

XXXII CONGRESSO NAZIONALE AIRO  
XXXIII CONGRESSO NAZIONALE AIRB  
XII CONGRESSO NAZIONALE AIRO GIOVANI

# AIRO2022

Radioterapia di precisione per un'oncologia innovativa e sostenibile

BOLOGNA, 25-27 NOVEMBRE  
PALAZZO DEI CONGRESSI

 Associazione Italiana  
Radioterapia e Oncologia clinica

 Società Italiana di Radiobiologia

 Associazione  
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## ***PARP INHIBITORS NEL TUMORE OVARICO IN ASSOCIAZIONE ALLA RADIOTERAPIA STEREOTASSICA***

Maura Campitelli

Policlinico A. Gemelli, Roma

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**Gemelli**  **ART**  
Fondazione Policlinico Universitario Agostino Gemelli IRCCS  
Università Cattolica del Sacro Cuore  
Advanced Radiation  
Therapy

 Associazione Italiana  
Radioterapia e Oncologia clinica

 Società Italiana di Radiobiologia

 Associazione  
Italiana di  
Radioterapia  
e Oncologia  
clinica



## DICHIARAZIONE

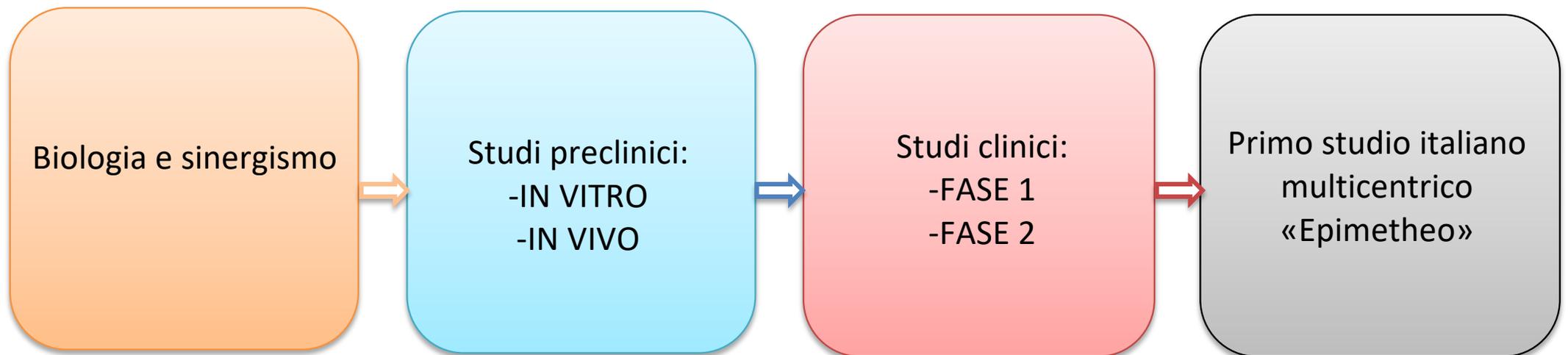
Relatore: MAURA CAMPITELLI

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 **(ASTRA ZENECA)**
- 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)**

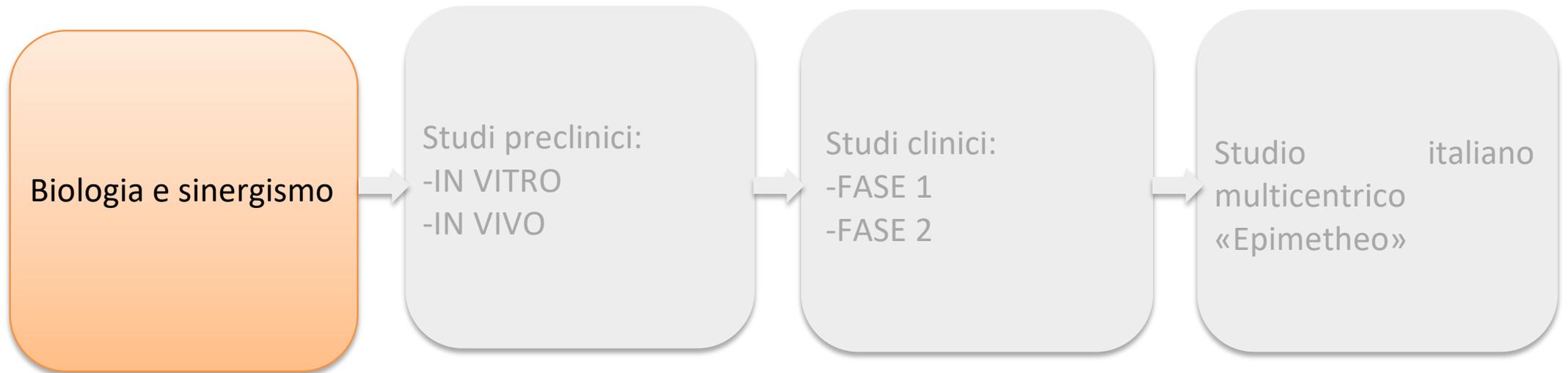


## ASSOCIAZIONE PARPi + SBRT





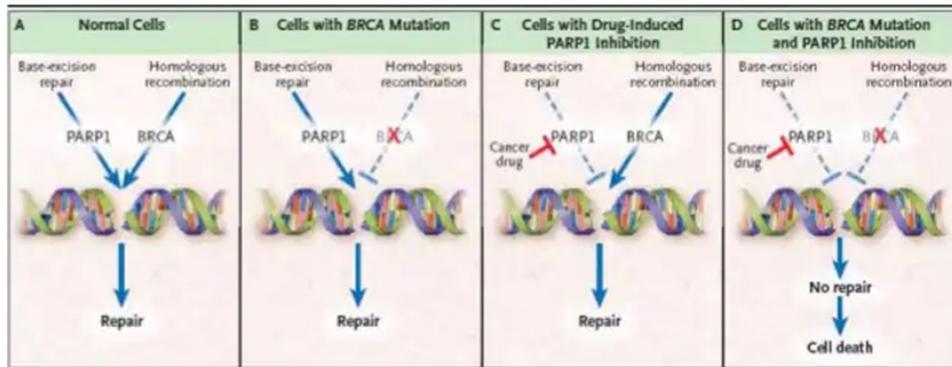
## ASSOCIAZIONE PARPi + SBRT





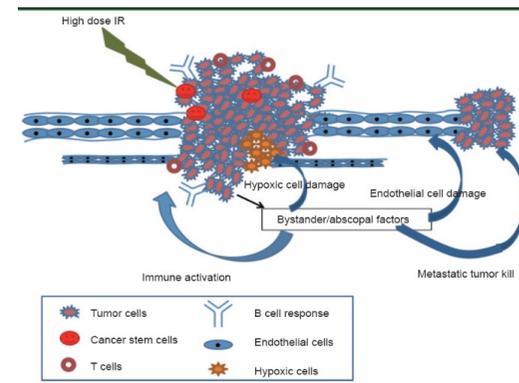
## MECCANISMI D'AZIONE

### PARPi



«Synthetic lethality»

### RT stereotassica



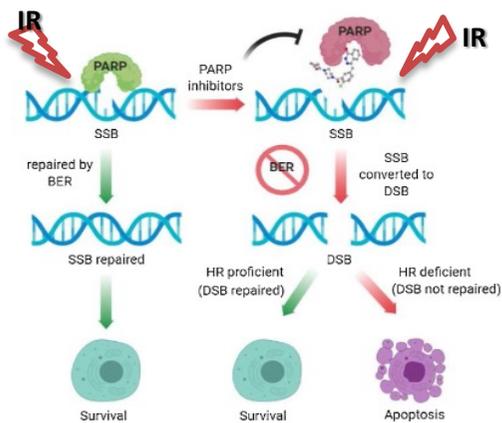
- relazione non lineare tra dose ed effetto citotossico
- Una o poche frazioni a dosi elevate hanno > effetto cell-killing della stessa dose data con frazionamenti convenzionali

## INTERAZIONE COMPLESSA

Igelhart JD and Silver DP, NEJM 2009

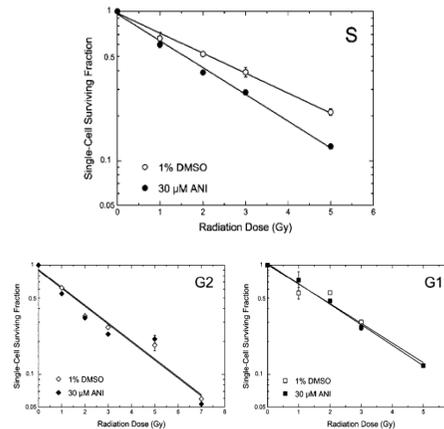
## MECCANISMI D'INTERAZIONE

### MOLECOLARE



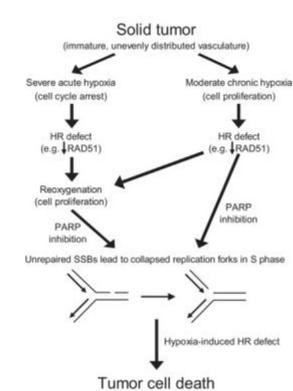
- Impedisce riparazione SSB
- Promuove la conversione SSB → DSB

### CELLULARE



radiosensibilizza la fase S del ciclo cellulare

### TISSUTALE

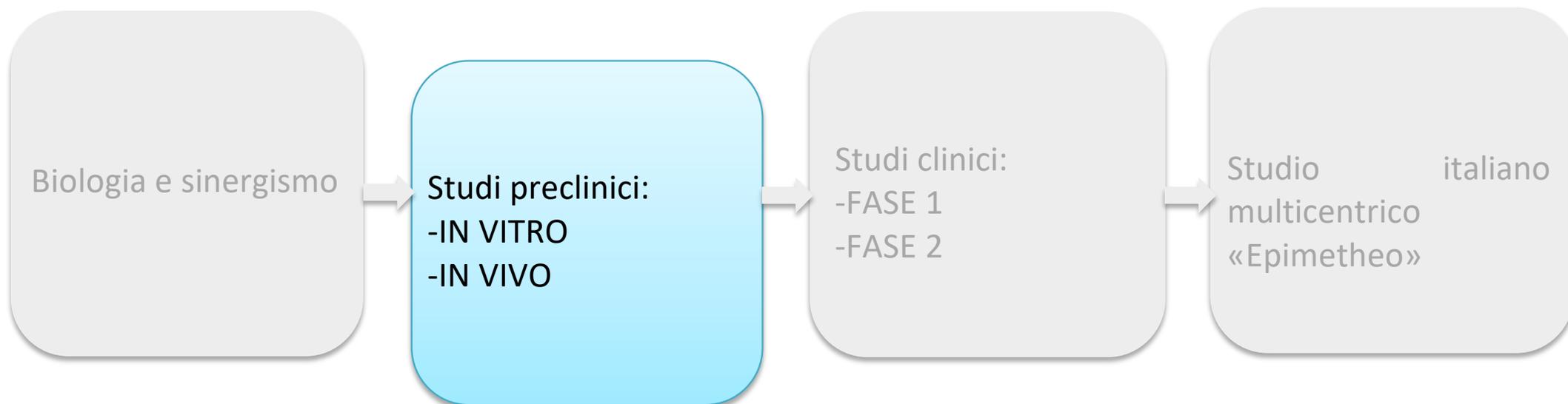


- Effetto sul microambiente tumorale
- superamento della resistenza all'ipossia tumorale

(zone ipossiche → deficit di HR (down-regulation di Rad51) → > sensibilità ai PARPi  
*contextual synthetic lethality*)



## ASSOCIAZIONE PARPi + RT





## STUDI DI CLONOGENICITA'

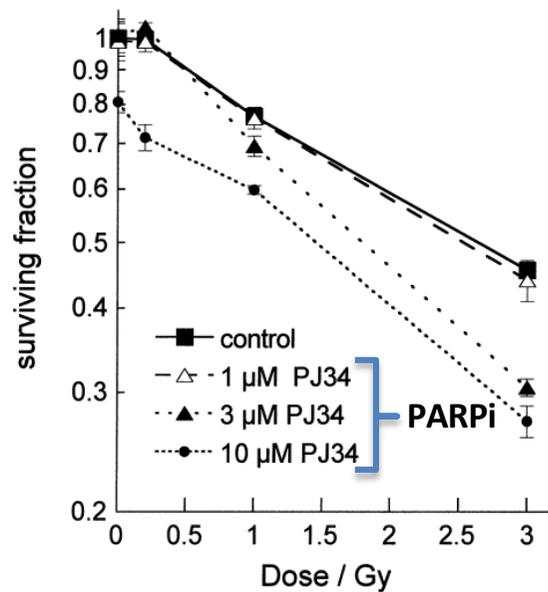
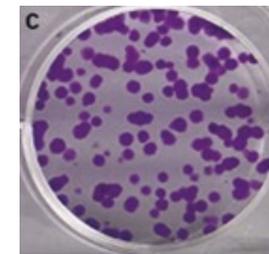
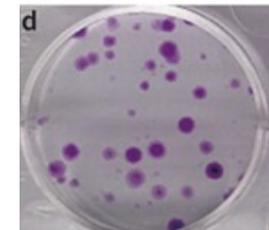
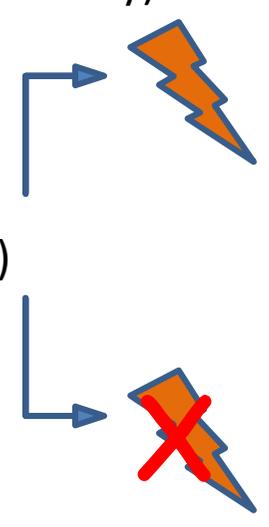


Fig. 2. Clonogenic survival of exponentially growing U373-MG glioma cells irradiated at 0.3, 1, and 3 Gy in the presence of three different concentrations of PARP inhibitor PJ34. Mean values  $\pm$  SEM of three measurements shown.

(0,05-2 Gy)

PARPi (1-10 $\mu$ M)

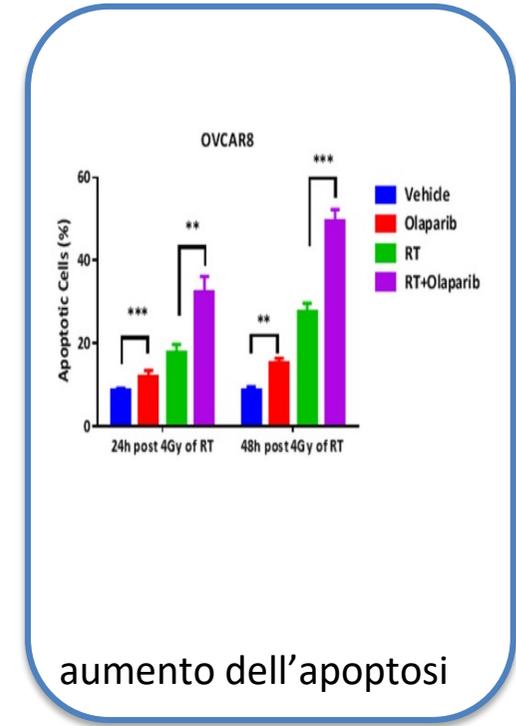
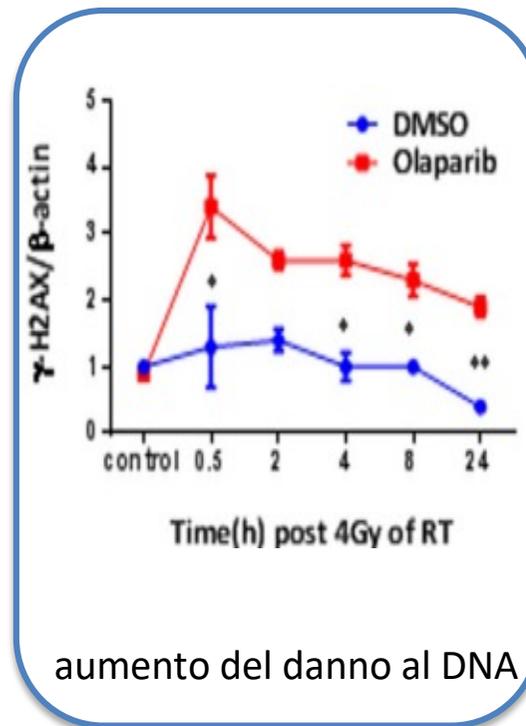
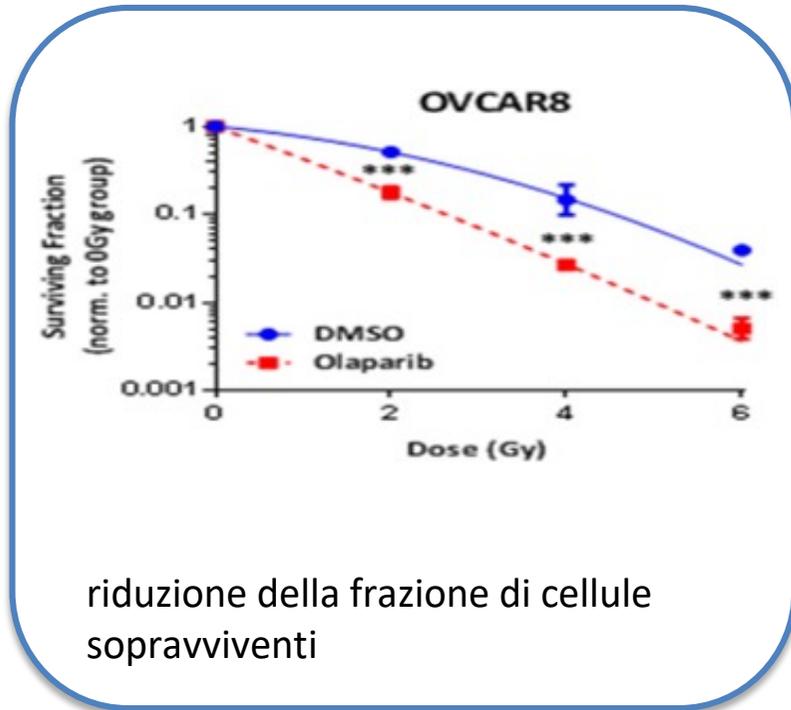


Chalmers A et al. *IJROBP*, 2004

Barreto-Andrade JC et al. *Mol Cancer Ther*, 2011

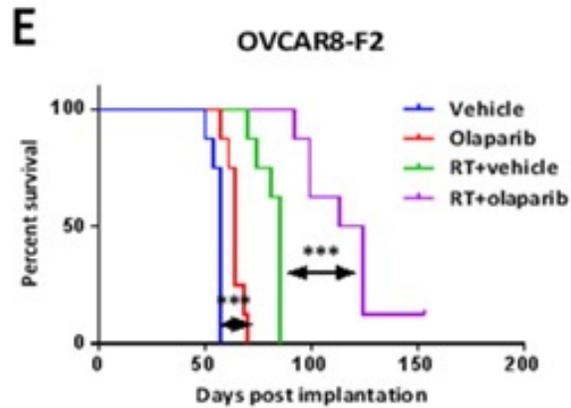
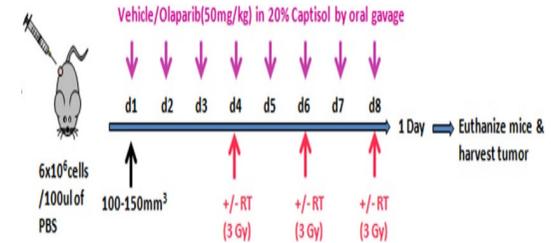


## Radiosensibilizzazione indotta dai PARPi

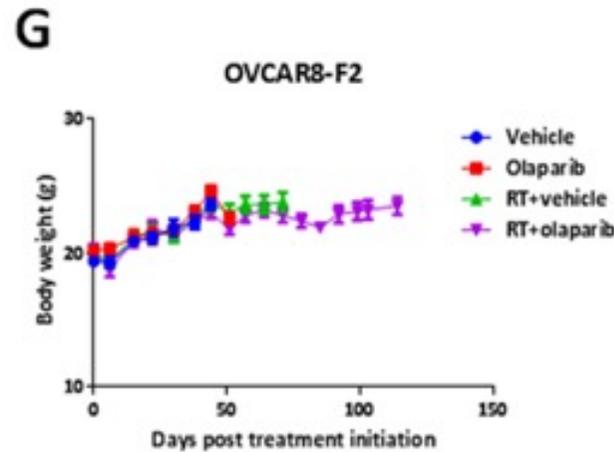




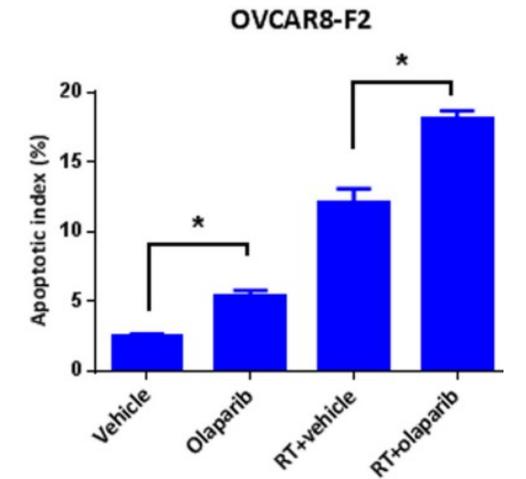
## ASSOCIAZIONE PARPi + RT in vivo



Ritarda crescita tumorale



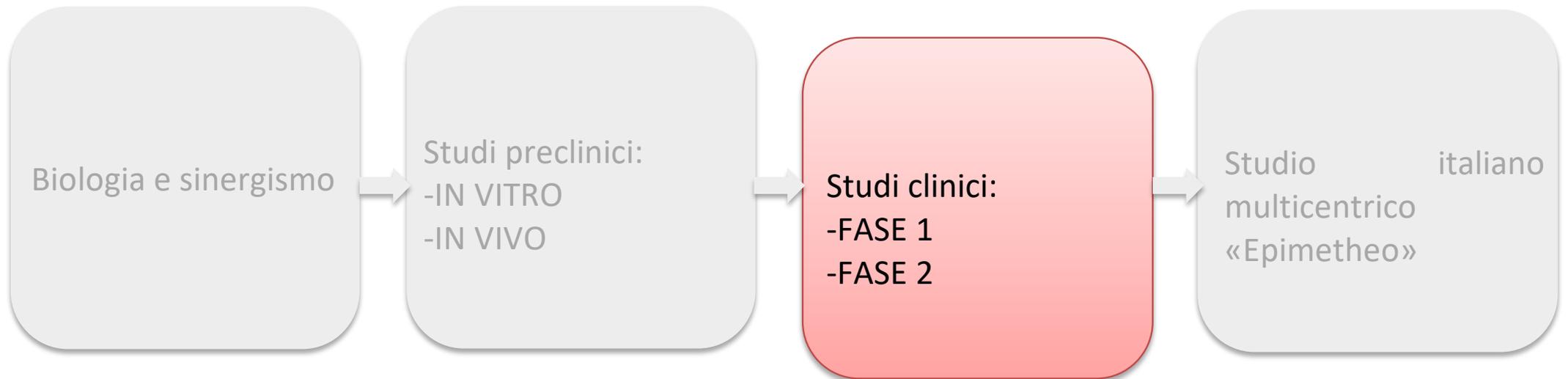
Non tossica



Aumenta indice apoptotico



## ASSOCIAZIONE PARPi + RT



## ASSOCIAZIONE PARPi + RT

Table 1 Current Clinical Trials Evaluating PARPi-Radiotherapy Combinations

PARPi	Cancer Site	Trial Title	Sponsor and Trial ID	Phase and Status
Olaparib AZD-2281	HNSCC	Phase I Trial of Olaparib (AZD2281) in Combination With C25 and Radiation Therapy in Patients With Locally Advanced, Stage IVA-B Squamous Cell Carcinomas of the Head/Neck With Heavy Smoking Histories	University of Colorado, Denver NCT01758731	Phase I Reported
		Olaparib Dose Escalation Trial in Patients Treated With Radiotherapy for Stage II-III Laryngeal and Stage II-III HPV-negative Oropharyngeal Squamous Cell Carcinoma	The Netherlands Cancer Institute NCT02229656	Phase I Active, not recruiting
		A Phase I Trial of Olaparib in Addition to Cisplatin-based Concurrent Chemoradiotherapy for Patients With High Risk Locally Advanced Squamous Cell Carcinoma of the Head and Neck (HNSCC)	University College, London NCT02308072	Phase I Active, not recruiting
	NSCLC	Olaparib Dose Escalating Trial in Patients Treated With Radiotherapy With or Without Daily Dose Cisplatin for Locally Advanced Non-small Cell Lung Carcinoma	The Netherlands Cancer Institute NCT01562210	Phase I Reported
		ES-SCLC	A Phase I Study of Olaparib and Low Dose Thoracic Radiotherapy for Extensive Stage Small Cell Lung Cancer	Memorial Sloan Kettering Cancer Centre NCT03532880
	Oesophagus		Radiotherapy & Olaparib in COmbination for Carcinoma of the Oesophagus. A Phase I Trial (ROCOCO)	The Christie NHS Foundation NCT03532880
	Pancreas	A Phase I study of olaparib in combination with radiotherapy for pancreatic cancer (PIONEER)		
	Breast	A Phase II Randomized Trial of Olaparib vs Radiotherapy Alone for Locally Advanced Breast Cancer		
			Olaparib Dose Escalation in Combination With Radiotherapy for Regional Lymph Nodes in Patients With Breast Cancer	
	GBM	GBM	A Phase I of Olaparib With Radiation Therapy in Patients With Inflammatory, Loco-regionally Advanced or Metastatic TNBC (Triple Negative Breast Cancer) or Patient With Operated TNBC With Residual Disease	Institut Curie NCT03109080
Short-course radiotherapy plus olaparib for newly diagnosed glioblastoma in patients unsuitable for radical chemoradiation: a randomized phase II clinical trial preceded by a lead-in phase I dose escalation study (PARADIGM)			NHS Greater Glasgow and Clyde ISRCTN52658296	Phase I/II Recruiting
Soft tissue sarcoma	NSCLC	OlaPARib and RADiotherapy or olaparib and radiotherapy plus temozolomide in newly-diagnosed Glioblastoma stratified by MGMT status: 2 parallel phase I studies (PARADIGM-2)	NHS Greater Glasgow and Clyde ISRCTN51253312	Phase I Recruiting
		Phase I/II Study of Concomitant Radiotherapy With Olaparib and Temozolomide in Unresectable High Grade Gliomas Patients (OLA-TMZ-RT-01)	Centre Francois Baclesse NCT03212742	Phase I/II Recruiting
Velparib ABT-888	NSCLC	A Phase II Study of Olaparib With Concomitant Radiotherapy in Locally Advanced/Unresectable Soft-tissue Sarcoma (RADIOSARP)	Institut Bergonié NCT02787642	Phase I Recruiting
		A Dose Finding Study Followed by Phase II Randomized, Placebo-Controlled Study of Velparib (ABT-888) Added to Chemoradiotherapy With Carboplatin and Paclitaxel for Unresectable Stage III Non-small Cell Lung Cancer (NSCLC), (NCI Study Number 8811)	National Cancer Institute NCT01386385	Phase I/II Active, not recruiting
Breast	Pancreas	A Phase I Study of Velparib (ABT-888) in Combination With Gemcitabine and Intensity Modulated Radiation Therapy in Patients With Locally Advanced, Unresectable Pancreatic Cancer (VelGemRad)	Cedars-Sinai Medical Center NCT01908478	Phase I Reported
	Breast	A Phase I Study of Velparib Administered Concurrently With Chest Wall and Nodal Radiation Therapy in Patients With Inflammatory or Loco-regionally Recurrent Breast Cancer	University of Michigan Rogel Cancer Center NCT01477489	Phase I Reported
		Pre-Operative PARPi and Irradiation (POPI) in Women With an Incomplete Response to Neoadjuvant Chemotherapy for Breast Cancer	Richard Zellars NCT01618357	Phase I Recruiting

Table 1 (Continued)

PARPi	Cancer Site	Trial Title	Sponsor and Trial ID	Phase and Status	
Brain metastases	Brain metastases	A Randomized, Double-Blind, Phase 2, Dose-Ranging Study to Evaluate the Safety and Efficacy of Velparib and Whole Brain Radiation Therapy vs Placebo and Whole Brain Radiation Therapy in Subjects With Brain Metastases From Non-Small Cell Lung Cancer	AbbVie (prior sponsor, Abbott) NCT01657799	Phase II Reported	
		A Phase I Study Evaluating the Safety, Tolerability and Pharmacokinetics of ABT-888 in Combination With Whole Brain Radiation Therapy in Subjects With Brain Metastases	AbbVie (prior sponsor, Abbott) NCT00649207	Phase I Completed	
	GBM	A Phase I/II Trial of Temozolomide and ABT-888 in Subjects With Newly Diagnosed Glioblastoma Multiforme	Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins NCT00770471	Phase I/II Completed	
		A Phase 2 Study of Velparib (ABT-888) and Local Irradiation, Followed by Maintenance Velparib and Temozolomide, in Patients With Newly Diagnosed High-Grade Glioma (HGG) Without H3 K27M or BRAFV600 Mutations	National Cancer Institute NCT03581292	Phase II Recruiting	
	Rectal	A Phase I/II Study of ABT-888, An Oral Poly(ADP-ribose) Polymerase Inhibitor, and Concurrent Radiation Therapy, Followed by ABT-888 and Temozolomide, in Children With Newly Diagnosed Diffuse Intrinsic Pontine Glioma (DIPG)	National Cancer Institute NCT01514201	Phase I/II Completed	
		An Open-Label Phase 1b Study of the Safety and Tolerability of Velparib in Combination With Capecitabine and Radiation in Subjects With Locally Advanced Rectal Cancer (LARC)	AbbVie (prior sponsor, Abbott) NCT01589619	Phase Ib Reported	
	Fractionated Whole Solid Malignancies With Epithelial Ovarian, Endometrial, Cervical, and Uterine Cancer	Breast	A Phase I Study of Olaparib in Combination With Radiotherapy in Patients With Metastatic Pancreatic Cancer	National Cancer Institute NCT02921256	Phase II Active, not recruiting
			A Phase I Study of Niraparib Administered Concurrently With Postoperative RT in Triple Negative Breast Cancer Patients (UNIT)	National Cancer Institute NCT01264432	Phase I Reported
	GBM	Cervix	Efficacy and Safety of Niraparib Combined With Radiotherapy in Patients With Recurrent Glioblastoma	Massachusetts General Hospital NCT04409002	Phase II Recruiting
			Phase I/II Study of Niraparib With Radiotherapy for Treatment of Metastatic Invasive Carcinoma of the Cervix (NIVIX)	Massachusetts General Hospital NCT03945721	Phase I Recruiting
Prostate	GBM	Randomized Phase II Trial of Niraparib With Standard Combination Radiotherapy and Androgen Deprivation Therapy (ADT) in High Risk Prostate Cancer (With Initial Phase I) (NADIR)	Tanjin Huaerui Hospital NCT04715620	Phase II Recruiting	
		A Multi-Center Trial of Androgen Suppression With Abiraterone aCetate, LEuprolide, PARP Inhibition and Stereotactic Body Radiotherapy (ASCLEPlus): A Phase I/2 Trial in High Risk and Node Positive Prostate Cancer	Michelle S Ludwig NCT03444342	Phase I/II Recruiting	
Pamiparib BGB-290	ES-SCLC	A Phase 1b/2 Study to Assess the Safety, Tolerability and Efficacy of BGB-290 in Combination With Radiation Therapy (RT) and/or Temozolomide (TMZ) in Subjects With First-line or Recurrent/Refractory Glioblastoma	NRG Oncology NCT04037254	Phase I/II Recruiting	
		A Phase I/2 Clinical Trial of Pamiparib in Newly-Diagnosed and Recurrent Glioblastoma Patients	University of Michigan Rogel Cancer Center NCT04194554	Phase I/II Recruiting	
Talazoparib BMMN-673	Gynae	A Phase I Study of Talazoparib and Consolidative Thoracic Radiotherapy for Extensive Stage Small Cell Lung Cancer	BtGene NCT03150862	Phase Ib/II Active, not recruiting	
		A Phase I Study of Talazoparib in Combination With Radiation Therapy for Locally Recurrent Gynecologic Cancers	Nader Sanai NCT04614909	Phase I/II Recruiting	
Rucaparib AG-014699	Breast	A Phase I Study of Rucaparib Administered Concurrently With Postoperative Radiotherapy in Patients With Triple Negative Breast Cancer With an Incomplete Pathologic Response Following Neoadjuvant Chemotherapy	University Health Network, Toronto NCT04170946	Phase I Recruiting	
			M.D. Anderson Cancer Centre NCT03968406	Phase I Recruiting	
			Memorial Sloan Kettering Cancer Centre NCT03542175	Phase I Recruiting	

37 studi: 7 pubblicati



## Studi pubblicati fase 1 e 2\*

### NO SBRT

#### Favorevoli

- **retto** (fase 1 PARPi + capecitabina + RT\*)
- **mammella** (fase 1 RADIOPARP Trial; RT \*)
- **pancreas** (fase 1 PIONEER study PARPi + capecitabina + RT \*)

- \*RT convenzionale (50-50.4 Gy/2-1.8 Gy/fx)
- CHT radiosensibilizzante convenzionale (CAPECITABINA)

#### Sfavorevoli

- **polmone** (fase 1 PARPi+cisplatino+ RT ipofraz 2.75Gy/fx)
- **testa-collo** (fase 1 PARPi+ cetuximab+ RT 2.1 Gy/fx)
- **pancreas** (fase 1 VelGemRad trial; RT 2.4 Gy/fx)
- **carcinosi peritoneale** (fase 1 PARPi+ LDFWAR 60cGy x 2/die)

- Ipofrazionamenti su GRANDI VOLUMI
- Vicinanza con acute responding normal tissue (mucosa esofagea e tenue, midollo)
- Associazione con cisplatino o cetuximab o gemcitabina

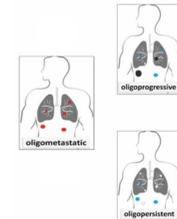
\* Ref su ClinicalTrials.gov diapo 13



## E nelle neoplasie ovariche...

la **stereotassi** può essere impiegata ad intento **curativo** in tumori sensibili ai **PARPi** in cui il ruolo della RT era stato finora limitato dalle tossicità tardive delle irradiazioni sull'addome in toto (vantaggio di **alte dosi/fx su piccoli volumi**)

## ...nella malattia oligometastatica/persistente/recidivante



The Oncologist®

Radiation Oncology

**A Large, Multicenter, Retrospective Study on Efficacy and Safety of Stereotactic Body Radiotherapy (SBRT) in Oligometastatic Ovarian Cancer (MITO RT1 Study): A Collaboration of MITO, AIRO GYN, and MaNGO Groups**

GABRIELLA MACCHIA<sup>a,†</sup>, ROBERTA LAZZARI<sup>b,†</sup>, NICOLETTA COLOMBO<sup>c</sup>, CONCETTA LALISCIA<sup>d</sup>, GIOVANNI CAPELLI<sup>e</sup>, GIUSEPPE ROBERTO D'AGOSTINO<sup>f</sup>, FRANCESCO DEDDATO<sup>g</sup>, ERNESTO MARANZANO<sup>h</sup>, EDY IPPOLITO<sup>i</sup>, SARA RONCHI<sup>b</sup>, FABIOLA PAIAR<sup>d</sup>, MARTA SCORSETTI<sup>e,j</sup>, SAVINO CILLA<sup>j</sup>, ROSSANA INGARGIOLA<sup>b,k</sup>, ALESSANDRA HUSCHER<sup>l</sup>, ANNA MARIA CERROTTA<sup>m</sup>, ANDREI FODOR<sup>n</sup>, LISA VICENZI<sup>o</sup>, DONATELLA RUSSO<sup>p</sup>, SIMONA BORGHESI<sup>q</sup>, ELISABETTA PERRUCCI<sup>r</sup>, SANDRO PIGNATA<sup>s</sup>, CYNTHIA ARISTEI<sup>t</sup>, ALESSIO GIUSEPPE MORGANTI<sup>†</sup>, GIOVANNI SCAMBIA<sup>u,v</sup>, VINCENZO VALENTINI<sup>w,x</sup>, BARBARA ALICIA JERECEK-FOSSA<sup>b,x,††</sup>, GABRIELLA FERRANDINA<sup>u,v,††</sup>

261 pazienti, 449 lesioni

FUP mediano: 22 mesi

CR+PR: **89%**

2y-LPFS: **81.9%**; 2y-PFS: 15.4; 2y-OS:**73.6%**

Macchia G et al. The Oncologist 2020; 25(2):e311-e320



## E nelle neoplasie ovariche...

NIH U.S. National Library of Medicine

*ClinicalTrials.gov*

NCT04593381

Efficacy and Safety of **Stereotactic Body Radiotherapy** (SBRT in Oligo-metastatic/Persistent/Recurrent **Ovarian Cancer** (MPR-OC): a **Prospective, Multicenter** Phase II Study (MITO-RT3/RAD)

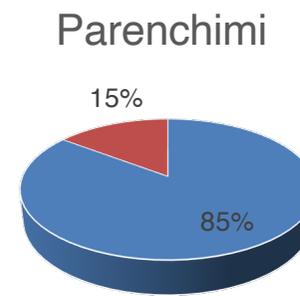
15 centri



265 lesioni (155 pazienti) a novembre 2022



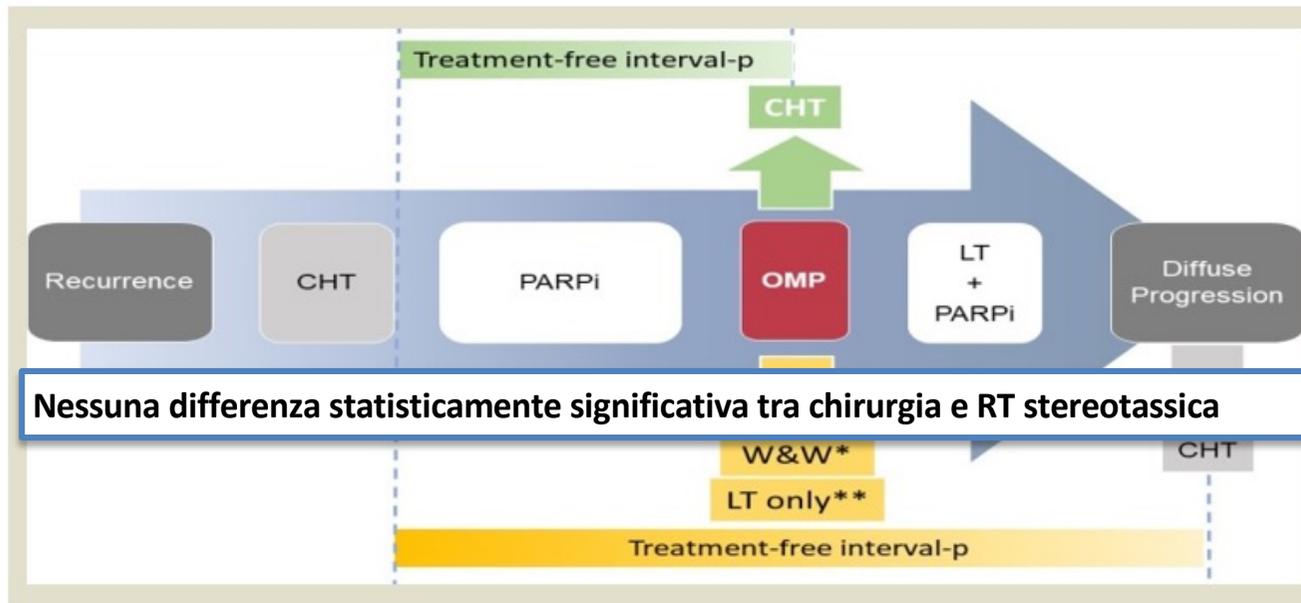
■ Attuali ■ Rimanenti



■ Attuali ■ Rimanenti



## Unico studio clinico pubblicato sull'associazione PARPi-trattamento locale (CH o SBRT)



Nessuna differenza statisticamente significativa tra chirurgia e RT stereotassica

### Conclusion

Patients with recurrent ovarian cancer who have an oligometastatic progression during PARPi maintenance treatment, may continue to benefit from PARPi, if combined with local treatment



## Associazione PARPi e SBRT nelle neoplasie ovariche...

### *Studio EPIMETHEO* (colui che agisce prima di pensare)

Primo studio italiano multicentrico retrospettivo che associa i **PARPi alla radioterapia stereotassica** nella malattia ovarica oligometastatica/persistente/recidivante volto a valutarne l'**efficacia**, il **profilo di tossicità** e l'**intervallo libero da CHT (durata del mantenimento con PARPi)**

#### Centri

- Policlinico Universitario A. Gemelli IRCCS – Roma
- Gemelli-Molise – Campobasso
- Ospedale Vito Fazzi – Lecce
- UPMC San Pietro FBF - Roma

Da Maggio 2019 a gennaio 2022

56 pazienti e 107 lesions (69 linfonodi e 38 parenchimi)



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SABATO 26 NOVEMBRE 2022

14.00 - 15.00

COMUNICAZIONI ORALI 5

SALA BIANCA

Moderatori: F. Marletta, V. De Sanctis

CO40

RADIOTERAPIA STEREOTASSICA IN PAZIENTI AFFETTI DA NEOPLASIA OVARICA  
IN PROGRESSIONE DURANTE TERAPIA DI MANTENIMENTO  
CON PARP-INIBITORI: EVENTI AVVERSI ED ATTIVITÀ DALLO STUDIO  
RETROSPETTIVO "EPIMETHEO"

*G. Macchia, M. Campitelli, D. Russo, D. Pezzulla, S. Lucci, A. Nardangeli,  
A. Di Stefano, G. Ronzino, C. Federico, V. Salutari, S. Cilla, M.A. Gambacorta, G. Ferrandina  
(Campobasso, Roma, Lecce, Napoli)*

# GRAZIE!

**ESTRO 2023** | 12-16 May 2023  
Vienna, Austria

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