CDK 4/6 inhibitors combined with radiotherapy: A review of literature

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A B S T R A C T

Cyclin-dependent kinase 4 and 6 inhibitors (CDK4/6i) namely palbociclib, ribociclib and abemaciclib were granted approval by the European Medicines Agency (EMA) between 2017 and 2018. They are currently prescribed in combination with hormone therapy to treat hormone receptor positive, HER2 negative metastatic or locally advanced breast cancer. Their combination with radiotherapy raises safety concerns as preclinical data enlightened their possible synergistic effect. Moreover, data about toxicity when combining CDK4/6i with radiotherapy are scarce. This review of literature focused on the use of CDK4/6i combined with radiotherapy. It aimed at listing every published data about such combination so as to understand its possible resulting toxicity in metastatic breast cancer.

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1. Introduction

Since 2017, cyclin 4 and 6 dependent kinase inhibitors (CDK4/6i) have been used to treat women with ER-positive, HER2-negative metastatic or locally advanced breast cancer. Their combination with hormone therapy such as aromatase inhibitors or fulvestrant produce a synergistic effect, which prevents cancer cell division [1–7]. Palbociclib was granted European approval based on the PALOMA 2 and 3 trials [8–10]. Ribociclib received European approval based on MONALEESA 2 and 3 trials [11–15]. Recently, an improvement in overall survival (OS) was reported in MONALEESA-7 [16]. Abemaciclib received European approval based on MONARCH 2 and 3 studies [17–19]. The latest update of MONARCH 2 showed a significant improvement of OS. Tolerance remained the same whatever the combined hormone therapy. CDK4/6 inhibitors (CDK4/6i) pharmacological characteristics are listed in Table 1.

Metastatic breast cancer patients often need palliative radiotherapy. A study about the benefit of curative-intent radiotherapy on primary tumor or oligometastases is currently ongoing and, its
preliminary results are promising [20–23]. Yet, little is known about the safety of the combination of CDK4/6i and radiotherapy. Preclinical studies suggested CDK4/i had a radiation-sensitizing effect on human cancer cell lines as they inhibited repair mechanisms of double DNA stand breaks [24–37]. Indeed, CDK4/6i may increase radiotherapy antitumor effect by first, controlling cell progression from G1 phase to the more radioresistant S phase and secondly, by inhibiting repair mechanisms of DNA double-strand break [24–37]. Moreover, when radiotherapy and CDK4/6i were combined, markers of DNA damage (γH2AX) and apoptosis (cPARP) increased. Conversely, acute gastrointestinal toxicity in mice was observed with concomitant palbociclib and fractionated abdominal radiotherapy [34]. Grade 3 enterocolitis was observed in one patient after palbociclib and palliative radiotherapy combination [35]. Thus, a careful analysis of every clinical data is required before lightening the radiotherapy-CDK4/6i combination. Such step will be all the more crucial as CDK4/6i could be used in other cancers [25]. Data about toxicity due to the combination of CDK4/6i with radiotherapy are rare. This review of literature aimed at listing reported toxicities caused by CDK4/6i combined with radiotherapy.

2. Materials and methods

A systematic assessment of literature articles was performed by searching in Pubmed Medline and Cochrane databases until January 1st 2020. The following keywords were used: “CDK4/6i”; “palbociclib”; “ribociclib”; “abemaciclib”; and “radiotherapy”, “radiation”, “radiation therapy”. As to in vivo and in vitro studies, they were excluded. Nine hundred and eighteen articles were identified. After focusing on titles and abstracts, 19 articles remained. Then, after focusing on CDK4/6i, only 7 articles were included in the final analysis.

3. Results

The 7 publications described the outcome of 92 radiotherapy procedures combined with CDK4/6i in 59 patients. Thirty-five patients (59%) received palliative radiotherapy for bone, brain or liver metastases from breast cancer. Twenty-four patients (41%) had curative radiotherapy for oligometastatic disease. Some studies pooled patients who had received different CDK4/6i and different types of radiotherapy treatments. Other studies analysed the number of irradiated sites. Two studies pooled patients who had different treatment protocols including concurrent, pre or post CDK4/6i combined with radiotherapy. The characteristics of all 7 studies included are summarized in Table 2.

### Table 1

| CDK4/6 inhibitors | Palbociclib | Ribociclib | Abemaciclib |
|-------------------|-------------|------------|-------------|
| **Approval**      | - Hormone receptor positive, HER2 negative metastatic or locally advanced breast cancer | - Hormone receptor positive, HER2 negative metastatic or locally advanced breast cancer | Hormone receptor positive, HER2 negative metastatic or locally advanced breast cancer |
|                   | - in combination with aromatase inhibitors or fulvestrant (in pre- or post-menopausal patients combined with LH-RH agonist) | - in combination with aromatase inhibitors or fulvestrant (in pre- or post-menopausal patients combined with LH-RH agonist) | In combination with aromatase inhibitors or fulvestrant (in pre- or post-menopausal patients combined with LH-RH agonist) |
|                   | - women treated with hormone therapy before | - as first-line treatment or after hormone therapy | - as first-line treatment or after hormone therapy |
| **Most frequent side effects** | **All grades:** Neutropenia, infections, leucopenia, fatigue, nausea, stomatitis, anaemia, alopecia et diarrhoea. | **Grade 3 and 4:** Neutropenia, leucopenia, anemia, fatigue, infections | **All grades:** Diarrhoea, infections, neutropenia, anemia, fatigue, nausea, vomiting, lack of appetite |
|                   | Grade 3 and 4: Neutropenia, leucopenia, anemia, fatigue, infections | | Grade 3 and 4: Neutropenia, diarrhoea, leucopenia, anemia and infections |
| **Dose schedule**  | 1 cycle = Daily dose 125 mg (1 pill) for 21 days + 7 days without treatment | 1 cycle = Daily dose 600 mg (3 pills) for 21 days + 7 days without treatment | 150 mg twice a day, without interruption |
| **Half-life**      | 28.8 h | 32 h | 24.8 h |
| **5 half-lives**   | 6 days | 6.7 days | 5.2 days |
| First Author | Dates of publication | Molecule | Design | Number of patients | Combination Radiotherapy | Radiation-induced toxicity grade ≥ 2 or treatment delay |
|--------------|----------------------|----------|--------|--------------------|--------------------------|--------------------------------------------------|
| **PALBOCICLIB** | | | | | | |
| [38] Hans S | 01-2018 | Palbociclib plus Fulvestrant | Retrospective cohort | N = 5 | Concurrent | - Palliative: 4 patients with bone metastases: 20 Gy/5fr (1 sacral iliac, 1 scapula, 2 vertebra) - Curative: 1 patient with liver metastases: 60 Gy/10fr |
| [35] Kawamoto | 10-2018 | Palbociclib + Fulvestrant | Case report | N = 1 | Concurrent | 30 Gy/10fr, Left iliac bone and first sacral vertebrae. Bloating, bloody diarrhoea and grade 3 colitis confirmed by CT scan and colonoscopy, to the irradiation field. No acute/late toxicity at 14.7 months |
| [39] Chowdhary | 1-2019 | Palbociclib + Fulvestrant (n = 6) or + letrozole (n = 10) | Retrospective cohort | N = 16 | 4 before RT (25.0%), 5 concurrently (31.3%), 7 after RT (43.8%), | - 3 whole brain, 30 Gy/10fr to 35 Gy/14fr - 1 stereotactic radiosurgery frontal cavity 25 Gy/5fr - 1 mediastinum IMRT 36 Gy/18fr - 18 bone (11 axial skeleton, 4 pelvis, 3 extremity) - 1 Right calvarium IMRT 37.5 Gy/15fr - 1 cervical vertebral SBRT 18 Gy/1fr Exophagitis after 5 fr, dermatitis grade 2 after 20 fr dysphagia grade 3 requiring a break in treatment. 1 month hospitalization and finish the radiation without palbociclib 20 Gy/10fr. 2 early interruptions due to grade 2 skin toxicity (6.3%) |
| [40] Messer JA | 5-2019 | Palbociclib plus Fulvestrant | Case report | N = 1 | Concurrent | - supraclavicular lymph node, 60 Gy/30fr, 3D-CRT |
| [41] Ippolito | 5-2019 | Palbociclib plus Letrozole or Fulvestrant | Retrospective cohort | N = 3 (5 rt) | Concurrent | - 11 patients undergoing palliative bone radiotherapy (median dose 30 Gy, 8–36 Gy). - 5 oligo metastatic patients (31.2%) treated with higher doses (median dose 50 Gy, range 39.6–60 Gy). - 19 3D-CRT, 2 IMRT, 3 VMAT 2 radionecrosis (5%), 2 early interruptions due to grade 2 skin toxicity (6.3%) |
| [42] Figura | 8-2019 | Palbociclib (n = 10; 67%) or -Abemaciclib (n = 5; 33%) | Retrospective cohort | N = 15, 42 sites irradiations | Concurrently 18/43% before 19/43% after 9/36% | 2 radionecrosis (5%), |
| **RIBOCICLIB** | | | | | | |
| [43] Meattini | 12-2018 | Ribociclib plus Letrozole | Retrospective cohort | N = 5 | Concurrent | - bone metastases (femoral neck, hip, lumbar and cervical spine) - 1 VMAT (30 Gy/5fr) - 4 3D-CRT (20 Gy/5fr) 1 grade 2 diarrhea, right hip ribociclib suspension 2 weeks No toxicity at 3 months |

(continued on next page)
Table 2 (continued)

| First Author | Dates of publication | Molecule | Design | Number of patients | Combination | Radiotherapy | Radiation-induced toxicity |
|--------------|----------------------|----------|--------|-------------------|-------------|--------------|----------------------------|
| [41] Ippolito | 5-2019 | -Palbociclib (n = 10; 67%) or -Abemaciclib (n = 5; 33%). | Retrospective cohort | N = 15 (42 treatments) | Concurrent 18 (43%) | -Median follow-up 9 month Technique: Stereotactic Body Radiotherapy (IMRT 6Mv) | 2 radionecrosis (5%) |
| [42] Figura  | 8-2019 | -Palbociclib plus Letrozole or Fulvestrant -n = 3 (5 tt) | Retrospective cohort | N = 16 | Concurrent | -11 patients undergoing palliative bone radiotherapy (median dose 30 Gy, 8–36 Gy) -5 oligo metastatic patients (31.2%) treated with higher doses (median dose = 50 Gy, range 39.6–60 Gy) -19 3D-CRT 2 IMRT 3 VMAT | 2 early interruptions (one grade 2 dermatitis (6.3%)) |

Abbreviations: fr: fraction; tt: treatment.

report [35] about a patient with no medical history of digestive tract disease. He received palbociclib + fulvestrant concurrently with 3D conformal radiotherapy (30 Gy/10fr) on the left iliac bone and first sacral vertebrae. Three days after radiotherapy completion, the patient experienced grade 3 colitis. CT scan and colonoscopy revealed bowel wall thickening corresponding to inflammatory disorders. The patient had no radio-sensitizing comorbidity such as an inflammatory intestinal disease and no radio-sensitizing treatment. The doses on the colon were limited (Dmax = 31.9 Gy so 106.3% of the prescribed dose, V10Gy = 21 cc, V20Gy = 18 cc). Palbociclib was therefore suspected of causing this unusual toxicity in radiation fields. In January 2019, a retrospective study reported outcome of 16 breast cancer patients with bone metastases radiotherapy and palbociclib [39]. Six patients had concurrent fulvestrant and ten had letrozole. Palbociclib was administered at different times from radiotherapy. Eleven patients had sequential treatment combination (palbociclib was prescribed before radiotherapy in 4 patients (25%) and after in 7 patients (43.8%)) whereas 5 patients had a concurrent administration (31.2%). The irradiated sites were bone (11 axial skeleton among which 2 stereotactic radiosurgery, 4 pelvic, 3 extremities), brain (3 whole brain radiotherapy, 1 stereotactic radiosurgery) and mediastinum (1). Bone stereotactic radiosurgery delivered 18 Gy/1fraction on C2 vertebrae and 30 Gy/3 fractions on the left iliac bone. A dose of 25 Gy/5 fractions brain stereotactic surgery was delivered post-surgery. Other treatments were mostly 3D conformational (2 IMRT in 16 patients) which delivered 30–37 Gy in 10–15 fractions. Median follow-up was 14.7 months. Pain relief and local control were achieved in all patients. Before radiotherapy, 4 patients developed leucopenia (25%), 5 had neutropenia (31.3%) and 1 developed thrombopenia (6.3%). After radiotherapy, 5 patients developed leucopenia (31.3%), 1 patient showed neutropenia (6.3%) and 3 patients developed thrombopenia (18.8%). Usual palbociclib induced hematological toxicities were grades 1 to 2. No grade ≥ 2 acute or late radio-induced dermatological, neurological or gastrointestinal toxicity was observed. No significant increase in acute or late toxicities with CDK4/6i and radiotherapy combination was reported but when palbociclib was administered alone. In addition, toxicity remained the same regardless of the irradiated site, the type of hormone therapy and the chronology of palbociclib and radiotherapy initiation. Authors concluded that, as toxicity was low, the radiotherapy/palbociclib combination could be used safely. The results of a 2019 case report about 60 Gy, 30 fractions curative-intent radiotherapy were less reassuring [40]. The patient with metastatic breast cancer received radiation treatment to a metastatic supraclavicular and axillary lymph node field. 3-D conformal radiotherapy was performed on one treatment field. It was combined with concurrent palbociclib-fulvestrant. No customized bolus was used during radiotherapy. The maximum dose was 63.6 Gy, the equivalent of 106% of the prescribed dose. After 5 fractions, the patient developed oedema although the planned doses to esophagus were limited (Dmax esophagus = 27 Gy, Dmean = 9 Gy). After 40 Gy (20 fractions), she developed grade 2 skin toxicity. In vivo dosimetry showed no significant difference from planned dosimetry. The following day, the patient developed grade 3 dysphagia and dermatitis as well as grade 2 pain requiring IV hydration in hospital. Palbociclib and radiotherapy were stopped for 1 month. The remaining 20 Gy were delivered without restarting palbociclib and it was well-tolerated. No information was available regarding the management of hormone therapy. Palbociclib was restarted 1 month after radiotherapy completion. Six months later, images showed no sign of disease and side effects had totally healed. In May 2019, Ippolito et al. published a retrospective evaluation of the early toxicity of concurrent radiotherapy combined with palbociclib or ribociclib in metastatic breast cancer patients [41]. Thirteen out of the 16 patients (81.3%) received palbociclib combined with letrozole or fulvestrant. Most patients (68.7%) received palliative radiotherapy to bones. The median dose was 30 Gy (range: 8–36 Gy). Five patients (31.2%) received higher doses (median dose 50 Gy, range: 39.6–60 Gy) on oligo-metastatic or oligo-progressive cancer sites. The most common toxicity was hematologic. Neutropenia was common (grade 2 = 12.5%, grade 3 = 25%, grade 4 = 6.3%). Sixty per cent of the patients with grade ≥ 3 neutropenia had already experienced neutropenia during previous cycles of palbociclib. Because of hematologic side effects, 1 patient suspended palbociclib 7 days earlier. Among the 13 patients on palbociclib, 2 (15.3%) suspended radiotherapy because of acute
side effects. One patient with skin metastases suspended chest wall radiotherapy 1 week (at 48 Gy out of 50 Gy prescribed) due to grade 2 skin toxicity. Another one suspended radiotherapy for 2 days but authors provided no information about irradiated site and type of toxicity in the article. Besides, radiotherapy characteristics in these 2 patients were not available. Median follow-up was 6.3 months. All patients experienced pain relief. Authors’ conclusion was that high-grade hematological toxicities were the same as those expected with these systemic treatments and had no impact on the radiotherapy treatment for most patients. In August 2019, Figura et al. published a retrospective analysis of 15 patients who received stereotactic radiotherapy for 42 brain metastases. Radiotherapy was performed within the 6 months pre- or post-CDK4/6i treatment (n = 10 palbociclib (67%), n = 5 abemaciclib (33%)) [42]. Dose and fractionation were heterogeneous (from 24 Gy in 1 fraction to 20 Gy in 5 fractions). Two radiation courses out of 42 (5%) led to clinical radionecrosis after 4 fractions. It was managed with steroids and bevacizumab. Radiotherapy dose,
CDK4/6i and combined hormonal therapy were not reported. Local control after one year was 88%. Stereotactic radiation to brain metastasis was well tolerated during CDK 4/6i administration.

Twenty-eight patients received concurrent palbociclib and radiotherapy combination only. Two clinical cases presented with grade 3 colitis, grade 2 dermatitis and grade 3 dysphagia [35,40]. The remaining 26 patients from the retrospective studies experienced grade 2 skin toxicity which led to 2 early treatment interruptions [38,39,41]. Such data is summarized in Table 2.

### 3.2. Ribociclib

A retrospective study was published in 2018. Five patients received palliative radiotherapy on breast cancer bone metastases. It was combined with ribociclib and letrozole as first-line treatment [43]. 3-D conformal radiotherapy was performed in 4 patients (20 Gy, 5 fractions on lumbar spine, hip and femur) whereas VMAT was chosen once (30 Gy, 5 fractions on the femur). Radiotherapy was concurrent to first cycle of ribociclib. Toxicities were assessed 3 weeks post-radiotherapy. Grade 3–4 neutropenia was reported after VMAT femoral neck. Grade 3–4 diarrhea/vomiting were reported after right hip radiation. Treatment fields and dosimetry were not reported. However, given the treated locations, such side effects probably resulted more from systemic treatment than radiotherapy. Ribociclib had to be suspended for 2 weeks in both patients. Letrozole was continued. Pain was relieved in 100% of the cases. At 3-month assessment, 3 patients were stable, 2 had partial response. No other abnormal toxicity was reported.

In Ippolito et al. study, 3 patients out of 16 were prescribed ribociclib in combination with letrozole. One patient on ribociclib concurrent to radiotherapy experienced grade 2 neutropenia. No other radio-induced toxicity was reported but the irradiated sites, the radiotherapy technique and doses combined with ribociclib were specified in the article. Every data is summarized in Table 2.

### 3.3. Abemaciclib

In the retrospective analysis by Figura et al. about brain metastases radiotherapy with curative intent, 5 out of the 15 patients received abemaciclib [42]. No information about CDK4/6i subgroups was given thus it is impossible to know if the patients experiencing radionecrosis after 4 fractions were on abemaciclib or palbociclib. Such data is summarized in Table 2.

### 4. Discussion

With emergence of CDK4/6i along with their expanding indications, it seems essential to understand the role played by and the risks of the combination of radiotherapy with CDK4/6i. We aimed at bringing together every published data about this issue and, to our knowledge; this article is the first attempt to try to do so.

In many cancer subtypes, preclinical studies [24–37] suggested that CDK4/6i have a radiation-sensitizing effect on tumor cells. In daily practice, CDK4/6i have been prescribed for more than 2 years in metastatic breast cancer. The issue of their safe combined use with palliative or curative radiotherapy has only been evaluated through limited retrospective data. Like in pre-clinical studies, the most tested molecule was palbociclib as it was the first to be granted approval. This review of literature included 59 patients among whom 46 had radiotherapy + palbociclib (79%), 8 had radiotherapy + ribociclib (13.5%) and 5 had abemaciclib + radiotherapy (8.47%) (Table 3). Whatever the goal of these therapeutic combinations – to relieve pain, to control irradiated lesions – it was always achieved when reported. Radiotherapy technique and doses were common practices. In more than 50% of the cases, CDK4/6i were administered concurrently. Regarding toxicities, 4 out of the 59 patients (6.77%) had > grade 3 acute toxicities due to radiotherapy, 2 (3.38%) had > grade 2 severe toxicities which required temporary radiotherapy suspension. Severe toxicities were therefore reported in more than 10% of the patients, which seemed unacceptable in first-line metastatic treatment. Hematological toxicity was related to CDK4/6i when combined with radiotherapy in 18.6% of the cases analysed in our review. The number of hematological toxicities did not seem to inflate with radiotherapy.

In addition, only one study evaluated late toxicities (over 3 months) caused by ribociclib + radiotherapy [43]. Indeed, late toxicity due to concurrent CDK 4/6i requires further investigations. Indeed, without confirmed safety proof, it seems wiser to suspend CDK4/6i 5 half-lives before and after radiotherapy. This can easily be achieved as CDK4/6i molecules have a short half-life that requires between 5 and 7 days arrest (Table 1). Meanwhile, hormone-therapy can be pursued during radiation course.

Currently prospective clinical data about CDK4/6i and radiotherapy are scarce. Additional safety data should be reported in open and ongoing clinical trials testing CDK4/6i-radiotherapy combination The ongoing prospective phase 2 ASPIRE trial is assessing radiotherapy combined with palbociclib and hormone therapy for bone metastases in breast cancer patients whereas PALATINE prospective trial will assess local breast treatment, (surgery and/or radiotherapy) in advanced breast cancer (Table 4).

### 5. Conclusion

Most pre-clinical data showed CDK4/6i have a synergistic radiosensitizing effect. Such data seems to be in accordance with retrospective clinical studies, which show that more than 10% of severe toxicities occur in radiation fields. Precautionary principle requires CDK4/6i are suspended five half-lives before and after radiotherapy. The results of ongoing prospective clinical trials assessing the combination of CDK4/6i and radiotherapy are expected to bring additional answers about its safe use.

### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

### References

[1] IBRANCE (palbociclib), inhibiteur de protéine kinase. Haute Aut Santé n.d. https://www.has-sante.fr/jcms/c_2964747/fr/ibrance-palbociclib-inhibiteur-de-proteine-kinase (accessed September 19, 2019).

[2] KISQALI. Haute Aut Santé n.d. https://www.has-sante.fr/jcms/c_2827573/fr/kisqali (accessed September 19, 2019).

[3] VERZENIOS. Haute Aut Santé n.d. https://www.has-sante.fr/jcms/c_2892921/fr/verzenios (accessed September 19, 2019).

[4] Lapenna S, Giordano A. Cell cycle kinases as therapeutic targets for cancer. Nat Rev Drug Discov 2009;8:547–66. https://doi.org/10.1038/nrd2907.

[5] Beaver JA, Amir-Kordesian L, Charlab R, Chen W, Palmby T, Tilley A, et al. FDA Approval: palbociclib for the treatment of postmenopausal patients with estrogen receptor-positive, HER2-negative metastatic breast cancer. Clin Cancer Res Off J Am Assoc Cancer Res 2015;21:4760–6. https://doi.org/10.1158/1078-0432.CCR-15-1185.

[6] Shah A, Bloomquist E, Tang S, Fu W, Bi Y, Liu Q, et al. FDA Approval: ribociclib for the treatment of postmenopausal women with hormone receptor-positive, HER2-negative advanced or metastatic breast cancer. Clin Cancer Res Off J Am Assoc Cancer Res 2018;24:2999–3004. https://doi.org/10.1158/1078-0432.CCR-17-2250.

[7] FDA OKs Abemaciclib for ER+, HER2- Breast Cancer. Cancer Discov 2017:7:OF1. https://doi.org/10.1158/2155-6253.CD-RB2017-141.

[8] Cristofanilli M, Turner NC, Bondarenko I, Ro J, Im S-A, Masuda N, 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. https://doi.org/10.1016/S1470-2045(15)00613-0.

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[9] Finn RS, Crown JP, Lang I, Boer K, Bondarenko IM, Kulyk SO, et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/B-18): a randomised phase 2 study. Lancet Oncol 2015;16:25-35. https://doi.org/10.1016/S1470-2045(14)71159-3.

[10] Turner NC, Slamon DJ, Ro J, Bondarenko I, Im S-A, Masuda N, et al. Overall survival with palbociclib and fulvestrant in advanced breast cancer. N Engl J Med 2018;379:1926-36. https://doi.org/10.1056/NEJMoa1802677.

[11] Janni W, Alba E, Bachet J, Diab S, Gil-Gil M, Beck T, et al. 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;169:69-79. https://doi.org/10.1007/s10549-017-4658-x.

[12] Yardley DA. MONALEESA clinical program: a review of ribociclib use in different clinical settings. Future Oncol 2019;15:2673-86. https://doi.org/10.21273/fon-2019-0130.

[13] Hortobagyi GN, Stemmer SM, Burris HA, Yap YS, Sonke GS, Paluch-Shimon S, 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. Ann Oncol Off J Eur Soc Med Oncol 2019. https://doi.org/10.1016/j.annonc.2019.06.078.

[14] Slamon DJ, Neven P, Chia S, Fasching PA, De Laurentiis M, Im S-A, et al. Phase III randomized study of ribociclib and fulvestrant in hormone receptor-positive, human epidermal growth factor receptor 2–negative advanced breast cancer: MONALEESA-3. J Clin Oncol 2018;36:2465-72. https://doi.org/10.1200/JCO.2018.81.3542.

[15] Hortobagyi GN, Stemmer SM, Burris HA, Yap YS, Sonke GS, Paluch-Shimon S, et al. Ribociclib as first-line therapy for HR-positive, advanced breast cancer. N Engl J Med 2016;375:1738-48. https://doi.org/10.1056/NEJMoa1609725.

[16] Im S-A, Lu Y-S, Bardea A, Harbeck N, Colleoni M, Franke F, et al. Overall survival with ribociclib plus endocrine therapy in breast cancer. N Engl J Med 2019;381:307-16. https://doi.org/10.1056/NEJMoa1901765.

[17] Johnston S, Martin M, Leo AD, Im S-A, Awada A, Forrester T, et al. MONARCH 3 final PFS: a randomized study of abemaciclib as initial therapy for advanced breast cancer. Npj Breast Cancer 2019;5:1-8. https://doi.org/10.1038/s41523-018-0097-2.

[18] Cozzi MP, Toi M, Campone M, Söhn J, Paluch-Shimon S, Husser J, et al. MONARCH 3: abemaciclib as initial therapy for advanced breast cancer. J Clin Oncol Off J Am Soc Clin Oncol 2017;35:3638-46. https://doi.org/10.1200/JCO.2017.75.6159.

[19] Sledge GW, Toi M, Neven P, Söhn J, Inoue K, Pivot X, 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 Off J Am Soc Clin Oncol 2017;35:2875-84. https://doi.org/10.1200/JCO.2017.73.2785.

[20] Olson R, Senan S, Harrow S, Gadea S, Louise A, Haasbeek C, et al. Quality of life outcomes after stereotactic ablative radiotherapy (SABR) versus standard of care treatments in the oligometastatic setting: a secondary analysis of the SABR-COMET randomized trial. Int J Radiat Oncol Biol Phys 2019;105:943–7. https://doi.org/10.1016/j.ijrobp.2019.08.041.