

Ribociclib: a valuable addition to treatment options in breast cancer?



CrossMark

Rupert Bartsch

To cite: Bartsch R. Ribociclib: a valuable addition to treatment options in breast cancer? *ESMO Open* 2017;2:e000246. doi:10.1136/esmoopen-2017-000246

Received 10 July 2017
Accepted 10 July 2017

Antihormonal treatment is regarded as the prototype of targeted therapy. As early as 1896, George Thomas Beatson proposed surgical oophorectomy for the treatment of patients with locally advanced, inoperable breast cancer.¹ While the underlying biological mechanisms were not understood in those days, the identification of steroid hormones² and eventually the oestrogen receptor (ER)³ led to the successful utilisation of endocrine treatment in breast cancer. Besides the partial ER-antagonist tamoxifen, the therapeutic armamentarium today consists of aromatase inhibitors (AIs) and the pure antioestrogen fulvestrant; medical ovarian-function suppression with GnRH analogues may be added in premenopausal patients, with surgical oophorectomy still being an alternative.

In early stage breast cancer, endocrine therapy reduces recurrence rates by 50% and breast cancer mortality by one-third⁴; in advanced disease, the sequential administration of non-cross-resistant drugs allows for the delay of cytotoxic chemotherapy. Still, in metastatic disease, secondary resistance will gradually develop with cells becoming insensitive to further endocrine intervention. To improve activity of endocrine therapy by delaying or reversing endocrine resistance, several treatment strategies were developed. Among them, small-molecule inhibitors of cycle-dependent kinases (CDK) 4 and 6 appear to be the most promising. Indeed, cell-cycle control is frequently dysregulated in breast cancer cells resulting in uncontrolled proliferation, and the first CDK4/6 inhibitor commercially available—palbociclib (Ibrance)—yielded impressive results when added to endocrine therapy alone in both treatment-naïve and pretreated patients.^{5 6} Of note, this intervention was relatively well tolerated and the main toxicity consisted of neutropaenia, which was easily manageable and resulted in a very low febrile neutropaenia rate.

With ribociclib (Kisqali), a second CDK4/6 inhibitor has now received EMA approval (pending European Commission decision) in combination with an aromatase inhibitor as initial endocrine therapy. The approval is based on results from the MonaLEESA-2 trial⁷; in this prospective randomised placebo-controlled phase III study, a total of 668 patients were randomly assigned 1:1 to endocrine therapy consisting of the AI letrozole with or without ribociclib. Combination treatment resulted in a statistically significant and clinically relevant prolongation of progression-free survival (PFS) from 16 to 25.3 months (HR 0.568; 95% CI 0.457 to 0.704).⁸ These data are comparable to the results of palbociclib in the phase III first-line PALOMA-2 study⁵ and suggest a class effect; furthermore, toxicity was similar as well with some subtle differences and the noted exception of a higher hepatotoxicity rate and a relatively rare but potentially deleterious QTc prolongation in patients receiving ribociclib. This problem necessitates liver-function parameter and ECG monitoring and proper patient and physician education regarding forbidden comedication. Given these facts, is ribociclib just a ‘me-too’ drug with a somewhat less favourable safety profile? To answer this question, a broader perspective is required.

In general, should every patient with ER-positive human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer receive a CDK4/6 inhibitor where available? Over the entire course of the disease, the answer is clearly ‘yes’ and as expected, the most impressive results in terms of PFS prolongation by CDK4/6 inhibitors were observed in early treatment lines, suggesting that CDK4/6 inhibitors should be given early on. Critics of such a ‘best first’ approach, however, may argue that the PFS HR remains similar also in later lines⁶; there is currently no proven overall survival (OS) benefit and little is known about the sensitivity to further endocrine intervention on progression on a CDK4/6-inhibitor. Finally,

Department of Medicine I,
Clinical Division of Oncology,
Comprehensive Cancer Center
Vienna, Medical University of
Vienna, Vienna, Austria

Correspondence to
Professor Rupert Bartsch;
rupert.bartsch@meduniwien.
ac.at

the costs of these drugs are currently prohibitive for the healthcare systems of many countries, thereby increasing disparities in European healthcare standards and implicating the need for reliable predictive makers. This shows that further data on the optimal use of CDK4/6 inhibitors in patients with ER-positive HER2-negative metastatic breast cancer is urgently required.

With two drugs of this class now available (and a third, somewhat different, is upcoming), the chance for generating this pertinent information sooner than later is considerably greater as manufacturers will strive to increase physicians' confidence with their respective drugs. This may also increase the readiness to support investigator-initiated trials, thereby benefiting the academic community as well as offering the chance for trials designed by patients' needs rather than commercial interest. In addition, having more than one CDK4/6-inhibitor available will result in reduced drug costs which again will benefit European patients and healthcare systems.

So, is ribociclib just a 'me-too' drug? Given the above-mentioned points, the answer appears to be 'no' and ribociclib is a most welcome addition to the therapeutic armamentarium.

Competing interests BS has served on advisory boards for Novartis and Pfizer and has received lecture honoraria and travel support from Novartis and Pfizer.

Provenance and peer review Commissioned; internally peer reviewed.

Open Access This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which

permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

© European Society for Medical Oncology (unless otherwise stated in the text of the article) 2017. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

REFERENCES

1. Beatson G. On the treatment of inoperable cases of carcinoma of the mamma: suggestions for a new method of treatment, with illustrative cases. *Lancet* 1896;148:104–7.
2. Butenandt A. Über Progynon ein krystallisiertes weibliches Sexualhormon. *Naturwissenschaften* 1929;17:879.
3. Jensen EV, Suzuki T, Kawashima T, *et al*. A two-step mechanism for the interaction of estradiol with rat uterus. *Proc Natl Acad Sci U S A* 1968;59:632–8.
4. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005;365:1687–717.
5. Finn RS, Martin M, Rugo HS, *et al*. Palbociclib and letrozole in advanced breast cancer. *N Engl J Med* 2016;375:1925–36.
6. Turner NC, Ro J, André F, *et al*. PALOMA3 Study Group. Palbociclib in Hormone-Receptor-Positive Advanced Breast Cancer. *N Engl J Med* 2015;373:209–19.
7. Hortobagyi GN, Stemmer SM, Burris HA, *et al*. Ribociclib as first-line therapy for HR-positive, advanced breast cancer. *N Engl J Med* 2016;375:1738–48.
8. Hortobagyi GN, Gabriel N, Salomon M, *et al*. Updated results from MONALEESA-2, a phase 3 trial of first-line ribociclib + letrozole in hormone receptor-positive (HR+), HER2-negative (HER2-), advanced breast cancer (ABC). *J Clin Oncol* 2017. ASCO Annual Meeting, Chicago, USA. Abstract 1038.