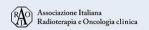


AIRB - UTILIZZO E TIMING DEI FARMACI DI PRECISIONE IN CORSO DI RADIOTERAPIA

# RAZIONALE RADIOBIOLOGICO IN TERMINI DI EFFICACIA

Luisa Bellu

Radiotherapy and Radiosurgery Department,
IRCCS Humanitas Research Hospital — Rozzano - Milan HUMANITAS









# No commercial disclosures









# **OUTLINE**

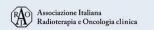
- > RADIOBIOLOGICAL RATIONALE
- ASSOCIATION RT AND EGFR-INHIBITORS/ TKI

  HER2-INHIBITORS

  BRAF/MEK-INHIBITORS

  VEGF-INHIBITORS

  PARP-INHIBITORS



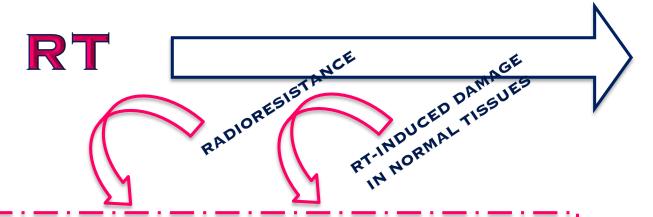


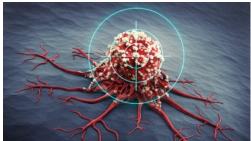




AIRB - UTILIZZO E TIMING DEI FARMACI DI PRECISIONE IN CORSO DI RADIOTERAPIA:

#### RAZIONALE RADIOBIOLOGICO IN TERMINI DI EFFICACIA





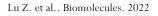
#### RT - TARGET AGENTS COMBINATION

radiosensitizing drugs could improve RT therapeutic index

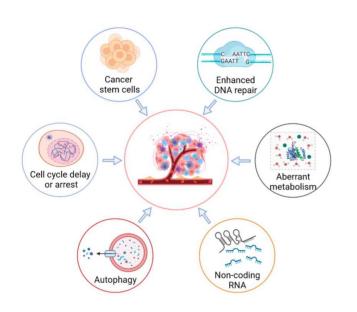
improving tumour control and decreasing side effects







AIRB - Utilizzo e timing dei farmaci di precisione in corso di radioterapia: RAZIONALE RADIOBIOLOGICO IN TERMINI DI EFFICACIA



**PROLIFERATION** 

TRASFORMATION
INVASION/MIGRATION

SURVIVAL



HER2-inhibitors

EGFR-inhibitors/TKI

BRAF/MEK-inhibitors

PARP-inhibitors

CDK-inhibitors

Maier P. et al. Int J Mol Sci. 2016 Maier P. et al. Strahlenther Onkol. 2014

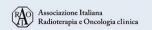








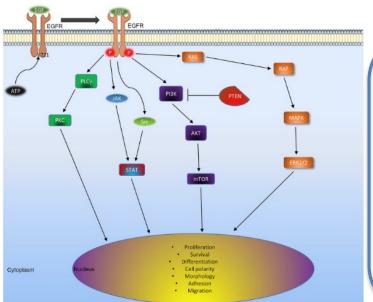
## RT + EGFR INHIBITORS/TKI







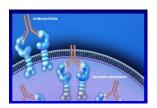
# **EGFR**



#### EGFR-INHIBITORS/TKI

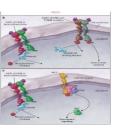
MONOCLONAL ANTIBODIES
TARGETING EGFR

Cetuximab Panitumumab
Approved for RAS wild-type
metastatic colorectal cancer and
H&N cancers



SMALL-MOLECULE
TYROSINE-KINASE INHIBITOR

Erlotinib Gefitinib Osimertinib
Efficacy in NSCLC, renal cell carcinoma,
and other cancers types.



Cuneo KC et al. 2015 - Hutchinson RA, et al. 2015 Zulkifli AA et al. *Mol Cell Endocrinol*. 2017 Yarden Y, et al. Nat Rev Cancer. 2012 - Mendelsohn et al., 2000









#### **RT - EGFR INHIBITORS**

Preclinical studies: anti EGFR

Anti-EGFR can potentiate RT efficacy

inducing cell-cycle arrest in the more radiosensitive G1 phases,

inhibiting radiation-induced damage repair

Preclinical studies: TKI

TKI could increase sensitivity to RT

Exposure of tumor cells to ionizing radiation

**EGFR** dimerization and auto phosphorylation

**EGFR** internalization and traslocation into the nucleus

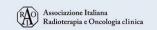
activation of RAS/RAF/MAPK pathway

activation of PI3K/AKT pathway

**RADIORESISTANCE** 

Inhibition of their upstream receptor EGFR increase radiosensitivity

Tao Y, et al J Clin Oncol. 2018 - Xing DT et al. Cancers (Basel). 2021 Banerjee R. et al. Mol Ther. 2022









#### **RT - TKI INTERACTION**

#### Preclinical studies

EGFR-TKI could increase radiosensitivity, radiotherapy could increase sensitivity to EGFR-TKI

A secondary mutation (T790 M) under chronic EGFR-TKI exposure can limit the therapeutic response

Plasma T790m mutation could be detected ≈ 2 months prior to PD: distant reseeding of T790m-positive tumor cells may be an **early event in disease progression** 

Cancer cells with **T790 m** mutation show **improved sensitivity to radiation** exposure

RT prior to tumor progression may reduces systemic reseeding of resistant clones T790M cells: potentially promising strategy to alleviate T790m-mediated EGFR-TKI resistance

Ramalingam SS, et al. N Engl J Med. 2020 Mok T, et al. Ann Oncol. 2020 Tang Y. et al. Lung Cancer. 2020.







#### RT - EGFR INHIBITORS/TKI

#### Clinical studies

RT-Cetuximab association superior outcome versus CT-RT and currently indicated in selected patients with HNSCC

Author and year	Strady type	N	Tumor site and stage (if analiable)	RT technique, dese, fractionarion	Contribution (concent), other)	Philady Endpoint	Troutment outcome
Bonner et al. (2000)	Phase III	211	LASCOR	-790y/88 fs	CERT (CROP) + /- Gia	LHC .	Median LBC 244 YE 144 months
				-72.76.84(y) 63.64 ft (hydro della)			(P = 0.001) 5-yy G0 45.6% to 36.4% $(P = 0.01)$
				-776/JP (t			
Ang et al. (2014)	Phase III	548	LA-90CHN	ART	CE-RESCRIPT A A DIS	PRS	3-py 295; 72.8% vs 49.2%
				726y/40 fx			(7 < ,000)
				-087			3-yy 00: 85.6% vs 68.1% (F < .00)
Tao et al. (2010)	Phase III	406	LASCON	SDCRT/DIRT	Gia = CT RT to Gia = RT	PRE	$3\gamma\gamma$ PFG 52.7% vs 40.5% $P=.81$
Lebbour et al. (2013)	Phone II E	114	(non-pulpable 50 NSS) stars III-N James Presidences	790y/08 fx 100Y7	Industry CT CT 8T (CDSP) + / On		3-yy Oli 88.8% vs 54.8% (F = 0.13 3-mondo LP: 92% vs 92%
	PRAIR II F.		NO.	799v / 30 h	marine Con Charles (Case) 17: On	Lar.	
							15 months 00: 92% to \$9%
Married or all (2010)	Phone II II	35	LASCON.	MOST WAT	CEAT (CROP) 1 / On	10	(P = NE) 2 op 10: 100% to 72.9%
Megha it is, carso	Phase II Fo	35	LASON	795v:75 (s	Cr-ar scales 17- Ox	66	
							2 cy 00: 180% to 77.8%
Tourier of Chicago	Phone ET	805	0000	MIT	ET a CODE IN	06	(P = NE) See (NE MARK to PP NE)
man in in card to	reas II	-00	SPC4	795x/35 fx	RT = CDDF to RT = CD		198 L46; 995 CLL0-2.00
Assists et al. (2019)	Phon II	-	LANCON	DET	Industries	PRE	OR 1.72 995 CI 1.29-2.20 2 or PTS 705
region is in call 10	reas II	**	LAWLING.	799x 79 fs		P	3 yr 1916 70% 3 yr 0% 74%
					(workly) Manadaanse		
					- Crs (5 months)		
Geoffreis et al. (2016)	Phase III	379	LA SCORN	RT .		295	Median PS 125 vs 115 monto
			( » N/M	795y-25 fx	(Carbo+5-PU)		(7 = 9.74) Median (6) 12.8 to 26.6 membe
							Median 06: 228 to 246 membe (F = 0.40)
Marrier (2007)	Phase II	90	9900	DAT	Induzion	P95	
			MPV+	683 Cp/23 fs or	CDOF + FAC + Cis		-2 yy PRIL RON
				S4Sy/2P fix Of QL to industrial	Committee ET + On Invokini		-2 yy 08: 94%
Covinda et al.a (2011)	Phase II E	300	Stage III NOCIC		CT- RT (Carboptoin + PEM) + /- Cin	00	19 worth OE 58% to 54%
San des Herrel et al. (2004)			Stee II NICIC	790y/W/W	COST (COOP) + /- Ox	LOI	(P = A47) (BIC 84% vs 92% (P = 0.36)
Bradley et al. (2007)	Phase III	144	Stage III NOCIC	60 Gy/30 fx to 74 Gy/37 fx	CE: RT (Carleplana + PAC) + /- Cra	06	Median OG 25 to 24 monto
Nobsesser et al. (2004)	Phone II II	202	Steer B.H. MICH.	ART MIGNISH IN	CONTROLOGO LA DA	06	(P = 9.2%) Median OG 33 to 30 months
			100 000	100 00 00 00 00	C		
							2 cy 00; 68.8% to 58.8% (P = 9.84)
Deedson et al. (2012)	Phase II R	165	High tisk noted cancer	MORT	CT-RT (CAPRIC) + A Cts	· ·	5-yr 00: 27.7% to 27.2% (F = 1.80) (B: 14% to 18% (F = 574)
				45/5x/25 fs + book 35/25x/3 fs			
Sultan et al. (2000)	Plan II	60	-57 emphaged oncer -3 gades career	10 CKT 50.4 Cp (28 lb	CT- RT (Carboplasia = PAC) = Cts	Substy-Efficacy	CCR 79%
Gode et al. (2004)	Phase E	79	Flogs III	DOKT	POLIFORO + CIX	OKK	068-77%
			3030 w 331	56.4 Gy/30 fs			pOli 40% Medica Oli 21 A months
					CD-RT (CDOP+3-FS) + /- CW	OK .	
Gody et al. (2013)	Phone E. Cl.	214					(P = 6.630)
				56 Cg / 25 fs			
Cooley at al. (2003) Sunbandingson at al. (2007)			This and or N + BC	SECULUS IN SECULUS SECULUS IN	CE-RE (CDEP = PAC) = $\wedge$ Ga	OK .	2 pp 06 48% to 60% 3 to 06 28% to 38%
Sunbandages et al. (2007)	Phase El	344	The and or N + HC	50.4 Gy 28 ts		_	5-py-06: 38% to 38% (P = AT)
			T3 4 and or N + BC	50.4 Gy GH Is 50.4 Gy GH Is	Industria CE o CEAT (CERT o TWO	OK PFS	3-39 GG 28% to 38% (P = AT) Modes PS-2-5 to 2 years (P = 6.1)
Sunbandages et al. (2007)	Phase El	344	The and or N + HC	10007 514 Gr 28 ft 10007 65 Gr 28 ft 10007 (1007		_	3.55 06: 20% to 30% (P = AT) Modes PS: 2.5 to 2 years (P = 6.1) Modes 66: 5.1 to 3 years (P = 8.85) Art 180: 67% to 15% (P = 8.86)
Sunhanding an et al. (2007) Rahmdor et al. (2001) Graft et al. (2005)	Phase III Phase III Phase II R	344	Ti-4 and or N + BC (Ti-4a (90% (N+) BC Li-5008N	20087 56.4 Gy 38 fs 20087 45 Gy 35 fs 30082 9887 70 72 Gy 36-33 fs	Induction CE = CE &T (CEOP + TXT) + /- On = 5 CE - RE (CEOP) ++ CE - RE (PAN)	PES SAC	3-39-00: 20% to 36% (P = AT) Modas PSS: 2.5% 2 years (P = 0.1) Modas GS 5.1 vs 3 years (P = 0.0) 2-39-38C: 62% vs 55% (P = 0.0) 2-39-38C: 67% vs 65% (p = 0.0)
Southendingum et al. (2017) Referedor et al. (2011)	Phote III	344	T3 4 and or N + BC (T3 4a (99% (N +) BC	20003 56.4 Gy-38 fs 10003 10003 10003 9897 76.72 Gy-36-33 fs 10003 9897	Induction CE = CE NY (CROP + TXY)	HS	3-39-06: 28% to 38% (P = AT) Modes PIS: 2.5 to 2 years (P = 6.1 Modes OF S.1 to 3 years (P = 6.8) 2-39-38C: 54% to 54% (P = 8.06) 2-39-06: 72% to 65% (P = 6.06) 2-30-75% 77% to 75%.
Sunhanding an et al. (2007) Rahmdor et al. (2001) Graft et al. (2005)	Phase III Phase III Phase II R	344	Ti-4 and or N + BC (Ti-4a (90% (N+) BC Li-5008N	20087 56.4 Gy 38 fs 20087 45 Gy 35 fs 30082 9887 70 72 Gy 36-33 fs	Induction CE = CE &T (CEOP + TXT) + /- On = 5 CE - RE (CEOP) ++ CE - RE (PAN)	PES SAC	5 yy $60$ : $20%$ to $50%$ ( $P = 40%$ ) (P = 40%) Modess $P(S : 2.5$ to $2$ years $(P = 0.1)$ Modess $60$ : $51$ to $3$ years $(P = 0.0)$ 2 yy $100$ : $62%$ to $52%$ $(P = 0.0)2$ yy $60$ : $72%$ to $95%$ to $(P = 0.0)2$ yy $100$ : $72%$ to $72%$ $(P = 0.0)(P = 3.3)2$ or $(98)$ $(97)$ to $(97)$ to $(97)$
Southernlargum et al. (2017) Radonaller et al. (2011) Genit et al. (2015) Sto et al. (2016)	Place EI Place EI Place EI Place EI	366 366 351	T14 and or N + RC  (T3.4a (99a (N +) RC  LA-SOCIN  LA-SOCIN	30087 56.4 Gy/GB fs 80 Gy/GB fs 30 GY/GB f	Induction CE= CERT (CERP = TXT) +/- On == 5 CE-RE (CERP) to CE-RE PANO CE-RE (CERP) to CE-RE PANO	HS SHC HS	5-yy 06: 28% to 38% (P = 47) Modas PS: 2.5 to 2 years (P = 6.1) Modas RS: 2.5 to 2 years (P = 6.1) Modas RS: 2.5 to 3 years (P = 8.55) 209 06: 75% to 56% (P = 000) 209 PS: 75% to 66% (P = 000) 209 PS: 75% to 68% to 85% to 85% 209 06: 85% to 88% to 85% to 85% 209 06: 85% to 88% to 85% to 85% 209 06: 85% to 88% to 85% 209 06: 85% to 88% to 85% to 85% 200 06: 85% to 85% to 85% to 85% to 85% 200 06: 85% to 85% to 85% to 85% to 85% 200 06: 85% to 85% to 85% to 85% to 85% 200 06: 85% to 85% to 85% to 85% to 85% 200 06: 85% to 85% to 85% to 85% to 85% to 85% 200 06: 85% to 85% to 85% to 85% to 85% to 85% 200 06: 85% to 85% t
Sunhanding an et al. (2007) Rahmdor et al. (2001) Graft et al. (2005)	Phase III Phase III Phase II R	366 366 351	Ti-4 and or N + BC (Ti-4a (90% (N+) BC Li-5008N	20087 56.4 Gy/36 fs 20087 61 Gy/35 fs 20082 (1987 75 Gy/36 St 36 20082 (1987 75 Gy/36 St 36	Induction CE = CE &T (CEOP + TXT) + /- On = 5 CE - RE (CEOP) ++ CE - RE (PAN)	PES SAC	5 yy $60$ : $20%$ to $50%$ ( $P = 40%$ ) (P = 40%) Modess $P(S : 2.5$ to $2$ years $(P = 0.1)$ Modess $60$ : $51$ to $3$ years $(P = 0.0)$ 2 yy $100$ : $62%$ to $52%$ $(P = 0.0)2$ yy $60$ : $72%$ to $95%$ to $(P = 0.0)2$ yy $100$ : $72%$ to $72%$ $(P = 0.0)(P = 3.3)2$ or $(98)$ $(97)$ to $(97)$ to $(97)$

Author and year	Study type	N	Tumor site	RT technique/dose/ fractionation	Combination (concomit, other.)	Primary Endpoint	Treatment outcome
Martins et al. (2013)	Phase II R	95	LA-SOCHN	IMRT 70 Gv/35 fs	CT-RT (CDDP) +/-E	CRR	CR: 40% vs 52% (P = 0.08)
Martinez et al. (2016)	Phase II R	90	NSCLC	3DCRT 66 Gy/33 fx	RT alone vs RT + E	Feasibility/ Tolerability	Median OS: 11.4 vs months (P = 0.835)
Herchenhorn et al. (2010)	Phase I/II	31	LA-SOCHN	TCT 70.2Gy/39 fx	CT-RT (CDDP) + E	Safety/Efficacy	3-yy PFS = 61% 3-yy OS: 72%
Yao et al. (2016)	Phase II	43	LA-SOCHN	DMRT 70 Gs/35 fs	CT-RT (weekly DOC) +E (daily,continued until 2-years)	DFS	3-yy DFS: 69.5% 3-yy OS: 83%
Hainsworth et al. (2009)	Phase II	60	LA-SOCHN	3DCRT 68.4Gy/38 fx	Induction BEV/5-FU/Carbo/PAC → CT-RT (PAC + BEV) + E	PFS	3-yy PFS: 71% 3-yy OS: 82%
Lilenbaum et al. (2015)	Phase II	75	Unresectable NSCLC	3DCRT 66 Gv/33 fx	Induction Carbo/Paclitaxel → RT + E	os	Median 06: 17 mon 1-vv 06: 57%
Ramella et al. (2013)	Phase 1-E	60	Unresectable NSCLC	3DCRT 59.4Gy/33 fx	CT-RT + Erlotinib	Feasibility/ Tolerability	Median OS: 23.3 m Median PS: 4.7 mc
Herman et al. (2013)	Phase II	46	Resectable PA	IMRT 50.4Gy/28 fx	$CT-RT\;(CAP)\;+\;E\toGEM\;+\;E$	RIS	Median RFS: 15.6 months Median OS: 24.4 m
Hammel et al. (2016)	Phase III	133	Unresectable PA	3DCRT 54 Gy/30 fs	Induction GEM alone vs GEM + E → CT vs CT-RT	os	Median OS: 13.6 vs months (P = 0.09)
Nogueira-Rodrigues et al. (2014)	Phase II	36	LACC	3DCRT 45Gy/25 fx +	CT-RT (CDDF) +E	Safety/Efficacy	2-yy 05: 91.7% 2-yy PFS: 80.6%
				24 Gv/4 fx			
Blaszkowsky et al. (2014)	Phase II	32	LARC	3DCRT 50.4Gy/28	CTRT (5-FU-BEV) + E	Safety/Efficacy	3-yy DFS: 75.5%
Zhao et al. (2016)	Phase II	21	Inoperable ESCC	IMRT 60Gv/30 fs	CT-RT (weekly PAC) + E	Safety/Efficacy	Median 06: 22.9 m
lyengar et al. (2014)	Phase II	24	Stage IV NSCLC	SBRT 27-33 Gy/3 fx 35-40 Gy/5 fx 19-20/1 fx	SBRT + E (1 week before and during)	PFS	Median PFS: 14.7 months Median OS: 20.4 mc
Welsh et al. (2013)	Phase II	40	204	3DCRT 35 Gy/14 fx	WERT + E (then maintained until neurological progression)	MST	MST: 11.8 months
Zhuang et al. (2013)	Phase II R	54	am.	30 Gy/10 fs	WERT +/-E	LPFS	Median LPFS: 6.8 vs months (P = 0.003) Median OS: 8.9 vs 1 months (P = 0.02)
Lee et al. (2013)	Phase II R	80	RM	3DCRT 20 Gy/5 fx	WERT +/-E	nPFS	Median nPFS: 1.6 vs months Median OS: 2.9 vs 3 months (P = 83)
Pesce et al. (2012)	Phase II R	59	BM	3DCRT 30 Gy/10 fs	WERT + TMZ vs WERT + G	os	Median OS: 4.9 vs t months
Wang et al., (2014)	Phase II	14	Stage IV NSCLC	SBRT 48-60 Gy/3 fx	SBRT + G (1 week before and until progression)	Tolerability/ Efficacy	Median PSS: 7 mon Median OS: 19 mon

No clear evidence supporting routinely concomitant integration of TKI (old gen) and RT.

Still no data available on Osimertinib and RT: ongoing trials

# Clinical Trials.gov

Randomized Phase II Trial of Osimertinib With or Without Local Consolidation Therapy for Patients With EGFR-Mutant Metastatic NSCLC (NORTHSTAR)

Radiation During Osimertinib Treatment: a Safety and Efficacy Cohort Study (NSCLC) (NCT05089916)

A Multicentre Single-arm Phase II Trial Assessing the Safety and Efficacy of First-line Osimertinib and Locally Ablative Radiotherapy in Patients With Synchronous Oligo-metastatic EGFR-mutant Non-small Cell Lung Cancer (NCT04908956)

Arcangeli S. et al. Crit Rev Oncol Hematol. 2019 - Tao Y, et al J Clin Oncol. 2018 - Xing DT et al. Cancers (Basel). 2021









#### RT + HER2 INHIBITOR





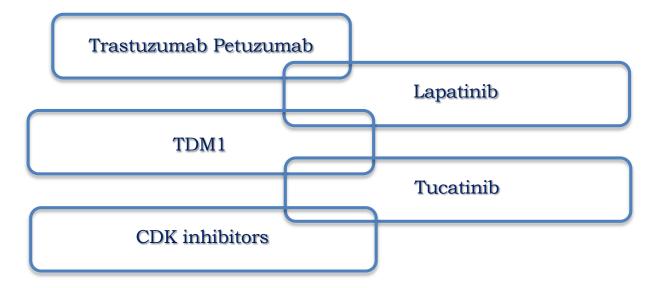




# HER1/3/4 HER2 p27 rapid degradation survival cancer cells' growth migration

# HER2

#### **HER2-INHIBITORS**



Mignot F. et al. Radiother Oncol. 2017 Vu T. et al. Front Oncol. 2012 Weiner and Adams, 2









#### RT - HER2 INHIBITORS INTERACTION

## Preclinical studies

## **HER2-overexpression** is correlated with **radioresistance**

Activation of STAT3-survivin signaling

Deregulation cell cycle
DNA repair accelerator
Resistance to apoptosis

RADIORESISTANCE

Down-regulation of HER2 can restore radiosensitivity

Mignot F. et al. Radiother Oncol. 2017 Liang et al. Pietras et al. ,









#### RT - HER2 INHIBITORS INTERACTION

## Clinical studies

	п	Median follow up (months)	Early dermat	itis (%)		Early esopha	gitis (%)		Late skin toxicity (%)		Late esophi toxicit		LVEF	Clinical congestive heart failure
Grade Retrospective studies			1	2	3	1	2	3	<2	≥2	<2	≥2		
Belkacémi et al. [42]	146	16	37°	35	6	64"	24	11	48°	51	883	12	≥Grade 2 : 10%* 6%*	-
Shaffer et al. [43]	44	15	-	-	-	-	-	-	-	-	-	-	Median decrease (MD): 4%	3 patients 4.5%
Meattini et al. [45]	95	52	20"	13.7	0	1.12	0	0	22.1° F 18.9 Lym 1.1 T 4.2	0	0	0	MD to the last follow-up: 2%	1 patient (atrial fibrillatio 1.1%
Cao et al. [44]	64	6.7° 26°	-	-	-	-	-	-	-	-	-	-	MD to the last follow-up: 3% Grade 1°: 7.8%	0
Prospective studies														
Jacob et al. [50]	308	50	73.4	21.8	3.9	8.4	1.3	0.3	F: 18.6 Lym: 6.7 T: 4.9	F: 7 T: 3.5	0.4	0	≥Grade 2: 2.9%*	0.6%
Halyard et al. [49]	935	44	-	-	4.3	-	-	0	-	-	-	-	-	2.7%
														1.7 %
Horton et al. [54]	12	38	-	-	16.7	-	-	-					1 patient	0

Confirm of radio-sensitizing effect and a good safety profile for Trastuzumab-RT

Target	Name	Number	Recruitment Status	Endpoint
Estrogen receptor (ER) Tamoxifen + locoregional RT	CONSET trial	NCT00896155	Unknown	Pulmonary fibrosis
Tumor growth Trastuzumab Emtansine (T-DM1) + brain RT	BIRTH trial	NCT02135159	Completed	Brain radionecrosis
Tumor angiogenesis				
Bevacizumab + brain RT	A-Plus	NCT02185352	Active, not recruiting	Brain-specific progression free survival
Cell cycle				
Palbociclib + locoregional RT	PALATINE	NCT03870919	Recruiting	Overall survival
DNA repair				
Olaparib +/- locoregional RT		NCT03598257	Recruiting	Invasive Disease-Free Survival

Main ongoing randomized clinical trials testing the combination of targeted treatments and RT in breast cancers

Promising data on Lapatinib+ RT in brain mets

T-DM1 no clear indication of administered concurrently with RT:

increase the risk of brain radionecrosis



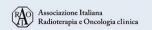








#### RT + BRAF/MEK INHIBITOR





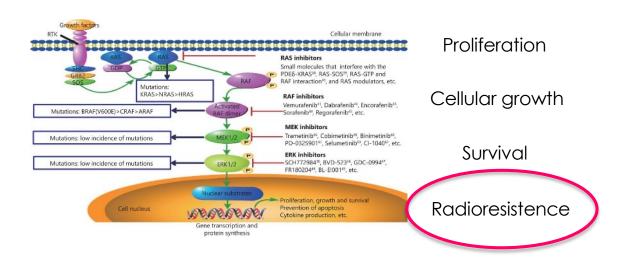




## **BRAF**

Part of the RAS-RAF-MEK-ERK pathway

BRAF mutation → constitutive activation of the Ras/Raf/MAPK pathway



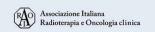
**BRAF-INHIBITORS** 

Vemurafenib

Dabrafenib

Li Y et al. Cancer Biol Med. 2019

Yarden Y. et al. Nat Rev Cancer. 2012









#### RT - BRAF INHIBITORS INTERACTION

## Preclinical studies

Inhibition of the MAPK pathway



**Reduction** in lethal DNA damage repair

Cell cycle arrest in G1

**Increase** of RT induced **apoptosis** 

#### Clinical studies

RT + BRAFi

remarkable increases in treatment efficacy

but risk of toxicity:

stop BRAFi during the same days of RT

Li Y et al. Cancer Biol Med. 2019

Yarden Y. et al. Nat Rev Cancer. 2012

Seeley AR, et al Melanoma Res. 2015

Consensus Guidelines from ECOG 2016









## RT + VEGF INHIBITORS







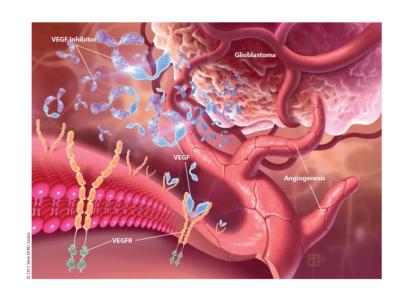


## **VEGF**

Involved in both vasculogenesis and angiogenesis Crucial for development and metastasis of tumors

# **VEGF-inhibitors**

Bevacizumab
Sorafenib
Sunitinib Pazopanib
Axitinib Everolimus



Polivka et al., 2017

Ostergaard and Tietze, 2013

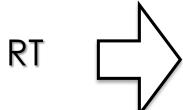




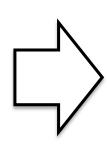


#### RT AND VEGF- INHIBITORS INTERACTION

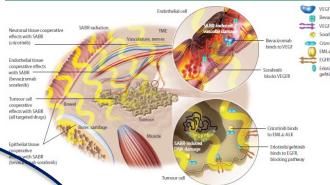
#### Preclinical studies



† ceramide signalling pathway in microvascular endothelial cells



Tumour radiation resistance through regulation of endothelial apoptosis



Anti-angiogenic drugs

Normalization of vascular tumor bed

Revers of hypoxia in tumor microenvironment

**Improve** tumour **oxygenation** status

Prevention of RT-induced re-vascularisation

Facilitation of RT-induced endothelial cells apoptosis

enhance

tumour response to RT

Zeng J, et al Lancet Oncol. 2014









#### RT AND VEGF- INHIBITORS INTERACTION

## Clinical studies

Only one randomized trial showed outcome advantages in HGG patients (PFS, not OS)

No clear indication to concurrent administration with RT

Author and year	Study type	N	Tumor site	RT technique/dose/ fractionation	Combination (concomit, other)	Primary Endpoint	Treatment outcome
Avallone (2015)	Phase II	46	LARC	3DCRT 45 Gy/25 fx	CT-RT (OXATOM-FUFA)+ BEV	TRG1	TRG1: 50% 5- yy PFS: 80% 5- yy OS: 85%
Willett (2009)	Phase I-II	32	LARC	3DCRT 50.4 Gy/28 fx	CT-RT (5-FU) + BEV	Safety/Efficacy	pCR: 16% 5-yy DFS: 75%
Cmne (2010)	Phase II	25	LARC	3DCRT 50.4 Gy/28 fx	CT-RT (CAP) + BEV	Safety/Efficacy	5-yy OS: 100% pCR: 32%, 2- yy DFS: 69% 2- yy OS 95%
Gasparini (2012)	Phase II	43	LARC	3DCRT 50.4 Gy/28 fx	CT-RT (CAP) + BEV	Safety/Efficacy	pCR: 14% 3- vv DFS: 75%
Spigel (2012)	Phase II	66	stage II/III rectal cancer	3DCRT 50.4 Gy/28 fx	CT-RT (5-FU) + BEV	DFS	2-yy (Preop) DFS: 979 2-yy (adjuv) DFS: 899
Salazar (2015)	Phase II R	90	LARC	3DCRT 45 Gy/25 fx	CT-RT (CAP) +/- BEV	pCR	pCR: 11% vs 16% (P = 0.54)
Kennecke (2012)	Phase II	42	high-risk rectal cancer	3DCRT 50.4 Gy/28 fx	CT-RT (CAPOX)+BEV	TRG1	TRG1: 18.4%
Dellas (2013)	Phase II	70	LARC	3DCRT 50.4 Gy/28 fx	CT-RT (CAPOX)+BEV	Safety/Efficacy	pCR: 17.4%
Landry (2013)	Phase II	57	LARC	3DCRT 50.4 Gy/28 fx	CT-RT (CAPOX)+BEV	Safety/Efficacy	pCR: 17%
Verstraete (2015)	Phase II R	82	LARC	3DCRT 45 Gy/25 fx	CT-RT (BEV + CAP)+/- OX	pCR	pCR: 8% vs 27% (P = 0.05)
Velenik (2011)	Phase II	61	LARC	3DCRT 50.4 Gy/28 fx	CT-RT (CAP) + BEV	pCR	pCR: 13%
Noguè (2011)	Phase II	47	LARC	3DCRT 50.4 Gy/28 fx	CT-RT (CAP) + BEV	pCR	pCR: 36%
Dipetrillo et al. (2012)	Phase II	26	LARC	3DCRT 50.4 Gy/28 fx	Induction FOLFOX + BEV →CT-RT (5-FU-OX) + BEV	pCR	pCR: 20% 3- yy OS: 95%
Vivaldi et al. (2016)	Phase II	48	LARC	3DCRT 50.4 Gy/28 fx	Induction FOLFOXIRI + BEV $\rightarrow$ CT-RT (CAP or 5-FU) + BEV	ORR	ORR: 89%









## RT + PARP INHIBITORS

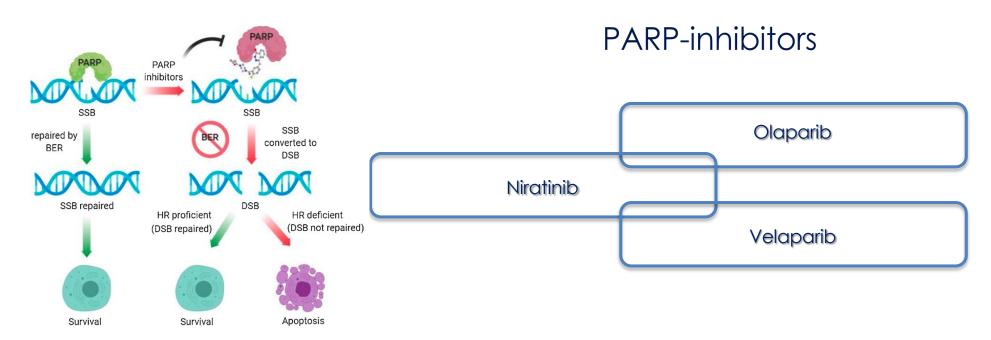




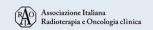


# POLY ADP-RIBOSE POLYMERASE (PARP)

PARP acts in repairing endogenous SSB occur frequently during cells proliferation



Zheng F. et al. Biomed Pharmacother. 2020, Chalmers A. et al. Int J Radiat Oncol Biol Phys. 2004









#### RT - PARP INHIBITORS INTERACTION

#### Preclinical studies

## Clinical studies

Clinical data are limited: further studies required to assess clinical advantages and safety of the combination. DSB

Activation and PARP-mediated
DNA damaged repair

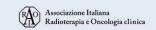
RADIORESISTANCE

PARP- inhibitors

Could enhanced radiosensitivity

Chalmers A. et al. Int J Radiat Oncol Biol Phys. 2004

Mao Y. Et al. Cancer Med. 2018









# CONCLUSIONS

> Potential advantages:

Attacking cancer cells by multiple mechanisms decrease risk of tumour resistance Allow for attacking not only known local disease but also potential micrometastases

> Timing:

different for each drugs and still not clearly defined

Prospective clinical trials, with longer-term results are needed to confirm efficacy, safety, and timing of association









# TAKE HOME MESSAGE

Precision drugs and RT combination promising challenge for the near future













