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REVIEW

CDK4/6 inhibitors in breast cancer: differences in toxicity profiles and impact on agent choice. A systematic review and meta-analysis

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ABSTRACT

Introduction: CDK4/6 inhibitor approval for hormone-responsive breast tumors has significantly changed therapeutic algorithms, with three drugs currently approved.

Areas covered: Here, we analyze the toxicity profiles of palbociclib, ribociclib, and abemaciclib through a systematic review and meta-analysis. Palbociclib and ribociclib showed high rates of hematological toxicity, primarily neutropenia, and were associated with a low rate of severe infections. Abemaciclib was associated with a high rate of gastrointestinal toxicities, primarily diarrhea, of grade 1–2 in most cases. Ribociclib was associated with a high rate of hepatic, and respiratory toxicity and with QTc prolongation. The toxicity rate of ribociclib was higher in metastatic patients than non-metastatic patients, with approximately 33% more grade 3–4 toxicities and 21% more grade 3–4 neutropenic events. A 5% higher risk of diarrhea was observed in postmenopausal patients. Pre-treated patients did not show a higher toxicity rate for palbociclib/ribociclib than previously untreated patients, while a 26% higher risk of any grade neutropenia and 6% higher risk of grade 3–4 diarrhea were observed with abemaciclib.

Expert opinion: Considering the similar efficacies and indications of palbociclib, ribociclib, and abemaciclib, the evaluation of their toxicity profiles may facilitate treatment choice.

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KEYWORDS
Breast cancer; CDK4/6 inhibitors; palbociclib; ribociclib; abemaciclib; meta-analysis

1. Introduction

With the advent of personalized medicine, new molecular targeted therapies have recently been introduced into clinical practice. Among them, cyclin-dependent kinases 4 and 6 (CDK4/6) in breast cancer have increasing importance, with the approval in recent years of three CDK4/6 inhibitors: palbociclib, ribociclib, and abemaciclib [1–5].

CDK4/6 are involved in regulation of the cell cycle and, in particular, in the transition from G1 to S phase [6]. In particular, D cyclins form a complex with CDK4 or 6, which becomes active and phosphorylates retinoblastoma protein (RB), a negative cell cycle inhibitor. When phosphorylated, RB releases the transcriptional factor EF2, which in turn regulates the expression of genes involved in cell cycle progression [6]. The cyclin D-CDK4/6-RB pathway is frequently disrupted in cancer, notably in breast cancer, with some differences between the subtypes. The cyclin D1 gene (CCND1) is amplified in approximately 15% of breast cancers, primarily luminal types (58% in luminal B and 29% in luminal A) but also in HER2-enriched subtypes (38% of cases) [7–9]. Moreover, CDK4 gain has been observed in approximately 25% of luminal B cancers and in 14% of luminal A, while RB loss is present in 20% of basal-like tumors, leading to CDK4/6 inhibitor resistance [7,10]. Upstream oncogenic signaling leads to the activation of the cyclin D1–CDK4/6 complex and estrogens induce the expression of cyclin D1, causing this pathway to be one of the major contributors to tumor progression in hormone receptor (HR)-positive breast cancer [11–13].

Breast cancer is the most common cancer and the leading cause of cancer-related death in women worldwide [14]. The majority of patients, approximately 70%, are HR-positive and HER2-negative [15]. In this group of patients, a benefit with CDK4/6 inhibitors has been observed in several clinical trials, leading to their approval for the treatment of metastatic tumors in combination with endocrine therapy (ET) [13]. In other settings, primarily HER2-positive or non-metastatic patients, the use of these drugs is currently being explored [16–22].

Actually, all three CDK4/6 inhibitors are approved in combination with aromatase inhibitors (AI) or fulvestrant for treating metastatic HR-positive/HER2-negative breast cancer (FDA and EMA approval), while abemaciclib is also approved as a monotherapy (FDA approval). Their mechanism of action and efficacy are similar, with some differences in their toxicity profiles. In this systematic review and meta-analysis, we explored the safety profiles of palbociclib, ribociclib, and abemaciclib in clinical trials and as in real-life clinical cohorts.

2. Methods

2.1. Literature search and data extraction

A systematic literature search was performed on May 24, 2020, in MEDLINE using the following keywords: ‘palbociclib breast

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Article highlights

- Palbociclib and ribociclib show a high rate of neutropenia, that is rapidly reversible and associated with a low rate of infection.
- Abemaciclib shows a high rate of gastrointestinal side effects, such as diarrhea and abdominal pain, which, although of low grade, can have a great impact on the patient quality of life.
- CDK4/6 inhibitors show a higher rate of toxicity in metastatic patients, probably due to their poorer general condition but also to the longer duration of treatment, than non-metastatic patients.
- Palbociclib and ribociclib do not seem to be more toxic in pretreated patients than in previously untreated patients, while abemaciclib seems to be associated with a higher rate of any grade neutropenia and grade 3-4 diarrhea.
- The toxicity profiles of palbociclib and ribociclib in pre- and post-menopausal patients are similar, with only a slight increase observed in the risk of diarrhea in postmenopausal patients.

cancer,' 'ribociclib breast cancer' and 'abemaciclib breast cancer.' All publications were collected and sorted by a medical oncologist (OCE). Full-text analysis and data extraction were performed by a reviewer (OCE) and verified by a second reviewer (GJ).

The following inclusion criteria were used to select articles for the final analysis: clinical studies on breast cancer patients, regardless of stage of the disease or the treatment line; clinical studies using currently approved doses for palbociclib (125 mg QD d1-21 q28), ribociclib (600 mg QD d1-21 q28) or abemaciclib (150 mg BID in combination with ET or 200 mg BID in monotherapy); studies in which CDK4/6 inhibitors were administered in combination with ET or as a monotherapy; and studies for which safety data of at least one adverse event were reported in the article in the form of percentage or number of patients reporting each toxicity. All of the following types of studies were included in the analysis: Phase I, Phase II, Phase III trials, expanded access programme (EAP), compassionate use programme and retrospective analysis. Exclusion criteria were as follows: studies not published in extenso; meta-analyses and literature reviews; studies where the administered dose of palbociclib, ribociclib, or abemaciclib was not that currently approved; studies in which CDK4/6 inhibitors were administered in concomitance of treatment other than ET or with radiotherapy, and studies where adverse effects were not reported.

The following data were included in the database: the total number of patients in the CDK4/6 arm; the stage of disease of patients included in the study (metastatic/non-metastatic); menopausal status; whether previous treatment had been administered; the number of events for any grade and grade 3–4 for toxicities of all types, neutropenia, leucopoenia, anemia, thrombocytopenia, infection, febrile neutropenia, AST and ALT increase, renal toxicity, diarrhea, vomiting, nausea, constipation, abdominal pain, stomatitis, dysgeusia, decreased appetite, fatigue, arthralgia, back pain, dizziness, headache, rash, hot flushes, pruritus, respiratory impairment, alopecia, thromboembolic event, and QTc prolongation. The number of severe adverse events (SAEs) and of toxic deaths was also collected.

Data extraction was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [23].

2.2. Statistical analysis

A one-sample proportion was used to obtain the pooled effect for each toxicity. Random and the fixed effect models were used to perform the analysis. Absolute risk (AR) and the 95% confidence interval (CI) were used to present the results. In the tables and in figures both random and fixed effect models are presented, while in the text, we presented results derived from the random effect model, which better fit our data considering the heterogeneity among the studies. Heterogeneity was assessed by means of the Higgins' I^2 statistic. The quality of each publication was assessed using the Cochrane risk of bias tools, Rob-2 for randomized trials, and ROBINS-1 for nonrandomized trials [24,25]. Publication bias was assessed with Egger's test.

In the first part of the analysis, data derived from palbociclib, ribociclib, and abemaciclib were analyzed separately. In the second part of the analysis, we analyzed data derived from metastatic and non-metastatic patients, from patients in pre- and post-menopausal status, and from previously untreated and in pre-treated patients.

The analysis was conducted using Comprehensive Meta-Analysis software v3.

3. Results

3.1. Article selection

A systematic literature search performed in MEDLINE identified 1024 records. A screening procedure identified 40 articles (Figure 1), that were included in the final database after exclusion of duplicates (323), non-clinical studies (612), post-hoc or subgroup analysis (17), articles in which toxicities were not detailed (16), combination with drugs other than endocrine therapy (8), study design (3), and report on other cancer types (2). Ultimately, 27 studies were included in the meta-analysis.

The type of study, the population included, the treatment arm, and the number of patients in the CDK4/6-inhibitor arm are summarized in the Table 1. The quality of each trial was assessed according to the Cochrane risk of bias tools and is reported in Table 1.

3.2. Safety results with palbociclib, ribociclib and abemaciclib

The absolute number of events for each toxicity was collected for all the studies and analyzed separately for palbociclib, ribociclib, and abemaciclib.

Of the 27 studies included in the meta-analysis, 20 were on palbociclib, including 2683 patients, 4 on ribociclib, including 1203 patients, and 3 on abemaciclib, including 906 patients.

Overall, for Palbociclib, 2 Phase III trials, 9 Phase II, 1 Phase I, 1 EAP, 2 compassionate use programs, and 5 retrospective studies were analyzed; for ribociclib, 3 Phase III and 1 Phase II trials were analyzed; and for abemaciclib, 2 Phase III and 1 Phase II trials were analyzed [18,19,22,26–58].

Publication bias was assessed with Egger's test and is reported in Tables 2 and 3.

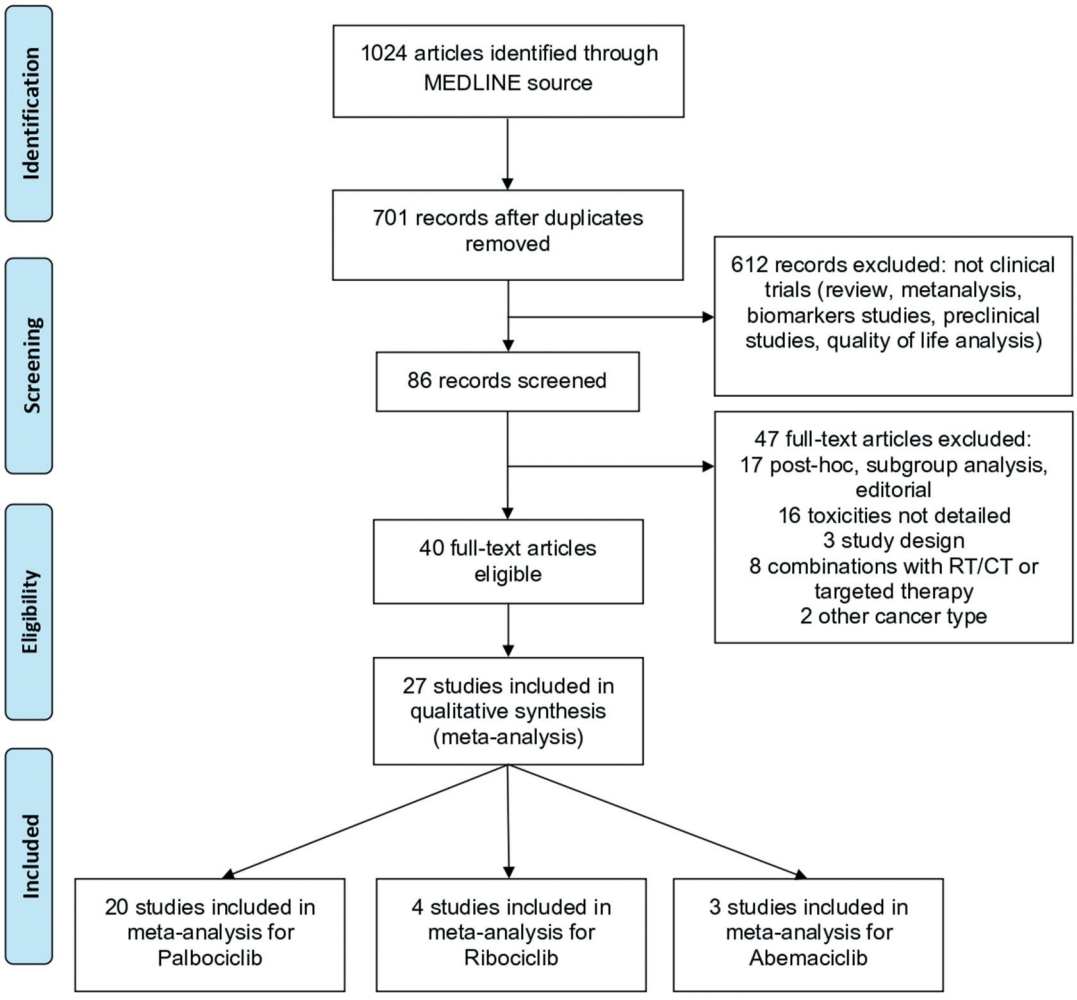

Figure 1. Consort diagram for article selection according to PRISMA guidelines.

The three drugs were comparable in terms of any grade toxicities, with an absolute risk (AR) of 0.981 (95% CI 0.972–-0.987; p < 0.0001) for palbociclib, 0.984 (95% CI 0.971–0.991; p < 0.0001) for ribociclib, and 0.979 (95% CI 0.966–0.987; p < 0.0001) for abemaciclib (Table 2). Abemaciclib showed a lower risk of grade 3–4 toxicities, with an AR of 0.592 (95% CI 0.557–0.626; p < 0.0001) compared to an AR of 0.763 (95% CI 0.634–0.857; p < 0.0001) for palbociclib and an AR of 0.739 (95% CI 0.629–0.825; p < 0.0001) for ribociclib (Table 3).

The most common toxicities were hematologic for palbociclib and ribociclib and gastrointestinal for abemaciclib (Table 2 and Table 3).

We observed an AR of 0.854 (95% CI 0.800–0.895; p < 0.0001) for any grade and 0.605 (95% CI 0.543–0.664; p 0.001) for grade 3–4 neutropenia with palbociclib; an AR of 0.760 (95% CI 0.702–0.810; p < 0.0001) and 0.586 (95% CI 0.531–0.638; p 0.002) for any grade and grade 3–4 neutropenia, respectively, with ribociclib; and 0.605 (95% CI 0.400–-0.779; p 0.317) and 0.225 (95% CI 0.175–0.283; p < 0.0001) for any grade and grade 3–4 neutropenia, respectively, with abemaciclib (Figure 2 and Figure 3). Considering the publication bias found for any grade neutropenia in palbociclib studies (Egger's test p 0.006), presumably due to the inclusion of retrospective studies, a second analysis was performed including only Phase I–III trials, which found similar results. Twelve studies with 1621 patients were analyzed, yelding an AR with a random effect model of 0.857 (95% CI 0.-777–0.912; p < 0.0001; *I2* 91%), without publication bias (Egger's test p 0.107). Despite the high rate of neutropenia, primarily for palbociclib and ribociclib compared to abemaciclib, the rate of infection was low, with some differences observed between the three drugs: AR 0.313 (95% CI 0.205–-0.446; p 0.007), AR 0.541 (95% CI 0.498–0.585; p 0.064), AR 0.385 (95% CI 0.329–0.443; p < 0.0001) for any grade infection with palbociclib, ribociclib, and abemaciclib, respectively; AR 0.049 (95% CI 0.034–0.070; p < 0.0001), AR 0.056 (95% CI 0.037–0.082; p < 0.0001) and AR 0.038 (95% CI 0.023–0.063; p < 0.0001) for grade 3–4 infection with palbociclib, ribociclib, and abemaciclib, respectively. Considering only Phase I–III trials for palbociclib with a random effect model, we obtained an AR of 0.361 (95% CI 0.228–0.519; p 0.083; I^2 93%; Egger's test p 0.091) for any grade infection and an AR of 0.055 (95%

Table 1. Trials included in meta-analysis for Palbociclib, Ribociclib, and Abemaciclib.

Palbociclib								
Study reference	Type of study	Population/line of treatment	Treatment arms	N of pts evaluable for toxicity	PFS/DFS in CDK4/6 arm	OS in CDK4/6 arm	ORR in CDK4/6 arm	Overall risk of bias (ROB-2/ROBINS-1)
PALOMA-2 [24,25]	Phase III	Postmenopausal HR+/HER2- MBC, first line	Palbociclib-letrozole *vs* placebo-letrozole	444	27.6 m	NR	42.1%	Low
PALOMA-3 [28–30]	Phase III	Any menopausal status, HR+/HER2- MBC, after ET	Palbociclib-fulvestrant *vs* placebo-fulvestrant	345	9.5 m	34.9 m	19%	Low
PALOMA-1 [31]	Phase II R	Postmenopausal HR+/HER2- MBC, first line	Palbociclib-letrozole *vs* letrozole	83	20.2 m	37.5 m	43%	Some concerns
NeoPAL [18]	Phase II R	HR+/HER2- stage II–III BC, neoadjuvant	Palbociclib-letrozole *vs* FEC → docetaxel	53	NR	NR	NR	Some concerns
PALLET [22]	Phase II R	Postmenopausal HR+/HER2- primary BC ≥ 2.0 cm, neoadjuvant	Letrozole *vs* letrozole → palbociclib-letrozole *vs* palbociclib → palbociclib-letrozole *vs* palbociclib-letrozole	201	NR	NR	54.3%	Some concerns
KCSG-BR15 -10 [32]	Phase II R	Premenopausal HR+/HER2- MBC, first/second/third line	Palbociclib- exemestane-gonadotropin *vs* Capecitabine	92	20.1 m	NR	37%	Some concerns
TREnd [33]	Phase II R	Postmenopausal HR+/HER2- ABC, progressed after one or two prior ETs	Palbociclib *vs* palbociclib-same ET previously received	58 57	6.5 m 10.8 m	NR NR	7% 10%	Some concerns
NeoPalAna [19]	Phase II single arm	Pre- and post-menopausal HR+/HER2- BC, neoadjuvant	Palbociclib-anastrozole	41	NR	NR	52%	Moderate
Takahashi et al. [34,35]	Phase II single arm	Postmenopausal HR+/HER2- MBC, first line	Palbociclib-letrozole	42	35.7 m	NR	47.6%	Moderate
Mayer et al. [36]	Phase II single arm	Stage II–III HR+/HER2- early BC, adjuvant	Palbociclib-ET (AI or tamoxifen)	162	NR	NR	NR	Moderate
De Michele et al. [37]	Phase II single arm	ABC positive for retinoblastoma (Rb) protein, no limit to the number of prior therapies allowed	Palbociclib	37	3.7 m	NR	5%	Moderate
Tamura et al. [38]	Phase I	Postmenopausal HR+/HER2- ABC, first line	Palbociclib-letrozole	6	NR	NR	NR	Moderate
Stearns et al. [39]	EAP	Postmenopausal HR+/HER2- MBC, first or later line	Palbociclib-letrozole	334	NR	NR	NR	Moderate
Ban et al. [40]	Compassionate Use program	Postmenopausal HR+/HER2-ABC, heavily pretreated	Palbociclib ± AI	24	4.8 m	11 m	0%	Serious
Maurer et al. [41]	Compassionate Use program	HR+/HER2- MBC, after ≥ 4 treatment lines	Palbociclib-ET	34	3.1 m	NR	7.1%	Serious
Bui et al. [42]	Retrospective	HR+/HER2- MBC progressed on previous ET	Palbociclib-Fulvestrant or AI	46	10 m	NR	NR	Serious
Pizzuti et al. [43]	Retrospective	HR+/HER2- MBC, all the lines of treatment	Palbociclib-ET	423	12 m	24 m	31%	Serious
Watson et al. [44]	Retrospective	Pre- and post-menopausal HR+/HER2- MBC, all the lines of treatment	Palbociclib-ET	64	NR	NR	17%	Serious
du Rusquec et al. [45]	Retrospective	HR+/HER2- MBC, after everolimus	Palbociclib-fulvestrant	60	5.8 m	NR	26.7%	Serious
Herrscher et al. [46]	Retrospective	HR+/HER2- MBC, heavily pretreated	Palbociclib-fulvestrant	77	7.6 m	NR	30%	Serious
Ribociclib								
Study reference	**Type of study**	**Population/line of treatment**	**Treatment arms**	**N of pts evaluable for toxicity**	**PFS/DFS in CDK4/6 arm**	**OS in CDK4/6 arm**	**ORR in CDK4/6 arm**	
MONALEESA-2 [47,48]	Phase III	postmenopausal HR+/HER2- recurrent/MBC, first line	Ribociclib-letrozole *vs* Placebo-letrozole	334	25.3	NR	52.7%	Low
MONALEESA-3 [49,50]	Phase III	Postmenopausal or man HR+/HER2- ABC, first or second line	Ribociclib-fulvestrant *vs* placebo-fulvestrant	483	20.5 m	NR	32.4%	Low

(*Continued*)

Table 1. (Continued).

Study reference	Type of study	Population/line of treatment	Treatment arms	N of pts evaluable for toxicity	PFS/DFS in CDK4/6 arm	OS in CDK4/6 arm	ORR in CDK4/6 arm	Overall risk of bias (ROB-2/ROBINS-1)
Palbociclib								
MONALEESA-7 [51,52]	Phase III	premenopausal HR+/HER2- ABC, no previous CDK4/6, allowed neo/adjuvant or up to one line of CT	Ribociclin-TAM/NSAI-goserelin *vs* TAM/NSAI-goserelin	335	23.8 m	NR	41%	Low
CORALLEEN [53]	Phase II R	Postmenopausal Luminal B stage I–IIIA HR+/HER2- BC, neoadjuvant	Ribociclib-letrozole *vs* AC → Paclitaxel	51	NR	NR	57.2%	Some concerns
Abemaciclib								
Study reference	**Type of study**	**Population/line of treatment**	**Treatment arms**	**N of pts evaluable for toxicity**	**PFS/DFS in CDK4/6 arm**	**OS in CDK4/6 arm**	**ORR in CDK4/6 arm**	
MONARCH-2 [54,55]	Phase III	Pre- and post-menopausal HR+/HER2- ABC progressed while receiving ET (neo/adjuvant of first line)	Abemaciclib-fulvestrant *vs* placebo-fulvestrant	446	16.4 m	46.7 m	48.1%	Low
MONARCH-3 [56,57]	Phase III	Postmenopausal HR+/HER2- ABC, first line	Abemaciclib-NSAI *vs* placebo-NSAI	328	18.2 m	NR	59%	Low
MONARCH-1 [58]	Phase II single arm	HR+/HER2- heavily pretreated MBC	Abemaciclib	132	6 m	17.7 m	19.7%	Moderate

Abbreviations: N = number; pts = patients; PFS = progression free survival; DFS = disease free survival; OS = overall survival; ORR = overall response rate; HR = hormone receptors; MBC = metastatic breast cancer; m = months; NR = not reported; ET = endocrine therapy; R = randomized; BC = breast cancer; FEC = 5-fluorouracil-epirubicine-cyclophosphamide; ABC = advanced breast cancer; AI = aromatase inhibitor; CT = chemotherapy; NSAI = non-steroidal aromatase inhibitor; AC = doxorubicine-cyclophosphamide

Table 2. Meta-analysis for the most common toxicities of any grade in clinical trials with Palbociclib, Ribociclib, and Abemaciclib.

	Palbociclib								Ribociclib								Abemaciclib							
		Random effect model		Fixed effect model			Egger's	N pts	Random effect model		Fixed effect model			Egger's			Random effect model		Fixed effect model			Egger's	
Toxicities	N pts	AR (95% CI)	P value	AR (95% CI)	P value	I^2	test	P value	AR (95% CI)	P value	AR (95% CI)	P value	I^2	test	N pts		AR (95% CI)	P value	AR (95% CI)	P value	I^2	test		
All toxicities	1683	0.981 (0.972–0.987)	< 0.0001	0.981 (0.972–0.987)	< 0.0001	0%	0.277	720	0.984 (0.971–0.991)	< 0.0001	0.984 (0.971–0.991)	< 0.0001	0%	0.368	774		0.979 (0.966–0.987)	< 0.0001	0.979 (0.966–0.987)	< 0.0001	0%	NA		
Neutropenia	2649	0.854 (0.800–0.895)	< 0.0001	0.753 (0.734–0.771)	< 0.0001	90%	0.006	1203	0.760 (0.702–0.810)	< 0.0001	0.749 (0.723–0.773)	< 0.0001	72%	0.110	906		0.605 (0.400–0.779)	0.317	0.486 (0.452–0.520)	0.405	97%	0.165		
Leucopoenia	2424	0.571 (0.431–0.701)	0.320	0.419 (0.396–0.443)	< 0.0001	96%	0.253	1152	0.326 (0.299–0.353)	< 0.0001	0.326 (0.299–0.353)	< 0.0001	0%	0.329	906		0.328 (0.198–0.491)	0.039	0.298 (0.269–0.330)	< 0.0001	95%	0.515		
Anemia	2602	0.356 (0.272–0.450)	0.003	0.301 (0.282–0.320)	< 0.0001	94%	0.122	1203	0.200 (0.167–0.238)	< 0.0001	0.203 (0.182–0.227)	< 0.0001	50%	0.204	906		0.322 (0.272–0.399)	< 0.0001	0.313 (0.284–0.344)	< 0.0001	63%	0.065		
Thrombocytopenia	2544	0.324 (0.258–0.399)	< 0.0001	0.276 (0.258–0.295)	< 0.0001	90%	0.112	869	0.088 (0.066–0.117)	< 0.0001	0.089 (0.072–0.110)	< 0.0001	26%	0.151	578		0.188 (0.183–0.277)	< 0.0001	0.175 (0.146–0.209)	< 0.0001	78%	NA		
Infection	1443	0.313 (0.205–0.446)	0.007	0.449 (0.421–0.476)	< 0.0001	95%	0.040	1152	0.541 (0.498–0.585)	0.064	0.544 (0.515–0.573)	0.003	56%	0.278	906		0.385 (0.329–0.443)	< 0.0001	0.397 (0.366–0.430)	< 0.0001	65%	0.102		
Diarrhea	2299	0.144 (0.103–0.197)	< 0.0001	0.200 50.183–0.219)	< 0.0001	88%	0.019	1203	0.258 (0.181–0.355)	< 0.0001	0.292 (0.266–0.318)	< 0.0001	90%	0.451	906		0.853 (0.809–0.888)	< 0.0001	0.847 (0.821–0.869)	< 0.0001	60%	0.451		
Constipation	2159	0.121 (0.085–0.170)	< 0.0001	0.162 (0.146–0.180)	< 0.0001	88%	0.031	1203	0.212 (0.158–0.279)	< 0.0001	0.232 (0.209–0.257)	< 0.0001	82%	0.352	774		0.153 (0.118–0.195)	< 0.0001	0.152 (0.128–0.179)	< 0.0001	56%	NA		
Nausea	2538	0.195 (0.151–0.247)	< 0.0001	0.263 (0.245–0.281)	< 0.0001	88%	0.006	1203	0.382 (0.277–0.501)	0.051	0.431 (0.403–0.460)	< 0.0001	93%	0.429	906		0.420 (0.383–0.459)	< 0.0001	0.423 (0.391–0.456)	< 0.0001	23%	0.228		
Vomiting	962	0.158 (0.110–0.220)	< 0.0001	0.182 (0.159–0.209)	< 0.0001	68%	0.060	1203	0.229 (0.158–0.320)	< 0.0001	0.265 (0.240–0.291)	< 0.0001	89%	0.316	906		0.258 (0.210–0.312)	< 0.0001	0.265 (0.238–0.295)	< 0.0001	64%	0.512		
Stomatitis	2492	0.206 (0.149–0.279)	< 0.0001	0.239 (0.221–0.258)	< 0.0001	92%	0.307	NA	NR	NA	NR	NA	NA	NA	NA		NR	NA	NR	NA	NA	NA		
Disgeusia	534	0.083 (0.040–0.163)	< 0.0001	0.100 (0.076–0.129)	< 0.0001	38%	0.286	NA	NR	NA	NR	NA	NA	NA	NA		NR	NA	NR	NA	NA	NA		
Decreased appetite	1765	0.140 (0.089–0.214)	< 0.0001	0.152 (0.135–0.172)	< 0.0001	90%	0.608	1203	0.137 (0.091–0.201)	< 0.0001	0.157 (0.137–0.179)	< 0.0001	85%	0.387	906		0.265 (0.237–0.295)	< 0.0001	0.265 (0.237–0.295)	< 0.0001	0%	0.755		
Abdominal pain	1265	0.082 (0.050–0.133)	< 0.0001	0.095 (0.079–0.113)	< 0.0001	83%	0.442	NA	NR	NA	NR	NA	NA	NA	906		0.300 (0.241–0.368)	< 0.0001	0.319 (0.289–0.350)	< 0.0001	75%	0.090		
AST increase	1133	0.138 (0.100–0.188)	< 0.0001	0.130 (0.112–0.152)	< 0.0001	68%	0.912	720	0.173 (0.107–0.267)	< 0.0001	0.152 (0.127–0.180)	< 0.0001	84%	0.307	774		0.143 (0.103–0.195)	< 0.0001	0.142 (0.119–0.169)	< 0.0001	70%	NA		
ALT increase	1126	0.123 (0.086–0.174)	< 0.0001	0.120 (0.103–0.139)	< 0.0001	77%	0.890	720	0.214 (0.108–0.380)	0.002	0.171 (0.144–0.201)	< 0.0001	93%	0.206	906		0.156 (0.128–0.188)	< 0.0001	0.155 (0.132–0.180)	< 0.0001	33%	0.689		
Renal alteration	161	0.076 (0.018–0.266)	0.001	0.110 (0.060–0.193)	< 0.0001	68%	0.461	818	0.070 (0.019–0.221)	< 0.0001	0.102 (0.082–0.126)	< 0.0001	94%	NA	906		0.261 (0.093–0.549)	0.100	0.233 (0.204–0.265)	< 0.0001	98%	0.405		
Rash	1058	0.152 (0.109–0.209)	< 0.0001	0.182 (0.159–0.208)	< 0.0001	66%	0.024	1203	0.187 (0.146–0.238)	< 0.0001	0.186 (0.165–0.209)	< 0.0001	72%	0.862	774		0.130 (0.093–0.177)	< 0.0001	0.129 (0.107–0.155)	< 0.0001	67%	NA		
Hot flushes	1288	0.277 (0.191–0.382)	< 0.0001	0.258 (0.234–0.284)	< 0.0001	92%	0.530	868	0.171 (0.101–0.273)	< 0.0001	0.183 (0.158–0.211)	< 0.0001	89%	0.832	NA		NR	NA	NR	NA	NA	NA		
Fatigue	2641	0.452 (0.389–0.516)	0.140	0.448 (0.429–0.468)	< 0.0001	88%	0.912	1203	0.283 (0.202–0.381)	< 0.0001	0.318 (0.0.292–0.346)	< 0.0001	90%	0.437	906		0.397 (0.366–0.430)	< 0.0001	0.397 (0.366–0.430)	< 0.0001	0%	0.559		
Arthralgia	2289	0.185 (0.127–0.260)	< 0.0001	0.248 (0.228–0.269)	< 0.0001	93%	0.051	1152	0.288 (0.236–0.346)	< 0.0001	0.286 (0.260–0.312)	< 0.0001	77%	0.353	774		0.142 (0.093–0.210)	< 0.0001	0.142 (0.119–0.169)	< 0.0001	82%	NA		
Back pain	590	0.158 (0.117–0.210)	< 0.0001	0.169 (0.140–0.201)	< 0.0001	49%	0.358	1152	0.198 (0.159–0.242)	< 0.0001	0.198 (0.176–0.222)	< 0.0001	69%	0.986	774		0.123 (0.073–0.201)	< 0.0001	0.125 (0.103–0.151)	< 0.0001	86%	NA		
Headache	2256	0.151 (0.109–0.205)	< 0.0001	0.210 (0.192–0.230)	< 0.0001	88%	0.009	1152	0.237 (0.206–0.270)	< 0.0001	0.236 (0.212–0.261)	< 0.0001	39%	0.656	906		0.182 (0.145–0.226)	< 0.0001	0.190 (0.165–0.217)	< 0.0001	54%	0.124		
Alopecia	1531	0.159 (0.111–0.224)	< 0.0001	0.237 (0.215–0.260)	< 0.0001	88%	0.005	1203	0.234 (0.159–0.329)	< 0.0001	0.239 (0.159–0.329)	< 0.0001	91%	0.871	774		0.208 (0.115–0.349)	< 0.0001	0.212 (0.184–0.243)	< 0.0001	94%	NA		
Pruritus	NA	NR	NA	NR	NA	NA	NA	869	0.148 (0.084–0.250)	< 0.0001	0.164 (0.141–0.191)	< 0.0001	88%	0.717	NA		NR	NA	NR	NA	NA	NA		
Dizziness	1309	0.123 (0.088–0.170)	< 0.0001	0.149 (0.130–0.171)	< 0.0001	71%	0.044	NA	NR	NA	NR	NA	NA	NA	NA		NR	NA	NR	NA	NA	NA		
Respiratory toxicity	1087	0.144 (0.120–0.172)	< 0.0001	0.147 (0.127–0.169)	< 0.0001	26%	0.111	818	0.311 (0.207–0.439)	0.004	0.327 (0.295–0.360)	< 0.0001	92%	NA	NA		NR	NA	NR	NA	NA	NA		
Thromboembolism	409	0.041 (0.005–0.256)	0.003	0.046 (0.026–0.080)	< 0.0001	92%	NA	534	0.039 (0.013–0.107)	< 0.0001	0.046 (0.031–0.068)	< 0.0001	23%	NA	NA		NR	NA	NR	NA	NA	NA		
QTc prolongation	930	0.008 (0.002–0.032)	< 0.0001	0.011 (0.005–0.032)	< 0.0001	66%	0.243	1203	0.073 (0.043–0.123)	< 0.0001	0.088 (0.072–0.106)	< 0.0001	82%	0.405	NA		NR	NA	NR	NA	NA	NA		

Abbreviations: N = number; pts = patients; AR = absolute risk; CI = confidence interval; NA = not applicable; NR = not reported

Table 3. Meta-analysis for the most common grade 3–4 toxicities in clinical trials with Palbociclib, Ribociclib, and Abemaciclib.

	Palbociclib							Ribociclib							Abemaciclib						
		Random effect model		Fixed effect model					Random effect model		Fixed effect model					Random effect model		Fixed effect model				
Toxicities	N pts	AR (95% CI)	P value	AR (95% CI)	P value	I^2	Egger's test	N pts	AR (95% CI)	P value	AR (95% CI)	P value	I^2	Egger's test	N pts	AR (95% CI)	P value	AR (95% CI)	P value	I^2	Egger's test
All toxicities	1554	0.763 (0.634–0.857)	< 0.0001	0.728 (0.702–0.751)	< 0.0001	95%	0.656	720	0.739 (0.629–0.825)	< 0.0001	0.70 (0.738–0.800)	< 0.0001	86%	0.314	774	0.592 (0.557–0.626)	< 0.0001	0.592 (0.557–0.626)	< 0.0001	0%	NA
Neutropenia	2619	0.605 (0.543–0.664)	0.001	0.576 (0.556–0.596)	< 0.0001	88%	0.314	1203	0.586 (0.531–0.638)	0.002	0.594 (0.566–0.622)	< 0.0001	67%	0.405	906	0.225 (0.175–0.283)	< 0.0001	0.240 (0.213–0.269)	< 0.0001	70%	0.028
Leucopoenia	2424	0.195 (0.128–0.286)	< 0.0001	0.248 (0.228–0.270)	< 0.0001	94%	0.245	1152	0.175 (0.143–0.213)	< 0.0001	0.175 (0.154–0.198)	< 0.0001	60%	0.983	906	0.104 (0.072–0.149)	< 0.0001	0.100 (0.081–0.121)	< 0.0001	70%	0.341
Anemia	2548	0.040 (0.032–0.050)	< 0.0001	0.041 (0.034–0.051)	< 0.0001	8%	0.007	1203	0.034 (0.025–0.046	< 0.0001	0.034 (0.025–0.046	< 0.0001	0%	0.175	906	0.065 (0.040–0.103)	< 0.0001	0.069 (0.054–0.089)	< 0.0001	55%	0.059
Thrombocytopenia	2642	0.037 (0.023–0.058)	< 0.0001	0.042 (0.034–0.053)	< 0.0001	69%	0.241	869	0.010 (0.005–0.019	< 0.0001	0.010 (0.005–0.019	< 0.0001	0%	0.782	578	0.029 (0.016–0.052)	< 0.0001	0.031 (0.019–0.049)	< 0.0001	13%	NA
Infection	1379	0.049 (0.034–0.070)	< 0.0001	0.056 (0.045–0.070)	< 0.0001	36%	0.048	1152	0.056 (0.037–0.082)	< 0.0001	0.060 (0.048–0.076)	< 0.0001	61%	0.025	774	0.038 (0.023–0.063)	< 0.0001	0.039 (0.027–0.055)	< 0.0001	49%	NA
Febrile neutropenia	1966	0.023 (0.017–0.031)	< 0.0001	0.023 (0.017–0.031)	< 0.0001	0%	0.021	1203	0.014 (0.009–0.023)	< 0.0001	0.014 (0.009–0.023)	< 0.0001	0%	0.564	906	0.010 (0.005–0.021)	< 0.0001	0.010 (0.005–0.021)	< 0.0001	1%	0.301
Diarrhea	2299	0.011 (0.007–0.018)	< 0.0001	0.011 (0.007–0.018)	< 0.0001	0%	0.291	1203	0.015 (0.008–0.027)	< 0.0001	0.016 (0.010–0.025)	< 0.0001	29%	0.418	906	0.135 (0.092–0.192)	< 0.0001	0.131 (0.111–0.156)	< 0.0001	77%	0.809
Constipation	2201	0.006 (0.001–0.032)	< 0.0001	0.037 (0.023–0.060)	< 0.0001	86%	0.0007	1203	0.009 (0.005–0.017)	< 0.0001	0.009 (0.005–0.017)	< 0.0001	0%	0.352	774	0.006 (0.003–0.015)	< 0.0001	0.006 (0.003–0.015)	< 0.0001	0%	NA
Nausea	2514	0.010 (0.006–0.015)	< 0.0001	0.010 (0.006–0.015)	< 0.0001	0%	0.045	1203	0.016 (0.009–0.027)	< 0.0001	0.016 (0.010–0.026)	< 0.0001	14%	0.355	906	0.022 (0.014–0.034)	< 0.0001	0.022 (0.014–0.034)	< 0.0001	0%	0.533
Vomiting	962	0.008 (0.004–0.016)	< 0.0001	0.008 (0.004–0.016)	< 0.0001	0%	0.948	1203	0.020 (0.011–0.036)	< 0.0001	0.022 (0.015–0.033)	< 0.0001	43%	0.421	906	0.011 (0.006–0.021)	< 0.0001	0.011 (0.006–0.021)	< 0.0001	0%	0.581
Stomatitis	2468	0.012 (0.008–0.018)	< 0.0001	0.012 (0.008–0.018)	< 0.0001	0%	0.161	NA	NR	NA	NR	NA	NA	NA	NA	NR	NA	NR	NA	NA	NA
Disgeusia	534	0.005 (0.001–0.025)	< 0.0001	0.005 (0.001–0.025)	< 0.0001	0%	0.122	NA	NR	NA	NR	NA	NA	NA	NA	NR	NA	NR	NA	NA	NA
Decreased appetite	1765	0.012 (0.006–0.026)	< 0.0001	0.019 (0.012–0.028)	< 0.0001	49%	0.051	1203	0.008 (0.004–0.019)	< 0.0001	0.009 (0.005–0.018)	< 0.0001	21%	0.322	906	0.013 (0.008–0.023)	< 0.0001	0.013 (0.008–0.023)	< 0.0001	0%	0.759
Abdominal pain	1265	0.009 (0.004–0.019)	< 0.0001	0.010 (0.005–0.018)	< 0.0001	13%	0.221	NA	NR	NA	NR	NA	NA	NA	906	0.021 (0.014–0.033)	< 0.0001	0.021 (0.014–0.033)	< 0.0001	0%	0.290
AST increase	1133	0.029 (0.020–0.041)	< 0.0001	0.029 (0.020–0.041)	< 0.0001	0%	0.131	720	0.054 (0.033–0.087)	< 0.0001	0.052 (0.038–0.072)	< 0.0001	50%	0.665	774	0.029 (0.018–0.047)	< 0.0001	0.029 (0.019–0.044)	< 0.0001	26%	NA
ALT increase	1126	0.034 (0.020–0.056)	< 0.0001	0.032 (0.023–0.045)	< 0.0001	45%	0.863	720	0.097 (0.051–0.178)	< 0.0001	0.088 (0.069–0.112)	< 0.0001	83%	0.655	906	0.046 (0.028–0.073)	< 0.0001	0.049 (0.036–0.065)	< 0.0001	52%	0.466
Renal alteration	119	0.017 (0.003–0.082)	< 0.0001	0.017 (0.003–0.082)	< 0.0001	0%	0.023	818	0.009 (0.002–0.036	< 0.0001	0.012 (0.006–0.024)	< 0.0001	55%	NA	906	0.014 (0.007–0.027)	< 0.0001	0.015 (0.008–0.026)	< 0.0001	18%	0.494
Rash	1058	0.009 (0.005–0.017)	< 0.0001	0.009 (0.005–0.017)	< 0.0001	0%	0.684	1203	0.009 (0.004–0.020)	< 0.0001	0.010 (0.005–0.018)	< 0.0001	30%	0.501	774	0.010 (0.005–0.021)	< 0.0001	0.010 (0.005–0.021)	< 0.0001	0%	NA
Hot flushes	1288	0.003 (0.001–0.009)	< 0.0001	0.003 (0.001–0.009)	< 0.0001	0%	0.002	868	0.003 (0.001–0.012)	< 0.0001	0.003 (0.001–0.012)	< 0.0001	0%	0.974	NA	NR	NA	NR	NA	NA	NA
Fatigue	2553	0.033 (0.024–0.047)	< 0.0001	0.034 (0.027–0.043)	< 0.0001	42%	0.252	1203	0.020 (0.013–0.031)	< 0.0001	0.020 (0.013–0.030)	< 0.0001	9%	0.420	906	0.034 (0.015–0.076)	< 0.0001	0.036 (0.025–0.051)	< 0.0001	79%	0.813
Arthralgia	2289	0.008 (0.005–0.013)	< 0.0001	0.008 (0.005–0.013)	< 0.0001	0%	0.346	1152	0.008 (0.004–0.015)	< 0.0001	0.008 (0.004–0.015)	< 0.0001	0%	0.0009	774	0.002 (0.000–0.010)	< 0.0001	0.002 (0.000–0.010)	< 0.0001	0%	NA
Back pain	590	0.012 (0.006–0.026)	< 0.0001	0.012 (0.006–0.026)	< 0.0001	0%	0.416	1152	0.020 (0.012–0.033)	< 0.0001	0.020 (0.013–0.031)	< 0.0001	34%	0.362	774	0.008 (0.004–0.017)	< 0.0001	0.008 (0.004–0.017)	< 0.0001	0%	NA
Headache	2256	0.006 (0.004–0.011)	< 0.0001	0.006 (0.004–0.011)	< 0.0001	0%	0.215	1152	0.006 (0.003–0.014)	< 0.0001	0.006 (0.003–0.014)	< 0.0001	0%	0.029	906	0.008 (0.004–0.016)	< 0.0001	0.008 (0.004–0.016)	< 0.0001	0%	0.947
Pruritus	NA	NR	NA	NR	NA	NA	NA	869	0.004 (0.001–0.023)	< 0.0001	0.005 (0.001–0.016)	< 0.0001	41%	0.683	NA	NR	NA	NR	NA	NA	NA
Dizziness	1309	0.006 (0.003–0.012)	< 0.0001	0.006 (0.003–0.012)	< 0.0001	0%	0.399	NA	NR	NA	NR	NA	NA	NA	NA	NR	NA	NR	NA	NA	NA
Respiratory toxicity	1087	0.012 (0.007–0.021)	< 0.0001	0.012 (0.007–0.021)	< 0.0001	0%	0.425	818	0.020 (0.012–0.032)	< 0.0001	0.020 (0.012–0.032)	< 0.0001	0%	NA	NA	NR	NA	NR	NA	NA	NA
Thromboembolism	409	0.012 (0.005–0.029)	< 0.0001	0.012 (0.005–0.029)	< 0.0001	0%	NA	534	0.022 (0.012–0.039)	< 0.0001	0.022 (0.012–0.039)	< 0.0001	0%	NA	NA	NR	NA	NR	NA	NA	NA
QTc prolongation	930	0.002 (0.001–0.009)	< 0.0001	0.002 (0.001–0.009)	< 0.0001	0%	0.646	1203	0.019 (0.010–0.037)	< 0.0001	0.023 (0.016–0.034)	< 0.0001	45%	0.256	NA	NR	NA	NR	NA	NA	NA

Abbreviations: N = number; pts = patients; AR = absolute risk; CI = confidence interval; NA = not applicable; NR = not reported

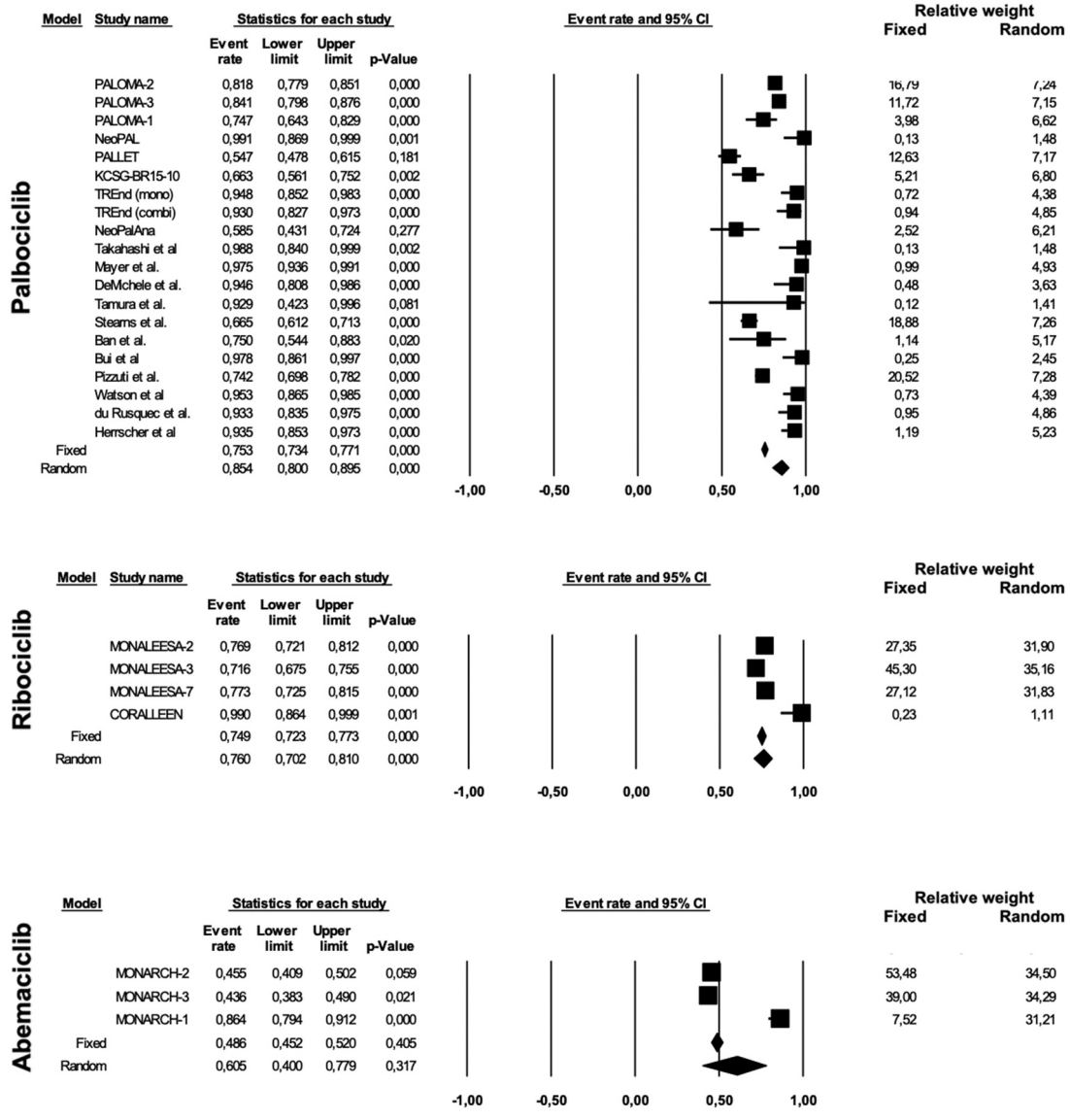

Figure 2. Absolute risk for any grade neutropenia for palbociclib, ribociclib and abemaciclib.

CI 0.037–0.080; p < 0.0001; I^2 28%; Egger's test p 0.010) for grade 3–4 infection. Febrile neutropenia was observed at a higher rate in the palbociclib group (AR 0.023, 95% CI 0.-017–0.031, p < 0.0001) than in the ribociclib (AR 0.010, 95% CI 0.005–0.021, p < 0.0001) and abemaciclib (AR 0.008, 95% CI 0.002–0.032, p < 0.0001) groups. Considering only Phase I–III trials, the AR with a random effect model for febrile neutropenia with palbociclib was 0.016 (95% CI 0.010–0.025; p < 0.0001; I^2 0%; Egger's test p 0.236).

Concerning gastrointestinal toxicities, the most common was diarrhea, with ARs for any grade toxicity of 0.144 (95% CI 0.103–0.197, p < 0.0001), 0.258 (95% CI 0.181–0.355, p < 0.0001) and 0.853 (95% CI 0.809–0.888, p < 0.0001) for palbociclib, ribociclib and abemaciclib, respectively (Figure 4). Considering the publication bias found for any grade diarrhea in palbociclib studies (Egger's test p 0.019), phase I–III trials alone (9 studies with 1465 patients) were analyzed, revealing an AR with a random effect model of 0.183 (95% CI 0.141–-0.233; p < 0.0001; I^2 75%; Egger's test p 0.003). However, diarrhea observed in the abemaciclib group was of low grade in the majority of cases. In fact, the AR of grade 3–4 diarrhea was 0.011 (95% CI 0.007–0.018, p < 0.0001) for palbociclib, 0.015 (95% CI 0.008–0.027, p < 0.0001) for ribociclib and 0.135 (95% CI 0.092–0.192, p < 0.0001) for abemaciclib (Figure 5).

Abemaciclib also showed a higher risk of other gastrointestinal toxicities, primarily nausea (AR for any grade toxicity 0.195, 0.382 and 0.420 for palbociclib, ribociclib, and abemaciclib, respectively), decreased appetite (AR for any grade toxicity 0.140, 0.137 and 0.265 for palbociclib, ribociclib and abemaciclib, respectively) and abdominal pain (AR for any grade toxicity 0.082 for palbociclib and 0.300 for abemaciclib, insufficient data reported to perform the meta-analysis for ribociclib).

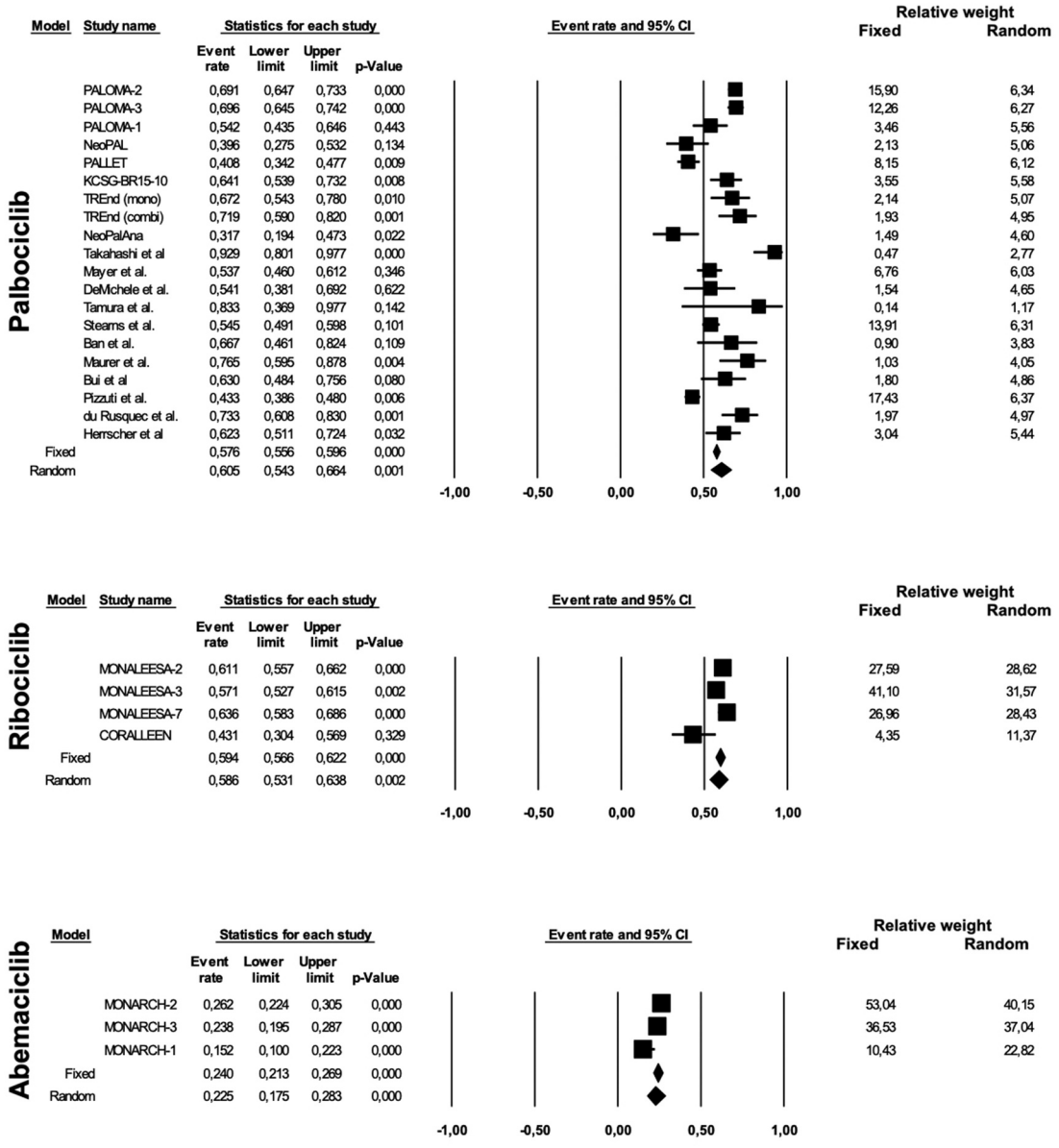

Figure 3. Absolute risk for grade 3–4 neutropenia for palbociclib, ribociclib and abemaciclib.

Renal alterations were also more frequent in the abemaciclib group, with an AR for any grade toxicity of 0.076, 0.070, and 0.261 for palbociclib, ribociclib, and abemaciclib, respectively. In the majority of studies, the parameter reported for renal function evaluation is the increase of creatinine level, with the exception of three studies, one for palbociclib, and two for ribociclib, in which the parameter evaluated was not specified in the articles [45,49–52].

Ribociclib showed a higher risk of hepatic toxicity, than palbociclib and abemaciclib, primarily for grade 3–4 adverse events: AR for grade 3–4 ALT increase with palbociclib 0.034, 0.097 for ribociclib and 0.046 for abemaciclib; and AR for AST increase of 0.029, 0.054, and 0.029 for palbociclib, ribociclib, and abemaciclib, respectively.

Any grade arthralgia was also more frequently observed in patients treated with ribociclib: AR 0.185, 0.288, and 0.142 for palbociclib, ribociclib, and abemaciclib, respectively.

Ribociclib exhibited a higher absolute risk compared to palbociclib for respiratory toxicity (AR for any grade respiratory toxicity 0.311 and 0.144; AR for grade 3–4 respiratory toxicity 0.020 and 0.012 for ribociclib and palbociclib, respectively) and QTc prolongation (AR for any grade QTc prolongation 0.073 and 0.008; AR for grade 3–4 QTc prolongation 0.019 and 0.002 for ribociclib and palbociclib, respectively). Insufficient data were available for abemaciclib to perform the meta-analysis.

Conversely, a lower risk of any grade fatigue was observed in patients receiving ribociclib: AR 0.452, 0.283, and 0.397 for palbociclib, ribociclib, and abemaciclib, respectively.

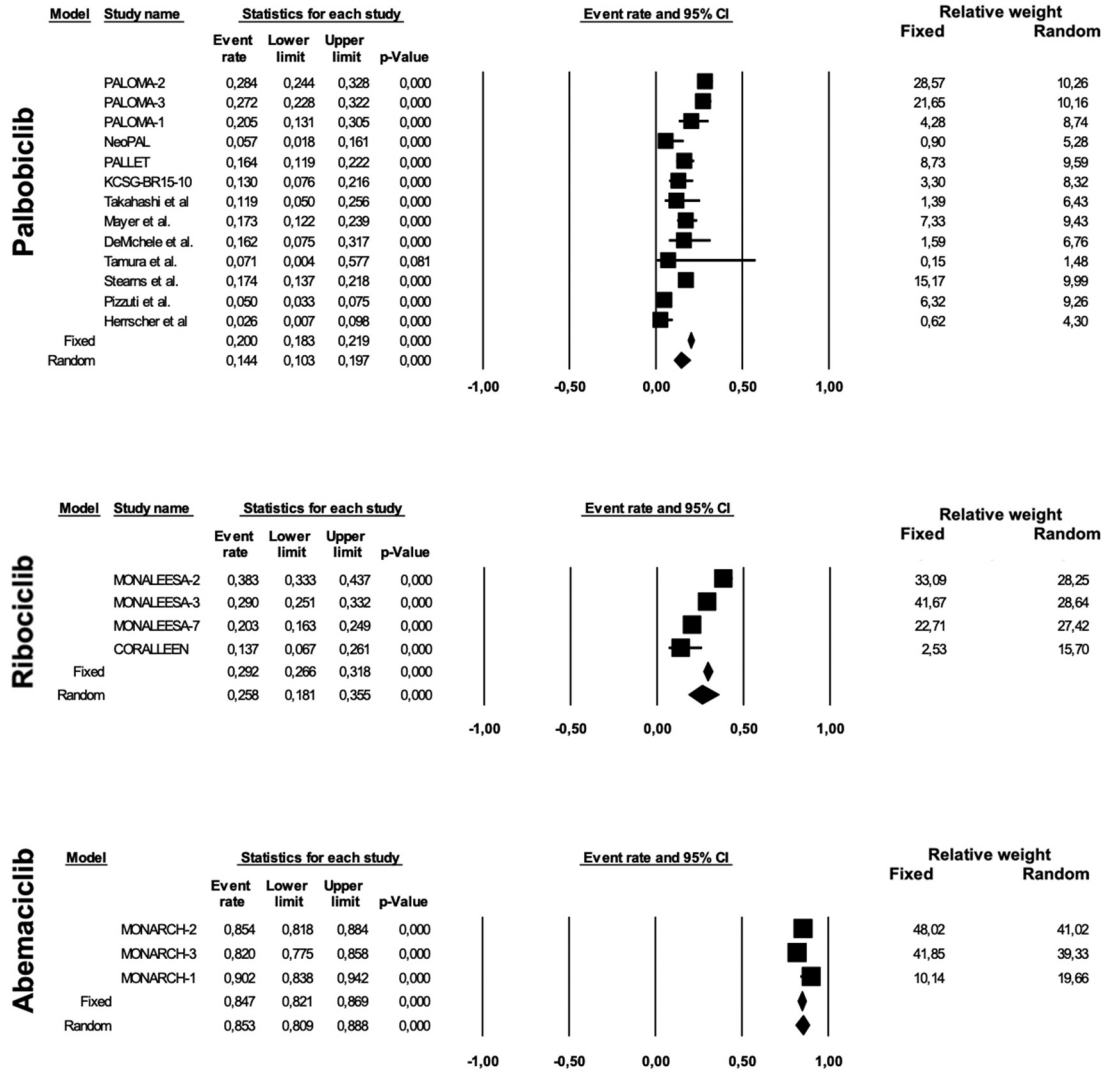

Figure 4. Absolute risk for any grade diarrhea for palbociclib, ribociclib and abemaciclib.

ARs for SAEs of 0.097 (95% CI 0.067–0.140; p < 0.0001; I^2 76%; Egger's test 0.013), of 0.195 (95% CI 0.133–0.276; p < 0.0001; I^2 87%; Egger's test 0.215) and of 0.246 (95% CI 0.215–0.280; p < 0.0001; I^2 22%; Egger's test p 0.939) for palbociclib, ribociclib, and abemaciclib, respectively, were observed.

Toxic death was a rare event, with an AR of 0.004 (95% CI 0.002–0.011; p < 0.0001; I^2 0%; Egger's test 0.332) for palbociclib, 0.003 (95% CI 0.001–0.009; p < 0.0001; I^2 0%; Egger's test 0.881) for ribociclib and 0.026 (95% CI 0.011–0.057; p < 0.0001; I^2 67%; Egger's test 0.439) for abemaciclib.

3.3. Safety results in metastatic and in non-metastatic patients

The safety profile was analyzed for metastatic patients and for non-metastatic patients. Overall, 19 trials including 3378 patients were analyzed for the metastatic group, and 5 trials including 792 patients for the non-metastatic group [18,19,22,26–35,37–53]. Trials with abemaciclib were excluded from analysis, because no trials were available in a non-metastatic setting [54–58].

Treatment with CDK4/6 inhibitors was associated with a similar rate of any grade toxicity (AR 0.981, 95% CI 0.-973–0.986, p < 0.0001, I^2 0% for metastatic patients and AR 0.990, 95% CI 0.970–0.997, p 0.001, I^2 0% for non-metastatic patients), with a lower incidence of G3-4 toxicities in the non-metastatic group (AR 0.818, 95% CI 0.756–0.867, p < 0.0001, I^2 88% and AR 0.492, 95% CI 0.413–0.572, p 0.852, I^2 37% for metastatic and non-metastatic patients, respectively).

For any grade neutropenia, AR was of 0.822 (95% CI 0.781–-0.857; p < 0.0001; I^2 84%) and 0.905 (95% CI 0.676–0.977; p 0.004; I^2 94%) for the metastatic and non-metastatic groups, respectively; while for grade 3–4 neutropenia, AR was 0.638 (95% CI 0,589–0.683; p < 0.0001; I^2 84%) for the metastatic and 0.430 (95% CI 0.358–0.506; p 0.070; I^2 59%) for the non-metastatic groups.

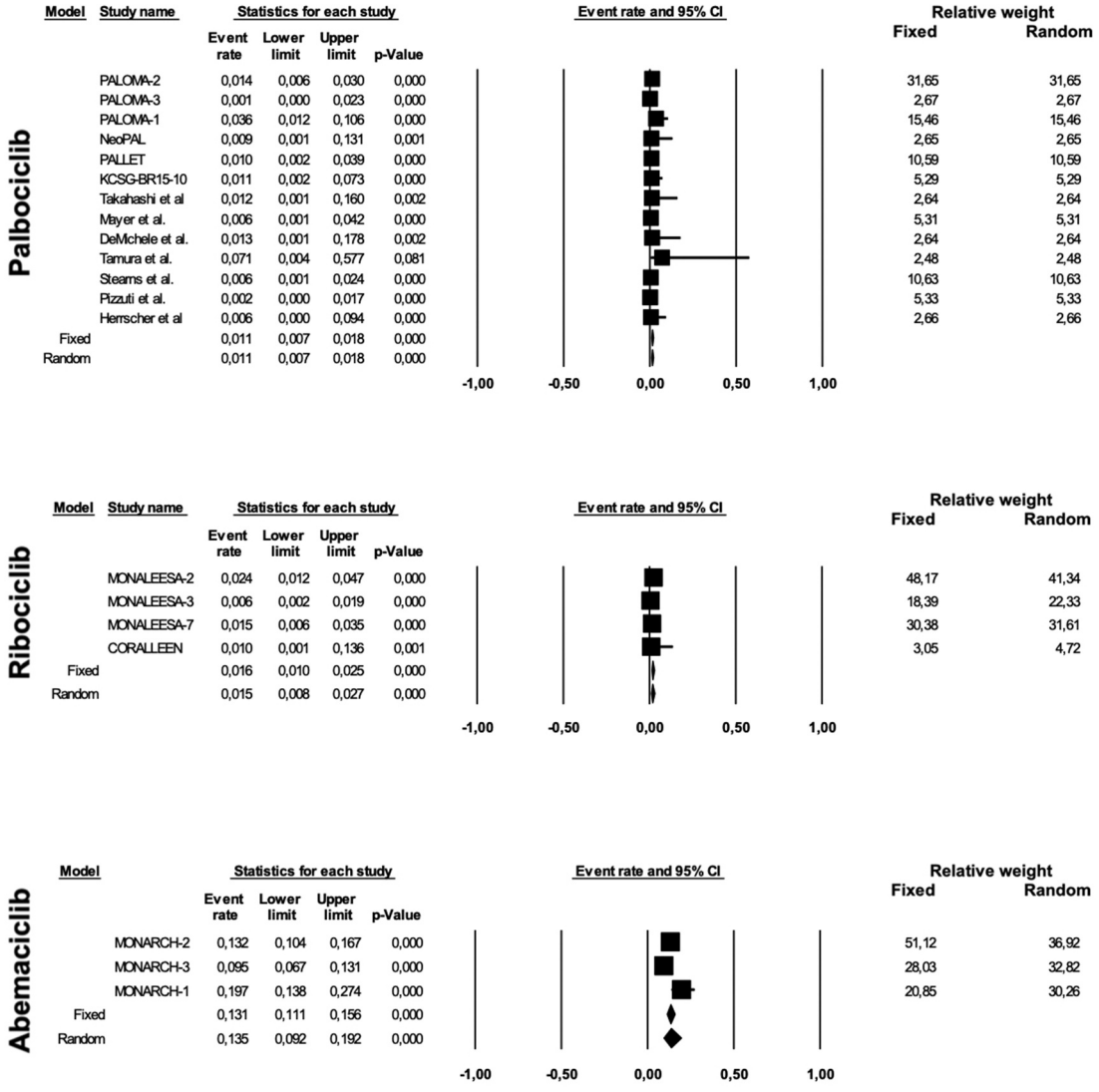

Figure 5. Absolute risk for grade 3–4 diarrhea for palbociclib, ribociclib and abemaciclib.

Differences in the risk of developing diarrhea were minimal. In fact, an AR for any grade diarrhea of 0.181 (95% CI 0.135–-0.239; p < 0.0001; I^2 92%) and of 0.152 (95% CI 0.114–0.199; p < 0.0001; I^2 28%) was observed for metastatic and non-metastatic patients, respectively. The AR for grade 3–4 diarrhea was also slightly higher in the metastatic group, with AR values of 0.013 (95% CI 0.008–0.020; p < 0.0001; I^2 25%) and 0.009 (95% CI 0.003–0.023; p < 0.0001; I^2 0%) in the metastatic and non-metastatic groups, respectively.

Publication bias was detected in metastatic patients for any grade neutropenia (p 0.001).

3.4. Safety results in pre- and in postmenopausal patients

Next, the safety profile was analyzed according to menopausal status. For this analysis, we considered only the studies in which menopausal status was declared and in which pre- and postmenopausal patients were not mixed. Overall, two studies including 427 patients were eligible for premenopausal status, and 11 studies including 2117 patients, were eligible for postmenopausal status [22,26,27,-,27,31–40,47–53]. Abemaciclib trials were excluded, because no trials exclusively in premenopausal status were available [54–58].

A single study showed data on all types of toxicities in premenopausal patients. In this single study, we observed an AR for any grade toxicity and grade 3–4 toxicity of 0.982 (95% CI 0.961–0.992) and 0.767 (95% CI 0.719–0.809), respectively. In postmenopausal patients, AR for any grade toxicity and G3-4 toxicity with random effect models of 0.983 (95% CI 0.974–-0.988; p < 0.0001; I^2 0%) and 0.793 (95% CI 0.664–0.882; p < 0.0001; I^2 95%) were observed, respectively.

Premenopausal women showed AR for any grade and grade 3–4 neutropenia of 0.727 (95% CI 0.609–0.820; p < 0.0001; I^2 78%) and 0.637 (95% CI 0.590–0.681;

p < 0.0001; I^2 0%), respectively. Postmenopausal women showed an AR for any grade neutropenia of 0.787 (95% CI 0.718–0.843; p < 0.0001; I^2 88%) and of 0.608 (95% CI 0.541–-0.670; p 0.002; I^2 85%) for grade 3–4 neutropenia.

The AR of developing any grade or grade 3–4 diarrhea was 0.174 (95% CI 0.113–0.257; p < 0.0001; I^2 0%) and 0.014 (95% CI 0.006–0.031; p < 0.0001; I^2 0%), respectively, in premenopausal patients, and 0.222 (95% CI 0.170–0.284; p < 0.0001; I^2 87%) and 0.015 (95% CI 0.009–0.024; p < 0.0001; I^2 19%), respectively, in postmenopausal women.

No publication bias was detected.

3.5. Safety results in previously untreated and in pretreated patients

The safety profile was next analyzed in pretreated and in previously untreated patients. We included five studies in the analysis in previously untreated patients, including 909 patients, and 14 studies in pretreated patients including 2469 patients [26–35,37–52]. Studies with abemaciclib were studied separately, considering its distinct toxicity profile.

Similar risks of all types of toxicities were observed between the two groups: AR 0.987 (95% CI 0.977–0.993; p < 0.0001; I^2 0%) in previously untreated and AR 0.977 (95% CI 0.967–0.984; p < 0.0001; I^2 0%) in pretreated for any grade toxicity; AR 0.813 (95% CI 0.778–0.844; p < 0.0001; I^2 21%) and AR 0.814 (95% CI 0.679–0.900; p < 0.0001; I^2 94%) for grade 3–4 toxicity, respectively.

With respect to neutropenia, we observed an AR of 0.794 (95% CI 0.734–0.843; p < 0.0001; I^2 57%) in previously untreated patients, an AR of 0.834 (95% CI 0.784–0.875; p < 0.0001; I^2 87%) in pretreated patients for any grade neutropenia and an AR of 0.676 (95% CI 0.576–0.762; p 0.001; I^2 81%) and of 0.626 (95% CI 0.570–0.679; p < 0.0001; I^2 84%) for grade 3–4 neutropenia, respectively.

A slightly higher risk of developing diarrhea was observed in previously untreated patients. In particular, we observed an AR of 0.255 (95% CI 0.179–0.350; p < 0.0001; I^2 82%) in previously untreated and 0.152 (95% CI 0.102–0.222; p < 0.0001; I^2 93%) in pretreated patients for any grade diarrhea, and an AR of 0.021 (95% CI 0.013–0.034; p < 0.0001; I^2 0%) and 0.009 (95% CI 0.005–0.015; p < 0.0001; I^2 0%) for grade 3–4 diarrhea, respectively.

Publication bias was observed in pretreated patients for any grade neutropenia (p 0.002).

Trials with abemaciclib were considered separately. Overall, two trials including 578 patients were performed in pretreated patients, and 1 trial including 328 patients in previously untreated patients [54–58]. We were unable to perform a meta-analysis in the previously untreated group, because only a single trial was available. Overall, we observed a higher rate of any grade neutropenia, albeit the p-value was not significant, and of grade 3–4 diarrhea in the pretreated group. In particular, the AR for any grade neutropenia was 0.694 (95% CI 0.238–0.943; p 0.419; I^2 98%) in pretreated patients *vs* 0.436 (95% CI 0.383–0.490; p 0.021) in previously untreated patients, while for grade 3–4 diarrhea it was 0.158 (95% CI 0.106–0.230; p < 0.0001; I^2 70%) *vs* 0.095 (95% CI 0.067–0.131; p < 0.0001), respectively. Publication bias was not evaluable, due to the low number of trials analyzed.

4. Discussion

The three CDK4/6 inhibitors palbociclib, ribociclib, and abemaciclib showed similar activity in clinical trials and are all approved in combination with AI or fulvestrant for treating woman with locally advanced or metastatic HR-positive/HER2-negative breast cancer as the initial therapy or after failure of previous ET. In pre- or peri-menopausal women, ET should be associated with a luteinizing hormone release hormone agonist (LHRH). Abemaciclib is also approved by the FDA as a monotherapy for treatment of both women and men with HR-positive/HER2-negative advanced or metastatic breast cancer after progression from ET and chemotherapy based on the results of the MONARCH-1 trial [58].

Palbociclib, ribociclib, and abemaciclib have a similar mechanism of action and are structurally related. They act by binding to the ATP-binding pocket of CDK4 and CDK6, and each drug has specific interactions with residues in the ATP-binding cleft [59]. They have a different half-maximal inhibitory concentration (IC_{50}) for CDK4 and 6, with consequent differences in toxicity profiles. The most common toxicity observed with CDK4/6 inhibitors is hematologic, primarily due to their action on CDK6, which is a key regulator of hematopoietic precursor proliferation [59,60]. Neutropenia following the administration of CDK4/6 inhibitors occurs due to a cytostatic effect on the cell cycle in contrast to that induced by chemotherapy, which is characterized by DNA damage and consequent induction of hematopoietic cell apoptosis [13]. CDK4/6 inhibitor-induced neutropenia is quickly reversible with the discontinuation of treatment. Therefore, palbociclib and ribociclib are administered for three consecutive weeks followed by a week's break, to allow recovery of hematopoietic progenitors. Conversely, abemaciclib can be administered continuously. In fact, abemaciclib has a higher affinity for CDK4 with an IC_{50} of 2 nM compared to the IC_{50} for CDK6, which is five-fold higher [61]. Consequently, abemaciclib shows a lower rate of hematopoietic toxicity than either palbociclib or ribociclib.

In this analysis, we focused on the most common toxicities with CDK4/6 inhibitors. We included in our analysis all studies in which CDK4/6 inhibitors were administered at FDA-approved doses, including compassionate use programs and retrospective real-life clinical cohorts. In this way, we studied a population more similar to that treated in daily clinical practice without the bias of stringent patient selection in clinical trials [62]. The disadvantage of this approach is that we found many real-life cohorts for palbociclib, which is the oldest of the three drugs, but not for ribociclib and abemaciclib, and the inclusion of retrospective cohorts increases the heterogeneity between studies. We analyzed the three CDK4/6 inhibitors separately, unlike in a previous meta-analysis published by Costa and colleagues, to compare the safety profiles of the three drugs [63]. Although such an analysis does not

have the validity of a direct comparison, it is able to collect and synthesize all safety data in the literature. Moreover, we analyzed all the types of toxicities, not only hematological or gastrointestinal toxicities, as in two previously published meta-analyses [62,64]. Likewise, our work is distinct from another previously published meta-analysis in which the authors analyzed only grade 3–4 adverse events because we also analyzed low-grade toxicities [65]. Moreover, in our meta-analysis, we investigated the two most common toxicities (neutropenia and diarrhea) in some subgroups based on stage, menopausal status, and line of treatment.

As expected, we observed a higher rate of hematological toxicity in the palbociclib and ribociclib groups than in the abemaciclib group, which was associated with a low rate of severe infections. As expected, we observed a higher rate of febrile neutropenia with palbociclib and ribociclib compared to abemaciclib, even though it was an uncommon event. Abemaciclib showed a higher rate of gastrointestinal toxicity, primarily diarrhea, and abdominal pain. Although these adverse effects are of low grade in most cases, they have a major impact on patient quality of life, unlike neutropenia, which is rapidly reversible and not associated with a high rate of infection. Compared to palbociclib and abemaciclib, ribociclib exhibited a higher rate of hepatic toxicity, respiratory toxicity, and QTc prolongation. The latter in particular is usually dose-dependent and reversible [13]. However, special attention needs to be paid to these toxicities, as they can be fatal. Moreover, abemaciclib is associated with a high rate of increased creatinine, even though that it was not considered a good parameter for assessing renal toxicity. In fact, abemaciclib inhibits the secretion of renal tubular transporters, but does not affect glomerular function [13,58]. Abemaciclib is also associated with a risk of thromboembolic events, although this is not reported in our meta-analysis due to insufficient data shown in the trials included in the final analysis [13].

The results of the subgroup analysis performed in our meta-analysis were interesting. These showed an increase of approximately 33% in the risk of grade 3–4 toxicity of any type and of approximately 21% in grade 3–4 neutropenia in metastatic patients treated with palbociclib and ribociclib. Pretreated patients compared to previously untreated patients receiving palbociclib or ribociclib do not appear to have an increased risk of developing toxicity, while those receiving abemaciclib showed an increase of approximately 26% in neutropenia and 6% in grade 3–4 diarrhea. Finally, postmenopausal patients seem to have a slight increase in risk of approximately 5% for developing diarrhea, compared to premenopausal patients. The major limitation to this subgroup analysis is the small sample size. These results should be confirmed in large prospective studies.

5. Expert opinion

The introduction of CDK4/6 inhibitors for the treatment of hormone-responsive metastatic breast tumors has significantly changed therapeutic algorithms in recent years. The first FDA approval was granted to palbociclib in 2017, followed by ribociclib and abemaciclib. Currently, one of the primary concerns is the choice between these three drugs in individual patients.

Although CDK4/6 inhibitors are generally safe and manageable drugs, with a low rate of severe complications, specific characteristics of their toxicity profile could drive clinical choice. Beyond the most common toxicities, hematologic for palbociclib and ribociclib, and gastrointestinal for abemaciclib, other less frequent adverse events should be considered in treatment decisions. In particular, the higher risk of hepatic toxicity, QTc prolongation, and respiratory injury for ribociclib advises against using these drugs in the presence of lung or liver comorbidities or in the presence of concomitant treatment that prolongs the QT interval. Similarly, considering the difficulties in easily evaluating renal function by creatinine level with the use of abemaciclib, caution advice for the use of this drug in specific situations should be posed.

While hazard ratios for progression-free survival (PFS) were very similar in all trials comparing CDK4/6 inhibitors plus endocrine therapy to placebo plus endocrine therapy, no palbociclib trial, two ribociclib trials (MONALEESA-3 and 7) and two abemaciclib trials (MONARCH-2 and nextMONARCH) showed statistically significant overall survival (OS) differences [49,51,54,66]. It is impossible to conclude whether impact on OS was influenced by differences in study design, patient population, statistical power and/or availability of salvage therapy at the different trial centers. No head-to-head comparison is currently available for the CDK4/6 inhibitors.

Interestingly, the CDK4/6 inhibitors seem to be even better tolerated in early-stage cancer, likely due to the better baseline clinical condition or to the limited number of treatment cycles compared to metastatic patients. For this reason, use of these drugs in an early phase seems to be an excellent therapeutic alternative for patient quality of life, to delay the start of toxic treatment. None of these drugs are currently approved for this indication, but several clinical trials have been published or are ongoing. Three clinical trials studied palbociclib in the neoadjuvant setting, in combination with letrozole in the NeoPAL and in PALLET trials, and in combination with anastrozole in the NeoPalAna trial [18,19,22]. Addition of palbociclib to ET enhanced cell cycle arrest without increasing the response rate in this setting [18,19,22]. Ribociclib plus letrozole showed an efficacy in molecular downstaging by PAM50 for HR-positive/HER2-negative patients treated in neoadjuvant setting in the CORALLEEN trial [53]. Similarly, in the NeoMonarch trial, the association between abemaciclib and anastrozole led to a Ki67 reduction in the neoadjuvant setting [67].

In light of their efficacy in the metastatic phase and due to increase efficacy and delay resistance to adjuvant ET, CKD4/6 inhibitors are currently being studied in phase III trials after surgery: PALLAS (NCT02513394) and PENELOPE (NCT01864746) for palbociclib, NATALEE for ribociclib (NCT03701334) and MONARCH E for abemaciclib (NCT03155997) [68–71]. The results from PALLAS trials were recently presented at 2020 ESMO Congress. In this trial, 5760 patients were randomized to receive adjuvant ET with or without palbociclib, resulting in similar invasive disease-free survival (iDFS) between the two arms [72]. In contrast, the MONARCH E trial met the primary endpoint of iDFS with

adjuvant abemaciclib plus ET compared to ET alone [73]. Long-term follow-up of both trials is extremely important as many events in an interim analysis with limited follow-up are likely related to patients with primary endocrine resistance, and in this context, the reported monotherapy activity of abemaciclib may be of importance.

The use of CDK4/6 inhibitors is progressively expanding in the field of breast disease. In recent years, several trials have been launched to investigate the role of these drugs in other settings, such as in other breast cancer subtypes and/or in combination with other molecules, such as trastuzumab.

In the monarcHER trial, abemeciclib was studied in association with trastuzumab and fulvestrant in heavily pretreated HR-positive/HER2-positive locally advanced or metastatic breast cancer, resulting in increased PFS compared to standard chemotherapy plus trastuzumab and demonstrating that a chemotherapy-free regimen could be an option in this group of patients [16]. Analogously, ribociclib was studied in combination with trastuzumab in heavily pretreated advanced breast cancer in a Phase Ib/II trial, in which 13 patients were evaluated for safety [20]. The NA-PHER2 trial investigated the combination of palbociclib with pertuzumab, trastuzumab, and fulvestrant showing promising results in neoadjuvant setting, with a significant reduction in Ki67 expression [17]. The data on triple-negative breast cancer (TNBC) are less convincing, due to the frequent loss of RB that makes this subtype less sensitive to CDK4/6 inhibition. However, preclinical data suggested that selection based on specific biomarkers could lead to identification of patients sensitive to palbociclib. In particular, epidermal growth factor receptor (EGFR), its partner membrane type-4 matrix metalloproteinase (MT4-MMP), and RB are co-expressed in approximately 50% of TNBCs and predict sensitivity to palbociclib and erlotinib, with additive effects from their combination [74]. Moreover, a specific subset of TNBC expressing the androgen receptor (AR), representing one-third of all TNBC, seems to have proliferative activity dependent on CDK4/6 and to be sensitive to CDK4/6 inhibitors [75,76]. In this subset of tumors, palbociclib seems to enhance the activity of enzalutamide in vitro [77]. A phase I–II trial exploring the combination ribociclib-bicalutamide is actually being conducted in this group of patients (NCT03090165) [78].

In conclusion, in view of the efficacy and good tolerance observed, we think an effort must be made to expand application of these drugs to other subtypes and lines of treatment. Of course, the highest priority is to define the role of these agents in the adjuvant setting with the aim of curing more patients.

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