

Onderbouwend	Stof	Effect	Code
<p>Sun W. Clin Pharmacol Drug Dev 2017;6:614-6. doi: 10.1002/cpdd.356.</p> <p>antacidum: aluminiumOH 400 mg, magnesiumOH 400 mg, simeticon 40 mg/5ml</p>	<p>palbociclib + rabeprazol</p> <p>palbociclib + rabeprazol famotidine, antacidum</p>	<p>#1 lege maag, effect op palbociclib rabeprazol: ↓AUC<sub>inf</sub> met 62% en C<sub>max</sub> met 80%. GIC: getallen uit tabel 4. Regime: palbociclib 125 mg 1x na 10 uur vasten en daarna nog 4 uur vasten, alleen of met rabeprazol 40 mg ged. 7 dagen; cross over, wash out ten minste 10 dagen, 25 vrijwilligers</p> <p>#2 met ontbijt, effect op palbociclib rabeprazol: ↓AUC<sub>inf</sub> met 13% en C<sub>max</sub> met 41% famotidine: ↓AUC<sub>inf</sub> met 4% en C<sub>max</sub> met 5% antacidum: ↑AUC<sub>inf</sub> met 5%, ↓C<sub>max</sub> met 4% GIC: getallen uit tabel 6. Regime: fixed sequence, 3 period, wash out ten minste 10 dagen, 27 vrijwilligers; A→B→C (n=14) of antacidum A→D→E (n=13); A palbociclib 125 mg 1x met ontbijt B als A icm famotidine 20 mg 10h voor en 2h na palbociclib C als A icm rabeprazol 40 mg ged. 7 dagen D als A, 30 ml antacidum 2h voor palbociclib E als A, 30 ml antacidum 2h na palbociclib</p> <p>Auteurs: food intake effectively mitigated the impact of acid-reducing agents on palbociclib exposure. Palbociclib free base capsule should be taken with food, and acid-reducing agent use does not need to be avoided. Palbociclib free base capsule is a weak base drug with highly pH-dependent solubility.</p>	3A
SPC Ibrance	palbociclib + rabeprazol	getallen uit Sun 2017.	
<b>Overig</b>	<b>Stof</b>	<b>Effect</b>	
SPC Ibrance	palbociclib + PPI, H2-antagonist, antacidum	rabeprazol: innemen met voedsel, bij voorkeur een maaltijd. H2-antagonist, antacidum: geen klinisch relevant effect verwacht bij inname palbociclib met voedsel.	

Retrospective analyses	Stof	Effect
<p>Agostinetto E. ESMO Open 2025;10:104096.</p> <p>PALLAS trial: either 2 y of palbociclib (125 mg orally 1dd on days 1–21 of a 28-day cycle) with ongoing standard provider or patient-choice adjuvant endocrine therapy (tamoxifen or aromatase inhibitor, with or without concurrent luteinising hormone-releasing hormone agonist), or endocrine therapy alone, without masking.</p>	<p>palbociclib + PPI</p>	<p>- 525 of 2840 (18.5%) patients treated with palbociclib + endocrine therapy had concomitant PPI; this was not significantly associated with survival outcomes (iDFS, distant relapse-free survival, overall survival);</p> <p>- all-grade neutropenia rates were numerically lower in patients who initiated a PPI before study start compared with patients never initiating PPIs (adjusted OR 0.81, 95% CI 0.60-1.09).</p> <p>Methods: exploratory analysis of PALLAS including patients who received at least one dose of palbociclib capsules. We aimed to determine the association of concomitant PPI use with iDFS, distant relapse-free survival and overall survival. The association between PPI use and neutropenia was also investigated. PPI intake was significantly associated with older age, post-menopausal status, use of aromatase inhibitors, higher BMI, and worse Eastern Cooperative Oncology Group status (all <math>P &lt; 0.001</math>).</p> <p>Conclusions: our exploratory analysis did not demonstrate worse survival outcomes in patients receiving concomitant palbociclib and PPIs in PALLAS.</p>
<p>Lee JE. JAMA Netw Open 2023;6(7):e2324852.</p> <p>progression-free survival (PFS) and overall survival (OS)</p> <p>hazard ratio (HR)</p>	<p>palbociclib + PPI</p>	<p>retrospective cohort study:</p> <p>- median clinical PFS in the concomitant PPI group was shorter than that of the nonconcomitant PPI group (25.3 vs 39.8 months (<math>P &lt; .001</math>), HR was 1.76 (95% CI, 1.46-2.13). Concomitant use of PPI was also associated with shorter OS (HR, 2.71 [95% CI, 2.07-3.53]). Both clinical PFS and OS in the concomitant PPI group were consistently poor in patients receiving endocrine-sensitive and endocrine-resistant treatment.</p> <p>Methods: retrospective cohort study with nationwide claims data in South Korea; women with breast cancer, 344 with concomitant PPI and 966 nonconcomitant PPI; 84.8% were treated with letrozole and anastrozole (endocrine sensitive); and 15.2% were treated with fulvestrant (endocrine resistant).</p> <p>Conclusions and relevance: These findings suggest that concomitant use of PPIs with palbociclib may hinder the complete therapeutic benefits of palbociclib in patients with breast cancer.</p>
<p>Eser K. BMC Cancer 2022;22:516.</p> <p>ribo = NN M848, zie capecitabine</p> <p>Palbociclib and ribociclib are weak bases so their solubility depends on different pH. The solubility of palbociclib dramatically decreases to <math>&lt; 0.5</math> mg/ml when pH is above 4,5 but ribociclib's solubility decreases when pH increases above 6,5.</p>	<p>palbociclib, ribociclib + PPI</p>	<p>observational study</p> <p>- palbociclib: PFS of the patients using PPIs was shorter than patients not using (13.04 months vs. unreachable, <math>p &lt; 0.001</math>). Multivariate analysis: taking PPIs was an independent predictor of shortening PFS (<math>p &lt; 0.001</math>).</p> <p>- ribociclib: PFS of the patients using PPIs was shorter than patients not using (12.64 months vs. unreachable, <math>p = 0.003</math>). Univariate analysis: taking PPIs was single statistically independent predictor of shortening PFS (<math>p = 0.003</math>).</p> <p>Methods: observational study, all data collected from real-life retrospectively; 217 hormone receptor-positive, HER2-negative mBC patients treated with endocrine treatment (letrozole or fulvestrant) combined palbociclib (<math>n=105</math>) or ribociclib (<math>n=112</math>) alone or with PPI; CDK inhibitor treatment was added to fulvestrant 102 patients (47%), to letrozole 115 patients (53%). In the Palbociclib arm fulvestrant/letrozole ratio was 53.3/46.7%, in the ribociclib arm it was 41.07/58.93%. Of 105 patients who received palbociclib, 65 were on concomitant PPI therapy, 40 were not. Of the 112 patients who received ribociclib, 61 were on concomitant PPI therapy, 51 were not.</p> <p>Conclusions: concomitant usage of PPIs was associated with shorter PFS in mBC treated with both ribociclib and especially palbociclib. If it needs to be used, PPI selection should be made carefully and low-strength PPI or other ARAs (eg H2 antagonists, antacids) should be preferred.</p>

<p>Del Re M. ESMO Open. 2021 Oct;6(5):100231.</p> <p>(zie 2 ingezonden reacties hieronder)</p> <p>PFS: progression-free survival mBC: metastatic breast cancer</p>	<p>palbociclib + PPI</p>	<p>retrospective observational study: -patients taking PPIs had a shorter PFS than those taking palbociclib and endocrine therapy alone, 14.0 vs 37.9 months (<math>P &lt; 0.0001</math>); -multivariate analysis confirmed concomitant PPIs as the only independent predictive factor for shorter PFS (<math>P = 0.0002</math>). PFS was significantly longer in estrogen-sensitive mBC with no concomitant PPIs compared with patients taking PPIs or estrogen-resistant patients, with and without PPIs (<math>P &lt; 0.0001</math>). Methods: retrospective observational study with 112 patients affected by estrogen receptor-positive, human epidermal growth factor receptor 2-negative mBC, who were candidates for first-line treatment with palbociclib; 56 belonged to the 'no concomitant PPIs' group and 56 to the 'concomitant PPIs' group; 71 were endocrine-sensitive and received palbociclib and letrozole, and 43 were endocrine-resistant and were treated with palbociclib and fulvestrant. The most prescribed PPI was lansoprazole. Conclusions: The present study demonstrates that concomitant use of PPIs in mBC patients treated with palbociclib has a detrimental effect on PFS. Therefore, it is recommended to prescribe PPIs with caution in these patients, strictly adhering to the indications in the summary of product characteristics.</p>
<p>Letter: Altundag K. ESMO Open 2022 Feb;7(1):100382. Reply: Del Re M. ESMO Open 2022 Feb;7(1):100381.</p> <p>Origineel (zie hierboven) Del Re M. ESMO Open. 2021 Oct;6(5):100231.</p>	<p>palbociclib + PPI</p>	<p>- Ingezonden Altundag: the authors did not give detailed information about the number of metastatic sites in both groups. It would be expected that cases with higher metastatic sites might have a higher chance of decreased PFS. Second, worse outcome in PFS in patients with receiving palbociclib plus PPIs may be a class effect and not be generalizable to other oral CDK-4 and 6 inhibitors (abemaciclib or ribociclib). This issue merits further investigation. Reply Del Re: we are pleased to clarify that the number of metastatic sites has been considered in the univariate analysis reported in Table 2 and it was not found to significantly impact on patient survival. Few additional data have been published about the class-effect of PPIs on CDK4/6 inhibitors and are in agreement with our findings; furthermore, preliminary unpublished data from our group suggest that PPIs have no effect on the PFS of ribociclib-treated patients. Considering the small number of subjects and the limitations that retrospective studies may have, however, the effect of PPIs on CDK4/6 inhibitors deserves further investigation.</p>

<p>Letter: Beechinor R. ESMO Open 2022 Feb;7(1):100393. Reply: Del Re M. ESMO Open 2022 Feb;7(1):100381.</p> <p>Origineel (zie hierboven) Del Re M. ESMO Open. 2021 Oct;6(5):100231.</p>	<p>palbociclib + PPI</p>	<p>- Ingezonden Beechinor: there are several critical considerations omitted in this analysis that call into question these findings and the resulting conclusions presented: #1 the authors have failed to recognize and account for the negative impact PPIs have on overall mortality; #2 the magnitude of reduction in PFS demonstrated is not likely biologically plausible given the purported mechanism suggested for this interaction.</p> <p>Reply Del Re: #1 it should be made clear that the effect of PPIs on cancer mortality has been evaluated within observational studies, which cannot exclude residual confounding factors including disease stage, treatment delivered to patients, sociodemographic or lifestyle characteristics; moreover, the link between PPI use and increased risk of mortality is not supported by evidence of causality. A significant bias is the use of PPIs within different clinical settings as well as the lack of information about the specific indications for PPIs and other drugs used during hospitalization, as stated by the authors themselves.</p> <p>Moreover, the effect of specific disease may be relevant, such as in the case of colorectal cancer mortality of PPI users versus non-users.</p> <p>#2 regarding the magnitude of the reduction in PFS, we invite the authors to consider the PFS in the population stratified by endocrine status and not the overall population. The PALOMA-2 study reported a difference in PFS of 24.8 vs 14.5 months, and the relative cohort of patients in our study had a PFS of not reached vs 20 months. Considering the PALOMA-3 trial, median PFS was 11.2 vs 4.6 months, whereas it was 16.4 vs 6.3 months in the population of our study. Obviously, with our population being numerically smaller and mirroring real-life practice, a slight difference in survival data is reasonable.</p> <p>Regarding the criteria used to enroll patients, all centers included subjects given palbociclib capsules as per approved label and with complete clinical data available for analysis.</p>
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### Opmerkingen

Werkgroep Interacties Oncologische middelen 25-6-25: retrospectieve analyses waaruit blijkt dat een PPI de uitkomst op PFS/OS negatief lijkt te beïnvloeden niet meer voorleggen (zijn niet-onderbouwend). Data uit de retrospectieve analyses overrulen de kinetische data niet. Als een patiënt een PPI nodig heeft, dan geef je die.

GIC 2019: ook gezocht voor andere 'clibben'.

-Ribociclib: dit heeft niets opgeleverd. De absorptie wordt niet beïnvloed door voedsel.

-Abemaciclib: zwakke base met pH-afhankelijke oplosbaarheid, bij pH 6.8 is deze lager dan bij lagere pH. Geen studie naar interactie met zuurverlagers uitgevoerd. Vlg fabrikant is hoogste dosis 200 mg oplosbaar in minder dan 250 ml tot pH 6.8, waarschijnlijk hebben zuurverlagers hier geen effect op.

Risicofactoren	
Mitigerende factoren	

	Interactie	Actie	Datum
Beslissing WG OncolA	Ja	Nee	10 april 2019

# Alpelisib + Secretieremmers/Antacida

B

Onderbouwend	Stof	Effect	Code
SPC + EPAR Piqray	alpelisib + ranitidine	↓ AUC alpelisib met 21% en ↓ Cmax met 36% na combinatie met ranitidine en inname met vetarme maaltijd. ↓ AUC alpelisib met 30% en ↓ Cmax met 51% na combinatie met ranitidine en inname op nuchtere maag. Regime: alpelisib 300 mg eenmalig, 21 gezonde personen.	2A

Overig	Stof	Effect
SPC en EPAR Piqray	alpelisib + antacida / zuurremmers	uit farmacokinetisch populatie-onderzoek in fase-1 en fase-3 studies bleek geen significant effect van combinatie met zuurverminderende middelen, waaronder protonpompremmers, H2-receptorantagonisten en antacida, op de farmacokinetiek van alpelisib. Daarom kan alpelisib gelijktijdig met zuurverminderende middelen worden toegediend, mits alpelisib onmiddellijk na het eten wordt ingenomen.

## Opmerkingen

Werkgroep Interacties Oncologische middelen 2-12-20: naar verwachting zal het effect met een PPI groter zijn, maar dat is niet onderzocht.

GIC 2023: + antacida. Antacida: hoewel kinetische gegevens ontbreken, is het aannemelijk dat bij deze signaaltransductieremmers sprake is van eenzelfde effect. Voor de gekoppelde signaaltransductieremmers is de interactie aangetoond met een PPI of een H2-antagonist. Dit is ook gedaan bij de Ja/Ja-interactie TKI's + Antacida, M 823 en bij de Ja/Nee interactie TKI's + Antacida, M1336.

Pubmed: -

Risicofactoren	
Mitigerende factoren	

	Interactie	Actie	Datum
Beslissing WG OncolA	Ja	Nee	2 december 2020

# Vismodegib + Secretieremmers/Antacida

C

Onderbouwend	Stof	Effect	Code
Malhi V. Cancer Chemother Pharmacol 2016;78:41-9. doi: 10.1007/s00280-016-3020-z.	vismodegib + rabeprazol	afname vismodegib steady-state AUC0-24h met 14% (402→346 umol*h/l) Regime: vismodegib 150 mg 1dd ged. 7 dagen (n = 22), of rabeprazol 20 mg/dag op dag 1-4 en vismodegib icm rabeprazol 20 mg op dag 5-11 (rabe 2 uur vóór vismo) (n = 24); gezonde vrijwilligsters. Auteurs: vismodegib kan worden gecombineerd met acid-reducing agents.	3A
SPC + EPAR Erivedge	vismodegib + rabeprazol	daling spiegel vismodegib met 33% na combinatie met rabeprazol 20 mg/dag gedurende 7 dagen. Deze afname is klinisch niet significant. Klinisch significante farmacokinetische (PK) interacties tussen vismodegib en middelen die de pH verhogen worden niet verwacht.	2A

## Opmerkingen

Werkgroep Interacties Oncologische middelen 27-1-2016: ga je in kliniek niets mee doen.

GIC 2023: + antacida. Antacida: hoewel kinetische gegevens ontbreken, is het aannemelijk dat bij deze signaaltransductieremmers sprake is van eenzelfde effect. Voor de gekoppelde signaaltransductieremmers is de interactie aangetoond met een PPI of een H2-antagonist. Dit is ook gedaan bij de Ja/Ja-interactie TKI's + Antacida, M 823 en bij de Ja/Nee interactie TKI's + Antacida, M1336.

PubMed search november 2017: behalve Malhi 2016 geen gegevens.

Risicofactoren	
Mitigerende factoren	

	Interactie	Actie	Datum
Beslissing WFG	Ja	Nee	27 januari 2016