Associazione Italiana Radioterapia e Oncologia clinica

Società Italiana di Radiobiologia

UTILIZZO DI INIBITORI DI CICLIN KINASI IN COMBINAZIONE CON LA RADIOTERAPIA NEI TUMORI DELLA MAMMELLA ORMONO RESPONSIVI

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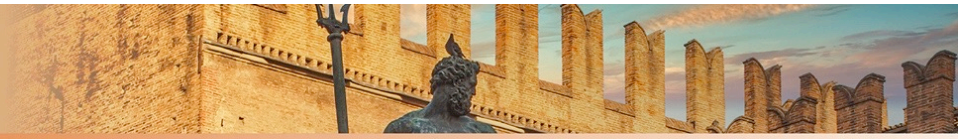
ISTITUTO NAZIONALE TUMORI
IRCCS – Fondazione Pascale

RETE ONCOLOGICA CAMPANA

Associazione Italiana Radioterapia e Oncologia clinica

Società Italiana di Radiobiologia

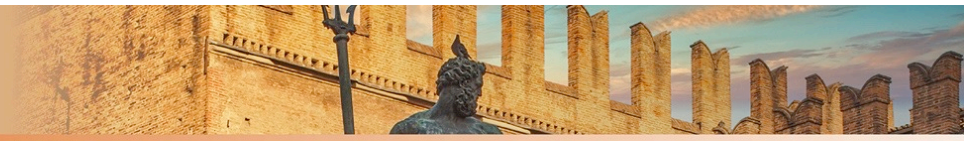


DICHIARAZIONE

Relatore: SARA FALIVENE

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



Role of the Combination of Cyclin-Dependent Kinase Inhibitors (CDKI) and Radiotherapy (RT) in the Treatment of Metastatic Breast Cancer (ME Risks in Cli

Ambrogio Gagliano, Angel
Giacomo Fisichella, Paolo

Immunotherapy ar metastatic bre

Francisco J Esteva, Var

Observational Study > Clin Breast Cancer. 2020 Dec;20(6):495-502.
doi: 10.1016/j.clbc.2020.05.013. Epub 2020 May 26.

Cyclin-Dependent Kinase 4/6 Inhibitors Combined With Radiotherapy for Patients With Metastatic Breast Cancer

Ivica Ratosa [1], Miha Orazem [2], Erika Scoccimarro [3], Mateja Steinacher [4], Luca Dominici [3], Michele Aquilano [3], Cecilia Cerbai [3], Isacco Desideri [3], Domen Ribnikar [5], Tanja Marinko [6], Lorenzo Livi [3], Icro Meattini [3]

The Breast 60 (2021) 163–167
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journal homepage: www.elsevier.com/brst

Safety of cyclin-dependent kinase4/6 inhibitor combined with palliative radiotherapy in patients with metastatic breast cancer

Kristine N. Kim [a], Payal Shah [b], Amy Clark [b], Gary M. Freedman [a], Sana Dastgheyb [a], Andrew R. Barsky [a], Alexandra D. Dreyfuss [a,c], Neil K. Taunk [a,*]

Lancet Oncol 2019; 20: e175-8

Journal of Neuro-Oncology
https://doi.org/10.1007/s11060-019-0

CLINICAL STUDY

CDK 4/6 inhibitors and stereotactic radiation in the manage of hormone receptor positive breast cancer brain metastases

Homan Mohammadi[1] · Daniel E. Oliver[1] · John A. Arrington · James K. Liu[3] · Hatem Soliman[4] · Peter A. F

Review Article

Clinical and Translational Radiation Oncology 26 (2021) 79–85

CDK 4/6 inhibitors combined with radiotherapy: A review of literatur

Claire Bosacki [a], Wafa Bouleftour [b], Sandrine Sotton [b], Alexis Vallard [a], Elisabeth Daguenet, Hamza Ouaz [a], Iohel Cojoracu [a], Dariush Moslemi [a], Mona Molekzadehmoghani [a], Nicolas

CDKI 4/6 are utilized in locally advanced or as first-line therapy for metastatic hormone receptor positive breast cancer. However, there are limited data on safety of combined radiotherapy (RT) and CDK4/ 6 inhibition.

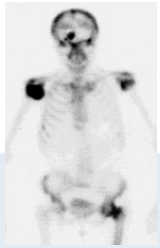
Pre-clinical evidences of CDK4/6 inhibitors + Radiotherapy

Preclinical studies suggested CDK4/6i had **a radiation-sensitizing effect** on human cancer cell lines

Indeed, CDK4/6i may increase radiotherapy antitumor effect
- by controlling cell progression from G1 phase to the more radioresistant S phase
- by inhibiting repair mechanisms of DNA double-strand break.

Compared to monotherapy, *palbociclib* during or after RT maintained a high percentage of G2/M cells, increased the proportion of apoptotic cells, and decreased the proportion S2 cells.

Moreover, when radiotherapy and CDK 4/6i were combined, markers of DNA damage (γH2AX) and apoptosis (cPARP) increased.

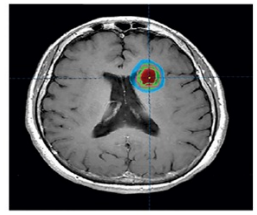


Pre-clinical data reveals penetration of *abemaciclib* across the blood-brain barrier. Interim results of a prospective trial have demonstrated anti-tumor activity in HR+/HER2- BC brain metastases with the use of CDK4/6i

Whittaker et al. revealed *palbociclib* combined with RT worked synergistically to significantly increase of apoptotic cell death and impede colony formation in glioblastoma mouse models.

Given the prolonged half-life of CDK4/6i, there is reasonable concern regarding the tolerance when combined with stereotactic RT in early mouse studies.

Prospective studies are ongoing to assess the efficacy of CDK4/6i in the treatment of brain metastasis.

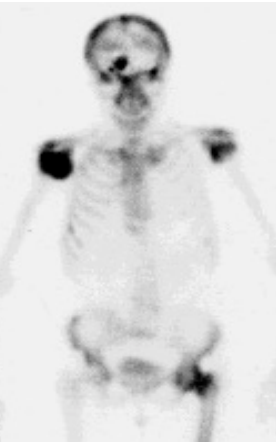


Clinical findings about CDK4/6 i + RT

- In the PALOMA clinical trials, RT was applied to < 25% of bone marrow, and palbociclib treatment was interrupted during palliative RT, pausing 1 day before RT and resuming treatment 1 week later.

- In clinical trials that led to approval of CDK 4/6i use with ET, no specific subanalysis was conducted to assess toxicity in a subset of patients who had received palliative RT while receiving CDK4/6i treatment.

- Small single-institution studies of ABC patients treated with a combination of CDK4/6i and RT to the bone and/or visceral metastatic sites recently reported a tolerable toxicity profile.



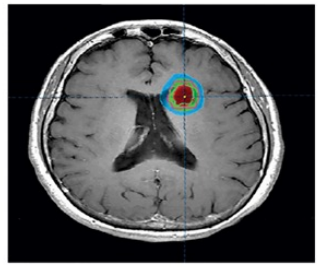
Evidences from clinical trials in BC brain metastases

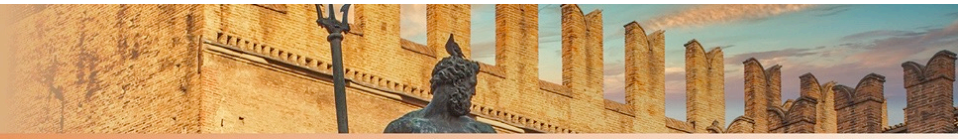
- Current clinical trials have two frequent vulnus: the exclusion of patients with brain metastases and the prospective lack of sites of disease progression.

- In HR+ metastatic disease, **PALOMA-2** enrolled 2 patients with stable brain disease out of 666 recruited, 1 per arm, with no loco-regional progression

- In endocrine-resistant metastatic disease, **PALOMA-3** enrolled 5 patients with stable brain disease; in addition, 2 patients had brain disease progression to treatment failure but no further clinical data are available

- **CompLEEment-1** is a real-world phase 3b study that recruited 51 patients out of 3,246 with brain metastases





- Multicentric retrospective study
- Breast cancer
- Palliative RT or adiuvant RT within 15 days of CDKI 4/6
- Primary endpoint: toxicity CTCAE v5

- 41 patients → 50 site
- 11 adjuvant treatments
- 39 palliative treatments → 18 SRS/SRT

CKI	n pz°	INTENT	n ° treatment
RIBOCICLIB	22	MTX	20
		ADJ	6
PALBOCICLIB	17	MTX	18
		ADJ	4
ABEMACICLIB	2	MTX	1
		ADJ	1
tot pz	41	tot treatment course	50

SITE	n°	mean dose
Breast/chest wall	11	50 Gy (45-60 Gy in 20-30 fx)
MTX brain	10	23,4 Gy (21-24 Gy in 1-3 fx)
MTX spine	14	25 Gy (20-30 Gy in 3-10 fx)
MTX bone other site	13	30 Gy (20-40 Gy in 3-5 fx)
MTX node	1	30 Gy in 3 fx
MTX lung	1	32,5 Gy in 5 fx

RT TECNIQUE	n°
SRS/SRT mtx	18
3D/VMAT mtx	21
3D/VMATadj	11
tot	50

TIMING	n°
CONCOMITANT	28
SEQUENTIAL	22
tot	50

- One acute G3 hematologic toxicity occurred with interruption of CDKi before the RT course.
- No increased hematologic toxicity was attributable to RT with no G3 hematologic toxicities rates before, during, and 3-6 months after RT completion.

The use of RT within 2 weeks of CDK4/6 inhibitors had low acceptable toxicity and high efficacy, suggesting that it is safe for palliation of metastatic breast chance

Prospective studies are ongoing to assess the efficacy of CDK4/6i in the treatment of brain metastasis.