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

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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  
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37 radiotherapy (RT) with palliative approach.

38 There are no available published data regarding the combination of ribociclib and palliative RT. We reported our  
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## 63 **Viewpoints and Debates**

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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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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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95 **Conflicts of interest statement**

96 None declared.

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98 **References**

- 99 [1]. Hortobagyi GN, Stemmer SM, Burris HA, Yap YS, Sonke GS, Paluch-Shimon S, Campone M, Blackwell KL,  
100 André F, Winer EP, Janni W, Verma S, Conte P, Arteaga CL, Cameron DA, Petrakova K, Hart LL, Villanueva  
101 C, Chan A, Jakobsen E, Nusch A, Burdaeva O, Grischke EM, Alba E, Wist E, Marschner N, Favret AM,  
102 Yardley D, Bachelot T, Tseng LM, Blau S, Xuan F, Souami F, Miller M, Germa C, Hirawat S, O'Shaughnessy  
103 J. Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer. *N Engl J Med* 2016;375:1738-  
104 48. doi: 10.1056/NEJMoa1609709.
- 105 [2]. Wei L, Leibowitz BJ, Wang X, Epperly M, Greenberger J, Zhang L, Yu J. Inhibition of CDK4/6 protects  
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107 Epub 2016 Oct 4.
- 108 [3]. Hans S, Cottu P, Kirova YM. Preliminary results of the association of Palbociclib and radiotherapy in  
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- 110 [4]. Janni W, Alba E, Bachelot T, Diab S, Gil-Gil M, Beck TJ, Ryvo L, Lopez R, Tsai M, Esteva FJ, Auñón PZ,  
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- 114 [5]. Kassem L, Shohdy KS, Lasheen S, Abdel-Rahman O, Bachelot T. Hematological adverse effects in breast  
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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 <sup>o</sup>	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.

<sup>o</sup>If pain at palliative radiation start.

## Highlights

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