Capecitabine + Secretieremmers/Antacida M 848A

RFS = recurrence-free survival, OS = overall survival, PFS = progression-free survival, HR = hazard ratio

Onderbouwend	Stof	Effect	Code
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Overig	Stof	Effect
van Doorn L. Clin Pharmacol Ther 2022;111:455-60.	capecitabine + esomeprazol	- esomeprazol 3h vóór capecitabine:↑ $AUC_{0\text{-}inf}$ capecitabine 1.19x en Cmax 1.09x, en t1/2 0.46→0.63h - esomeprazol 3h vóór en C tegelijk cola:↑$AUC_{0\text{-}inf}$ 1.03x en ↓Cmax met 5%; tegelijk cola 'did not completely reverse the effects observed after esomeprazole' (relative difference 3.3% (95% CI -16.3 to 27.4%, P = 1.00). Regime: B) capecitabine alleen (capecitabine 2dd ged. 2 weken en 1 week rust); A) capecitabine met esomeprazol 40 mg 1dd 3 h vooraf ged. 4 dagen; C) capecitabine tegelijk met cola (Coca cola Classic®), en esomeprazol 3 hours before; studie (randomized crossover) met 22 patienten Auteurs: capecitabine exposure is not negatively influenced by esomeprazole cotreatment. Therefore, altered capecitabine pharmacokinetics do not explain the assumed worse clinical outcome of PPI-cotreated patients with cancer.
Kitazume Y. Sci Rep 2022;12:6561. CapeOX: capecitabine and oxaliplatin	capecitabine + PPI	retrospective observational study with consecutive patients with stage II-III CRC who received adjuvant capecitabine monotherapy or CapeOX between 2009-2014. The primary endpoint was the difference in relapse-free survival (RFS) between patients who received PPIs and those who did not. Overall survival (OS) was the secondary endpoint. Methods: data from 606 patients were evaluated, 54 of whom had received a PPI. PPI-treated patients tended to have poorer RFS and OS than patients treated without PPIs. The hazard ratio for RFS with capecitabine monotherapy was 2.48 (95% CI: 1.22-5.07). These results were consistent with sensitivity analyses performed using propensity score adjustment and IPTW methods. Co-administration of PPIs may reduce the effectiveness of capecitabine and negatively impact patients with stage II-III CRC.

<table>
<tr>
<td>Jeong SH.
Cancer Chemother Pharmacol 2022;90:381-8.</td>
<td>capecitabine + PPI</td>
<td>Several observational studies, mostly retrospective, have reported inferior survival outcomes among patients on capecitabine who concomitantly use PPI. This association is yet to be definitively established. The leading mechanism of interaction postulated in these reports has focussed on the pH altering effects of PPI and how this could diminish capecitabine absorption. We highlight the long-term effects of PPI on health outcomes, and how PPI use itself could lead to poorer outcomes, independent of capecitabine.
Table 1: summary/review of outcomes
<table>
<tr><th>References</th><th>Study size (n)</th><th>Capecitabine + PPI versus no PPI</th></tr>
<tr><td>Sun et al. (2016) [3]</td><td>298</td><td>Worse outcome</td></tr>
<tr><td>Chu et al. (2017) [4]</td><td>545</td><td>Worse outcome</td></tr>
<tr><td>Rhinehart et al. (2019) [5]</td><td>70</td><td>Worse outcome</td></tr>
<tr><td>Kitazume et al. (2022) [7]</td><td>606</td><td>Worse outcome</td></tr>
<tr><td>Wong et al. (2019) [6]</td><td>389</td><td>Worse outcome</td></tr>
<tr><td>Kim et al. (2021) [8]</td><td>482</td><td>No effect*</td></tr>
<tr><td>Wang et al. (2017) [9]</td><td>671</td><td>No effect</td></tr>
<tr><td>Kichenadasse et al. (2021) [10]</td><td>5,262</td><td>No effect</td></tr>
<tr><td>Menon et al. (2021) [11]</td><td>508</td><td>No effect</td></tr>
<tr><td>Zhang et al. (2017) [12]</td><td>125</td><td>Improved outcome</td></tr>
<tr><td>Bridoux et al. (2022) [13]</td><td>149</td><td>No effect</td></tr>
<tr><td>Roberto et al. (2019) [14]</td><td>61</td><td>No effect</td></tr>
<tr><td>Yang et al. (2017) [15]</td><td>891</td><td>No effect</td></tr>
<tr><td>Lu et al. (2019) [16]</td><td>72</td><td>No effect</td></tr>
</table>
*This study reported significantly worse outcomes for PPI users receiving capecitabine compared to those receiving 5-FU plus PPI
Conclusion: we suggest taking this high impact and clinically relevant question back to the bench for further scrutiny. We believe the scope of investigation should be broadened to study other alternative DDI mechanisms, such as altered renal elimination or potential effects on transport of capecitabine's active metabolites into tumour cells.</td>
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<tr>
<td>Patel A.
World J Gastroenterol 2021;27:7716-33.

CRC: colorectal cancer

FOLFOX: 5FU, leucovorin, oxaliplatin</td>
<td>capecitabine + PPI</td>
<td>systematic review (CRC), based on the patients, interventions, comparisons, outcome models and performed according to PRISMA guidelines. MEDLINE, EMBASE, Scopus, and Web of Science databases were searched. 28 studies met the inclusion criteria, categorized as basic research studies (n = 12), epidemio-logical studies (n = 11), and CRC treatment studies (n = 5).
- basic research: data indicate that PPI do not stimulate CRC development via the trophic effect of gastrin but instead may paradoxically inhibit it. These studies also suggest that PPI may have properties beneficial for CRC treatment. PPI appear to have anti-tumor properties (ome-/pantoprazole), and are potential T lymphokine-activated killer cell-originated protein kinase inhibitors (panto-/ilaprazole), and chemosensitizing agents (pantoprazole). However, these mechanisms have not been confirmed in human trials.
- epidemiological studies suggest that there is no causal association between PPI use and increased CRC risk.
- CRC treatment studies show that concomitant PPI and capecitabine use may reduce the efficacy of chemotherapy resulting in poorer oncological outcomes, while also suggesting that pantoprazole may have a chemosensitizing effect with the FOLFOX regimen.
Conclusion: an unexpected inhibitory effect of PPI on CRC carcinogenesis by way of several potential mechanisms is noted. Prospective studies are warranted to delineate this relationship and assess the role of individual PPI agents.</td>
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</table>

Viñal D. Clin Transl Oncol 2020;22:1288-94.	capecitabine + PPI	systematic review - a systematic literature search on the main databases up to November 2019. Results: 9 studies met our inclusion criteria: 8 retrospective studies and 1 phase II clinical trial; 4 out of 9 studies reported a shorter efficacy outcome in uni- or multivariate analysis when capecitabine was taken concomitantly with PPI than alone. Conclusions: the clinical evidence reported on the use of capecitabine concomitantly with PPI is scarce and shows conflicting results. While awaiting further data, avoiding misuse of PPI in patients taking capecitabine is recommended
Takemura M. Anticancer Res 2022;42:2591-8. HFS: Hand-foot syndrome	capecitabine + PPI	Retrospectief: -lower incidence of severe HFS in patients who received PPIs (18%) than in patients who did not receive PPIs (43%, p=0.001), and also lower discontinuation rate of capecitabine due to HFS (p=0.003); -multivariate analysis revealed that concomitant PPIs use was an independent factor that significantly contributed to the prevention of severe HFS (OR=0.265, p=0.003); -no significant difference in median PFS and OS values was observed between patients treated with and without PPIs. Methods: we analyzed the effects of PPIs on the development of severe HFS (grade ≥2), progression-free survival (PFS), and overall survival (OS) in 195 patients on capecitabine for breast cancer (50 patients (26%) were treated with PPIs, 145 patients (74%) did not receive PPIs). Conclusion: concomitant use of PPIs could ameliorate capecitabine-induced HFS in patients with breast cancer.
Sekido M. Cancer Chemother Pharmacol 2019;83:1127-35. CapeOX: capecitabine and oxaliplatin	capecitabine + rabeprazol	- no significant effects of rabeprazole on AUC divided by capecitabine dose for capecitabine and its 3 metabolites - rabeprazole did not affect the proliferation inhibition of colon cancer cells by the respective capecitabine metabolites. Methods: CapeOX without (n=9) or with (n=5) rabeprazole 20 mg/day: capecitabine 1000 mg/m^2 2dd 1 h after rabeprazole on day 1, oxaliplatin (and bevacizumab) administration on day 1 was shifted to day 2 for PK analysis of the first capecitabine dose; prospective study with patients administered adjuvant CapeOX for postoperative CRC, and metastatic CRC patients receiving CapeOX with/without bevacizumab.

Chu MP. JAMA Oncol 2017;3:767-73. Correction: JAMA Oncol 2017;3:1742. See letters in *JAMA Oncol*, 29098276, 29098281 and 29098270. Reply in *JAMA Oncol*, 29098275. PFS: Progression-free survival OS: overall survival DCR disease control rate TRIO-013: RCT that compares CapeOx with or without lapatinib in 545 patients with GEC; 229 received PPIs (42%) and were evenly distributed between arms. GEC: ERBB2/HER2-positive metastatic gastroesophageal cancer	capecitabine + PPI	secondary analysis of TRIO-013 1) **CapeOx geen lapatinib** *PFS mnd* *OS mnd* *DCR* -met PPI 4.2 9.2 72% -geen PPI 5.7 11.3 83% -HR 1.55 1.34 Multivariate analysis: PPI-treated patients had poorer PFS (HR 1.68) and OS (HR 1.41) considering age, race, disease stage, and sex. **2) CapeOx met lapatinib** *PFS mnd* *OS mnd* *DCR* -met PPI 5.7 9.6 x -geen PPI 6.8 13.8 x -HR 1.08 1.26 n.s. PPIs had less effect on PFS and OS. Multivariate analysis: PPIs affected OS (HR 1.38) but not PFS (HR 1.14) Methods: secondary analysis of TRIO-013, PPI use was identified by medication records. Primary study outcome: PFS and OS between patients treated with PPIs vs patients who were not. Secondary outcomes included disease response rates and toxicities. Conclusions: this secondary analysis confirms previous retrospective data that concomitant use of gastric acid suppressants such as PPIs with capecitabine may lower the antitumor efficacy of capecitabine. This negative association is strongest when taking into consideration reduced DCR coupled with lower PFS and OS in CapeOx-treated patients.
Sun J. Clin Colorectal Cancer 2016;15,:257-63.	capecitabine + PPI's	statisch significante afname in 5-jaars RFS met PPI tov zonder PPI (74% vs 83%; HR 1.89). Geen significant verschil in OS, dit is mogelijk gerela-teerd aan de korte follow-up en de beschikbaarheid van effectieve palliatieve combinatie chemotherapie regimes. Methode: retrospectieve studie van 298 patiënten met colorectale kanker stage II-III op capecitabine, waarvan 77 (26%) met PPI en 221 (74%) zonder PPI. Auteurs: pH verandering voorkomt mogelijk dissolutie en absorptie. → Werkgroep: confouding by indication, multivariate analyse verdunt effect, onbekend wanneer PPI is ingenomen
Reigner B. Cancer Chemother Pharmacol 1999;43:309-315.	capecitabine + antacida	inname Maalox direct na capecitabine (B) of met een tussenpoos van 2 uur (C) had geen effect op tmax en t½ van capecitabine en metabolieten; kleine toename Cmax en AUC capecitabine en 5'-DFCR (1.1-1.3x, statistisch niet significant). Regime: 1-malig capecitabine 1250 mg/m^2 alleen (A), idem en direct gevolgd door Maalox 20 ml (B), idem en na 2 uur gevolgd door Maalox 20 ml (C), washout 6-8 dagen; 12 patiënten met solide tumoren.
SPC Xeloda	capecitabine + antacida	kleine toename spiegel capecitabine en metaboliet 5'-DFCR door antacidum met aluminium- en magnesiumhydroxide, geen effect op de 3 belangrijkste metabolieten (5'-DFUR, 5-FU en FBAL). → GIC: komt overeen met Reigner 1999. PPI/omeprazol, pH, zuurgraad: niet genoemd.

Opmerkingen
Stockley: absorptie capecitabine wordt niet beïnvloed door aluminium/magnesium-bevattende antacida.
PubMed: niets gevonden voor cimetidine, famotidine, nizatidine, ranitidine.
Werkgroep: theoretisch, 'slechte patiënten' gebruiken een PPI; er is geen onderbouwing voor een interactie.

	Interactie	**Actie**	**Datum**
Beslissing WG OncoIA	Nee	Nee	2 oktober 2024

Abirateron + Secretieremmers/Antacida B

Onderbouwend	Stof	Effect	Code
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Overig	Stof	Effect
Bethlehem C. Nederlands Platform voor Farmaceutisch Onderzoek 2018;3:A1673. https://www.knmp.nl/resolveuid/520c765afb2e405e88bb13a428af83c4	abirateron + antacida/ secretieremmers	op klinische eindpunten geen verschil in wel/geen gebruik maagzuurremmer (oa tijd tot PSA-progressie en progressievrije overleving) Methode: retrospectieve cohortstudie: 111 patiënten op abirateron zonder (n=49) of met (n=62) maagzuurremmer* ten minste 2 weken gelijktijdig met abirateron. *ATC A02: antacida, H2-antagonisten, PPI. Auteurs: studie beschouwen als hypothesegenererend. Geen abirateronspiegels gemeten. Een prospectieve farmacokinetische studie kan worden overwogen om de gegevens van dit onderzoek te bevestigen. GIC: na 2 weken kun je weinig zeggen over PSA-progressie en overleving.
SPC Zytiga		geen informatie

Opmerkingen
Stockley: prod.info.

PubMed: verder niets.

Risicofactoren	
Mitigerende factoren	

	Interactie	Actie	Datum
Beslissing WG OncoIA	Als A		

Ribociclib/Talazoparib + Secretieremmers/Antacida C

Onderbouwend	Stof	Effect	Code
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Overig	Stof	Effect
SPC Talzenna EPAR p. 57	talazoparib + secretieremmers	Uit een farmacokinetische populatieanalyse bleek dat gelijktijdige toediening van zuurremmende middelen, waaronder protonpompremmers en H2-antagonisten of andere zuurremmende middelen, geen significante invloed had op de absorptie van talazoparib. Rubriek Kinetiek: er wordt niet verwacht dat zuurremmende middelen een significant effect hebben op de blootstelling aan talazoparib, aangezien de oplosbaarheid van talazoparib voldoende is bij alle pH's tussen 1 en 6,8. 28% van de patiënten in het hoofdonderzoek gebruikte zuurremmende middelen, hoofdzakelijk protonpompremmers.
Samant TS. Clin Pharmacol Ther 2019;104: 374-83.	ribociclib + PPI's	The influence of proton pump inhibitors (PPIs) on ribociclib bioavailability was assessed using 1) biorelevant media solubility, 2) physiologically based pharmacokinetic (PBPK) modeling, 3) noncompartmental analysis (NCA) of clinical trial data, and 4) population PK (PopPK) analysis. This multipronged approach indicated no effect of gastric pH changes on ribociclib PK and served as a platform for supporting ribociclib labeling language, stating no impact of gastric pH-altering agents on the absorption of ribociclib, without a dedicated drug–drug interaction trial.
SPC Kisqali	ribociclib en pH	ribociclib is zeer goed oplosbaar bij of onder een pH van 4,5 en in biologisch relevante milieus bij een pH tussen 5,0 en 6,5. Gelijktijdige toediening van ribociclib en geneesmiddelen die de pH in de maag verhogen is niet in een klinisch onderzoek onderzocht; er is echter in populatiefarmacokinetisch onderzoek en niet-compartimenteel farmacokinetisch onderzoek geen verandering van de absorptie van ribociclib waargenomen.

Opmerkingen
Stockley: the pharmacokinetics of ribociclib do not appear to be affected by proton pump inhibitors.

PubMed: niets.

Risicofactoren	
Mitigerende factoren	

	Interactie	Actie	Datum
Beslissing WG OncoIA	als A		