AIRB - Utilizzo e timing dei farmaci di precisione in corso di radioterapia

Razionale radiobiologico in termini di efficacia

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HUMANITAS
CANCER CENTER

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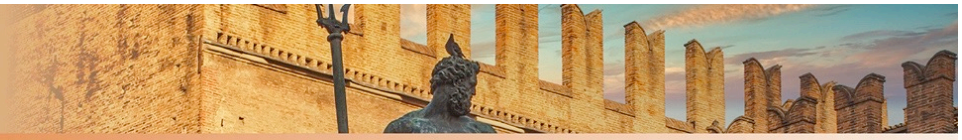
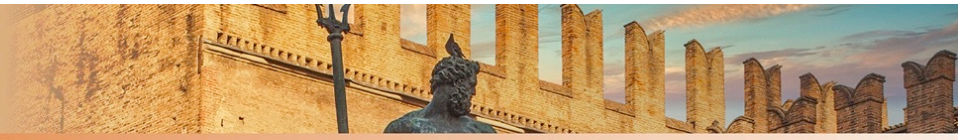
Società Italiana di Radiobiologia



No commercial disclosures

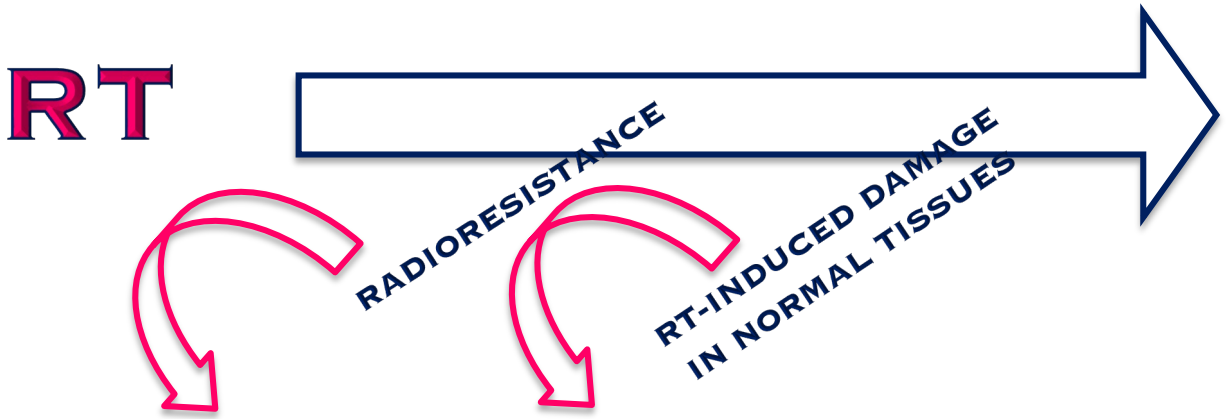


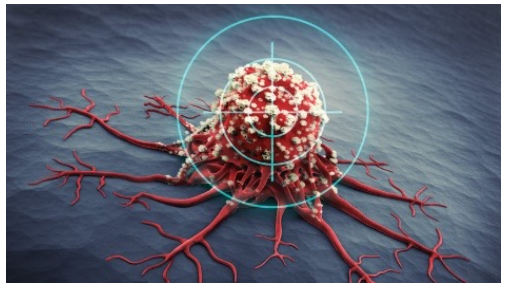
OUTLINE

- 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





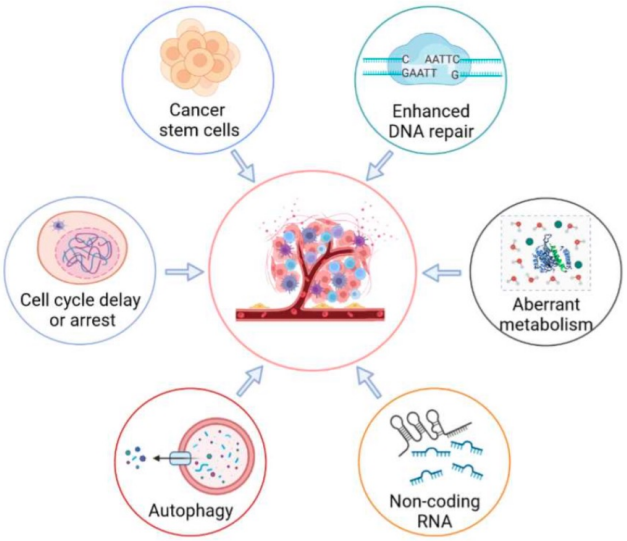
RT – Target agents combination

radiosensitizing drugs could improve RT therapeutic index

improving tumour control and decreasing side effects

Lu Z. et al.. Biomolecules. 2022

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



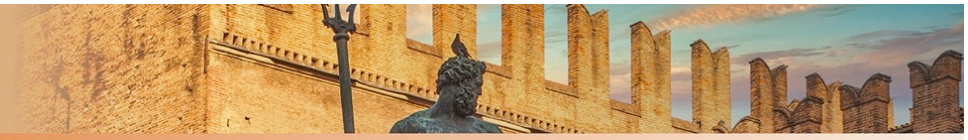
PROLIFERATION

TRASFORMATION
INVASION/MIGRATION

SURVIVAL

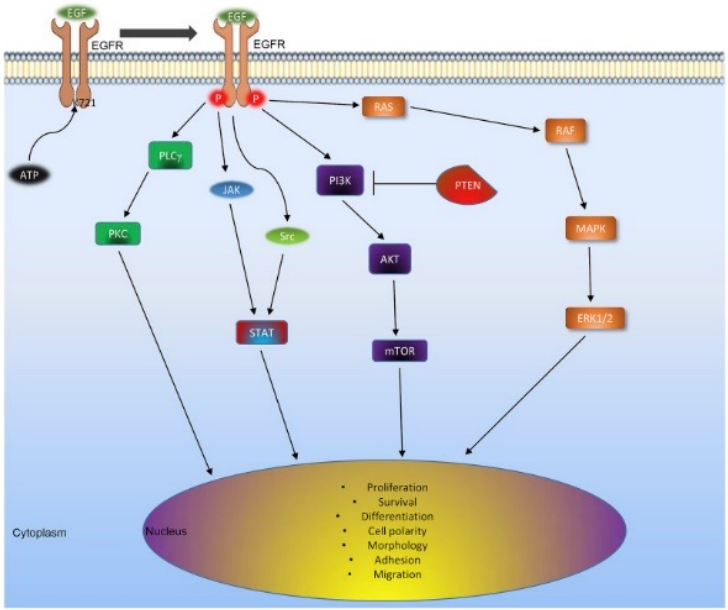
- VEGF-inhibitors
- HER2-inhibitors
- EGFR-inhibitors/TKI
- BRAF/MEK-inhibitors
- PARP-inhibitors
- CDK-inhibitors

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



RT + EGFR inhibitors/TKI

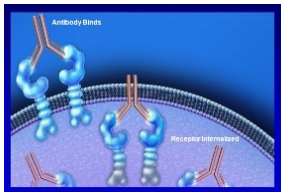
EGFR



EGFR-INHIBITORS/TKI

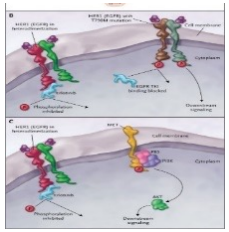
MONOCLONAL ANTIBODIES TARGETING EGFR

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 → activation of **RAS/RAF/MAPK pathway**

EGFR internalization and traslocation into the nucleus → 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

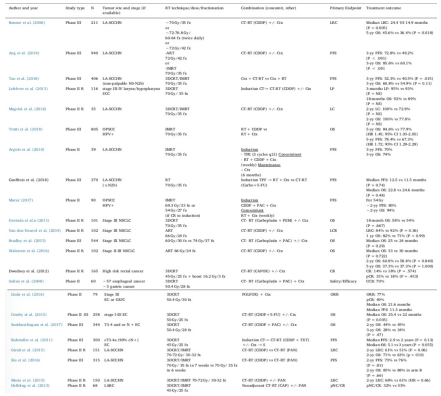
RT prior to tumor progression
may reduces systemic reseeding of resistant clones T790M cells:
potentially promising strategy to alleviate T790m-mediated EGFR-TKI resistance

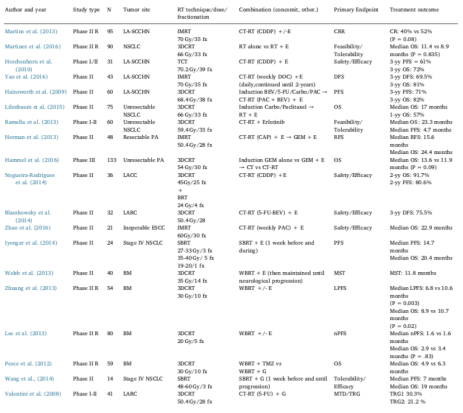
Ramalingam SS, et al. N Engl J Med. 2020 Mok T, et al. Ann Oncol. 2020 Tang Y. et al. Lung Cancer. 2020.

RT - EGFR INHIBITORS/TKI

Clinical studies

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





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

Still no data available on Osimertinib and RT: ongoing trials

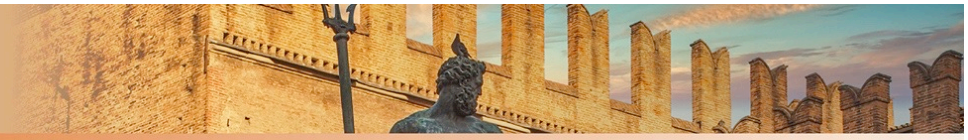
Arcangeli S. et al. *Crit Rev Oncol Hematol*. 2019 - Tao Y, et al *J Clin Oncol*. 2018 - Xing DT et al. Cancers (Basel). 2021

ClinicalTrials.gov

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

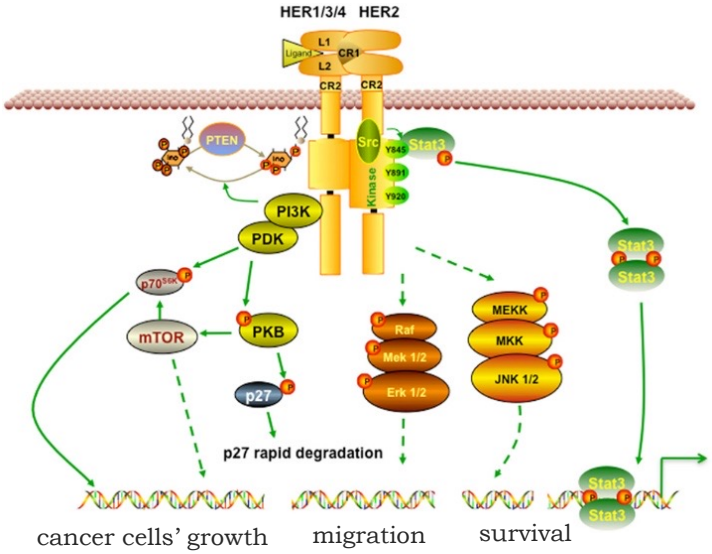
Radiation During Osimertinib Treatment: a Safety and Efficacy Cohort Study (NSCLC) (NCT05089916)

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)



RT + HER2 INHIBITOR

HER2



HER2-INHIBITORS

- Trastuzumab Petuzumab
- Lapatinib
- TDM1
- Tucatinib
- CDK 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**

Increased HER2 levels in cancer cells

Activation of **STAT3-survivin signaling**

activation of **PI3K/AKT** pathway

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

	n	Median follow up (months)	Early dermatitis (%)			Early esophagitis (%)			Late skin toxicity (%)		Late esophageal toxicity (%)		LVEF	Clinical congestive heart failure
Grade			1	2	3	1	2	3	<2	≥2	<2	≥2		
Retrospective studies														
Belkacémi et al. [42]	146	16	37[a]	35	6	64[a]	24	11	48[a]	51	88[a]	12	≥Grade 2 : 10%[a] RR[a]	–
Shaffer et al. [43]	44	15	–	–	–	–	–	–	–	–	–	–	Median decrease (MD): 4%	3 patients 4.5%
Meattini et al. [45]	95	52	20[a]	13.7	0	1.1[a]	0	0	22.1[a] F 18.9 Lym 1.1 T 4.2	0	0	0	MD to the last follow-up: 2%	1 patient (atrial fibrillation) 1.1%
Cao et al. [44]	64	6.7[a] 26[a]	–	–	–	–	–	–	–	–	–	–	MD to the last follow-up: 3% Grade 1[a]: 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%[a]	0.6%
Halyard et al. [49]	935	44	–	–	4.3	–	–	0	–	–	–	–	–	2.7%[a] 1.7 %[b]
Horton et al. [54]	12	38	–	–	16.7	–	–	–					1 patient	0

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

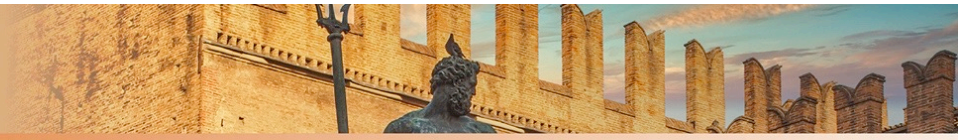
Target	Name	Number	Recruitment Status	Endpoint
Estrogen receptor (ER) Tamoxifen + locoregional RT	CONSET trial	NCT00896155	Unknown	Pulmonary fibrosis
Tumor growth Trastuzumab Emtansine (T-DM1) + brain RT	BIRTH trial	NCT02135159	Completed	Brain radionecrosis
Tumor angiogenesis Bevacizumab + brain RT	A-Plus	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

Beddok A. et al. Cancers 2021

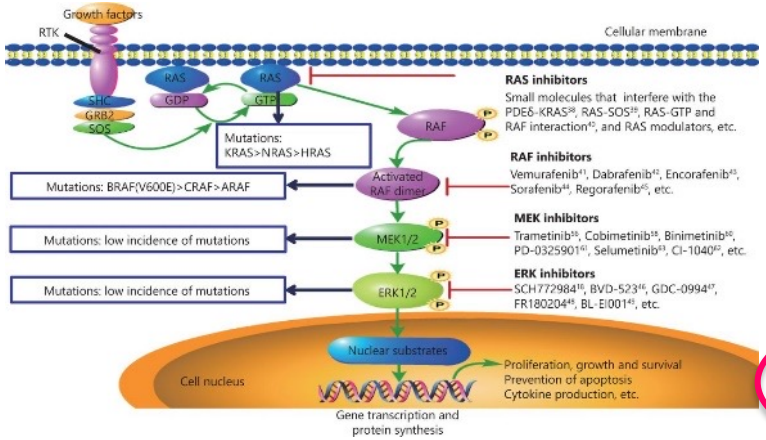


RT + BRAF/MEK INHIBITOR

BRAF

Part of the RAS-RAF-MEK-ERK pathway

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



Proliferation

Cellular growth

Survival

Radioresistence

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

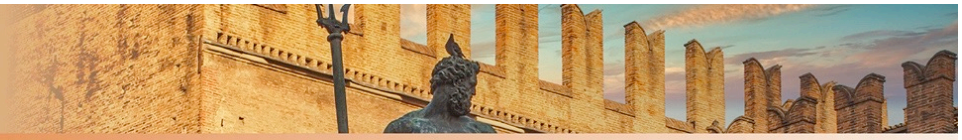
RT + BRAFi

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

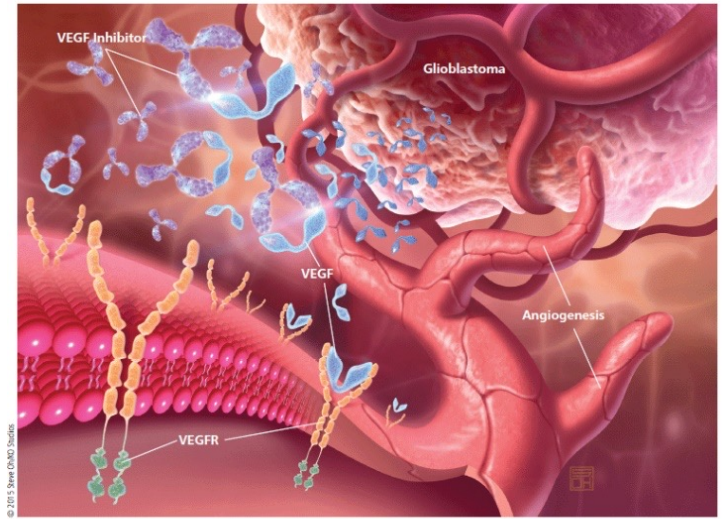
VEGF

Involved in both vasculogenesis and angiogenesis

Crucial for development and metastasis of tumors

VEGF-inhibitors

- Bevacizumab
- Sorafenib
- Sunitinib Pazopanib
- Axitinib Everolimus



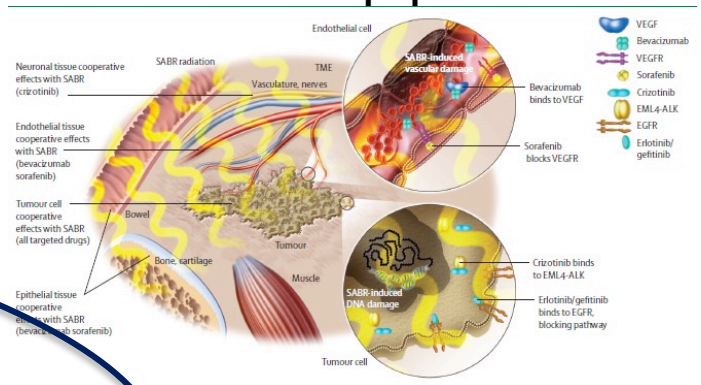
Polivka et al., 2017

Ostergaard and Tietze, 2013

RT AND VEGF- INHIBITORS INTERACTION

Preclinical studies

RT → ↑ **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

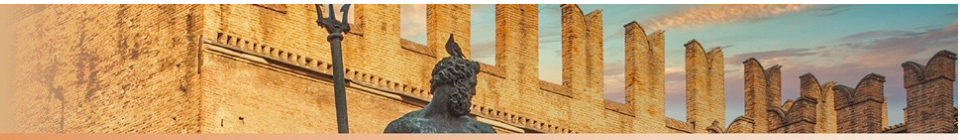
RT AND VEGF- INHIBITORS INTERACTION

Clinical studies

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

No clear indication
to concurrent administration with RT

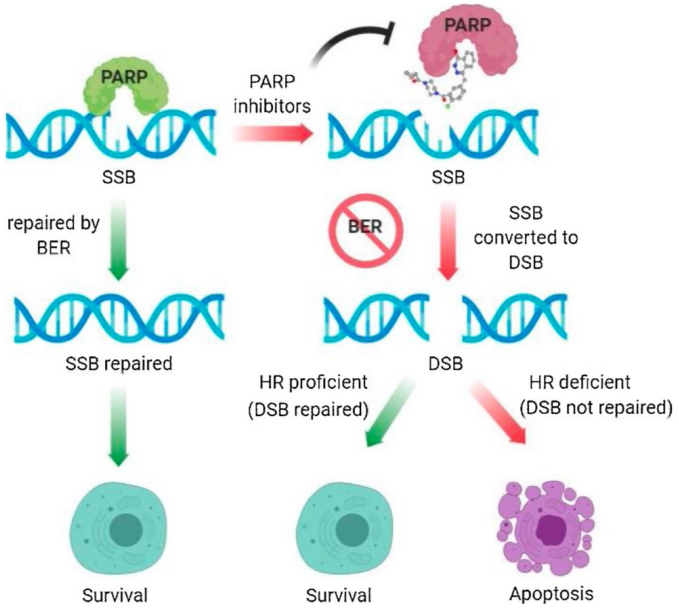
Author and year	Study type	N	Tumor site	RT technique/dose/ fractionation	Combination (concomit. other)	Primary Endpoint	Treatment outcome
Avallone (2015)	Phase II	46	LARC	3DCRT 45 Gy/25 fx	CT-RT (OXATOM-FUFA) + BEV	TRG1	TRG1: 50% 5- yy PFS: 80% 5- yy OS: 85%
Willett (2009)	Phase I-II	32	LARC	3DCRT 50.4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



RT + PARP INHIBITORS

Poly ADP-ribose polymerase (PARP)

PARP acts in repairing endogenous SSB occur frequently during cells proliferation



PARP-inhibitors

- Olaparib
- Niratinib
- Velaparib

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

RT – PARP INHIBITORS INTERACTION

Preclinical studies

Exposure of tumor cells to ionizing radiation

DSB

Activation and PARP-mediated
DNA damaged repair

RADIORESISTANCE

Clinical studies

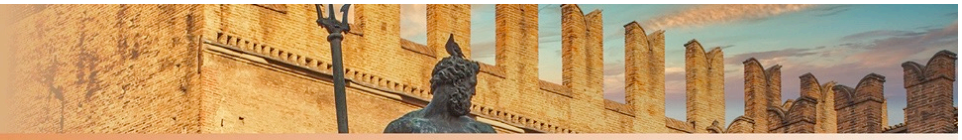
Clinical data are limited:
further studies required to assess clinical advantages and safety of the combination.

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

Grazie

Associazione Italiana
Radioterapia e Oncologia clinica

Società Italiana di Radiobiologia

BOLOGNA, 25-27 NOVEMBRE
PALAZZO DEI CONGRESSI