Cancer Management and Research

Dovepress

open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Thromboembolic Events in Patients with HER2-Negative, Hormone Receptor-Positive, Metastatic Breast Cancer Treated with Ribociclib Combined with Letrozole or Fulvestrant: A Real-World Data

Hikmat Abdel-Razeq[1,2], Baha' Sharaf[1], Rama AlMasri[3], Rashid Abdel-Razeq[1], Faris Tamimi[1], Omar Khader[1], Osama Salama[1], Mahmoud Abunasser[1], Sarah Edaily[1], Hazem Abdulelah[1]

[1]Department of Internal Medicine, King Hussein Cancer Center, Amman, Jordan; [2]Department of Internal Medicine, School of Medicine, The University of Jordan, Amman, Jordan; [3]Department of Internal Medicine, Istishari Hospital, Amman, Jordan

Correspondence: Hikmat Abdel-Razeq, Department of Internal Medicine, King Hussein Cancer Center, 202 Queen Rania Al Abdullah Street, Amman, Jordan, Tel +962 79 643 3993, Fax +962 6 535 3001, Email habdelrazeq@khcc.jo

Purpose: Cyclin dependent kinase (CDK) 4/6 inhibitors (palbociclib, ribociclib and abemaciclib) modulate endocrine resistance and are integral treatment for patients with advanced hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer. Since their approval, CDK4/6 inhibitors are widely used in clinical practice. Thromboembolic events (TEE) were not a major issue in patients treated on clinical trials utilizing these agents. However, conflicting data started to emerge describing higher than expected rates of both arterial and venous thrombosis in patients treated with CDK4/6 inhibitors. In this study, we report our experience on TEE in patients treated with one of these agents (ribociclib) in real-world settings.

Patients and Methods: All consecutive patients with metastatic breast cancer (mBC) treated with ribociclib combined with letrozole or fulvestrant were retrospectively reviewed. All episodes of radiologically confirmed arterial or venous thrombosis were recorded. TEE was considered ribociclib-related if diagnosed while patients are on the drug, or within 4 weeks after the last dose.

Results: A total of 305 patients, median age (range), 49 (22–87) years were enrolled. All patients had metastatic disease, and most (n=241, 79.0%) were with visceral metastasis. Ribociclib was used for a median duration of 7 months (range: 1–45) and was used beyond the first-line setting in 110 (35.9%) patients. TEE were confirmed on 6 (1.97%) patients; 3 were pulmonary embolism, 2 cerebral venous sinus thrombosis (CVST), and one case of limb ischemia and all were symptomatic. Similar rates of TEE were noted prior to initiation, and after stopping ribociclib.

Conclusion: In real-world settings, breast cancer patients treated with ribociclib, combined with aromatase inhibitors or fulvestrant, may not be at higher risk for thromboembolic events. However, unusual sites of thrombosis, like CVST, may raise some concerns.

Keywords: CDK4/6 inhibitors, letrozole, fulvestrant, thrombosis, patient stratification, prediction

Introduction

Thromboembolism is commonly encountered in patients with cancer and is considered the second leading cause of mortality in this group of patients, too.[1,2] Risk is much higher among patients on active anti-cancer therapy including chemotherapy, immunotherapy, targeted therapy and endocrine therapy.[3,4] Multiple studies had shown that patients with TEE at diagnosis, or while on active therapy with anti-cancer drugs, have worse disease prognosis than cancer patients without.[5] Pathogenesis of thrombosis among cancer patients is complex and involves multiple factors related to the patients and underlying comorbidities, cancer itself and its therapy.[6–8]

Received: 11 December 2021
Accepted: 23 February 2022
Published: 8 March 2022

Breast cancer is the most common cancer diagnosed among women worldwide.[9–11] More than 70% of breast cancers are hormone receptor (HR)-positive, for which endocrine therapy (ET) is the preferred initial treatment for patients with no visceral crisis, and for those with low burden disease.[12] Despite recent advances in early detection and awareness, 5–20% of patients present with de novo metastatic disease and another 20% will develop systemic relapse; months to years after their initial diagnosis.[13] Patients with low-volume disease and without visceral crisis are usually treated with ET. Until few years ago, tamoxifen, aromatase inhibitors and fulvestrant were the only available options for upfront or subsequent endocrine therapy. However, majority of such patients acquire resistance to endocrine therapy. Cyclin-dependent kinases 4/6 (CDK4/6) inhibitors modulate this resistance and have become a corner stone in the treatment regimens of patients with advanced HR-positive, HER2-negative breast cancer. Since their first approval in 2015,[14] CDK4/6 inhibitors (palbociclib, ribociclib and abemaciclib) are widely used in clinical practice and had resulted in remarkable improvement in the way we treat metastatic HR-positive, HER2-negative breast cancer; both endocrine-resistant,[15–18] and endocrine sensitive tumors.[19–22] In addition to significant prolongation of time to disease progression, recent updates from the previously published studies have also shown significant improvement in overall survival (OS), as well.[17,23] Such dramatic outcomes were seen regardless of the companion endocrine therapy;[24] aromatase inhibitors, or fulvestrant and in both pre- and postmenopausal women.[25,26]

Though TEE were not a major issue among patients treated on clinical trials with the three CDK4/6 inhibitors, conflicting data recently started to emerge describing higher than expected rates of both arterial and venous thrombosis in patients treated with these drugs.

In this study, we use real world data to study TEE rates in patients treated with ribociclib, one of these CDK4/6 inhibitors, in real-world settings.

Methods

The study is a retrospective analysis of individual patients' data. All consecutive patients with pathologically confirmed diagnosis of metastatic breast cancer (mBC), treated and followed at our institution were reviewed. Patients should have been on ribociclib plus an aromatase inhibitor (letrozole) or fulvestrant for at least 3 months at time of data collection. Data were collected from patients' electronic medical records and from radiology department archives. Clinical and pathological features known to increase the risk of TEE were reviewed. All image-confirmed arterial or venous thrombosis were recorded. Thromboembolic event was considered ribociclib related if diagnosed while patients on the drug or within 4 weeks after the last dose. Deep venous thrombosis (DVT) was diagnosed by Doppler ultrasound, while pulmonary embolism (PE) was diagnosed by computed tomography (CT) angiogram. Routine screening for venous thromboembolism (VTE) among asymptomatic patients was not performed. However, incidental PE, found on imaging studies performed for other purposes, like staging, were counted.

The research was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). Because of the retrospective nature of the study and the lack of personal details of participants that compromise anonymity, consent was waived and the study was approved by King Hussein Cancer Center Institutional Review Board (IRB).

Results

During the study period, 305 patients were enrolled. Median age (range) was 49 (22–87) years, and 74 (24.3%) were 60 years or older, while 52 (17.0%) were younger than 40 years at time of TEE diagnosis. Except for 3 males, all patients enrolled were females. Majority (n=245, 80.3%) of the tumors were infiltrating ductal carcinoma (IDC), while 46 (15.1%) were infiltrating lobular carcinoma (ILC), and 89 (29.2%) were high-grade (grade-3).

All patients had metastatic disease; 168 (55.1%) were de novo metastasis, while the others had a recurrent disease. Most (n=241, 79.0%) patients had visceral metastasis at time of ribociclib therapy, including liver (n=67, 22.0%), lung (n=79, 25.9%), brain (n=17, 5.6%) with 70 (23.0%) had 3 or more sites of metastasis. Though bone metastasis was reported on 241 (79.0%), it was the only site of metastasis (bone-only disease) in 64 (20.9%), Table 1.

Ribociclib was used in combination with letrozole in first-line setting in 195 (63.9%) and with fulvestrant in 110 (35.9%) patients who failed one or more lines of ET, or chemotherapy. Median duration of ribociclib therapy was 7

Table 1 Patients' Characteristics (n=305)

Characteristics		Number	Percentage
Age (Years)	Median (Range) Years	49 (22–87)	
	< 40	52	17.0
	40–49	104	34.1
	50–59	75	24.6
	60–69	54	17.7
	≥ 70	20	6.6
Gender	Female	302	99.0
	Male	3	0.98
Timing of metastasis	De novo	168	55.1
	Recurrent	137	44.9
Site of metastasis	Bone	241	79.0
	Bone-only	119	39.0
	Liver	67	22.0
	Lung	79	25.9
	Brain	17	5.6
	Serosal surfaces	49	16.1
	Bone marrow	5	1.6
Number of metastatic sites	1	127	41.6
	2	108	35.4
	3	42	13.8
	≥ 4	28	9.2
Smoking history	Current smoker	30	9.8
	Prior smoker	15	4.9
	Never smoked	219	71.8
	Unknown	41	13.4
Pathology	IDC	245	80.3
	ILC	46	15.1
	Others	14	4.6
Tumor grade	I	22	7.2
	II	173	56.7
	III	89	29.2
	NA	21	6.9

(*Continued*)

Table 1 (Continued).

Characteristics		Number	Percentage
ECOG performance status	Zero	192	63.0
	1	97	31.8
	2	10	3.3
	3–4	2	0.6
	NA	4	1.3

Abbreviations: IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; NA, not available; ECOG, Eastern Cooperative Oncology Group.

(range 1–45) months, with 56 (18.4%) patients were on the drug for 18 or more months. A total of 178 (58.4%) had complete response (CR), partial response (PR) or stable disease (SD), Table 2.

Episodes of TEE were confirmed in 6 (1.97%) patients; 3 were PE (two were bilateral), and all were symptomatic, while two patients had cerebral venous sinus thrombosis (lateral sagittal sinus and superior sagittal sinus). One patient had arterial thrombosis manifested as lower limb ischemia. Thromboembolic events were diagnosed as early as 15 days after starting ribociclib and ET, and as late as 6 months later. Among the 6 patients with TEE, other risk factors for TEE were identified including active smoking in 3, recent hospital admission (within 30 days of TEE) in one, and the recent cancer diagnosis (≤ 6 months) in 5 patients, Table 3. Seven (2.3%) more patients had a confirmed diagnosis of TEE prior

Table 2 Endocrine Therapy

Characteristics		Number	Percentage
Line of therapy	First Line	195	63.9
	Beyond first line	110	36.1
Companion ET	Letrozole	195	63.9
	Fulvestrant	110	36.1
Duration of ribociclib therapy (months)	Median (Range)	7 (1–45)	
	< 6 Months	139	45.5
	6–12 Months	66	21.6
	12–18 Months	44	14.4
	≥ 18 Months	56	18.4
Ribociclib dose reduction	Yes	44	14.4
	No	261	85.6
Response to ribociclib	Complete response (CR)	1	0.3
	Partial response (PR)	105	34.4
	Stable disease (SD)	72	23.6
	Disease progression (DP)	68	22.2
	Not available	59	19.3

Abbreviation: ET, endocrine therapy.

Table 3 Confirmed Cases of Thromboembolic Events

Case Number	Age (Years)	Smoking	Site of VTE	Time to TEE	Endocrine Therapy Companion	Type of Metastasis	Metastatic Site	Other Risk Factors for TEE
1	43	No	Lateral sinus thrombosis	6 months	AI/GnRHa	Recurrent	Brain, Lymph Nodes	Cancer diagnosis < 6 months
2	64	No	Bilateral PE	3 months	AI	De novo	Bone, Leptomeningeal, Bone Marrow	Cancer diagnosis < 6 months,
3	65	No	Bilateral PE	1 month	Fulvestrant	De Novo	Peritoneal Ascites	Hospital admission within 30 days of TEE
4	67	Yes	Superior sagittal sinus thrombosis	15 days	AI	De Novo	Bone, Liver, Pleura	Cancer diagnosis < 6 months Dyslipidemia, Diabetes
5	77	Yes	PE	3 months	AI	Recurrent	Bone	Cancer diagnosis < 6 months
6	77	Yes	Lower limb ischemia	1 month	AI	Recurrent	Lung, Bone, Pleural effusion	Cancer diagnosis < 6 months

Abbreviations: TEE, thromboembolic events; AI, aromatase inhibitors; GnRHa, gonadotropin releasing hormone agonists; PE, pulmonary embolism.

to starting ribociclib therapy and another 4 (1.3%) patients had confirmed episodes after stopping the drug; range 2–7 months.

All patients were treated with low-molecular heparin (LMWH) with no complications. Given the small number of patients with TEE, no clinical or pathological predictors could be used to identify subgroups of patients at higher risk for TEE while on ribociclib.

Discussion

Since the introduction of CDK4/6 inhibitors, millions of patients with metastatic breast cancer were treated with these drugs in combination with aromatase inhibitors or fulvestrant. Common adverse events associated with such combination are familiar, predictable, manageable and were fully addressed in published clinical trials and clinical practice guidelines.[27,28] However, thromboembolic events; venous or arterial were not part of these adverse events.

Patients with metastatic breast cancer are at higher risk for TEE by virtue of their age and advanced-stage disease, which may affect their mobility and may result in frequent hospitalization. Additionally, both tamoxifen and aromatase inhibitors, in their own, may increase such risk. Recent reports about the higher incidence of both arterial and venous thrombosis among such patients are of a concern. However, such events are not as obvious as other commonly encountered adverse events with these drugs like neutropenia, thrombocytopenia, anemia, fatigue, diarrhea and elevated liver enzymes.[29,30]

One meta-analysis included 8 randomized controlled trials and a total of 4557 eligible patients. The study arms were ET plus a CDK4/6 inhibitor (palbociclib, ribociclib or abemaciclib) or ET plus placebo. Venous thromboembolic events were recorded in 56 (2%) in the CDK4/6 inhibitor plus ET arm, compared to only 10 (0.5%) in the control arm; the pooled relative risk (RR) for VTE was 2.62 [95% Confidence Interval (CI) 1.21–5.65; P= 0.01]. Over a median follow-up of up to 36 months, RR increased to 3.18 (95% CI 1.22–8.24; P= 0.02). Subgroup analysis showed that most of the reported VTE were among patients treated with abemaciclib (RR=6.77, 95% CI 1.61–28.43), less with ribociclib (RR=2.19, 95% CI 0.80–5.97) and palbociclib (RR=2.33, 95% CI 0.36–15.19), Table 4.[31]

Another study used the Food and Drug Administration (FDA) pharmacovigilance database to retrospectively assess TEE in real world practice.[32] The study again raised a concern about a potential class effect for venous thrombosis, especially PE.

Table 4 Summary of Published Studies

Clinical Trial	Study Arms	Number of Patients Included	End Point	Thrombosis Rate	Relative Risk (RR) 95% CI	P-value
All CDK4/6 inhibitors	CDK4/6 arms	2793	VTE	56 (2%)	2.62 1.21–5.65	0.01
	Control	1764		10 (0.5%)		
PALOMA	Palbociclib	872	VTE	14 (1.6%)	2.33 0.36–15.19	0.38
	Control	471		3 (0.6)		
MONALEESA	Ribociclib	1153	VTE	13 (1.12%)	2.19 0.80–5.97	0.13
	Control	909		5 (0.55%)		
MONARCH	Abemaciclib	768	VTE	29 (3.77%)	6.77 1.61–28.43	0.009
	Control	384		2 (0.5%)		

Note: Data from Thein et al.[31]
Abbreviations: CI, confidence interval; CDK4/6, cyclin dependent kinase; VTE, venous thromboembolism.

However, a distinctive risk for arterial events were noted in patients treated with ribociclib, including myocardial infarction (MI), cerebral ischemia, transient ischemic attacks (TIA), paraplegia, and paraparesis, which tend to happen sooner than the other CDK4/6 inhibitors; 1 vs 6 months, respectively. The study also showed that abemaciclib was associated with a higher risk for DVT, which was well noted in many randomized clinical trials,[33] including the more recently published monarchE study, which used abemaciclib for high-risk node positive early-stage (nonmetastatic) breast cancer; VTE rate was 2.3% in patients randomized to the abemaciclib arm compared to only 0.5% in the control arm.[34] Palbociclib, on the other hand, was associated with higher risk of cerebrovascular accidents and cardiovascular comorbidities.

Different conclusions were drawn from another study that also used the US FDA Adverse Event Reporting System (FAERS) database between January 2015 and December 2020. The study highlighted the possible association between CDK4/6 inhibitors and VTE. Patients treated with CDK4/6 inhibitors had 631 venous thromboembolic events [Reporting odd ratio (ROR) 1.44, 95% CI 1.33–1.55]. Risk was almost similar for both palbociclib (ROR 1.42, 95% CI 1.09–1.88) and ribociclib (ROR 1.41, 95% CI 1.29–1.54). Contrary to the previous study, abemaciclib was associated with the lowest risk (ROR 0.92, 95% CI 0.72–1.17).[35]

Our data, utilizing ribociclib with letrozole or fulvestrant, may not raise significant concerns regarding venous or arterial thrombosis. The few reported TEE are in line with what clinicians usually see in routine daily practice. Additionally, our TEE rates were similar to what patients had encountered prior to, and after stopping CDK4/6 inhibitors. However, the two cases of cerebral venous sinus thrombosis among a total of 6 confirmed cases of TEE, worth emphasis and closer look in future studies. Both patients were on aromatase inhibitors (letrozole), and one of them was also on Gonadotropin Releasing Hormone agonists (GnRHa), too. Cerebral venous sinus thrombosis is relatively rare;[36] puerperium,[37] contraception, hyperthyroidism,[38] meningitis, hypercoagulable state,[39] meningioma, multiple myeloma, Behcet's disease,[40] Crohn, ulcerative colitis,[41] and epidural anesthesia are among the known causes, and none were identified in our patients.

Our study, though represent a real-world data, is not without limitations. The retrospective nature and absence of randomization may miss some of the thromboembolic events. Additionally, our data is relevant to only one drug in this class of medications (ribociclib), and findings may not be generalized for the other two CDK4/6 inhibitors; palbociclib and abemaciclib. A better approach to answer the question under discussion is to collect data from all phase-3 studies on all CDK4/6 inhibitors (ribociclib, palbociclib and abemaciclib) and utilize artificial intelligence approach to stratify patients into different risk levels for TEE to better predict the occurrence of TEE utilizing clinical and biomarker data.

Conclusions

In real-world settings, breast cancer patients treated with ribociclib, in combination with aromatase inhibitors or fulvestrant, may not be at higher risk for arterial or venous thromboembolic events. Our TEE rates are similar to what patients had encountered prior to, and after stopping CDK4/6 inhibitors. However, the unusual sites of TEE reported in our cohort raises some concerns, and worth further investigations.

Abbreviations

CDK, cyclin dependent kinase; CI, confidence interval; CR, complete response; CT, computed tomography; CVST, cerebral venous sinus thrombosis; DVT, deep vein thrombosis; ET, endocrine therapy; FAERS, Food and Drug Administration Adverse Event Reporting System; FDA, Food and Drug Administration; GnRHa, gonadotropin releasing hormone agonists; HER2, human epidermal growth factor receptor 2; HR, hormone receptors; IDC, infiltrating ductal carcinoma; ILC, infiltrating lobular carcinoma; IRB, Institutional Review Board; LMWH, low-molecular heparin; mBC, metastatic breast cancer; OS, overall survival; PE, pulmonary embolism; PFS, progression-free survival; PR, partial response; ROR, reporting odd ratio; SD, stable disease; TEE, thromboembolic events; VTE, venous thromboembolism.

Data Sharing Statement

Data will be made available, as per the journal and publisher rules and regulations, from the corresponding author on reasonable request.

Ethics Approval and Informed Consent

This research was done in accordance with the ethical standards of the institutional and international research standards and with the 1964 Helsinki declaration and its later amendments. The study was approved by King Hussein Cancer Center Institutional Review Board (IRB). Because of the retrospective nature of the study and the lack of personal details of participants that compromise anonymity, consent was waived.

Consent for Publication

Given the retrospective nature of the study and the lack of personal details of participants that compromise anonymity, consent for publication was not sought from the participants, but obtained from the hospital administration.

Acknowledgments

The authors would like to acknowledge the help of our librarians, Mrs. Alice Haddadin and Mrs. Lubna Al-Useily.

Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article was submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Funding

No grants were received from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Abdol Razak NB, Jones G, Bhandari M, Berndt MC, Metharom P. Cancer-associated thrombosis: an overview of mechanisms, risk factors, and treatment. *Cancers*. 2018;10(10):380. doi:10.3390/cancers10100380
2. Prandoni P, Falanga A, Piccioli A. Cancer and venous thromboembolism. *Lancet Oncol*. 2005;6(6):401–410. doi:10.1016/S1470-2045(05)70207-2
3. Mulder FI, Horváth-Puhó E, van Es N, et al. Venous thromboembolism in cancer patients: a population-based cohort study. *Blood*. 2021;137(14):1959–1969. doi:10.1182/blood.2020007338

4. Moik F, Chan WE, Wiedemann S, et al. Incidence, risk factors, and outcomes of venous and arterial thromboembolism in immune checkpoint inhibitor therapy. *Blood*. 2021;137(12):1669–1678. doi:10.1182/blood.2020007878
5. Fuentes HE, Tafur AJ, Caprini JA. Cancer-associated thrombosis. *Dis Mon*. 2016;62(5):121–158. doi:10.1016/j.disamonth.2016.03.003
6. Khorana AA, Francis CW, Culakova E, Lyman GH. Risk factors for chemotherapy-associated venous thromboembolism in a prospective observational study. *Cancer*. 2005;104(12):2822–2829. doi:10.1002/cncr.21496
7. Khorana AA, Dalal M, Lin J, Connolly GC. Incidence and predictors of venous thromboembolism (VTE) among ambulatory high-risk cancer patients undergoing chemotherapy in the United States. *Cancer*. 2013;119(3):648–655. doi:10.1002/cncr.27772
8. Abdel-Razeq H, Mansour A, Abdulelah H, et al. Thromboembolic events in cancer patients on active treatment with cisplatin-based chemotherapy: another look! *Thromb J*. 2018;16(2). doi:10.1186/s12959-018-0161-9
9. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209–249. doi:10.3322/caac.21660
10. Ferlay J, Colombet M, Soerjomataram I, et al. Cancer statistics for the year 2020: an overview. *Int J Cancer*. 2021;149(4):778–789. doi:10.1002/ijc.33588
11. Lei S, Zheng R, Zhang S, et al. Global patterns of breast cancer incidence and mortality: a population-based cancer registry data analysis from 2000 to 2020. *Cancer Commun*. 2021;41(11):1183–1194. doi:10.1002/cac2.12207
12. Howlader N, Altekruse SF, Li CI, et al. US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. *J Natl Cancer Inst*. 2014;106(5):dju055. doi:10.1093/jnci/dju055
13. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. *Lancet*. 2015;386(10001):1341–1352. doi:10.1016/S0140-6736(15)61074-1
14. US Food & Drug Administration. Resources for Information; Approved Drugs: Palbociclib (IBRANCE); 2017.Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/palbociclib-ibrance. Accessed February 28, 2022.
15. 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 [published correction appears in Lancet Oncol. 2016;17 (4): e136][published correction appears in Lancet Oncol. 2016;17 (7): e270]. *Lancet Oncol*. 2016;17(4):425–439. doi:10.1016/S1470-2045(15)00613-0
16. 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 [published correction appears in Clin Cancer Res. 2018; 24(21):5485]. *Clin Cancer Res*. 2017;23(17):5218–5224. doi:10.1158/1078-0432.CCR-17-0754
17. Slamon DJ, Neven P, Chia S, et al. Overall survival with ribociclib plus fulvestrant in advanced breast cancer. *N Engl J Med*. 2020;382(6):514–524. doi:10.1056/NEJMoa1911149
18. 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):2875–2884. doi:10.1200/JCO.2017.73.7585
19. Rugo HS, Finn RS, Diéras V, et al. Palbociclib plus letrozole as first-line therapy in estrogen receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer with extended follow-up. *Breast Cancer Res Treat*. 2019;174(3):719–729. doi:10.1007/s10549-018-05125-4
20. Hortobagyi GN, Stemmer SM, Burris HA, et al. Updated results from MONALEESA-2, a Phase III trial of first-line ribociclib plus letrozole versus placebo plus letrozole in hormone receptor-positive, HER2-negative advanced breast cancer [published correction appears in Ann Oncol. 2019; 30(11):1842]. *Ann Oncol*. 2018;29(7):1541–1547. doi:10.1093/annonc/mdy155
21. Finn RS, Martin M, Rugo HS, et al. Palbociclib and letrozole in advanced breast cancer. *N Engl J Med*. 2016;375(20):1925–1936. doi:10.1056/NEJMoa1607303
22. Goetz MP, Toi M, Campone M, et al. MONARCH 3: abemaciclib as initial therapy for advanced breast cancer. *J Clin Oncol*. 2017;35(32):3638–3646. doi:10.1200/JCO.2017.75.6155
23. Turner NC, Slamon DJ, Ro J, et al. Overall survival with palbociclib and fulvestrant in advanced breast cancer. *N Engl J Med*. 2018;379(20):1926–1936. doi:10.1056/NEJMoa1810527
24. Llombart-Cussac A, Pérez-García JM, Bellet M, et al. Fulvestrant-palbociclib vs letrozole-palbociclib as initial therapy for endocrine-sensitive, hormone receptor-positive, ERBB2-negative advanced breast cancer: a randomized clinical trial. *JAMA Oncol*. 2021:e214301. doi:10.1001/jamaoncol.2021.4301
25. Neven P, Rugo HS, Tolaney SM, et al. Abemaciclib plus fulvestrant in hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer in premenopausal women: subgroup analysis from the MONARCH 2 trial. *Breast Cancer Res*. 2021;23(1):87. doi:10.1186/s13058-021-01463-2
26. Tripathy D, Im SA, Colleoni M, et al. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial. *Lancet Oncol*. 2018;19(7):904–915. doi:10.1016/S1470-2045(18)30292-4
27. Yang L, Xue J, Yang Z, et al. Side effects of CDK4/6 inhibitors in the treatment of HR+/HER2- advanced breast cancer: a systematic review and meta-analysis of randomized controlled trials. *Ann Palliat Med*. 2021;10(5):5590–5599. doi:10.21037/apm-21-1096
28. NCCN Clinical practice guidelines in oncology. Breast cancer, version 8; 2021. Available from: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed November 01, 2021.
29. Hu W, Sung T, Jessen BA, et al. Mechanistic investigation of bone marrow suppression associated with palbociclib and its differentiation from cytotoxic chemotherapies. *Clin Cancer Res*. 2016;22(8):2000–2008. doi:10.1158/1078-0432.CCR-15-1421
30. Chandrasekhar S, Fradley MG. QT interval prolongation associated with cytotoxic and targeted cancer therapeutics. *Curr Treat Options Oncol*. 2019;20(7):55. doi:10.1007/s11864-019-0657-y
31. Thein KZ, Htut TW, Ball S, Swarup S, Sultan A, Oo TH. Venous thromboembolism risk in patients with hormone receptor-positive HER2-negative metastatic breast cancer treated with combined CDK 4/6 inhibitors plus endocrine therapy versus endocrine therapy alone: a systematic review and meta-analysis of randomized controlled trials. *Breast Cancer Res Treat*. 2020;183(2):479–487. doi:10.1007/s10549-020-05783-3
32. Raschi E, Fusaroli M, Ardizzoni A, Poluzzi E, De Ponti F. Thromboembolic events with cyclin-dependent kinase 4/6 inhibitors in the FDA adverse event reporting system. *Cancers*. 2021;13(8):1758. doi:10.3390/cancers13081758

33. Rugo HS, Huober J, García-Sáenz JA, et al. Management of abemaciclib-associated adverse events in patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: safety analysis of MONARCH 2 and MONARCH 3 [published correction appears in Oncologist. 2021; 26(3):e522]. *Oncologist*. 2021;26(1):e53–e65. doi:10.1002/onco.13531
34. Johnston SRD, Harbeck N, Hegg R, et al. Abemaciclib combined with endocrine therapy for the adjuvant treatment of HR+, HER2-, node-positive, high-risk, early breast cancer (monarchE). *J Clin Oncol*. 2020;38(34):3987–3998. doi:10.1200/JCO.20.02514
35. Yan MM, Wu SS, Qi YP, et al. Association between cyclin-dependent kinase 4/6 inhibitors and venous thromboembolism: analysis of F.A.E.R.S. *Expert Opin Drug Saf*. 2021:1–7. doi:10.1080/14740338.2021.1981856
36. Weimar C, Masuhr F, Hajjar K. Diagnosis and treatment of cerebral venous thrombosis. *Expert Rev Cardiovasc Ther*. 2012;10(12):1545–1553. doi:10.1586/erc.12.126
37. Cole B, Criddle LM. A case of postpartum cerebral venous thrombosis. *J Neurosci Nurs*. 2006;38(5):350–353. doi:10.1097/01376517-200610000-00005
38. Nagumo K, Fukushima T, Takahashi H, Sakakibara Y, Kojima S, Akikusa B. [Thyroid crisis and protein C deficiency in a case of superior sagittal sinus thrombosis]. *Brain Nerve*. 2007;59(3):271–276. Japanese.
39. Zhang Z, Long J, Li W. Cerebral venous sinus thrombosis: a clinical study of 23 cases. *Chin Med J*. 2000;113(11):1043–1045. PMID: 11776122.
40. Aguiar de Sousa D, Mestre T, Ferro JM. Cerebral venous thrombosis in Behçet's disease: a systematic review. *J Neurol*. 2011;258(5):719–727. doi:10.1007/s00415-010-5885-9
41. Katsanos AH, Katsanos KH, Kosmidou M, Giannopoulos S, Kyritsis AP, Tsianos EV. Cerebral sinus venous thrombosis in inflammatory bowel diseases. *QJM*. 2013;106(5):401–413. doi:10.1093/qjmed/hcs229