Response to Abemaciclib After 10 Lines of Therapy Including Palbociclib in Metastatic Breast Cancer: A Case Report With Literature Review

Isabella O. Wender • Kayla Haines • Mohammad Jahanzeb

Received: July 24, 2020 / Published online: September 2, 2020 © The Author(s) 2020

ABSTRACT

Metastatic breast cancer (BC) is considered incurable, and it is generally treated with sequential single-agent therapies to control it with palliative intent. Cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) are used in the frontline setting of hormone receptor (HR)-positive, HER2-negative BC, and guidelines discourage the use of a second-line CDK4/6i after failure of first-line use of this class of drugs due to lack of data supporting this practice. We report a case of a postmenopausal woman with HR-positive and HER2-negative advanced BC who was treated with four lines of hormonal therapy and more than five chemotherapy regimens, with progression. Palbociclib was used in the sixth-line therapy and discontinued after 5 months. We then tried abemaciclib in the 11th-line setting, where it induced a response that lasted 16 months.

Keywords: Breast carcinoma; Cyclin-dependent kinase; Metastatic breast cancer

Key Summary Points

While metastatic breast carcinoma is incurable, palliative therapy, chosen according to surface markers, is still warranted in patients with adequate performance status and organ function.

National Comprehensive Cancer Network Breast Cancer Guidelines recommend multiple lines of systemic therapy to palliate advanced breast cancer after failure of three lines of hormonal therapy, where clinicians should assess the value of ongoing treatment, risks and benefits, and patient preferences before moving to supportive care. Some patients are offered additional therapy if they maintain an excellent performance status and desire more treatment, especially if there are viable options.
We report a case of a postmenopausal woman with breast carcinoma with 9-year survival, where we tried multiple lines of systemic therapy, most with response or stabilization followed by progression. Palbociclib plus letrozole was her sixth line of therapy, then we tried abemaciclib, another cyclin-dependent kinase 4/6 inhibitor, in the 11th line therapy and achieved a sustained benefit for 16 months.

With this brief report we can raise awareness about this option and allude to this lack of complete cross-resistance between these two CDK4/6 inhibitors.

INTRODUCTION

Excluding nonmelanoma skin cancer, breast cancer (BC) is the most common cancer diagnosed in women and is the second leading cause of cancer death among women after lung cancer [1, 2]. Metastatic disease is generally considered incurable, but it is known that we can control the disease with sequential single-agent therapies (unless there is a rapid tempo of disease, life-threatening visceral involvement and large tumor burden). We report a case of a postmenopausal woman with estrogen-receptor (ER)-positive, progesterone-receptor (PR)-negative and HER2-negative BC. She was treated with four lines of hormonal therapy (HT) and more than five chemotherapy regimens, with initial response or stabilization, followed by progression. Palbociclib, a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i), was used in the sixth line and discontinued after 5 months. After the 10th-line therapy we tried abemaciclib, another CDK4/6i, and it induced a response including in the liver.

CASE REPORT

A 70-year-old white woman was diagnosed in October 2010 with metastatic right-sided BC, hormone-receptor-positive (ER-positive, PR-negative) and HER2-negative, with widespread bone metastasis. The patient underwent palliative radiation to her lumbar spine with 10 meV photon beam via an anterior-posterior/posterior-anterior (AP-PA) technique, 2 Gy per day to 30 Gy, elapsed count of 12 days in March and April of 2011. She received denosumab for prevention of skeletal-related events and also chemotherapy with vinorelbine from December 2010 to May 2011, which was poorly tolerated and caused a rare occurrence of near total alopecia. She was then started on letrozole, but after 2 years the cancer progressed. She was given fulvestrant until July 2014, with progression again. Tamoxifen was started in August 2014 and discontinued in December of the same year because of progression.

In January 2015 she developed left lower extremity swelling and underwent a left lower extremity venous duplex ultrasound. The image showed a left inguinal mass measuring $4.9 \times 2.5 \times 6.8$ cm with a complex hypoechoic center and abnormal vascularity, compatible with necrotic lymphadenopathy, and additional lymph nodes were present. A left inguinal lymph node mass biopsy was performed and revealed small lymphocytes in a marginal zone pattern and occasional colonization of reactive follicles. By immunohistochemistry, lymphocytes were positive for CD20 and BCL2, and negative for CD3, CD5 and CD10. A diagnosis of marginal-zone lymphoma was made, an indolent B-cell non-Hodgkin lymphoma. A bone marrow biopsy at that time showed involvement of the same lymphoma. She was given rituximab for 4 weeks until April 2015, and from June through October 2015 she received bendamustine with rituximab every 28 days. The patient had a complete response with no recurrence of her lymphoma.

Lymphoma treatment ended in October 2015, and a PET-CT from November 2015 showed progression in her bony disease. She started letrozole with palbociclib until April 2016 with progression. She was placed on capecitabine, which she received from May 2016 to September 2016, but the cancer progressed. The patient had exhausted her HT options, so we switched to chemotherapy and...
re-treated her with vinorelbine at a lower dose of 20 mg/m² given every other week, which she tolerated better, but after 3 months the disease progressed. She received liposomal doxorubicin for a year from November 2016 with a good clinical response, but the drug had to be stopped because of reaching the maximum recommended cumulative dose over which the risk of cardiotoxicity would be significantly increased. She was then treated with gemcitabine from November 2017 to March 2018, but PET-CT from March showed widespread hypermetabolic liver and osseous metastases with increasing metabolism compared to the prior exam, with the majority of the lesions showing increasing metabolism, as well as new hypermetabolic osseous lesions. Due to these findings, gemcitabine was discontinued and she started eribulin.

The next PET-CT scan in May 2018 showed widespread hypoattenuating hypermetabolic liver and new osseous metastases, with progression. She was given paclitaxel but progressed with new liver lesions. A liver biopsy was done in June 2018 and pathology reported metastatic carcinoma consistent with breast primary, immunoperoxidase stains positive for cytokeratin AE1/AE3, ER (100% with strong intensity), clone SP1, PR (20% with weak intensity) and GATA-3. FoundationOne genomic testing from the liver biopsy showed stable microsatellite status and low tumor mutational burden, and other genomic findings: CCND1, C11orf30, FGF19, FGF3, FGF4 amplifications and AXIN1 R533_H534insQVHH and MAP2K4 splice site 336_393 6del64 mutations. Paclitaxel was discontinued and she started abemaciclib 200 mg BID in August 2018, but the dose had to be reduced to 150 mg BID due to diarrhea. She was treated with abemaciclib 150 mg twice daily beginning 08/09/2018, with initial response followed by stable disease, while working full-time as an accountant. The patient progressed on abemaciclib in late January 2020 confirmed by a new PET-CT. She maintained Eastern Cooperative Oncology Group (ECOG) I performance status. After discussion with the patient and her family, she was given a reduced dose of irinotecan. When she returned for follow-up on day 8, she presented with complaints of shaking chills, fever and weakness, which she had been having for a few days but had not notified anyone. The patient was admitted to the hospital for intravenous antibiotics for febrile neutropenia but died of sepsis the day after admission (day 9 of cycle 1). Table 1 summarizes the patient’s treatment chronology.

Informed consent was obtained from the patient and her family for the inclusion of her medical and treatment history within this case report.

DISCUSSION

The American Cancer Society reports a 5-year relative survival rate for metastatic BC of 27% based on women diagnosed between 2009 and 2015 [3]. Although patients with HR-positive disease have longer survival, statistics show us that long-term survival for stage IV disease is quite uncommon [4]. Here we report an unusual patient with a more than 9-year survival after being diagnosed with bone metastasis from primary right-sided BC, who later developed liver metastases and a non-Hodgkin lymphoma that had to be treated with bendamustine and rituximab.

The use of multiple lines of HT before resorting to chemotherapy in patients with HR-positive and HER2-negative advanced disease is recommended by National Comprehensive Cancer Network (NCCN) and European School of Oncology (ESO)-European Society of Medical Oncology (ESMO) current treatment guidelines for breast cancer [5, 6]. After failure of three lines of HT, multiple lines of systemic therapy can be used to palliate BC considering risks and benefits [6].

CDK4/6i (abemaciclib, palbociclib and ribociclib) are typically employed and have the best efficacy if given in the front-line therapy in patients with HR-positive, HER2-negative advanced disease. Literature has demonstrated that patients who received CDK4/6i plus HT versus HT alone as the first-line setting had longer progression-free survival, but they were not available when our patient presented in 2010 [7–10]. Palbociclib plus letrozole was her 6th line of therapy.
Abemaciclib is the only CDK4/6i approved for single-agent use in the subsequent-line therapy of metastatic HR-positive and HER2-negative BC [11]. However, NCCN Clinical Practice Guidelines and 4th ESO-ESMO International Consensus Guidelines for BC state that a second-line CDK4/6i should not be tried after failure of the first-line use of these agents due to lack of data supporting this practice. Since our patient maintained a good performance status and desired more therapy after four HT regimens, including letrozole and palbociclib, and more than five chemotherapy regimens, it seemed reasonable to try abemaciclib due to lack of other good options and a significant interval since prior exposure to a CDK4/6 inhibitor. Since the patient started this therapy, additional data emerged from multiple institutions indicating activity of abemaciclib after failure of palbociclib in a prior line of therapy [12–15] as summarized in Table 2. The purpose of this report is to raise awareness about this option and to allude to this lack of complete cross-resistance between the two CDK4/6 inhibitors.

| Agents                        | Start date | End date     | Reason for discontinuation       |
|-------------------------------|------------|--------------|----------------------------------|
| Vinorelbine                   | December 2010 | May 2011     | Progression                      |
| Letrozole                     | May 2011   | June 2013    | Progression                      |
| Fulvestrant                   | June 2013  | July 2014    | Progression                      |
| Tamoxifen                     | August 2014| December 2014| Progression                      |
| Letrozole and palbociclib     | January 2016| April 2016   | Progression                      |
| Capecitabine                  | May 2016   | September 2016| Progression                      |
| Vinorelbine                   | September 2016| November 2016| Progression                      |
| Liposomal doxorubicin         | November 2016| November 2017| Maximum allowable cumulative dose reached |
| Gemcitabine                   | December 2017| March 2018   | Progression                      |
| Eribulin                      | April 2018 | May 2018     | Progression                      |
| Paclitaxel                    | May 2018   | July 2018    | Progression                      |
| Abemaciclib                   | August 2018| December 2019| Progression                      |
| Irinotecan                    | January 2020| January 2020 | Death                            |

After 10 lines of therapy, our patient had a good response with abemaciclib alone, remaining on this treatment for almost 16 months, while palbociclib plus HT had controlled her disease for only 5 months.

Mariotti et al. described metastatic BC patients who responded to abemaciclib after previous exposure to palbociclib. They reported 19 patients who received a mean of 5.6 prior therapies, including palbociclib plus HT (fulvestrant or letrozole), before trying abemaciclib in combination with HR or as a single agent. Four cases (21%) had longer progression-free survival (PFS) on abemaciclib compared to prior palbociclib PFS, and although no partial or complete response was observed, 33% had stable disease [15].

Evidence for giving abemaciclib as a single agent in subsequent lines of therapy of refractory HR-positive and HER2-negative metastatic BC is found in the MONARCH 1 trial [11]. Abemaciclib demonstrated positive anti-tumor activity in 26 patients of a total of 132 who previously progressed on or after HT and chemotherapy. MONARCH 1 excluded patients previously treated with CDK4/6i; however, our
patient was previously exposed to palbociclib and progressed on it, but she still had good clinical benefit from abemaciclib. Additionally, we administered more than five chemotherapy regimens in the metastatic setting in our patient, while MONARCH 1 administered no more than two lines of chemotherapy during metastatic disease.

It is important to discuss why our patient might have responded to abemaciclib despite failing palbociclib. There are some structural differences between abemaciclib and the other two CDK4/6i, palbociclib and ribociclib. Besides being considered agents from the same drug class, it is known that abemaciclib has greater selectivity for CDK4 than for CDK6 and that it can inhibit other kinases which are not inhibited by the other two CDK4/6i, such as CDK9/7/2/1, GSK3α/β and CAMK2γ/δ. It is suggested that inhibition of these kinases by abemaciclib overcomes known mechanisms of resistance to CDK4/6 inhibition. Moreover, these agents have some differences in pharmacokinetics. Abemaciclib has the ability to induce cell death and apoptosis and arrest in the G2 phase of the cell cycle, and it is the most effective inhibitor of CDK4/6. Nonetheless, the three agents seem to have similar anti-tumor activity [16].

### Table 2

| Study ID | Design | Findings |
|----------|--------|----------|
| Wander et al. 2018 [12] | Evaluated patients (pts) of one institution with HR+/HER2− metastatic BC (MBC) who had received abemaciclib following an initial course of palbociclib-based therapy | Twelve pts were included. Five pts (41.7%) had early progression on abemaciclib, while three (25%) had ongoing benefit (progression-free survival [PFS]) greater than 120 days. Three pts had recently initiated abemaciclib therapy (less than 120 days prior to the current analysis). A subset of pts derived clinical benefit with continued exposure to CDK4/6i |
| Wander et al. 2019 [13] | Evaluated clinical outcomes in pts with HR+/HER2− MBC who received abemaciclib following progression on prior palbociclib at four US academic centers | Twenty-one pts (36%) had abemaciclib treatment duration exceeding 6 months (alone or combined), including 10 who remained on treatment at interim analysis (range 181–413 days). This is the first multi-center experience demonstrating a substantial proportion of pts with clinical benefit with abemaciclib after prior CDK4/6i exposure |
| Tamragouri et al. 2019 [14] | Performed a chart review of pts with HR+, HER2− MBC who progressed on palbociclib and were subsequently treated with abemaciclib with or without fulvestrant | Twenty-one pts were included. The clinical benefit rate for using abemaciclib after previous exposure to palbociclib was 29% (6/21). All pts received abemaciclib alone, demonstrating some activity of this agent in pts previously treated with palbociclib |
| Mariotti et al. 2019 [15] | Analyzed the efficacy of abemaciclib-based therapy (ABT) after exposure to palbociclib in estrogen receptor-positive MBC patients | Twenty-two pts who progressed on palbociclib were included. Five (22.7%) pts had durable response to abemaciclib. Of those, two (33.3%) had longer PFS compared to prior palbociclib PFS. Abemaciclib can result in durable response in selected pts who progressed on palbociclib |
Navarro-Yepes et al. suggested a differential mechanism of resistance to abemaciclib versus palbociclib. Western blot analysis revealed dose-dependent downregulation of ERα, Rb, p-Rb and p27 in palbociclib-resistant cells, which were only partially cross-resistant to abemaciclib. Also, a key mediator of DNA repair (Rad51) was downregulated only in abemaciclib-resistant cells. The authors examined the combination of abemaciclib plus niraparib, a PARP inhibitor, in organoid cultures created from patient-derived xenograft (PDX) models with surrogate palbociclib-resistance cells, and found significantly reduced viability, number and density of these organoids. In vivo, with the same PDX models, the treatment reduced the rate of tumor growth and increased survival [17].

Among metastatic BC patients, there are clearly some exceptional cases, such as this patient who remained fully functional and a productive member of society, that deserve consideration from their providers. Besides the heavy treatment with chemotherapy regimens and the previous exposure to another CDK4/6i, abemaciclib showed a 16-month response and 11-month longer PFS than palbociclib-based therapy. This lack of complete cross-resistance between these two CDK4/6i should be better investigated.

The US Food and Drug Administration approved the first CDK4/6i, palbociclib, less than 5 years ago, and now we see ongoing trials to find more uses for these agents [18]. There are some ongoing studies that will generate prospective data regarding response to CDK4/6i after failure in a prior line of therapy. The MAINTAIN trial (NCT02632045) will investigate whether there is continued benefit for remaining on a CDK4/6i at the time of switching to anti-estrogen therapy in a randomized open-label trial [19]. Another study, a phase II trial with 100 participants in a single group assignment, will determine the role of continuing palbociclib treatment in combination with another type of HT (fulvestrant) after disease progression with palbociclib plus an aromatase inhibitor (NCT02738866) [20].

Investigations into the use of CDK4/6i with novel drugs can also be found. The TRINITI-1 study (NCT02732119), a single-arm open-label trial, is looking to determine whether ribociclib in combination with everolimus and exemestane is effective in treating men and post-menopausal women with HR+, HER2– locally advanced or metastatic BC following progression on a CDK4/6i [21]. Initial results of TRINITI-1 were already presented, and it achieved its primary efficacy end point with clinical benefit and tolerability [22]. The PACE trial (NCT03147287) is a phase II research study which is recruiting patients with metastatic HR-positive HER2-negative BC to evaluate the activity of fulvestrant alone, fulvestrant and palbociclib, or fulvestrant, palbociclib and avanbulam combined, in participants who previously stopped responding to prior palbociclib and HT. Trials are ongoing and results are expected [23].

CONCLUSION

Our case report shows an unusually durable response in such a late line of therapy in this 70-year-old woman with metastatic right-sided BC. The patient responded to abemaciclib as her 11th-line therapy after previous exposure to palbociclib. This illustrates the potential for reintroducing a dissimilar member from the same class of a drug that had been used many lines before in unusual patients who exhibit long-term survival, have responded to several agents before, and have run out of new options. As we look for the best treatment for our patients, it is important to develop individualized therapeutic strategies based on their performance status, biology of disease, individual track record and personal preferences.

ACKNOWLEDGEMENTS

We thank the patient for giving us the opportunity to report her medical case.
Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Authorship Contributions. I Wender and K Haines were responsible for data acquisition, analysis and manuscript drafting and editing. M Jahanzeb was responsible for study conception and design, patient clinical examination, data analysis and manuscript review.

Disclosures. I Wender and K Haines have nothing to disclose. M Jahanzeb is speaker and consultant for Pfizer and Novartis.

Compliance with Ethics Guidelines. Informed consent was obtained verbally from the patient for the inclusion of her medical and treatment history within this case report. The patient’s family was also notified of this case submission and consented. This case report was performed in line with the principles outlined in the Declaration of Helsinki of 1964 for all human or animal experimental investigations.

Open Access. This article is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License, which permits any non-commercial use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by-nc/4.0/.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424.

2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin. 2018;68(1):7–30.

3. American Cancer Society Web Page. Cancer.org. Available at: https://www.cancer.org/cancer/breast-cancer/understanding-a-breast-cancer-diagnosis/breast-cancer-survival-rates.html. Accessed 3 Jun 2019.

4. Miller KD, Nogueira L, Mariotto AB, et al. Cancer treatment and survivorship statistics, 2019. CA Cancer J Clin. 2019;69(5):363–85.

5. Network NCC. Breast Cancer (Version 3.2019). https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed 28 Oct 2019.

6. Cardoso F, Senkus E, Costa A, et al. 4th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4). Ann Oncol. 2018;29(8):1634–57.

7. Finn RS, Crown JP, Lang I, et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of estrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. Lancet Oncol. 2015;16:25–35.

8. Cristofanilli M, Turner NC, Bondarenko I, et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative, metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. Lancet Oncol. 2016;17:425–39.

9. Sledge GW Jr, Toi M, Neven P, et al. MONARCH 2: Abemaciclib in combination with fulvestrant in women with HR+/HER2– advanced breast cancer who had progressed while receiving endocrine therapy. J Clin Oncol. 2017;35(25):2875–84.

10. 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.

11. Dickler MN, Tolaney SM, Rugo HS, et al. MONARCH 1, a phase II study of Abemaciclib, a CDK4 and CDK6 inhibitor, as a single agent, in patients...
with refractory HR+/HER2- metastatic breast cancer. Clin Cancer Res. 2017;23(17):5218–24.

12. Wander SA, Spring LM, Stein CR, et al. Abemaciclib after prior palbociclib exposure in patients with metastatic hormone-receptor positive (HR+)/HER2-breast cancer. In. 2018 San Antonio Breast Cancer Symposium; San Antonio, TX; December 4–8, 2018. Abstract P-06-18-39. https://www.abstracts2view.com/sabcs/view.php?nu=SABCS18L_1832.

13. Wander SA, Zangardi M, Niemierko A, et al. A multicenter analysis of abemaciclib after progression on palbociclib in patients (pts) with hormone receptor-positive (HR+)/HER2- metastatic breast cancer (MBC). J Clin Oncol. 2019;37(15 suppl): 1057.

14. Tamragouri K, Cobleigh MA, Rao RD. Abemaciclib with or without fulvestrant for the treatment of hormone receptor-positive and HER2-negative metastatic breast cancer with disease progression following prior treatment with palbociclib. J Clin Oncol. 2019;37(15 suppl): e12533.

15. Mariotti V, Khong HT, Soliman HH, et al. Efficacy of abemaciclib (abema) after palbociclib (palbo) in patients (pts) with metastatic breast cancer (MBC). J Clin Oncol. 2019;37(15 suppl): e12521-e12521 2521.

16. Lee KA, Shepherd STC, Johnston SRD. Abemaciclib, a potent cyclin-dependent kinase 4 and 6 inhibitor, for treatment of ER-positive metastatic breast cancer. Fut Oncol. 2019;15(29):3309-26.

17. Navarro-Yepes J, Chen X, Bui T, Kettner NM, Hunt KK, Keyomarsi K. Abstract PD2-05: differential mechanisms of acquired resistance to abemaciclib versus palbociclib reveal novel therapeutic strategies for CDK4/6 therapy-resistant breast cancers. Cancer Res. 2020. https://doi.org/10.1158/1538-7445.SABCS19-PD2-05.

18. US FDA. FDA Approved Drug Products (abemaciclib, palbociclib, ribociclib). https://www.accessdata.fda.gov/scripts/cder/daf/ Accessed 4 Jul 2020.

19. ClinicalTrials.gov Web Page. Bethesda (MD): National Library of Medicine (US). 2000 Feb 29 -. Identifier NCT02632045, Study of Efficacy of Ribociclib After Progression on CDK4/6 Inhibition in Patients With HR+ HER2- Advanced Breast Cancer (MAINTAIN); 2016 Mar. Available from: https://clinicaltrials.gov/ct2/show/NCT02632045. Cited Nov 2019.

20. ClinicalTrials.gov Web Page. Bethesda (MD): National Library of Medicine (US). 2000 Feb 29 -. Identifier NCT02738866, Palbociclib With Fulvestrant for Metastatic Breast Cancer After Treatment With Palbociclib and an Aromatase Inhibitor; 2016 Oct. Available from: https://clinicaltrials.gov/ct2/show/NCT02738866. Cited Nov 2019.

21. ClinicalTrials.gov Web Page. Bethesda (MD): National Library of Medicine (US). 2000 Feb 29 -. Identifier NCT02732119, Study of Ribociclib With Everolimus + Exemestane in HR+ HER2- Locally Advanced/Metastatic Breast Cancer Post Progression on CDK 4/6 Inhibitor. (TRINITI-1); 2016 Jun. Available from: https://clinicaltrials.gov/ct2/show/NCT02732119. Cited Nov 2019.

22. Bardia A, Hurvitz SA, DeMichele A, et al. Triplet therapy (continuous ribociclib, everolimus, exemestane) in HR-+/HER2-advanced breast cancer postprogression on a CDK4/6 inhibitor (TRINITI-1): Efficacy, safety, and biomarker results. J Clin Oncol. 2019;37(15):e1016–e10161016.

23. ClinicalTrials.gov Web Page. Bethesda (MD): National Library of Medicine (US). 2000 Feb 29. Identifier NCT03147287, Palbociclib After CDK and Endocrine Therapy (PACE). 2017 May. Available from: https://clinicaltrials.gov/ct2/show/NCT03147287. Cited Apr 2020.