Graziosi et al. Systematic Reviews (2026) 15:36
https://doi.org/10.1186/s13643-025-03046-0

Systematic Reviews

RESEARCH

Open Access

Pharmacokinetic interactions and clinical implications of PPIs and CDKIs in breast cancer: a systematic review and meta-analysis

Agnese Graziosi[1,5*†], Roberto Pane[1,2†], Emanuele Tinazzo[1], Marco Basso[1], Matteo Avantaggiato[1], Alice Schianchi[1,3], Mattia Canella[1], Mauro Melis[1], Alessandro Nani[1], Marzia Del Re[4], Romano Danesi[5], Arianna Pani[5†], Riccardo Giossi[6†] and Diego Fornasari[1†]

Abstract

Background Breast cancer is the fourth leading cause of cancer mortality worldwide. New drugs, such as cyclin-dependent kinase 4/6 inhibitors (CDKIs), increase the life expectancy of receptor-positive (HR+) and human epidermal growth factor receptor 2 negative (HER2-) breast cancer patients. This class acts to limit the G1/S transition in tumor cells, inducing tumor cell death. Owing to the basic nature of CDKIs, their solubilities are pH dependent and could be influenced by the concurrent use of acid-reducing agents such as proton pump inhibitors (PPIs). This meta-analysis aims to assess the impact of co-administering PPIs on the pharmacokinetics and clinical efficacy of CDKIs in breast cancer patients.

Methods Four databases with English-language restriction were searched for concomitant CDKIs and PPIs keywords from their inception date to 2024 March 7th. Prospective, retrospective, randomized or nonrandomized clinical studies and observational longitudinal studies with at least one outcome of interest were included. The outcomes included pharmacokinetic variables, progression-free survival (PFS), and overall survival (OS).

Results We included three pharmacokinetic studies conducted in patients enrolled in clinical trials and seven clinical studies evaluating survival outcomes. When coadministered with palbociclib, PPIs significantly reduced the serum maximum concentration (Cmax) (MD -35.37 ng/mL; 95%CI from -67.59 to -3.16) and increased the clearance (CL/F) (MD 61.24 L/h; 95%CI from 14.66 to 107.82). Ribociclib Cmax and AUC did not significantly differ among the PPIs users. However, the overall PFS favored PPIs non-users (HR 1.74; 95%CI from 1.28 to 2.37). Consistently, coadministration of PPIs with CDKIs significantly increased the likelihood of reduced OS (HR 1.99; 95%CI from 1.18 to 3.33). The effect was confirmed only for the palbociclib subgroup (HR 2.11; 95%CI from 1.17 to 3.81). No data were available for OS evaluation with ribociclib. A single study on abemaciclib revealed nonsignificant differences (HR 1.30; 95%CI from 0.53 to 3.19), with similar results for OS.

Conclusions PPI use in HR+/HER2- breast cancer patients treated with palociclib should be avoided. When strictly necessary, ribociclib may be preferred to palbociclib, even though closer monitoring is strongly advised.

†Agnese Graziosi and Roberto Pane contributed equally as first authors.

†Arianna Pani, Riccardo Giossi and Diego Fornasari share co-senior authorship.

*Correspondence:
Agnese Graziosi
agnese.graziosi@unimi.it
Full list of author information is available at the end of the article

Systematic review registration PROSPERO identifier number CRD42024506456.
Keywords Proton pump inhibitors, Cyclin-dependent kinase 4/6 inhibitor, Breast Cancer, Drugs Interaction

Background

In 2022, breast cancer accounted for nearly 2.3 million new cases in women globally and was the fourth most common cause of cancer-related mortality [1]. Approximately 70% of cases are hormone receptor-positive (HR+) and human epidermal growth factor receptor 2 negative (HER2−) [2]. Almost a decade ago, the approval of the first cyclin-dependent kinase 4/6 inhibitor (CDKI) established a milestone in the treatment of HR+/HER2- advanced breast cancer [3]. The mechanism of action of CDKIs is to prevent retinoblastoma protein (Rb) phosphorylation and the consequent activation of E2F transcription factor through their binding to the CDK4/6-Cyclin D-p21/p27 complex, thus preventing progression from the G1 phase to the S phase and inducing a senescence-like status in tumor cells. Other indirect mechanisms of action have been proposed and are discussed elsewhere [4, 5]. Currently, three CDKIs are available in clinical practice: palbociclib, ribociclib, and abemaciclib. Despite some chemical and pharmacological differences, they have shown remarkable benefits in terms of progression-free survival (PFS) and overall survival (OS) in combination with aromatase inhibitors or fulvestrant [6–20]. Due to the basic nature of CDKIs, their solubility is pH-dependent, thus, their absorption could be influenced by the concurrent use of acid-reducing agents, such as proton pump inhibitors (PPIs) [21–24]. PPIs are widely used drugs and influence the bioavailability of several anticancer drugs, such as tyrosine kinase inhibitors and immune checkpoint inhibitors, by increasing the gastric pH [23, 25]. Some studies have investigated whether the use of PPIs could influence the clinical outcomes of patients taking CDKIs [26–33]. However, the results revealed discrepancies in terms of PFS and/or OS. For this reason, we conducted a systematic review and meta-analysis to evaluate the effects of PPIs on the bioavailability and pharmacokinetics (PK) of CDKIs and the resulting clinical outcomes.

Methods

Search strategy and study selection

We searched PubMed, Embase, the Cochrane Library, and Web of Science from their inception date to 7th March 2024, with English-language restrictions, to retrieve eligible studies. The search strategy included "palbociclib", "ribociclib", "abemaciclib", and "PPI" as keywords, both as MeSH and free terms with related synonyms, combined with Boolean operators, as applicable. The complete search strategy is available in Supplementary Table S2. Three investigators (A.G., R.P. and E.T.) independently screened the retrieved records by title and abstract. All potentially relevant articles were read in full for a final decision on inclusion. Any discrepancies were collegially discussed and resolved. Eligibility criteria were defined according to the PICO framework. The population included patients with breast cancer treated with CDKIs. The intervention was the concomitant use of PPI. The comparator was CDKIs treatment without PPIs. Outcomes of interest included pharmacokinetic parameters (Cmax, AUC, CL/F) and survival outcomes, either PFS or OS. No restrictions were applied regarding the specific quantitative study design; thus, randomized controlled trials, nonrandomized clinical trials, and prospective or retrospective observational studies were eligible if they reported at least one outcome of interest.. In addition, the reference lists of relevant systematic reviews and meta-analyses were manually screened to identify any additional eligible studies not captured by the electronic search. Non-English-language studies, conference abstracts, noncomparative case series, case reports, systematic reviews, and meta-analyses were excluded. Our study was registered on PROSPERO (CRD42024506456), and we followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement for the realization of this work as shown in the PRISMA checklist (Supplementary Table S1) [34].

Data extraction and assessed outcomes

Data concerning the authors, study year, study design, number of participants and relative repartition in study arms, including CDKIs and PPIs and the relative number of participants exposed, sex, mean/median study age, Eastern Cooperative Oncology Group (ECOG) performance score, endocrine sensitivity, menopausal status, presence of metastatic disease, previous treatment lines, Ki-67 status, feeding state at the moment of the CDKI assumption, and clinical outcomes were extracted. The PK outcomes included the serum maximum concentration (Cmax) expressed in ng/mL, the area under curve (AUC) expressed in mg·h/mL, and the apparent oral clearance (CL/F) expressed in L/h. PK outcomes have been extracted as arithmetic or geometric means with associated standard deviation (SD) or percentual coefficient of variation (CV%). Clinical outcomes included PFS and OS expressed as hazard ratios (HR) with associated 95% confidence interval (95%CI). When both adjusted and unadjusted results were provided in the included studies, we extracted adjusted results to be included in our meta-analysis.

Risk of bias assessment

The Cochrane Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool was used to independently assess the risk of bias of each article that satisfied the eligibility criteria by two pairs of authors (M.A and M.C.; A.G. and R.P.). The tool is divided into 7 bias domains: confounding, selection of participants in the study, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported result. For the ROBINS-I tool, the prespecified confounding domains we considered relevant to address in the in included studies were age, sex, menopausal status, ECOG score, previous lines of treatment, presence of metastasis, sites of metastasis, and Ki-67. We also checked for the fed state at the moment of the treatment assumption; however, we did not consider it necessary to control for this latter variable. Since we wanted to investigate the possible interaction effect of PPIs on the efficacy and pharmacokinetics of CDKIs, we decided that our study aimed to verify the adhering to the intervention [35]. Controversies were resolved through discussion among all the authors. The risk of bias figures was realized with the online robvis tool.

Statistical analysis

When at least 2 studies had available data, we performed a random-effects generic inverse variance to estimate pooled HR and mean differences (MD) with associated 95%CI. We assessed heterogeneity with I^2 statistics. Publication bias was assessed with funnel plots. Cochrane RevMan 5.4 software was used for all analyses [36].

Summary of findings

We used GRADEproGDT to produce a summary of findings for our meta-analysis. The quality of evidence was independently evaluated with the GRADE method by two authors (R.P. and R.G.), and discrepancies were resolved by discussion.

Results

Study characteristics

The systematic literature search identified a total of 251 articles (Fig. 1). After checking for duplicates, 91 were removed. At the end of the screening process, 34 articles were read in full. Ten studies met the eligibility criteria and were ultimately included in the meta-analysis [26–28, 30–33, 37–40]. One study reported our outcomes of interest but did not provide usable results for quantitative analysis; hence it was included in the systematic review and narratively discussed [29].

Among those, three evaluated the effect of PPI coadministration on the PK of CDKIs in a total of 173 participants (81 receiving palbociclib and 92 ribociclib). Among them, 73 received concomitant PPIs (42.4%). The enrolled participants were either all male, close to equity, all female, or not reported. Race was not reported in the majority of the included articles. Only one study specified races with a higher prevalence of white participants [37]. One study developed a highly predictive PK model for CDKIs starting from randomized open-label study samples (NCT04484064) [40]. Another study evaluated the effects of PPIs on the PK of CDKIs in patients from three different clinical trials, a randomized parallel trial (NCT01872260) and two nonrandomized single-group assignment trials (NCT01898845 and NCT01237236) [38]. A third study reported the results of two other phase I, open-label, crossover trials (NCT02097329, NCT01918176) [37]. The characteristics of the included PK outcome studies are detailed in Table 1 and Supplementary Figure S1.

The remaining 7 articles included in the meta-analysis, delved into the effects of concomitant PPI administration on CDKI survival outcomes (i.e., PFS and/or OS). All of them were retrospective observational studies, enrolling a total of 2185 participants (1775 receiving palbociclib, 376 receiving ribociclib, and 34 receiving abemaciclib) with HR+/HER2- breast cancer, mostly females (99.9%), recruited from several countries worldwide (Supplementary Figure S1), and with a mean age ranging between 25 and 92 years. Race was not reported in any of the studies included in the exam. Of them, 763 received concomitant PPI (34.9%). The characteristics of included survival outcome studies are detailed in Table 2.

Risk of bias assessment for PK outcomes

We assessed the ROBINS-I for all six studies reported by the three included papers. Overall, one paper was considered at serious risk of bias due to confounding for lacking information about baseline variables, unclear definitions in the process of participant selection and classification of the intended intervention, and lack of information about cointerventions (bias due to deviation from the intended intervention). A second paper, reporting data from three different studies, was considered a critical risk of bias. All three studies had a critical risk of bias due to confounding and deviations from intended interventions, since baseline variables and cointerventions were not reported; additionally, they were considered at serious

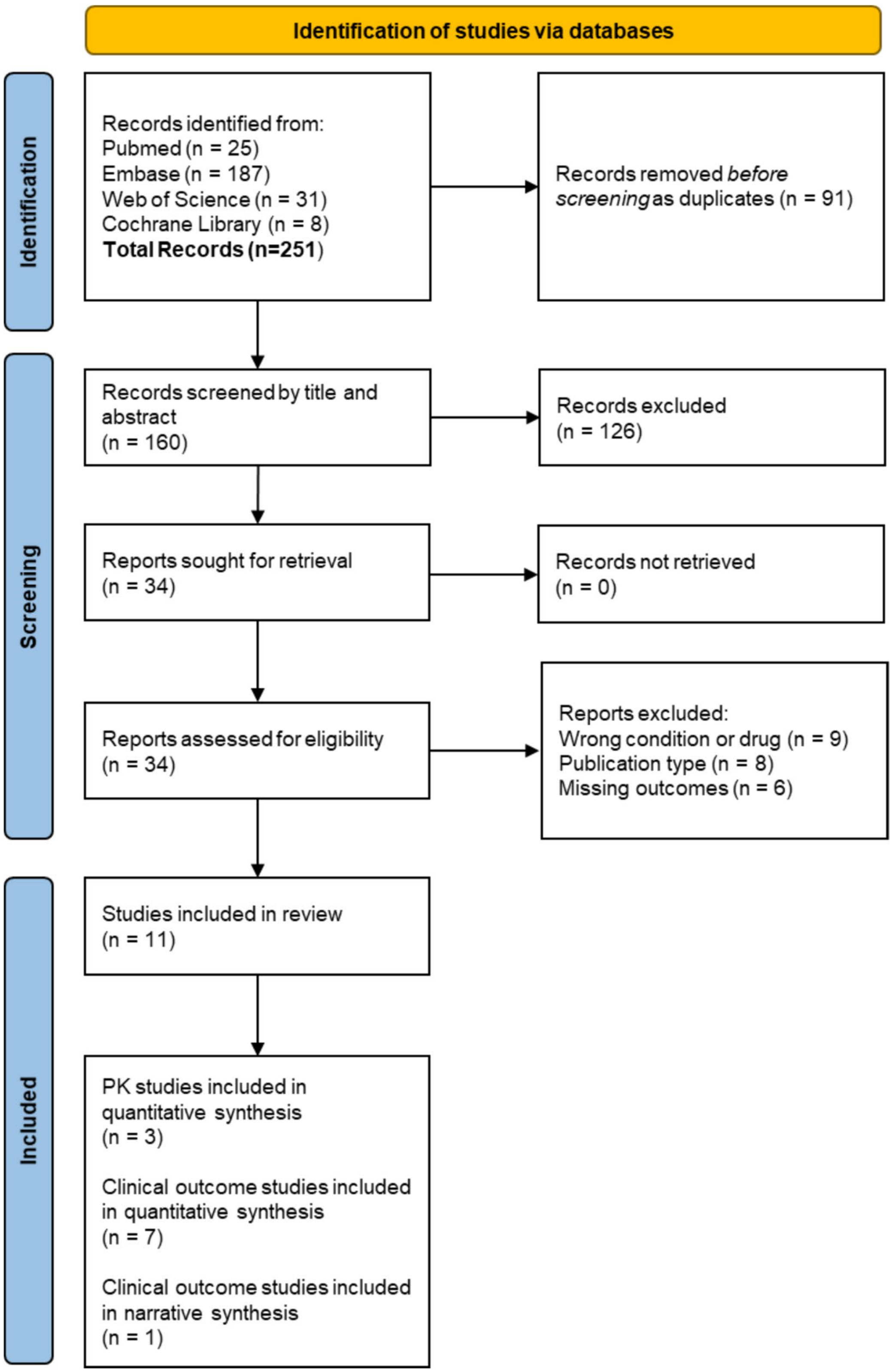

Fig. 1 PRISMA flow chart

Table 1 PK outcome studies characteristics and results

Study, year	Study design	Sex (%)	Age, mean (SD)	Race (n)	Treatment arm (n)	Reported PPI	Cmax,Mean (SD)	Cmax, gMean (CV%)	AUC, gMean (SD)	AUC, gMean (CV%)	CL/F, Mean (SD)
Courlet, 2022 [40]	NRCT	F (100)	65 (4.6)	NA	Palbociclib (33)	\	NA	NA	NA	NA	67 (3.35)
					Palbociclib + PPI (11)	NA	NA	NA	NA	NA	131 (5.24)
Samant, 2018a [21, 38]	NRCT	NA	NA	NA	Ribociclib (10/13)[a]	\	NA	1.62×10^3 (53.2)	NA	21.1 (57.2)	NA
					Ribociclib + PPI (8/10)[a]	NA	NA	1.78×10^3 (34.6)	NA	24.7 (30.6)	NA
Samant, 2018b [21, 38]	NRCT	NA	NA	NA	Ribociclib (6/6)[a]	\	NA	3.5×10^3 (65.8)	NA	55.1 (68.6)	NA
					Ribociclib + PPI (2/2)[a]	NA	NA	2.7×10^3 (53.0)	NA	42.6 (28.7)	NA
Samant, 2018c [21, 38]	NRCT	NA	NA	NA	Ribociclib (46/48)[a]	\	NA	1.87×10^3 (60.3)	NA	23.7 (61.3)	NA
					Ribociclib + PPI (12/13)[a]	Rabeprazole	NA	2.05×10^3 (74.7)	NA	25.9 (79.1)	NA
Sun, 2017a [22]	OLCO	F (42.3)	45.4 (8.1)	W (25), B (1), O (0)	Palbociclib (22)	\	65.28 (21.50)	61.74 (36)	1.971 (0.55)	1.90 (38)	66.78 (20.37)
		M (57.7)			Palbociclib + PPI (23)	Rabeprazole	13.37 (6.14)	12.25 (44)	0.723 (0.29)	0.673 (40)	176.2 (61.81)
Sun, 2017b [37]	OLCO	M (100)	34.9 (7.4)	W (3), B (15), O (9)	Palbociclib (14)	\	51.76 (7.84)	51.21 (15)	1.551 (0.30)	1.524 (20)	80.78 (16.04)
					Palbociclib + PPI (14)	NA	32.72 (12.78)	30.30 (44)	1.352 (0.42)	1.302 (28)	94.51 (23.15)

Abbreviations: AUC area under curve, *B* black, *CL/F* apparent oral clearance, *Cmax* serum maximum concentration, *CV%* percentual coefficient of variation, *F* female, *gMean* geometric mean, *M* male, *NA* not available, *NRCT* non-randomized clinical trial, *O* other, *OLCO* open-label crossover trial, *PPI* proton pump inhibitor, *W* white, *SD* standard deviation

Cmax, AUC, and CL/F values are reported as ng/mL, mgh/mL, and L/h, respectively. When not reported as gMean, Cmax and AUC values are given as arithmetic mean and SD

[a] The first number in brackets refers to the sample size reported for AUC measurements while the second number refers to the sample size reported for Cmax measurements

Table 2 Survival outcome studies characteristics and results

Study, year	Study design	Sex (%)	Age, mean (SD/range)	Treatment arm (n)	ECOG (n)	Endocrine sensitive (n)	Menopause (n)	Metastatic sites (n)	Reported PPI (n) [b]	PFS, HR (95%CI)	OS, HR (95%CI)
Çağlayan, 2023 [30]	OR	F (100)	55.5 (12.8)	Palb (21) Ribo (20)	NA	16	NA	NA	Es; La; Om; Pa (NA)[a]	2.54 (1.14–5.64)	NA
				Palb + PPI (29) Ribo + PPI (16)	NA	20	NA	NA			
Del Re, 2021 [33]	OR	NA	63 (35–86)	Palb (56)	ECOG 0–1 (55) ECOG 2 (1)	35	45	V (31) NV (25)	Es (1); La (42); Om (11); Pan (2)[a]	2.77 (1.62–4.75)	NA
				Palb + PPI (56)	ECOG 0–1 (54) ECOG 2 (2)	36	48	V (24) NV (32)			
Del Re, 2022 [32]	OR	NA	59.1 (9.7)	Ribo (78)	ECOG 0–1 (73) ECOG 2 (5)	62	60	V (41) NV (26)	Es (3); La (34); Om (6); Pa (7)[a]	1.17 (0.65–2.14)	NA
				Ribo + PPI (50)	ECOG 0–1 (47) ECOG 2 (3)	44	37	V (36) NV (24)			
Eser, 2022a (palbociclib) [31]	OR[a]	NA	59 (32–8)	Palb (40) Palb + PPI (65)	ECOG 0–1 (85)[a] ECOG 2 (6)[a]	57[a]	55[a]	V (46)[a] NV (45)[a]	Es (26); La (12); Om (15); Pa (46); Ra (27)[a]	7.85 (2.67–23.05)	NA
Eser, 2022b (ribociclib) [31]	OR[a]	NA	53 (32–87)	Ribo (51) Ribo + PPI (61)	ECOG 0–1 (106)[a] ECOG 2 (20)[a]	58[a]	87[a]	V (71)[a] NV (55)[a]	Es (26); La (12); Om (15); Pa (46); Ra (27)[a]	2.90 (1.38–6.40)	NA
Lee, 2023 [27]	OR[a]	F (100)[a]	NA	Palb (966) Palb + PPI (344)	NA	819[a]	951[a]	V (253)[a] NV (264)[a]	De; Es; Il; La; Om; Pa; Ra (NA)[a]	1.76 (1.46–2.13)	2.71 (2.07–3.53)
Odabas, 2023a (palbociclib) [28]	OR[a]	F (99.0)[a]	58 (25–92)	Palb (63) Palb + PPI (57)	ECOG 0–1 (122)[a] ECOG 2–3 (12)[a]	47[a]	92[a]	V (63)[a] NV (71)[a]	Es (20); La (31); Om (6); Pa (21); Ra (8)[a]	0.98 (0.59–1.65)	NA
Odabas, 2023b (ribociclib) [28]	OR[a]	F (99.0)[a]	56 (31–84)	Ribo (71) Ribo + PPI (29)	ECOG 0–1 (81)[a] ECOG 2–3 (6)[a]	39[a]	73[a]	V (45)[a] NV (41)[a]	Es (20); La (31); Om (6); Pa (21); Ra (8)[a]	1.71 (0.78–3.78)	NA
Takahashi, 2024a (palbociclib) [26]	OR[a]	F (99.0)[a]	70 (62–75)	Palb (35) Palb + PPI (43)	OG 0–1 (53)[a] ECOG 2 (3)[a]	NA	52[a]	V (36)[a] NV (20)[a]	Es (10); La (25); Om (3); Ra (8); Vo (10)[a]	0.94 (0.61–1.46)	1.47 (0.82–2.62)
Takahashi, 2024b (abemaciclib) [26]	OR[a]	F (99.0)[a]	71 (60–75)	Abem (21) Abem + PPI (13)	OG 0–1 (52)[a] ECOG 2 (4)[a]	NA	48[a]	V (34)[a] NV (22)[a]	Es (10); La (25); Om (3); Ra (8); Vo (10)[a]	1.3 (0.53–3.17)	1.22 (0.33–4.47)

Abbreviations: 95%CI 95% confidence interval, *Abem* abemaciclib, *CDKI* cycline-dependent kinase inhibitors, *De* dexlansoprazole, *ECOG* Eastern Cooperative Oncology Group performance score, *Es* esomeprazole, *F* female, *Il* ilaprazole, *HR* hazard ratio, *La* lansoprazole, *NA* not available, *NV* non-visceral, *O* other, *Om* omeprazole, *OR* observational retrospective, *OS* overall survival, *Palb* palbociclib, *Pa* pantoprazole, *PFS* progression-free survival, *PPI* proton pump inhibitor, *Ra* rabeprazole, *Ribo* ribociclib, *SD* standard deviation, *V* visceral, *Vo* vonoprazan

[a] Values reported for the overall study population

[b] Reported PPI are to be considered for the CDKI + PPI treatment arm only

risk of bias due to selection of participants, classification of interventions, and missing data since the sample size varied on the basis of different reported outcomes and lacked data about selection and inclusion processes. The last paper, reporting data from two different studies was considered to have an overall moderate risk of bias, and was thus sound for a nonrandomized study. In contrast to the other included studies, we judged the bias in the measurement of the outcomes to be low since the data were collected in the context of prospective clinical trials. The risk of bias assessment for the PK outcome studies is detailed in Fig. 2.

Risk of bias assessment for survival outcomes

We considered almost all included studies at moderate risk of bias due to confounding since they did not control for Ki-67 except for one study, which we considered at low risk of bias for confounding [30]. One study was considered at serious risk of bias due to confounding since baseline-adjusted results were not reported [32]. Six studies were at moderate risk of bias in the selection of participants since they were unclear or lacked information on the timing of the follow-up and intervention start date. Five studies with limited information on the source of data, particularly if the information used to define intervention groups was recorded at the start of the intervention, were considered at moderate risk of bias for the classification of interventions. We considered five studies at moderate risk of bias due to deviations from the intended intervention since we did not find any reference to verification of adherence to the intervention. All studies were considered at moderate risk of bias in the measurement of outcomes domain because of their retrospective nature, since investigators' knowledge of the outcome in included patients was likely. All studies were considered at low risk of bias due to missing data and selection of the reported results. The risk of bias assessment for the clinical outcome studies is detailed in Fig. 3.

Pharmacokinetics outcomes

When coadministered with palbociclib, PPI significantly reduced the Cmax (MD −35.37 ng/mL; 95%CI from −67.59 to −3.16) and resulted in a nonsignificant reduction in the AUC (MD −0.72 mg·h/mL; 95%CI from −1.75 to 0.30), both with a low quality of evidence (Fig. 4a and b). Moreover, PPIs significantly increased the CL/F (MD 61.24 L/h; 95%CI from 14.66 to 107.82) (Fig. 4c). Comparable results were observed when the geometric means for Cmax and AUC were used (Supplementary Figure S2a and S2b), with very low-quality evidence. On the other hand, the Cmax and AUC of ribociclib did not significantly differ among the PPI users (MD 0.15 mg/mL; 95%CI from −0.34 to 0.64 and MD 2.43 mg·h/mL; 95%CI from −4.74 to 9.61, respectively) (Fig. 5a and b), with a low quality of evidence. No PK outcome data for abemaciclib are currently available. Due to the different risk of bias of the studies included in the CL/F pooled estimates, we performed a sensitivity analysis excluding the study with a higher risk of bias, resulting in a similar effect size, however, it was not statistically significant (Supplementary Figure S3). Funnel plots for the evaluation of publication bias for PK outcomes are presented in Supplementary Figure S4. A summary of the findings of the PK outcome studies is presented in Table 3.

Survival outcomes

In the overall analysis, the concomitant administration of PPIs with CDKIs resulted in significantly increased hazards for reduced PFS (HR 1.74; 95%CI from 1.28 to 2.37) with moderate quality of evidence (Fig. 6). Consistently, subgroup analyses yielded similar results with concomitant PPIs resulting in significantly increased hazards for reduced PFS both for palbociclib (HR 1.77; 95%CI from 1.09 to 2.86) and ribociclib (HR 1.73; 95%CI from 1.01 to 2.96), with low quality of evidence due to inconsistency and imprecision, respectively. Assessed only in a single study, the concomitant administration of PPIs with abemaciclib resulted in nonsignificant differences in the hazard for PFS (HR 1.30; 95%CI from 0.53 to 3.19), whose quality of evidence was judged very low for very serious imprecision due to severely limited sample size [26].

Similarly, the concomitant administration of PPIs with CDKIs resulted in significantly increased hazards for reduced OS (HR 1.99; 95%CI from 1.18 to 3.33) with a moderate quality of evidence (Fig. 7). This result was mainly based on the effect estimates of the palbociclib subgroup, which resulted in a significantly increased hazard for reduced OS in patients co-administered with PPIs (HR 2.11; 95%CI from 1.17 to 3.81), with a moderate quality of evidence. No data were available for OS evaluation with ribociclib. The single abemaciclib study revealed nonsignificant differences in hazards for OS (HR 1.22; 95%CI from 0.33 to 4.51), with very low quality of evidence due to very serious imprecision. Funnel plots for the evaluation of publication bias for survival outcomes are presented in Supplementary Figure S5. A summary of findings for survival outcomes is presented in Table 4.

To explain the heterogeneity observed among the studies, we attempted to pool univariate analyses of the included studies for age, ECOG score, metastatic site, endocrine sensitivity, and menopausal status, when available. Unfortunately, these findings did not show any relevant results that could explain this phenomenon (Supplementary Figure S6).

One retrospective study enrolling 82 patients receiving palbociclib, of whom 32 concomitantly received PPIs,

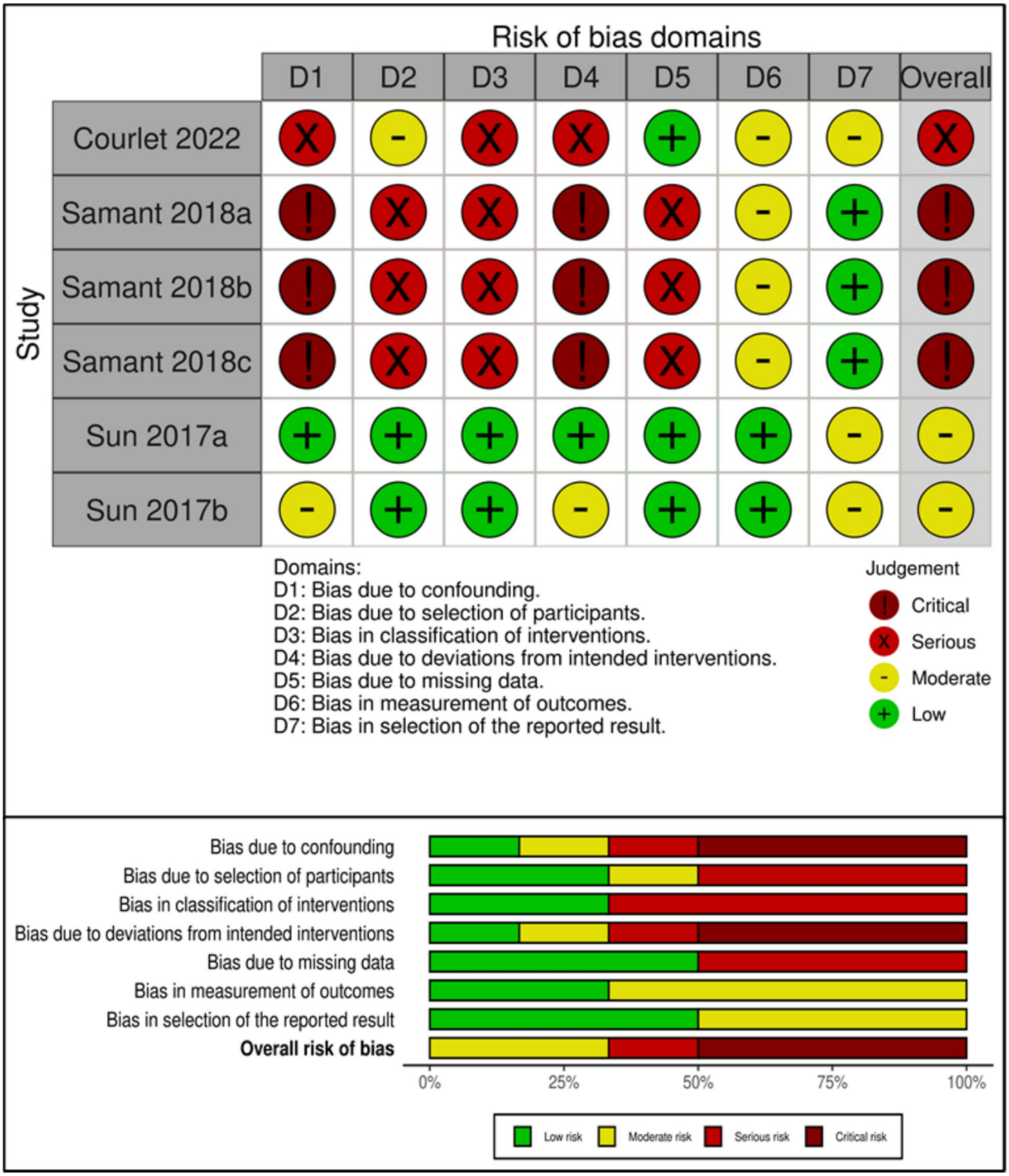

Fig. 2 Risk of bias assessment for PK outcome studies

did not provide usable results for our quantitative analysis [29]. For this reason, we decided to narratively discuss its results. The study did not show significant differences in median PFS between groups (median 20.6 months; 95%CI from 16.07 to not estimable for the no PPI use arm and median 21.0 months; 95%CI from 15.15 to not estimable for the PPI use arm, $p=0.95$). The median OS was not reached and thus was not analyzed.

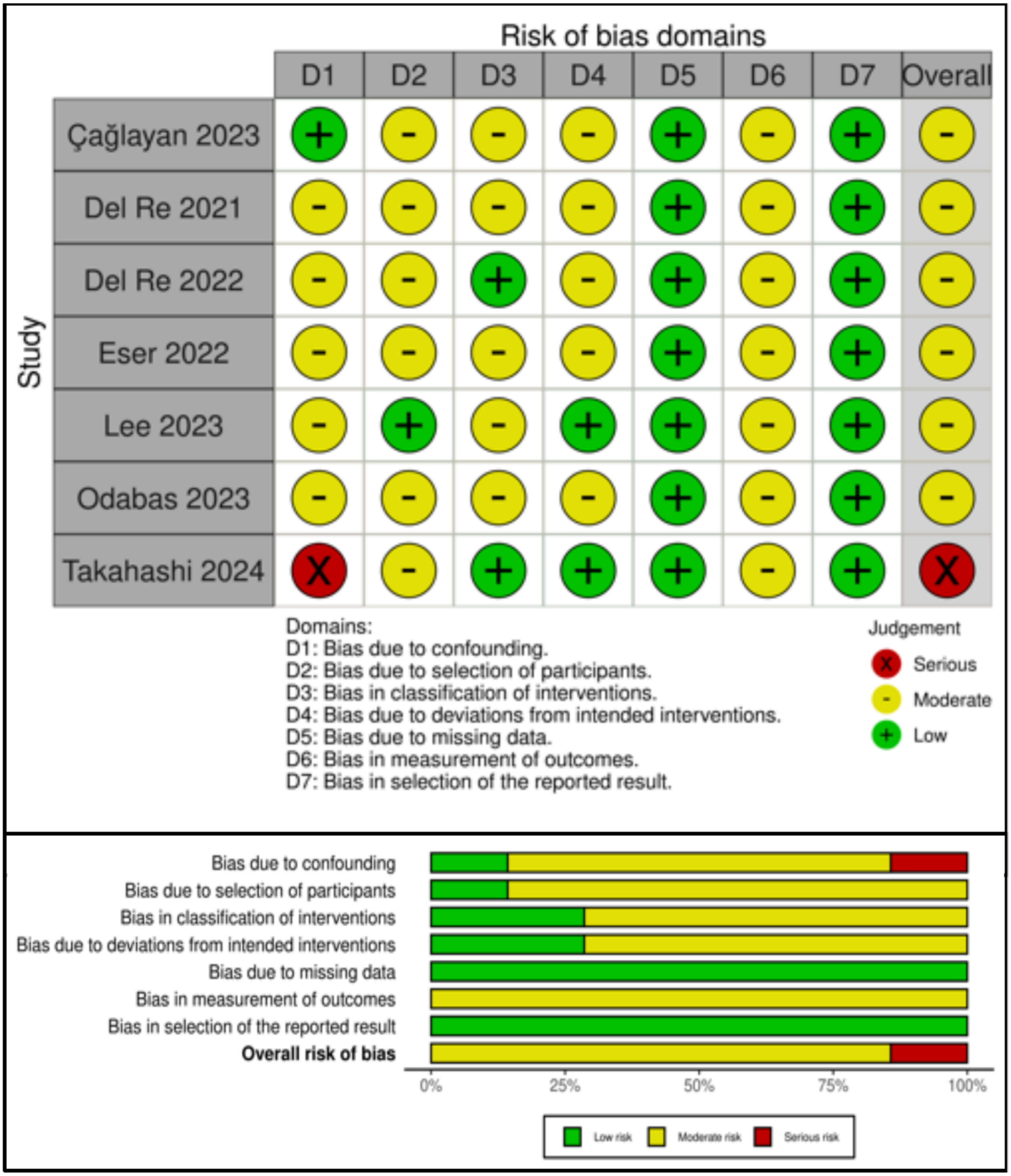

Fig. 3 Risk of bias for survival outcome studies

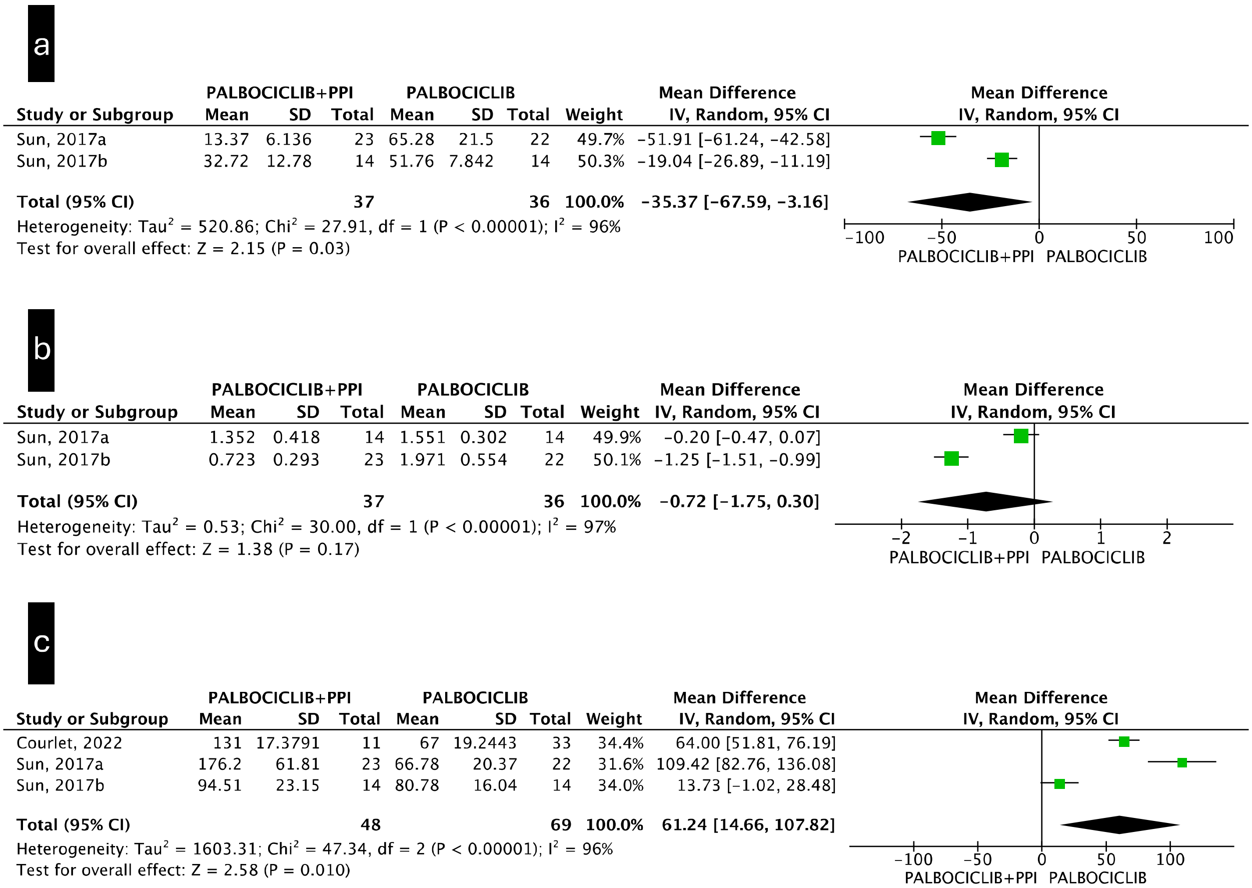

Fig. 4 Mean difference ("palbociclib + PPI"- "palbociclib") meta-analysis for pharmacokinetic outcomes of palbociclib: **a** palbociclib, the mean difference of the arithmetic mean Cmax [ng/mL]; **b** palbociclib, the mean difference of the arithmetic mean AUC [mgh/mL]; **c** palbociclib, mean difference of the arithmetic mean CL/F [L/h]

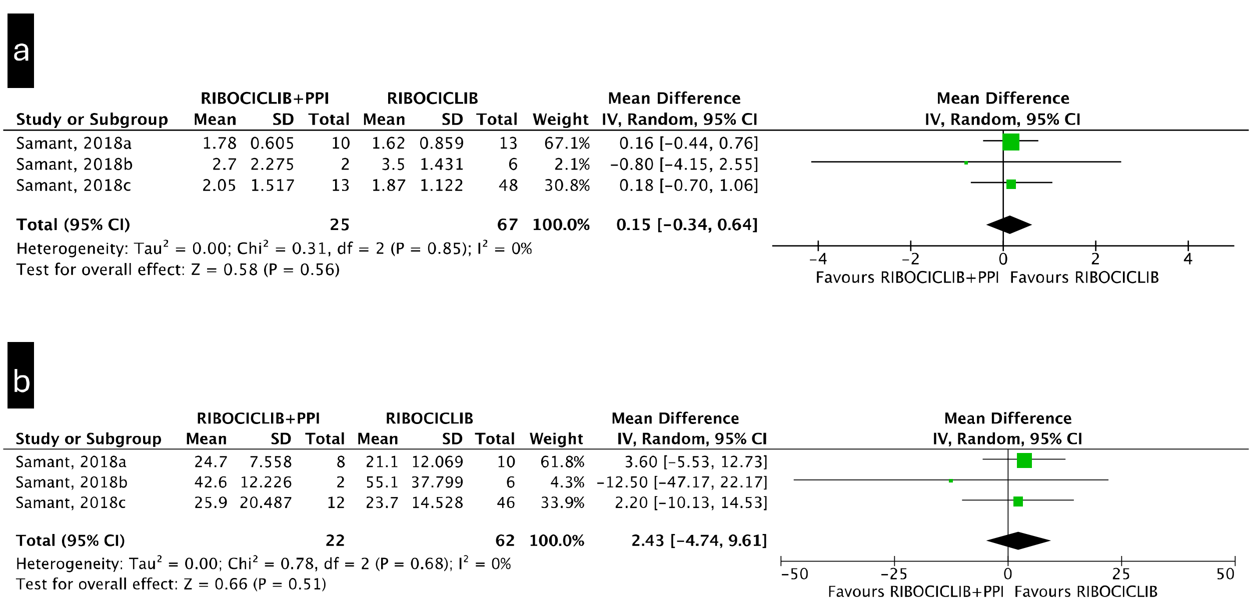

Fig. 5 Mean difference ("ribociclib + PPI"- "ribociclib") meta-analysis for pharmacokinetic outcomes of ribociclib: **a** Ribociclib mean difference of the geometric mean Cmax [mg/mL]; **b** Ribociclib mean difference of the geometric mean AUC [mgh/mL]

Table 3 Summary of findings for PK outcomes

Outcomes	Relative effect (95%CI) with PPI added to CDKI	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Palbociclib Cmax	MD −35.37 ng/mL (−67.59 to −3.16)	73 (2 non-randomised studies)	⨁⨁◯◯ Low[a,b]	The evidence suggests PPI added to palbociclib result in a reduction of palbociclib Cmax
Palbociclib AUC	MD −0.72 mgh/mL (−1.75 to 0.3)	73 (2 non-randomised studies)	⨁⨁◯◯ Low[b,c]	The evidence suggests PPI added to palbociclib may reduce palbociclib AUC
Palbociclib CL/F	MD 61.24 L/h (14.66 to 107.82)	117 (3 non-randomised studies)	⨁◯◯◯ Very low[d,e,f]	PPI added to palbociclib may increase palbociclib CL/F but the evidence is very uncertain
Ribociclib Cmax	MD 0.15 mg/mL (−0.34 to 0.64)	92 (3 non-randomised studies)	⨁⨁◯◯ Low[g]	The evidence suggests that PPI added to ribociclib result in little to no difference in Cmax
Ribociclib AUC	MD 2.43 mgh/mL (−4.74 to 9.61)	84 (3 non-randomised studies)	⨁⨁◯◯ Low[g]	The evidence suggests that PPI added to ribociclib result in little to no difference in AUC

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

Explanations:

[a] Serious inconsistency ($I^2 = 96\%$)

[b] Serious imprecision due to small sample size and large confidence interval ranging from limited to considerable clinical impact

[c] Serious inconsistency ($I^2 = 97\%$)

[d] One study did not report baseline confounding variables between the population and was considered ad serious risk of bias. However, we chose not to downgrade for risk of bias since a sensitivity analysis excluding this study substantially confirmed the estimated results

[e] Serious inconsistency ($I^2 = 96\%$)

[f] Serious imprecision due to small sample size and large confidence interval

[g] Serious risk of bias due to possible confounding, selection of participants, classification of intervention, deviations from intended interventions, and missing data

Abbreviations: 95%CI 95% confidence interval, *AUC* area under curve, *CDKI* cycline-dependent kinase inhibitors, *CL/F* apparent oral clearance, *Cmax* serum maximum concentration, *PPI* proton pump inhibitors

Discussion and conclusions

Acidic gastric pH is a fundamental condition for the absorption of weak base, such as palbociclib, ribociclib, and abemaciclib. Del Re et al. reported that palbociclib and ribociclib, as expected for weak bases, possess pH-dependent solubilities. Palbociclib solubility decreases from 0.5 mg/mL to 0.05 mg/mL as the pH increases from 3 to 5 [37]. Ribociclib solubility is influenced by pH changes from 2.4 mg/mL when the pH is between 5 and 6 to 0.3–0.8 mg/mL when the pH is ≥ 6.8 [32]. Abemaciclib showed a pH-dependent solubility ranging from 5 mg/mL at pH 6 to 1.58 mg/mL at pH 6.8. Notably, these pH changes are expected to occur with the use of PPIs [41]. Because the decreased gastric solubility may be responsible for the reduced drug absorption, the limited influence of pH on ribociclib may explain the nonsignificant effect on tha Cmax and AUC of the combination of PPIs with ribociclib, at the same time, the sensitivity of palbociclib to pH changes could explain our meta-analysis results indicating that the concomitant use of PPIs reduces palbociclib Cmax and AUC mean values.

We also observed a significant increase in HR for both PFS and OS in the case of co-assumption of CDKI and PPI. PFS and OS are reduced in patients who receive concomitant PPIs with palbociclib confirming the pharmacokinetic data underlying the reduced absorption of CDKIs. In contrast, in our meta-analysis, the subgroup analysis of ribociclib produced pooled estimates for PFS similar to those of the palbociclib subgroup, even if the pharmacokinetic analysis did not demonstrate a significant modulation of ribociclib absorption. However, the sample sizes of studies investigating survival outcomes with ribociclib were remarkably inferior to those of palbociclib, thus reducing the certainty of the evidence due to imprecision. Other authors have shown that the therapeutic index of ribociclib is broader than that of palbociclib, making its efficacy less influenced by pH fluctuations [42]. However, the discrepancy in survival outcomes without significant PK variations remains unresolved. Nevertheless, since PK outcomes and survival outcomes were assessed in different patients and studies, conducting studies investigating both outcomes in the same

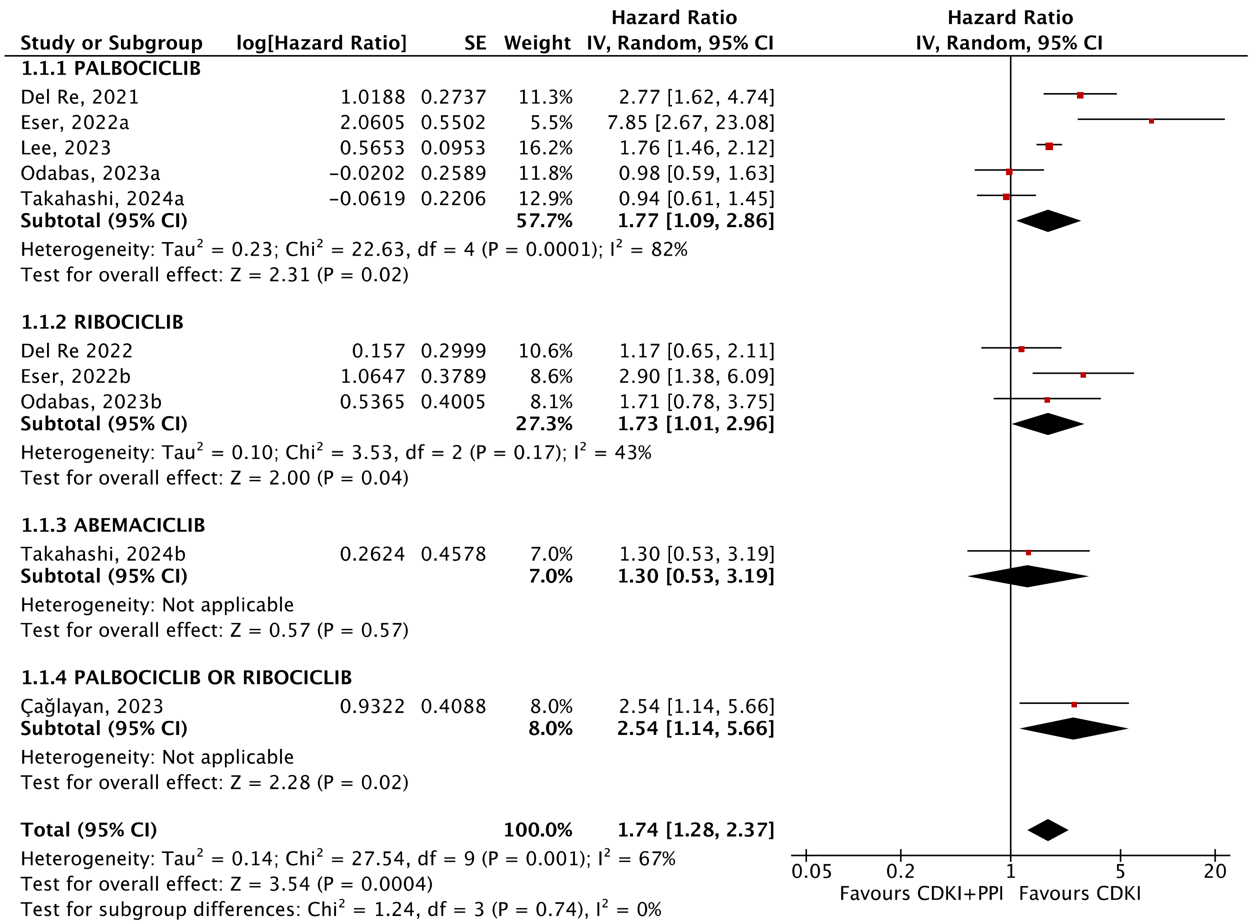

Fig. 6 Meta-analysis of PFS outcomes. Hazard of PFS in PPI and CDKI users vs CDKI users

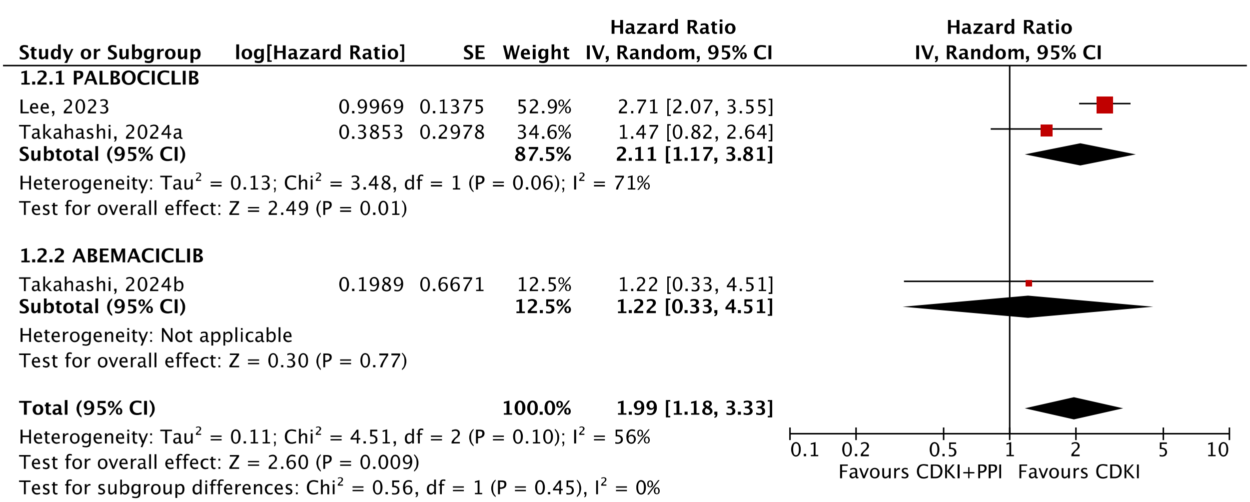

Fig. 7 Meta-analysis of OS outcomes. Hazard ratio of OS in PPI and CDKI users vs CDKI users

Table 4 Summary of findings for survival outcomes

Outcomes	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
PFS Overall	HR 1.72 (1.27 to 2.32)	2185 (7 non-randomized studies)	⨁⨁⨁◯ Moderate[a]	Concomitant use of PPI with CDKI may reduce PFS
PFS palbociclib	HR 1.77 (1.09 to 2.86)	1775 (5 non-randomized studies)	⨁⨁◯◯ Low[a,b]	Concomitant use of PPI with palbociclib may result in PFS reduction
PFS ribociclib	HR 1.73 (1.01 to 2.96)	376 (3 non-randomized studies)	⨁⨁◯◯ Low[a,c]	Concomitant use of PPI with ribociclib may result in PFS reduction
PFS abemaciclib	HR 1.30 (0.53 to 3.19)	34 (1 non-randomized study)	⨁◯◯◯ Very low[a,d]	The evidence is very uncertain about the effect of concomitant use of PPI in addition to abemaciclib on PFS
OS Overall	HR 1.99 (1.18 to 3.33)	1422 (3 non-randomized studies)	⨁⨁⨁◯ Moderate[a]	Concomitant use of PPI with CDKI may reduce OS
OS palbociclib	HR 2.11 (1.17 to 3.81)	1388 (2 non-randomized studies)	⨁⨁⨁◯ Moderate[a,e]	Concomitant use of PPI with palbociclib may result in OS reduction
OS abemaciclib	HR 1.22 (0.33 to 4.51)	34 (1 non-randomized study)	⨁◯◯◯ Very low[a,d]	The evidence is very uncertain about the effect of concomitant use of PPI in addition to abemaciclib on OS

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

Abbreviations: 95%CI 95% confidence interval, *CDKI* cycline-dependent kinase inhibitors, *Cmax* serum maximum concentration, *HR* hazard ratio, *OS* overall survival, *PFS* progression-free survival, *PPI* proton pump inhibitors

[a] We considered the overall ROBINS-I serious; the judgement was mainly due to the absence of adjustment for Ki-67 in the majority of included studies (i.e., bias due to confounding). However, we did not consider this relevant enough to downgrade for risk of bias

[b] Serious inconsistency ($I^2 = 81\%$), with some studies reporting no substantial effect and others reporting large effect

[c] Serious imprecision due to limited sample size

[d] Very serious imprecision due to severely limited sample size and 95%CI ranging from substantial benefit to substantial harm

[e] Inconsistency was moderately high for this comparison (i2 = 71%); however, since the direction of the effect was similar in included studies, our judgement was to not downgrade for inconsistency

patients could improve the mechanistic interpretation of the effects of PK on clinical efficacy and limit bias due to confounding factors.

Limited data are available for other processes such as the distribution or metabolism of these molecules, which could explain the interaction between PPIs and CDKIs. CDKIs are metabolized mainly by CYP3A4 with palbociclib and ribociclib being weak and moderate-to-strong inhibitors of this enzyme, respectively. CYP3A4 is partially inhibited by some PPIs such as lansoprazole and rabeprazole [43, 44]. Unfortunately, the limited amount of data for specific PPIs prevented us from performing subgroup analyses of different PPIs to estimate any metabolic interactions. The formation of a metabolite with grater activity than the parent drug could, for example, explain what was previously reported for ribociclib. An interesting study revealed that ribociclib possesses several functional sites that can be targeted by several cytochromes [45]. Recently, James et al. reported that this molecule is metabolized primarily by CYP3A4 (54%) and flavin-containing monooxygenase 3 (FMO3, 36%) producing LEQ803 and CCI283 as the main metabolites, respectively [46]. However, data on files by Novartis suggest that these and other minoritarian metabolites are clinically irrelevant even if they are pharmacologically active [47]. Therefore, the decrease in the efficacy of ribociclib in combination with PPIs cannot be explained by metabolic interference.

The excretion of CDKIs varies between molecules, being mainly renal for palbociclib and ribociclib and biliary for abemaciclib. Data for CL/F are available only for palbociclib [37, 40]. PPI co-administration significantly increased palbociclib clearance and elimination. However, CL/F is the ratio between the clearance value (CL) and the absorbed fraction or bioavailability (F). Since an AUC reduction in PPI users implies a reduction in F, the observed effect on CL/F seems to be related mainly to a decrease in F rather than a real increase in clearance. These findings support the idea that elimination is less involved in the mechanism by which PPIs interact with the bioavailability and efficacy of CDKIs. Given that ribociclib has chemical properties similar to those of palbociclib, it is reasonable to expect a similar behavior for excretion. However, considering the different mechanisms of elimination, it is difficult to imagine any clinically relevant effects of PPIs on abemaciclib excretion, and further PK and clinical studies are pivotal for a better understanding.

Our meta-analysis has several inevitable limitations. First, the outcomes themselves are limited since the reported outcomes are only PFS and, in few cases, OS. The evaluation of other outcomes, such as disease stability or complete/partial response, would provide better insights into the relationship between PPIs and CDKIs. A second weak point is represented by currently available clinical data since they come from observational retrospective studies. These surely allow us to observe the effects in a real-world context, but they are also impacted by uncontrolled confounding variables that only clinical trials, or at least very sound, prospective observational studies can avoid (e.g., fed-state, ethnicity, drug formulation, administered PPI, Ki-67, concomitant medications leading to possible drug–drug interactions with CDKIs). Finally, the sample size of individual studies is highly variable among different CDKIs. This led to better clinical and pharmacokinetic definitions of the effects of PPIs on palbociclib, followed by ribociclib and abemaciclib. The limited number of patients, especially those treated with abemaciclib, does not allow us to clearly state any clinical involvement of the PPI interaction in the PK data.

We carried out two parallel meta-analyses exploring both PK and clinical outcomes related to co-administration of PPIs with CDKIs. Our results are based only on published scientific articles with exploitable results. We pointed out how PPIs are able to reduce CDKI absorption as well as decrease their clinical efficacy. However, while this effect is clearn for palbociclib, some doubts remain for ribociclib, and even more for abemaciclib. The co-administration of PPIs with abemaciclib is currently being studied in only one study and can thus be considered almost unexplored. Prospective studies are strongly advised to clarify whether the negative interaction is class- or molecule-related. These data suggest that PPI and CDKI co-administration should be avoided unless it is strictly indicated. In these cases, ribociclib or abemaciclib seem to be better options than palbociclib, even though closer monitoring is strongly advised.

Abbreviations

CDKI	Cyclin-dependent kinase 4/6 inhibitor
CDKIs	Cyclin-dependent kinase 4/6 inhibitors
HR+	Receptor-positive
HER2-	Receptor 2 negative
PPIs	Proton pump inhibitors
PFS	Progression-free survival
OS	Overall survival
CL/F	Increased the clearance
PRISMA	Reporting Items for Systematic Reviews and Meta-analysis
Cmax	Serum maximum concentration
SD	Standard deviation
CV%	Percentual coefficient of variation
95%CI	95% Confidence interval
HR	Hazard ratios
ROBINS-I	The Cochrane Risk of Bias in Non-randomized Studies of Interventions
MD	Mean differences
CL	Clearance value
PK	Pharmacokinetics

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13643-025-03046-0.

Supplementary Material 1.

Acknowledgements
We would like to thank Pr. Csaika, director of Centre de Recherche et d'Innovation en Sciences Pharmaceutiques cliniques (Lausanne, Switzerland), for the extremely prompt and kind response to our question about her scientific contribution [40].

Authors' contributions
AG, RP, ET, and MB conceived the study. AG, RP, and RG designed the study. AG, RP, and RG did the analysis. RP, MB and RG drafted the manuscript. AG, ET, MA, AS, MC, and MDR revised the manuscript. AG edited the manuscript. All authors had full access to and verified the data and had final responsibility for the decision to submit for publication.

Funding
No external funds were used to support this work. The authors have no relevant financial interests to declare that are relevant to the content of this article.

Data availability
Not applicable.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
Riccardo Giossi received support for congress participation from Mylan, acted as a consultant for Daiichi-Sankyo, and received fees for speaking from Alexion-AstraZeneca, outside this work. Marzia Del Re received fees as speaker bureau from: Roche, Astra Zeneca, Novartis, Menarini, Pfizer, Lilly, MSD, BMS, Astellas, Amgen, Daiichi Sankyo; and advisory roles from Roche, Astra Zeneca, Menarini, Daiichi Sankyo, Amgen, Qiagen. The other authors have no disclosures.

Author details
[1]Department of Medical Biotechnology and Translational Medicine, Postgraduate School of Clinical Pharmacology and Toxicology, Università Degli Studi Di Milano, Milan, Italy. [2]SC Territorial Pharmacy, Pharmaceutical Department, ASL Alessandria, Alessandria, Italy. [3]Division of Clinical Pharmacology and Toxicology, Institute of Pharmacological Sciences of Southern Switzerland, Ente Ospedaliero Cantonale, Lugano, Switzerland. [4]Saint Camillus International University of Medical and Health Sciences, Rome, Italy. [5]Department of Oncology and Hemato-Oncology, University of Milan, Milan, Italy. [6]Poison Control Center and Clinical Pharmacology Unit, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy.

Received: 28 October 2024 Accepted: 15 December 2025
Published online: 30 December 2025

References

1. Ferlay J, Colombet M, Soerjomataram I, Parkin DM, Piñeros M, Znaor A, et al. Cancer statistics for the year 2020: An overview. Int J Cancer. 2021;149(4):778–89. Available from: https://pubmed.ncbi.nlm.nih.gov/33818764/. Cited 2024 Sep 4.
2. Howlader N, Altekruse SF, Li CI, Chen VW, Clarke CA, Ries LAG, et al. US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. J Natl Cancer Inst. 2014;106(5). Available from: https://pubmed.ncbi.nlm.nih.gov/24777111/. Cited 2024 Sep 4.
3. Beaver JA, Amiri-Kordestani L, Charlab R, Chen W, Palmby T, Tilley A, et al. FDA Approval: Palbociclib for the Treatment of Postmenopausal Patients with Estrogen Receptor-Positive, HER2-Negative Metastatic Breast Cancer. Clin Cancer Res. 2015;21(21):4760–6. Available from: https://pubmed.ncbi.nlm.nih.gov/26324739/. Cited 2024 Sep 4.
4. Kent LN, Leone G. The broken cycle: E2F dysfunction in cancer. Nat Rev Cancer. 2019;19(6):326–38. Available from: https://pubmed.ncbi.nlm.nih.gov/31053804/. Cited 2024 Sep 4.
5. Watt AC, Goel S. Cellular mechanisms underlying response and resistance to CDK4/6 inhibitors in the treatment of hormone receptor-positive breast cancer. Breast Cancer Res. 2022;24(1). Available from: https://pubmed.ncbi.nlm.nih.gov/35248122/. Cited 2024 Sep 4.
6. Cristofanilli M, Rugo HS, Im SA, Slamon DJ, Harbeck N, Bondarenko I, et al. Overall Survival with Palbociclib and Fulvestrant in Women with HR+/HER2- ABC: Updated Exploratory Analyses of PALOMA-3, a Double-blind, Phase III Randomized Study. Clin Cancer Res. 2022;28(16):3433–42. Available from: https://pubmed.ncbi.nlm.nih.gov/35552673/. Cited 2024 Sep 4.
7. Finn RS, Martin M, Rugo HS, Jones S, Im SA, Gelmon K, et al. Palbociclib and Letrozole in Advanced Breast Cancer. N Engl J Med. 2016;375(20):1925–36. Available from: https://pubmed.ncbi.nlm.nih.gov/27959613/. Cited 2024 Sep 4.
8. Goetz MP, Toi M, Huober J, Sohn J, Trédan O, Park IH, et al. Abemaciclib plus a nonsteroidal aromatase inhibitor as initial therapy for HR+, HER2- advanced breast cancer: final overall survival results of MONARCH 3. Ann Oncol. 2024;35(8):718–27. Available from: https://pubmed.ncbi.nlm.nih.gov/38729566/. Cited 2024 Sep 4.
9. Hortobagyi GN, Stemmer SM, Burris HA, Yap YS, Sonke GS, Paluch-Shimon S, et al. Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer. N Engl J Med. 2016;375(18):1738–48. Available from: https://pubmed.ncbi.nlm.nih.gov/27717303/. Cited 2024 Sep 4.
10. Hortobagyi GN, Stemmer SM, Burris HA, Yap YS, Sonke GS, Hart L, et al. Overall Survival with Ribociclib plus Letrozole in Advanced Breast Cancer. N Engl J Med. 2022;386(10):942–50. Available from: https://pubmed.ncbi.nlm.nih.gov/35263519/. Cited 2024 Sep 4.
11. Johnston S, Martin M, Di Leo A, Im SA, Awada A, Forrester T, et al. MONARCH 3 final PFS: a randomized study of abemaciclib as initial therapy for advanced breast cancer. NPJ Breast Cancer. 2019;5(1). Available from: https://pubmed.ncbi.nlm.nih.gov/30675515/. Cited 2024 Sep 4.
12. Kappel C, Elliott MJ, Kumar V, Nadler MB, Desnoyers A, Amir E. Comparative overall survival of CDK4/6 inhibitors in combination with endocrine therapy in advanced breast cancer. Sci Rep. 2024;14(1). Available from: https://pubmed.ncbi.nlm.nih.gov/38326452/. Cited 2024 Sep 4.
13. Lu YS, Im SA, Colleoni M, Franke F, Bardia A, Cardoso F, et al. Updated Overall Survival of Ribociclib plus Endocrine Therapy versus Endocrine Therapy Alone in Pre- and Perimenopausal Patients with HR+/HER2- Advanced Breast Cancer in MONALEESA-7: A Phase III Randomized Clinical Trial. Clin Cancer Res. 2022;28(5):851–9. Available from: https://pubmed.ncbi.nlm.nih.gov/34965945/. Cited 2024 Sep 4.
14. Neven P, Fasching PA, Chia S, Jerusalem G, De Laurentiis M, Im SA, et al. Updated overall survival from the MONALEESA-3 trial in postmenopausal women with HR+/HER2- advanced breast cancer receiving first-line ribociclib plus fulvestrant. Breast Cancer Res. 2023;25(1). Available from: https://pubmed.ncbi.nlm.nih.gov/37653397/. Cited 2024 Sep 4.
15. Slamon DJ, Neven P, Chia S, Fasching PA, De Laurentiis M, Im SA, et al. Phase III Randomized Study of Ribociclib and Fulvestrant in Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: MONALEESA-3. J Clin Oncol. 2018;36(24):2465–72. Available from: https://pubmed.ncbi.nlm.nih.gov/29860922/. Cited 2024 Sep 4.
16. Slamon DJ, Neven P, Chia S, Fasching PA, De Laurentiis M, Im SA, et al. Overall Survival with Ribociclib plus Fulvestrant in Advanced Breast Cancer. N Engl J Med. 2020;382(6):514–24. Available from:https://pubmed.ncbi.nlm.nih.gov/31826360/. Cited 2024 Sep 4.
17. Sledge GW, Toi M, Neven P, Sohn J, Inoue K, Pivot X, et al. MONARCH 2: Abemaciclib in Combination With Fulvestrant in Women With HR+/HER2- Advanced Breast Cancer Who Had Progressed While Receiving Endocrine Therapy. J Clin Oncol. 2017;35(25):2875–84. Available from: https://pubmed.ncbi.nlm.nih.gov/28580882/. Cited 2024 Sep 4.
18. Tripathy D, Im SA, Colleoni M, Franke F, Bardia A, Harbeck N, et al. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial. Lancet Oncol. 2018;19(7):904–15. Available from: https://pubmed.ncbi.nlm.nih.gov/29804902/. Cited 2024 Sep 4.
19. Turner NC, Ro J, André F, Loi S, Verma S, Iwata H, et al. Palbociclib in Hormone-Receptor-Positive Advanced Breast Cancer. N Engl J Med. 2015;373(3):209–19. Available from: https://pubmed.ncbi.nlm.nih.gov/26030518/. Cited 2024 Sep 4.
20. Turner NC, Slamon DJ, Ro J, Bondarenko I, Im SA, Masuda N, et al. Overall Survival with Palbociclib and Fulvestrant in Advanced Breast Cancer. N Engl J Med. 2018;379(20):1926–36. Available from:https://pubmed.ncbi.nlm.nih.gov/30345905/. Cited 2024 Sep 4.
21. Samant TS, Dhuria S, Lu Y, Laisney M, Yang S, Grandeury A, et al. Ribociclib Bioavailability Is Not Affected by Gastric pH Changes or Food Intake: In Silico and Clinical Evaluations. Clin Pharmacol Ther. 2018;104(2):374–83.
22. Sun W, Klamerus KJ, Yuhas LM, Pawlak S, Plotka A, O'Gorman M, et al. Impact of Acid-Reducing Agents on the Pharmacokinetics of Palbociclib, a Weak Base With pH-Dependent Solubility, With Different Food Intake Conditions. Clin Pharmacol Drug Dev. 2017;6(6):614–26.
23. Raoul JL, Moreau-Bachelard C, Gilabert M, Edeline J, Frénel JS. Drug-drug interactions with proton pump inhibitors in cancer patients: an under-recognized cause of treatment failure. ESMO Open. 2023;8(1):100880. https://doi.org/10.1016/j.esmoop.2023.100880. Cited 2024 Sep 4.
24. Lu Y, Yang S, Ho YY, Ji Y. Ribociclib Population Pharmacokinetics and Pharmacokinetic/Pharmacodynamic Analysis of Neutrophils in Cancer Patients. J Clin Pharmacol. 2021;61(8):1054–68.
25. Uchiyama AAT, Silva PAIA, Lopes MSM, Yen CT, Ricardo ED, Mutão T, et al. Proton Pump Inhibitors and Oncologic Treatment Efficacy: A Practical Review of the Literature for Oncologists. Curr Oncol. 2021;28(1):783–99. Available from: https://pubmed.ncbi.nlm.nih.gov/33546228/. Cited 2024 Sep 4.
26. Takahashi K, Uozumi R, Mukohara T, Hayashida T, Iwabe M, Iihara H, et al. Proton Pump Inhibitors and Cyclin-Dependent Kinase 4/6 Inhibitors in Patients With Breast Cancer. Oncologist. 2024;29(6):e741-9. Available from: https://pubmed.ncbi.nlm.nih.gov/38340010/. Cited 2024 Sep 4.
27. Lee JE, Kwon SH, Kwon S, Jung HI, Nam JH, Lee EK. Concomitant Use of Proton Pump Inhibitors and Palbociclib Among Patients With Breast Cancer. JAMA Netw Open. 2023;6(7):E2324852. Available from: https://pubmed.ncbi.nlm.nih.gov/37477917/. Cited 2024 Sep 4.
28. Odabas H, Dogan A, Ozcelik M, Yildirim S, Ozkerim U, Turan N, et al. Does Proton Pump Inhibitors Decrease the Efficacy of Palbociclib and Ribociclib in Patients with Metastatic Breast Cancer? Medicina (Kaunas). 2023;59(3). Available from: https://pubmed.ncbi.nlm.nih.gov/36984558/. Cited 2024 Sep 4.
29. Schieber T, Steele S, Collins S, Berger M, Fleming M, McLaughlin E, et al. Effect of Concurrent Proton Pump Inhibitors With Palbociclib Tablets for Metastatic Breast Cancer. Clin Breast Cancer. 2023;23(6):658–63. Available from: https://pubmed.ncbi.nlm.nih.gov/37296062/. Cited 2024 Sep 4.
30. Çağlayan D, Koçak MZ, Geredeli Ç, Tatlı AM, Göksu SS, Eryılmaz MK, et al. The effect of concomitant use of proton pump inhibitors with CDK 4/6 inhibitors on survival in metastatic breast cancer. Eur J Clin Pharmacol. 2023;79(2):243–8. Available from: https://pubmed.ncbi.nlm.nih.gov/36520173/. Cited 2024 Sep 4.
31. Eser K, Önder AH, Sezer E, Çil T, İnal A, Öztürk B, et al. Proton pump inhibitors may reduce the efficacy of ribociclib and palbociclib in metastatic breast cancer patients based on an observational study. BMC Cancer. 2022;22(1). Available from: https://pubmed.ncbi.nlm.nih.gov/35525929/. Cited 2024 Sep 4.
32. Del Re M, Crucitta S, Omarini C, Bargagna I, Mongillo M, Palleschi M, et al. Concomitant administration of proton pump inhibitors does not

significantly affect clinical outcomes in metastatic breast cancer patients treated with ribociclib. Breast. 2022;66:157–61. Available from: https://pubmed.ncbi.nlm.nih.gov/36283134/. Cited 2024 Sep 4.
33. Del Re M, Omarini C, Diodati L, Palleschi M, Meattini I, Crucitta S, et al. Drug-drug interactions between palbociclib and proton pump inhibitors may significantly affect clinical outcome of metastatic breast cancer patients. ESMO Open. 2021;6(5). Available from: https://pubmed.ncbi.nlm.nih.gov/34509802/. Cited 2024 Sep 4.
34. Moher D, Liberati A, Tetzlaff J, Altman DG, Antes G, Atkins D, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7). Available from: https://pubmed.ncbi.nlm.nih.gov/19621072/. Cited 2024 Sep 4.
35. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;355. Available from: https://pubmed.ncbi.nlm.nih.gov/27733354/. Cited 2024 Sep 4.
36. Tantry TP, Karanth H, Shetty PK, Kadam D. Self-learning software tools for data analysis in meta-analysis. Korean J Anesthesiol. 2021;74(5):459–61. Available from: https://pubmed.ncbi.nlm.nih.gov/33677944/. Cited 2024 Sep 4.
37. Sun W, Klamerus KJ, Yuhas LM, Pawlak S, Plotka A, O'Gorman M, et al. Impact of Acid-Reducing Agents on the Pharmacokinetics of Palbociclib, a Weak Base With pH-Dependent Solubility, With Different Food Intake Conditions. Clin Pharmacol Drug Dev. 2017;6(6):614–26. Available from: https://pubmed.ncbi.nlm.nih.gov/28430398/. Cited 2024 Sep 4.
38. Samant TS, Dhuria S, Lu Y, Laisney M, Yang S, Grandeury A, et al. Ribociclib Bioavailability Is Not Affected by Gastric pH Changes or Food Intake: In Silico and Clinical Evaluations. Clin Pharmacol Ther. 2018;104(2):374–83. Available from: https://pubmed.ncbi.nlm.nih.gov/29134635/. Cited 2024 Sep 4.
39. Lu Y, Yang S, Ho YY, Ji Y. Ribociclib Population Pharmacokinetics and Pharmacokinetic/Pharmacodynamic Analysis of Neutrophils in Cancer Patients. J Clin Pharmacol. 2021;61(8):1054–68. Available from: https://pubmed.ncbi.nlm.nih.gov/33713359/. Cited 2024 Sep 4.
40. Courlet P, Cardoso E, Bandiera C, Stravodimou A, Zurcher JP, Chtioui H, et al. Population Pharmacokinetics of Palbociclib and Its Correlation with Clinical Efficacy and Safety in Patients with Advanced Breast Cancer. Pharmaceutics. 2022;14(7). Available from: https://pubmed.ncbi.nlm.nih.gov/35890213/. Cited 2024 Sep 4.
41. Eli Lilly Canada Inc. PRODUCT MONOGRAPH INCLUDING PATIENT MEDICATION INFORMATION VERZENIO® Abemaciclib tablets. 2019;270898.
42. Goldstein MJ, Peters M, Weber BL, Davis CB. Optimizing the Therapeutic Window of Targeted Drugs in Oncology: Potency-Guided First-in-Human Studies. Clin Transl Sci. 2021;14(2):536–43. Available from: https://pubmed.ncbi.nlm.nih.gov/33048459/. Cited 2024 Sep 4.
43. Strand DS, Kim D, Peura DA. 25 Years of Proton Pump Inhibitors: A Comprehensive Review. Gut Liver. 2017;11(1):27–37. Available from: https://pubmed.ncbi.nlm.nih.gov/27840364/. Cited 2024 Sep 4.
44. Li XQ, Andersson TB, Ahlström M, Weidolf L. Comparison of inhibitory effects of the proton pump-inhibiting drugs omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole on human cytochrome P450 activities. Drug Metab Dispos. 2004;32(8):821–7. Available from: https://pubmed.ncbi.nlm.nih.gov/15258107/. Cited 2024 Sep 4.
45. Alsubi TAAMBADHAHKA. In silico and in vitro metabolism of ribociclib: a mass spectrometric approach to bioactivation pathway elucidation and metabolite profiling. RSC. 2020;10:22668–83.
46. James AD, Schiller H, Marvalin C, Jin Y, Borell H, Roffel AF, et al. An integrated assessment of the ADME properties of the CDK4/6 Inhibitor ribociclib utilizing preclinical in vitro, in vivo, and human ADME data. Pharmacol Res Perspect. 2020;8(3). Available from: https://pubmed.ncbi.nlm.nih.gov/32524755/. Cited 2024 Sep 4.
47. Food and Drug Administration (FDA). NDA/BLA Multi-disciplinary Review and Evaluation NDA. 2017.

Publisher's Note