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1 **Ribociclib plus letrozole and concomitant palliative radiotherapy for metastatic breast cancer**

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16 **Keywords:** breast cancer; concomitant radiotherapy; ribociclib; safety.

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32 **Abstract**

33 Ribociclib is a CDK4-6 inhibitor recently approved by the Food and Drug Administration (FDA) and the European
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35 significant improvement in progression-free survival when compared to endocrine therapy alone. However, having a
36 challenging toxicity profile in comparison with exclusive endocrine therapy, safety may be a concern when combined to
37 radiotherapy (RT) with palliative approach.

38 There are no available published data regarding the combination of ribociclib and palliative RT. We reported our
39 preliminary experience on the first five patients treated at the Radiation Oncology Unit of the Florence University
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63 **Viewpoints and Debates**

64 Ribociclib (Kisqali[®]; Novartis, Basel, Switzerland) is a CDK4-6 inhibitor recently approved by the Food and Drug
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72 There are no available published data regarding the combination of ribociclib and palliative RT in a clinical setting. A
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79 Main patients' series characteristics are summarized in *Table 1*. In all cases, RT was prescribed with palliative/analgesic
80 intent due to symptomatic bone metastases. Two patients had bone-only disease, three patients both bone and visceral
81 disease (two lung, one liver).

82 Hematological and non-hematological **toxicities were assessed during the second 21-days cycle of ribociclib, following**
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86 Ribociclib treatment suspension was required in two cases, for two weeks. Treatment recovery (first dose reduction;
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Conflicts of interest statement

None declared.

References

[1]. Hortobagyi GN, Stemmer SM, Burris HA, Yap YS, Sonke GS, Paluch-Shimon S, Campone M, Blackwell KL, André F, Winer EP, Janni W, Verma S, Conte P, Arteaga CL, Cameron DA, Petrakova K, Hart LL, Villanueva C, Chan A, Jakobsen E, Nusch A, Burdaeva O, Grischke EM, Alba E, Wist E, Marschner N, Favret AM, Yardley D, Bachelot T, Tseng LM, Blau S, Xuan F, Souami F, Miller M, Germa C, Hirawat S, O'Shaughnessy J. Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer. *N Engl J Med* 2016;375:1738-48. doi: 10.1056/NEJMoa1609709.

[2]. Wei L, Leibowitz BJ, Wang X, Epperly M, Greenberger J, Zhang L, Yu J. Inhibition of CDK4/6 protects against radiation-induced intestinal injury in mice. *J Clin Invest* 2016;126:4076-87. doi: 10.1172/JCI88410. Epub 2016 Oct 4.

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[4]. Janni W, Alba E, Bachelot T, Diab S, Gil-Gil M, Beck TJ, Ryvo L, Lopez R, Tsai M, Esteva FJ, Auñón PZ, Kral Z, Ward P, Richards P, Pluard TJ, Sutradhar S, Miller M, Campone M. First-line ribociclib plus letrozole in postmenopausal women with HR+ , HER2- advanced breast cancer: Tumor response and pain reduction in the phase 3 MONALEESA-2 trial. *Breast Cancer Res Treat.* 2018 Feb 5. doi: 10.1007/s10549-017-4658-x.

[5]. Kassem L, Shohdy KS, Lasheen S, Abdel-Rahman O, Bachelot T. Hematological adverse effects in breast cancer patients treated with cyclin-dependent kinase 4 and 6 inhibitors: a systematic review and meta-analysis. *Breast Cancer* 2018;25:17-27. doi: 10.1007/s12282-017-0818-4.

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101 C, Chan A, Jakobsen E, Nusch A, Burdaeva O, Grischke EM, Alba E, Wist E, Marschner N, Favret AM,
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Table 1

Table 1. Main patients and treatments characteristics.

Case	Age	PS	RT treated site	Dose (Gy)/Fx	Technique	Ribociclib cycle	G3-4 hematological toxicity*	G3-4 non hematological toxicity*	RT suspension required	Pain relief ^o	Ribociclib suspension required*	Weeks of suspension
1	71	0	Left femoral neck	30/5	VMAT	1	Neutropenia	No	No	Yes	Yes	2
2	55	0	Bilateral femoral neck	20/5	3DCRT	1	No	No	No	Yes	No	0
3	76	2	Right hip	20/5	3DCRT	1	No	Diarrhea Vomiting	No	Yes	Yes	2
4	79	1	Lumbar spine (L2-L3)	20/5	3DCRT	1	No	No	No	Yes	No	0
5	36	0	Cervical/thoracic spine (C3-T2)	20/5	3DCRT	1	No	No	No	Yes	No	0

Abbreviations: PS, performance status; Dose/fx, total dose (Gy)/number of fractions; G3-4, grade 3-4; RT, radiotherapy; VMAT, volumetric modulated arc therapy; 3DCRT, 3-dimensional conformal radiotherapy.

*Toxicity recorded after the cycle of combined treatment ribociclib/letrozole with palliative radiation.

^oIf pain at palliative radiation start.

Highlights

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