Associazione Italiana Radioterapia e Oncologia clinica

Società Italiana di Radiobiologia

Re-irradiazione: razionale clinico E biologico nell' integrazione con le terapie sistemiche

INTEGRAZIONE CON TARGETED THERAPY

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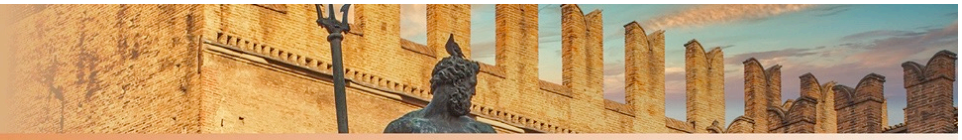
Società Italiana di Radiobiologia



DICHIARAZIONE

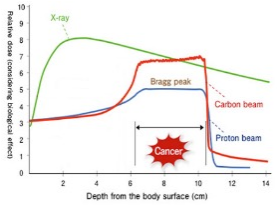
Relatore: ROSSANA INGARGIOLA

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario NIENTE DA DICHIARARE
- Consulenza ad aziende con interessi commerciali in campo sanitario NIENTE DA DICHIARARE
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario NIENTE DA DICHIARARE
- Partecipazione ad Advisory Board NIENTE DA DICHIARARE
- Titolarità di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario NIENTE DA DICHIARARE
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario NIENTE DA DICHIARARE
- Altro

REIRRADIATION

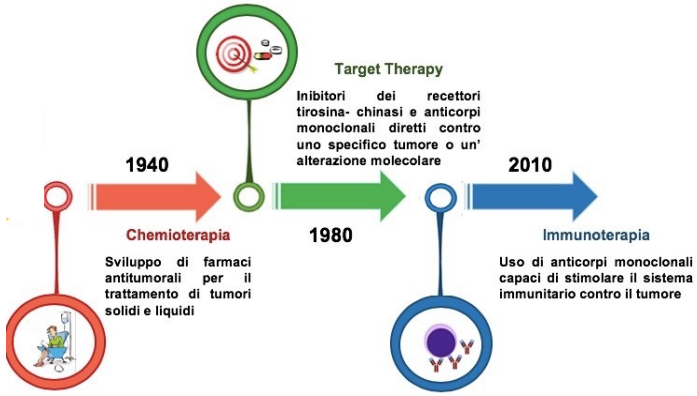
The improvement of modern radiotherapy (RT) tecquiniques:



IMRT **SRT** **PARTICLE THERAPY**

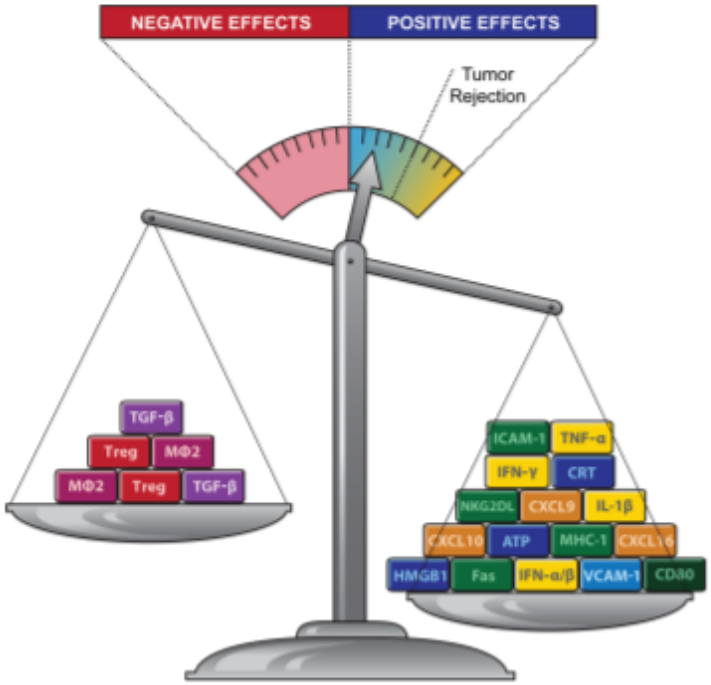
PRECISION CANCER MEDICINE

- Immunotherapy
- Target therapy



IMMUNOSUPPRESSIVE

IMMUNOSTIMULATORY



*"**positive effects of RT often predominate over negative** ones but are **insufficient** to shift the balance of the immunosuppressive tumor microenvironment to achieve tumor rejection **in the absence of targeted immunotherapy**"*

Formenti SC, Demaria S. J Natl Cancer Inst. 2013

RADIORESISTANCE

- **Intrinsic** resistance naturally present before the treatment has started
- **Acquired** resistance is induced by the irradiation, in which the tumor cells or tissues adapt and induce changes developing radiation resistance

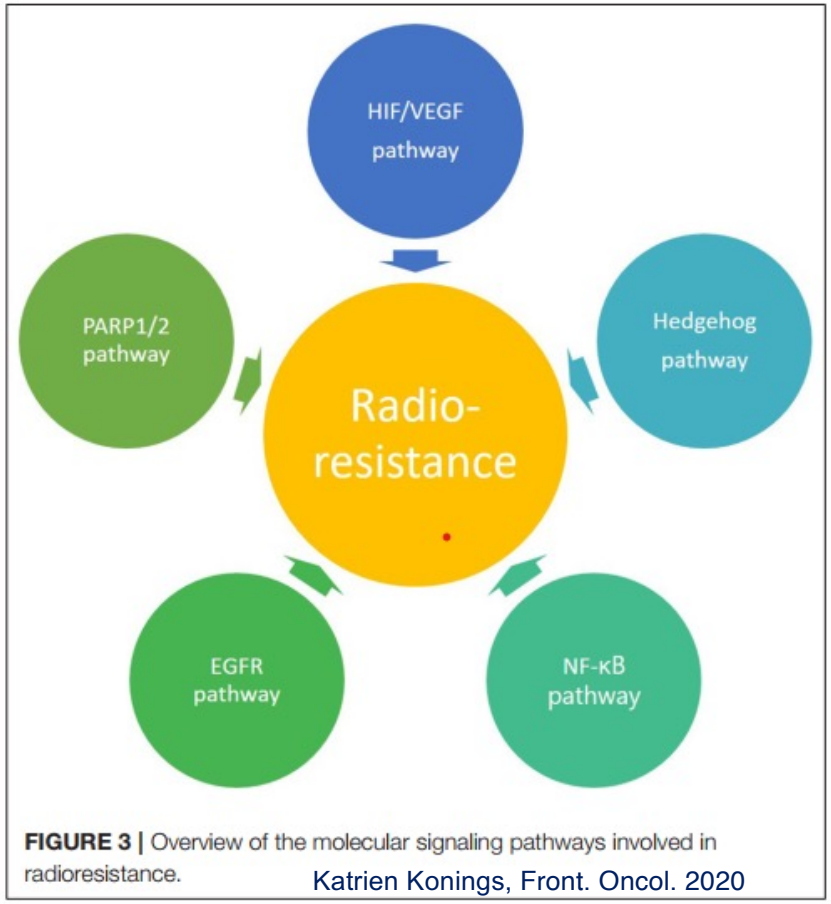


FIGURE 3 | Overview of the molecular signaling pathways involved in radioresistance.

Katrien Konings, Front. Oncol. 2020

Hypoxia, cancer stem cells, and specific signaling pathways of **EGFR**, NFκB, as well as DNA damage signalling involving **PARP**, are mechanisms of radioresistance for which pharmacological targets have been identified.

Cetuximab

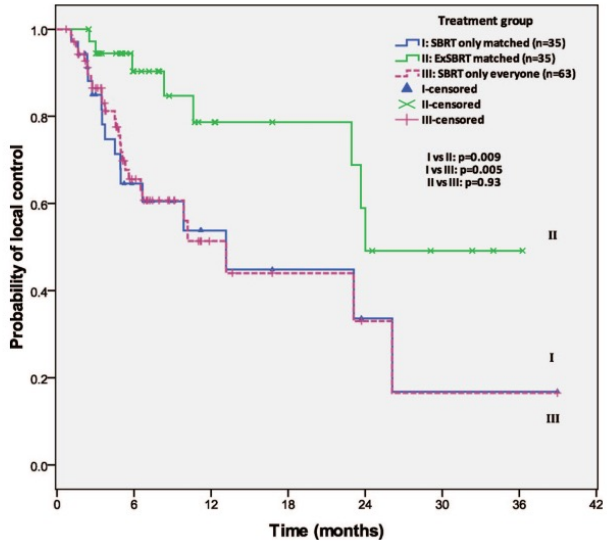
- 35 patients
- Cetuximab weekly + SRT 20-44 Gy
- Cetuximab conferred an OS advantage (24.5 vs. 14.8 months)
- **No increase in grade 3/4 toxicities**

ORIGINAL ARTICLE Am J Clin Oncol 2011

Concurrent Cetuximab With Stereotactic Body Radiotherapy for Recurrent Squamous Cell Carcinoma of the Head and Neck

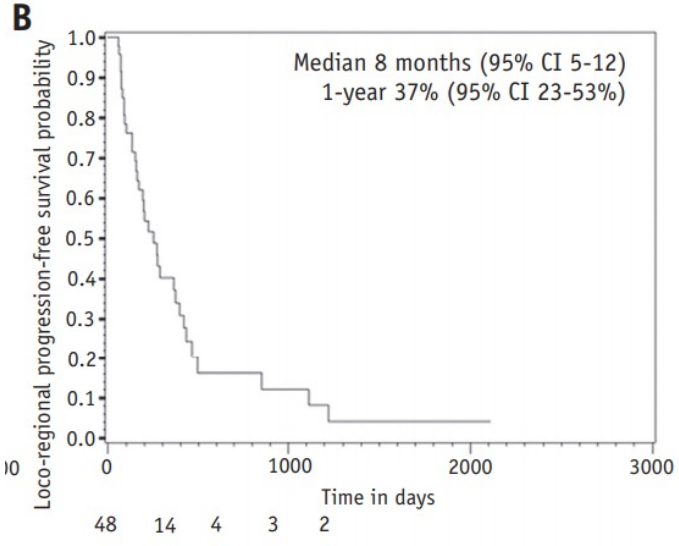
A Single Institution Matched Case–Control Study

Dwight E. Heron, MD, FACRO, Jean-Claude M. Rwigema, BS,* Michael K. Gibson, MD,†*
Steven A. Burton, MD, Annette E. Quinn, RN, MSN,* and Robert L. Ferris, MD, PhD‡*



A Prospective Phase 2 Trial of Reirradiation With Stereotactic Body Radiation Therapy Plus Cetuximab in Patients With Previously Irradiated Recurrent Squamous Cell Carcinoma of the Head and Neck

- 50 patients
- Cetuximab weekly (400 mg/m$_2$ on day 7 and then 250 mg/m$_2$) plus **SBRT** (40-44 Gy in 5 fractions on alternating days over 1-2 weeks)



1-year locoregional PFS was 37%

(95% CI: 23%-53%)

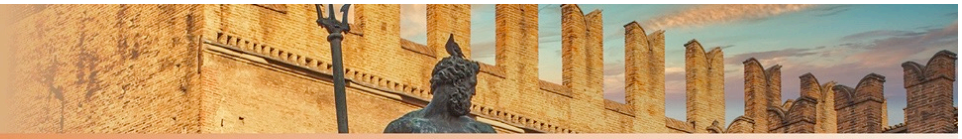


Table 2 Patients experiencing grade 3+ treatment-related toxicity

Toxicity description and grade	Time (mo)	Prior treatment	Reirradiation interval (mo)	Site of recurrence	Recurrence volume (cm^3)	Treatment platform
Acute grade 3 rash	<1	Concurrent cetuximab plus RT of 70 Gy	9	Base of tongue	33	Trilogy
Acute grade 3 mucositis requiring admission and G-tube placement	1-3*					
Acute and late grade 3 dysphagia requiring G-tube dependence	2-death	Concurrent Cisplatin/5FU and RT 64.8 Gy	12	Tonsil	45	TrueBeam
Acute grade 3 moist desquamation	<1	Total laryngectomy and adjuvant concurrent cetuximab plus RT of 59.4 Gy	264	Stoma and submental	45	TrueBeam
Late grade 3 esophageal stricture to tracheoesophageal fistula	6-death					
Late grade 3 leakage extending into neopharynx requiring feeding tube	3.5-death	Definitive RT at 66 Gy Salvage laryngectomy	35	Base of Tongue	135	TrueBeam

Abbreviations: G-tube = gastrostomy tube; RT = radiation therapy.
* The patient died at 3 months with a feeding tube.

Toxicity

Acute and late grade 3 toxicity was observed

in 6% of patients respectively.

- Acceptable tumor control and survival results compared to historic results for conventional reirradiation plus chemotherapy and chemotherapy alone with or without cetuximab,
- Low rates of acute toxicity
- Potentially improved patient compliance due the short overall treatment time

Bevacizumab

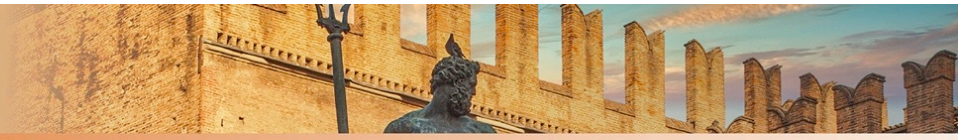
Acta Neurochirurgica (2021)

Radiotherapy versus combination radiotherapy-bevacizumab for the treatment of recurrent high-grade glioma: a systematic review

Daniel P. Kulinich [1,2] · John P. Sheppard [1,2] · Thien Nguyen [1,2] · Aditya M. Kondajji [1,2] · Ansley Unterberger [1,2] · Courtney Duong [1,2] · Adam Enomoto [1,2] · Kunal Patel [1,2] · Isaac Yang [1,2,3,4,5,6,7]

- 1399 patients
- 954 patients receiving reRT alone/ 445 patients receiving reRT + BVZ
- BVZ therapy improved OS (2.51, 95% CI [0.11, 4.92] months, P = .041) but no significant improvement in PFS (1.40, 95% CI [- 0.36, 3.18] months, P = .099).
- Patients receiving BVZ also had significantly lower rates of RN (2.2% vs 6.5%, P < .001).

Data on the combination of bevacizumab and SRT at extra-cranial locations is scarce but indicates that the use of concurrent abdominal SRT and bevacizumab should be practised with caution



Tki inhibitors

Multi receptor tyrosine kinase inhibitors (sorafenib, sunitinib)

Published in final edited form as:
Target Oncol. 2014 June ; 9(2): 145–153. doi:10.1007/s11523-013-0280-y.

Concurrent sunitinib and stereotactic body radiotherapy for patients with oligometastases

cancers

MDPI

Article

Is the Concurrent Use of Sorafenib and External Radiotherapy Feasible for Advanced Hepatocellular Carcinoma? A Meta-Analysis

Chai Hong Rim [1,*,†], Sunmin Park [1,†], In-Soo Shin [2] and Won Sup Yoon [1]

EGF-R-inhibitors (gefitinib, erlotinib, lapatinib)

ORIGINAL ARTICLE

Gefitinib Combined With Stereotactic Radiosurgery in Previously Treated Patients With Advanced Non–Small Cell Lung Cancer

Zhen Wang, MSc, Xi-Xu Zhu, MD,* Xin-Hu Wu, MSc,* Bing Li, PhD,* Tian-Ze Shen, MSc,* Qing-Tao Kong, MSc,† Jing Li, MSc,* Zhi-Bing Liu, MSc,* Wan-Rong Jiang, MSc,* Yang Wang, BSc,* and Bo Hou, BSc**

ALK-Inhibitors (crizotinib, ceritinib, alectinib)

Clinical Investigation: Thoracic Cancer

Stereotactic Radiation Therapy can Safely and Durably Control Sites of Extra-Central Nervous System Oligoprogressive Disease in Anaplastic Lymphoma Kinase-Positive Lung Cancer Patients Receiving Crizotinib

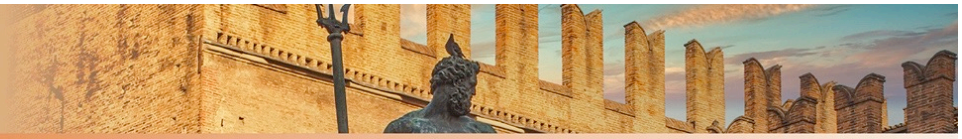
Gregory N. Gan, MD, PhD,* Andrew J. Weickhardt, MBBS, DMedSc,† Benjamin Scheier, MD,† Robert C. Doebele, MD, PhD,† Laurie E. Gaspar, MD, MBA,* Brian D. Kavanagh, MD, MPH,* and D. Ross Camidge, MD, PhD†

Neuro-Oncology

Neuro-Oncology 17(2), 296–302, 2015
doi:10.1093/neuonc/nou146
Advance Access date 22 July 2014

Significance of targeted therapy and genetic alterations in *EGFR*, *ALK*, or *KRAS* on survival in patients with non–small cell lung cancer treated with radiotherapy for brain metastases

Kimberley S. Mak, Justin F. Gainor, Andrzej Niemierko, Kevin S. Oh, Henning Willers, Noah C. Choi, Jay S. Loeffler, Lecia V. Sequist, Alice T. Shaw, and Helen A. Shih



Systematic or Meta-analysis Studies

Cancer Treatment Reviews 53 (2017)

Toxicity of concurrent stereotactic radiotherapy and targeted therapy or immunotherapy: A systematic review

Stephanie G.C. Kroeze [a,*], Corinna Fritz [a], Morten Hoyer [b], Simon S. Lo [c], Umberto Ricardi [d], Arjun Sahgal [e], Rolf Stahel [f], Roger Stupp [f], Matthias Guckenberger [a]

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[d] Department of Oncology, University of Turin, Regione Gonzole 10, 10043 Orbassano, Italy
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[f] Department of Oncology, University Hospital Zurich, Rämistrasse 100, 8091 Zurich, Switzerland

Cetuximab not add toxicity

Cranial SRT combined with **Sorafenib of Sunitinib** appears to be safe but one grade 5 toxicity has been observed for sunitinib.

Concurrent treatment is mostly well tolerated in cranial SRT, the relatively scarce literature on extracranial SRT shows a potential risk of increased toxicity when SRT is combined with **EGFR-targeting tyrosine kinase inhibitors and bevacizumab.**

High rates of severe toxicity were observed for the combination with BRAF-inhibitors.

BRAF/MEK inhibitors

Increased dermatologic, pulmonary, neurologic, hepatic, esophageal, and bowel toxicity from the combination.

BRAFi and MEKi recommendations:

- Hold 3 days before and after fractionated RT.
- Hold 1 day before and after SRS.

RT recommendations:

- Consider dose per fraction <4 Gy unless using a stereotactic approach or the patient has very poor prognosis/performance status.

CME ASTRO

International Journal of Radiation Oncology biology • physics
www.redjournal.org

Critical Review

Avoiding Severe Toxicity From Combined BRAF Inhibitor and Radiation Treatment: Consensus Guidelines from the Eastern Cooperative Oncology Group (ECOG)

Christopher J. Anker, MD,* Kenneth F. Grossmann, MD, PhD,† Michael B. Atkins, MD,‡ Gita Suneja, MD,§ Ahmad A. Tarhini, MD, PhD,‖ and John M. Kirkwood, MD‖

cancers 2021 MDPI

Article

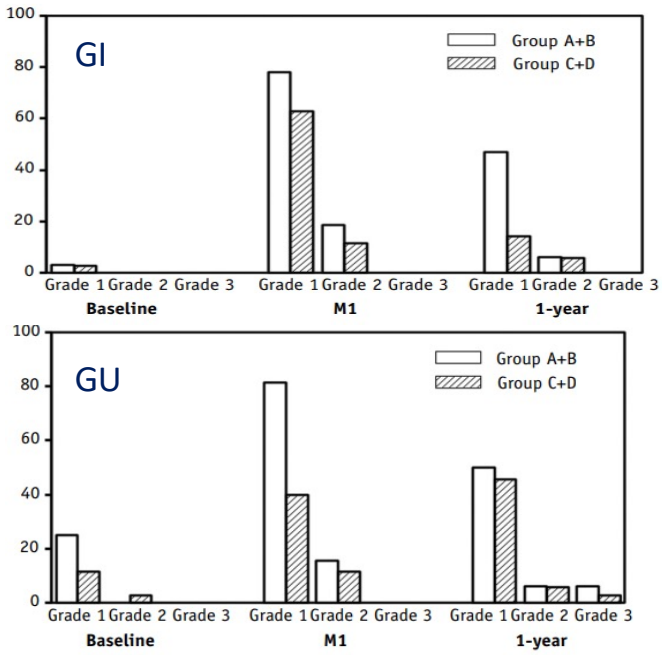
Continued versus Interrupted Targeted Therapy during Metastasis-Directed Stereotactic Radiotherapy: A Retrospective Multi-Center Safety and Efficacy Analysis

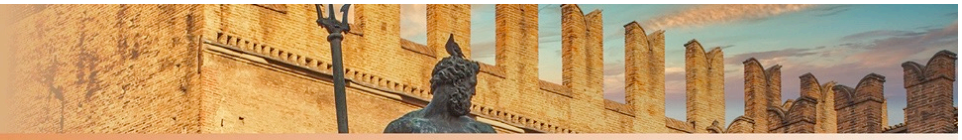
Stephanie G. C. Kroeze [1,*], Corinna Fritz [1], Jana Schaule [1], Oliver Blanck [2], Klaus Henning Kahl [3], David Kaul [4], Shankar Siva [5], Sabine Gerum [6], An Claes [7], Nora Sundahl [8], Sonja Adebahr [9,10], Susanne Stera [11], Markus M. Schymalla [12], Nasrin Abbasi-Senger [13], Daniel Buergy [14], Michael Geier [15], Marcella Szuecs [16], Fabian Lohaus [17], Guido Henke [18], Stephanie E. Combs [19] and Matthias Guckenberger [1]

Hormone Therapy

Early Toxicity of a Phase 2 Trial of Combined Salvage Radiation Therapy and Hormone Therapy in Oligometastatic Pelvic Node Relapses of Prostate Cancer (OLIGOPELVIS GETUG P07)

- 67 patients
- 54 Gy in 1.8 Gy fractions - 66 Gy in 2.2 Gy
- G2 GU acute toxicity occurred in 9/67 patients (13.4%)
  G2 GU late toxicity occurred in 4/67 patients (6%)
- G2 GI acute toxicity occurred in 10/67 patients (14.9%)
  G2 GI late toxicity occurred in 4/67 patients (6%)
- Half patients had received prior prostatic irradiation, they did not exhibit increased urinary or digestive toxicity





Clinical & Experimental Metastasis (2021) 38:227–230
https://doi.org/10.1007/s10585-021-10072-4

COMMENTARY

Check for updates

Integrating stereotactic body radiation therapy (SBRT) and systemic treatments in oligoprogressive prostate cancer: new evidence from the literature

Giulio Francolini[1] · Mauro Loi[1] · Beatrice Detti[1] · Isacco Desideri[2] · Monica Mangoni[1,2] · Gabriele Simontacchi[1] · Icro Meattini[1,2] · Lorenzo Livi[1,2]

La radiologia medica (2022) 127:912–918
https://doi.org/10.1007/s11547-022-01511-7

RADIOTHERAPY

Check for updates

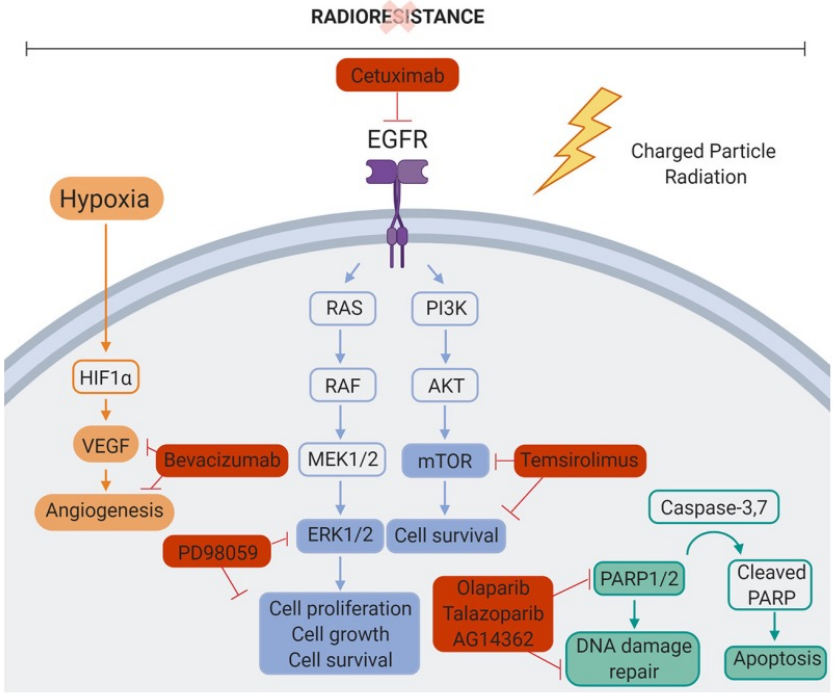
Study protocol and preliminary results from a mono-centric cohort within a trial testing stereotactic body radiotherapy and abiraterone (ARTO-NCT03449719)

Giulio Francolini[1] · Beatrice Detti[1] · Vanessa Di Cataldo[1] · Pietro Garlatti[1] · Michele Aquilano[3] · Andrea Allegra[3] · Sara Lucidi[3] · Cecilia Cerbai[3] · Lucia Pia Ciccone[3] · Viola Salvestrini[3] · Giulia Stocchi[3] · Barbara Guerrieri[3] · Luca Visani[2] · Mauro Loi[1] · Isacco Desideri[3] · Monica Mangoni[3] · Icro Meattini[3] · Lorenzo Livi[3]

SBRT + Abiraterone treatment was safe and well tolerated.

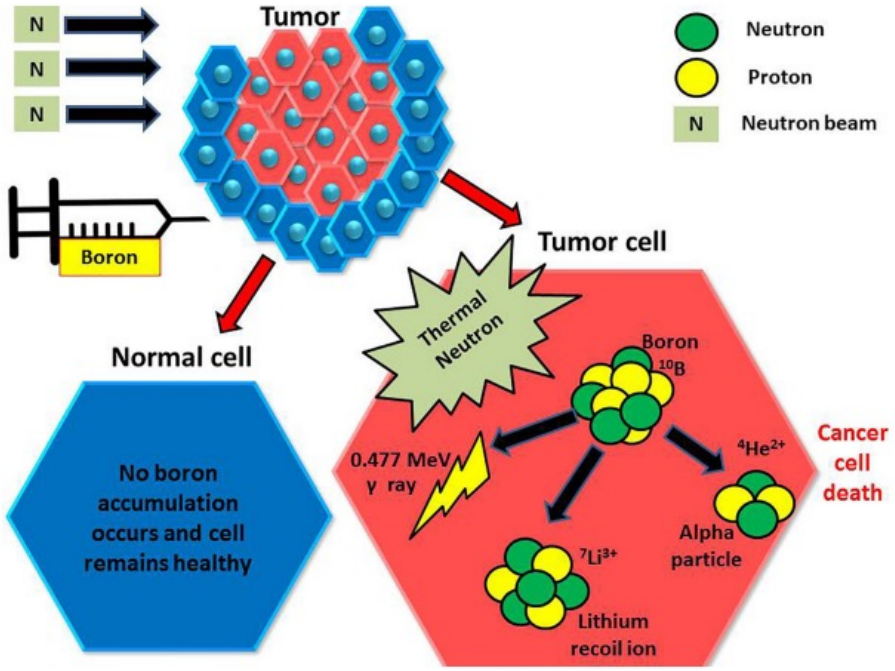
PARTICLE THERAPY

- **Charged particle** modulate the activity of some of molecular pathways than photons
- **Carbon ion** irradiation is able to reduce hypoxia-induced radioresistance. High LET radiation can eradicate hypoxic tumor cells more effectively than low-LET radiation. This is also reflected in the oxygen enhancement ratio (OER).
- A handful *of in vitro* studies have shown that particle radiation (protons or carbon ions) is more effective against CSCs than photon radiation.



BNCT Boron neutron capture therapy

- BncT is a biologically **targeted type**
- It theoretically should be **selectively destroy tumor cells** dispersed in normal tissue
- BNCT has been studied in malignant brain tumors, **recurrent tumors of the head and neck region**, and cutaneous melanomas.
- The most efficacious boronated compound remains unclear. Nowadays two agents are used: **sodium borocaptate (BSH) and boronophenylalanine (BPA)**



Malouff et al, Front.Onc 2021

TAKE HOME MESSAGES

- The identification of **specific genetic, biological disease features** and molecular pathways involved in radioresistance mechanism might help to facilitate the development of **personalised radiotherapy prescriptions.**
- Literature date are still **lacking to guide the clinical practice** in order to define **the best combination strategy** and future studies are needed.
- Whenever possible, we encourage **enrollment in clinical trials**
- Considering the potential superior role of **particle therapy** in treating radioresistant cancers, clinical studies about the combination of targetable pathways and particle radiation are necessary.

Radiation oncologist, medical oncologist and surgeon have to work together to identify the better terapeutical strategy

Grazie per l'attenzione