity	Tumor outcome	Comments

Selection criteria for full-text article review

Publications were eligible for inclusion in the full text review if the following criteria were satisfied: (1) published as a full article in peer-reviewed journals; (2) any histology; (3) photon external beam RT techniques with or without concurrent innovative biological agent; (4) follow-up of at least one year; (5) at least one of the considered outcomes (efficacy and/or safety) reported; (6) articles written in English language; (7) articles with patients treated with radical or palliative intent.

The following studies were included: interventional, observational, prospective, retrospective.



Finally, two Authors collected data emerging from Phase III Trial comparing innovative drug plus Radiotherapy vs Radiotherapy alone or Drug alone and reported TAKE HOME MESSAGES (emerging from Randomized trial), KEY MESSAGES (emerging from all the data reviewed) and a SUMMARY EBM TABLE (with the potential Strength of Recommendation of the association of radiotherapy with a specific innovative drug) according to SIGN Criteria.

3. <u>Results</u>

3.a First Explored Monoclonal Antibodies combined with Radiotherapy

- anti EGFR (cetuximab, panitumumab)

LB-RC

The epidermal growth factor receptor (EGFR) is a receptor tyrosine kinase belonging to the ErbB family. EGFR consists of an extracellular domain, a single transmembrane region, and a cytoplasmic kinase domain (1). There are several known ligands for EGFR including EGF, TGF α , HB-EGF, amphiregulin, betacellulin, epigen, and epiregulin (2). Upon ligand binding, EGFR forms a dimer and specific tyrosine residues are phosphorylated promoting signal transduction (3) through many pathways including PI3k/Akt (4), Ras-MAPK (5), STAT (6) and PLC γ (7). Activation of these pathways promotes several cellular processes including proliferation, migration and invasion, transformation, differentiation, and angiogenesis (8). Overexpression or upregulation of EGFR is seen in many types of malignancies including lung (9), head and neck (10), esophageal (11) and



colorectal cancers (12) and is directly implicated in disease initiation and progression, resistance to therapy, and poor prognosis.

Due to its important role in cell proliferation and other cellular processes, EGFR is an attractive target for cancer therapy.

Several EGFR targeted drugs are FDA approved for clinical use including the antibodies cetuximab and panitumumab.

Potential interaction with radiotherapy:

The mechanism of radiosensitization with EGFR inhibitors is complex; ionizing radiation (IR) 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 sensitivity of cells to IR (13) EGFR's role in the radiation response include also the activation of pro survival pathways and enhance cell proliferation (14-16).

PRE CLINICAL DATA:

The ability of cetuximab as a radiosensitizer has been demonstrated in head and neck cancer and in vitro in colon rectal cancer cell lines (17).

Some preclinical data identify a favorable interaction when combining radiation and panitumumab in upper aerodigestive tract tumor models, both *in vitro* and *in vivo*. Panitumumab increased radiosensitivity, radiation-induced apoptosis and augmented radiation induced DNA damage in different cell lines studied (HNSCC lines UM-SCC-1 and SCC-1483 as well as the NSCLC line H226), it inhibited radiation-induced EGFR phosphorylation and downstream signaling through MAPK and STAT3 (18).



CETUXIMAB

Cetuximab with radiotherapy was approved only in head and neck cancer but clinical trials were conducted also in lung and gastrointestinal cancer.

Clinical data on efficacy and toxicity.

- NSCLC:

In locally advanced NSCLC available data are based mainly on Phase II and randomized controlled trial (RCT), where cetuximab has been investigated associated to chemotherapy concomitant to radiotherapy; Blumenschein et al designed a phase II trial with concomitant carboplatin and paclitaxel +RT with interesting outcomes (OS 2 years: 49%) but reported six G5 adverse events possibly related to treatment (19); Govidan et al and Van De Heuvel et al completed a RCT in pts received chemotherapy (carboplatin, permetrexed in the first and CDDP in the second) and RT with or without cetuximab with no difference in OS but increased toxicity in cetuximab arm (20-21). An extremely important randomized trial is by Bradley et al, patients has been randomized to RT (high or standard dose) and concurrent carboplatin and paclitaxel with or without cetuximab with no survival benefit (25 vs 24 months) and Cetuximab was associated with a higher rate of G3 or worse toxic effects, moreover there were more treatment-related deaths in cetuximab group and in the high-dose chemoradiotherapy (CTRT) (22). A subgroup analysis revealed that in pts with increased EGFR expression the addition of cetuximab improved OS (42 vs 21 months, p=0.032). Lastly, Walraven at al concluded a phase II RCT of hypofractionated RT concomitant to low dose CDDP with or without cetuximab; no significant difference has been registered in two arms as regards median OS (23).



GASTROINTESTINAL CANCER:

Some phase I trials evaluated the addition of cetuximab to chemoradiotherapy in locally advanced rectal cancer; Hofheinz et al performed a phase I trial of preoperative RT with capecitabine, irinotecan and cetuximab and Machiels et al with capecitabine and cetuximab, both these regimens seem to be tolerable and safe with no unexpected toxicities but no improve in pCR (24-25). These data have been confirmed by several phase II trial, even when Kras status is taken into account. Dwedney et al concluded a RCT of radiochemotherapy (CAPOX) with or without cetuximab; addition of cetuximab did not improve the primary end point of CR or PFS but significantly improved radiological response and OS (26). Also Sun et al, in a phase II trial, did not refer any difference in pCR rate, 3-year DFS rate or 3-year OS rate between KRAS WT patients and KRAS-mutated patients (27).

In esophageal cancer EGFR overexpression is common, two phase II trial evaluated safety and efficacy of concomitant cetuximab adding to chemoradiotherapy in locally advanced patients: Safran et al obtained 70% of <u>clinical</u> complete response adding cetuximab to paclitaxel and carboplatin with no increase in esophagitis or other radiation-enhanced toxicity (28), Lledo et al obtained 40.5% of clinical complete response and 37% of partial clinical response adding cetuximab to FOLFOX and RT and reported one treatment related death due to oesophagitis (29). The randomized trial of Crosby et al reported worse toxicity and decreased survival adding cetuximab to CTRT (5FU/CDDP) (30).

Other studies evaluated cetuximab as induction treatment and its subsequent association with neoadjuvant or radical CTRT, with rate of pathologic complete response wide (6-40%) and conflicting results regarding toxicity, some studies reported poor tolerability and high treatment related mortality (10%) (31) versus others with no increased mortality (32).



- HEAD AND NECK CANCER:

In 2006 a first relevant randomized trial has been published, Bonner et al compared RT alone versus RT + Cetuximab with improved local control and survival in sperimental arm; the other two relevant data that emerged from this study were that younger patients with oropharynx tumor and those who developed severe acneiform rash had better outcomes than patients not having these characteristics (33).

Thereafter data regarding Cetuximab in head and neck cancer are increased and several studies have been performed to study cetuximab and RT versus standard CTRT or associated with CTRT. In this latter setting from retrospective and phase II trials it seems that Cetuximab increased toxicity, especially cutaneous rash, with no difference in outcomes, this data are confirmed also by Ang et al in a RCT with no improvement of progression free survival but more toxicity with the addition of cetuximab to CTRT (34).

Another question is whether or not cetuximab can replace CT as a radiation sensitizer; Lefebre et al published a RCT in patients with cancer of larynx or hypopharynx that received induction CT followed by CT or Cetuximab concurrent to RT: no difference between the two arms in terms of outcomes was registered (35). Another recent RCT by Magrini et al compared CTRT vs RT + Ctx in pts with SCCHN with scarce compliance, necessity of more nutritional support and increase toxicity in sperimental arm (36).

The last question is the use of cetuximab in induction setting, Agiris et al incorporate Ctx in induction, concomitant and maintenance scheme with promising 3 year PFS and OS (70% and 74%) and more manageable toxicity compared to standard induction scheme (TPF) (37), recently also Marur et al evaluated ctx in induction and concomitant phase in the subset of



p16/HPV+ oropharyngeal squamous cell carcinoma with 70% of patients achieved a primary site clinical complete response to IC (38).

Table 1- Radiotherapy and cetuximab in HNSCC

Drug (dose)	Author and year	Study type	N	Tumor site	RT technique/dose/fractionati on	Combination (concomit, other.)	Toxicity	Tumor outcome	Comments
Cetuximab	Bonner 2006	RC T	211	HN	-70Gy/35 fx - 72-76.8Gy/ 60-64 fx twice daily -72 Gy/42 fx	RT vs RT +Ctx	8% GIII-IV acneiform rash, 1% GIII-IV voice alteration, 1% GIII- IV infusion reaction	LRC 2yy: 50% Median LRC: 24.4 months OS 3yy: 55% Median OS: 49 months	Ctx improved LRC and OS
Cetuximab	Pfister 2006	Pilot phase II	22	HN	70Gy to GTV 54 Gy to subclinical disease	Concomitant + CDDP	G5 pneumonia, 1 death of unknown cause G4: arrhytmia 5%, infection 5% G3-4: Acne like reaction 10%, Hypersensitivity 5%	OS 3yy: 76% PFS 3yy: 56% LRC 3yy: 71%	Study close due to significant AEs
Cetuximab	Berger2008	Case report	1	HN	72 Gy/45 fx/42days 3DCRT	Concomitant after 44 Gy	G4 dermatitis	/	



Cetuximab	Balermpas 2009	Prospective	7	HN	54-50.4 Gy/28-30 fx Re-RT	Concomitant	G3 acneiform rash in 2 pts, G3 abacterial salivary gland infiammation in 1 pts	PD in 1 pts, SD in 3 pts, PR in 2 pts, 1 death due to pneumonia
Cetuximab	Pryor 2009	Prospective	13	HN	70Gy/ 35 fx 3DCRT	concomitant	G3-4: Skin reaction 77 % Mucositis 77%	
Cetuximab	Argiris 2010	Prospective	39	HN	70-74 Gy	Induction with docetaxel+ CDDP, <u>concomitant</u> +CDDP, <u>mainteinance</u>	G3-4 mucositis: 54% Neutropenia: 36%, Infection:21% In field dermatitis:27%	PFS 3yy: 70% OS 3yy: 74%
Cetuximab	Buiret 2010	retrospectiv e	46	HN	70Gy/ 35 fx 66Gy/33 fx 2DRT	concomitant	No G4-5 toxicity	Tolerability Safety
Cetuximab	Koukourakis 2010	Phase I	43	HN	56.7Gy/ 21 fx 3DRT	<u>Concomitant</u> + CDDP+ Amifostine	- G3-4 mucositis in 16.2%, - Interruption of cetuximab due to acneiform rash in 23.3%	Feasibility
Cetuximab	Kuhnt 2010	Phase I	18	HN	30Gy/15fx +1.4Gy twice up to 70.6Gy	Concomitant + CDDP	G3: Mucositis 57% Dysphagya 37% In fiels dermatitis 37% Skin rash 6%	Safety and tolerability
Cetuximab	Koutcher 2011	retrospectiv e	49	HN	69.96 Gy/33 fx IMRT	concomitant	G3-4 late toxicity in 21.3%	LRF 2yy 39.9% FFS 2yy 44.5%
Cetuximab	Studer 2011	Prospective	99	HN	70 Gy/35 fx or 69.60 Gy/33 fx or 66 Gy/33 fx SIB -IMRT	concomitant	G3-4 dermatitis: 35%	



Cetuximab	Walsh 2011	Retrospectiv e	48	HN	66-70 Gy/33-35 fx	concomitant	Acute toxicity: 74% mucositis ≥G3 62% dermatitis ≥G3	/	
Cetuximab	Zwicker 2011	Retrospectiv e	10	HN recurrent	Median dose 50.4 Gy/28 fx IMRT	Concomitant	1 fatal infield bleeding 1 flap necrosis 30% G3 dermatitis	OS 1 yy: 40% LRC 1 yy: 44% DMFS 1 yy: 75%	Reirradiation in recurrent HN
Cetuximab	Suntharaling am 2012	Phase II	43	HN	70.2 Gy/ 39 fx 3DCRT-IMRT	<u>Concomitant</u> + Paclitaxel + carboplatin	G3: 79% mucositis, 9% rash, 16% dermatitis, 19% leukopenia, 19% neutropenia	LRC 3 yy: 72% OS 3 yy: 59% DFS 3 yy: 58%	
Cetuximab	Matuschek 2013	Phase II	55	HN postsurgery	61.6 Gy/ 28 fx IMRT	Concomitant+ CDDP+5FU and <u>sequential</u>	-G3-4 mucositis, radiation der- matitis, and skin reactions outside the radiation portals were 46, 28, and 14% of patients, respectively. - 1 toxic death occurred (peritonitis at day 57). - 22% of patients discontinued cetuximab within the last 2 weeks or at the end of RTCT		
Cetuximab	Ley 2013	Retrospectiv e	29	HN	70 Gy/35 fx IMRT/Tomo	Concomitant		DSS 3 yy: 31% Recurrent disease was more common in the cetuximab group compared with the cisplatin group	DSS was superior in the patients given CDDP with definitive RT compared to cetuximab with definitive RT due to a lower risk of



									recurrent disease in the CDDP group.
Cetuximab	Lartigao 2013	Phase II	60	Recurrent HN	36 Gy/ 6fx	concomitant	Cutaneous toxicity 84%, G3=9%	OS 1yy: 47.5%	There was 1 toxic death from hemorrhage and denutrition
Cetuximab	Lefebvre 2013	RCT	116	HN Larynx/Hypophary nx	70 Gy/ 35 fx	Induction CT -> RT+CDDP vs RT+Ctx	Treatment compliance was higher in Ctx arm.	No significant difference in LP at 3 months (95% vs 93%), LFP (87% vs82%), and OS at 18 months (92% vs 89%).	
Cetuximab	Huang 2013	Retrospectiv e	31	HN	70 Gy/35 fx IMRT	concomitant		- LRR and DM rates of IMRT/cetuxima b were higher but not significantly different as compared to that of IMRT/platinum (2-year LRR, 33 vs. 23 %, P = 0.22, respectively; 2- year DM, 17 vs. 11 %, P = 0.40, respectively) - IMRT/cetuxima b had significantly inferior CSS and OS compared to IMRT/	IMRT/cetuxima b and IMRT/platinum had nearly identical results for all the endpoints: 2-year LRR: 26 vs 25 %, P = 0.56, respectively; 2- year DM: 6 % for both, P = 0.92; 2-year CS: 69 % for both, P = 0.66; 2-year OS: 57 vs 64 %, P = 0.24, respectively



								platinum (2- year CSS, 67 vs. 84 %, P = 0.04, respectively; 2-year OS, 58 vs. 83 %, P = 0.001, respectively	
Cetuximab	Ang 2014	RCT	940 (444 in ctx arm)	HN stage III-IV		RT+CDDP vs RT+CDDP +Ctx	Cetuximab +CDDP+RT resulted in more frequent interruptions in RT (26.9% vs 15.1%); and more G3-4 radiation mucositis (43.2% v 33.3%, respectively), rash, fatigue, anorexia, and hypokalemia, but not more late toxicity.	No differences between arms in 30-day mortality, 3- year PFS, 3- year OS, LR failure or distant metastasis	Adding cetuximab to radiation- cisplatin did not improve outcome and hence should not be prescribed routinely
Cetuximab	Zhang 2014	Retrospectiv e	46	Hypopharyngeal SCC	IMRT	Concomitant+CDDP		The 3-year local control survival, DFS, OS, and LP survival rates were 66.8%, 59.0%, 68.9%, and 86.7%, respectively	
Cetuximab	Hu 2014	Retrospectiv e	54	HN	70 Gy/35 fx IMRT	Concomitant	 Skin acne related to cetuximab treatment was noted in 68.5% of patients in the BioRT group. radiation dermatitis occurred more frequently in the 	LR relapse rates 13% The 3-year relapse-free survival rate was 65.5% 3 yy OS 70.9%	



							SDCCRT group (69.8%) than in the BioRT group (48.1%; <i>P</i> = 0.033). - The incidence of mucositis was similar in the two groups (88.8% versus 87.0%; <i>P</i> = 0.747)		
Cetuximab	Levy 2014	Retrospectiv e	71	HN	70 Gy/35 fx 3DCRT-IMRT	Concomitant	BRT patients had more G3–4 skin complications	CRT was independently associated with an improved LRC (2-year LRC: 76 % for CRT vs. 61 % for BRT) and DC (2-year LRC: 81 % for CRT vs. 68 % for BRT) in comparison with BRT ($p <$ 0.001 and $p = 0.01$ in the MVA).	
Cetuximab	Fury 2014	Phase I	25	HN	70 Gy IMRT	Concomitant +paclitaxel		2-year failure- free survival (FFS) is 65%	
Cetuximab	Feng 2014	Retrospectiv e	28	Nasopharyngeal cancer	66-70 Gy/30-31 fx 3DCRT-IMRT	Concomitant + CDDP	- G3–4 oral mucositis occurred in 71.4 %. - G3 RT related dermatitis occurred in 25%. - G3 and G4 cetuximab-related acneiform Rashes in 14.3% and 3.6%. These	PFS 2 yy: 89.3 %	



Cetuximab	Egloff 2014	Phase II	60	HN	70 Gy/35 Fx 2D-3DCRT	Concomitant + CDDP	grade 3–4 skin and mucosal toxic effects were manageable and reversible. Most common G≥3 toxicities included mucositis (55%), dysphagia (46%) and neutropenia (26%); one attributable G5 toxicity	- Median PFS was 19.4 months, 2-year PFS 47% - OS 2 yy: 66%	
Cetuximab	Xu 2015	RCT	21	Nasopharyngeal cancer	70.4-66 Gy/ 32-30 fx IMRT	Induction CT-> cetuximab +RT vs CDDP + RT	occurred. G3-G4 toxicity: oral mucositis , acneiform rash , dysphagia, radiation dermatitis were 80.9%, 33.3%.47.6% vs 47.8%, 0%,13% and 0% in CDDP arm	DFS 3 yy 78.3% in cetuximab arm and 85.7% in CDDP arm	ERT was not more efficacious than CRT but was more likely to cause acute adverse events in LA NPC. Because of the unexpectedly high rates of grade 3/4 mucositis observed in the ERT arm, the study was closed ahead of schedule.
Cetuximab	Thomson 2015	Phase I/II	27	HN Stage II-III	62.5 Gy/ 25 fx IMRT	Concomitant	Acute toxicities (G3): pain (81%), oral mucositis (78%) and dysphagia (41%). Late toxicities (G3): pain (11%), problems with	Median f up: 47 months OS: 70%	



							teeth (8%) and weight loss (4%).		
Cetuximab	Taberna 2015	Prospective	43	HN	Median dose 70 Gy/35 fx 2D/3DCRT/IMRT	Concomitant			
Cetuximab	Strom 2015	Retrospectiv e	38	HN	76-70 Gy/35-38 fx IMRT	Concomitant		LRC 2 yy: 90% OS 2 yy: 89% Distant metastasis rate 2 yy: 12%	no difference in locoregional control, distant metastasis rate, or overall survival between patients treated with concurrent CIS or CTX.
Cetuximab	Tomohiro Sakashita 2015	Retrospectiv e	14	HN	40 Gy/20 fx +sequential boost of 30 Gy/15 fx	Concomitant	Grade ≥ 3 mucositis/stomatit is was 64.3% Grade ≥3 radiation dermatitis 43%	/	
Cetuximab	Dornoff 2015	Retrospectiv e	33	HN Re-RT	Median dose of re-RT 50.4 Gy/ 28 fx 3DCRT	Concomitant	one gastrostomy- associated peritonitis 24.2 % of these patients developed grade 3 acne.	 OS 1yy rates with cetuximab were 44.4% LCR 1 yy were 46.4% FFM 1 yy rates 73.6% 	Haematological toxicity \geq G3 occurred more often in the CDDP group (p < 0.001), pain \geq G3 was increased in the cetuximab group (p = 0.034).
Cetuximab	Voichita Bar- Ad 2016	Prospective phase II	602	HN	70 Gy/35 fx or 66-60 Gy/33- 30 fx	Concomitant + CDDP or docetaxel	G2-4 rash in 63.6%		G2 to 4 cetuximab rash was associated with better



									survival. This observation was noted mainly in p16- negative patients. G2 to 4 acute in-field radiation dermatitis was associated with higher rate of late G2 to 4 skin fibrosis
Cetuximab	Bibault 2016	Prospective	29	HN	IMRT	Concomitant	-34.5% G3 acute dermal toxicity in the cetuximab group vs 10.3% in the non-cetuximab -Cetuximab was not significantly associated with more grade 3 mucositis	no significant difference in local relapse- free survival or OS	
Cetuximab	Montal 2016	Retrospectiv e	202	HN	70 Gy/35fx	Concomitant			
Cetuximab	Goshi Nishimura 2016	Phase II	9	HN	70.2-66.6 Gy/39 fx 1.8 Gy/fx	<u>Concomitant</u> + docetaxel+ CDDP	severe neutropenia in five patients (56 %) and leukopenia in seven patients (78 %);		the safety of this treatment was questionable, and terminated the study.
Cetuximab	Suntharaling am 2016	Phase II	43	HN	70.2 Gy/39 fx IMRT/3DCRT	Concomitant + Carboplatin+paclitax el	G3 mucositis (79%), rash (9%), leucopenia (19%), neutropenia (19%), and RT dermatitis (16%).	The 3-year actuarial overall survival and disease- free survival were 59% and 58%	The addition of CTX to weekly PC and daily RT was well tolerated



Cetuximab	Wu 2016	Retrospectiv e	56	Nasopharyngeal cancer	74-70 Gy/33 fx IMRT	Concomitant	CRT arm had more significant decrease in white blood cell, platelet, hemoglobin, and severe vomiting, while more severe skin reactions and mucositis were shown in BRT arm.	5-year OS rates of 79.5% 3-year and 5- year PFS was 82.1%, 74.6% i	BRT was not less efficacious than traditional CRT
Cetuximab	Mesia 2016	Phase II	73	Laryngeal SCC	70 Gy/35 fx 3DCRT	Concomitant to RT post induction CT	In 47% AEs G3-4, the most frequent were mucositis, radio- dermatitis, odynophagia, dysphagia, and skin toxicity outside the radiation field. There was only 1 toxicity- related death (local bleeding during concomitant treatment)	SFL 3 yy: 70 % OS yy: 78% Laringectomy free survival. 72%	Cetuximab added to RT in patients with stage III and IVA laryngeal cancer who respond to TPF could improve functional larynx preservation.
Cetuximab	Magrini 2016	RCT	35	HN	70 Gy/35 fx 3DCRT/IMRT	RT+CDDP vs RT+ Ctx	 Severe cutaneous toxicity of G3 or worse was more common in the CTX arm. 4 patients in the CTX arm versus none in the CDDP arm had a break of more than 10 days in RT Patients treated with CTX needed more nutritional support during 	Respective 1- and 2-yy LC rates were 64% and 53% in the CTX arm Respective 1- and 2-yy OS rates were 75% and 68% in the CTX arm	



							treatment		
Cetuximab	Shanti- Marur 2017	Phase II	90 (80 evaluable)	OPSCC HPV+	69.3 Gy in 33 fx or 54 Gy/27 fx if CR to induction IMRT	Induction + CDDP+paclitaxel_and concomitant +	In 54 Gy group: G3 mucositis (30%), dysphagia (15%), acneiform rash (12%), radiation dermatitis (7%), and lymphopenia (12%). In 69.3 Gy group: mucositis (47%), dysphagia (29%), acneiform rash (24%), radiation dermatitis (12%), thromboembolism (6%), and lymphopenia (29%).	For 54 Gy -PFS 2 yy: 80% - OS 2 yy: 94%	

RCT: randomized control trial, LRC: loco regional control, OS: overall survival, PFS: progression free survival, AEs: adverse events, PD: progression disease, SD: stable disease, PR: partial response, DSS: disease specific survival, LP: Larynx preservation, LFP: larynx function preservation, BRT: bioradiotherapy



Table 2 - Radiotherapy and cetuximab in LUNG Cancer

Drug	Author and	Study	Ν	Tumor	RT	Combination (concomit,	Toxicity	Tumor	Comments
(dose)	year	type		site	technique/dose/fractionation	other.)		outcome	
Cetuximab	Hughes 2008	Phase II	12	Stage IIIA or B	64 Gy/32 fx 3DCRT	Concomitant post induction CT (platinum based)	One pts experienced G3 lethargy following the first cetuximab dose and one a G2 skin reaction following the third dose of cetuximab	PR: 58%,CR: no	Inoperable pts
Cetuximab	Jatoi 2010	Phase II multicentric	57	NCLC Stage IIIA or B	60 Gy/30 fx	Concomitant	31 patients experienced G3+ adverse events (fatigue, anorexia, dyspnea, rash, and dysphagia)	-Median survival: 15.1 months -Median time to cancer progression: 7.2 months -26% PR, CR no	Pts no candidates for CTRT Age>65 yy or younger but ECOG 2
Cetuximab	Jensen 2011	Phase II prospective	31	NSCLC stage IIIA or B	66 Gy/33fx IMRT	Concomitant and maintenance	Mild toxicity: - G3 pneumonitis: 3.3%, - any G3 acute toxicity: 36.7%	- Median OS: 19.6 months - Median PFS: 8.5 months - PR 63%, CR no - OS 1- and 2- year: 66.7% and 34.9%	Pts no candidates for concomitant CTRT or refused
Cetuximab	Hallqvist 2011	Phase II multicentric	71	NSCLC Stage IIIA or B	68 Gy/34 fx 3DCRT	Concomitant post induction CT (CDDP/docetaxel)	-Esophagitis G1–2: 72%; G3: 1.4% Hypersensitivity reactions G3/4: 5.6% - Febrile neutropenia G3/4: 15.4% - Skin reactions G1/2: 74%; G3: 4.2% Diarrhoea G1/2:	- Median survival: 17 months - 1-, 2- and 3- year OS of 66%, 37% and 29% - PR 16%, CR 7%	Medically Inoperable or unresectable pts



							38%; G3:11.3%. - Pneumonitis G1/2: 26.8%; G3: 4.2%; G5: 1.4%.		
Cetuximab	Blumenschein 2011	Phase II multicentric	87	NSCLC Stage IIIA or B	63 Gy/ 35 fx 2D-3DCRT	Concomitant + carboplatin/ paclitaxel	-G4 hematologic toxicities: 20%, -G3 esophagitis:8% pneumonitis G3-4: 7% - There were six grade 5 events	Median OS 22.7 months, 2 yy OS: 49.3% PR 33%, CR 29%	3/6 G5 AEs had unacceptable study deviations in TRT planning, with volume of lung receiving at least 20 Gy of 65%, 40%, and 50%, respectively.
Cetuximab	Govidan 2011	RCT multicentric	101 (53 in cetuximab arm)	Stage III A or B	70 Gy/35 fx 3DCRT	Concomitant + carboplatin/permetrexed vs carboplatin/permetrexed	G3-4 non hematologic AEs were 46% and 6, in arm A vs 53% and 9%, in arm B. Two patients in arm A and three patients in arm B experienced grade 5 AEs	The 18-month OS rate: 58% in arm A vs 54% in arm B.	Inoperable pts
Cetuximab	Ramalingan 2013	Phase II multicentric	40	NSCLC stage III	73.5 Gy/35 fx	Concomitant and maintenance+carboplatinum and paclitaxel	G3 rash: 3pts One patient died of pneumonitis, possibly related to cetuximab	-The median OS: 19.4 months PFS: 9.3 months. -The best overall response rate: 67% (31 evaluable patients)	
Cetuximab	Dingeman 2014	Phase I	25	Stage III	45 Gy/ 30 twice daily fx of 1.5 Gy -> 2 Gy/fx until a mean lung dose of 19 Gy or	concomitant + CDDP/ vinorelbina post induction CT (Gemcitabin/ carboplatin)	12/25 patients experienced G3+ toxicity	Metabolic remissions in 19 of 22 patients.	



					another normal		(esonhagitis 3 rash		
					tissue constraint		1 diarrhea 1		
					Maximal dose: 69Gy in 6 weeks		cough 1 dyspnea		
					3DCRT		1 vomiting 1 and		
					SDent				
							ombolism 1)		
Cotuvinash	Van dan	DCT	10/51	Ctogo	66 Cu/24 fr		empolisin 1).		
Cetuximab	vuii ueii	RC1	10(51	Stage				-OLCR Was 64%	
	neuvei 2014		DOLII		3DCR1/IIVIR1	RT+CDDP+Clx (Affil B)	drill B		
			arms)				only anorexia	92% in Arm B (p	
							significantly	= 0.36).	
							different between	- 1 yy LPFI: 69 %	
							the two treatment	(arm A) vs 82	
							groups.	%(armB)	
							Late toxicities:	- 1 yy OS:	
							primarily	73%(armA) vs	
							pulmonary toxicity	71%(armB)	
							(0% vs. 4%) and		
							esophagus toxicity		
							(6%		
							vs. 8%) for Arm A		
							and Arm B		
Cetuximab	Wanebo 2014	Phase II	63	Stage	72-68 Gy/ 36- 34 fx	Induction and concomitant +	G4 toxicity: 21pts	-OS 3 yy: 78%	there were no
				III-IV	2D-3DCRT/IMR	paclitaxel and	G3 toxicity: 43 pts	- EFS 3yy: 55%	treatment
						carboplatinum	Toxicity was	-Disease	related
							primarily	progression:	deaths.
							hematologic and	37% -> local in	
							radiation-related	16%, regional in	
							(mucositis,	8%,	
							dysphagia,	local and	
							dermatitis); 11	regional in 3%,	
							patients had G3	and distant in	
							rash.	8%	
Cetuximab	Bradley 2015	RCT	544 (257	Stage	74 Gy/37 fx or 60 Gy/30 fx	Concomitant	No statistical	in patients who	74 Gy/35Gy
			with ctx)	III		+paclitaxel/carboplatin vs	differences in G3 or	received	fractions with
						paclitaxel/carboplatin	worse toxic effects	cetuximab	concurrent
1							between	median OS: 25	chemotherapy
1							radiotherapy	months	was not
							groups.	compared with	better than
1							Cetuximab was	24 months in	60Gy plus
							associated with a	those who did	concurrent
1							higher rate of G3 or	not	chemotherapy
			1	1		1			. /
							worse toxic effects		and might be



							treatment-related deaths in the high- dose chemoradiotherapy and cetuximab group		harmful.
Cetuximab	Liu 2015	Phase I-II	24	Stage III	66-60Gy/33-30fx	Induction and concomitant +vinorelbine and CDDP	Severe (G3 or high) AEs in 81% pts (mostly haematologic). Severe non- haematologic toxicities including nausea/vomiting, intestinal obstruction, pulmonary infection and esophagitis, each of which was detected in <7% of patients	- median survival: 26.7 months - 1- and 2-year survival rates of 88.9% and 51.9% - median PFS: 13.5 months	
Cetuximab	Walraven 2016	RCT	102	Stage II-III	66Gy/24 fx 3DCRT/IMRT	CDDP vs CDDP+Cetuximab		-Median OS: 31.5 months -Not significantly different between arms A and B (33 vs 30 months). - 1-, 2- and 5- yyr OS: 74.5%, 59.4% and 37.3%	



PR: partial response, CR: complete response, CTRT: chemoradiotherapy, OS: overall survival, PFS: progression free survival, AE: adverse event, LPFI: local progression free interval, EFS: event free survival

Table 3- Radiotherapy and cetuximab in GASTROINTESTINAL CANCERS

Drug	Author	Study	Ν	Tumor site	RT	Combination (concomit,	Toxicity	Tumor	Comments
(dose)	and year	type			technique/dose/fractionatio	other.)		outcome	
					n				
Cetuximab	Machiels	Phase	40	Rectal	45 Gy/25 fx	Concomitant +	acneiform rash:87%,	pCR: 5%	
	2007	I-II		cancer	3DCRT	capecitabine	diarrhea:65%,		
				T3-4 or N+			fatigue: 57%.		
							G3 diarrhea: 15%.		
							Three G4 AEs: one		
							myocardial		
							infarction, one		
							pulmonary		
							embolism and one		
							pulmonary infection		
							with sepsis.		
Cetuximab	Bertolini	Phase	40	Rectal	40-50.4 Gy/25-28 fx	Concomitant +5FU	- 77% acnelike rash	pCR:8%	
	2009	II		cancer T3-4	3DCRT		- dose reduction/		
				N0-1			interruption in 15%		
							-> 2 for G3 acnelike		
							rash, 2 for G3		
							gastrointestinal		
							toxicity, and 2 for		
							refusal.		
Cetuximab	Velenik	Phase	40	Rectal	45 Gy/25 fx	Concomitant+	-G1/2 acneiform	pCR 8%	
	2010	II		cancer stage	3DCRT	capecitabine	skin rash: 86%		
				-			-G3		
							radiodermatitis:16%		
							, diarrhea:11% and		
							hypersensitivity: 5%		



Cetuximab	Dwedney 2012	RCT	16 5	Rectal cancer High risk operable	45 Gy/25 fx+ boost 16.2 Gy/3 fx 3DCRT	Concomitant +CAPOX vs CAPOX	G3-5 diarrhoea 1- 10% Rash 0-9%	 addition of cetuximab did not improve the primary end point of CR or PFS. Cetuximab significantly improved RR and OS 	
Cetuximab	Sun 2012	Phase	63	Rectal cancer T3-4	45 Gy/25 fx 3DCRT	Concomitant+capecidabin e	Acneiform rash: 82.5% Radiodermatistis G3: 16% Diarrhoea G3: 6% Acneiform rash G3: 6% Dry skin infection G3:3%	- pCR: 12.7% - DFS Зуу 76.2% - OS 3 уу 81%	The down- staging rate in patients KRAS wild-type was significantly higher than patients KRAS mutation - no significant difference in pCR rate, 3-yy DFS rate or 3- yy OS rate between KRAS WT patients and KRAS- mutated patients.
Cetuximab	Eisterer 2014	Phase II	31	Rectal cancer T3-4	45 Gy/25 fx 3DCRT	Concomitant+capecitabine	Diarrhoea G3:10% Rash G3: 6% Rectal pain G3: 3% Diarrhoea G4: 6%,	pCR: 0 R0-resection was possible in 27 of 31 (86%) patients	



Cetuximab	Hofheinz 2006	Phase I	20	Rectal cancer T3-4	50.4 Gy/28 fx 3DCRT	Concomitant + irinotecan + capecitabine	Diarrhoea G3: 20%	pCR: 26% R0: 95%	
				or N+					
Cetuximab	Horisber	Phase	50	Rectal	50.4 Gy/28 fx	Concomitant +	G2/3/4 AEs;	4 patients	
	ger 2009	П		cancer T3-4	3DCRT	capecitabine + irinotecan	 leukocytopenia 	had a pCR	
				or N+			6/2/2,		
							 nausea/vomiting 		
							4/2/0,		
							- diarrhea 34/30/0,		
							- proctitis 26/2/0,		
							- 个liver		
							transaminases		
							8/10/0		
							- achelike skin rash		
Caturina a h	Kim 2011	Dhasa	20	Destal	50 4 Cu/20 fr	Concernitent	46/6/0.	-CD 22 10/	
Cetuximab	KIM 2011	Phase	39	Recial	30.4 Gy/28 IX	Conconniant +		DES 2000	
		11			SDCKT			20 0%	
								OS 3 WV	
								94 7%	
								54.770	
Cetuximab	Rodel	Phase	58	Rectal	50.4 Gy/28 fx	Concomitant+	G3 toxicity:	pCR: 9%	
	2008	1-11		cancer T3-4,		capecitabine+oxaliplatin	- diarrhoea 17%,		
				N0-+ , M1			- radiation		
							dermatitis 8%		
							- transaminitis,		
							infection/fever: 6%;		
							-ieuкopenia, acne-		
							like rash:4%;		
							- 2 death multi-		
							deficient) 2%		
						1	uencient) 2%		



Cetuximab	Fokas	Phaas	45	Rectal		Concomitant+		1, 3, 5 yy	
	2013	e I-II		cancer		capecitabine+oxaliplatin		OS: 91.1%,	
								88.9%,	
								86.7%	
								1,3,5 yy CSS:	
								97.6%,	
								95.2%,	
								90.3%	
								1,3,5 уу	
								DFS: 90.7%,	
								88.3%,	
								88.3%	
Cetuximab	Bazarbas	Pilot	15	Rectal	50.4 Gy/28 fx	Concomitant+	Significant G3-4	4- year RFS	
	hi 2016	study		cancer T3-4		capecitabine	toxicity was mainly	80%	
				or N+			cetuximab-induced	4 years OS	
							skin reactions	93%.	
							(33%), radiation-		
							induced skin toxicity		
							(13%) and diarrhea		
							(20%).		
Cetuximab	SAFRAN	Phase	60	Esophageal	50.4 Gy/28 fx	Concomitant + paclitaxel	G3 dermatologic	complete	Cetuximab can
	2008	П		and	3DCRT	+carboplatin	toxicity:23%	clinical	be safely
				proximal			Consisting of a	response	administered
				gastric			painful, pruritic	after CTRT:	with CTRT for
				cancer T2/4,			acneiform rash on	70%	esophageal
				N0/+			the face outside of		cancer.
							the radiation field.		Dermatologic
							G3/4 esophagitis		toxicity and
							were 12% and 3%,		hypersensitivit
							respectively.		y reactions
							3 patients had G3/4		were
							cetuximab		associated with
							hypersensitivity		the addition of
							reactions		cetuximab.
							and were not		Inere was no
							assessable for		increase in
							response		esophagitis or
									other



									radiation- enhanced toxicity
Cetuximab	De vita 2011	Phase II	40	esophageal cancer	50.4/28 fx 3DCRT	Neoadjuvant +FOLFOX and concomitant	G3/4 toxicity was skin (30%) and neutropenia (30%).	pCR: 27% The 36- month survival rates were 85% and 52% in patients with pCR or PR vs 38% and 33% in patients with SD or PD.	
Cetuximab	Ruhstalle r 2011	Phase IB/II	28	locally advanced esophageal cancer	45 Gy/25 fx 3DCRT	Induction and concomitant+CDDP	no limiting toxicity occurred, rash was not exacerbated within the RT field, and the main G3 toxicities were esophagitis (7patients), anorexia (3), fatigue (3), and thrombosis (2).	complete or near complete pathologic regression: 68%	
Cetuximab	Tomblyn 2012	Phase II	21	Unresectabl e esophageal cancer	50.4 Gy/ 28 fx 3DCRT	Induction and concomitant + CDDP/irinotecan	G3/4 toxicity, respectively: 52.4% hematologic, 23.8% fatigue, 19.0% nausea, 19.0% dehydration, and	2 yy OS and PFS were 33.3% and 23.8% overall response	treatment- related mortality approached 10%



							19.0% anorexia Two deaths were due to protocol treatment	rate among 17 evaluable patients was 17.6%, including 6% confirmed complete responders and 12% unconfirme d partial	
Cetuximab	Crosby 2013	RCT	25 8	Esophageal cancer stage I-III	50 Gy/25 fx 3DCRT	CDDP/ fl uoropyrimidine+ RT vs CDDP/ fl uoropyrimidine + RT + Cetuximab	Patients who received CRT plus cetuximab had more non- haematological G3- 4 toxicities [79% vs 63%) The most common G3- 4 toxicities were: low white blood cell count [11%] in the CRT plus cetuximab group vs 16% in the CRT only group, low absolute neutrophil count 12% vs 19%, fatigue 20% vs 19%, and dysphagia 27% vs 29%	responders. The CRT plus cetuximab group had shorter median overall survival (22·1 vs 25·4 months)	



Cetuximab	Lledo 2016	Phase II	79	Oesophageal cancer	50.4 Gy/30 fx 3DCRT	FOLFOX and weekly cetuximab on week 1e10 with concurrent radiotherapy	G4/4 toxicities: neutropenia (28%), oesophagitis (12%), rash (11%), allergy (9%). There was one treatment related	Overall response rate: 77% with 40% CR OS 1 yy:70%	
							death due to oesophagitis with gastrointestinal bleeding.	40%	
Cetuximab	Deutsch 2013	Phase II	16	Locally advanced anal cancer	45 Gy/ 25 fx + boost 20 Gy/10fx 3DCRT/IMRT	Concomitant +5FU +CDDP (no ctx in boost phase)	G 3/4 acute toxic effects: 88% -> general (81%), digestive (56%), dermatological (31%), infectious (25%), haematological (19%); and three patients suffered from six G3/4 late toxic effects.	1-year CFS: 67% 1 yy PFS: 62% 1 yy OS: 92%	The trial was prematurely stopped after the declaration of 15 serious adverse events in 14 out of 16 patients
Cetuximab	Sparano 2016	Phase	45	Anal canal Stage I-III HIV+	45-54 Gy/ 25-30 fx IMRT	Concomitant + CDDP and 5FU	G4 toxicity occurred in 26%, and 4% had treatment- associated deaths	3 yy LRF: 20% 3 yy PFS: 72% 3 yy OS: 79% The complete response rate was 62% and the overall response rate was 67%	Although addition of cetuximab may result in less LRF, the 20% recurrence and 26% G4 toxicity rates indicate the continued need for more- effective and less-toxic therapies.


Cetuximab	Garg	Phase	61	Anal canal	45-54 Gy/ 25-30 fx	Concomitant + CDDP and	G3-4 AEs: 10%,	The 3 yy LRF	
	2017	П		stage I-III	IMRT	5FU	including	rate: 23%	
						(first 28 pts induction CT)	G3 diarrhea in 68%,	The	
							neutropenia in 50%	objective	
							, nausea in 32% ,	response	
							dehydration in 32%	rate was	
							hypokalemia in 24%	65%	
							, infection in 18%,		
							anemia in 15%,		
							thrombocytopenia		
							in 12%		

pCR: pathologic complete response, PFS: progression free survival, OS: overall survival, RR: radiological responce , CSS: , RFS: relapse free survival, CFS:

colostomy free survival, ORR: overall response rate, LRF: loco regional failure



PANITUMUMAB

Clinical data on efficacy and toxicity:

Panitumumab is a fully human monoclonal antibodies that binds the EGFR with high affinity. It has been tested in locally advanced head and neck cancer in 3 randomized controlled trial: Girald et al in a phase II trial randomized patients to received CTRT or RT+ Panitumumab with a local control rate at 2 years lower but not significantly different with panitumumab (51% vs 61%) and similar rate of serious toxicity (39); Siu et al compared standard CTRT versus panitumumab associated to accelerated RT with the PFS of panitumumab plus accelerated-fractionation RT that was not superior to standard arm and non inferiority was not proven (40).

At last Mesia et al evaluated CTRT with or without Panitumumab with no significant difference between the two groups (LRC without and with panitumumab 68% vs 61%) but higher toxicity in sperimental arm (43% vs 32%) (41).

In gastrointestinal cancer it has been tested mainly in phase II study for locally advanced esophageal cancer in neoadjuvant setting associated to chemo-radiotherapy and in locally advanced rectal cancer with promising results but also increase toxicity (42-44).



Table 4- Radiotherapy and panitumumab

Drug	Author	Stud	N	Tumor	RT	Combination	Toxicity	Tumor outcome	Comments
(dose)	and year	У		site	technique/dose/fractionatio	(concomit,			
		type			n	other.)			
Panitumumab	Wirth 2010	Phase	19	HN Stage III- IVB	70 Gy/ 35 fx IMRT	concomitant + carboplatin+ paclitaxel	Mucositis G3-4 most significant toxicity Nearly all patients experienced G1-2 oral pain and xerostomia and G3 dysphagia. PEG in all patients but 100% experienced G1-2 weight loss (median weight loss 11%). G1-2 dermatitis 58% and G3 in 42%	overall complete clinical response rate was 95%. At median follow- up of 21 months 95% remained disease free.	
							95% experienced		
Panitumumab	Girald 2015	RCT	151 (90 with panitumumab)	HN Stage III-IV	70-72 Gy/ 30-32 fx 3DCRT/IMRT	RT+CDDP vs RT+panitumuma b	The most frequent G3–4 AEs was mucosal inflammation 40% vs 42% Dysphagia 32% vs 40% radiation skin injury 11% vs 24%. Serious AEs were reported in 40% vs 34%	2 yy LRC was 61% (CDDP) vs 51% (panitumumab)	Panitumumab cannot replace cisplatin in the combined treatment with radiotherapy
Panitumumab	Mesia 2015	RCT	150 (87 in panitumumab)	HN stage III-IV	70-72 Gy/ 30-32 fx 3DCRT/IMRT	RT+CDDP vs RT+CDDP +panitumumab	The most frequent G–4 AEs were dysphagia 27% in chemoradiotherap y group <i>vs</i> 40% in	2 yy LRC was 68% in the chemoradiotherap y group and 61% in the panitumumab	the addition of panitumumab to standard fractionation radiotherapy and



							the panitumumab	plus	cisplatin did not
							group	chemoradiotherap	confer any benefit
							Mucosal infl	y group	
							ammation 24% vs		
							55%, and radiation		
							skin injury 13%] <i>vs</i>		
							31).		
							Serious AEs were		
							reported in 32% in		
							the		
							chemoradiotherap		
							y group and in 43		
							in the		
							panitumumab		
Panitumumab	Siu 2017	RCT	315 (156 vs	HN	70 Gy/ 35 fx in 7 weeks vs 70 Gy/	RT standard	Incidence of any	- 2-year PFS was 73	
			159)		35 fx in 6 weeks	+CDDP vs RT	G3-5	in arm A and 76 in	
					3DCRT/IMRT	+Panitumumab	nonhematologic	arm B	
							AEs was 88%in	- 2 yy OS was 85%	
							arm A and 92%in	in	
							arm B (<i>P</i> = .25).	arm A and 88% in	
								arm B	
Panitumumab	Lockhart	Phase	65	ADK distal	50.4 Gy in 28 fractions of 1.8 Gy	Concomitant +	48.5% had toxicity	PCR rate was	
	2013	П		Esophagus	each	CDDP + docetaxel	≥G4. Lymphopenia:	33.3% and near-	
				T3N0M0		in neoadjuvant	43%	pCR was 20.4%.	
				T2/3N1M0	EBRT	setting	- The incidence of		
				, or T2-			skin rash of any	At median follow-	
				3N0/			grade was 94.3%,	up of 26.3 months,	
				1M1a			with 5.7% of	median OS:	
							patients	19.4months and 3-	
							experiencing a G3-	year OS: 38.6%	
							4 rash		
							- Skin toxicity led		
							to a dose reduction		
							in 11 patients and		
							dose delay in 5		
							patients		
							- Adult respiratory		
							distress syndrome		
							was encountered		
							in two cases		
							(3.7%).		



Panitumumab	Kordes	Phase	90	esophagea	41.4 Gy in 23 fractions	Concomitant +	Main G3 toxicities	pCR rate of 22%.	primary aim was
	2014	П		l cancer		carboplatin	were rash (12%),	•	unmet,
				cT1N1M0		+paclitaxel in	fatigue (11%), and		
				or cT2-3N0		neoadjuvant	non-febrile		
				to -2M0		setting	neutropenia (11%).		
Panitumumab	vanZweed	Phase	14	Locally	50.4 Gy/28 fx	Concomitant +	Neutropenia: 33%,	PR 23%	designed to
	en 2015	I		advanced	3DCRT/VMAT	gemcitabine	fatigue: 17%,	Median PFS 8.9	investigate the
				pancreatic			nausea 17%, and	months	maximum-
				cancer			vomiting: 17%		tolerated dose,
									safety,
									and activity of
									panitumumab
									added to
									gemcitabine-based
									chemoradiotherap
									у
Panitumumab	Helbling	RCT	68 (40 vs 28)	Rectal	45 Gy/25 fx	CRT vs CRT	The most common	pNC/CR was	
	2013			cancer	3DCRT/IMRT	+Panitumumab	grade ≥3 toxic	achieved in 53%	
				wilde type		in neoadjuvnt	effects in the P +	treated with P +	
				locally		setting	CRT/CRT arm were	CRT vs 32% treated	
				advanced			diarrhea (10%/6%)	with CRT alone	
							and anastomotic	pCR 10% vs 18%	
							leakage (15%/4%).	pNCR 43% vs 14%	
Panitumumab	Mardjuadi	Phase	19	cT3-4/N +	45 Gy/25 fx	Concomitant		no pCR was	
	2015	II		KRAS wild-				observed	
				type					
				locally				41% had grade 3	
				advanced				Dworak	
				rectal				pathological tumor	
				cancer				regression.	



SUMMARY:

EGFR targeted therapies and radiation have been studied in cancers originating from different sites; it is important to know that these therapies are linked to specific toxicity that in same case has been severe and not linked to benefit in non selected population. To improve the effectiveness of EGFR directed therapies with chemoradiation both proper patient selection and proper drug scheduling are needed. Given the important role EGFR plays in locally advanced squamous cell carcinoma of the head and neck and the well-defined role of EGFR in the response to radiation therapy, this receptor remains an important target.

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IM, CB, LL

Trastuzumab – Pertuzumab

Mechanisms of actions

Human epidermal growth receptor factor 2 (HER2) targeting immunotherapeutic agents, comprising of HER2 specific humanized monoclonal antibodies, pertuzumab and trastuzumab, have acquired a central position as targeted anticancer modalities and are currently being extensively studied (1). 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 (2). 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 (3). Preclinical models suggested that trastuzumab recruits immune effector cells that are responsible for antibody-dependent cytotoxicity (4). The finding that animals deficient in immune-cell–activating Fc receptors (on effector cells) do not have a response to trastuzumab provides support for this hypothesis (5). Preoperative administration of trastuz-umab has been reported to increase tumor infiltration by lymphoid cells and modulation of in vitro antibody-dependent cytotoxicity (6).

Studies in an animal model 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 (7-8). Pertuzumab (a newer antibody that binds farther from the cell membrane) appears to be more efficient because of increased inhibition of hetero-dimerization (9).



Potential interaction with radiotherapy

Formenti et al. explored the potential association between several known molecular markers and pathological response from the original tumors following a regimen of preoperative concurrent treatment with paclitaxel and radiation, and found that only HER2 and estrogen receptor seemed to be significantly associated with the extent of pathological response to the regimen, that is, tumors with low levels of HER2 and negative estrogen receptors were more likely to respond to the regimen (10) In a phase II prospective trial Horton JK et al providing evidence for a radio-sensitizing effect of trastuzumab in breast cancer and a good safety profile of combination between trastuzumab and radiotherapy (11). Although there is emerging evidence regarding the radio-sensitizing effects of trastuzumab, little information exists on the clinical complications seen in some patients receiving concurrent anti-HER2 therapy and radiation therapy. Katz DA et al reported two cases of patients with HER2-positive metastatic breast cancer who developed radiation-related complications likely caused by the radiosensitizing effects of anti-HER2 therapy. These 2 cases suggest that the gastrointestinal tract may be more vulnerable when exposed to concurrent radiation therapy and anti-HER2 therapy (12). Likewise, Michaelson MD et al. showed an encouraging response rate (62% of CR) for HER2/neu-targeted therapy, but they report a certain increase in adverse events those population (33% of AE) (13). **Preclinical data**

In preclinical studies, HER2 overexpression in breast cancer was associated with radio-resistance relative to controls (low HER2 expression) (14-15). HER2 inhibitors demonstrated modest radio-sensitization in several studies (16-17). When HER2 is exogenously overexpressed in normal breast cancer cell lines, the HER2-overexpressing cells acquire radio-resistance



compared with their parental counterparts, a phenomenon that can be reversed with exposure to trastuzumab (18-19). Alanyali et al. studied the interactions between RT and trastuzumab in HER2 positive breast cancer cell line MDA-MB-453. In their preliminary study the cell viability at 24 and 48 hours were significantly decreased (p=0.0012) compared to single exposures (trastuzumab or irradiation), indicating that trastuzumab sensitizes HER2 positive breast cancer cells to irradiation (20).

Clinical data on efficacy and toxicity

Despite widespread use of both trastuzumab and radiation in HER2-positive breast cancer, the combination of these two has undergone only limited study in the context of clinical trials. Early phase II data from a multicenter French study suggested the potential for cardiac toxicity with concurrent administration of trastuzumab and radiation (21), although a subsequent phase II study did not reproduce such toxicity and indicated potential for radio-sensitization (22). The Brown University Oncology Group performed a pilot study of trastuzumab added to chemo-radiation in patients with locally advanced adenocarcinoma of the esophagus. In the setting, trastuzumab has demonstrated safety and promising efficacy (23). In addition, the RTOG 0524 study (paclitaxel and radiation with or without trastuzumab in treating patients after surgery for bladder cancer) showed encouraging response rates in patients with HER2-positive muscle-invasive bladder cancer who were treated with radiation, paclitaxel, and trastuzumab but also demonstrated increases in certain toxicities including marrow suppression (24).



X.5. SUMMARY:

At present Trastuzumab concurrent with RT could be safely administered, however is worth of notice that in the randomized trial published on this topic pts were not randomized versus RT alone.

Table 5- Radiotherapy and Trastuzumab

Drug (dose)	Author &	Study	N	Tumor site	RT	Combination	Toxicity	Tumor	Comments
	year	type			techniques/dose/fractionation	(concomitanti,other)		Outcome	
Trastuzuma	Michaelson	phase I/II	68 (20	Bladder	3D-CRT.Radiation therapy was	Paclitaxel (days 1, 8, 15, 22, 29,	Acute AE 35%	The CR rate at	Our
b (4 mg/kg	MD et al.,		gruppo 1	cancer	administered in 1.8 Gy	36, 43), at a dosage of 50	group 1 (1 G5	1 year 72% for	experience
loading	2016		trastuzuma		fractions once daily, 5	mg/m2	colic	Group 1 and	suggests a
dose; 2			b)		days/week, for a total of 36		perforation, 3	68% Group 2.	reasonable
mg/Kg					fractions, asfollows: 1.8 Gy		GI G3) and		safety
subsequent					small pelvic fields x 22		30.4% group 2		profile to
weekely					fractions, then reduction to				this
dose					whole bladder for 1.8 Gy x 8				regimen.
					fractions, and finally a				Based on
					reduction to the bulky tumor				experience
					area with margin (partial				in other
					sparing of the bladder if				malignancie
					possible) for an additional 6				s, future
					fractions at 1.8 Gy. Total dose				studies of
					was 64.8 Gy.				her2/neu-
									based
									treatment
									in urothelial
									cancer
									should
									probably
									focus on
									FISH-
									positive
									cancers.



Trastuzuma	Belkacémi Y	Phase II	146	Breast cancer	median dose to the whole	Endocrine therapy was	51% developed	no efficacy	
b (32 (23%)	et al., 2008				breast or the chest wall was 50	administered in 74 HR+	grade 2	data	
and 114					Gy (25 fractions). A 10- to 16-	patients. It consisted of	dermatitis.		
(77%) of					Gy boost (5-8 frz)to the tumor	tamoxifen [with or without	Grade 2		
the 146					bed in 68 patients using	luteinizing hormone-releasing	esophagitis was		
patients					electron beams. Internal	hormone (LH-RH) agonists] and	observed in 16		
received a					mammary chain (IMC) nodes	aromatase inhibitors in 34	of 136 patients		
weekly and					were irradiated in 103 of 146	(46%) and 40 (54%) patients,	(12%).		
a 3-weekly					patients (71%): median dose	respectively.	According to		
T schedule,					was 50 Gy in 25 fractions		the CTC v3.0		
respectively					delivered mainly by a mixed		scale and HERA		
. The					photon–electron technique (93		trial criteria, 9		
median					of 103, 90%). Supraclavicular		of 92 patients		
dose of T					nodes were irradiated in 122 of		(10%) and 6 of		
before RT					146 patients (84%): median		111 patients		
was 1600					dose was 46 Gy in 23 fractions		(6%), respectivel		
mg (range:					delivered following mixed		y, had a grade <u>></u>		
0–4312					photon-electron beams,		2 of LVEF		
mg).					electrons alone, or using		decrease.		
					teletherapy unit in 77 (63%), 35		Multivariate		
					(29%), and 1(8%) patients,		analysis		
					respectively.		revealed three		
							unfavorable		
							prognostic		
							factors: weekly		
							Т		
							administration		
							(for the risk of		
							LVEF		
							decrease;P =		
							0.004 and 0.04,		
							according to		
							HERA and CTC		
							v3.0		



Trastuzuma	Safran H et	Phase I/II	10	Esonhageal	The total dose of radiation	cisplatin 25 mg/m2 and	There was only	The complete	
h (doco		Fildselyli	15	cancor	therapy was E0.4 Cy in 1.80 Cy	naclitaval E0 mg/m2 wookly for	one incidence	clinical	
b (uose	ai, 2010			Cancer	fractions given once doily for F	C weeks with rediction thereby	of Crade 4		
					dave a service of for 20 freetiers	(DT)	of Graue 4	response for	
1.5, 01 2					days per week for 28 fractions,	(KT)	esopriagitis and	patients with 3	
mg/kg					on days 1–38. 3D-CRT		one of Grade 3	IHC .	
weekly for							esophagitis.	or an increase	
5 weeks							There were no	in HER2 gene	
after an							cardiac	copy number	
initial bolus							toxicities.	was 8 of 14	
of 2, 3, or 4							Prophylactic	(57%). The 2-	
mg/kg.)							feeding tubes	year survival	
							were not used.	was 50%.	
							Other Grade		
							3/4 toxicities		
							included		
							nausea,		
							dehydration,		
							neutropenia,		
							hypersensitivity		
							to paclitaxel,		
							and infection.		
							Four patients		
							received 1 year		
							of maintenance		
							trastuzumab.		
							There were no		
							complications		
							from		
							maintenance		
							treatment		
	Halvard M et	Phase III	2148 (group	Breast cancer	Whole-breast BT was required				
	al 2009	i nase in	C 489)	Breast cancer	after segmental mastertomy				
	u., 2005				with a dose of 45.0 to 50.4 Gy				
					in 25 to 28 fractions of 1.8 to				
					20 Gy Boost dose to the				
					primary tumor excision site				
					primary tumor excision site				
				1	was optional.		1	1	



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Bevacizumab

DG, LC

Bevacizumab (BEV; Avastin; Genentech, South San Francisco, CA) is a humanized monoclonal antibody that inhibits vascular endothelial growth factor (VEGF) and was the first antiangiogenic therapy used in patients with cancer. In combination with chemotherapy or biological drugs, BEV was associated with prolonged overall survival (OS) in phase III trials of metastatic colorectal and non–small-cell lung cancers and with prolonged progression-free survival (PFS) in recurrent glioblastoma, metastatic breast, renal cancers compared with placebo or chemotherapy alone.

The safety and efficacy of the association with radiotherapy have been also investigated in different clinical trials, especially concerning brain, lung and gastrointestinal tumors. Since ionising radiation induces the expression of a range of proangiogenic factors, including VEGF, it appears that radiation-induced up-regulation of signaling via the VEGF receptor (VEGFR) pathway may contribute to radiotherapy failure by enhancing the rate of vascular repair (1). Sensitization of tumor cells to radiotherapy has been demonstrated with monoclonal antibodies directed against VEGFR (2).

HIGH-GRADE GLIOMA (GB)

The intense and aberrant vascularization and the high resistance to radiotherapy (RT) and chemotherapy (CT) has made GB a main candidate for efficacy studies of BEV. The current standard of care for patients with newly-diagnosed GB is represented by neurosurgery and subsequent fractionated RT plus concomitant temozolomide, followed by systemic temozolomide in the adjuvant setting (3). Despite this multimodal treatment, the median survival of patients with GB is still no longer than 15 months and 6-month PFS, due relapsed or progressive disease in 9% to 21% of patients with an objective response (OR) rate



less than 10%. During the past decade the genetic and epigenetic abnormalities of mutated genes and cellular signaling pathways involved in high-grade glioma development and progression have been object of several studies. Also, the GB microenvironment, especially tumor angiogenesis and aberrations in anticancer immune responses, and their involvement in cancer development and progression, were extensively investigated (4) and conducted studies have revealed potential new targets in cancer cells and in the surrounding tumor microenvironment that can be therapeutically influenced by the small molecules and monoclonal antibodies (5).

Excessive microvascular proliferation and vascular endothelial growth factor (VEGF) overexpression have been identified in tumor tissues from patients with GB. Higher intra-tumoral and plasma VEGF concentrations were then associated with high-grade malignancy and poor prognosis, correlating with rapid disease progression and presence of early recurrence of GB (6).

BEV was extensively examined in clinical trials for treatment of recurrent as well as newly-diagnosed GB, as a single agent and in various combinations with CT and other targeted therapeutics (7). In addition, based on a well tolerated treatment with a high clinical response rates and prolonged PFS (8-9), in 2009 BEV was approved by the US Food and Drug Administration (FDA) for the treatment of recurrent GB.

Subsequently, combination of BEV with standard treatment for newly-diagnosed GB, included radiotherapy, was also examined for newly-diagnosed GB in preliminary studies (10-11). Based on the encouraging results of these studies, one phase II and two large phase III clinical trials were conducted (Table 1). Seventy patients with newly diagnosed GB were enrolled in the prospective, multicenter single-arm phase II study combined BEV with standard of the care radiation therapy and temozolomide for the treatment of newly diagnosed GB(12). An improved PFS (13.6 vs. 7.6 mounts) without improved



OS (19.6 vs 21.1 months) were reported compared to the control group. Toxicity related to radio-chemotherapy treatment was similar then in historical trials, without increased toxicities probably due to the addition of BEV in the radiotherapy phase.

AVAglio (NCT00943826)(13) and RTOG-0825 (NCT00884741) (14) phase III trials evaluated BEV -containing regimes compared to standard regimen alone (RT plus temozolomide) for patients with newly-diagnosed GB. In AVAglio trails, BEV was associated with a 4.4-month increase in median PFS (BEV=10.6 months vs. Placebo=6.2 months; P<0.001) without a significant effect on OS (P=0.10). In addition, in the BEV group the baseline health-related quality of life and performance status were maintained longer with a lower requirement of glucocorticoid. On the others hands, with a median follow-up of 12.3 months in the BEV group and 8.5 months in the placebo group, more patients had grade 3 or higher adverse events in the BEV than in the placebo group (66.8% vs. 51.3%) and grade 3 or higher adverse events were often associated with BEV (32.5% vs. 15.8%).

Similar trend toward improvement, with a 3.4-month extension of PFS, without a significant difference in OS between the study (P=0.21) was confirmed in the, randomized, placebo-controlled Radiation Therapy Oncology Group (RTOG)-0825 study, investigating the addition of BEV to standard radiotherapy–temozolomide therapy as first-line treatment for glioblastoma. During chemoradiotherapy, grade 3 or higher hematological toxicity was reported in term of lymphopenia, occurring in approximately 10% of patients in both arms, neutropenia (7.3% vs. 3.7%) and thrombocytopenia (10.2% vs. 7.7%) more common in the BEV group. In addition, in contrast with the results of the AVAglio trial, a greater deterioration in



neurocognitive function, as well as in perceived cognitive function was recorded in patients receiving BEV, suggesting either unrecognized tumor progression or BEV -related neurotoxicity.

Data from these 3 clinical trials were evaluated in a meta-analysis aimed to assess the effect of BEV plus temozolomideradiotherapy treatment for newly diagnosed glioblastoma with different MGMT methylation status (15). Since, MGMT methylated and unmethylated patients showed improved PFS in the BEV group and similar OS, the available data from these trials were insufficient to determine the synergistic effects of combining BEV with standard radio-chemotherapy on improving survival in patients with different MGMT methylation status.

Since the poor prognosis of unresectable GB, the efficacy and safety of BEV were evaluated in this setting of patients. The phase II, randomized, multicentric GENOM 009 study compared 2 cycles of temozolomide before radiation therapy and concomitant temozolomide plus maintenance with the addition of BEV to one arm, during the neo-adjuvant and concomitant phase, in patients with unresected GB, aiming to evaluate the efficacy in terms of response treatment rate, PFS, as well as toxicity, maintenance of neurological status, and completion of radiotherapy. Preliminary results showed an acceptable safety on 20 patients (16). Moreover, updated results was shown at the 2014 ASCO Annual Meeting, reporting an increased clinical partial response (7.1% vs. 25.6%, P=0.001), with a tendency towards improved of PFS (2.2 vs. 4.8 m, P=0.29), OS (7.7 m vs. 10.8 m, P=0.12) and 1-year survival (29.6% vs. 48.9%, P=0.06) in experimental arm. More toxicities occurred in the BEV arm, but a significant difference was observed only for stomatitis (P=0.02) (17).



Instead, the intensification of BEV with other drugs in this setting of patients had not been showed advantages, at the expense of greater toxicity. The TEMAVIR randomized phase II trial was conducted to evaluate BEV plus irinotecan as neoadjuvant and adjuvant treatment to chemoradiation with temozolomide and BEV in naive unresectable GB, compared to control standard treatment arm (temozolomide concomitant and adjuvant to radiation treatment)(18). Primary aim was improving in the 6 month PFS from 50% to 66% without increased toxicity. Due to the not achieved primary aim (50.0% alive patients without progression at 6 months in the experimental arm), with similar median overall survival between the two arms (11.1 months) and the reported toxicities in the BEV plus irinotecn arm (three fatal intracranial bleedings, three bile duct or digestive perforations/infections, and six thrombotic episodes), the authors concluded that neo-adjuvant and adjuvant BEV plus irinotecn, combined with temozolomide based radio-chemotherapy, is currently not recommended until further evaluation in the first-line treatment of unresectable GB.

SUMMARY:

In patients with newly diagnosed GB, phase II-III trials not showed an OS advantage with first-line use of BEV in addition to standard radio-chemotherapy treatment, although PFS was prolonged. Furthermore, higher rates of neurocognitive decline, increased symptom severity, and decline in health-related quality of life were found over time among patients who were treated with BEV. Based on these clinical data, at this time, the use of BEV concomitant to radiotherapy for newly diagnosed GB is not endorsed. Preliminary results on few patients with unresectable GB by phase II trials showed an acceptable safety with an increased clinical partial response and a tendency towards improved of PFS, OS and 1-year survival. More consistent date are needed. The intensification of BEV with other drugs (i.e. irinotecan), in naive



unresectable GB, combined with temozolomide based radio-chemotherapy, is currently not recommended until further

evaluation in the first-line treatment of unresectable GB, due unacceptable increased toxicity.

Table 6- Radiotherapy and Bevacizumab in newly-diagnosed GB.

	Author and	Study type	Ν	Tumor site	RT	Combination	Toxicity	Tumor	Comments
	year				technique/dose/fractionation	(concomit, other.)		outcome	
Bevacizumab (10 mg/ kg q2w) Vs historic control	Lai A, 2011	Phase II, multicenter single-arm, compared to historical control group	70 vs. 110	newly diagnosed glioblastoma	60 Gy/ 2 Gy, 5 days a week	Concomitant oral Temozolomide (75 mg/m2/day, 6 weeks); Maintenance 10 mg/kg bevacizumab q2w + 150–200 mg/m ² temozolomide/day, 5 days q4w, total of 24 4- week cycle; 10 mg/kg bevacizumab monotherapy q2w	overall hematologic and non- hematologic toxicities comparable to control grade 3 or higher hypertension and venous thrombosis/pulmonary embolism = 11- 19%	median PFS= 13.6 vs. 7.6 months; OS: 19.6 vs. 21.1 months ;	Until disease progression, or completion of adjuvant therapy
Bevacizumab (10 mg/ kg q2w) Vs Placebo	Chinot OL, 2014. AVAglio (NCT00943826)	Phase III, randomized, placebo- controlled	458 vs. 463	newly diagnosed glioblastoma	60 Gy/ 2 Gy, 5 days a week	Concomitant oral Temozolomide (75 mg/m2/day, 6 weeks); Maintenance 10 mg/kg bevacizumab q2w or placebo + 150–200 mg/m ² temozolomide/day, 5 days q4w, total of 6 4- week cycle; bevacizumab monotherapy at 15 mg/kg q3w or placebo.	grade 3 or higher adverse events: 66.8% vs. 51.3%; grade 3 or higher adverse events often associated with Bevacizumab (32.5% vs. 15.8%).	median PFS: 10.6 vs. 6.2 months; (P<0.001). OS: (16.8 vs 16.7 months; P=0.10). 1 and 2 year OS: 72.4 vs	Until disease, progression severe treatment- related toxicity or completion of adjuvant therapy



								66.3% (P=0.049) and 33.9% vs 30.1% (P=0.24).	
Bevacizumab (10 mg/ kg q2w) Vs Placebo	Gilbert MR, 2014. RTOG-0825 (NCT00884741)	Phase III, randomized, placebo- controlled	320 vs. 317	newly diagnosed glioblastoma	60 Gy/ 2 Gy, 5 days a week	Concomitant oral Temozolomide (75 mg/m2/day, 6 weeks); Maintenance 10 mg/kg bevacizumab, q2w or placebo + 150–200 mg/m ² temozolomide/day, 5 days q4w, total of 6–12 4-week cycle	grade 3 or higher neutropenia (7.3% vs. 3.7%) and thrombocytopenia (10.2% vs. 7.7%)	median PFS= 10.7 vs. 7.3 months; (P = 0.007). OS: (15.7 vs 16.1 months; (P = 0.21).	Until disease progression or unacceptable toxic effects developed

NON SMALL CELL LUNG CANCER (NSCLC)

Antiangiogenic agents, including both monoclonal antibodies (e.g. BEV) and multi-targeted TKIs (e.g. sunitinib, sorafenib and vandetanib), have been investigated also in the management of NSCLC (19) (Table 2).

Disappointing results were reported in a phase II trial investigating BEV in combination with chemoradiotherapy for unresectable stage III NSCLC, due to the occurrence of trachea-oesophageal fistulae. The enrollment was early stopped when 2 of the 5 patients underwent radiotherapy plus BEV and pemetrexed/carboplatin concomitant and adjuvant chemotherapy, followed by maintenance BEV, developed trachea-oesophageal fistulae (20). High rates of trachea-oesophageal fistulae were seen in the similar independent phase II clinical trial conducted for patients with small-cell lung cancer (SCLC) (20). In total, 4



confirmed, and a 5 suspected trachea-oesophageal fistulae were identified among a total of 34 patients (29 with SCLC and 5 with NSCLC).

Similar results have been reported in a subsequently phase I-II trial evaluating induction and concurrent carboplatin/paclitaxel chemotherapy plus BEV and thoracic conformal radiation therapy to 74 Gy (21). Grade 3 or 4 esophagitis was reported in 29% of patients, with one patient with grade 3 trachea-oesophageal fistula. Consolidation therapy with erlotinib and BEV was also programmed, but not administered due the high rate toxicity.

Although high rates of ulceration and bleeding have been seen when combining BEV with chemo-radiotherapy also in other tumour types (22-23), similar rates have not been seen in studies with BEV and chemotherapy alone (24). Based on these considerations, the risk of fistula formation seems so related to the combination of BEV with radiotherapy, probably due to the inhibition of healing of mucosal injury in the radiation field owing to the antiangiogenic effects of BEV.

SUMMARY:

Preliminary phase I-II trials in NSCLC showed that, due to serious toxicity risks, BEV should be not suitable for use during radiotherapy, especially in patients with squamous cell carcinoma histology and with central thoracic lesions and, at present, BEV cannot be recommended for routine clinical use.



Table 7- Radiotherapy and Bevacizumab in NSCLC

Drug (dose)	Author	Study	Ν	Tumor site	RT	Combination	Toxicity	Tumor	Comments
	and	type			technique/dose/fractionation	(concomit, other.)		outcome	
	year				-				
CarboplatinAUC_5, Pemetrexed 500 mg/m2, and Bevacizumab 15 mg/kg each i.v. weeks 1 and 4	Spigel DR. 2010	Phase II	5	Unresectable Stage III NSCLC	3DCRT 61.2 Gy, 1.8 Gy in 34 fraction	Concurrent Bevacizumab + RT plus chemotherapy (Carboplatin+ Pemetrexed) followed by consolidation (Bevacizumab + Carboplatin + Pemetrexed) and maintenance (Bevacizumab)	2 of 5 patients: trachea-oesophageal fistulae, one of whom died	Not assessed due to early trial closure	Trial stopped early for toxicity
Carboplatin AUC 2 and Paclitaxel 45 mg/m2 weekly with Bevacizumab 10 mg/kg	Socinski MA. 2012	Phase I-II	45	Stage III NSCLC	3DCRT 74 Gy, 2 Gy in 37 fraction	Induction chemotherapy (carboplatin AUC 6, paclitaxel 225 mg/m2, and bevacizumab 15 mg/kg on days 1 and 22) followed by concurrent chemotherapy (carboplatin AUC 2 and paclitaxel 45 mg/m2 weekly with bevacizumab 10 mg/kg every other week for four doses) and maintenance bevacizumab (15 mg/kg every 3 weeks) + erlotinib (150 mg daily)	grade 3 or 4 esophagitis= 29% of patients grade 3 tracheoesophageal fistula = one patient	median PFS=10.2 months (95% Cl, 8.4 to 18.3 months) OS = 18.4 months (95% Cl, 13.4 to 31.7 months)	Maintenance therapy with bevacizumab and erlotinib was not feasible



Rectal cancer

Multimodality approach, including neoadjuvant chemo-radiotherapy (CT-RT), as well as short-course RT, has improved local control of locally advanced rectal cancer (LARC), with limited impact on distant recurrence. In fact, risk of distant metastases remains a clinical challenge and treatment intensification could be implemented. Since the addition of cytotoxic drugs to fluoropyrimidine-based CT-RT had shown disappointing results on survival outcome, targeted agents integration into neoadjuvant treatment thus could offer a rational approach. Some clinical and pre-clinical evidences suggest a chemosensitizing activity of anti-VEGF agents related to the reduction of tumor vessel abnormalities and vessel density, and to the enhancing of tumor blood flow, resulting in more cancer cells oxygenation (25-26). BEV has been tested with pre-operative RT or CT-RT in LARC in several phase II trials (Table 3)(27). Most of them had as primary endpoint pathologic complete response (pCR), that seems to have an impact on local control, disease free survival and overall survival, ranging between 15-25% with neoadjuvant CT-RT (27).

Many Phase II study evaluating the safety profile of BEV concomitantly with fluoropyrimidine based CT-RT (45-50.4 Gy in 25-28 fractions) showed promising results, in terms of acceptable grade toxicity (grade 3 or 4 diarrhea = 0-22 %), even though a moderate rate of major post-operative complications, in terms of wound complications, delayed wound healing, and infection or abscess, requiring surgical intervention, was reported. Moreover, a slight benefit by the BEV addition seems to be achieved in term of pCR (range= 14-32%, in the different phase II trials). Concerning the impact in terms of long-term outcome conclusions are difficult to draw due to the phase I-II design of available trials (22, 28-32). Only one randomized phase II study was conducted to compare Capecitabine based CT-RT with or without BEV. Grade 3-4 toxicity rates were



somewhat (but non-significantly) higher in the BEV arm compared with the control arm (18% vs 13%; P = 0.50), without any grade 3-4 hematological toxicity. BEV arm was also associated with a slightly more frequency in post-operative complications (43% vs 37%) and a higher (but non-significantly) pCR rate (16% vs 11%, P = 0.54).

Additional phase II trials evaluating the advantage of adding BEV to neoadjuvant regimens integrated with Oxaliplatin (33-37) showed similar toxicities to those reported in previous CT-RT Oxaliplatin studies without BVZ. Diarrhea (4-24%) was the most common grade 3 or 4 toxicity during the treatment with an acceptable rate of major post-operative complications (6-10%). An advantage in terms of pCR was also not observed (range = 8-21%), with the exception of the study by Avallone et al.

Finally, phase II trials was also conducted aiming to test the safety and efficacy of BEV as induction treatment followed by neoadjuvant CT-RT chemotherapy (38-41). Since the high pCR rate reported (36% in the Phase II AVACROSS study and 38% in TRUST trial preliminary results), induction BEV followed by CT-RT seems to offer a promising strategy for multimodality approach to LARC. On the other hand, preoperative toxicity rate, probably related to the long induction treatment with BEV and chemotherapy before the start of CT-RT, was relevant and should not underestimate.

The safety of BEV concomitantly with CT-RT was probably not been adequately evaluated, due to the phase II design of available trials. Most regimens showed that BEV was almost safe and active when administered prior to and concurrent CT-RT. In several trials, BEV seemed to have an important impact on a not negligible increased risk of major post-operative complications, in term of delayed wound healing and infections, and consequently deserves particular attention in future



trials. Moreover, since a slight increased pCR rate with long-term outcomes improvement has been reported only in some of these studies, a clear benefit from the addition of BEV in terms of pCR was not demonstrate. The percentage of patients with a pCR varied between 13% and 50%, stressing the importance of a good selection of patients for this treatment intensification. Based on these available clinical date, at this time the use of BEV concomitant to RT-CT for neoadjuvant treatment of rectal cancer is not endorsed and since the lack of phase III data in rectal cancer patients BEV is currently not recommendable to use outside clinical trials. Results from ongoing studies are expected for more consistent data.

Drug (dose)	Author	Study type	Ν	Tumor	RT	Combination (concomit,	Toxicity	Tumor	Comments
	and year			site	technique/dose/fractionation	other.)		outcome	
Bevacizumab (5 or 10 mg/kg) days 14, 1, 15, 29	Willett CG 2009	Phase I- non randomized Phase II	32	rectum	50.4 Gy in 28 fractions	5FU 225 mg/m ² /d days 1– 38	grade 3 or 4 diarrhea = 22 % major post-operative complications = 4%	pCR = 16% 5-year DFS = 75%. 5-year OS = 100%	
Bevacizumab (5 mg/kg) days 1, 15, 29	Crane CH 2010	non randomized Phase II	25	rectum	50.4 Gy in 28 fractions	Cap 900 mg/m ² b.i.d. days 1–38	grade 3 or 4 toxicity = 0% major post-operative complications = 12%	pCR = 32%, 2-years DFS = 69% 2-years OS = 95%	
Bevacizumab (5 mg/kg) days 1, 15, 29	Gasparini G 2012	non randomized Phase II	43	rectum	50.4 Gy in 28 fractions	Cap 825 mg/m ² b.i.d. days 1–38	grade 3 or 4 diarrhea = 7 % major post-operative	pCR = 14% radical tumor resection =	

Table 8- Radiiotherapy and Bevacizumab in preoperative radio-chemotherapy for rectal cancer.



							complications = 2%	95%	
								sphincter- sparing surgery = 72.1% 3-years DFS = 75%	
Bevacizumab (5 mg/kg) days 1, 15	Spigel DR 2012	non randomized Phase II	35	rectum	50.4 Gy in 28 fractions	5FU 225 mg/m ² /d days 1– 42	grade 3 or 4 toxicities: diarrhea = 9% thrombocytopenia = 6% major post-operative complications = 3%	pCR = 29% 1-years DFS = 85%	
Bevacizumab (5 mg/kg) vs no Bevacizumab	Salazar R 2015	randomized Phase II	90	rectum	45 Gy in 25 fractions	Cap 825 mg/m ² b.i.d. days 1–35	grade 3-4 toxicity = 18%vs 13%; P = 0.50	pCR = 16% vs 11%, P = 0.54	
Bevacizumab (5 mg/kg) days 1, 15, 29	Kennecke H 2012	non randomized Phase II	42	rectum	50.4 Gy in 28 fractions	Cap 825 mg/m ² b.i.d. days 1–14 and 22–35; OX 50 mg/m ² days 1, 8, 22, and 29	grade 3 or 4 toxicities: diarrhea = 24% major post-operative complications = 10%	pCR = 18.4%	
Bevacizumab (5 mg/kg) days 1, 15, 29	Dellas K 2013	non randomized Phase II	70	rectum	50.4 Gy in 28 fractions	Cap 825 mg/m ² b.i.d. days 1–14 and 22–35; OX 50 mg/m ² days 1, 8, 22, and 29	grade 3 or 4 toxicities: diarrhea = 4%	pCR = 17%	
Bevacizumab (5 mg/kg) days 1, 15, 29	Landry JC 2013	non randomized Phase II	57	rectum	50.4 Gy in 28 fractions	Cap 825 mg/m ² b.i.d. days 1–38; OX 50 mg/m ² weekly × 5 weeks	grade 3 or 4 toxicities: diarrhea = 13% major post-operative complications = 6%	pCR = 17%	
Bevacizumab (5 mg/kg) days 4, 11	Avallone A, 2015	non randomized Phase II	46	rectum	45 Gy in 25 fractions	OX 100 mg/m ² + Tom 2.5 mg/m ² days 1, 15 and 29; 5FU 800 mg/m ² + LFA 250 mg/m ² days 2, 16 and 30	grade 3 or 4 toxicities: diarrhea = 6% neutropenia = 30% major post-operative complications = 10%	pCR = 50% 5-years PFS = 80% 5-years OS = 85%	
Bevacizumab (5 mg/kg)	Verstraete M 2015 (AXEBeam	randomized Phase II	82	rectum	45 Gy in 25 fractions	Cap 825 mg/m ² b.i.d. days 1–38; - /+ OX 50 mg/m ² weekly ×	nr	pCR = 27% vs 8%, P = 0.05	



	study)					5 weeks			
Induction Bevacizumab (5 mg/kg); Plus concomitant Bevacizumab (5 mg/kg) days 1, 15, 29	Velenik V 2011	non randomized Phase II	61	rectum	50.4 Gy in 28 fractions	Cap 825 mg/m ² b.i.d. days 1–38	grade 3 or 4 toxicities: dermatitis = 10 % proteinuria = 6.5% leucocytopenia = 4.9% major post-operative complications = 10%	pCR = 13%	
Induction: Bevacizumab (5 mg/kg);+XELOX × 4 Plus concomitant Bevacizumab (5 mg/kg) days 1, 15, 29	Noguè N 2011	non randomized Phase II (AVACROSS study)	47	rectum	50.4 Gy in 28 fractions	Cap 825 mg/m ² b.i.d. days 1–38	grade 3 or 4 toxicities: diarrhea = 11% neutropenia = 6% major post-operative complications = 24%	pCR = 34%	
Induction: Bevacizumab (5 mg/kg);+FOLFOX× 2 Plus concomitant Bevacizumab (5 mg/kg) days 1, 15, 29	Dipetrillo T 2012	non randomized Phase II	26	rectum	50.4 Gy in 28 fractions	5FU200 mg/m ² /d days 1– 38; OX 40 mg/m ² weekly × 6 weeks	grade 3 or 4 toxicities: diarrhea = 44% neutropenia = 20% major post-operative complications = 0%	pCR = 19% 3-years DFS= 65% 3-years OS = 95%	
Induction: Bevacizumab (5mg/kg);+FOLFOXIRI Plus concomitant Bevacizumab (5 mg/kg) days 1, 15, 29	Vivaldi C 2013	(TRUST trial)	15	rectum	50.4 Gy in 28 fractions	Cap 825 mg/m ² b.i.d. days 1–38 or 5FU 225 mg/m ² /d days 1–38	major post-operative complications = 1%	pCR = 38%	

-FU = 5-fluorouracil; Cap = Capecitabine; OX = Oxaliplatin, LFA = folinic acid, XELOX: Capecitabine and oxaliplatin FOLFOX: 5-fluorouracil and oxaliplatin; FOLFOXIRI: 5-FU,oxaliplatin and irinotecan; pCR = pathologic complete response; LCR = local control rate; DFS = disease-free survival; major post-operative complications: anastomotic leak, pelvic hematoma and abscess requiring drainage, delayed healing of perineal incision, ileus, and wound infection; OS= overall survival.

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3.b Small molecules

- TKI (tinib) Erlotinib, Gefitinib, Afatinib

FA, RM

Mechanisms of actions

Epidermal growth factor receptors (EGFR) represent a member of the HER-family, including ErbB2, ErbB3 and ErbB4. The activation of signaling mediated by EGFR has been shown to have a relationship with the initiation, progression and poor prognosis of Non Small Cell Lung Cancer (NSCLC). In NSCLC, deletions in exon 19 and amino-acid substitution in exon 21 are two most common EGFR-activating mutations, conferring sensitivity to EGFR-tyrosine kinase inhibitor therapy (TKI), resulting in higher response rates comparing to patients with non-mutated EGFR profile (1,2). Thus, mutations in EGFR play a role as both biomarkers and rational targets for tailored-therapy. First-generation of EGFR-TKIs, Gefitinib and Erlotinib, have the capability to combine with the ATP-binding sites, thus blocking EGFR-induced activation of downstream signaling. The second-generation of EGFR-TKIs, such as Afatinib and Dacomitinib, show a greater affinity for the EGFR kinase domain also inhibiting other members of the EGFR family, such as ErbB2, ErbB3 and ErbB4 (3).

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Preclinical data and potential interaction with radiotherapy

Preclinical data indicate that EGFR-overexpression represents a possible reason of radioresistance in different tumors. The association between radiotherapy (RT) and EGFR inhibitors can improve tumor control compared to RT alone (1). Specifically, RT in combination with anti-EGFR has been shown to be able to promote a reduction in the S-phase fraction (the most radioresistant cell cycle phase), inducing accumulation of cells in G1 and G2 phases (1). In addition, the combination RT/TKIs allows reducing Poly-(ADP-ribose)-polymerase (PARP) activity with subsequently increasing cellular sensitivity to oncological treatment (2).

The main action of radiation is represented by the cell-killing by means of DNA damage. Anti-EGFR drugs reduce radiationinduced expression of DNA repair proteins (1). 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 TKIs block EGFR, the complex does not enter into the nucleus, resulting in the inhibition of DNA repair (3). The potential impact of anti-EGFR on the DNA damage repair is amplified in vivo setting, compared to in vitro evidences, due to the delivery of multiple versus single fractions of RT (1). Finally, anti-EGFR drugs



influence cancer cell clonogenic survival, with a modest but consistent reduction in clonogenic survival when the drug is administered before RT (3-4).

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line. Int J Colorectal Dis. 2014 Jan;29(1):31-41.

Clinical data on efficacy and toxicity

Population

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



Of these, 143 patients affected by brain metastases from NSCLC were treated with RT/Erlotinib whereas in 30 cases Gefitinib was combined with RT. Iyengar et al (18) explored the feasibility and tolerability of stereotactic body RT (SBRT) and Erlotinib in the oligometastatic setting by NSCLC, whereas Wang et al. (22) evaluated a similar approach using a combination of SBRT/Gefitinib in previously treated patients with advanced NSCLC. No studies of RT in combination with Afatinib were found.

Intervention

Regarding the modality of adopted RT, all head and neck patients were treated with radical intent. IMRT with conventional fractionation was performed in 149 cases; a 3-dimensional conformal RT (3DCRT) was used in the remaining 104. In case of NSCLC patients, RT with definitive intent was delivered with conventional fractionation by means of 3DCRT technique. Looking at the pancreatic patients, all cases were candidate to a neoadjuvant approach using a conventional fractionation. In a single-phase II study (13) for a total of 48 enrolled patients, the impact of IMRT was analyzed. All rectal cancer patients were treated with neoadjuvant intent using a conventional fractionation by means of 3DCRT. Available data regarding brain metastases seem quite heterogeneous in terms of TKI-using (Erlotinib or Gefitinib) and RT adopted schedules. Concerning this last point, three fractionations are mostly used (i.e. 30 Gy/10, 20 Gy/5, 35 Gy/14) [19-21, 23]. Finally, Erlotinib and Gefitinib in combination with SBRT were evaluated in two esperiences (18,22) in the setting of oligometastatic NSCLC.

Comparison and Outcomes



A direct comparison in terms of oncological outcomes when TKI is associated with RT comparing to TKI alone is not available. Four randomized phase II studies (6,7,19,23) and a single randomized phase III trial [10] compared RT with or without TKIs. Martins et al. (6) evaluated the impact of Cisplatin-irradiation with or without Erlotinib in 204 locally advanced HNC patients. At a median follow up of 26 months, the addition of Erlotinib to Cisplatin-RT did not increase the toxicity, but failed to increase the objective response or progression free-survival rates. In the multicenter randomized controlled open-label trial by Martinez and colleagues (7), the concurrent addition of Erlotinib to RT in 90 locally advanced NSCLC patients versus RT alone was analyzed. Compared to RT-alone, the association of Erlotinib/RT showed a higher cancer specific survival and complete response, without benefits in terms of PFS and OS. No increased toxicity was observed when Erlotinib was added to RT. In the context of locally advanced pancreatic cancer, the LAP07 trial (10) is a two-steps randomized phase III trial. In the first step, patients were randomized to receive induction chemotherapy with Gemcitabine or Gemcitabine plus Erlotinib for 4 cycles. In the second step, patients with controlled tumor (stable or objective response) were randomly assigned to chemo-RT versus chemotherapy alone. In both arms, Erlotinib maintenance therapy was administered. Although no significant difference in OS was found, chemo-RT was associated with decreased local progression and no increase in severe toxicity.

Finally, in the SAKK 70/03 randomized phase II trial (23), patients with brain metastases from NSCLC were randomly assigned to receive whole brain irradiation combined with Gefitinib versus Temozolamide. A total of 59 patients were enrolled. At a median follow up of 34 months, median OS was 6.3 months in the Gefitinib arm versus 4.9 months in the Temozolamide treated group. No relevant toxicity was observed.



Table 9 summarized the oncological outcomes and the tolerability regarding the major studies evaluating the association of RT and TKIs.

SUMMARY:

Tolerability profile of the association between TKI and RT seems to be acceptable. Regarding effectiveness, some data are promising, but in summary, no evidences support the routinely concomitant integration of TKIs and RT.

No data are available concerning Afatinib and RT, thus, their combination in daily clinical practice is recommended only within clinical trials.



Table 9- Radiotherapy and TKIs

Drug	Author and	Study type	Ν	Tumor site	RT	Combination	Toxicity	Tumor	Comments
(dose)	year				technique/dose/fractionation	(concomit, other)		outcome	
	[Reference]								
Erlotinib (150 mg)	Herchenhorn et al. 2010 [1]	Phase I/II single arm dose escalation	31	Head and neck	Telecobalt therapy/ 70.2 Gy/39	Erlotinib was started orally 1 week before chemo (Cisplatin)- radiation and continued daily until the last day of chemo-radiation	Grade3-4: In-field dermatitis (52%) Nausea (48%) Vomiting (39%) Xerostomia (29%)	Pathologic complete response 74%	
Erlotinib (150 mg)	Yao et al. 2016 [2]	Phase II	43	Head and neck	IMRT/70 Gy/35	Erlotinib was started orally 2 weeks before radiation and continued daily until 2-years (Docetaxel)	Grade3-4: In-field dermatitis (37%) Nausea and vomiting (16%) Mucositis (35%) Dysphagia (49%)	Complete response 83%	
Erlotinib (100 or 150 mg)	Arias de la Vega et al. 2008 [3]	Phase I dose escalation	13	Head and neck	3DCRT/63Gy/35	Erlotinib was started orally during radiation (Cisplatin)	Grade3-4: In-field dermatitis (8%) Mucositis (50%)	Not reported	
Erlotinib (150 mg)	Hainsworth et al. 2009 [4]	Phase II single arm	60	Head and neck	3DCRT/68.4Gy/38	Erlotinib was started orally during radiation (Cisplatin, Paclitaxel, Bevacizumab)	Grade3-4: In-field dermatitis (37%) Nausea and vomiting (8%) Mucositis (27%) G5: 1.6%	3-year progression free survival and Overall Survival were 71% and 82%, respectively	
Erlotinib (50, 100 or 150 mg)	Ahn et al. 2016 [5]	Phase I dose escalation	11	Head and neck	IMRT/70 Gy/35	Erlotinib was started orally on day 1 of induction chemotherapy and continuing until the last day of radiation therapy (Cisplatin, Bevacizumab)	Grade3-4: In-field dermatitis (23%) Nausea and vomiting (8%) Mucositis (38%)	At a median follow up of 24 months local control was 70%	
Erlotinib (150 mg)	Martins et al. 2013 [6]	Randomized Phase II	95	Head and neck	IMRT/70 Gy/35	Erlotinib was started orally during radiation therapy (Cisplatin)	Grade3-4: rash (13%) Pain (19%) Gastrointestinal	Complete response of 52%	The use of Erlotinib was not associated with an



							(48%)		improvement in PFS. There was no statistical difference in overall survival or locoregional control between the two arms
Erlotinib (150 mg)	Martinez et al. 2008 [7]	Randomized Phase II	23	NSCLC	3DCRT/66Gy/33	Erlotinib was started orally during radiation therapy	21.7% developed severe toxicity caused directly by erlotinib	Complete response of 41.5% and a response rate of 84.9%)	Erlotinib with RT shoved an extended cancer specific survival, and higher complete response. Erlotinib did not increase the toxicity of RT
Erlotinib (150 mg)	Lilenbaum et al. 2015 [8]	Phase II	75	NSCLC	3DCRT/66Gy/33	Erlotinib was started orally during radiation therapy	Esophagitis: 5% Pulmonary: 1%, Nausea/vomiting: 4%	Disease control rate was 93% 12-months PFS: 47% 12-months OS: 57%	
Erlotinib (150 mg)	Ramella et al. 2013 [9]	Not specified	60	NSCLC	3DCRT/59.4Gy/33	Erlotinib was started orally during radiation therapy	Esophagitis: 2% Pulmonary: 8%, Rush: 7%	Median OS and PFS were 23.3% and 4.7 months respectively	
Erlotinib (100 mg)	Hammel et al. 2016 [10]	Phase III randomized trial	133	Unresectable Pancreatic cancer (patients with progression free-disease after a first randomizzation)	3DCRT/54Gy/30	Erlotinib was started orally during radiation therapy and continued as maintenance (Gemcitabine)	Chemo-RT was associate with no increase in grade 3 or 4 toxicity except for nausea	No significant difference in OS. Chemo-RT was associate with decreased local progression	



Erlotinib	Chadha et al.	Phase I	17	Unresectable	3DCRT/50.4Gy/28	Erlotinib was started	Grade 3 acute	Of the five
(from 100	2016	dose		Pancreatic		orally during radiation	toxicity	patients who
mg)	[11]	escalation		cancer		therapy	developed in 3	underwent
						(Capecitabine and	patients (2	surgery, 3
						Bevacizumab)	diarrhea and 1	patients had
							rash)	pathological
								response
Erlotinib	Jiang et al.	Phase I	18	Unresectable	3DCRT/50.4Gy/28	Erlotinib was started	None	No objective
(from 50	2014	dose		Pancreatic		orally during radiation		response was
mg)	[12]	escalation		cancer		therapy (Capecitabine)		observed.
								Median PFS was
								0.59 year,
								median OS was
								1.1 years
Erlotinib	Herman et	Phase II	48	Resectable	IMRT/50.4Gy/28	Erlotinib was started	Grade 3: 31%	Median
(100 mg)	al.			Pancreatic		orally during radiation	Grade 4: 2%	recurrence-free-
	2014			cancer		therapy (Capecitabine)		survival was 15.6
	[13]							months
								1-year and 2-
								years local
								recurrence free-
								survival were
								86.9% and 44.4%
								respectively
Erlotinib	Nogueira-	Phase II	36	Locally	3DCRT/45Gy/25	Erlotinib was started	Grade 3: Rash in	94.4% achieved a
(150 mg)	Rodrigues et			advanced	Brachytherapy 24 Gy/4	orally during radiation	14%	complete
	al.			cervical cancer		therapy (Cisplatin)	Diarrhea 8%	response
	2014						Hematological	2-year and 3-
	[14]						8%	year overall and
							Proctitis 8%	progression free
							Vaginal fistulae	survival were
							5.5%	91.7% and 80.6%
								and 80% and
								73.8%
								respectively
Erlotinib	Blaszkowsky	Phase I/II	32	Locally	3DCRT/50.4Gy/28	Erlotinib was started	Grade3-4	33% achieved a
(100 mg)	et al. 2014			advanced rectal		orally during radiation	occurred in	pathological
	[15]			cancer		therapy (5-Fluorouracil	46.9%, grade 3-4	complete
						and Bevacizumab)	diarrhea in 18.8%	response
								No local
								recurrences at 3-
								years
								3-years disease



								free survival was	
								75.5%	
Erlotinib	Das et al.	Phase I	18	advanced rectal	3DCRT/50.4Gy/28	Erlotinib was started	No grade 3-4	44% achieved a	
(50 <i>,</i> 100 mg)	2014			cancer		orally during radiation		pathological	
	[16]					therapy (5-Fluorouracil		complete	
						and Bevacizumab)		response	
Erlotinib	Zhao et al.	Phase II	21	Inoperable	IMRT/60Gy/30	Erlotinib was	Grade 4	38% achieved a	
(100 mg)	2016			esophageal		administered daily for 60	pulmonary	pathological	
	[17]			carcinoma		beginning at the start of	toxicity was	complete	
						radiotherapy (Paclitaxel)	observed in 1	response	
							patient	2-years local	
								progression free	
								survival was	
								52.4%	
								PFS was 42.8%	
								OS was 67%	
Erlotinib	lyengar et al.	Phase II	24	Oligometastatic	27-33 Gy/3	Erlotinib was	Grade 3: 8%	There were 3	A total of 52
(100 mg)	2014			phase	35-40 Gy/ 5	administered 1 week	Grade 4: 4%	local failures	lesions were
	[18]				19-20/1	before and during SBRT	Grade 5: 4%	after SBRT	treated with
						_		presenting at 9	SBRT
								months after	
								treatment.	
								Median PFS was	
								14.7 months	
								Median OS was	
								20.4 months	
Erlotinib(100	Lee et al.	Phase II	80	Brain	3DCRT/20 Gy/5	Erlotinib or matched	Grade ¾ were	No advantage in	
mg)	2014	randomized		metastases		placebo were taken	similar between	intracranic PFS	
	[19]					concurrently with WBRT.	the two arms of	and OS for	
						Thereafter, Erlotinib was	the study, except	concurrent	
						maintained at the dose of	for rush and	WBRT	
						150 mg until neurological	fatigue		
						progression			
Erlotinib(100	Welsh et al.	Phase II	40	Brain	3DCRT/35 Gy/14	Erlotinib was	Grade 3:	Overall response	
mg)	2013			metastases		administeredconcurrently	Headache 2.5%	rate was 86%	
	[20]					with WBRT.		At a median	
						Thereafter, Erlotinib was		follow up of 28.5	
						maintained at the dose of		months median	
						150 mg until neurological		survival time was	
						progression		11.8 months	
Erlotinib(150	Zhuang et al.	Phase II	23	Brain	3DCRT/30 Gy/10	Erlotinib was	Grade 3:	Objective	



mg)	2013 [21]			metastases		administeredconcurrently with WBRT	dizziness	response rate was 95% Median local progression free- survival 10.6 months Median OS was 10.7 months	
Gefitinib (250 mg)	Wang et al. 2014 [22]	Prospective	14	Lung metastases	SBRT/48-60 Gy/3	Gefitinib was administered for the duration of the SBRT and continued at the same dose as maintenance	Grade 3: Esophagitis 7% Pneumonitis 7%	1-year local control and OS were 84% and 70% respectively	
Gefitinib (250 mg)	Pesce et al. 2012 [23]	Phase II randomized	16	Brain metastases	3DCRT/30 Gy/10	Gefitinib was administered for the duration of the WBRT without interruption until disease progression	No grade ≥ 3	Median 1-year OS was superior in Gefitinib arm 6.3 months	Brain metastases from NSCLC were randomized between Gefitinib in combination with WBRT and Temozolamide in combination with WBRT
Gefitinib (250/ 500 mg)	Valentini et al [24]	Phase I-II	41	Locally advanced rectal cancer	3DCRT/50.4 Gy/28	Gefitinib was administered with chemo (5FU) radiotherapy	Grade 3+ gastrointestinal toxicity in 8 patients (20.5%), Grade 3+ skin toxicity in 6 (15.3%), and Grade 3+ genitourinary toxicity in 4 (10.2%).	TRG1 was recorded in 10 patients (30.3%) andTRG2 in 7 patients (21.2 %)	Gefitinib can be associated with 5-FU– based preoperative CTRT at the dose of 500 mg without any life- threatening toxicity and with a high pCR but 250 mg would be



				moro
				more
				tolerable dose
				in a
				neaoadjuvant
				approach.

IMRT: Intensity modulated Radiotherapy; 3DCRT: three-dimensional conformal Radiotherapy; PFS: progression free-survival, OS: overall survival; LC: local control; NSCLC: non small cell lung cancer, SBRT: stereotactic body radiotherapy; WBRT: Whole brain Radiotherapy; TRG Tumor Regression Grade

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9.

- TKI (nib)



SR, RDA, MF, CG

Sunitinib

Mechanisms of actions

Sunitinib is a tyrosine kinase inhibitor (TKI) that targets multiple receptors such as VEGF receptor 1,2 and 3, PDGF receptor alpha and beta, c-KIT, FLT-3, RET, CSF-1R, leading to de-activation of multiple signaling pathways involved in tumor growth and survival, angiogenesis and immune escape (1).

At present time sunitinib is approved and currently adopted, for treatment of metastatic renal cell carcinoma, pancreatic neuroendocrine tumors, and imatinib resistant gastro-intestinal stromal tumors (GIST).

Potential interaction with radiotherapy

Acting on multiple targets, sunitinib could enhance apoptosis and reduce clonogenic survival when given together with RT either on tumor cells (2,3) and in endothelial cells (4,5). This effect is strictly related to the presence of at least one of the target receptors on tumor cells (6).

Moreover, the effect on tumor perfusion by normalizing the tumor vasculature is another important rationale in combinig sunitinib and irradiation, as well as the VEGF expression induced by RT as a vasculare rebound effect and tumor re-growth (7-

9).

Preclinical data



In pre-clinical tumor model both RT and sunitinib reduce tumor proliferation, while RT induced tumor cell apoptosis and sunitinib decreased tumor angiogenesis. Combined together these effects are potentiated (10).

In a xenograft mouse model of renal cancer (11) and squamous cell carcinoma (12), dynamic contrast-enanched (DCE) MRI revealed an improvement of tumor perfusion after three days of sunitinib and a synergistically tumor growth delay when irradiation was applied on day 4. Those effects are improved when compared to single modality (IR or sunitinib only).

Other data (10,13) suggest that giving RT before sunitinib allowed a dose reduction in sunitinib while maintaining comparable anti-tumor effect.

All these data confirm the synergistic effect in combining RT and sunitinib, underlining a possible effect of timing on tumor control.

Clinical data on efficacy and toxicity

Sunitinib is generally delivered at 50 mg/daily in a 6-weeks schedule (4 weeks on and 2 weeks off).

A phase I (14) and II trials (15) have been published, where sunitinib in a 6 weeks schedule was delivered with image-guided radiotherapy (IGRT).

In the phase I trial published by Kao et al (14), sunitinib was administered from day 1 to day 28 (starting from 25 mg daily), while radiotherapy was delivered with IGRT at day 8 starting with 40 Gy in 10 fractions to different tumor location (most common treatment were bone, liver, lung). Maximum tolerated dose was 37.5 mg for sunitinib and 50 Gy in ten fractions for IGRT.



These results were adopted in the following phase II trial published by Tong et al (15) where 25 patients with different tumor types (most frequent head and neck, liver, lung, kidney and prostate) have been treated, recording a median progression free-survival (PFS) of 9.5 months and median overall survival (OS) of 22-23 months (obtained from survival curve). Grade 3 or more toxicity was recorded in 28% of patients, mostly neutropenia, thrombocytopenia, liver function test abnormalities and bleeding, including one fatal gastrointestinal hemorrhage likely related to sunitinib rather than irradiation.

Taken together these phase I and II trials (16), 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 weeks schedule in very different tumors (head and neck, hepatocellular, 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%) liver (13%). Moreover, 39% of patients received maintenance sunitinib. Four-years local control (LC), distant control (DC), PFS and OS were 75%, 40%, 34% and 29% respectively. On multivariate analysis kidney or prostate primaries were the only significant factors. Thirty-three per cent of patients experienced a grade 3 or more toxicity, and two fatal hemorrhages were recorded. Surprisingly, compared to sunitinib alone, combining sunitinib and RT resulted in further reduction of haemopoiesis, even the methods to evaluate this end-point is quite doubtful (17).

Staehler et al (18) explored the adoption of high dose hypo-fractionated RT concurrently with sunitinib in progressive metatstatic renal cell carcinoma. RT was delivered in median 12 fraction with 3.5 Gy daily fraction up to 40 Gy in 22 patients during standard 50 mg sunitinib on a 6 weeks 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. One grade 4 cardiac toxicity was



seen (cardiac failure due to hypertension). The difference between radiation intended dose (40 Gy in 5 Gy daily fractions) and effectively delivered dose (40 Gy in 3.5 Gy fractions) underlines as radiation should be optimized according to organ at risk from an expert point of view, thus unlikely reproducible.

Similarly, the same author (19) published a case series among 106 patients with cerebral or spinal metastases treated with radiosurgery (SRS) concurrently to sunitinib or sorafenib. In 51 patients with cerebral metastases, radiosurgery was delivered at 20 Gy in single fraction with a 2-years LC of 96.6%. Five patients (9.8%) experienced an adverse event within 6-weeks after SRS, 3 convulsions and 2 bleeding into the treated cranial lesion. Moreover, no radiation-related necrosis was recorded but one patient, receiving sunitinib, experienced a fatal cerebral bleeding 3 months after SRS. Fifty-five patients received a single 20 Gy SRS to spinal lesions concurrently with sunitinib and sorafenib with a 2-years LC of 90.4%. One patients developed temporary abdominal pain within 6 weeks after SRS. A decrease in pain score was observed too.

Ahluwalia et al. (20) explored in 14 patients enrolled in a phase II trial, the adoption of sunitinib after SRS for 1-3 brain metastases. They reported a 1-year LC in central nervous system of 34%, and severe toxicities in 8 out of 14 patients (57%), not likely caused by the radiation therapy.

These data on feasibility of SRS with sunitinib in brain metastases have been recorded in a small case series report on 5 patients by Kusuda Y et al (21).

Furthermore, 5 studies report results on innovative combination of RT and sunitinib, such as in soft tissue sarcoma, recurrent high grade glioma and prostate cancer.

Three studies (22-24) explored the inclusion of sunitinib concurrently with RT in soft tissue sarcoma (STS).



Jakob J et al (22) explored in a phase I trial the dose limiting toxicity of sunitinib concurrently with neoadiuvant RT in 9 patients with locally advanced STS located in retroperitoneum (4), lower legs (3) or trunk (2). Sunitinib started 2 weeks before RT, that was delivered to lesion by IMRT at 50.4 Gy in 28 fractions. Recommended sunitinb dose is 37.5 mg daily given continuously during IMRT, and no cumulative toxicity was recorded.

In a similarly case-series, Jacob J et al (23) adopted this sunitinib regimen in 16 patients with STS (10 retroperitoneal and 6 of the extremities) who underwent to neoadjuvant sunitinib and IMRT followed by tumor resection 5-8 weeks after treatment completion, recording 4 grade 3-4 hematological toxicity and one grade 3 hand-foot syndrome. Fourteen patients underwent surgery with 13 R0 and 1 R1 resections, and 4 patients (28%) required re-interventions due to post-operative complications: one repeated seroma and one lymphatic fistula in STS of extremities, and one anastomotic lekeage and septic bleeding from pelvic abscess for retroperitoneal one's.

Lewin J et al (24) pointed out the toxicity related to this combination in 9 patients with STS of the extremities that lead to a premature study closure of a phase I trial. In their trial 7 patients have been treated with sunitinib 50 mg 2 weeks before RT and 25 mg during RT, and 2 patients with 37.5 mg continuously. RT was delivered at 1.8 Gy fraction up to 50.4 Gy. Independent Data and Safety Monitoring Committee prematurely closed the trial for six grade 3-4 dose limiting toxicity, mainly unexpected liver toxicity. Moreover, 7 patients (78%) experienced late lymphedema and skin fibrosis in two cases graded as grade 3 toxicity. Finally, with a median follow-up of 3.7 years, 6 out 9 patients had local relapse.

Wuthrick EJ et al (25) explored the adoption of re-irradiation concurrently with 37.5 mg daily of sunitinib in 11 patients with recurrent high grade glioma after surgery and RT. Radiotherapy was delivered as hypo-fractionated stereotactic RT (fSRT)



generally up to 35 Gy in 10 fractions, while low-dose sunitinib was delivered concurrently starting on day 1 of RT up the end of treatment, including weekends. Only one patient experienced a grade 3-4 toxicity (stomatitis), while median PFS and OS were 5.8 months and 11 months respectively.

Corn PG et al (26) explored in a phase I trial of patients with localized high risk prostate cancer, the maximum tolerated dose of continuous sunitinib 1 month before, 2 months during, and 1 month after RT in a standard RT plus androgen deprivation therapy schema (ADT delivered as neoadjuvant, concurrent and 2 years adjuvant). Only 1 among 7 patients completed treated with sunitinib at 37.5 mg daily and two grade 3 GI toxicity were recorded, while 6/7 completed the 25 mg step. Thus, 25 mg daily of sunitinib was accepted as MTD and recommended for a phase II trial.

Finally, there are several case reports that describe synergistic and beneficial effect of combining RT and sunitinib (27-30), and radiation recall toxicity such as pneumonitis (31) and dermatitis (32).

SUMMARY:

According to these data sunitinib given together with irradiation, should be reduced to 37.5 mg daily in a classical 6-week schedule or to 25 mg daily if a continuous schedule is applied. Particular attention should be adopted to dose-constraint for organ at risk, maybe applying those of [14], with particular caution when GI or airways are included or are next to treated lesion [33].



However, some concerns remain according to rare but severe side effects such as perforations of GI tract and hemorrhages, along with the fact that published studies generally include in their cohorts oligometatastatic patients, leaving the doubt of what would be better between a combination strategy or high-dose RT only.

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Sorafenib

Mechanisms of actions

Sorafenib is an inhibitor of multiple kinases that blocks tumor cell proliferation by targeting the Raf/MAPK/ERK signaling pathway. It exerts an antiangiogenic effect by interfering with the tyrosine kinases of vascular endothelial growth factor receptor 2 (VEGFR2), VEGFR3, and platelet-derived growth factor receptor β (PDGF β) (1,2).

After a large phase III trial demonstrating safety and survival benefits in patients with advanced hepatocellular carcinoma (HCC), sorafenib has become the first clinically approved drug for HCC (3). It has also shown clinical activity against advanced renal cell carcinoma (RCC) and is considered to be a standard second-line therapy in this setting (4).

Potential interaction with radiotherapy

Several studies have found that vascular endothelial growth factor receptor (VEGF) can be induced in cancer cells by ionizing radiation, contributing to protection of tumor blood vessels from radiation-mediated cytotoxicity, and thereby to tumor radioresistance (5). In addition, expression of VEGF and VEGF receptors (VEGFR) observed in several cell lines may act as an autocrine growth factor-receptor loop, stimulating cell proliferation in an angiogenesis-independent manner (6). The mechanism of sorafenib action provides a strong rationale for its combination use with radiotherapy.

Preclinical data

Huang et al. recently have shown that sorafenib overcomes radiation resistance in HCC and identified that STAT3 signaling pathway plays a significant role in mediating the effect of sorafenib on radiosensitivity. STAT3 has a critical role in liver inflammation and tumor progression because it can be triggered by cytokines and growth factors such as endothelial growth



factor receptor (EGFR), fibroblast growth factor receptor (FGFR), and PDGFR through tyrosin phosphorylation. By downregulating phospho-STAT3, sorafenib reduced the expression levels on STAT3-related proteins (Mcl-1, survivin, and cyclin D1) in a dose-dependent and time-dependent manner (7).

Moreover, sorafenib has been shown to sensitize both human colorectal and oral carcinomas to radiation in tumor-bearing mouse models via the inhibition on nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) and its downstream effectors proteins. Treatment resistance found in HCC has been related to NF-kB activation. Thus, NF-kB has been proposed to play a crucial role in controlling the dynamic balance between radiation-induced apoptosis and resistance. Both sorafenib and radiation could trigger cell deaths through apoptotic pathways; however, radiation also induces NF-kB activity via ERK phosphorylation and results in upregulations of NF-kB downstream proteins. Sorafenib has been proved to inhibit both endogenous and radiation-induced NF-kB activity and avoids the development of radioresistance in HCC (8). Accordingly, pretreatment of sorafenib plus radiotherapy could provide the better tumor growth inhibition than any single or combination treatments.

So far little is known about the effects of sorafenib when combined with irradiation with respect to cellular radiosensitivity, which is the key determinant of tumor radioresponse. The clinical experience using this combined treatment has been limited.

Clinical data on efficacy and toxicity (table)

Two studies examined the combination of sorafenib and concurrent stereotactic radiotherapy (SRT). In the retrospective study of Staehler et al. 61 patients with spinal and cerebral metastases from RCC were treated with stereotactic radiosurgery



(SRS) and simultaneous sorafenib. The high local tumor control rate of over 98% after SRS adds a valuable palliative tool to the therapeutic approach of metastatic RCC. No radiation-related necrosis was noted. Local skin toxicity was not found. SRS did not alter the adverse effect profile of the underlying anti-angiogenic therapy, and did not induce other adverse events (9). Brade et al. evaluated sorafenib and SRT of intrahepatic HCC. Sixteen patients were treated at 2 sorafenib dose levels. The authors observed severe toxicity that was potentially caused by the concurrent SRT. Grade 3 toxicity was observed in 9 of 16 patients (56%). Two patients developed grade 4 toxicity (13%), consisting of liver failure and small bowel obstruction. One patient died after an upper GI haemorrhage. Sorafenib had to be discontinued in 4 patients and 13 out of 16 patients required a dose modification (10). Interestingly, in a recent phase 2 study, Chen et al reported results on 40 patients with unresectable locally advanced HCC treated with conventionally fractionated radiotherapy (2-2.5 Gy per daily fraction; dose range 40-60 Gy) with concurrent and sequential sorafenib. Complete and partial response rate were 55% with 2-year in-field progression-free survival of 39%. Four patients (10%) and six patients (15%) developed treatment-related hepatic toxicity grade 3 or higher during the concurrent and sequential phase, respectively. No high-grade luminal toxicity was reported, suggesting that dose per fraction may play an important role in this type of toxicity (11).

In a report by Kasibhatla et al. three consecutive patients with RCC experienced disease progression on sorafenib therapy and received palliative radiotherapy for painful metastatic or locally recurrent disease, while undergoing sorafenib therapy. None reported significant acute or late side effect at follow-up of 3,6 and 8 months after radiotherapy and sorafenib, with a complete pain relief. In this report the combination was well tolerated and resulted in excellent clinical and radiologic responses (12).



Overt gastrointestinal bleeding from chronic radiation-induced duodenitis is rare. In literature a case report of hemorrhagic duodenitis caused by radiation and sorafenib treatment was cited. The precide mechanisms for the pathogenesis are unclear, but direct radiation effects on the microvasculature are suggested to lead to gastrintestinal mucosal damage. The improvement of radiation-induced hemorrhagic duodenitis after discontinuation of sorafenib suggests that the drug had contributed to the bleeding (13).

Recently, a rare case of radiation recall dermatitis (RRD) induced by sorafenib was reported. It consisted of erythematous skin lesions 1-2 weeks after the initiation of the drug, predominantly in areas where the skin ws irradiated with an equivalent dose > 30 Gy. The therapy was sorafenib discontinuation, treatment with topical steroids and oral antihistamines (14). **SUMMARY:**

In summary, cranial SRT combined with sorafenib appears to be safe. For extra-cranial SRT, liver SRT combined with sorafenib is associated with a high risk of severe toxicity, which has not been observed with conventionally fractionated radiotherapy. The combination should be used with caution and needs further investigation.

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Pazopanib

Mechanisms of actions

Pazopanib is an oral kinase inhibitor. It has an important antiangiogenic role because it has been shown to inhibit the intracellular tyrosine kinase of vascular endothelial growth factor receptor -1, -2 and -3 (VEGFR-1, VEGFR-2, VEGFR-3) and also the platelet-derived growth factor receptor (PDGFR- α and $-\beta$) receptor tyrosine kinases including vascular endothelial growth factor receptors. The anti-tumor effect is also characterized by the blockage of secondary signaling pathways and target such as Fibroblast growth factor receptors (FGFR-1 and -3), Stem cell factor receptor (c-Kit), Interleukin-2 receptor-inducible T-cell kinase (Itk), Leukocyte-specific protein tyrosine kinase (Lck), Transmembrane glycoprotein receptor tyrosine kinase (c-Fms) (1).

Pazopanib plays a role in kidney cancer as first-line treatment option or after failure of cytokine therapy (2), and in patients with advanced soft tissue sarcoma (STS) who have received prior chemotherapy (3,4).

Potential interaction with radiotherapy

Pazopanib inhibiting VEGF should improve, as other compounds done, vessels quality enhancing tumor oxygenation, and finally resulting in increased radiation efficacy (5).

Preclinical data



In the only pre-clinical study published, Meredith et al observed a synergistic effect in athymic nude mice on human lung cancer cell line adding Pazopanib (100 mg/kg) 7 days before radiation and continued for 28 days. Daily radiation was 0.5, 1, 2, or 3 Gy ×5 days (6).

Clinical data on efficacy and toxicity

Very few data are available on concomitant treatment of pazopanib and RT.

In a phase I trial, Haas et al (7) evaluated once daily pazopanib (escalation cohorts 400, 600 and 800 mg) for 6 weeks and 50 Gy neoadiuvant RT in advanced soft tissue sarcoma. Twelve patients have been enrolled, and the last cohort has been reached (800 mg daily). Hepatotoxicity was the the main limiting factor with no additional toxicity within radiation ports. No tumor reduction was observed and 2 patients experienced delayed wound healing.

Goyal et al (5) observed toxicity and results in patients with breast cancer who received adjuvant chemotherapy and pazopanib and irradiation. In 12 cases pazopanib was delivered concurrently with RT and their reselts were compared in a 2:1 matter with other patients who received RT only. Authors stated that no more radiation toxicity was observed in pazopanib patients, but the association does not fit any treatment indication.

Finally two case reports observed a complete response of a gastric metatstases from renal cancer treated with pazopanib and RT (30 Gy in 10 fractions (8)), and a case of radiation recall dermatitis (9).

SUMMARY:

Data on pazopanib and concurrent RT are rare and of low evidence, thus supporting no reccomandation or at least the one's of other drugs in the same family.



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Axitinib

Mechanisms of actions

Axitinib has the ability to inhibit VEGFR-1, 2 and 3 selectively which subsequently leads to the recruitment of ATP. ATP in turn binds to the so-called ATP-binding pocket of VEGFR, causing activation of the VEGF signaling pathway, which ultimately results in cellular effects that are pivotal for angiogenesis. It is one of the most powerful anti-angiogenic drug (1). In a randomized, phase III clinical trial, axitinib was shown to benefit patients with mRCC after failure of one previous systemic therapy. Compared with sorafenib, axitinib led to a statistically significant and clinically meaningful longer PFS time (6.7 months versus 4.7 months; hazard ratio [HR], 0.665; one-sided p < .0001) in this study group.

Due to these results Axitinib is indicated for the treatment of advanced renal cell carcinoma (RCC) after failure of one prior systemic therapy (EMA and AIFA indication only after sunitibib or citochin in second line) (2).

Potential interaction with radiotherapy

Inhibition of VEGFRs have been shown to sensitize to radiation endothelial cells (3,4); thus the administration of axitinib prior to irradiation could act as radio-enhancement. On the other site, some data (5) showed that axitinib significantly increase tumor hypoxia, having a potential detrimental effect.

Preclinical data

Rao et al (6) explored axitinib with single dose RT in vitro and in vivo, recording, in sarcoma or radioresistant melanoma cells, an increased tumor growth delay and complete response mainly when axitinib is delivered 1 hour before RT.



Fenton and Paoni (5) evaluated how sequencing of axitinib and fractionated radiotherapy could affect results. The study showed a benefit in adding axitinib to fractionated RT in tumor growth delay and tumor vasculature, but failed to demonstrate any sequencing between treatment modalities.

Finally, Hillman et al (7) observed in a murine xenograft of lung tumor, a radioprotective effect of axitinib on radiation pneumonitis and an enhancing effect on tumor cells.

Clinical data on efficacy and toxicity

No clinical data on axitinib and concurrent RT are available.

SUMMARY:

The absence of clinical data on axitinib and concurrent RT supports the use of this combination in a clinical trial only.

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- TABLE 10- Radiotherapy and TKI (nib)

Drug	Autho	Study type	Ν	Tumor	RT	Combination	Toxicity	Tumor	Comments
(dose)	r and			site	technique/dose/fractionatio	(concomit,		outcome	
	year				n	other.)			
Sunitinib (25-37.5-50 mg/die, 6weeks cycle)	Kao 2009	Phase I	21	Different sites	IGRT/40-50 Gy/10 fx	Before/Concurren t	3 DLTs @ 50mg/die	1 years PFS 44%	One rectal bleeding; one fatal tracheal necrosis
Sunitinib (37.5 mg/die, 6weeks cycle)	Tong 2012	Phase II	25	Different sites	IGRT/50 Gy/10 fx	Before/Concurren t	Grade 3 or more 28% mostly hematological and liver tests	Median PFS: 9.5 months	One fatal gastrointestinal hemorrhage
Sunitinib (50 mg/die, 6weeks cycle) Sorafenib (400 mg/die)	Staehl er 2011	Retrospective	106	Brain, spine	SRS/20Gy/fx	Concurrent	9.8% adverse event within 6-weeks after SRS, 3 convulsions and 2 bleeding into the treated cranial lesion	2-years LC of 96.6	One fatal cerebral bleeding 3 months after SRS
Sunitinib (50 mg/die, 6weeks cycle)	Staehl er 2012	Retrospective	22	Body	Hypofractionation/40 Gy/12 fx	Concurrent	13.6% Grade 3-4 toxicity	Median duration of disease stabilization of 14.7 months	One grade 4 cardiac toxicity
Sunitinib (37.5 or 50 mg/die, 6weeks cycle)	Ahluw alia 2015	Phase II	14	Brain mets (1- 3)	SRS	1 months after SRS	severe toxicity 57%	1-year LC = 34%	
Sunitinib (25-37.5 mg/die, 6weeks cycle)	Jakob 2016	Phase I	9	Soft Tissue Sarcoma	IMRT/50.4Gy/28/fx	Concurrent	1 DLTs (lymphopenia)	1 partial response	All 9 pts were operated
Sunitinib (25-37.5	Jakob 2015	Cohort study	16	Soft Tissue	IMRT/45-50.4Gy/25-28 fx	Concurrent	4 grade 3-4 hematological	14/16 pts underwent	4 patients (28%) required re- interventions due to post-operative



mg/die, 6weeks cycle)				Sarcoma			toxicity and one grade 3 hand-foot syndrome	surgery	complications
Sunitinib (50 mg mg/die, 2weeks before RT and 25 mg/die during RT)	Lewin 2014	phase Ib/II	9	Soft Tissue Sarcoma	EBRT/50.4Gy/28 fx	2 weeks neoadjuvant and concurrent	Closed by IDSMC for 6 DLTs	One partial response	6 out 9 patients had local relapse
Sunitinib (37.5 mg/die during RT)	Wuthri ck 2014	Case-series	11	high grade glioma	hypo-fractionated stereotactic RT/35Gy/10 fx	Concurrent	10 patients grade 1-2 toxicity only	Median PFS 5.8 months Median OS 11 months	One grade 4 mucositis (oral ulcer)
Sunitinib (12.5 or 25 mg/die 4 weeks before RT, 8 weeks during RT and 4 weeks after RT)	Corn 2013	Phase I trial	17	Prostate cancer	Standard RT/75.6 Gy/42 fx	Neoadjuvant (4weeks), concurrent (8weeks) and adjuvant (4 weeks)	2 grade 3 toxicity (GI)	PSA post-RT<0.2 ng/ml in 13 pts	37.5 mg of sunitinib was the DLT
Sorafenib (200-400 mg/die)	Brade 2016	Phase I trial	16	нсс	SBRT/33.5Gy/6fx	Neoadjuvant (1 week), concurrent (2 weeks) adjuvant (up to 12 weeksfor whole sorafenib)	9 events of grade 3 or more toxicity	Median survival and in-field local progression not, at a median follow-up of 11 months	One liver failure, one small bowel obstruction, one fatal GI bleed/HCC rupture
Sorafenib (400 mg twice daily)	Chen 2014	Phase II	40	нсс	Standard RT/40-60 Gy/ 2-2.5 Gy fx	Concurrent and adjuvant (up to 6 months)	25% of grade 3 or higher toxicity	CR+PR=55% 2-year in-field progression-free survival = 39%.	One gastric or duodenal ulcer (grade 3)



- Cyclin dependant kinase(CDK) inhibitors (ciclib) – FA, RM (Palbociclib, Abemaciclib, Ribociclib)

Mechanisms of actions

Cyclin-dependent kinases (CDKs) represent promoters of the cell cycle, due to the mitogenic signals mediated by CDK4 and CDK6. Specific cyclins and CDK complexes regulate cell cycle progression by managing the transition through the cell cycle; thus, inhibition of CDKs can represent an important target for novel agents. Palbociclib, Abemaciclib and Ribociclib were introduced as a new generation of CDK inhibitors with high selective inhibition to CDK4 and CDK6, blocking ATP binding to CDK4/6 enzymes (1). The slight conformational differences between the adenosine triphosphate (ATP)-binding pockets of individual CDKs allow for the design of highly selective CDK4/6 inhibitors. Compared to pan-CDK inhibitors, Palbociclib fits tightly into the ATP-binding pocket, resulting in a larger binding interface with its target and, thus, to a possible increased activity (2).

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Preclinical data and potential interaction with radiotherapy



Two generations of CDK inhibitors are categorized: 1) a first-generation molecules, relatively nonselective with unacceptable toxicity profile; 2) a second-generation CDK inhibitors, designed to target CDK4/6 complex, showing a higher clinical activity with acceptable toxicity profile in patients affected by metastatic breast cancer.

Palbociclib, a first-in-class CDK4/6 inhibitor, was approved by the U.S. Food and Drug Administration in combination with letrozole in the first-line setting for the treatment of metastatic breast cancer as well as in combination with fulvestrant in metastatic breast cancer patients progressed on previous endocrine therapy. Other CDK4/6 inhibitors, including Ribociclib and Abemaciclib, remain under investigation as monotherapy and in combination with endocrine therapies (1).

In vivo studies showed that the inhibition of CDK4/6 complex results in decreased expression of E2F-dependent genes and Ki-67 staining with a concentration-dependent arrest of Retinoblastoma (Rb) protein-positive tumors in G1-phase. Palbociclib has been shown to be able to inhibit thymidine incorporation into the DNA of Rb-positive human breast carcinomas. However, there was no activity against Rb-negative cells, suggesting there are no targets besides CDK4/6. Preclinical studies with palbociclib, as well as the newer CDK4/6 inhibitors, such as Ribociclib and Abemaciclib, show a reversible halt of the cell cycle with selectivity in breast cancer cell lines (2).

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Clinical data on efficacy and toxicity

No clinical data are available in literature regarding the association between RT and CDK inhibitors. Thus, a combination in daily clinical practice is recommended only within clinical trials.



- poli-ADP-ribose polymerase (PARP) inhibitor (parib) (rucaparib, veliparib, olaparib, niraparib)

FA, RM

Mechanisms of actions

Poly ADP-ribose polymerase inhibitors (PARP) is a family of enzymes that utilize beta nicotinamide adenine dinucleotide to covalently add Poly ADP-ribose (PAR) chains onto target proteins. This form of post-translational modification has the ability to alter the function of target proteins and it has been found to be involved in several cellular processes including chromatin modification, transcription regulation and control of cell mitosis (1).

PARP1/2 inhibitors can selectively target tumor cells with defects in BRCA1 or BRCA2 suppressor genes that normally maintain the integrity of the genome by mediating a DNA repair process, known as homologous recombination (HR). In the absence of BRCA genes function and HR, tumor cells is unable to repair DNA lesions with subsequently tumor cells death (2). **REFERENCES:**

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Preclinical data and potential interaction with radiotherapy

The effectiveness of PARP inhibitors have shown to be able to selectively target 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 (1). 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 (2). 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 to identify a biomarker for response to a combination PARP inhibitors/RT remain to be determined with the intent to facilitate the application of this combination in clinical practice (3).

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Clinical data on efficacy and toxicity

Two phase I studies are available in literature exploring the combination of Velaparib and RT. In the trial by Reiss et al. (1), low dose fractionated RT was associated to Velaparib in 22 patients affected by peritoneal carcinomatosis from advanced solid tumor malignancies. Patients were treated with Velaparib at the dosage of 80-320 mg daily. Low dose RT consisted of 21.6 Gy in 36 fractions (0.6 Gy twice daily). Median OS and PFS were 13 months and 4.5 months, respectively. Disease stabilization longer than 24 weeks was observed in 33% of cases. Authors identified a more favorable responsive category, representing by the ovarian cancer. Non-hematological treatment related Grade 3-4 toxicities was 4%.

In the phase I study by Mehta and colleagues (2), Velaparib was tested in association with whole brain irradiation in 81 patients affected by brain metastases. Most common primary tumors were NSCLC and breast cancer. Whole brain irradiation consisted of 30-37.5 Gy in 10-15 fractions. Velaparib was administered at the dosage of 10-300 mg orally. The addition of Velaparib to whole brain irradiation did not identify new toxicities when compared to whole brain irradiation alone. Preliminary efficacy results were better than predicted by a nomogram-model hypothesized by the Authors themselves.

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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.



-PI3K/mTOR dual inhibitors

SR, RDA, CG,MF

Mechanisms of actions

Everolimus is an oral inhibitor of mammalian target of rapamycin (mTOR) pathway, an important intracellular signal that, through the PI3K/AKT pathway, promotes cell growth and cell proliferation. The drug binds to an intracellular protein, FKBP-12, resulting in an inhibitory complex formation with mTOR complex 1 (mTORC1) and thus inhibition of mTOR kinase activity (1). The mTOR pathway is dysregulated in several human cancers.

There is also a connection between the PI3K pathway and angiogenesis. Hypoxia leads to HIF-1α (hypoxia-inducible factor 1) stabilization and is a major stimulus for increased vascular endothelial growth factor (VEGF) production by tumor cells. However, activation of the PI3K/AKT pathway in tumor cells can also increase VEGF secretion, both by hypoxia-inducible factor 1 (HIF-1) dependent and independent mechanisms. Many agents have been developed that can inhibit PI3K and/or mTOR signaling in tumor cells, and these drugs have effects on angiogenesis as well as on tumor cell proliferation and survival (2).

Inhibitors targeting the PI3K/AKT pathway have been developed and, as predicted, these agents can decrease VEGF secretion and angiogenesis.



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 (3), 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 (4).

Temsirolimus is another m-TOR inhibitor that binds the same target of Everolimus such as the intracellular protein FKBP-12 and the protein-drug complex inhibits the activity of mTOR that controls cell division, and is currently approved in advanced renal cell carcinoma (RCC) patients with multiple adverse risk features (5).

Potential interaction with radiotherapy

Sinergistic effect of everolimus and radiotherapy has been reported by several investigators and can be summarized in three points.

First of all, it is well known that radiosensitivity of solid tumors is determined not only by intrinsic tumor cell factors but also by the microvascular network that provides oxygen to the tumor (6,7).

Tumor growth and metastasis are largely dependent from tumor microvasculature network. Tumor cells produce growth factors that stimulate proliferation and migration of endothelial cells and so the formation of new blood vessels (8). However, blood flow is heterogeneous and even if the vascular density is high, the architecture is irregular and so ipoxic tumor areas are frequent inside the tumor. These hypoxic areas are radioresistant. The effect of radiation on micorvasculature is both anti- and pro-angiogenetic. From one hand, radiotherapy induces apoptosis of endothelial cells, by



the other hand it is responsible for the releasing of proangiogenetic factors (9). Theoretically, the mechanism of action of mTor inhibitors is in the perturbation of the proangiogenetic factors' release and also targeting tumor endothelial cells. In this way microvascular endothelial cell are sensitized to radiation. Moreover, everolimus-induced apoptosis of vascular endothelial cells was also followed by thrombus formation that leads to tumor necrosis.

Another mechanism of mTOR-mediated radiosensitation is the promotion of autophagy. Usually, mTOR proteins inhibit autophagy so the mTOR inhibitors block this process and favour radiation induced autophagy of cancer cells (10-11).

The last reported machanism of radiosensitation linked to mTOR inhibitors is mediated by EGFR cascade. Radiation induces activation of the EGFR family resulting in signal traduction through the PI3K patway and AKT (12). The subsequent phosphorylation of mTOR plays a pivoltal role in regulation of translational processes. Thus, mTOR inhibition interrupts the radiation-induced stress response of tumor cells and cycle progression and cell proliferation are blocked

Preclinical data

PI3K/Akt/mTOR pathway can be activated as response to radiotherapy (13,14). Some studies confirms in vitro and in vivo radiosensitization in different tumor models (14-17) inhibiting angiogenesis (15,18) and sensitizing tumor vasculature to ionizing radiation (19). Taken together, these findings suggest that combining mTOR inhibition with radiation results in radio-sensitization of both tumor cells and vascular endothelial cells (20).

The study from Manegold et al (12) showed that in vitro proliferation of Human Umbilical Vascular Endothelial Cells (HUVEC) seemed to be most sensitive to a combination of mTOR inhibition and radiotherapy whereas tumor cells showed some resistance. In particular, cells proliferation was reduced by 37% and 83% at low and high dose of everolimus in comparison



with controls. Moreover, single dose of radiation decreased the proliferation by 17% and 72% at 0.25 and 2Gy, respectively. The strongest reduction was achieved by pretreating HUVEC with higher concentration of everolimus and higher dose of radiation. Pancreatic tumor cells seemed to be more radioresistant to mTOR inhibition with reduction in cell proliferation in the range in 8-24% while and in colon cancer cells reduction in proliferation was achieved in 82% using high dose of everolimus and in 70% using radiotherapy single dose of 2Gy. It is important also to underlines that induction mTOR inhibition two days before the beginning of high dose fractionated radiotherapy resulted in improved tumor growth control in vivo. These results confirm that mTOR inhibition can interrupt the radiation-induced stress response of tumor cells that should protect tumor microvasculature against radiation damage.

A recent publication confirmed that everolimus and radiotherapy may be an effective modality to overcome radioresistant tumors via targeting tumor endothelial cells (21). The Authors previously established a clinically relevant radioresistant cell line; these cells continue to proliferate with daily x-ray exposures of 2 Gy for more than 30 days in vitro. They hypothesized that also resistant tumors can be controlled by radiotherapy and everolimus enhancing authopagy. The results showed that everolimus and fractionated radiotherapy inhibited tumor growth of resistant cells. The volume shrunk after five days of treatment. Moreover everolimus and radiotherapy significantly decreased microvessel density and also induced morphological changes of microvessels, in particular disrupted vessels and erythrocyte extravasation were observed. An higher thrombus density occurred and the evidence of a central necrosis area, together with the observation of endothelial cells with condensed chromatin, suggested that endothelial cells death induced by everolimus and radiotherapy was



apoptosis. So, even if the hypothesis of enhanced autophagy was not confirmed, the combined treatment overcomes radioresistance via targeting vascular endothelial cells rather than tumor cells.

Clinical data on efficacy and toxicity

To the best of our knowledge, the available clinical data of the association between everolimus and radiation are not sufficient to reach a definitive and sharable conclusions. The quality of the reported literature is quite low, with just one phase II trial, some phase I studies and several case reports. Hovewer, some considerations to orient in clinical practice can be proposed.

Case reports

The first case report on a possible toxic interaction between mTOR inhibitors and radiotherapy has been published in 2011 by Bourgier et al (22). In their experience the authors documented three cases of radiation recall syndrome, which is defined as an inflammatory reaction within a previously irradiated volume.

In the first case, a metastatic breast cancer patient received palliative irradiation to bone metastases from the 12th dorsal vertebra to the 3rd lumbar vertebra (TD = 30 Gy/10 fractions) and two months later started with paclitaxel, trastuzumab, and everolimus. Four months after the initiation of everolimus, grade 3 gastric hemorrhage and grade 2 anemia occurred and the mucosal reaction with ulceration was documented in the radiation filed.

In the second metastatic pancreatic patient, a grade 2 colitis and grade 3 bladder stenosis occurred two weeks after the start of everolimus. This patient was treated 4 years before with radiotherapy for prostate cancer and chronic ulceration of the



anterior anorectal junction was found as the cause of the colitis. Moreover, obstructed bladder was also reported. Review of radiotherapy portals confirmed that the lesions were within the irradiated area.

The last woman, was an ovary carcinoma patient treated with pelvic surgery, multiple lines of chemotherapy and pelvic radiotherapy three year before the start of temserolimus. Four weeks after she presented with a subocclusive syndrome associated with grade 2 colitis documented at the computed tomography scan.

These three overreaction cases highly suggestive of radiation recall syndrome occurred months after exposure to mTOR kinase inhibitors within pre-irradiated areas. In particular should be noted that the toxic effects were always in the gastroenteric tract.

It is well known that everolimus cause stomatitis (4) and probably the radiation mucosal damage can be exacerbated by the association. In this setting, careful and long-term examination of gastroenteric side-effects may yield higher-than-anticipated radiation recall syndrome rates.

A similar effect was reported in 2013 by Miura et al. (23). They published a case report on another unexpected toxicity from everolimus and radiotherapy association. Also in this patient the toxicity was in the gastroenteric tract, in particular it was a radiation-induced esophagitis exacerbated by everolimus. A metastatic renal carcinoma patient received radiotherapy to thoracic vertebral metastases from T6 to T10 because of back pain. Due to vertebral progression, treatment with everolimus was started. One week later everolimus was discontinued and RT delivered. Everolimus was reinitiated immediately after RT. One week later the patient complained of dysphagia, nausea and vomiting and the endoscopic examination showed erosive esophagitis corrisponding to the irradiation filed. However, the same patient one year before everolimus received a first line



treatment with sunitinib too. The role of radiotherapy in patients pretreated with sunitib has also to be defined (see the dedicated paragraph)

A radiation-recall dermatitis with the everolimus/exemestane combination has been reported 10 years after adjuvant wholebreast radiotherapy in a caucasian 58-year-old female (24). Three days later the commencement of everolimus/exemestane for an asymptomatic disease-progression, she developed an acute G2 dermatitis within the previously irradiated field which resolved completely after temporary suspension of the doublet and systemic corticosteroid and local dexpanthenol.

A case report on pituitary metastasis from renal cell carcinoma treated with surgery, radiotherapy and target therapy (sunitinib, axitinib, everolimus and sorafenib) has been reported (25). The combined treatment has been well tolerated and patient died 5 years after the initial diagnosis of renal carcinoma and 30 months after the diagnosis of pituitary metastasis, without toxicity.

A complete response in metastatic renal carcinoma after radiotherapy and everolimus was reported in 2016 (26). A 54-yearold man with metastatic renal carcinoma started with sorafenib interrupted after only four months due to hematologic toxicity. Because of groin relapse underwent radiotherapy (30 Gy in 10 fractions) and started with sunitinib. After two years, vertebral progression was documented and the patient performed D3-D4 radiotherapy (20 Gy in 5 fractions) and started with everolimus and bisphosphonates. The treatment was well tolerated and after 3 months a partial response was observed. After 12 months a complete regression of the paravertebral lesion was obteined but also a compete response of lung nodules and inguinal node metastasis were reported.

Phase I-II Trials



Thoracic radiotherapy for NSCLC patients in combination with mTOR inhibitors has been investigated in two phase I trials (27,28). The first study enrolled nine patients with stage III locally advanced disease treated with sirolimus and radiotherapy but it was terminated prematurely because of loss of funding. None of the patients developed dose-limiting toxicities except one patient who experienced grade 3 dysphagia.

In 2015 a complete phase I trial was published (28). In twenty-six patients everolimus was escalated at incremental steps and administered weekly (10, 20 or 50 mg) or daily (2.5, 5 or 10 mg) one week before, during radiotherapy and 3.5 weeks after the completion of radiotherapy. In the weekly group, everolimus could be administered safely up to the maximum planned weekly dose of 50 mg while in the daily group there were five patients with G3-4 interstitial pneumonitis related to treatment. In the conclusion the authors themselves recommend in previously untreated and unselected NSCLC patients, a phase II dose of everolimus in combination with thoracic radiotherapy of 50 mg/week, even if pulmonary toxicity should be carefully monitored. Pneumonitis is a known side effect of mTOR inhibitors and may occur in the absence of thoracic radiotherapy. The incidence of all- and high grades toxicity was 10.4% and 2.4% respectively (29). Thus combining everolimus with thoracic radiotherapy can be tricky and the exact impact on lung damage needs to be further explored. Fury et al. (30) reported a phase I trial of everolimus plus weekly cisplatin and intensity modulated radiotherapy in head and neck cancer patients. The most common grade \geq 3 treatment-related adverse event was lymphopenia (92%), mucositis (functional 62%, clinical 31%), pain in the oral cavity (31%) and disphagia (23%). The maximum tolerated dose recommended

for phase II studies was everolimus 5 mg/day.



The combined treatment was also tested in a phase I study on locally advanced cervix cancer (31). This phase I study aimed to treat three dose levels with daily doses of everolimus (2.5, 5 and 10 mg/day), cisplatin and radiotherapy. Patients received everolimus from day -7 up to the last day of brachytherapy. The MTD of everolimus in combination with cisplatin and radiotherapy has been defined as 5 mg/day. The dose limiting toxicities reported were grade 4 acute renal failure, grade 3 rash and grade 4 neutropenia. In thirteen patients, ten experienced diarrhea and nausea as the most frequent adverse events, even if G3 was reported just one patient. The data regarding safety and response rates support further studies.

Very recently a phase I trial of everolimus and radiation therapy for salvage treatment of biochemical recurrence in prostate cancer patients following prostatectomy has been published (32). Safety and tolerability of the concurrent treatment after a two weeks period of everolimus have been reported. Common acute toxicities included G1-G2 mucositis (56%), G1-2 fatigue (39%), G1-2 rash (61%) and G1 urinary symptoms (61%). Acute G3 toxicities occurred in 22% of cases (rash and hematological toxicities) and no patients had G3 or greater cronic toxicity. So at daily doses \leq 10 mg everolimus does not appear to increase salvage radiation-related normal tissue toxicity.

The most numerous experience investigating the association between everolimus and radiotherapy has been reported in glioblastoma patients. Both NCCTG and RTOG published phase II studies in 2011-2013 and 2015, respectively (33-35). The initial two phase I trials investigated the safety and tolerability of everolimus in combination with radiotherapy and temozolamide in two different schedule: weekly in NCCTG study and daily in the RTOG trial. They reported a recommended dose for phase II trials in the weekly and in the daily administration of 70 mg and 10 mg, respectively. In the first experience, the most common toxicities were G3 fatigue, G4 hematologic toxicity, and G4 liver dysfunction and throughout therapy on 18



patients, 16% patients experienced G4 and 30% patients had G3 toxicities attributable to treatment. In the daily administration among 25 patients, a similar percentages have been reported with 28% of patients experiencing a G3 and 17% a G4 toxicity. DLTs included gait disturbance, febrile neutropenia, rash, fatigue, thrombocytopenia, hypoxia, ear pain, headache, and mucositis. In the weekly phase I NCCTG trial fourteen patients had stable metabolic disease, and 4 patients had a partial metabolic response. So the efficacy of the association was tested in a phase II trial enrolling 104 patients, with 100 evaluable cases (35). Weekly everolimus was associated with 57% of patients having at least one grade 3+ adverse event and 23% having a grade 4 adverse event. The study did not meet its predetermined criterion for a successful survival endpoint (65% OS12months) and had similar survival compared with historical phase II trials. The RTOG 0913 trial is currently testing daily dosing of everolimus with stardard chemoradiation, so the results for the phase II portion of this trial may provide grater insight into the potential differences in efficacy for daily versus weekly everolimus dosing schedules.

Finally, one of the initial applications for mTOR inhibitors was in trasplanted patients because of their effective immunosoppressive potential. So the risk of infectious during cancer therapy is a clear concern as demonstrated by Sakaria et al investigating the role of temserolimus in glioblastoma patients (36). Hovewer, the risk of infectious did not seemed to be increased with everolimus in both weekly and daily administration trials althought this difference may be attributed to prophylaxis against pneumocystis jiroveci/carinii pneumonitis.



Table 11- Radiotherapy and PI3K/mTOR inhibitors

Drug	Author	Study	Ν	Tumor site	RT	Combination	Toxicity	Tumor	Comments
(dose)	and	type			technique/dose/fractionation	(concomit,		outcome	
	year					other.)			
Everolimus (10, 20 or 50 mg weekly or 2.5, 5, 10 mg daily)	Deutsch 2015	Phase I	26	NSCLC	EBRT/66Gy/33fx	Neoadjuvant (1 week), concurrent, adjuvant (3.5 weeks)	Five G3-4 interstitial pneumonitis in daily everolimus	2-yr PFS 12% 2yr-OS 31%	One fatal pneumonitis
Everolimus (5 mg daily)	Fury 2013	Phase I	13	Head and neck	IMRT/66-70Gy/30-33fx	Concurrent + weekly Cisplatin 30 mg/m2	More common grade 3-4 toxicity: mucositis 62%, pain 23-31% and disphagia 23%	2-yr PFS 85% 2yr-OS 92%	
Everolimus (2.5, 5, 10 mg daily)	De Melo <i>,</i> 2016	Phase I	13	Cervical cancer	EBRT/45Gy/25fx followed by BRT/24Gy/4fx	Neoadjuvant (1 week) and concurrent (EBRT and BRT)	2 DLTs at 10 mg daily More frequent grade 3-4 toxicity was hematological	11 CR (9 confirmed by PET/CT)	5 mg/daily was MTD
Everolimus (2.5, 5, 10 mg daily)	Narayan, 2017	Phase I	18	Prostate cancer, biochemical recurrence	EBRT/66Gy/37fx	Concurrent	No DLTs 22% of grade 3 toxicity	2-ys BCR-free survival 74.9%	
Everolimus (70 mg/wk)	Ma, 2015	Phase II	100	Glioblastoma	EBRT/6Gy/30fx	Neoadjuvant (1 week) and concurrent with RT+TMZ	grade 3+ 57% grade 4, 23%	1-yr OS 64% median TTP 6.4 month	

SUMMARY:

There are no sufficient clinical data to adequately judge the risks and potential benefits of a combined use of mTORinhibitors with radiotherapy. As long as this is the case, it can be assumed, as in other anti-angiogenic compounds, that the combinational may lead to wound healing deficits, increased bleeding and thrombosis. Particularly caution should be



given when RT involved GI tracts even when RT is applied to a new patient or when a new patient receives PI3K/mTOR inhibitors after RT.

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- BRAF inhibitors



CG, MF,RDA,SR

Mechanisms of actions

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 abuot 60% of melanona cells. The most common mutation in BRAF is caused by a single amino acid substitution of valine for glutamine at codon 600, representing the majority of BRAF mutations found in human cancer. (1)

The promise of molecularly targeted therapy for melanoma began with the discovery of these mutations.

The BRAF activity as an oncogene, and thus its attractiveness as a therapeutic target, has been confirmed in some studies, which showed that BRAF is an important activator of MEK-ERK signaling in cancer cells, regardless of RAS, resulting in induction proliferation and inhibition of apoptosis (2).

Vemurafenib (PLX4032) was the first selective BRAF inhibitor approved in cancer. Is a low molecular weight, orally available inhibitor of some mutated forms of BRAF serinethreonine kinase, including BRAF V600E. It is indicated for the treatment of patients affected by advanced melanoma with BRAF V600 mutation (3).



Dabrafenib (GSK2118436) is a potent and reversible ATP-competitive inhibitor that selectively inhibits the BRAF V600E kinase. Preclinical data have demonstrated that Dabrafenib inhibits the MAPK pathway in the BRAF V600E melanoma cells, which leads to a decrease of proliferation and regression in xenograft mouse models and significantly improved progression-free survival compared with standard chemotherapy regimens (4).

Potential interaction with radiotherapy

Inhibition of BRAF has been associated with radiosensitization in vitro.

Sambade et al (5) 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 B-RAF inhibitors in combination with radiation could provide improved radiotherapeutic response in B-Raf mutant melanomas.

Preclinical data

Desgupta et al, have assessed the interaction between PLX4720, a specific BRAF V600 inhibitor and some human carcinoma cell lines (melanoma, colon and thyroid carcinoma) demonstrating additive activity between radiation and PLX4720. In cells with BRAF V600E mutations, PLX4720 caused cell cycle arrest at G1, and, when combined with radiation, caused a combined G1 and G2 cell cycle arrest; this pattern of cell cycle effects was not seen in the BRAF wild type cell line (6).

Hecht et al (7) evalueted radiosensitivities in 35 blood samples of melanoma patients with or without BRAF inhibition. Each blood sample was divided into two portions, one of which was irradiated with 2 Gy and the other was not. Chromosomal aberrations were then analyzed via three-color fluorescence in situ hybridization (FISH). Again, patients who were or had



taken BRAFi demonstrated increased radiosensitivity. Interestingly, this increased effect was significantly associated with Vemurafenib but not with Dabrafenib.

Clinical data on efficacy and toxicity

Radiosensitization by combined treatment with BRAF inhibitors and radiotherapy has been described as an increase in the occurrence and severity of skin disorders, which was restricted to the irradiated areas in the vast majority of cases. In addition, enhanced radiation toxicity within the irradiated target areas has also been reported.

Skin toxicities

The radiosensitizing effect of BRAF inhibitors probably also sensitizes melanoma cells, maybe even to a greater extent than keratinocytes.

In a multicenter study conducted by Hecht et al. (7) a total of 161 melanoma patients from 11 European skin cancer centers were evaluated for acute and late toxicity, of whom 70 received radiotherapy with concomitant BRAF inhibitor treatment by vemurafenib or dabrafenib, or sequential application of these drugs.

Any acute or late toxicity appeared in 57% of radiotherapies with concomitant BRAF inhibitor therapy. Skin toxicity appeared frequently whereas other toxicities were rare. With radiotherapy and concomitant BRAF inhibitor therapy the rate of acute radiodermatitis grade≥2 was in 36% and follicular cystic proliferation in 12.8%.

Non-skin toxicities included hearing disorders (4%) and dysphagia (2%).

It was also evaluated the correlation between the dermatitis and the type of BRAF inhibitor. Concomitant treatment with vemurafenib induced acute radiodermatitis grade≥2 more frequently than treatment with dabrafenib (40% versus 26%,



P=0.07) but G3 toxicities were similar. Follicular cystic proliferation only appeared in patients taking vemurafenib. In some cases the dose was reduced precautionary immediately before the radiotherapy (5 patients) or following the appearance of the first adverse event (10) but These dose reductions did not reduce radiation induced skin toxicity during concomitant treatment compared with full dosage (P= 0.4). The largest subgroup of patients treated with radiotherapy and concomitant BRAF inhibitors received WBRT.

Following whole-brain radiotherapy, radiodermatitis grade≥2 was 44% and 8% (P < 0.001) for patients with and without BRAF inhibitor therapy, respectively. No toxicities were reported after stereotactic treatment.

In line with these findings, analysis of chromosomal breaks ex vivo indicated significantly increased radiosensitivity for patients under vemurafenib (P = 0.004) and for patients switched from vemurafenib to dabrafenib (P = 0.002), but not for patients on dabrafenib only.

Radiation recall reactions have been reported too.

Forshner et al. (15) described a case of a patients subjected to whole brain radiation therapy with a cumulative dose of 30 Gy (3 Gy x 5fr/week, 6 MV photons, 2D opposing lateral fields). The radiation was well tolerated without any skin toxicity. After completion of radiotherapy, patient started treatment with vemurafenib 960 mg twice a day, and developed two weeks later multiple itchy vesicles and papules on an erythematous swelling of the scalp, sharply defined to the prior irradiated area and consistent with radiation recall reaction.

Similar reactions have been reported in other cases in several areas (see Table 1).



SKIN TOXICITY - TAKE HOME MESSAGE

BRAF inhibitors increase the risk of G2-3 dermatitis with RT. Patients receiving conventionally fractioned radiotherapy with concomitant dabrafenib have a moderately increased risk of acute radiodermatitis compared with a larger increase in patients taking vemurafenib. Patients under treatment with BRAFi, need careful dermatologic control and receive early supportive care, if necessary.

Mucosal Toxicity

Severe non-cutaneous radiosensitizing effects with vemurafenib have been described too.

Peuvrel et al (8) described a patient treated with hypofractionated palliative RT to a primary rectal adenocarcinoma concurrently with vemurafenib given for metastatic melanoma. Patient developed grade 3 anorectitis and diarrhea, with severe pain refractory to morphine and corticosteroids and finally colostomy was required 10 months after RT. Merten and colleagues (9) reported a case of G3 esophagitis that required hospitalization for parenteral nutrition. This patients received RT for spine metastases concurrently with vemurafenib.

MUCOSAL TOXICITY - TAKE HOME MESSAGE

The risk of mucosal toxicity with association of BRAFi and RT, is higher than radiotherapy. To reduce toxicity should organs at risk should not be involved in the RT fields; anyway, the radio-sensitizing effect of BRAFi, suggest to avoid the association.



HEPATIC TOXICITY

Vemurafenib alone could cause hepatic toxicity involving transaminase increase.

A case of exceptional fatal liver toxicity after radiotherapy of the lumbar vertebra was reported by Anker and collegues after 20 Gy of RT administered in five fractions to the painful bone metastases. Aposterior-anterior (PA) beam to T10 to L1 ; vemurafenib was stopped for 4 days before and 2 days after radiation.

Five weeks later the patient developed lower extremity weakness, and a lumbar spine MRI showed cauda equina compression at L4. She received 8 Gy of RT to L2 to L5 using a PA field, but vemurafenib was only withheld for 2 days because of the emergent nature of the treatment. After some weeks she developed worsening abdominal pain and an acute drop in hematocrit. Accumulation of a large subcapsular hepatic hematoma and hemoperitoneum consistent with hepatic hemorrhage were detected on CT imaging. The patient died 2 days later. The mean liver dose was only 2.7 Gy.

The authors raccomend withholding Vemurafenib for 7 days before and after Radiotherapy (10).

Other reports involving radiotherapy with concurrent vemurafenib and dabrafenib to the same region but without severe hepatoxicity (11-12-13).

LIVER TOXICITY -TAKE HOME MESSAGE

Althoug the probability of hepatotoxicity would seem low because only 1 case has been reported, the association between RT with BRAFi it may cause severe side effects.


LUNG TOXICITY

Baroudjian et al. (14) described a case of an hemopneumothorax after radiotherapy of the right axillary area, which ultimately led to the death of the patient 1 month after radiotherapy with a prior vemurafenib therapy.

Radiation recall pneumonitis may occur from RT and BRAFi association. Forshner et al. described pneumonitis in patients treted with vemurafenib and RT(15).

A patient received adjuvant radiotherapy of right axilla and right supraclavicular, infraclavicular and pectoral regions (50 Gy; 2Gy/fr). The estimate skin dose was between 30-40 Gy; the mean lung dose and the lung volume receiving 20 Gy, were 6.9 Gy and 12.4% respectively. Four weeks after radiotherapy, started systemic therapy with vemurafenib 960 mg twice a day for progression disease.

After 3 weeks of treatment, the patients developed a dry and obsessing cough with emergence of parenchymal changes with predominant ground glass appearance of the right upper lung corresponding to the radiation dose distribution.

Another patient, treated for an obstruction of the left main bronchus. The MLD and V20 were 17.4 Gy and 32.9 % respectively. During radiotherapy the patient developed dysphagia and cough . Three weeks later start treatment with Vemurafenib 960 mg twice a day and 4 weeks later the patients developed shortness of breath leading to hospitalization. In



the CT scan of the thorax were found consolidations most prominent in the irradiated paramediastinal as a radiation pneumonitis.

A treatment with prednisolone was started in combination with antibiotic therapy for 10 days with consequent improvement of the symptoms.

The authors saw no pulmonary symptoms in 5 other patients treated with axillary RT followed by vemurafenib.

A case of severe pleural toxicity after 20 Gy in 4 consecutive fractions was reported in patient who took concurrently vemurafenib for right axillary lymphadenopathy (15). The patient experienced grade 3 dermatitis followed by CR at 1 month, but a hemothorax leading to death 1 month later raises suspicion of a severe hemorrhagic pulmonary/pleural toxicity. Although a second patient had no toxicity despite a higher dose of 30 Gy in 6 daily fractions to the pleural surface, the risk of hemorrhage should be noted.

Take Home message

The risk of radiation recall pneumonitis, pleural hemorrhage, or both is low. It requires careful assessment of patients undergoing the combination treatment in order to detect early symptoms such as fever, cough and chest pain.

Vigilance in detecting symptoms of RRP (cough, fever, shortness of breath, and chest pain) is recommended.

Concurrent stereotactic radiotherapy and BRAFi

There are no randomized studies comparing stereotactic radiotherapy (SR) with or without BRAFi.

Patel et al (16) retrospectively compared the outcomes and toxicities of melanoma brain metastases patients treated with Vemurafenib/Dabrafenib and stereotactic radiosurgery (15 patients) or with radiosurgery alone (87 patients). They included



patients treated with VMF 12 days before SRS or DAB 2 days before SRS. 14 patients were treated with VMF and one patient with dabrafenib.

Radiation necrosis was higher in the SRS + BRAFi cohort. At 1 year 22.2 vs. 11%, p<0.001). Symptomatic Radionecrosis was higher in patients receiving BRAFi (at 1 year: 28.2 vs.

11.1%, P< 0.001), without difference in the rate of local recurrence.

Ly and colleagues (17), in a report of 52 patients with known BRAF mutation status, identified 17 patients treated with BRAFi with a washout period initiated before and after SRS (median, 7 days; range, 1-20 days). At a median follow-up time of 10.5 months, no patient had radionecrosis. BRAFi treatment for patients with BRAF mutant melanoma was associated with a decreased rate of freedom from hemorrhage at 1 year: 77.0% versus 39.3% (P=.0003). However, despite this difference, OS was not significantly different between patients who did and did not receive BRAFi.

Out of 80 lesions treated in 24 patients with BRAFi held 2 to 3 days before and after started radiotherapy.

Ahmed et al (18) reported only 1 episode of hemorrhage that led to a craniotomy 2 months after SR.

Gaudy et al. (19), reported no case of radiation-induced necrosis and no scalp radiation dermatitis in 24 patients received BRAF-I and Gamma-Knife .Median survival from first gamma knife radiosurgery under BRAF-I and first dose of BRAF-I were 24.8 and 48.8 weeks, respectively.

A prospective study was conducted by Wolf and colleagues (20) who evaluate the impact of BRAF inhibitors on survival outcomes in patients receiving stereotactic radiosurgery for melanoma brain metastases.



They collected treatment parameters and outcomes for 80 patients with melanoma brain metastases who underwent SRS with 18 Gy in 1 fraction. Of 80 patients analysed, 35 patients harbored the BRAF mutation and 45 patients did not.

No significant difference in hemorrhage (16% after BRAF and SRT vs. 8% after SRT alone, ns). Patients with BRAF-M treated with both SRS and BRAF inhibitors, at or after SRS, have increased overall survival from the time of SRS.

In 2 patients who received SRS to 24 Gy concurrently with BRAFi (1 vemurafenib, 1 dabrafenib) did not show evidence of necrosis or hemorrhage at magnetic resonance imaging (MRI) 3 months after SRS (21).

In a single center retrospective study conducted by Xu et al (22), analyzed the impact of Braf mutation status and use of BRAFi (dabrafenib or vemurafenib) in conjunction with stereotactic radiosurgery in 65 patients of which 17 were treated with BRAFi. Among them 12 (71%) received vemurafenib, while 5 patients dabrafenib. It is important to emphasize that not all patients were treated concomitantly. Only 2 patients received Vemurafenib during the radiotherapy, while 10 other patients received it at median of 5.5 months after stereotactic RT (range 1 week to 10 months) and 3 had to discontinue vemurafenib due to the development of a severe rush. 4 patients received dabrafenib at a median of 4.5 months after the initial SRS (range 4-6 months) and only one received the drug 8 days before and again 8 days after radiotherapy.

Median survival times after diagnosis and treatment, were favorable in patients with BRAF mutation and treated with radiotherapy and BRAFi compared with the patients with wild type BRAF (median survival 23 months ,vs 8 month and 13 vs 5 months respectively). Following radiotherapy no significant difference was found respect the rate of intratumoral hemorrhage or tumor necrosis in the 3 groups. 6/17 (35%) of patients of the concomitant therapy group.



Narayana et al. (23) analyzed retrospectively twelve patients whith BRAF mutation, treated with either stereotactic radiosurgery or whole brain radiation therapy prior to or along with vemurafenib at a dose of 960 mg orally twice a day. Radiographic responses were noted in 36/48 (75 %) of index lesions with 23 (48 %) complete responses and 13 (27 %) partial responses. There were 2 deaths caused by cerebral edema, but did not but it is not specified if it was correlated with the concurrent treatment.

There is few data on the combination of BRAFi and extracranial SRT.

Eilsmark et al. described recall radiation-induced myelitis in the thoracic spine caused by radiotherapy followed radiosensitization by dabrafenib 8 months after sterotactic radiotherapy to a large central left sided pulmonary lung metastasis; treatment was given with 56 Gy in 8 fraction; The dose to the spinal cord did not exceed 33.5 Gy.(24).

In contrast Stefan and collegues (25) described the case of a patient treated with sterotactic radiotherapy for a L3 metastases. Concomitant stereotactic radiation that focused on the third lumbar vertebra, using the Cyberknife system that delivered 10 Gy in one fraction, was started 1 month after vemurafenib. The absolute maximal doses accepted were 11.62 Gy for the spinal canal, 10.26 Gy for the spinal cord, 13.3 Gy for the skin, 6.66 Gy for the large bowel and 8.16 Gy for the small bowel.

The patient, received steroids for several weeks, showed a partial response without neurological, skin or mucosal toxicity, 8 months after completion of this combination. This case suggests that stereotactic radiation sparing normal tissues and might be safer than conventional fractionated radiation with vemurafenib



BRAIN TOXICITY TAKE HOME MESSAGE

Data on intracranial neurologic toxicity are conflicting and the risk of brain radionecrosis does not appear increased with BRAFi; nevertheless the toxicity reported by some recent studies recommends caution.

New radiation therapy techniques, such as stereotactic radiation, could allow association with BRAFi in association with RT. Precaution is always advisable when radiation is associated with BRAFV600 inhibitors and clinical studies assessing these new techniques are needed.

Clinical data on efficacy

Some authors have shown that the combination of radiotherapy and BRAFi, can determine an increase of therapeutic efficacy and not only the toxicity.

Interesting results, have been reported in 6 patients with unresectable disease, treated with induction vemurafenib and then receiving radiation therapy (median dose 57 Gy, conventional fractionation), with 3 patients receiving debulking interval surgery (26). With 29 months' follow-up, local control was 100%. The 3 patients who experienced relapse received salvage therapy to become free of disease at latest follow-up.

Lee and colleagues (27) reported a case report in which a patient with positive cerebral spinal fluid cytology developed after 4 months of vemurafenib, underwent to whole brain irradiation (30 Gy in 10 fr)m with vemurafenib held 7 days before and after radiootherapy. With a follow up of 18 moinths after RT, the cerebral spinal fluid was still negative without skin or non-



dermatitis skin toxicity. The authors hypothesized that RT could have have altered the permeability of the blood brain barrier allowing greater absorption of the drug in the spinal fluid.

Baroudjian et al (14) reported a complete metabolic response in a patient who had progression in the axilla, after radiotherapy 30 Gy in 6 fractions with concomitant vemurafenib.

On the contrary, Satzger (12) described the experience of 4 patients treated with BRAF (3 dabrafenib and 1 vemurafenib) who reported severe skin toxicity with infield progression disease.

SUMMARY:

The introduction of small molecule BRAFV600 kinase inhibitors represents a milestone in the targeted therapy of patients with metastatic melanoma by a significant increase in therapeutic efficacy in terms of overall and progression-free survival compared with conventional chemotherapy. Clinical investigations and prospective clinical trial are needed to provide definitive evidence-based data regarding the safety and efficacy of the combination of radiotherapy and BRAF inhibitors.

The data we have are now insufficient to make strong recommendations about the concomitant use of BRAFi and radiotherapy, and the reports of unexpected severe toxicity suggest paying specific attention when RT and BRAFi are given even not concurrently but in shorter time.

Until more prospective data are available, the consensus recommendations of the Eastern Cooperative Oncology Group (ECOG) include the following for all patients receiving a BRAFi, MEKi, or both BRAFi and MEKi (eg, vemurafenib/dabrafenib and trametinib/cobimetinib) (28).



For drug:

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

For RT:

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

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Summary of case reports and clinical series on radiosensitizing effects of the BRAF inhibitors dabrafenib and vemurafenib in patients with NON BRAIN metastases.									
Table 1									
Radiosensitizing effect	Radiosensitizing Report by first effect author		Start of BRAFi treatment	Specified adverse reaction and time of onset					
Acute skin reaction	Satzger et al.	4	Dabrafenib (n = 3) or vemurafenib (n = 1) 2–8 months before RT	Radiodermatitis (grade 2–3) during (n = 2) or after (n = 2) RT					
	Ducassou et al.	1	Vemurafenib (240 mg twice/day) before RT	Intensive erythema 4 days after RT					
	Baroudjian et al.	1	Vemurafenib 1 month before RT	Radiodermatitis (grade 3) and possibly hemopneumothorax after RT					
Radiation recall skin	Braunstein wt al.	1	Vemurafenib 6 weeks after RT	Ulceration, erythema and scar dehiscence 2 weeks after BRAFi					

Table 12- Radiotherapy and BRAF inhibitors



Reaction				
	Hourier et al.	1	Vemurafenib 1 or 23 days after RT	Multiple epidermal cysts 3 months after BRAFi
	Conen et al	1	Vemurafenib 5 weeks after RT	Maculopapular rash, edema erythema 1 week after BRAFi
	Wang et al.	1	Vemurafenib 1months after RT	Keratosis, folliculocentric papules 8 days after Brafi
	Boussemart et al.	2	Vemurafenib 1 or 23 days after RT	Pruriginous erythematous vescicles 10 days after BRAFi and pruriginous
				rectangular eczematous plaque 7 days after BRAFi
Extra-dermatologic reaction	Peuvrel et al.	1	Vemurafenib during RT	Pelvic radiodermatitis (G2) anorectitis amd diarrhea after RT
	Merten et al.	1	Vemurafenib during RT	Skin hyperpigmentation (G2) and esophagitis (G3) after RT
	Anker et al.	1	Vemurafenib before and after RT	Severe liver toxixity after RT
	Forsher et al.	2	Vemurafenib 3 and 4 weeks after RT	Radiation recal pneumonitis 3 and 4 months after radiotherapy

- Hedgehog signalling pathway inhibitor (erivedge, sonidegib) SP, AS

Mechanisms of actions

The Hedgehog (Hh) signalling pathway is involved in cell proliferation and differentiation during embryonic period; oppositely, it is largely suppressed in the adult. Reactivation during adult period results in carcinogenesis and metastasis phenomena. Aberrant activation of the pathway has been found in several disparate tumours, such as cervical cancer (1-3). Interestingly, the Hh pathway has been implicated in resistance to both chemotherapy and radiation (4). Vismodegib (GDC-0449) selectively inhibits the hedgehog (HH) signalling pathway. There are three HH signalling molecules in vertebrates: Indian HH (which is expressed in the intestine and chondrocytes), Desert HH (which is expressed in Sertoli cells), and the better-known Sonic HH, involved in different processes. The HH signalling pathway is made up of 3 elements:

- HH ligands,



- the inhibitory receptor Patched (PTCH),
- the signalling receptor Smoothened (SMO) (5).

The PTCH protein negatively regulates the pathway, whereas the SMO protein positively regulates the pathway and is permanently activated in the absence of PTCH. SMO also activates some transcription factors (Gli), which enter the nucleus and activate the transcription of genes involved in cell growth: these ones control PTCH and Gli via a negative feedback mechanism. This mechanisms allow the activation of the pathway, resulting in proliferation, apoptosis, and epidermal differentiation. Proteolyzed Gli factors are transcription inhibitors: their proteolysis occurs with the binding to microtubules and to suppressor of fused (Sufu) proteins which, if linked to Gli, stop the activation of the target genes of the HH pathway (6-8).

Translating these steps in clinical picture, it has been found that in sporadic BCC, mutations induced by UV radiation can be found in the HH pathway: in particular, 80% are caused by inactivation of *PTCH1*, 10% by *SMO* gain-of-function mutations, and just 1% by *Sufu* mutations (5). To treat this condition, vismodegib was the first small molecule inhibitor of SMO in the hedgehog pathway, approved for use in January 2012 for locally advanced and metastatic BCC unsuitable for conventional treatment (9). It acts inactivating SMO, preventing the activation of Gli and reducing cell proliferation and tumour growth: the effect of Vismodegib administration in BCC patients is a significant decrease in HH-signalling, as demonstrated by a highly significant decrease in GLI1 messenger RNA in biopsy specimens from BCCs in patients treated for 1 -month. As a consequence, vismodegib treatment reduced tumour proliferation and the rate of appearance of new lesions (10). On the other hand, sonidegib blocks Hedgehog signalling by selective inhibition of *SMO* expression (11,12).



Resistance to treatment has been reported in cases with mutations in other genes involved in the HH pathway, mainly in the presence of PTCH1 and heterozygous SMO mutations (PTCH1-W844 C) [13-15]. Brinkhuizen et al. (16) found 2 SMO mutations: c.842G[T (p.Trp281Leu) in exon 4 and c.961G[A(p.Val321Met) in exon 5. Pricl et al. (17) detected 2 new mutations: SMO G497 W and SMO D473Y; the first one results in a conformational rearrangement of the protein at the drug entry site which determines obstruction, while the second mutation alters the binding site geometry. Mutations may cause also different mechanisms. Recently, Sharpe et al. (18) observed that some mutations can led to hyperactivation of the HH pathway and these mutations affect 2 regions of the SMO gene: the drug binding pocket and a distal location, suggesting possible cross-resistance. Other mutations involve the target HH gene cyclin D1 (CCND1) (15,19) and compensatory upregulation of IGF-1R/PI3 K can determine resistance to SMO inhibitors. In other words, resistance to vismodegib has been demonstrated to be caused mainly by somatic mutations in PTCH and in SMO, by mutations located distally to this transmembrane receptor, and also through SMOindependent Gli activation and compensatory upregulation of IGF-1R/PI3 K [20]. Moreover, patients who have SHH pathway mutations downstream of SMO do not respond to Sonidegib at all (21).

In recent years, targeted therapies have been evaluated in patients affected by medulloblastoma presenting mutations in the Sonic Hedgehog (SHH) pathway (22): consequently, antagonists of SMO may entry into clinical trials also for this disease.

Potential interaction with radiotherapy

Vismodegib may interfere with wound healing because Hh plays a role in tissue regeneration (23), so it has been hypothesized vismodegib may slow wound healing induced by irradiation.



Available radiation approaches for BCC are the following: brachytherapy (24); collimated beams of orthovoltage for superficial treatments; electrons with more deeply penetrating energy; high-energy electrons and photons for deep tumours. Pollom et al. (25) successfully combined vismodegib treatment with high-energy irradiation. In a previous study, radiotherapy was combined with vismodegib to treat squamous cell carcinoma tumours not responding to vismodegib alone (26). After the first experiences, it has been thought that patients could not tolerate more than 6 months of therapy (27), even if improvement could persist for more than a year after the end of the dual treatment.

Several theories have been proposed to explain resistance to Vismodegib and Sonidegib. First of all, depletion of Hh may lead to changes in the stroma layer so that it removes a constraint to tumoral growth; this condition, considering the stage of the tumour and the context of the treatment, may be crucial for reaching the efficacy of Hh inhibition (28,29). Additionally, differences in stromal component between the primary lesion and metastatic ones may impact drug efficacy, since the lower stromal content which characterizes some metastatic lesions may impair the efficacy of Hh inhibition in advanced or metastatic disease (30). In this context, pre-clinical cervical cancer experiments evaluating short term Hh inhibition to standard radiochemotherapy (RTCT) for localised treatment naive disease, have demonstrated improvements in tumour and metastases control. The addition of these molecules to RTCT is justified by emerging studies dealing with the relationship between DNA repair and the Hh pathway, which demonstrate that inhibition of the activity of GLI can interfere with DNA repair in cancer, suggesting that Hh/GLI functions can have a role in permitting tumour cells to survive even when DNA damage induced by RTCT occurs (4). Pre-clinical studies of Chaudary et al. (31) give the final kick for combining Hh inhibition with RTCT.



Preclinical data

Mice with mutations in Ptch1 or Smo genes leading to constitutive activation of the Hh pathway can develop BCC and medulloblastoma (32). The activity of an Hh antagonist (Hh-Antag) was first explored in Ptch1+/- Trp53-/- mice (33), a spontaneous medulloblastoma model, where it demonstrated to inhibit the Hh pathway with tumour regression and improved survival. Moreover, in subcutaneous allograft models generated from Ptch1+/- mice, it was demonstrated that vismodegib administration could result in complete regression of tumours (34,35). Interestingly, it was observed that a high suppression of the pathway (>90%) was required to obtain tumour regression (33,36). These results in preclinical models supported the testing of these molecules in patients.

To measure effects of inhibitors in combination with the SHH antagonist NVP-LDE225 (Selleck Chemicals, S2151), tumour cells were cultured with increasing doses of Sonidegib (37) for 48hrs and [methyl-3H]thymidine assays were performed (37). Chaudary et al. (31) evaluated Sonidegib addition to RTCT. They investigated tumour growth delay, metastasis and GI toxicity using orthotopic cervical cancer xenografts models. Radiation therapy was delivered to the xenografts (2Gy/day over 3 weeks) and weekly cisplatin 4mg/kg concurrently, with or without Sonidegib (60mg/kg daily for 3 weeks). They observed that Sonidegib administered with RTCT was well tolerated and resulted in delayed tumoral growth and reduction of metastatic spreading, with no increase in acute GI-toxicity with respect to RTCT alone. Their data support an additional therapeutic role for targeting Hh in patients undergoing RTCT.



Clinical data on efficacy and toxicity

The discovery of receptor targeted molecules in the Hedgehog pathway led to the approval of the two Hedgehog pathway inhibitors (HPI) vismodegib and sonidegib by the U.S. Food and Drug Administration (FDA) for the treatment of adults with locally advanced BCC (laBCC) which includes either locally recurrent advanced BCC after surgery or those who are not candidate for surgery or radiation. Vismodegib was also approved for patients with metastatic BCC (mBCC). The availability of these agents as highly targeted therapy represents a success in translational medicine. In a phase I clinical trial, Von Hoff et al. (38) observed respective response rates of 60% and 50% for locally advanced and metastatic BCCs treated with vismodegib, respectively. The phase II study with 96 aBCC patients leading to FDA approval demonstrated a response rate of 30 % in patients with metastatic BCC and 43 % response rate in locally advanced BCC [39]. These results were confirmed in a subsequent study on 119 aBCC patients (40). Gill et al. studied patients with locally advanced periocular BCC, with response rates in about half of all cases (41).

In the 3 largest studies of vismodegib efficacy and safety (42-44), median duration of treatment has ranged from 6.5 to 12.9 months with the median time to response approximately 2.5 months (45). The SafeTy Events in VIsmodEgib (STEVIE) study is an international multicentre open-label study, containing important data regarding safety and efficacy of vismodegib (44). Interim results confirmed the results of the previous studies and progression free survival of 20.2 months (496 patients). Among the patients evaluated, 134 ones received RT prior to Vismodegib administration. Adverse effects include muscle cramps, taste disturbance, weight loss, fatigue and alopecia. Three similar class effects are seen with other novel hedgehog pathway inhibitors (eg sonidegib) and the possibility of dose alteration to reduce adverse events is under investigation (44):



in particular, oral sonidegib at the dose of 200 mg daily has shown a promising risk-benefit profile for aBCCs (46). Chang et al. (43) studied 119 patients with aBCC undergoing vismodegib for a median of 5.5 months. Objective responses occurred in 46.4% of laBCC and 30.8% of patients with mBCC. Response was negatively associated with prior systemic therapy in patients with laBCC in a significant manner. The most common adverse events in this study were muscle spasms (70.6%), dysgeusia (70.6%), alopecia (58.0%), and diarrhoea (25.2%).

Among sequential schemes of treatment, Block et al. (47) reported a case of laBCC treated with trimodality therapy (vismodegib, radiotherapy, and local excision), resulting in excellent outcome and facial cosmesis, without requiring extensive resection or reconstructive surgery; Jacobsen et al. (45) has reported resolution with vismodegib of relapsing BCC after fourteen months from previous RT; finally, the cases reported by Amici et al. (48) elicited the possible interest of radiotherapy in combination or after tumour debulking by vismodegib.

Among concurrent schemes with vismodegib and RT, Pollom et al. (25) reported 2 cases of recurrent aBCC treated with concurrent RT and vismodegib. Concurrent treatment was found to be well tolerated and efficacious and both patients had no evidence of progressive disease at last follow-up (Table). Raleigh et al. (49) described the case of a patient affected by auricular laBCC treated with induction vismodegib and radiation, reaching durable local control of disease and acceptable acute toxicity. Schulze et al. (50) studied four patients who received vismodegib and radiotherapy (50.4-66Gy) in combination. 3/4 patients had recurrent BCC whereas the remaining one had locoregional lymph node involvement. 3 of the 4 patients experienced a CR; one showed SD for 6 months and then experienced PD. The combination of therapy was well tolerated with no relevant adverse effects due to drug-radiation interaction.



Inhibition of Hh has demonstrated successful results in BCC exhibiting activation of the Hh pathway secondary to an activating mutation (44); oppositely, in other tumours not exhibiting this ligand-independent activation, molecules targeting the Hh pathway has employed with less success. In fact, drugs targeting the Hh pathway has also been explored for the treatment of pancreatic cancer, where upregulation of SHH occurs in over 70% of tumours. In pancreatic cancer, a ligand dependent paracrine mechanism determines activation of the Hh pathway (51). In 2008, Olive et al. (28) demonstrated that inhibition of the Hh pathway could disrupt the desmoplastic stroma, facilitating the delivery and increasing the efficacy of chemotherapy in pancreatic cancer.

The approval of sonidegib by the FDA was based on the demonstration of durable objective response rate (ORR) from the Phase II, multicenter, randomized and double-blinded BOLT clinical trial, which evaluated the treatment with two different doses of sonidegib in patients with locally advanced or mBCC [46]: in total, 230 patients were evaluated, 79 in the 200 mg sonidegib group and 151 in the 800 mg sonidegib group; interestingly, sonidegib was administered after RT in 19 patients of the 200 mg group and 49 of the 800 mg group.

Sonidegib is available in 200mg capsules for the treatment of patients that are 18 years or older with laBCC that has recurred following surgery or radiation therapy, or those who are not candidates for surgical resection or radiation therapy. Obviously, Sonidegib is contraindicated in women during pregnancy or breast-feeding since Hedgehog signalling plays an important role in early periods of life. Sonidegib has high tissue penetration and the ability to cross the blood–brain barrier as per first preclinical studies. The main dose-limiting toxicity was elevated serum creatine kinase reported in 1/5 patients under treatment. Muscle spasm is the most commonly reported adverse event for patients under sonidegib (52).



Sonidegib is currently evaluated not only in BCC patients, but also in clinical trials for management of myelofibrosis, leukaemia and solid tumours sharing mutations in loss of function in PTCH or gain of function in Smo like in BCC. Currently there are several ongoing clinical trials studying sonidegib in patients with recurrent or refractory medulloblastoma.

The BOLT trial showed both 200 mg and 800 mg of sonidegib demonstrated durable clinical benefit with acceptable safety and tolerability; however, the 200 mg subpopulation showed having a more favourable benefit-to-risk profile (46). Among patients with the greatest inhibition of *GLI1* expression from baseline, those treated with 800 mg sonidegib had a greater risk of grade 2 or worse increases in creatine kinase levels with respect to patients under 200 mg sonidegib. The 12-month analysis confirmed efficacy in patients with advanced BCC with no additional safety problems. At the time of primary analysis, a total of 144 patients (63%) had discontinued the treatment largely due to adverse events and an additional 35 patients (77.8%) had discontinued the treatment in the 12-month follow-up (53). Both sonidegib and vismodegib have shown similar percentage of adverse events of any grade at 12-month follow-up. In the STEVIE trial, another multicenter, open-label study evaluating safety in patients with advanced BCC under 150 mg oral vismodegib capsule once a day in 28-day cycles, also recorded similar safety profile in a larger patient series (n = 499) at the time of interim analysis (44). All these findings support the use of these agents in clinical practice.



Table 13- Radiotherapy and VISMODEGIB AND SONIDEGIB

Drug	Author	Study type	N	Tumour	RT	Combination	Toxicity	Tumour outcome	Comments
(dose)	and			site	technique/dose/fractionation	(concomit,			
	year					other.)			
Vismodegib	Pollom EL et al, 2015	Case report	2	Left nasal tip BCC	VMAT 66Gy/33Fx	Concomitant	Grade 1 dermatitis and mucositis during RT; taste changes, loss of appetite, muscle cramping, and fatigue after 3 months	Stable disease (9 months)	
				left lower eyelid and lateral canthalBCC	51 Gy in 17 fractions using mixed 6- MeV and 9-MeVelectrons	Concomitant	Grade 1 dermatitis. Vismodegib stopped 2 weeks after completion of RT because of increased fatigue, weight loss, and shortness of breath.	Disease free at 12- month follow-up, with dry eye managed by eye drops as his only radiation- associated toxic effect.	RT after 2 months of Vismodegib therapy
Vismodegib	Raleigh DR et al, 2015	Case report	1	Right ear BCC	IMRT/70Gy/35Fx	Concomitant	At follow-up 13 months after the end of treatment, mild fibrosis, mild erythema and inflammation of the periauricular soft tissues, mild-to- moderate	Disease free	RT started after 12 weeks of monotherapy



							conductive hearing loss.		
Vismodegib	Schulze B et al, 2015	Case series	4	Facial BCC	Case 1: 54.0 Gy (single fraction: 2 Gy per fraction) followed by interstitial HDR brachytherapy boost of 2 × 6 Gy. Case 2: definitive RT in combination with vismodegib (66Gy/2Gy per fraction). Case 3: RT (55Gy/ 2.75 Gy per fraction). With regard to the lymph node involvement, the planning target volume encompassed the right- sided lymph node levels I and II. Case 4: RT (55Gy/ 2.75 Gy per fraction).	Concomitant	Radiodermatitis occurred in all four cases (1/4 grade-3 skin reaction). Alopecia and dysgeusia occurred in one patient only. One patient only. One patient, whose BCC was located next to the right eye, developed a persistent blepharitis and epiphora, which was still ongoing at the last follow-up visit.	3 CR; 1 SD for 6 months and then PD	Vismodegib was taken once a day (150 mg) during the entire time of irradiation and beyond upon instructions of the attending dermatologist.
Vismodegib	Block AM et al, 2015	Case report	1	Right cheek BCC	(3DCRT) with a 4-field technique 50Gy in 20Fx	Vismodegib followed after 4 months by RT	Grade 1 fatigue and grade 2 moist skin desquamation	PR	Treated with skin bolus
Vismodegib	Jacobsen AA et al, 2016	Case report	1	Left eye BCC	Not described	Vismodegib after RT	Not described	PD after RT, CR after Vismodegib	
Vismodegib	Basset- Seguin N et al, 2015	Multicenter trial	499 pts	laBCC	Not described	Vismodegib after RT in 134 pts	Treatment was discontinued in 80% of pts; 36% had adverse events, and 51 (10%) requested to stop treatment. Median duration of vismodegib exposure was 36.4 weeks.	70 (14%) had PD. Of the 31 patients who died, 21 were the result of adverse events. As assessed by investigators, 302 (66.7%) of 453 patients with IaBCC had an overall response (153 CR and 149 PR); 11 (37.9%) of 29 patients with mBCC	

							Adverse events in 98% of patients: the most common were muscle spasms, alopecia, dysgeusia, weight loss, asthenia, decreased appetite, ageusia, diarrhoea, nausea, and fatigue. Most adverse events were grade 1 or 2. Serious	had an overall response (two CR, nine PR).	
							adverse events in 108 (22%) of patients.		
Vismodegib	Chang AL et al, 2014	Multicenter trial	119	laBCC or mBCC	Not described	Vismodegib after RT in 55 pts	Mean follow-up for safety was 6.5 months, with muscle spasms (70.6%), dysgeusia (70.6%), alopecia (58.0%), and diarrhoea (25.2%) as the most common adverse events.	Objective responses occurred in 46.4% of locally advanced BCC and 30.8% of patients with metastatic BCC. Response was negatively associated with prior systemic therapy in patients with locally advanced BCC (P = 0.002).	
Vismodegic	Amici JM et al, 2015	Case report	2	laBCC	45Gy/15Fx/5weeks	RT between Vismodegib cycles	Grade-2 ageusia, grade-1 cramps, alopecia Not reported after RT	PR	Article in French language
					Contact KT 40Gy/10Fx/5weeks	KI atter Vismodegib		improvement after 2 months	



Sonidegib	Migden MR et al, 2015	Multicentre, randomised, double- blind, phase 2 trial.	230 pts, 79 in the 200 mg sonidegib group, and 151 in the 800 mg sonidegib group.	laBCC or mBCC	Not described	Sonidegib after RT in 19 (200 mg group) and 49 (800 mg group) pts	Fewer adverse events leading to dose interruptions or reductions (25 [32%] of 79 patients vs 90 [60%] of 150) or treatment discontinuation (17 [22%] vs 54 [36%]) occurred in patients in the 200 mg group than in the 800 mg group. The most common grade 3–4 adverse events were raised creatine kinase (5 in the 200 mg group vs 19 in the 800 mg group vs 19 in the 800 mg group) and lipase concentration (four [5%] vs eight [5%]). Serious adverse events occurred in 11 of 79 patients in the 200 mg group and 45 of 150 patients in the 800 mg group	In the primary efficacy analysis population, 20 of 55 patients receiving 200 mg sonidegib and 39 of 116 receiving 800 mg sonidegib achieved an objective response. In the 200 mg sonidegib group, 18 patients who achieved an objective response, as assessed by central review, were noted among the 42 with locally advanced basal cell carcinoma and two among the 13 with metastatic disease. In the 800 mg group, 35 of 93 patients with locally advanced disease had an objective response, as assessed by central review, as did four of 23 with metastatic disease.	Median follow-up was 13-9 months. Per central Review by Chen et al (2016), 92.3% of patients (48/52) treated with sonidegib 200 mg and 90.1% of patients (91/101) treated with sonidegib 800 mg had laBCC tumour shrinkage by photograph per WHO criteria, demonstrating clinical benefit. In addition, 52.6% of responding patients treated with sonidegib 200 mg and 53.6% of responding patients treated with sonidegib 800 mg had a tumour response lasting longer than 6 months, with a median DOR of 20.2 and 19.8 months, respectively. Among 94 patients (16.0%) had PD and three patients (3.2%), all of which had significant cardiac risk factors, died from cardiac causes deemed to be unrelated to sonidegib.



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3.c Immune Check Point Blockade

AF, AM, MT,

The effects of radiation on tumor microenvironment and its interaction with the immune system appear as a complex balance of activating and suppressing signals (1). For clinical use, intense research is ongoing on how to best harness in different cancer subtypes the positive effects of radiotherapy (RT) on immune activation, particularly combining RT with agents such as immune checkpoint inhibitors (ICI) (1). This option could further expand the separate effects of ICI and of radiation alone, especially in metastatic/advanced disease. The combination of RT with ICI, such as ipilimumab (anti-CTLA-4), pembrolizumab or nivolumab (anti-PD-1), has been explored on different fronts across recent years. Preclinical studies have reported increased loco-regional control when radiation is combined with checkpoint blockade immunotherapy (2). Moreover, increased systemic disease control has been shown when combining radiation with both anti-CTLA-4 and anti-PD-1/PD-L1 inhibitors (3). A study investigating the combination of anti-CTLA-4 with RT in both humans and mouse models of metastatic melanoma showed that the induction of the abscopal effect is limited to a small proportion of patients, due to an acquired resistance to ipilimumab which is PD-1/PD-L1 mediated. The clinical component of this study was a phase I trial testing the combination of RT on a single lesion (6-8 Gy delivered over two or three fractions) followed by ipilimumab (4 cycles, beginning 3-5 days after the last RT fraction), showing a 36% overall abscopal response rate. Non-responding patients had an up-regulation of PD-L1, and the genetic elimination of PD-L1 from therapy-resistant melanoma cells dramatically



restored response to ipilimumab plus radiation. This study planted a seed for the sequential combination of radiation and both anti-CTLA-4 and anti-PD1/PD-L1 agents, as a promising strategy to evade immune resistance and trigger the abscopal effect at the highest degree. As well summarized by Ngiow et al, anti-PD-1/PD-L1 antibodies may combat adaptive immune resistance upon localized radiation plus anti-CTLA-4 therapy, and the superior activity of radiation and dual immune checkpoint blockade is mediated by non-redundant immune mechanisms (4).

New insights and clinical data on the combination between these agents and RT are emerging. We here summarize the clinical findings published so far.

Radiotherapy and ipilimumab

MELANOMA

Two pivotal clinical reports showed how the combination of RT and ipilimumab might obtain better disease control by enhancing the so-called abscopal effect on un-irradiated sites in advanced melanoma. Postow et al. (5) firstly described the case of a female patient treated with 4 doses of ipilimumab at 10mg/kg followed by maintenance ipilimumab every 12 weeks. After 1 year she had progressive disease on a para-spinal mass and spleen/thoracic lymph nodes, and received palliative fractionated RT on the para-spinal mass, while continuing ipilimumab. After 4 months, the targeted mass regressed and, remarkably, also a very good partial response was observed on the hilar lymph nodes and spleen lesions, with stable disease at 10 months. The authors performed immunological studies showing an increase in antibody response regressed are remarkable with an immune-mediated abscopal effect. Few months later, Hiniker et al. (6) reported on a case of a male



patient who first developed a nodal recurrence after resection of the primary tumor (at 3 years) and then had oligo-recurrent metastatic disease with 2 liver metastases at 4 years. He received 2 doses of ipilimumab followed by RT on 2 out of 7 metastases, followed by 2 more doses of ipilimumab. At 5 months, all liver lesions were in complete response. The patient later relapsed at the site of previous surgery (skin): he was simply observed, and the lesion completely resolved after 2 months. Investigators at the Memorial Sloan Kettering Cancer Centre (MSKCC) performed a retrospective analysis of 29 patients who received extra-cranial RT in combination with ipilimumab: no significant increase in adverse effects was observed, and patients receiving RT during maintenance ipilimumab had higher overall survival than those treated during the induction phase (7). A retrospective observational series on 23 patients treated with palliative RT after ipilimumab reported the occurrence of abscopal responses in 11/23 (52%); median time between ipilimumab and RT was 5 months, and median OS for patients obtaining an abscopal response was significantly higher than for non-responding patients (22.4 vs. 8.3 months) (8). Similar results were reported by Chandra et al, who showed an improved response on index lesions (outside radiation fields) in 68% of the cases (9). Multiple possible combinations of ICI and RT exist for advanced melanoma, especially in terms of sequence and timing (11).

Heterogenous results in terms of efficacy and toxicity of the combination of ipilimumab with radiotherapy for melanoma brain metastases have been reported (12). Few reports described successful outcomes in patients treated with ipilimumab and whole-brain radiation therapy (WBRT). Early reports included a 49-year-old patient who received ipilimumab 4 weeks after receiving 30 Gy WBRT, with a significant regression of brain metastases at 12 weeks after the initiation of ipilimumab (13), and a woman with lepto-meningeal disease who received 20 Gy WBRT followed by ipilimumab having a complete



radiographic response 2-3 months after completing treatment, without symptoms (14). Gerber et al reported on 13 patients receiving WBRT and ipilimumab, with a promising overall response rate, yet 10/10 patients with available imaging demonstrated new or increased intralesional bleeding (15). Investigators from the Dana-Farber Cancer Institute reported on 16 melanoma patients who received ipilimumab and either WBRT or stereotactic radiosurgery (SRS): surprisingly, extra-cranial target lesions achieved a response rate of 35% (16).

Researchers from the University of Michigan compared 33 patients with brain metastases receiving either SRS or WBRT and ipilimumab vs. 37 not receiving ipilimumab, showing improved survival for the combination of SRS and ipilimumab (17). Knisely et al. reported on 77 patients with brain metastases treated with SRS: patients who received ipilimumab had a median survival of 21.3 months vs. 4.9 months for those who did not. Survival was not significantly different whether the drug was given before or after SRS (18). In a similar study from New York University, on 58 patients treated with brain SRS, no difference in local tumor control, survival, or frequency of intracranial haemorrhage was reported for those who did or did not receive ipilimumab (19). Tazi et al reported on the combination of SRS and ipilimumab on 10 patients, showing promising survival results (comparable to those without brain metastases) (20). Investigators at the MSKCC also reported on 46 patients treated with ipilimumab and brain SRS: on multivariate analysis, prolonged survival was associated with the delivery of SRS during ipilimumab (21). It is important to note that the Authors documented an increase in brain metastasis size >150% in 40% of the treated lesions with SRS before or during ipilimumab and in 10% of the metastases treated with SRS after ipilimumab. Hemorrhage was observed after SRS during ipilimumab in 42% of brain metastases. Radionecrosis after SRS in combination with ipilumumab was documented in a small series of 3 patients, who were treated with a single dose of 20 Gy



(22). Cases of symptomatic radionecrosis were also reported in a larger series (5/46 patients) (21). The higher rate of increasing lesions, as well as radio-necrosis features among patients receiving SRS or WBRT in combination with ICI is a matter of debate, but many researchers believe that these findings could be an expression of greater local immune reactions.

NON-SMALL CELL LUNG CANCER

Ipilimumab has been tested against advanced non-small cell lung cancer in few trials in combination with chemotherapy (23). This trial did not offer specific information on the combined use of this drug with radiotherapy for metastatic disease. A single report showing promising results was published in 2013 by Golden et al, showing abscopal response in a case of advanced lung adenocarcinoma heavily pretreated with chemotherapy and receiving radiotherapy together with ipilimumab with palliative intent (24). Result are awaited from a prospective phase II study combining radiation and ipilimumab in metastatic lung cancer (NCT02221739).

PROSTATE CANCER

A multicentre, randomised, double-blind, phase 3 trial was published in which men with at least one bone metastasis from castration-resistant prostate cancer that had progressed after docetaxel treatment were randomly assigned in a 1:1 ratio to receive bone-directed radiotherapy (8 Gy in one fraction) followed by either ipilimumab 10 mg/kg or placebo every 3 weeks for up to four doses. 799 patients were randomly assigned (399 to ipilimumab and 400 to placebo), all of whom were included in the intention-to-treat analysis. Median overall survival was 11·2 months (95% CI 9·5-12·7) with ipilimumab and 10·0 months (8·3-11·0) with placebo (hazard ratio [HR] 0·85, 0·72-1·00; p=0·053). A piecewise hazard model showed that the



HR changed over time: the HR for 0-5 months was 1·46 (95% Cl 1·10-1·95), for 5-12 months was 0·65 (0·50-0·85), and beyond 12 months was 0·60 (0·43-0·86). Despite the primary endpoint was not met, longer follow-up would probably show a beneficial effect from RT. Dose and fractionation were also discussed as no preclinical data on the combination were available before study design, and probably the combination could be further optimized to harness at maximum the effect of radiation (25).

Radiotherapy and Pembrolizumab/Nivolumab

MELANOMA

Liniker et al (26) reported on 53 patients with metastatic melanoma treated either with nivolumab and pembrolizumab and SRS, WBRT or extracranial RT. Response in irradiated extracranial/intracranial SRS lesions was 44% for sequential treatment and 64% for concurrent treatment (*p*=0.448), without excess in toxicity. Out of 6 patients receiving SRS, one developed grade 3 radiation necrosis. Among 21 patients receiving WBRT, one developed Stevens–Johnson syndrome, one acute neurocognitive decline, and one significant cerebral edema in the site of the disease. Alomari et al. reported on two patients with brain metastases (one from melanoma and one from NSCLC): 1 was treated with SRS followed after 5 months by pembrolizumab, while the other with SRS followed by nivolumab and ipilimumab after 1 month [28]. Both patients appeared to have early clinical and radiologic progression of their treated lesions. Pathologic examination in both cases showed radiation-induced changes characterized by reactive astrocytosis and vascular wall infiltration by T lymphocytes. Ahmed et al. retrospectively analyzed a series of patients with both resected and unresectable melanoma brain metastases from two



prospective nivolumab protocols (27). Twenty-six patients received SRS. When compared with historical data, local brain metastases (BM) control was similar, whereas distant BM control appeared to be improved, and survival was longer than previously reported. Neurotoxicity was mild and regressed with steroids. Comparing these results with the study of Kiess et al. (21), the authors suggested that there might be a biological difference in post-radiation changes occurring in BMs receiving an anti-CTLA-4 therapy as opposed to an anti-PD-1 therapy.

The anti-PD1 Brain Collaboration (ABC) (ClinicalTrial.govNCT02374242) is an Australian randomized phase 2 trial exploring the activity of nivolumab alone or in combination with ipilimumab, in melanoma brain metastases. Eligible patients are immunotherapy naïve and with measurable brain lesions (5-40 mm). Cohorts 1 (n = 30) and 3 (n = 30) include patients with active brain metastases without prior local therapy and asymptomatic. Patients are randomized to either cohort 1: nivolumab only (3mg/kg Q2W) or cohort 3: nivolumab (1mg/kg Q3W x 4, then 3mg/kg Q2W) combined with ipilimumab (3mg/kg Q3W x 4). Cohort 2 (n = 16) includes patients with brain metastases who have either 1) failed local therapy with evidence of intracranial progression (new +/- progressed in previously treated lesions), 2) neurological symptoms related to brain metastases or 3) leptomeningeal disease. The primary endpoint is the best intracranial response. Secondary endpoints include best extracranial response, best overall response, intracranial PFS, extracranial PFS, overall PFS, and overall survival, as well as safety and tolerability. An additional two cohorts of nivolumab combined with stereotactic radiosurgery (< 4 brain metastases) or whole brain RT (> 5 brain metastases) will be recruited [29]. Another phase 2 trial (ClinicalTrial.gov NCT02320058) is also exploring the activity of the combination of ipilimumab and nivolumab in active melanoma brain metastases (30).


A retrospective study including patients with melanoma brain metastases treated with radiosurgery and pembrolizumb or ipilimumab or RT alone showed superior results in trems of disease control (response) for the combination of pembrolizumab and radiotherapy, without grade 3-4 acute toxicities (31).

OTHER CANCER SUBTYPES

Clinical data on the combination of anti PD-1 and RT in non-melanoma patients are even smaller. Preliminary reports on the safety of pembrolizumab plus RT seem to favor this approach, as no severe or enhanced toxicity was observed. A small study of 10 NSCLC patients with brain metastasis treated with sequential RT and pembrolizumab showed no grade 3-4 adverse CNS events (32). In a Phase II study the authors reported only mild drug-related toxicities in 26 patients affected by unresectable/recurrent metastatic colo-rectal cancer treated with pembrolizumab and ablative or palliative RT (33). Similarly, an exploratory study on 12 patients with metastatic renal cell carcinoma did not report an excess of toxicity combining pembrolizumab with radiation therapy (34). In the initial safety report of a phase II trial in patients with inoperable or unresectable stage III NSCLC treated with concurrent chemoradiation and consolidation with pembrolizumab, no enhanced severe toxicity was observed (35).

A secondary analysis of the Keynote 001 trial, testing the efficacy of pembrolizumab for advanced NSCLC, showed significantly better PFS and OS for patients who previousy received radiotherapy (HR 0.56 and 0.58, respectively). Only 13% of patients with previous thoracic radiotherapy had treatment-related pulmonary toxicity compared with 1% of those without, however the incidence of grade 3 or worse pulmonary toxicity with pembrolizumab was not affected by previous



thoracic radiotherapy (36). Anti-PD-1 related pneumonitis is a known complication, and its incidence varies from 2.7% to 6.6%; RT could possibly enhance PD-1 expression also in non-irradiated regions and increase the risk of side effects, even if this phenomenon is still unclear (37,38).

In a phase II trial including 9 patients with triple-negative metastatic breast cancer treated with RT and pembrolizumab, only mild toxicities were preliminarily reported (39).

Radiotherapy and durvalumab

LB, FM

Durvalumab is an FDA-approved immunotherapy known as a checkpoint inhibitor drug. It is a human immunoglobulin G1 kappa (IgG1 κ) monoclonal antibody that blocks the interaction of programmed cell death ligand 1 (PD-L1) with the PD-1 and CD80 (B7.1) molecules. Durvalumab is approved for the treatment of patients with locally advanced or metastatic urothelial carcinoma who either have disease progression during or following platinum-containing chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum- containing chemotherapy.

Levy et al (40) reported the results in terms of safety and efficacy of durvalumab in combination with radiotherapy (RT) in an expansion cohort of patients included in a phase 1/2 trial. They analyzed 10 patients that received durvalumab (10 mg/kg every 2 weeks via intravenous infusion) with concurrent palliative RT (3DCRT in 79% and intracranial stereotactic RT, 21%). RT was delivered at a median biologically-effective dose of 28 Gy (range, 6 e 92), in a median number of five fractions (range, 1-10) and over a median duration of 6 days (range, 1-14). Five patients reported an irradiation-related adverse event G1 or 2 (mucositis, vomiting, diarrhea or dermatitis) and one patient had two G2 AEs. There was no G3 or unexpected more RT-



related AEs. On 10/15 in-field (IF) evaluable lesions, the objective response rate was 60% (complete response, 2/10 and partial response, 4/10) and 4/10 stable disease. All evaluated in-field lesions had a tumour growth rate (TGR) decrease resulting in a significant decrease in the TGR between the two periods (before versus after RT; p < 0.01). Outfields disease evaluation retrieved 10/14 SD and 4/14 progressive disease (PD). There was no abscopal effect (40).

Antonia et al (41) reported the results of a very important RCT on locally advanced, unresectable NSCLC; this study compared durvalumab versus placebo as consolidation therapy in 709 patients with stage III NSCLC who did not have progression after two or more cycles of platinum based chemoradiotherapy.

Progression-free survival (primary endpoint) was significantly longer with durvalumab than with placebo: the median progression-free survival from randomization was 16.8 months with durvalumab versus 5.6 months with placebo (P<0.001). The secondary end points also favored durvalumab (the 12-month PFS was 55.9% versus 35.3%, and the 18-month PFS was 44.2% versus 27.0%). The response rate was higher with durvalumab than with placebo (28.4% vs. 16.0%; P<0.001), and the median duration of response was longer (72.8% vs. 46.8% of the patients had an ongoing response at 18 months). Safety was similar between the groups with G3 or 4 adverse events occurred in 29.9% of the patients who received durvalumab and 26.1% of those who received placebo.

The most frequent adverse events leading to discontinuation of durvalumab and placebo were pneumonitis or radiation pneumonitis (in 6.3% and 4.3%, respectively) and pneumonia (in 1.1% and 1.3%). In patients who received durvalumab, as compared with those who received placebo, pneumonitis or radiation pneumonitis of any grade occurred in 33.9% and 24.8%



and pneumonitis or radiation pneumonitis of grade 3 or 4 occurred in 3.4% and 2.6%; pneumonia of any grade occurred in 13.1% and 7.7%, and pneumonia of grade 3 or 4 occurred in 4.4% and 3.8% (41).

Conclusions

The combination of ipilimumab and RT is safe and effective for melanoma brain metastases. A trend towards a positive synergistic effect has been shown in a trial on metastatic prostate cancer patients with bone metastases. Still few data are available on the combination of anti-PD-1 agents and RT for brain metastases, but preliminary evidence suggests the absence of toxicity for brain RT, and possible enhanced efficacy (again in melanoma); for advanced NSCLC, initial data suggest a benefit for a sequential combination of radiotherapy and pembrolizumab, and the risk of pulmonary toxicity seems to be slightly higher but manageable. Moreover, in a Randomized Clinical Trial, adjuvant durvalumab, delivered sequentially after chemoradiotherapy, has led to an advance in the therapy of unresectable NSCLC, prolonging progression-free survival.

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3.d. Androgen pathway therapy

BJ, FA, RM, SM, MB

3.d.1 Abiraterone and Radiotherapy

FA-RM

Mechanisms of actions

Abiraterone acetate is a pro-drug of Abiraterone, an inhibitor of cytochrome P450/17 alpha-hydroxylase/17,20 lyase (CYP17). Abiraterone can inhibit androgen production deriving by testicles, adrenal glands and intratumoral autocrine androgens. This mechanism results in undetectable serum and intratumoral androgen levels (1). In addition, the inhibition of CYP17 decreases the production of endogenous glucocorticoids; thus, the association of Abiraterone acetate with low-dose prednisolone mitigate the subsequently potential adverse events.

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Preclinical data and potential interaction with radiotherapy

The androgen pathways represent crucial therapeutic targets in prostate cancer care. 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 prostate cancer growth; 3) abnormalities within the AR pathway, involving coactivators and corepressors that predispose to AR pathway activation (1). To date, there are broadly two new classes of hormonally active drugs in development: more effective AR antagonists, such as MDV3100, ARN-509, TOK-001, and inhibitors of the androgen biosynthetic pathway, such as Abiraterone.

Two potential interactions between Abiraterone and RT deserve to be largely investigated: a) an enhanced therapeutic effect in case of high-risk localized disease; b) postponing the subsequent systemic schedules in case of oligoprogressive castration resistant PC by means of SBRT (2).

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Clinical data on efficacy and toxicity

A single experience (1) has been published in literature regarding the concomitant use of RT and Abiraterone in men with localized disease. The study intervention consisted of 12 weeks of neoadjuvant LHRH analogue and Abiraterone followed by definitive RT. Twenty-two patients were enrolled. Most of them (86%) had high-risk PC. At a median follow up of 21 months (range, 3 – 37 months), 92% of patients had not experienced biochemical recurrence. Abiraterone was discontinued early in 6 patients for fatigue or atrial fibrillation or hypertension. No increased toxicity was observed when RT was concomitantly delivered with Abiraterone and there were no delays in RT duration attributable to concomitant Abiraterone administration. In the setting of metastatic PC, a post hoc exploratory analysis of the study COU-AA-301 was conducted to explore safety and tolerability profile by concomitant RT and Abiraterone. Data were presented at the American Urology Association (AUA)-Conference in 2012 by Saad et al. (2). In the COU-AA-301 trial, 11.1% of patients in the Abiraterone-arm were submitted to RT in distant-site of metastases. According to Their findings, RT in bone metastases can safely administered with Abiraterone in patients in which a localized progression at a single site is experienced, allowing to continue Abiraterone administration.

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SUMMARY:

Although the limited existing data, experiences here reported extrapolated from large series, such as the COU-AA-301 trial, confirmed the feasibility and promising synergistic effects by combining Abiraterone/RT in PC. Well-designed studies will add further potential confirmation of these findings.

3.d.2 Enzalutamide and Radiotherapy

Mechanisms of action of Enzalutamide and a combination of Enzalutamide and radiotherapy (RT)

The combination of Androgen Deprivation Therapy (ADT) and RT is a consolidate concept in the management of prostate cancer (PCa) patients, even if the mechanism of interaction between them is still not completely clarified (1). An in vivo study showed synergism with ADT and RT, mainly related to the capacity of ADT to decrease tumor hypoxia, that is a well-known predictive factor of radioresistance, and this could explain the radiosensitizing properties of ADT (2). Moreover recent studies have shown that androgen receptor (AR) regulates a transcriptional program correlated to DNA repair capable to induce radioresistance, enhancing DNA repair and decreasing DNA damage (3).

Among the newer agents targeting AR pathway Enzalutamide (MDV 3100) is a non-steroidal, second-generation (AR) antagonist that binds the AR with a higher affinity than Bicalutamide. It belongs, together with Abiraterone, to the class of

GM, **B**



next generation anti-androgens that have been recently approved for the treatment of metastatic castration resistant PCa (mCRPC) both in the pre- and post-chemotherapy setting, confirming that AR remains a critical therapeutic target for PCa cell (4-5).

Enzalutamide acts at different levels of the AR signaling pathway, it not only antagonizes the AR, but also prevents nuclear translocation and coactivator recruitment of the ligand–receptor complex, and induces tumor cell apoptosis (6).

The idea to combine RT and Enzalutamide arises from data suggesting that, following RT, androgen receptor enhances DNA damage repair and contributes to resistance of PCa cells to RT itself. Enzalutamide as a potent AR inhibitor could be considered a potential radiosensitizer and its mechanism of action in hormone resistant PCa cells could be partially due to inhibition of DNA damage repair. The results of a preclinical study demonstrated a significant enhancement of RT efficacy and confirm the rational for the ongoing combination clinical trials with RT (7).

In patients with PCa who underwent surgical resection, loss of the phosphatase and tensin homolog (PTEN) gene on pathologic specimens was correlated with higher Gleason score, advanced tumor stage, lymph node involvement, and castrate-resistance (8).

One potential mechanism by which PTEN loss may affect cell survival and oncogenesis specific to PCa involves a potential interaction between AR and PTEN. A recent study demonstrated that AR, a target of the PTEN and platelet-derived growth factor D (PDGF D) downstream signaling program, contributes to radiation resistance in human PCa cells (9). In addition, this study suggests that anti-androgens such as Enzalutamide may serve as radiation sensitizers for the treatment of PCa patients, 193



particularly so in patients with loss of PTEN or overexpression of PDGF-D.

Efficacy data of a combination of Enzalutamide and RT

Enzalutamide recently demonstrated an important clinical response in non-castrate resistant disease with a low toxicity profile and represents a promising drug in combination with RT in the earlier stage of PCa. In fact, preliminary phase II data presented by M. Smith and colleagues in 2016 (10) assessed the efficacy and safety of 25-weeks (~6-months) of Enzalutamide alone in PCa of all stages who had never received hormone therapy; presenting with non-castrate testosterone levels (230 ng/dL). Enzalutamide alone for 6-months achieved a high PSA response rate with efficacy similar to castration, but in contrast to castration, bone mineral density (BMD) remained stable and metabolic variables were not substantially impacted. These findings suggest that Enzalutamide monotherapy in men with hormone-naive PCa of varying severity provides a level of disease suppression and was generally well tolerate and provide a rationale for further investigation of clinical response and outcomes with Enzalutamide in non-castrated men with PCa (10).

Preliminary studies have shown significant volume reductions of the primary prostate tumors according to (18) F-FCH PET/CT evaluation. These findings suggest the potential role of Enzalutamide in management of localized PCa (11).

No data are currently available regarding the efficacy of a combination of RT and Enzalutamide.

Multiple prospective trials are currently looking at the use of Enzalutamide as a potential radiosensitizer, both in the curative and post-operative setting (as listed in Table 1).



Toxicity data of a combination of enzalutamide and RT

As far as drug toxicity is concerned, the available data come from large studies on Enzalutamide administrated in monotherapy in CRPC (see AFFIRM, PREVAIL etc.) (12-13) and from Expanded Access Program (EAP) (14).

The adverse events present in a greater proportion of patients treated with Enzalutamide compared with placebo in the AFFIRM study included seizures (0.6% vs 0%), cardiac disorders (8% vs 6%), and hypertension or significantly increased blood pressure above baseline (6.6 % vs 3.3%). In the EAP the most common side effects (>10%) were fatigue 39.1 % vs 9.9% in placebo arm, nausea (22% vs 2.4%), anorexia (14.8% vs 1.6%), anemia (14.8% vs 1.6%), peripheral edema (11.4% vs 0.2%), back pain (10.3% vs 2.8%), vomiting (10.3% vs 1.6%) and arthralgia (10.1% vs 1.8%).

Importantly, some of these adverse events may overlap with RT-induced toxicity (fatigue, nausea etc.) so the patients receiving Enzalutamide and RT should be carefully monitored for these symptoms. Enzalutamide-induced back pain can make difficult the evaluation of spine metastasis for palliative bone RT.

SUMMARY:

No data are currently available regarding the toxicity and the efficacy of a combination of RT and Enzalutamide. In the large studies (AFFIRM, PREVAIL etc.) the Enzalutamide treatment was stopped in case of skeletal events (including events that required RT), so no indirect data on the potential toxicity of a combination Enzalutamide and RT are available from these studies [12, 13].



Table 14: On-going prospective trials evaluating the combination RT and enzalutamide (www.clinicaltrial.govaccessed on the 7th May 2017)

Drug	Author	Study type	Clinical	Tumor site	RT	Combination	Toxicity	Tumor	Status	Comments
(dose)			trial.gov		technique/dose/	(concomit,		outcome		
			number		fractionation	other.)				
Enzalutamide	Robert Den Thomas Jefferson University	Phase I Evaluation of safety	NCT02023463	Prostate	IMRT or VMAT daily five days a week for 8 weeks	RT and HT in Treating Patients With Intermediate or High-Risk PCa	NR	NR	Ongoing Ending 2018	Single arm 6 months Enzalutamide + ADT (LHRH agonist with goserelin or leuprolide acetate) for 6 or 24 months after RT
Enzalutamide	Kevin D Courtney, UT Southwestern Medical Center	Phase II Evaluation of safety and PSA progression	NCT02064582	Prostate	EBRT will be delivered as per standard RT protocol	Enzalutamide and Hormone Therapy Before, During, and After Radiation for High Risk Localized PCa	NR	NR Secondary outcomes: Assess intra- tumoral androgen regulated gene expression pre and post combination therapy	Ongoing Ending 2019	Single arm Enzalutamide 160 mg daily for 6 months Leuprolide acetate 22.5mg every 3 months or 45mg every 6 months, RT as standard of care
Enzalutamide	Glenn Bubley, Beth Israel Deaconess Medical Center	Phase II Evaluation of efficacy	NCT02028988	Prostate	EBRT prescription doses to the PTV 75.6- 79.2 Gy delivered in 1.8 Gy fractions	Enzalutamide in combination with EBRT in Intermediate Risk PCa	NR	NR	Active not recruiting	Single arm 6 months of Enzalutamide plus EBRT
Enzalutamide	Paul Nguyen Dana Farber			Prostate		Enzalutamide in ADT With RT for	NR	NR		Randomized Experimental:



	Cancer Institute and ANZUP	Phase III Randomized Evaluation of efficacy	NCT02446444		EBRT 16 weeks after randomization (+/- brachytherapy boost)	High Risk, Clinically Localised, PCa (ENZARAD)			Ongoing Ending 2021	Enzalutamide and LHRHa for 24 months plus EBRT. Standard arm: Conventional Non-steroidal Anti-androgen (NSAA), by mouth, for 6 months from randomisation.
Enzalutamide	Andrew Armstrong, Duke University	Phase II Evaluation of efficacy	NCT02057939	Prostate (Biochemical recurrence)	PSA-only disease after prostatectomy receiving combined enzalutamide and standard (ADT) with salvage RT (final dose of approximately 66 Gy)	Salvage Therapeutic RT With Enzalutamide and ADT in Men With Recurrent PCa (STREAM)	NR	NR	Ongoing, but not recruiting participants	Single arm Enzalutamide and LHRH a 6 months plus EBRT
Enzalutamide	Phuoc Tran, The SKCCC at Johns Hopkins	Phase II Randomized Evaluation of efficacy	NCT02203695	Prostate (Biochemical recurrence)	Salvage RT ((3D- CRT)/IMRT 66.6- 70.2 Gy as 1.8 Gy M-F for 37-39 fx	Salvage RT Plus Enzalutamide for Biochemically recurrent PCa following radical prostatectomy	NR	NR	Ongoing Recruiting Ending 2025	Randomized Placebo- Controlled Double-Blind Study of Salvage RT Plus Placebo Versus Salvage RT Plus Enzalutamide in Men With High- Risk PSA- Recurrent PCa After Radical Prostatectomy

Legend: Not Reported (NR), Intensity-modulated radiation therapy (IMRT), Volumetric Arc Therapy (VMAT), Radiation Therapy (RT), Hormone



Therapy (HT), External Beam Radiation Therapy (EBRT), Luteinizing hormone releasing hormone agonist (LHRH agonist), Androgen Deprivation Therapy (ADT), Three dimensional conformal radiation therapy (3DCRT).

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3.d.3 Androgen pathway suppression – other "newest" drugs MB, SMM

As already described, second line hormonal treatment can overcome resistance to first line LHRH analogues and antiandrogen receptor (AR) drugs.

Abiraterone acts inhibiting CYP17 hydroxylase during the transformation of progesterone in 17 OH-progesterone (1), while Enzalutamide is a new generation antagonist of androgen receptor (AR) and inhibits the link between intracellular dihydrotestosterone (DHT) and androgen receptor (2).

Resistance to these drugs can develop, similarly to what happens after first line hormonal treatment. Some different resistance mechanisms (3) can involve up-regulation of intra-tumour CYP17 (4), the emergence of the v7 variant of AR (potentially exploitable as a predictor of resistance) (5) or of different single AR point mutations (eg mutations in ligand binding domain) (6).

The ongoing research aims at the development of new agents targeting different pathways, to enhance the activity of the already available drugs, to overcome the resistance mechanisms and to find new non cross-acting drugs, or the same pathway with a different approach.

Some of these drugs are already in advanced phases of development and showed promising results.



ARN-509 (APALUTAMIDE)

Mechanisms of actions

ARN-509 acts exactly on the same pathway of Enzalutamide (Fig.1), selectively and irreversibly binding itself to AR receptor, thus inducing a conformational change that inhibits the internalization of the receptor into the nucleus and DNA binding; however, ARN-509 demonstrated an higher therapeutic index (being more effective at lower doses). In addition, it seems to strongly reduce the main side effect of Enzalutamide (seizures), an effect probably mediated by the antagonism of the CNS based GABA_A receptor.

Considering its mechanism of action, also the way resistance to ARN-509 develops is very similar to that of Enzalutamide. It consists of the emergence of AR gene mutations, amplification and variants, maintaining disease progression. Sustained AR inhibition leads to alternative oncogenic signalling (as Akt, enhancer of zeste homolog 2, STAT3 and c-Met) and induction of glucocorticoid receptor, providing a survival advantage to cancer cells. (7).

Potential interaction with radiotherapy



There are no published clinical data about the interaction between ARN-509 and radiotherapy. Preclinical data obtained in prostate cancer-derived cell cultures seem to point to a synergistic cell killing of ARN-509 and radiotherapy; this additive effect seems mediated by the inhibition of DNA double strand breaks (DSB) repair mechanisms. LNCaP cells treated with ARN-509 showed decreased repair mediated by the DSB repair pathway nonhomologous end joining (NHEJ) (8,9). In reason of its likeness with Enzalutamide it would be possible to apply the results obtained from the ongoing studies using Enzalutamide with RT both in terms of efficacy and toxicity (NCT02023463 phase I trial and ENZARD trial) (10,11).

Preclinical data

Preclinical data showing ARN-509 has the same in-vitro activity of but higher in-vivo efficacy on animal models in comparison with the parent molecules were firstly published in 2009 (12). The results were then confirmed on animal preclinical models were ARN-509 demonstrated both higher antitumor activity and lower concentration in central nervous system in comparison with Enzalutamide, suggesting the same efficiency with lower doses and less neurologic toxicity (13,14,15).

Clinical data on efficacy and toxicity

Different studied tested the safety and efficacy of ARN 509.

The first phase I study showed that the drug was well tolerated. Fatigue G1-2 was reported in 47% of the cases, nausea/abdominal pain, grade 1-2 and G3 were reported in 26% and 3% of the patients, respectively. Other G2 toxicities, as diarrhoea and dyspnea, were reported in 6-10% of the patients. No G3-4 toxicities were reported. No seizures were reported.



Regarding the maximum tolerated dose, it was established at 240 mg/daily because the FDHT-PET/CT analysis demonstrated the maximum AR inhibition at this dose (16).

Two phase II study, recently published, confirmed the efficacy of ARN-509 in metastatic and non-metastatic CRPC. Rathkopf, D.E. et al treated 25 naïve patients with mCRPC and 25 previously treated with Abiraterone and concluded that the drug is safe, well tolerated and has clinical activity (80% of naïve patients and 43% of pre-treated patients remained on treatment for 6 month or longer) (17). Smith MR et al. published the results obtained with 51 high risk non metastatic CRPC treated with ARN-509, after a median follow-up of 28 months: 89% of the patients had a >=50% reduction of PSA after 12 weeks; median time to PSA progression was 24 months. Of the 33 patients discontinuing the drug, 22% had disease progression (PSA, radiographic or clinical) and 18% adverse events. The authors confirmed the results of the phase I study (favorable toxicity profile and absence of seizures) (18).

Two early (2013) Phase III studies addressing the efficacy of ARN-509 in metastatic and non- metastatic CRPC patients never recruited patients (SPARTAN, NCT01946204, and NCT02257736).

Twenty-two additional studies are testing the use of ARN-509 in different phases of the natural history of prostate cancer (19). They aim at defining:

- ARN-509 toxicity profile;
- the utility of this drug to decrease the number of positive biopsies in patients assigned to active surveillance;
- the efficacy of Apalutamide to downstage the disease in patients submitted to prostatectomy;



- its efficacy in association with other drugs;
- its efficacy in association with radiotherapy.

Two of these studies involve the use of radical radiotherapy. NCT02772588 is a single arm Phase II study promoted by MSKCC with the official title of: "ARN-509+Abiraterone Acetate +Leuprolide With Stereotactic, Ultra-Hypo-fractionated Radiation (AASUR) in Very High Risk Prostate Cancer: A Single Arm, Phase II Study". The study is currently recruiting (20).

The second one is a Phase III randomized, double-blind, placebo-controlled, multicenter study: "An Efficacy and Safety Study of JNJ-56021927 (Apalutamide) in High-risk Prostate Cancer Subjects Receiving Primary Radiation Therapy: ATLAS" (ID: NCT02531516), currently recruiting. Apalutamide plus GnRH agonist is compared with GnRH agonist among participants with high-risk, localized or locally advanced prostate cancer receiving primary radiation therapy (RT). Patients will be given either apalutamide (experimental) or bicalutamide 50 mg plus placebo as control group. The study is expected to enroll 1500 patients and results are awaited in 2026 (21).

SUMMARY:

Arn-509 mimics the action of Enzalutamide and is possibly designated to be used instead of it because of the lower dose required and lower neurological toxicity. No direct comparisons or mature data for apalutamide are however available.



In relation with its use with radiotherapy there are the same (limited) concerns than with enzalutamide and these can be related to the possibly overlapping abdominal toxicities.

ODM-201 (DAROLUTAMIDE)

Mechanisms of actions

ODM-201 is another AR antagonist (Fig.1) but its structure is different from Enzalutamide and ARN-509. ODM-201 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 significantly inhibits tumour growth in the murine VCaP CRPC xenograft model. Non-clinical data have also shown that ODM-201 in practice does not cross the blood–brain barrier, thus suggesting a low risk of seizure (22,23,24).

Another advantage of darolutamide is the activity against tumors characterized by known AR variants (25).

Potential interaction with radiotherapy



No published data are present regarding the possible interaction with radiation. No studies are on-going considering the use of ODM-201 in association with radiotherapy.

Preclinical data

In vitro data suggest that ODM-201 has a low potential for CYP-mediated drug–drug interactions. In HepaRG cells treated with 10 mM of each test compound, ODM-201 and ORM-15341 showed no induction of CYP3A4, whereas both enzalutamide and ARN-509 demonstrated potential induction. Further, ODM-201 showed no inhibition of CYP isoenzymes (CYP1A2, CYP2A6, CYP2B6, CYP3A4, CYP2C8, CYP2D6, CYP2C19 and CYP2C9) in human liver microsomes at clinically relevant concentrations (25).

Clinical data on efficacy and toxicity

Results of a Phase I study looking for the maximum tolerated dose between 6 levels of doses in 24 patients treated with this drug did not reach the MTD. Anticancer activity was noted across all of the six doses. The toxicity profile is relatively safe: the most common adverse events were fatigue or asthenia in ten of 24 patients (42%), diarrhoea in seven (29%), arthralgia in six (25%), back pain in six (25%), and headache in five (21%). Three patients (13%) reported eight adverse events of grade 3 (fracture, muscle injury, laceration, paralytic ileus, pain, presyncope, urinary retention, and vomiting) and one patient (4%) had a grade 4 adverse event (lymphoedema). None of these grade 3–4 adverse events was related to ODM-201 (26).



A subsequent phase II study included 112 patients with mCRPC (naïve to other treatments or already treated with abiraterone or chemotherapy) randomized to three dose levels (200mg/die vs 400mg/die vs 1400mg/die). The toxicity profile in the entire study (phase I and II) was reported in 44 (35%) patients, including fatigue or asthenia in 15 patients (12%), hot flush in six (5%), decreased appetite in five (4%), diarrhoea in three (2%), and headache in three (2%). No seizures were noted during the trial. Adverse events of grade 3 were reported in only 27 patients (22%) and adverse events of grade 4 in two (<2%). Good 12 weeks PSA response (\geq 50% decrease in PSA) was seen at all doses and in all treatment groups; worse response was seen in patients previously treated with CYP17 inhibitors in comparison with those naïve to both chemotherapy and CYP17 inhibitors. The best PSA responses were registered at 1400 mg/die in patients naive to both chemotherapy and CYP17 inhibitor. An higher percentage of non PSA responders (55%) was registered in patients already treated with CYP17 inhibitors (26).

A phase III trial was designed using a ODM-201 dose of 1200 mg/die is still ongoing (Efficacy and safety study of ODM-201 in men with high-risk non-metastatic castration-resistant prostate cancer - ARAMIS) (27). The ARAMIS study is comparing ODM-201 (600 mg administered twice daily) vs. placebo in patients with CRPC manifesting as a rising PSA level (but no radiologic evidence of metastatic disease) with a primary end point of metastasis-free survival.

Other studies are now testing ODM-201 in different settings:



- in association with Docetaxel and standard ADT in metastatic hormone sensitive prostate cancer. The official title of the ARASENS study is: "A Randomized, Double-blind, Placebo Controlled Phase III Study of ODM-201 Versus Placebo in Addition to Standard Androgen Deprivation Therapy and Docetaxel in Patients With Metastatic Hormone Sensitive Prostate Cancer". Primary end point is overall survival. Secondary end points are time to castration resistant prostate cancer and time to initiation of subsequent antineoplastic therapy; symptomatic skeletal event free survival, time to first symptomatic skeletal event, time to initiation of opioid use, time to pain progression; time to worsening of physical symptoms of disease, number of adverse events as a measure of safety and tolerability (28).
- as maintenance treatment versus placebo in patients with mCRPC previously treated with one novel hormonal agent first line and non-progressive disease after second line treatment with a taxane. Primary end points is radiographic progression-free survival at 12 weeks; secondary end points are radiographic progression-free survival every 12 weeks until disease progression, time to PSA progression, time to symptomatic/clinical disease progression, event free survival, overall survival, PSA response. The study is a randomized Phase II comparing maintenance with ODM-201 with watchful waiting (29).
- in hormone naive prostate cancer with the primary objective to demonstrate that ODM-201 produces prostate-specific antigen (PSA) response rates at 24 weeks (defined as ≥80% reduction compared to baseline) that are in the range of those achieved with 24 weeks of ADT. Secondary end-points are: change in hormone-treatment related symptoms using EORTC QLQ-PR25 evaluation, tumour response, 90% PSA response rate, evaluation of safety. This is an open label controlled randomized phase II study comparing ODM-201 and Androgen Deprivation Therapy (ADT) (30).



SUMMARY

Darolutamide (ODM-201) is an investigational drug active against known AR mutants causing resistance to already available second-generation antiandrogens, having minimal blood-brain barrier penetration. It therefore may have potential clinical advantages [31].

EPI-001

One of the resistance mechanisms to all the AR antagonists is the induction of mutations or deletions on the AR ligandbinding domain. While all the other second generation-AR antagonists (like Enzalutamide and Abiraterone) act by the link with the C-terminus of the AR protein, Epi-001 inhibits the NH₂-terminal domain of the same protein. Thus it could be potentially successful in treating patients resistant to the other drugs (Fig.1).

Mechanisms of actions

The AR is modular and the NH2-terminal domain (NTD) incorporates the transcriptional activation function in two units (TAU1 and TAU5) (32,33). These domains are very important from a functional and clinical point of view, since in CRPC AR



variant proteins are expressed, representing AR species composed of the AR NTD and central DNA binding domain (DBD), but lacking the regulatory ligand binding domain (LBD) and therefore constitutively active. This highlights the clinical need for new therapeutic agents that exert their action through non-LBD interfaces on the AR protein [34]. EPI-001, a Bisphenol-Adiglicydyl ether (BADGE) derivative, was identified as a specific inhibitor of the AR that bound covalently to an undetermined structural motif in the AR NTD and inhibits the growth of androgen sensitive PCa and CRPC cells *in vitro* and *in vivo*.

Potential interaction with radiotherapy

No data about the potential interaction with radiotherapy are available.

Preclinical data

In prostate cancer cell line studies, the drug inhibited proliferation of AR-dependent LNCaP cells but not AR- independent PC3 or DU145 cells. In a castrate LNCaP CRPC mouse xenograft study, EPI-001–treated mice had a decrease in mean tumor volume from 100 to 73 mm³ after 2 weeks, whereas control mice had an increase in mean tumor volume from 103 to 148 mm³. In a VCaP mouse xenograft model bearing amplified AR and AR splice variants, a sister compound (EPI-002) significantly decreased tumor growth when compared with both bicalutamide and control. This study also demonstrated that EPI-002 did not induce increased levels of full-length AR or AR splice variants, a phenomenon that has been observed with other AR-targeted therapies (35,36).



Clinical data on efficacy and toxicity

The drug is awaiting clinical development, and it is unclear whether one of these compounds or a sister analogue will be brought forward for further study.

Summary

It is not clear if its potential, important benefits could lead to clinical studies.

ORTERONEL

Orteronel (TAK-700) is included in a category of inhibitors of cytochrome P450 17α-hydroxylase/17,20-lyase (CYP17), a key enzyme in adrenal androgen synthesis (Fig.1). The same category includes ketoconazole, a non-selective CYP17 inhibitor, prescribed in the past as second line treatment for prostate cancer, and abiraterone acetate, largely used in metastatic CRPC. Orteronel (TAK-700) is a novel CYP17 inhibitor.

Mechanisms of actions

When circulating testosterone is at castrate-levels, prostate cells can yet convert the adrenal androgens such as DHEA and AED to DHT. A prostate tissue androgen study in patients who underwent ADT recorded high levels of testosterone and DHT,



sufficient to activate AR. Intraprostatic conversion of adrenal steroids into testosterone and DHT seemed to play a major role in this mechanism (37, 38, 39).

CYP17 is a key multifunctional cytochrome P450 enzyme involved in adrenal androgen synthesis, that we already indicated as the target of some new drugs for mCRPC. It is present in testes and adrenal glands synthesis, and its activity determines the molecule the substrate will be transformed in (sex steroids or glucocorticoids). The precursors of every steroid hormone is cholesterol, then converted to pregnenolone, which then enters the androgen formation pathway, or is converted to progesterone. CYP17 catalyses two key steps in the production of sex steroids: 17α -hydroxylase activity results in the conversion of pregnenolone and progesterone in the 17α - hydroxy derivatives, then converted by 17,20-lyase activity in DHEA and AED. Since CYP17 is needed also to produce glucocorticoids, 17α -hydroxylase activity blockage by a CYP17 inhibitor will block the formation of cortisol and its precursors.

While Abiraterone inhibits both the 17,20-lyase and 17α- hydroxylase activities of CYP17A1, Orteronel preferentially inhibits 17,20-lyase activity, which down-regulates androgenic steroid production in vitro and in vivo. This may in theory reduce the need for corticosteroid supplementation, as secondary mineralocorticoid excess induced by CYP17 inhibition may be more dependent on 17α-hydroxylase; this could lead to an improved toxicity profile and fewer treatment adverse event. The Orteronel-mediated intracellular depletion of testosterone together with inhibition of AR translocation by another agent

such as docetaxel may provide synergistic or additive effects against prostate cancer growth (40, 41).



Potential interaction with radiotherapy

No clinical data are published about the use of TAK-700 with radiotherapy. Just one study is registered on the NCT registry about the use of the drug in association with radiotherapy and hormonal treatment in high risk non-metastatic prostate cancer but it results as not recruiting (42).

Preclinical data

TAK-700, chemically 6-[(7S)-7-hydroxy-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-7-yl]-N-methyl-naphthalene-2-carboxamide is a selective, oral, non-steroidal androgen synthesis inhibitor. In preclinical studies, Orteronel has been shown to bind and inhibit the enzyme 17,20-lyase in the testes and in the adrenal glands and reduces the levels of testosterone and dihydroepiandrosterone (43).

Papers describing different in vitro/in vivo experiments are available. The main objectives were to assess the metabolic stability of Orteronel, its CYP related metabolism, cell permeability; moreover, a series of in vivo experiments in rats were performed on pharmacokinetic parameters, oral bioavailability, to define dose proportional oral pharmacokinetics and the effect of food on that and the route of elimination. Orteronel was found to be stable in various liver microsomes tested; its absorption was rapid after oral administration and the primary route of elimination has found to be urine (44).

Clinical data on efficacy and toxicity

In 2014 the results of a phase I/II trial regarding the use of Orteronel and prednisone in mCRPC were published (45). The phase I dose escalation followed the standard 3x3 schema: patients received open-label single-agent Orteronel in 28- day



cycles (continuous dosing) at 1 of 5 dose levels: 100, 200, 300, 400, or 600 mg twice a day. An additional cohort also received Orteronel 400 mg twice a day plus prednisone 5 mg.

Given the results of dose escalation study, in the phase II patients received open-label Orteronel daily in 28-day cycles in 4 parallel dose cohorts: 300 mg twice a day, 400 mg twice a day plus prednisone 5 mg twice a day, 600 mg twice a day plus prednisone 5 mg twice a day, or 600 mg every day in the morning.

In phase I, all patients experienced more than one treatment-related adverse event (TRAE). In phase II, all but 1 patient had a treatment related adverse event; fatigue, nausea, constipation, and diarrhoea were common. More than half of the patients had adverse events \geq Grade 3: fatigue (12%), hypokalemia (8%), hyperglycemia (5%), and diarrhea (4%) were the more frequently observed. Serious adverse events (SAE) were documented in about 25-30% of the patients in phases I and II, respectively, and were drug related in 5 and 7 patients. They included fatigue, hypertension (n=1); acute renal failure, hypokalemia, pneumonia, decreased hemoglobin, hyperglycemia, hyperkalemia, pain in extremity, sensory neuropathy, and DVT. Three on-study unrelated deaths were observed during phase II: two cardiac- related events and one infection.

At 12 weeks, PSA was evaluable in 84 phase II patients. Fifty-four percent of them had >=50% decline in PSA from baseline and 18 (21%) had >=90% decline in PSA. At 24 weeks, response rates slightly increased. The median time to PSA progression was >225 days in all 4 dose groups. Twenty percent of phase II patients with RECIST-evaluable radiographic lesions had unconfirmed partial responses, and 41% had stable disease.

A little later, in 2015, another Phase I/II trial was published where Orteronel was used in mCRPC in association with Docetaxel-prednisone (46). The doses in the phase I study were as follows: In cycle 1 (28 days), patients received Orteronel



200 or 400 mg orally (PO) BID without regard to food intake on days 1–28, docetaxel 75 mg/m2 intravenously (IV) on day 8, and prednisone 5 mg PO BID on days 8–28. From cycle 2 onwards, cycles were 21 days in length, and the first dose of each of the drugs was administered on day 1. Dose escalation from Orteronel 200 mg BID proceeded in a standard 3x3 design based on the occurrence of dose-limiting toxicities (DLTs) during cycle 1. In the cohort 1 one patient died due to Orteronel unrelated sepsis. In the cohort 2 (Orteronel 400 mg BID), 1 patient received <75 % of the planned dose due to drug-related grade 3 fatigue and asthenia on day 8, and then grade 3 decreased neutrophil count on day 15. One of the other 3 patients enrolled in cohort 2 received <75 % of the planned dose of Orteronel due to grade 3 hypophosphatemia. 400 mg BID was deemed to be the RP2D, and this dose was evaluated further in the phase 2 part of the study.

22 patients were evaluable for response after 4 cycles: PSA reduction of 90%, 50% and 30% were respectively 5 (23%), 13 (59%) and 15 (68%).

In 2016 R. Cathomas et al published the results of a phase II random comparison between maintenance treatments with TAK-700 vs placebo in mCRPC patients in response after docetaxel. Median radiographic progression-free survival (rPFS) was 8.5 and 2.8 months (P=0.02) in the Orteronel and placebo arm, respectively. PSA decline >=50% was seen in 57% on Orteronel and 4% on placebo. Toxicity was mainly mild, one patient on Orteronel developed transient grade 3 adrenal insufficiency and one grade 4 pneumonitis. The study was interrupted because of the negative results of the phase III studies (47). Two phase III trials were published in 2015 regarding the use of Orteronel+prednisone vs placebo+prednisone in the setting of mCRPC before (48) and after (49) the use of docetaxel, in comparison with placebo. Both failed to demonstrate advantage in overall survival, despite the advantages in terms of radiographic progression free survival. These studies induced the



interruption of further developments for this drug even if one phase III study is still ongoing comparing Androgen Deprivation Therapy + TAK-700 With Androgen Deprivation Therapy + Bicalutamide in Patients With Newly Diagnosed Metastatic Sensitive Prostate Cancer in terms of overall survival (50).

SUMMARY

Orteronel (TAK-700) is another CYP 17 inhibitor with some potentially interesting features, but two large Phase III trials studying its efficacy gave negative results.

GALETERONE (TOK-001)

Mechanisms of actions

In vitro, Galeterone increases AR protein degradation in prostate cancer derived cells expressing a T878A mutant AR. Galeterone, like enzalutamide, may be effective as a direct AR antagonist in CRPC. Both these agents blocks AR receptor chromatine binding. Moreover, it is a CYP17A1 lyase inhibitor (Fig.1). The main step forward in comparison with enzalutamide is the additional feature of an increase in AR receptor degradation, potentially suggesting a possible increased efficacy also with AR-receptor variants.


Potential interaction with radiotherapy

There are no data on the potential interactions of radiotherapy with galeterone.

Preclinical data

Galeterone is one of a family of Δ16-17 azolyl steroids studied as potentially more effective than ketoconazole since the early years of this century (51); the first preclinical studies demonstrated an important activity of the compound in the experimental setting. In the following years, the drug showed activity also against CRPC and enzalutamide-resistant prostate cancer cells in vitro and was finally tested in humans (52).

Clinical data on efficacy and toxicity

Two open-label phase I and II studies (ARMOR1 and ARMOR2-1) evaluated efficacy and toxicity of galeterone in patients with treatment-naive non-metastatic or metastatic CRPC. In ARMOR-1 49 patients were treated with increasing doses of Galeterone (650-2,600 mg) and about 20% obtained a PSA reduction \geq 50%, as opposed to more than 50% of the patients of ARMOR2 treated with a dose of 2,550-mg Fatigue, increased liver enzymes, gastrointestinal events, and pruritus, mostly mild or moderate, were the more common side effects, with no toxic effects related to mineralocorticoid excess (53). The ARMOR-2 was then completed and the results appeared promising, so that a Phase III trial was launched (54). A small subgroup analysis of these studies also suggested potential clinical efficacy against mCRPC AR variants.



ARMOR3-SV (NCT02438007) was then a study planned to randomize 148 metastatic CRPC patient not previously treated with Enzalutamide, Abiraterone or taxanes . In accordance with the Phase II results, only AR-V7-positive men (about 10% of the potentially eligible) could be randomized, and were allocated equally to receive enzalutamide 160 mg daily or galeterone 2,550 mg daily. Unfortunately, the study was ended by the sponsor in July 2016, since the independent Data Monitoring Committee suggested that the study was unlikely to meet its primary objective (improved radiographic progression free survival).

SUMMARY

Galeterone seems to have a mechanisms of action different from other drugs against mCRPC by adding to the inhibition of CYP 17 and the antagonistic effect toward AR with the novel mechanism of AR protein degradation. The early clinical trials demonstrated a reasonably good toxicity profile and at least a proof of principle of efficacy, also in enzalutamide-resistant patients, but the following Phase III study was ended by the sponsor in July 2016; at the time of this writing there are no other Phase III studies described in the literature.

SEVITERONEL (VT-464)

Mechanisms of actions

Seviteronel (VT-464) is a non-steroidal CYP17A1 inhibitor, directed mainly at 17,20-lyase blockade (10 times more selective for this enzyme than for 17α -hydroxylase and also > 50 fold more selective for 17,20 lyase than abiraterone) therefore having at least the theoretical advantage of a reduced need for glucocorticoid supplementation when given in clinic (55).



Preclinical data

In vitro, seviteronel appears to possess greater efficacy as an antiandrogen relative to abiraterone. Seviteronel has also been found to act as an antagonist of the androgen receptor, like abiraterone.

Potential interaction with radiotherapy

We are not aware of specific studies addressing this issue.

Clinical data on efficacy and toxicity

Seviteronel was firstly introduced in 2014 in Phase 2 clinical trials for prostate cancer. In January 2016, it was designated fast-track status by the U.S. FDA (56).

Four studies are currently recruiting or closed to recruitment:

- a) A Phase 1/2 Open-Label, Multiple-Dose Study (NCT 02012920) is evaluating safety, tolerability, pharmacokinetics/dynamics of VT-464 in CRPC patients, and is currently enrolling men with castration-resistant prostate cancer previously treated with both abiraterone and enzalutamide. The Phase I part of the study is closing and evaluating a dose escalation protocol (57).
- b) Another Phase 2 open-label study of VT-464 (NCT 02130700) is recruiting patients with mCRPC previously treated with enzalutamide and patients with breast cancer. The study consists of five cohorts: mCRPC patients in Cohort 1 must have never received prior chemotherapy. Patients in Cohort 2 must have received at least one (and not more) prior



course of chemotherapy for CRPC. Cohorts 3, 4 and 5 consist of breast cancer patients. The study is currently recruiting (58).

- c) A Phase 2 Open-Label Study (NCT02445976) to Evaluate the Efficacy and Safety of Once-Daily Oral VT-464 in Patients with Castration-Resistant Prostate Cancer Progressing on Enzalutamide or Abiraterone. This study is currently enrolling men with castration-resistant prostate cancer who were previously treated with enzalutamide, abiraterone or both (59).
- d) A Phase 1/2 Open-Label, Multiple-Dose Study (NCT02361086) to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Once-Daily VT-464 in Patients with Castration-Resistant Prostate Cancer. Enrollment for this study is complete (60).

Available safety data seem on the whole satisfactory. Syncopal, pre-syncopal and vasovagal episodes were however registered. Company-driven analysis were presented at ASCO-GU 2016 and Holter and ECG monitoring in patients receiving the drug showed that syncopal and pre-syncopal episodes were due to an increased parasympathetic tone, excluding a cardiac origin or arrhytmogenic potential (61).

SUMMARY:

To date, there is not sufficient clinical evidence to fully understand the potential clinical use of this drug. REFERENCES:

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Table 15 - Major studies with/without Radiotherapy and new drugs

Drug	Author and year	Study type	N	Tumor	RT technique/dose/fractionation	nbinati ncomi,	Toxicity	Tumor outcome	Comments
						Con (cor			
ARN-509 - Apalutamide	Rathkopf et al., J Clin Oncol 2013; 31:3525–30	Phase I 2013	30	Progressive mCRPC			G1-2 fatigue (47%); nausea/abdominal pain (G1-2 30%); non G3-4 tox		No maximum tolerated dose; it was evident a plateau in AR signaling blockade at 240 mg/daily
ARN-509- Apalutamide	Rathkopf et al., Clinical Cancer research DOI: 10.1158/1078- 0432.CCR-16- 2509 On line 17 February 2017	Phase II 2017	50	mCRPC (25 naïve, 25 already treated with ABI)	No RT	no	Confirmed the phase I tox	PSA decline >=50% in 80% of naïve patients and 43% after abiraterone	
ARN-509- Apalutamide	Smith, MR, et al., European Urology 2016, 70 : 963-970	Phase II 2016	51	51 non mCRPC with PSA rising	No RT	no	Confirmed the phase I tox	PSA decline >=50% in 12 w in 89% of the pts median Time to PSA progression: 24 m	
ODM-201- Duralutamide	Fizazi K., et al., Lancet Oncol 2014; 15:975– 85	Phase I 2014	24	Progressive mCRPC	No RT	No	Fatigue or asthenia 42%, diarrhoea 29%, arthralgia 25%), back pain in 25%,		No maximum tolerated dose;



						-			
							headache in 21%.		
							None of the grade		
							3–4 adverse		
							events were		
							related to ODM-		
							201		
ODM-201-	Fizazi K., et al.,	Phase	112	mCRPC (naïve	No RT	No	Fatigue or	Worse	200mg/die vs 400mg/die vs
Duralutamide	Lancet Oncol	П		or already			asthenia in 12%,	response was	1400mg/die
	2014; 15:975–	2014		treated with			hot flush 5%,	seen in	
	85			ABI or			decreased	patients	
				chemotherapy)			appetite in 4%,	previously	
							diarrhoea in 2%,	treated with	
							headache in 2%.	CYP17	
							No seizures were	inhibitors The	
							noted during the	best PSA	
							trial. Grade 3 tox	response was	
							in 22%, grade 4 in	registered at	
							<2%.	1400 mg in	
								naïve	
								patients.	
TAK-700	Dreicer, R., et	I	26	Progressive	No RT	Onteronel	SAE: 31%	NA	No MTD or DLT;
Orteronel	al Clin Cancer	2014		mCRPC		+/-	(hypertension,		
	Res; 20(5);					prednisone	nausea, vomiting,		
	1335–44,						deep vein		
	2014.						thrombosis,		
							fatigue, increased		
							amylase,		
							increased lipase,		
							diarrhea, skin		
							infection, and		
							dehydration (each		
							n=1)		



TAK-700	Same	II	97	mCRPC (25	No RT	Onteronel	SAE: 27% (fatigue	At 12	Overall, the steroid-free
Orteronel	reference as	2014		naïve, 25		+/-	(n=1) and	weeks→ 54%	regimen was well tolerated and
	the previous			already		prednisone	hypertension	had >=50%	did not have high
	study			treated with		-	(n=1); acute renal	decline in	discontinuation rates.
				ABI)			failure,	PSA and 21%	
							hypokalemia	had >=90%	
							(each n=2),	decline in	
							pneumonia,	PSA.	
							decreased		
							hemoglobin,		
							hyperglycemia,		
							hyperkalemia,		
							pain in extremity,		
							sensory		
							neuropathy, and		
							DVT (each n=1)		
TAK-700	Petrylak DP, et	1/11	14/24	mCRPC	No RT	Docetaxel-	Phase I: Fatigue,		Onteronel MTD: 400 mg/bid
Orteronel	al Invest New					prednisone	alopecia, diarrhea,		
	Drugs. 2015						nausea, dygeusia,		
	April ; 33(2):						and neutropenia –		
	397–408.						each reported in		
							≥39 % of patients		
TAK-700	R. Cathomas,	П	23 TAK-	mCRPC after	No RT		As reported in	Radiographic-	The study was discontinued
Orteronel	et al		700 vs	Docetaxel			phase I-II studies	PFS →8.5 m	
	Prostate		24					(TAK-700)	
	76:1519–		placebo					and 2.8 m	
	1527, 2016							(placebo)	
								(P=0.02)	
TAK-700	Fred Saad, et	III	781	mCRPC before	No RT	Prednisone	Lipase and	Median	OS 31,4 m (TAK-700) and 29,5 m
Orteronel	al., Lancet		TAK-	Docetaxel			amylase increase,	radiographic	(placebo) (p=0,31). No further
	Oncol 2015;		700 vs				fatigue and	PFS was 13,8	trials
	16: 338–48		779				pulmonary	m (TAK-700)	
			placebo				embolism (>= G3)	and 8,7 m	
								(placebo)	
								(P=0.0001);	
TAK-700	Karim Fizazi, ,	111	734	mCRPC after	No RT	Prednisone	Lipase and	rPFS was	Median OS 17.0 m (TAK-700) vs
Orteronel	et al., J Clin		IAK-	Docetaxel			amylase increase	8.3m (TAK-	15.2 m (placebo) p=0.190).
	Uncol 33:723-		/00 vs				(>= G3), nausea,	700) vs 5.7m	No differences in pain response.
	731., 2015		365				vomiting and	(placebo)	No further trials
			placebo				tatigue (all grades)	(p<0.001);	
								PSA50%	
								reduction	
								was 25%	



			(TAK-700) vs	
			v 10%	
			(placebo)	
			(p<0.001);	
			median time	
			to PSA	
			progression	
			5.5 m (TAK-	
			700) vs 2.9 m	
			(placebo)	
			(p<0.001)	



Fig. 1 - Androgen synthesis and function pathways and the site of action of the new antiandrogens





4.1 TAKE HOME MESSAGES FROM RANDOMIZED TRIALS - MOABS - CA, IP

Mo-Ab	Clinical setting	Randomized trials	Clinical results	Toxicity	Grade of recommendations
Cetuximab	Head and neck				
	cancer				
	RT+ cetuximab <i>vs</i> RT alone	(33)	Improved LC and OS, particularly in younger pts with oropharinx tumor whit severe acneiform rush	Severe acneiform rush	Cetuximab +RT better than RT alone, suggested only for pts unfit for RT+CT (positive strong)
	RT+CT+ cetuximab <i>vs</i> RT+CT	(34)	No difference in PFS and OS	More acute toxicity	The addiction of cetuximab to RT+CT (CDDP) did not improve outcome and hence should not be prescribed routinely (negative strong)
	induction CT -> RT+ cetuximab <i>vs</i> RT+CT	(35)	No difference in larynx preservation, larynx function preservation and OS	More skin toxicity in the cetuximab arm but higher treatment compliance	Induction CT followed by RT+ cetuximab is not superior to induction CT followed by RT+CT (negative strong)
	RT+ cetuximab <i>vs</i> RT+CT	(36)	No difference in LRC, patterns of failure, and survival	More serious adverse events related to treatment including deaths and more need for nutritional support more in the RT+ cetuximab arm	RT+CT is the standard treatment for pts with Head and neck cancer (positive strong)
	induction CT -> RT+ cetuximab <i>vs</i> RT+CT	(Xu 2015 citato nelle tabelle non in hibliografia)	No difference in PFS	More toxicity (mucositis, acneiform rash and dysphagia)	Induction CT followed by RT+ cetuximab is not superior to induction CT followed by RT+CT in pts with nasopharyngeal cancer (negative strong)
Cetuximab	Lung cancer (NSCLC)				(



_						
		RT+CT + cetuximab vs CT +RT	(20-23)	No differences in OS, except in one study in a subset of pts with high EGFR expression	Increased toxicity	Cetuximab +CT in lung cancer pts should be not routinely administered (negative strong)
	Cetuximab	Gastrointestinal cancer Rectal cancer				
		induction CT -> RT+ CT (capox) + cetuximab vs RT+ CT (capox) high risk patients Esophageal cancer	(26)	No differences in pCR or PFS (primary endpoints) but in radiological response and OS (secondary endpoints)	Increased toxicity (diarrhoea and rash)	Despite the results regardingthe secondary endpoints of the RCT, cetuximab +CT after preoperative CT should be not routinely administered in high risk rectal cancer pts (negative strong)
		RT+ CT (FOLFOX) + cetuximab vs RT+ CT (FOLFOX)	(30)	reduced Os in the cetuximab arm	More toxicity (non haematological)	Cetuximab + CT in oesophageal cancer pts should be not routinely administered (negative strong)

- → Randomized trials avalaible on H&N, Lung, Esophageal and Rectal cancers
- → At present Cetuximab is recommended only in head and neck cancer cancer pts unfit for standard radiochemotherapy since the addiction of Cetuximab to RT+CT is not superior to RT+CT and could lead to an increased toxicity. (recommendation by SIGN)



Mo-Ab	Clinical setting	Randomize d trials	Clinical results	Toxicity	Grade of recommendations
Panitumumab	Head and neck cancer				
	RT+ panitumumab <i>vs</i> RT+CT	(39)	Lower LC (ns)	Simlar toxicity rate and grade	RT+ panitumomab pts should be not routinely administered instead of RT+CT
	RT+ panitumumab vs RT+CT	(40)	Similar PFS and OS	Simlar toxicity rate and grade	RT+ panitumomab pts should be not routinely administered instead of RT+CT (negative strong)
	RT+CT+ panitumomab <i>vs</i> RT+CT	(41)	Similar LRC	Simlar toxicity rate and grade	Panitumumab should not be routinely added to RT+CT (negative strong)
	Gastrointestinal cancer Rectal cancer neoadjuvant setting wt KRAS RT+CT+panitumumab vs RT+CT	(44)	More pNC and CR	Increased toxicity (diarrhoea and anastomotic leakage)	Despite the results the promising results RT+CT+panitumumab in rectal cancer pts should be not routinely administered (only 68 pts were enrolled) (negative strong)

- → Randomized trials avalaible on H&N and Rectal cancers
- → At present Panitumumab should be not routinely administered in association with RT since the only randomized trial that demonstrated a clinical benefit evaluted only 68 pts affected by rectal cancer. (recommendation by SIGN)



Mo-Ab	Clinical setting	Randomized trials	Clinical results	Toxicity	Grade of recommendations
Trastuzumab	Breast cancer pts were randomly assigned to AC followed by weekly T with or without H followed by H with or without RT (The study was nor designed for RT+H vs RT alone evaluation, so pts were not randomized for RT)	(Haylard M et al 2009) manca numerazione bibliografia	not assessed	Not acute AEs, late AEs not assessed	concurrent RT (with modern techniques involving cardiac sparing) and trastuzumab may be continued. (positive weak)

- → Randomized trials avalaible on Breast cancer
- → At present Trastuzumab concurrent with RT could be safely administered, however is worth of notice that in the randomized trial published on this topic pts were not randomized versus RT alone. (recommendation by SIGN)

Mo-Ab	Clinical setting	Randomized	Clinical results	Toxicity	Grade of recommendations
		trials			
Bevacizumab	High – grade glioma				



bevacizumab+RT+CT (TMZ) <i>vs</i> RT+CT (TMZ)	(13- 15)	PFS was prolonged without advantages in OS	Increased toxicity (rate of grade 3 and AEs)	bevacizumab should not be routinely added to RT+CT (negative strong)
Gastrointestinal cancer Rectal cancer preoperative treatment: bevacizumab+RT+CT (CAP) vs RT+CT (CAP)	phase II (32)	similar rate of ypCR	similar toxicity rate	bevacizumab should not be routinely added to preoperative RT+CT (negative strong)

Table 1 – Take home messages: evidence based clinical recommendations (based on randomized trials: levels of evidence A) - monoclonal antibodies and radiotherapy

abbreviations: Mo-Ab, monoclonal antibodies; RT, radiotherapy; CT, chemotherapy; PFS, progression-free survival, LC, local control; O,S overall survival; pts, patients; LRC, locoregional control; wt, wild type; pNC, pathological near-complete; CR, complete response, ns, not significant; AEs, adverse events; A, doxorubicin; C, cyclophosphamide; T, paclitaxel; H, trastuzumab NSCLC, Non Small Cell Lung Cancer; TMZ, temozolomide; CAP, capecitabine; ypCR, pathologic complete response



- → Randomized trials avalaible on High Grade Gliomas and Rectal cancers
- → At present Bevacizumab should be not routinely administered in association with RT+CT since only one randomized trial showed an advantage in PFS but non in OS in pts affected by High – Grade Glioma (recommendation by SIGN)



TAKE HOME MESSAGES SMALL MOLECULES DRUGS - CA, IP

	Clinical setting	Randomized	Clinical results	Toxicity	Grade of recommendations
		trials			
	Head and neck				
Erlotinib	cancer				
	RT +CT (CDDP) erlotinib <i>vs</i> RT+ CT (CDDP)	(6)	no differences in CR rate and PFS	more cutaneous toxicity	erlotinib in Head and neck cancer cancer pts should be not routinely added to RT+CT (negative strong)
	NSCLC				
	RT +erlotinib <i>vs</i> RT	(7)	no differences in PFS or OS	no increased toxicity	RT+ erlotinib in locally advanced lung cancer pts should be not routinely administered (negative strong)
	Gastrointestinal				
	cancer				
	Pancreatic cancer	(1.2)			
	induction CT(gem) + erlotinib ->r andom	(10)	no differences in OS decreased local	no increased toxicity	RT+CT+ erlotinib in locally advanced pancreas cancer pts is safe, but should be not routinely administered
	RT+CT+ erlotinib vs		progression		(negative strong)
	CT+ erlotinib				
	Brain metastasis from NSCLC				
	RT +erlotinib <i>vs</i> RT+ pacebo	(19)	no differences in neurological PFS or OS	more cutaneous toxicity	RT+ erlotinib in lung cancer pts with brain metastases should be not routinely administered (negative strong)



- → Randomized trials avalaible on H&N, Lung, Pancreatic and NSCLC Brain Metastatic cancers
- → Erlotinib administered concomitant to RT or concomitant to CT+RT should be not routinely administred since an advantage in OS, PFS, CR and local progression was never obtained from the available randomized trials and since a more severe cutaneous toxicity was documented in Head and neck cancer pts and in pts with metastatic NSCLC. (recommendation by SIGN)

Small	Clinical setting	Randomized	Clinical results	Toxicity	Grade of recommendations
molecules		trials			
	Brain metastasis				
Gefitinib	from NSCLC				
	6 1				
	RT +gefitinib vs	(23)	poor outcome all arms	no increased toxicity	RT+ gefitinib in lung cancer pts with brain metastases
					should be not routinely administered (negative strong)

Table 2 – Take home messages: evidence based clinical reccomendations (based on randomized trials: levels of evidence A) - Small molecules and radiotherapy

abbreviations: RT, radiotherapy; CT, chemotherapy; CDDP, **Cisplatin**; CR, complete response; pts, patients; PFS, progression-free survival; NSCLC, Non Small Cell Lung Cancer; OS ,overall survival; gem, gemcitabine; TMZ, temozolomide;



- **Randomized trials avalaible on NSCLC Brain Metastatic cancer**
- Gefitinib concomitantly to RT should not be routinely administered since the only one randomized trial, testing RT+ gefitinib vs RT+TMZ, did not demonstrate a clinical benefit of gefitinib in pts affected by metastatic NSCLC (brain metastasis). (recommendation by SIGN)



TAKE HOME MESSAGES Immune Check Point Blockade drugs- CA, IP

Immune Check Point Blockade drugs	Clinical setting	Randomized trials	Clinical results	Toxicity	Grade of recommendations
Ipilimumab	Metastaic	(25)	PFS was prolonged without	Increased toxicity	Ipilimumab should not be
	castration-		advantages in OS (primary	(rate of grade 3-4	routinely added to RT
	resisten Prostate		endpoint); a post-hoc	and AEs)	(negative strong)
	cancer		subgroup analyses		
	(progressed after		suggested that ipilimumab		
	docetaxel		might be more effective in		
			pts with favourable		
			prognostic factors		
	+RT+ Ipilimumab				
	vs RT+ placebo				

 Table 3 – Take home messages: evidence based clinical reccomendations (based on randomized trials: levels of evidence A) - Immune Check Point

 Blockade drugs and radiotherapy

abbreviations: RT, radiotherapy; CR, complete response; pts, patients; PFS, progression-free survival; OS, overall survival; AEs, adverse events



- → Randomized trials avalaible on Castration Resistent Prostate Metastatic cancer
- → At present Ipilimumab should not be routinely added to RT since the only randomized trial showed an advantage in PFS but non in OS in pts affected by Metastatic castration-resisten Prostate cancer (progressed after docetaxel). (recommendation by SIGN)



5.0 Key Messages. AIRO POSITION PAPER "Radiotherapy and new drugs for solid tumors: what is known and what is not?"

5.1 Table: Wrap-up of Evidence and Strength of Recommendation

Cetuximab

- → Randomized trials avalaible on H&N, Lung, Esophageal and Rectal cancers
- → Cetuximab is recommended only in head and neck cancer pts unfit for standard radiochemotherapy. (level of evidence and recommendation by SIGN)

Panitumumab

- ➔ Randomized trials available on H&N and Rectal cancers
- → Panitumumab should be not routinely administered in association with RT (level of evidence and recommendation

by SIGN)

Trastuzumab

- → Randomized trials avalaible on Breast cancer
- → Trastuzumab concurrently with RT could be safely administered (level of evidence and recommendation by SIGN)

Bevacizumab

- → Randomized trials avalaible on High Grade Gliomas and Rectal cancers
- Bevacizumab should be not routinely administered in association with radio chemotherapy (level of evidence and recommendation by SIGN)



Erlotinib

- → Randomized trials avalaible on H&N, Lung, Pancreatic and NSCLC Brain Metastatic cancers
- → Erlotinib administered concomitant to RT or concomitant to CT+RT should be not routinely administered (level of

evidence and recommendation by SIGN)

Gefitinib

- → Randomized trials avalaible on NSCLC Brain Metastatic cancer
- → Gefitinib concomitantly to RT should not be routinely administered (level of evidence and recommendation by SIGN)

Afatinib.

No data are available concerning Afatinib and RT, thus, their combination in daily clinical practice is recommended only within clinical trials.

Sunitinib

- → Phase I-II studies are avalaible on renal, H&N, prostate,NSCLC and Pancreatic metastatic cancers
- → Sunitib concomitantly to RT should not be routinely administered (level of evidence and recommendation by SIGN)

(Sunitinib given together with irradiation should be reduced to 37.5 mg daily in a classical 6-week schedule or to 25 mg daily if a continuous schedule is applied. Particular attention should be adapted to dose-constraint for organ at risk, with particular caution when GI or airways are included or are next to treated lesion. Some concerns remain according to rare but severe side effects such as perforations of GI tract and hemorrhages, along with the fact that published studies generally include in their cohorts oligometastatic patients, leaving the doubt of what would be better between a combination strategy or high-dose RT only.)



Sorafenib.

- → Phase I-II studies are avalaible on HCC and metastatic colon rectal cancers
- → Sorafenib concomitantly to RT should not be routinely administered (level of evidence and recommendation by SIGN)

(Cranial SRT combined with sorafenib appears to be safe. For extra-cranial SRT, liver SRT combined with sorafenib is associated with a high risk of severe toxicity, which has not been observed with conventionally fractionated radiotherapy. The combination should be used with caution and needs further investigation)

PARP Inhibitors.

- → Phase I-II studies are avalaible on brain metastasis
- → PARP Inhibiors concomitantly to RT should not be routinely administered (level of evidence and recommendation

by SIGN)

(Although the mechanisms of interaction between PARP inhibitors and RT are intriguing, available data are far to be applicable in clinical practice. Further studies are advocated.)

CDK Inhibitors.

→ For CDK Inhibitors there are no clinical data available in literature regarding the association with RT (level of evidence and recommendation by SIGN)

(No clinical data are available in literature regarding the association between RT and CDK inhibitors. Thus, a combination

in daily clinical practice is recommended only within clinical trials.)



PI3K/mTOR dual inhibitors.

→ Phase I-II studies are avalaible on NSCLC, H&N, cervix, prostate and glioblatoma cancers

→ PI3K/mTOR inhibitors concomitantly to RT should not be routinely administered (level of evidence and

recommendation by SIGN)

(The association of PI3K/mTOR dual inhibitors (everolimus) with radiotherapy remains investigational due to lacking of mature literature data.)

BRAF inhibitors.

- → Phase I-II studies are avalaible on melanoma
- → BRAF concomitantly to RT should not be routinely administered (level of evidence and recommendation by SIGN)

(The data we have are now insufficient to make strong recommendations about the concomitant use of BRAFi and radiotherapy, and the reports of unexpected severe toxicity suggest paying specific attention when RT and BRAFi are given even not concurrently but in shorter time.

Until more prospective data are available, the consensus recommendations of the Eastern Cooperative Oncology Group (ECOG) include the following for all patients receiving a BRAFi, MEKi, or both BRAFi and MEKi (eg, vemurafenib/dabrafenib and trametinib/cobimetinib) (28).

For drug:

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

For RT:

- consider dose per fraction <4 Gy unless using a stereotactic approach or the patient has very poor prognosis/performance status;
- for adjuvant nodal basin RT, consider a dose ≤48 to 50 Gy in 20 fractions;



- for spine metastases, consider highly conformal RT when feasible and safe to minimize exit dose through visceral organs.

Data on intracranial neurologic toxicity are conflicting and the risk of brain radionecrosis does not appear increased with BRAFi; nevertheless the toxicity reported by some recent studies recommends caution. New radiation therapy techniques, such as stereotactic radiation, could allow association with BRAFi in association with RT. Caution is always advisable when radiation is associated with BRAFV600 inhibitors and clinical studies assessing these new techniques are needed)

Hedgehog Signalling pathway inhibitors.

- → Phase I-II studies are avalaible on basal cell carcinoma
- → Hedgehog Signaling pathway inhibitors concomitantly to RT should not be routinely administered (level of evidence

and recommendation by SIGN)

(The association of Hedgehog signalling pathway inhibitors (erivedge, sonidegib) with radiotherapy remain investigational and should be explored only in controlled clinical trial).

Ipilimumab.

- → Randomized trials avalaible on melanoma and Castration Resistent Metastatic Prostate cancer
- → Ipilimumab concomitantly to RT is recommended only in melanoma brain metastasis (level of evidence and recommendation by SIGN)

(The combination of Ipilimumab and Radiotherapy is safe and effective for melanoma brain metastases. A trend towards a positive synergistic effect for radiotherapy plus ipilimumab has been shown in a trial on metastatic prostate cancer patients with bone metastases. However, ipilimumab should not be routinely added to RT in pts with prostate cancer since the only randomized trial showed an advantage in PFS but not in OS in pts affected by Metastatic CRPC (progressed



after docetaxel)

Anti-PD1–PDL1 agents (Pembrolizumab, Nivolumab).

- → Phase I-II studies are avalaible on melanoma and NSCLC metastatic cancers
- → Anti PD1/PDL1 agents concomitantly to RT should not be routinely administered (level of evidence and recommendation by SIGN)

(Still few data are available on the combination of anti-PD-1 agents and RT, but preliminary evidence suggests the absence of toxicity for brain RT, and initial retrospective data favor the combination of radiosurgery with pembrolizumab over radiosurgery alone for melanoma brain metastases. A beneficial effect on PFS and OS was shown for advanced lung cancer when combining radiotherapy and pembrolizumab sequentially. The risk of pulmonary toxicity seems to be slightly higher for the combination, but manageable.)

Abiraterone.

→ Phase I-II studies are avalaible on prostate cancers

→ Abiraterone concomitantly to RT should not be routinely administered (level of evidence and recommendation by

SIGN)

(Although the limited existing data, experiences here reported extrapolated from large series, such as the COU-AA-301 trial, confirmed the feasibility and promising synergistic effects by combining Abiraterone/RT in PC.)

Enzalutamide.

→ No data are currently available regarding the toxicity and the efficacy of a combination of RT and Enzalutamide

(level of evidence and recommendation by SIGN)

(No data are currently available regarding the toxicity and the efficacy of a combination of RT and Enzalutamide. In the



large studies the Enzalutamide treatment was stopped in case of skeletal events (including events that required RT), so no indirect data on the potential toxicity of a combination Enzalutamide and RT are available from these studies.)

Androgen pathway suppression – other "newest" drugs

There is not sufficient clinical evidence to fully understand the potential clinical use of these drug. (level of evidence and recommendation by SIGN)



5.2 Summary Table. Association of New Drugs with Radiotherapy in clinical practice for solid tumors: Quality of Evidence and Strength of Recommendation

Innovative Drug	Levels of Evidences	Score of Recommendation	Question: Is the association with
	SIGN	SIGN	Radiotherapy recommended?
			Strength of Recommendation
			SIGN
Cetuximab	1+	A in HNSCC unfit for chemotherapy	Positive weak
	2+	B in other tumors	Negative strong
Panitumumab	1+	В	Negative strong
Trastuzumab	2+	В	Positive weak
Bevacizumab	1+	В	Negative strong
TKI (tinib)	1+ erlotinib	В	Negative strong
	1+ gefitinib	В	Negative strong
			lack of data for combination
TKI (nib)	3 sorafenib	D	Negative strong
			lack of data for combination
CDK Inhibitors	3	D	Negative strong
			lack of data for combination
PARP inhibitors	3	D	Negative strong
			lack of data for combination
P13K/mTtor dual inhibitors	3	D	Negative strong
			lack of data for combination
BRAF inhibitors	3	D	Negative strong
Hedgehog signaling inhibitors	3	D	Negative strong
			lack of data for combination
Immune Check Point Blockade	1+ prostate	В	Negative strong
	3 melanoma brain metastasis	D	Positive weak
			lack of data for combination
Androgen Pathway therapy	3 abiraterone	D	Negative weak
	3 enzalutamide	D	Negative strong
			lack of data for combination



6.0 Conclusions

As evident in the Sections 4.0 (Take Home Messages from Randomized Trial) e 5.1 (Key Messages) and 5.2 (Summary Table) of this position paper, for the majority of the associations of novel drug with radiotherapy, the Recommendations emerging from the literature data are "Negative Strong" for the standard use in clinical practice. This finding is mainly correlated with the lack of data to support these associations: for many drug-radiotherapy combinations the main reason of a negative recommendation is due to the absence of sufficient evidence from the literature. However, as specified by Altman DG et al published on BMJ in 1995 "Absence of Evidence Is not Evidence of Absence". Thus, for many associations the unavailable data advice that the novel drugs could be administered with caution or explored only in controlled clinical trials.

Conversely, for other associations of novel drugs with radiotherapy the Negative Strong Recommendations are truly correlated to an increased risk of new toxicities despite promising, although limited, clinical results in tumor control rate.

Overall, these findings means also that more controlled clinical researches are encouraged to exploit better the interactions between novel molecular agents and ionizing radiations for the cure of solid tumors.



Appendix 1. Innovative Drug half-lives. (generally, Radiotherapy is considered administered "concurrently" with Systemic Therapy when administered in a period less than five half-lives of the drug)

From Tallet AV et al, Ann Oncol in press 2017

Drug	Median Half-life
Vemurafenib	51.6 hours
Dabrafenib	8 hours (orally)
Trametinib	127 hours
Erlotinib	36.2 hours
Gefitinib	41 hours
Sunitinib	95 hours
Bevacizumab	480 hours
Trastuzumab	456 hours
Lapatinib	24 hours
Trastuzumab-emtansine	96 hours
Ipilimumab	370 hours
Pembrolizumab	600 hours
Nivolumab	578 hours