Therapeutic Advances in Medical Oncology

Review

Management of adverse events during cyclin-dependent kinase 4/6 (CDK4/6) inhibitor-based treatment in breast cancer

Ther Adv Med Oncol

2018, Vol. 10: 1–12

DOI: 10.1177/1758835918793326

Marc Thill and Marcus Schmidt

Abstract: Cyclin-dependent kinase (CDK) 4/6 inhibitors have shown great results in numerous clinical trials and have improved the clinical outcome for patients with hormone-receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer significantly. To date, three CDK4/6 inhibitors are approved by the US Food and Drug Administration (FDA): palbociclib, ribociclib and abemaciclib; the first two compounds are aproved by the European Medicines Agency (EMA) as well. In combination with endocrine therapy, all of them led to significantly improved progression-free survival compared with endocrine therapy alone. The aim of this article is to give an overview of the efficacy data and to describe the CDK4/6 inhibitor-based treatment-associated adverse events, including hematological and nonhematological adverse events. In addition, it describes the corrrect approach to patient monitoring and adverse event mangement and summarizes the current recommendations for dose reductions and dose interruptions regarding the key adverse events, such as neutropenia, diarrhea, QTc prolongation and hepatobiliary toxicity. Accurate patient monitoring and management of the side effects is crucial, as several clinical trials in early breast cancer are in progress and may lead to an additional approval in the neo-/adjuvant setting.

Keywords: abemaciclib, breast cancer, CDK4/6 inhibitor, clinical management, palbociclib, ribociclib, toxicity

Received: 14 January 2018; revised manuscript accepted: 5 July 2018.

Introduction

The family of cyclin-dependent kinases (CDKs) are critical regulators of cell-cycle progression. Cyclin D is a major transcriptional target of the estrogen receptor (ER) and the catalyst for CDK4 and 6. Its interaction with CDK4/6 facilitates the hyperphosphorylation of the retinoblastoma (Rb) gene product, which in turn leads to the transition from the G1 to the S phase. Alterations of the the cyclin D-CDK4/6-Rb pathway, such as cyclin-D-amplification, loss and mutation of Rb and loss of p16, are able to cause overactivation of CDK4/6 and that may attenuate senescence and promote cell-cycle progression.[1,2]

Palbociclib (Ibrance, Pfizer, New York, USA), Ribociclib (Kisquali, Novartis, Basel, Switzerland) and Abemaciclib (Verzenio, Eli Lilly, Indianapolis, USA) are small-molecule inhibitors of CDK4 and CDK6. The three compounds underwent extensive evaluation in the PALOMA (palbociclib), MONALEESA (ribociclib) and MONARCH (abemaciclib) trial programs in metastatic breast cancer, and several trials are in progress for neo-/adjuvant treatment (see Table 1).

The results of the PALOMA-1 trial (phase II)[3] and the confirmatory PALOMA-2 trial (phase III)[4] showed significantly longer progression-free survival (PFS) with palbociclib plus letrozole than with letrozole alone in first line. Moreover, the PALOMA-3 (phase III) significantly improved PFS in pretreated, post-, pre- and perimenopausal, metastatic breast cancer patients when combined with fulvestrant *versus* fulvestrant alone.[5]

Correspondence to:
Marc Thill
Department of Gynecology and Obstetrics, Breast Center, Agaplesion Markus Hospital, Wilhelm-Epstein-Strasse 4, 60431 Frankfurt am Main, Germany
marc.thill@fdk.info

Marcus Schmidt
Department of Obstetrics and Gynecology, University Medical Center Mainz, Germany

Table 1. Selected phase II and phase III trials of CDK4/6 inhibitors in advanced and metastatic breast cancer.

Trial [ClinicalTrials.gov identifier]	Patient population	Phase	Enrollment	Setting	Treatment	Results
PALOMA-1/TRIO-18 [NCT00721409][3]	Postmenopausal, HR+/HER2– ABC	2	165	1st line	Palbociclib* + letrozole *versus* letrozole alone	10.2 *versus* 20.2 months PFS
PALOMA-2 [NCT01942135][4]	Postmenopausal, HR+/HER2– ABC	3	666	1st line	Palbociclib* + letrozole *versus* letrozole alone	24.8 *versus* 14.5 months PFS
PALOMA-3 [NCT01942135][5]	Pre-, peri- and postmenopausal, HR+/HER2– ABC	3	521	2nd line or later	Palbociclib* + fulvestrant *versus* fulvestrant alone**	9.5 *versus* 4.6 months PFS
MONALEESA-2 [NCT01958021][6]	Postmenopausal, HR+/HER2– ABC	3	668	1st line	Ribociclib (600 mg daily, 3/1 schedule) + letrozole *versus* letrozole alone	Not reached *versus* 14.7 months (hazard ratio 0.56)
MONALEESA-7 [NCT02278120][7]	Pre- and perimenopausal	3	672	1st line	Ribociclib + letrozole + goserelin *versus* letrozole + goserelin alone	13.8 *versus* 13.8 months (hazard ratio 0.55)
MONARCH-1 [NCT02102490][8]	HR+/HER2– ABC	2	132	3rd line or later	Abemaciclib (200 mg every 12 h, continuously)	6 months PFS, ORR 19.7%
MONARCH-2 [NCT02107703][9]	Pre-, peri- and postmenopausal, HR+/HER2– ABC	3	669	Progress during neo-adjuvant/ adjuvant endocrine therapy (ET), ⩽12 months from end of adjuvant ET, or during 1st line ET for mBC	Abemaciclib (150 mg twice daily every 12 h, continuously) + fulvestrant *versus* fulvestrant alone**	16.4 *versus* 9.3 months PFS (hazard ratio 0.55)
MONARCH-3 [NCT02246621][10]	Postmenopausal HR+/HER2– ABC	3	493	1st line	Abemaciclib (150 mg twice daily, continuously) + anastrozol or letrozole *versus* anastrozol or letrozole alone	Not reached *versus* 14.7 months PFS (hazard ratio 0.54)

*Palbociclib dose was 125 mg daily administered orally on a 3/1 schedule in all studies.
**Goserelin (luteinizing hormone-releasing hormone analog) was coadministered with fulvestrant to premenopausal women in PALOMA-3 and MONARCH-2.
3/1, 3 weeks on, 1 week off; ABC, advanced breast cancer; ET, endocrine treatment; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor-positive; mBC, metastatic breast cancer; ORR, overall response rate; PFS, progression-free survival; Rb, retinoblastoma tumor suppressor protein.

The results for ribociclib within the MONALEESA trial program were similar. In the MONALEESA-2 trial (phase III) ribociclib in combination with letrozole *versus* letrozole alone led to a significant improvement of PFS in postmenopausal patients with first-line therapy.[6] Very recently, results of the MONALEESA-7 trial (phase III) have been presented and showed a significantly improved PFS of ribociclib plus tamoxifen/nonsteroidal aromatase inhibitor (NSAI) plus goserelin in

pre- and perimenopausal patients who had no prior endocrine therapy and at least one line of chemotherapy for advanced disease.[7]

Abemaciclib demonstrated a significantly improved PFS for second-line treatment of pre-, peri and postmenopausal patients in the MONARCH-2 (phase III) trial in combination with fulvestrant *versus* fulvestrant alone,[9] and in the MONARCH-3 (phase III) trial for first-line treatment in a postmenopausal patient population in combination with an NSAI.[10] Table 1 summarizes selected phase II and phase III trials.

The excellent efficacy data led to the approval of palbociclib, ribociclib and abemaciclib [US Food and Drug Administration (FDA) breakthrough therapy designation as single agent in October 2015] by the FDA and of palbociclib and ribociclib by the European Medicines Agency (EMA). Thereby, CDK4/6 inhibitor-based combination therapies were successfully brought to the clinic. Their use in daily routine requires a good understanding of the associated toxicity and both appropiate patient monitoring and effective side effect management. Altogether, the CDK4/6 inhibitor side effects are less severe compared with chemotherapy-associated side effects and through dose reductions and treatment interruptions, they are well managed.

CDK4/6 inhibitor dosage and drug metabolism

Palbociclib is started with 125 mg/day, with the first dose reduction to 100 mg/day and the final reduction to 75 mg.[11] Ribociclib is started with 600 mg/day, with the first dose reduction to 400 mg/day, and the second and final reduction to 200 mg/d.[12] Abemaciclib is started with 200 mg twice daily continuously when used as a monotherapy and 150 mg twice daily continuously in combination with endocrine treatment. The first dose reduction is 100 mg twice daily, and the second and final reduction is 50 mg twice daily.[13]

Palbociclib is recommended to be taken orally with food, as an empty stomach could influence the drug levels in terms of reducing them, which may compromise effectiveness.[6] In contrast, ribociclib or abemaciclib absorption is not affected by food intake.[6,13]

CDK4/6 inhibitor drug interaction

All three CDK4/6 inhibitors are metabolized primarily by CYP3A and SULT2A1 enzymes and are time-dependent inhibitors of CYP3A.[12–14] Administration of one of the three CDK4/6 inhibitors with a strong CYP3A inhibitor (e.g. itraconazole) should be avoided, as well as administration with strong (e.g. phenytoin, clarithromycin) or moderate (e.g. modafinil, diltiazem) CYP3A inducers.[12–14] CYP3A inhibitors may increase and CYP3A inducers might decrease plasma exposure to palbociclib, ribociclib and abemaciclib, which in turn could lead to an increased toxicity or decreased efficacy, respectively. As well, the hepatic metabolism of ribociclib is mediated by CYP3A and concomitant use of strong CYP3A inhibitors/inducers should be avoided. CYP3A inhibitors may increase and CYP3A inducers might decrease plasma exposure to palbociclib, which in turn could lead to an increased toxicity or decreased efficacy, respectively. Yu and coworkers developed a physiologically based pharmacokinetic (PBPK) model of palbociclib.[15] They verified this model with clinical drug–drug interaction (DDI) results of palbociclib with strong CYP3A inhibitor (itraconazole), inducer (rifampin), and a sensitive CYP3A substrate (midazolam). Furthermore, they predicted the DDI risk of palbociclib with moderate/weak CYP3A inhibitors. Their results have clearly showed that weak CYP3A inhibitors (e.g. fluoxetine) had an insignificant DDI risk with palbociclib, whereas moderate CYP3A inhibitors (e.g. verapamil) increase plasma palbociclib by ~40%. Conversely, a moderate CYP3A inducer (e.g. efavirenz) decreases plasma palbociclib by ~40%.

CDK4/6 inhibitor toxicity

The three CDK4/6 inhibitors show similar side effects with some exceptions.[3–5,16] Abemaciclib is structurally distinct from the other two CDK4/6 inhibitors and shows a greater selectivity for CDK4 compared with CDK6.[17] In enzymatic assays, it is 14 times more potent against CDK4 than CDK6. CDK4 is particulary important for breast tumorigenesis, while CDK6 plays a critical role in hematopoetic stem cell differentiation.[18,19] Therefore, it demonstrates a higher rate of diarrhea and fatigue, but a lower rate of hematologic adverse events, including neutropenia.[10,20] In contrast to current data for palbociclib, ribociclib

demonstrates a higher incidence of QT interval prologation.[6]

As summarized in Table 2, the most common side effects of palbociclib are neutropenia, leukopenia, fatigue and nausea, and these side effects are also common following ribociclib-based treatment. In the MONALEESA-2 trial, mostly neutropenia, leukopenia, nausea, infections, fatigue and diarrhea occurred.[6] Regarding grade 3/4 adverse events, neutropenia, leukopenia, hypertension, increased liver enzymes alanine transaminase/aspartate aminase (ALT/AST) and lymphopenia mostly occurred. Moreover, QTc prolongation was observed in 11 (3.3%) patients,[6] and in comparison with the latter two, abemaciclib had a higher rate of fatigue and gastrointestinal toxicities (see Table 2). The most common grade 3/4 side effects in the MONARCH-1 trial were leukopenia, neutropenia and diarrhea.[8] Diarrhea emerged in the MONARCH-1 trial in 90%, in MONARCH-2 in 86%, and in MONARCH-3 in 81.3%, but was manageable with conventional antidiarrheal agents or *via* dose reduction. To date, there is no evidence for a race- or ethnicity-dependent difference regarding toxicity in all published phase III trials of the three CDK4/6 inhibitors.[3,4,6,9,10] Table 2 summarizes the most common side effects that occur following CDK4/6 inhibition.

Treatment-related hematological adverse events of CDK4/6 inhibitors

Neutropenia

Due to bone marrow influence, the main CDK4/6-associated toxicities are neutropenia and leukopenia. It is the most common grade 3/4 adverse event observed in clinical trials. Anemia or thrombocytopenia is less frequent.[4–6,16,21,22] However, due to the greater CDK4 selectivity of abemaciclib, it has a 50% lower neutropenia rate (all grades) when compared with palbociclib and ribociclib.[10] All hematologic adverse events can generally be managed adequately with standard supportive care.[9,10] In contrast to chemotherapy, CDK4/6 inhibitor-associated neutropenia is rapidly reversible, as CDK4/6 inhibitors induce a cell-cycle arrest by decreasing the proliferation of hematopoetic stem cells and resumed proliferation following CDK4/6 dose reduction or interruption. This is different to chemotherapy, where bone marrow is suppressed *via* apoptotic cell death.[23] Utilizing an *in vitro* assay with human bone marrow mononuclear cells (hBMNC), the authors elegantly showed that palbociclib-induced bone marrow suppression occurred through cell-cycle arrest without DNA damage and apoptotic cell death that is usually seen with cytotoxic chemotherapies. Furthermore, palbociclib-induced bone marrow suppression was reversible upon palbociclib withdrawal and neither apoptosis level nor cell viability were alterated or affected.[24]

In the PALOMA-3 trial with a CDK4/6 inhibitor-based treatment consisting of palbociclib and fulvestrant, a grade 3/4 neutropenia usually resolved within 7 days.[25] As mentioned above, this kind of neutropenia is different to a chemotherapy-induced neutropenia, which is additionally characterized by missing pancytopenia and a lower infection rate.[5,16,22] In contrast to chemotherapy, there is no need for granulocyte-colony stimulating factor (GCSF). Chemotherapy-induced neutropenia grade 4 usually occurs in more than a third of the patients within the first four cycles, with a subsequent febrile neutropenia in up to 23%[26] and a mortality rate of approximately 5%.[27] In comparison with chemotherapy-induced neutropenia, both the rate of grade 4 neutropenia and febrile neutropenia is considerably lower in trials using CDK4/6 inhibitors.[3–7,9,10] Furthermore, neutropenia often decreases cycle by cycle, suggesting that a cumulative toxicity does not exist. This is in line with the mechanism of action outlined above.[22]

Dose modification/interruption. In all three PALOMA trials, palbociclib was given at 125 mg daily (with food) for 3 weeks followed by 1 week off. Ribociclib was initially dosed at 600 mg daily (preferable in the morning) in the same schedule within the MONALEESA trial program. Abemaciclib was given in MONARCH-2 and -3 at 150 mg twice daily (see Table 1). Initially, the dose of 200 mg twice daily, which is approved for monotherapy with abemaciclib, was also used in MONARCH-2. However, after a review of safety data and dose-reduction rates, the protocol was amended to reduce the starting dose to 150 mg for all patients.[9] Approximately half of the patients who had neutropenia had dose reductions, dose interruptions or cycle delays in the PALOMA-1 study.[22] However, only 6% were required to permanently discontinue treatment due to grade 3–4 neutropenia as per protocol. The frequency of grade 3–4 neutropenia decreased over time. In PALOMA-3, neutropenia was the most common

Table 2. Common side effects with CDK4/6 inhibitor-based treatment.

Treatment [ClinicalTrials.gov identifier]	Patients	Most common side effects (>30% any grade)	Most common side effects (⩾20% grade 3/4)
Palbociclib			
Palbociclib monotherapy [NCT01037790][21]	ABC, *n* = 37	Leukopenia (100%), neutropenia (92%), thrombocytopenia (76%), anemia (70%), lymphopenia (65%)	Neutropenia (54%), leukopenia (51%), lymphopenia (30%)
Palbociclib + letrozole, PALOMA-2 [NCT01942135][4]	HR+, HER2–, ABC, *n* = 444	All causality AEs: Neutropenia (80%), leukopenia (39%), fatigue (37%), nausea (35%), arthralgia (33%), alopecia (33%)	Neutropenia (66%), leukopenia (25%)
Palbociclib + fulvestrant, PALOMA-3 [NCT01942135][5]	HR+, HER2–, ABC, *n* = 345	All causality AEs: Neutropenia (81%), leukopenia (50%), infections (42%), fatigue (39%), nausea (32%)	Neutropenia (65%), leukopenia (28%)
Ribociclib			
Ribociclib monotherapy [NCT 01237236][21]	Advanced solid tumors/ lymphomas, *n* = 132	TEAEs: Neutropenia (46%), fatigue (45%), leukopenia (43%), nausea (42%), thrombocytopenia (30%)	Neutropenia (27%)
Ribociclib + letrozole, MONALEESA-2 [NCT02107703][6]	HR+, HER2–, ABC, *n* = 334	All-causality AEs: neutropenia (74%), nausea (52%), infections (50%), fatigue (37%), diarrhea (35%), alopecia (33%), leukopenia (33%)	Neutropenia (59%), leukopenia (21%)
Abemaciclib			
Abemaciclib monotherapy, MONARCH-1 [NCT02102490][8]	HR+, HER2–, ABC, *n* = 132	TEAEs: Leukopenia (91%), diarrhea (90%), neutropenia (88%), anemia (69%), fatigue (65%), nausea (64%), decreased appetite (46%), thrombocytopenia (41%), abdominal pain (39%), vomiting (35%)	Leukopenia (28%), neutropenia (27%), diarrhea (20%)
Abemaciclib + fulvestrant, MONARCH-2 [NCT02107703][9]	HR+, HER2–, ABC, *n* = 644	TEAEs: Diarrhea (86%), neutropenia (46%), nausea (45%), fatigue (40%), abdominal pain (35%)	Neutropenia (23.6%),
Abemaciclib + nonsteroidal aromatase inhibitor, MONARCH-3 [NCT02246621][10]	HR+, HER2–, ABC, *n* = 493	TEAEs: Diarrhea (81.3%), neutropenia (41.3%), fatigue (40.1%), infections and infestations (39.1%), nausea (38.5%)	Neutropenia (21.1%)

ABC, advanced breast cancer; AE, adverse event; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor-positive; TEAE, treatment-emergent adverse events.

grade 3 (55%) and 4 (10%) adverse event.[25] In the palbociclib arm, 28% of patients had one dose reduction and 6% of patients had two dose reductions. Dose modification appeared to be effective for reducing the risk for subsequent grades 3–4 neutropenia. The median duration of dose interruption or dose delay in the palbociclib arm was 6.0 or 2.5 days, respectively. Remarkably, neither dose modifications for grade 3–4 neutropenia [hazard ratio (HR) 0.87, 95% confidence interval (CI) 0.61–1.25] nor dose interruption or cycle delay (HR 0.84, 95% CI 0.61–1.17) had an adverse effect on PFS in PALOMA-3.[25] In the MONALEESA-2 trial, ribociclib had mostly

well-accepted side effects. Nevertheless, 7.5% of patients required permanent discontinuation of both ribociclib and letrozole because of adverse events.[6] In the MONARCH-2 trial patients received dose reductions in 42.9% and interruptions in 51.9% due to adverse events.[9] Table 3 summarizes dose modifications and management for neutropenia.

Altogether, most cases treated with palbociclib, ribociclib and abemaciclib resolved rapidly with interruptions or reductions.[6,9,10,28]

Monitoring/management of treatment-related hematological toxicities. Neutropenia usually emerges 15 days after the first dose of palbociclib and ribociclib,[11,16,25] and with abemaciclib, it occurs within the first two cycles and infrequently in later cycles.[10] Therefore, the timing of sufficient monitoring is important. For a correct evaluation of the different blood cell counts, examining the complete blood count prior to the start of CDK4/6 inhibitor-based treatment is recommended, at the beginning of each new treatment cycle and on day 14 of cycle 1 and 2.[29] For grade 3 (<50,000–25,000/mm^3) or grade 4 (<25,000 mm^3) thrombocytopenia palbociclib treatment was stopped until a recovery back to 50,000/mm,^{3} and then resumed at one dose level lower.[23] In case of a grade 3/4 thrombocytopenia or if recovery to 50,000/mm^3 took more than 2 weeks, two dose reductions were performed. For an anemia grade 3 (hemoglobin <8.0 g/dl) and grade 4 (urgent intervention indicated), treatment should be stopped until an improvement to grade 2 (hemoglobin <10.0–8.0 g/dl) or above is reached and then resumed at one dose level lower.[2] Beside accurate monitoring with subsequent dose modifications (see Table 3), clear communication between the patient and the therapist is mandatory to minimize any misunderstandings. Every breast cancer center has to find its own strategy to take care of the patient and a correct treatment adjustment, such as informational flyers, patient follow-up calls and visits in the center. It is important to build up increased awareness of side effects and any treatment-related specialties, such as avoiding contact to infectious people because of a mild increased risk of infection including influenza and upper respiratory infections,[22,25] and to report fevers above 38.3°C or a persistent fever of >38°C lasting ⩾1 h that occurs alongside the treatment with CDK4/6 inhibitors.

Treatment-related nonhematological adverse events

As well known from other agents used for the treatment of advanced and metastatic breast cancer, side effects, such as fatigue, nausea, vomiting and diarrhea occurred for every CDK4/6 inhibitor.[16,22,25] Additionally, in the case of ribociclib, QTc prologation is notable and increased liver enzymes, as well.

QTc prolongation

Long QT syndrome is a heart rhythm condition that can potentially cause fast, chaotic heartbeats. QTc prolongation can be distinguished into three clinically relevant categories. For men, the cut-off points are less than 430 ms (normal), 430–450 ms (borderline) and more than 450 ms (prolonged); and for women, less than 450 ms (normal), 450–470 ms (borderline), and more than 470 ms (prolonged).[30] Ribociclib prolongs the QT interval in a concentration-dependent manner and patients who are at risk of developing QTc prolongation should not be treated with ribociclib. In the MONALEESA-2 trial, QTc prologation to >480 ms was experienced by 3.3% (11 patients, including 1 with cardiac abnormalities at baseline and 6 with an increase of <60 ms from baseline) following a treatment combination of ribociclib and letrozole. Most changes were observed in the first cycle and were limited by proactive dose interruption or reduction.[6] Interestingly, palbociclib had no clinically relevant effect on the QTc interval in advanced breast cancer patients.[31]

QTc prolongation is well known from a lot of medicinal products. In routine use, patients eligible for treatment with ribociclib have to be checked according their cardiac status and their potentially QTc-prolonging concomitant medication. They should undergo electrocardiograms at baseline, day 14 in cycle 1 and day 1 in cycle 2, and have to be carefully monitored to limit the incidence of these events. Moreover, patients receiving ribociclib should be informed about QTc prolongation and motivated to share every associated symptom. Table 4 summarizes the QTc-related monitoring for ribociclib.

Elevation of liver enzymes

Another side effect observed with antiendocrine CDK4/6 inhibitor-based combination treatment

Table 3. Dose modifications and management for neutropenia.[11–13]

CDK4/6 inhibitor	Grade 1 or 2 (ANC 1000/mm^3–<LLN)	Grade 3 (ANC 500–<1000/mm^3)	Grade 3 (ANC 500–<1000/mm^3) febrile neutropenia*	Grade 4 (ANC < 500/mm^3)
Ribociclib				
Perform CBC before initiating treatment with ribociclib; monitor CBC every 2 weeks for the first two cycles, at the beginning of each subsequent four cycles, and as clinically indicated	No dose adjustment is required	Dose interruption until recovery to grade ⩽2; resume ribociclib at the same dose level; if toxicity recurs at grade 3, dose interruption until recovery, then resume ribociclib at the next lower dose level	Dose interruption until recovery of neutropenia to grade ⩽2; resume ribociclib at the next lower dose level	Dose interruption until recovery to grade ⩽2; resume ribociclib at the next lower dose level
Palbociclib				
CBC should be monitored prior to the start of palbociclib therapy and at the beginning of each cycle, as well as on day 14 of the first 2 cycles, and as clinically indicated	No dose adjustment is required	Day 1 of cycle: withhold palbociclib, repeat CBC monitoring within 1 week; when recovered to grade ⩽2, start the next cycle at the same dose; day 14 of first 2 cycles: continue palbociclib at current dose to complete cycle; repeat CBC on day 21; consider dose reduction in cases of prolonged (>1 week) recovery from grade 3 neutropenia or recurrent grade 3 neutropenia in subsequent cycles	Withhold palbociclib until recovery to grade ⩽2 (⩾1000/mm^3); resume at next lower dose	Withhold palbociclib until recovery to grade ⩽2; resume at next lower dose
Abemaciclib				
Monitor CBC prior to starting abemaciclib therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated	No dose modification is required	Suspend dose until toxicity resolves to ⩽grade 2; dose reduction is not required	No distinct recommendation in the prescribing information	Suspend dose until toxicity resolves to ⩽grade 2; resume at *next lower dose*

Extracted from ribociclib US prescribing information, March 2017,[12] palbociclib US prescribing information, March 2017,[11] abemaciclib US prescribing information, September 2017.[13]
*Grade 3 neutropenia with single episode of fever >38.3°C or above.
Grade according to CTCAE Version 4.03.
ANC, absolute neutrophil count; CBC, complete blood count; CDK, cyclin-dependent kinase; CTCAE, common terminology criteria for adverse events; LLN, lower limit of normal.

Table 4. QTc-related monitoring requirements for ribociclib.[12]

Dose modifications and management for QTc prolongation	
ECGs with QTcF >480 msec	Interrupt ribociclib treatment If QTcF prolongation resolves to <481 ms, resume treatment at the same dose level If QTcF ⩾481 ms recurs, interrupt dose until QTcF resolves to <481 ms then resume ribociclib at next lower dose level
ECGs with QTcF >500 msec	Interrupt ribociclib treatment if QTcF greater than 500 ms on at least two separate ECGs (within the same visit) If QTcF prolongation resolves to <481 msec, resume treatment at the next lower dose level Permanently discontinue ribociclib if QTcF interval prolongation is either greater than 500 ms or greater than 60 ms change from baseline and associated with any of the following: *Torsades de Pointes*, polymorphic ventricular tachycardia, unexplained syncope, or signs/symptoms of serious arrhythmia
ECGs should be assessed prior to initiation of treatment. Repeat ECGs at approximately day 14 of the first cycle and at the beginning of the second cycle, and as clinically indicated. In case of (QTcF) prolongation at any given time during treatment, more frequent ECG monitoring is recommended.	

Extracted from ribociclib US prescribing information, March 2017.[12]
ECG, electrocardiogram; QTcF, Fridericia's correction formula for prolongation of QT interval.

is an asymptomatic increase of the liver enzymes ALT and AST. Following the combination treatment of palbociclib and letrozole, hepatic failure and liver-related death was documented in two cases.[32] In the PALOMA-3 trial, grade 1/2 ALT increase in only 4% and grade 3 in 3% was observed.[5] However, in the MONALEESA-2 trial grade 3/4 ALT and AST elevations occurred in 9.3% and 5.7%, respectively, following a treatment combination of ribociclib and letrozole.[6] A concurrent elevation of total bilirubin was presented without deaths and with complete reversibility after treatment interruption. Under treatment combination of abemaciclib and nonsteroidal aromatase inhibitor within the MONARCH-3 trial, an ALT increase grade 3 and grade 4 was observed in 5.8 % and 0.6%, and an AST increase grade 3 in 3.8% and no grade 4.[10] Most cases were isolated and asymptomatic and reversible with dose adjustment.

Monitoring/management of treatment-related liver enzyme elevation. Regular liver function tests help to identify any abnormal liver function following CDK4/6 inhibitor-based treatment. Moreover, complementary and alternative concomitant medication, alcohol abuse and hepatitis in medical history have to be considered in every patient. For ribociclib, performing a liver function test before initiating treatment and monitoring liver function every 2 weeks is recommended for the first two cycles, at the beginning of each subsequent four cycles, and as clinically indicated.[12] If grade ⩾2 abnormalities are noted, more frequent monitoring is recommended. An AST or ALT elevation grade 1 [less than three times the upper limit normal (ULN)] leads to no dose adjustment. For grade 2 (more than three to five times the ULN) with a baseline value of grade <2, dose interruption until recovery to no more than baseline grade is required.[12] After recovery, treatment is to be resumed at next lower dose level. If baseline value was at grade 2, no dose interruption is required. However, a grade 3 elevation (more than 5–20 times the ULN) leads to a dose interruption until recovery.[12] Afterwards, treatment should be resumed at the next lower dose level. If grade 3 recurs, a discontinuation is recommended. Finally, grade 4 (more than 20 times the ULN) demands a treatment discontinuation. Table 5 summarizes the dose modifications and management of hepatobiliary toxicity of ribociclib.[12]

Gastrointestinal toxicities

Gastrointestinal CDK4/6 inhibitor-related side effects are nausea, vomiting and diarrhea. For palbociclib and ribociclib, theses toxicities are known to occur at low grades (Table 2). In contrast, abemaclib has a different gastrointestinal toxicity

Table 5. Dose modification and management for hepatobiliary toxicity.[12]

	Grade 1 (>ULN to 3× ULN)	Grade 2 (>3 to 5× ULN)	Grade 3 (>5 to 20× ULN)	Grade 4 (>20× ULN)
AST or ALT elevations from baseline, total bilirubin < 2× ULN	No dose adjustment required	Dose interruption until recovery to baseline grade, then resume at same dose level If grade 2 recurs, resume at next lower dose level*	Dose interruption until recovery to baseline grade, then resume at next lower dose level If grade 3 recurs, discontinue ribociclib	Discontinue ribociclib
Elevation in AST or ALT with total bilirubin increase in absence of cholestasis		Discontinue ribociclib, irrespective of baseline grade		

Extracted from ribociclib US prescribing information, March 2017.[12]
*No dose interruption if at grade 2 at baseline.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.

profile and a higher rate of grade 3 diarrhea. In the MONARCH-1 trial, using abemaciclib monotherapy, diarrhea was experienced in 90% of the patients, generally within 1 week of treatment initiation and led to dose reductions in 21% of the patients. The vast majority of cases did not last long and were resolved with a median duration of 7.5 days for grade 2 and 4.5 days for grade 3.[8] In the MONARCH-2 trial grade 1 and 2 diarrhea occured in 73% and grade 3 in 13.4%.[9] The events typically occurred, as in MONARCH-1, in the first treatment cycle, with a median duration of 6 days, and in 70.1% of the patients, treatment modifications were not required.[9] In an analysis presented at the American Society of Clinical Oncology meeting 2017, the authors showed a significant decrease of diarrhea grade 3/4 after cycle 4 and 5.[33]

Monitoring/management of treatment-related gastrointestinal toxicities. Diarrhea can weaken the patient due to loss of fluids and electrolytes. Therefore, diarrhea has to be monitored carefully. Blood tests can be helpful to identify alterations in electrolyte levels, and antidiarrheal medications, such as loperamide and diphenoxylate/atropine, should be used in a proactive manner to prevent complications. Nausea and vomiting should be treated with usual antiemetics (i.e. metoclopramide, serotonin 5-HT3 antagonists) if necessary.[22] However, therapists should be aware of ribociclib and the prescription of comedications due to the risk of QTc prolongation. Diarrhea should be treated in the beginning with hydration and dietary modifications, as long as no signs of infection are diagnosed. Later on, the treatment should be extended to antidiarrheal agents (loperamide, diphenoxylate/atropine, octreotide, etc.). In the MONARCH-3 trial, stopping abemaciclib medication until diarrhea resolved to at least grade 1 was recommended.[10] Table 6 summarizes the dose modifications and management for abemaciclib.

Influence on creatinine level

During the treatment with abemaciclib, reversible increases in serum creatinine have been observed in 98.3% of the patients (based on laboratory results); in 1.9%, the elevation reached even grade 3/4. Compared with patients who were treated with an aromatase inhibitor or with fulvestrant alone, a creatinine serum level increase was measured in 78.4% (all grades).[34] The reason for such an increase is an inhibition of renal transporters which are involved in the tubular sectretion of creatinine and the disposition of metformin.[35] *In vitro* data have shown that abemaciclib and its major metabolites inhibit organic cation transporter 2, multidrug and toxin extrusion protein 1 (MATE1) and MATE2-K. Further significant differences in other markers of renal function and an influence of the glomerular filtration rate as measured by iohexol clearance were not shown.[36] Usually, the increase of creatinine level occurs in the first month of treatment and stays elevated, but in a stable manner. After end of treatment, elevated serum level returns to baseline without alterations in other markers of renal function.

Pulmonary embolism

Thromboembolic events are a severe side effects and well known from several agents. Following CDK4/6 inhibitor-based combination treatment

Table 6. Dose modifications and management: diarrhea.[13]

At the first sign of loose stools, start treatment with antidiarrheal agents and increase intake of oral fluids	
Grade 1	No dose modification is required
Grade 2	If toxicity does not resolve within 24 h to ⩽grade 1, suspend dose until resolution; no dose reduction is required
Grade 2 that persists or recurs after resuming the same dose despite maximal supportive measures	Suspend dose until toxicity resolves to ⩽grade 1; resume at *next lower dose*
Grade 3 or 4 or requires hospitalization	Suspend dose until toxicity resolves to ⩽grade 1; resume at *next lower dose*

Extracted from abemaciclib US prescribing information, September 2017.[13]

some cases have also been found. Thromboembolic events have rarely been reported following palbociclib. In the PALOMA-1 trial, two patients (0.6%) suffered from a nonserious event and four patients (1.2%) had serious events (three pulmonary embolisms and one deep vein thrombosis).[37] In the PALOMA-3 trial, the following events were reported in 2% of the patients: pulmonary embolism, deep vein thrombosis, subclavian vein thrombosis, vena cava thrombosis.[25] Moreover, in the MONALEESA-2 trial, two cases of pulmonary embolism were reported[6] and in the MONARCH-3 trial, more thromboembolic events occurred in the abemaciclib/nonsteroidal aromatase inhibitor arm.[10] Therefore, patients should be monitored for signs and symptoms of a pulmonary embolism. Typical symptoms are shortness of breath, hypoxia, chest pain, rapid breathing, or rapid heart rate.

Alopecia

Alopecia is a noteworthy side effect for all three CDK4/6 inhibtors. In the PALOMA-2 trial, the possibilty of experiencing an alopecia at any grade 1/2 was 32.9% in the combinaton arm compared with 15.8% for letrozole alone.[22] In the PALOMA-3 trial, a more than twofold higher alopecia rate was observed for the CDK4/6 inhibitor-based treatment (14.8% *versus* 5.8%). In the MONARCH-2 trial, 15% of the patients under the combination of abemaciclib and fulvestrant experienced an alopecia grade 1/2 compared with 1.8% in the fulvestrant-only arm.[9] In the MONARCH-3 trial, alopecia occurred in 26.6% for all grades and 1.6% for grade 2 following the combination of abemaciclib plus NSAI compared with 10.6% in the standard arm with NSAI alone.[10] In the MONALEESA-2 trial, alopecia emerged in 33.2% *versus* 15.5% in the combination arm with ribociclib plus letrozole *versus* letrozole alone.[6] Therefore, patients should be informed about the possibility of an at least twofold higher alopecia rate grade 1/2.

Conclusion

In general, CDK4/6 inhibitors are well-tolerated agents. The main side effects associated with a CDK4/6-inhibitor-based combination treatment are similar, including neutropenia and gastrointestinal side effects. Nevertheless, some differences exist for palbociclib, ribociclib and abemaciclib. The most common side effect for palbociclib and ribociclib is neutropenia, but QTc prolongation and hepatobilary toxicity is noteworthy for ribociclib as well. Gastrointestinal toxicity is associated especially with abemaciclib. In contrast to chemotherapy, toxicity can be limited by dose reductions and dose modifications. Therefore, early and sufficient monitoring with regular clinical assessments and management of the side effects is crucial and the key to treating patients successfully, minimizing side effects and treatment interruptions, and avoiding a lack of confidence for this innovative treatment.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest

Marc Thill has received speaker honoraria by Pfizer and Novartis, consultant honoraria by Pfizer, Novartis and Lilly, travel reimbursement by Pfizer, Novartis and Lilly.

Marcus Schmidt has received speaker honoraria by Pfizer and Novartis, consultant honoraria by Pfizer and Novartis, and travel reimbursement by Pfizer and Novartis.

References

1. Sammons SL, Topping DL and Blackwell KL. HR+, HER2– Advanced breast cancer and CDK4/6 inhibitors: mode of action, clinical activity, and safety profiles. *Curr Cancer Drug Targets* 2017; 17: 637–649.
2. Spring LM, Zangardi ML, Moy B, *et al*. Clinical management of potential toxicities and drug interactions related to cyclin-dependent kinase 4/6 inhibitors in breast cancer: practical considerations and recommendations. *Oncologist* 2017; 22: 1039–1048.
3. 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 oestrogen receptor-positive, HER2- negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. *Lancet Oncol* 2015; 16: 25–35.
4. Finn R, Martin M, Rugo H, *et al*. Palbociclib and letrozole in advanced breast cancer. *N Engl J Med* 2016, 375: 1925–1936.
5. 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: 425–439.
6. Hortobagyi G, Stemmer S, Burris H, *et al*. Ribociclib as first-line therapy for HR-positive, advanced breast cancer. *N Engl J Med* 2016; 375: 1738–1748.
7. Tripathy D, Sohn J, Im S-A, *et al*. *First-line ribociclib vs. placebo with goserelin and tamoxifen or a nonsteroidal aromatase inhibitor in premenopausal women with hormone-receptor-positive, HER2-negative advanced breast cancer: results from the randomized phase III MONALEESA-7 trial. Paper presented at 2017 San Antonio Breast Cancer Symposium*, 6 December. San Antonio, TX. Abstract GS2–05.
8. 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: 5218–5224.
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: 2875–2884.
10. Goetz MP, Toi M, Campone M, *et al*. MONARCH 3: abemaciclib as initial therapy for advanced breast cancer. *J Clin Oncol* 2017; 35: 3638–3646.
11. IBRANCE. Prescribing information: palbociclib. New York, NY: Pfizer Inc, http://labeling.pfizer.com/ShowLabeling.aspx?id=2191 (March 2017).
12. KISQUALI. Prescribing information: ribociclib. East Hanover, NJ: Novartis Pharmaceuticals Corporation, https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/kisqali.pdf (March 2017).
13. VERZENIO. Prescribing information: abemaciclib. Indianapolis, IN: Eli Lilly and Company, http://pi.lilly.com/us/verzenio-uspi.pdf (September 2017).
14. Dhillon S. Palbociclib: first global approval. *Drugs* 2015; 75: 543–551.
15. Yu Y, Loi C, Hoffman J, *et al*. Physiologically based pharmacokinetic modeling of palbociclib. *J Clin Pharmacol* 2017; 57: 173–184.
16. Infante J, Cassier P, Gerecitano J, *et al*. A phase I study of the cyclindependent kinase 4/6 inhibitor ribociclib (LEE011) in patients with advanced solid tumors and lymphomas. *Clin Cancer Res* 2016; 22: 5696–5705.
17. Gelbert LM, Cai S, Lin X, *et al*. Preclinical characterization of the CDK4/6 inhibitor LY2835219: in-vivo cell cycle-dependent/independent anti-tumor activities alone/in combination with gemcitabine. *Invest New Drugs* 2014; 32: 825–837.
18. Malumbres M and Barbacid M. Cell cycle, CDKs and cancer: a changing paradigm. *Nat Rev Cancer* 2009; 9: 153–166.
19. Laurenti E, Frelin C, Xie S, *et al*. CDK6 levels regulate quiescence exit in human hematopoietic stem cells. *Cell Stem Cell* 2015; 16: 302–313.
20. Asghar U, Witkiewicz AK, Turner NC, *et al*. The history and future of targeting cyclin-dependent kinases in cancer therapy. *Nat Rev Drug Discov* 2015; 14: 130–146.
21. DeMichele A, Clark AS, Tan KS, *et al*. CDK4/6 inhibitor palbociclib (PD0332991) in Rb+ advanced breast cancer: phase II activity, safety,

and predictive biomarker assessment. *Clin Cancer Res* 2015; 21: 995–1001.

22. Finn RS, Crown JP, Ettl J, *et al.* Efficacy and safety of palbociclib in combination with letrozole as firstline treatment of ER-positive, HER2-negative, advanced breast cancer: expanded analyses of subgroups from the randomized pivotal trial PALOMA-1/TRIO-18. *Breast Cancer Res* 2016; 18: 67.
23. Hu W, Sung T, Jessen B, *et al.* Mechanistic investigation of bone marrow suppression associated with palbociclib and its differentiation from cytotoxic chemotherapies. *Clin Cancer Res* 2015; 22: 2000–2008.
24. Johnson S, Torrice C, Bell J, *et al.* Mitigation of hematologic radiation toxicitiy in mice through pharmacological quiescence induced by CDK4/6 inhibition. *J Clin Invest* 2010; 120: 2528–2536.
25. Verma S, Bartlett C, Schnell P, *et al.* Palbociclib in combination with fulvestrant in women with hormone receptor-positive/HER2- negative advanced metastatic breast cancer: detailed safety analysis from a multicenter, randomized, placebo-controlled, phase III study (PALOMA-3). *Oncologist* 2016; 21: 1165–1175.
26. Fontanella C, Bolzonello S., Lederer B, *et al.* Management of breast cancer patients with chemotherapy-induced neutropenia or febrile neutropenia. *Breast Care* 2014; 9: 239–245.
27. De Naurois J, Novitzky-Basso I, Gill M, *et al.* ESMO guidelines working group. Management of febrile neutropenia: ESMO clinical practice guidelines. *Ann Oncol* 2010; 21(Suppl. 5): v252–v256.
28. Vidula N and Rugo HS. Cyclin-dependent kinase 4/6 inhibitors for the treatment of breast cancer: a review of preclinical and clinical data. *Clin Breast Cancer* 2016; 16: 8–17.
29. Rugo HS, Diéras V, Gelmon KA, *et al.* Impact of palbociclib plus letrozole on patient-reported health-related quality of life: results from the PALOMA-2 trial. *Ann Oncol* 2018; 29: 888–894.
30. Van Noord C, Eijgelsheim M and Stricker BHC. Drug- and non-drug-associated QT interval prolongation. *Br J Clin Pharmacol* 2010; 70: 16–23.
31. Durairaj C, Ruiz-Garcia A, Gauthier ER, *et al.* Palbociclib has no clinically relevant effect on the QTc interval in patients with advanced breast cancer. *Anticancer Drugs* 2018; 29: 271–280.
32. Vuppalanchi R, Saxena R, Maria A, *et al.* Pseudocirrhosis and liver failure in patients with metastatic breast cancer after treatment with palbociclib. *Hepatology* 2017; 65: 1762–1764.
33. Sledge GW, Toi M, Neven P, *et al.* MONARCH-2: abemaciclib in combination with fulvestrant in patients with HR+/HER2- advanced breast cancer who progressed on endocrine therapy. *J Clin Oncol* 2017; 35(Suppl.): abstract 1000.
34. Chappell J, Turner K, Chiang AY, *et al.* *Abemaciclib inhibits renal transporters but does not affect glomeraular filtration rate*. American Society of Clinical Pharmacology and Therapeutics, Annual Meeting 2018 . *J Clin Pharm Ther* 2018; 100(Suppl.1): abstract 672.
35. Idkaidek N, Tawfiq A, Munther M, *et al.* Metformin IR versus XR pharmacokinetics in humans. *J Bioequiv Availab* 2011; 3: 233–235.
36. Krutzén E, Bäck SE, Nilsson-Ehle I, *et al.* Plasma clearance of a new contrast agent, iohexol: a method for the assessment of glomerular filtration rate. *J Lab Clin Med* 1984; 104: 955–961.
37. Turner NC, Ro J, Andre F, *et al.* Palbociclib in hormone-receptor-positive advanced breast cancer. *N Engl J Med* 2015; 373: 209–219.