CYP3A4: paclitaxel 7050/7051

95% CI = 95% confidence interval, AUC = area under the concentration-time curve, NM = normal metaboliser (two fully functional alleles (e.g. *1/*1), normal CYP3A4 enzyme activity), grade = grade according to the National Cancer Institute Common Toxicity Criteria for Adverse event (NCI-CTCAE), HR = hazard ratio, IM = intermediate metaboliser (one fully functional allele and one allele leading to an enzyme with reduced or absent activity (e.g. *1/*22); reduced CYP3A4 enzyme activity), nab-paclitaxel = nanoparticle albumin-bound paclitaxel, OR = odds ratio, PM = poor metaboliser (two alleles leading to an enzyme with reduced or absent activity (e.g. *22/*22); strongly reduced CYP3A4 enzyme activity)

Brief summary and justification of choices:
Paclitaxel is mainly metabolized by CYP2C8 to 6α-hydroxypaclitaxel and to a lesser extent by CYP3A4 to 3'-p-hydroxypaclitaxel. Both metabolites are inactive and are further metabolised to 6α,3'-p-dihydroxypaclitaxel by CYP3A4 and CYP2C8, respectively.
None of the 3 studies investigating the effect of genetically diminished CYP3A4 activity (intermediate or poor metabolisers (IM or PM)) on paclitaxel pharmacokinetics found an association between genetically diminished CYP3A4 activity and decreased clearance of paclitaxel (de Graan 2013 (35 IM+PM), Nakajima 2006 (8 IM), and Nakajima 2005 (2 IM)). The largest study investigating also the paclitaxel metabolites, showed the metabolism of paclitaxel by CYP3A4 to 3'-p-hydroxypaclitaxel to be decreased in IM (Nakajima 2006).
2 of 6 studies investigating the effect of IM and/or PM on neurotoxicity found an association (de Graan 2013 (35 IM+PM and 26 IM+PM) and Apellániz-Ruiz 2015 (7 IM without *22, 15 with *22); Shen 2023 (29 IM and 1 PM), Lam 2016 (17 IM and 1 PM), Demurtas 2021 (13 IM), and Ciruelos 2019 (5 IM with *22 and 2 IM with *20)). However, both studies finding an association showed inconsistent results. De Graan 2013 found an association with neurotoxicity score distribution only in females in the exploratory cohort (35 IM+PM) and in both males and females in the validation cohort (26 IM+PM). In addition, female IM+PM in the validation cohort not only showed a higher percentage of patients with neurotoxicity grade 3 than NM, but also a numerically higher percentage of patients without neurotoxicity (50% versus 31%). Results were based on a small number of patients with neurotoxicity grade 3 (2 in the exploratory cohort and 6 in the validation cohort). Apellániz-Ruiz 2015 found an association with neuropathy risk for 4 *1/*20 (either or not combined with 3 carriers of *8, *25, or *27), but not for 15 *1/*22. As in this study, most CYP3A4 IM in the Netherlands (and the rest of Europe) have the genotype *1/*22.
Demurtas 2021 (13 IM) showed no effect on all adverse events grade ≥ 2, haematological adverse events grade ≥ 2, gastrointestinal disorders grade ≥ 2, hepatotoxicity grade ≥ 2, infusion related reactions grade ≥ 2, mucositis grade ≥ 2, and skin reactions grade ≥ 2 either.
Two studies showed no effect of the *22 variant on the effectiveness of paclitaxel (Assis 2013 (6 IM(+PM) and Demurtas 2021 (approximately 6 IM in the effectiveness analysis)).
Based on the decreased CYP3A4 metabolism of paclitaxel in IM, the KNMP Pharmacogenetics Working Group concluded that there is a gene-drug interaction. However, based on both the clearance and AUC of paclitaxel being unaffected and clinical studies showing either no effect or inconsistent results, the KNMP Pharmacogenetics Working Group decided that there is insufficient evidence for a clinical effect of IM and PM, and thus for the usefulness of therapy adjustment (yes/no-interactions).
You can find an overview of the observed kinetic and clinical consequences per phenotype in the background information text of the gene-drug interactions in the KNMP Kennisbank. You might also have access to this background information text via your pharmacy or physician electronic decision support system.

The table below uses the KNMP nomenclature for NM, PM and IM. As a result, the nomenclature of the genotype groups in the table below can differ from the nomenclature used by the authors in the article.

Source	Code	Effect	Comments
ref. 1 Shen F et al. Cytochrome P450 oxidoreductase (POR) associated with severe paclitaxel-induced peripheral neuropathy in patients of European	3	168 women who developed paclitaxel-induced peripheral neuropathy grade 3-4 during paclitaxel containing adjuvant treatment were compared to 172 controls who did not develop paclitaxel-induced peripheral neuropathy. Treatment consisted of intravenous doxorubicin and cyclophosphamide every 2 or 3 weeks (at the discretion of the treating physician) for four cycles followed by 12 weeks of weekly paclitaxel (80 mg/m^2) alone, or the same chemotherapy with either concurrent bevacizumab or concurrent	Author's conclusion: 'There were no associations between CYP2C8, CYP3A4 or CYP3A5 metabolizer status with severe taxane-induced peripheral neuropathy.'

<table>
<tr>
<td>ancestry from ECOG-ACRIN E5103.
Clin Cancer Res 2023;29:2494-500.
PMID: 37126018.

ref. 1, continuation</td>
<td>PM: AA
IM: AA</td>
<td>plus sequential bevacizumab. Follow-up was until three months after the last dose of therapy. CYP3A4 genotype was unknown in 13 patients.
Prior treatment with a taxane was excluded, as were infection requiring parenteral antibiotics, therapeutic anti-coagulation, regular nonsteroidal anti-inflammatory medi-cation, and aspirin (325 mg/d), but co-medication with influence on CYP3A4 was not.
Analysis was performed by additive logistic regression, adjusting for age, body-surface area, treatment arm, and sequencing batch.

Genotyping:
- 297x NM
- 29x IM (28x IM (*1/*22), 1x unknown (*1/*2))
- 1x PM

Results:
<table><tr><td colspan="2">Result for PM versus IM versus NM:</td></tr><tr><td>peripheral neuropathy grade ≥ 3</td><td>NS</td></tr></table>
Note: Genotyping was for *2 and *22. *22 is the most important gene variant in this population from the USA with European ancestry. There is no information on the effect of *2, but this allele was only present in 1 of the 29 IM.</td>
<td></td>
</tr>
<tr>
<td>ref. 2
Demurtas S et al. Single nucleotide polymorphisms to predict taxanes toxi-cities and effective-ness in cancer patients.
Pharmacogenomics J
2021;21:491-7.
PMID: 33649523.</td>
<td>3

IM: AA</td>
<td>107 patients with solid tumours were treated with paclita-xel (n = 88) or nab-paclitaxel (n = 19) containing chemo-therapy. 72% of the paclitaxel users and 53% of the nab-paclitaxel users were treated with monochemotherapy.
Paclitaxel was used in combination with carboplatin, cisplatin, and 5-fluorouracil or as single agent; nab-pacli-taxel was administered alone or with gemcitabine. The association with a monoclonal antibody, such as trastuzu-mab, pertuzumab, or bevacizumab, was considered as monochemotherapy.
Adverse events grade 2-4 (haematological, neurotoxicity, gastrointestinal disorders, hepatotoxicity, infusion related reactions, mucositis, and skin reactions) were assessed.
Nab-paclitaxel is known to be associated with more frequent neurotoxicity than paclitaxel (47% versus 20% of patients in this study, 70% versus 21% of the patients receiving monochemotherapy).
Effectiveness was not evaluated in early stage (e.g. in patients receiving adjuvant chemotherapy after radical surgery), only in patients with advanced stage (locally advanced or metastatic disease) (n = 34 for paclitaxel and n = 19 for nab-paclitaxel). For patients with locally advan-ced or metastatic disease, the treatment was defined as effective when images demonstrated complete response, partial response or stable disease; neoadjuvant treatment was considered effective when the pathology report described no evidence of carcinoma or a carcinoma smal-ler in size than at the beginning of treatment.
Different treatment regimens were used and co-medica-tion with influence on CYP3A4 was not excluded.

Genotyping:
- 94x NM
- 13x IM

Results:
<table><tr><td colspan="2">Results for IM compared to NM:</td></tr><tr><td>all adverse events grade ≥ 2</td><td>NS</td></tr><tr><td>haematological adverse events grade ≥ 2</td><td>NS</td></tr></table></td>
<td>Author’s conclusion: ‘Despite the popula-tion was heterogene-ous, CYP3A4*22 and CYP2C8 SNPs may influence paclitaxel and nab-paclitaxel toxicity and ABCB1 c.3435 may affect taxanes effective-ness, even if any statistically significant was found.’</td>
</tr>
</table>

<table>
<tr>
<td>ref. 2, continuation</td>
<td></td>
<td>
<table>
<tr><td>neurotoxicity grade ≥ 2</td><td>NS</td></tr>
<tr><td>gastrointestinal disorders grade ≥ 2</td><td>NS</td></tr>
<tr><td>hepatotoxicity grade ≥ 2</td><td>NS</td></tr>
<tr><td>infusion related reactions grade ≥ 2</td><td>NS</td></tr>
<tr><td>mucositis grade ≥ 2</td><td>NS</td></tr>
<tr><td>skin reactions grade ≥ 2</td><td>trend for a higher risk (p = 0.077) (NS)</td></tr>
<tr><td>effectiveness (complete response, partial response or stable disease)</td><td>NS</td></tr>
</table>
Note: Genotyping was for *22. This is the most important gene variant in this Italian population.
</td>
<td></td>
</tr>
<tr>
<td>ref. 3
Ciruelos E et al.
A pilot, phase II, randomized, open-label clinical trial comparing the neurotoxicity of three dose regimens of nab-paclitaxel to that of solvent-based paclitaxel as the first-line treatment for patients with human epidermal growth factor receptor type 2-negative metastatic breast cancer.
Oncologist 2019;24:e1024-e1033.
PMID: 31023863.</td>
<td>3

IM: AA</td>
<td>60 breast cancer patients were treated with 4-week cycles of either 80 mg/m^2 paclitaxel on days 1, 8, and 15 (n = 14), 100 mg/m^2 nab-paclitaxel on days 1, 8, and 15 (n = 16), 150 mg/m^2 nab-paclitaxel on days 1, 8, and 15 (n = 14), or 150 mg/m^2 nab-paclitaxel on days 1 and 15 (n = 16). Genotyping results were only available for 57 patients. The median follow-up period was 23 months.
Associations between the genotypes and paclitaxel neuropathy were tested with cumulative paclitaxel dose analysis, which analyses the cumulative dose of paclitaxel up to the development of ≥ grade 2 neuropathy and censors patients with grade 0 or 1 at the total cumulative dose. Multivariate analyses adjusted for age and previous neuropathy events. The frequency of polyneuropathy (all grades) was lower with paclitaxel (50% of patients) and with 150 mg/m^2 nab-paclitaxel on days 1 and 15 (62.5%) than with nab-paclitaxel on days 1, 8, and 15 (81.3% and 78.6% for 100 and 150 mg/m^2, respectively).
Different treatment regimens were used and co-medication with influence on CYP3A4 was not excluded.

Genotyping:
*22 - 52x no *22 - 5x *22 heterozygous
*20 - 55x no *20 - 2x *20 heterozygous

Results:
<table>
<tr><td colspan="2">Association with paclitaxel-induced neurotoxicity grade ≥ 2:</td></tr>
<tr><td>*22</td><td>NS</td></tr>
<tr><td>*20</td><td>NS</td></tr>
</table>
Note: Genotyping was for *20 and *22. These are the most important gene variants in this Spanish population.
</td>
<td>Author’s conclusion: ‘Among the seven polymorphisms selected for genotyping, the variant alleles of EPHA5-rs7349683, EPHA6-rs301927, and EPHA8-rs209709 were associated with an increased risk of paclitaxel-induced neuropathy.’</td>
</tr>
<tr>
<td>ref. 4
Lam SW et al.
Genotypes of CYP2C8 and FGD4 and their association with peripheral neuropathy or early dose reduction in paclitaxel-treated breast cancer patients.
Br J Cancer 2016;115:1335-42.
PubMed PMID: 27736846.</td>
<td>3</td>
<td>172 women were treated with paclitaxel and bevacizumab without or with capecitabine. Paclitaxel was either given as 90 mg/m^2 on days 1, 8 and 15 of a repeated 4-week schedule for 24 weeks (n = 89), or as paclitaxel 90 mg/m^2 on days 1 and 8 of a repeated 3-week schedule for 24 weeks (n = 83). Paclitaxel dose was reduced to 60 mg/m^2 for a second occurrence of grade 2 treatment-related adverse events or any occurrence of grade 3 treatment-related adverse events. Paclitaxel was terminated at third occurrence of grade 2, second occurrence of grade 3 or at first occurrence of a grade 4 adverse event deemed paclitaxel-related. The median cumulative dose of paclitaxel was 1409 mg/m^2.
67% of patients experienced peripheral neuropathy grade ≥ 1. The rate of paclitaxel dose reduction was 46%.
Grade ≥ 1 was chosen as a cut-off of peripheral neuropathy, because of its gradual development in the weekly low dose paclitaxel schedule.
Capecitabine and bevacizumab do not increase the rates</td>
<td>Author’s conclusion: ‘We could not confirm CYP3A4 *22 as a possible risk factor for neurotoxicity grade ≥1 in female carriers.’</td>
</tr>
</table>

<table>
<tr>
<td>ref. 4, continuation</td>
<td>IM+PM:
AA</td>
<td>of paclitaxel-specific toxicities, like peripheral neuropathy. Co-medication with influence on CYP3A4 was not excluded.

Genotyping:
- 154x NM
- 17x IM
- 1x PM

Results:
<table>
<tr><td colspan="2">Results for IM+PM compared to NM:</td></tr>
<tr><td>peripheral neuropathy grade ≥ 1</td><td>NS</td></tr>
<tr><td>paclitaxel dose reduction</td><td>NS</td></tr>
</table>

Note: Genotyping was for *22. This is the most important gene variant in this Dutch population.</td>
<td></td>
</tr>
<tr>
<td>ref. 5
Apellániz-Ruiz M et al.
Whole-exome sequencing reveals defective CYP3A4 variants predictive of paclitaxel dose-limiting neuropathy. Clin Cancer Res 2015;21:322-8. PubMed PMID: 25398452.</td>
<td>3

IM: D</td>
<td>8 patients with grade 3 paclitaxel-induced peripheral neuropathy were analyzed together with 228 patients from a paclitaxel treated cohort. *22 genotyping was successful for only 231 of the patients. The 8 selected patients received paclitaxel weekly, the patients in the cohort either weekly or every 3 weeks. Different combination regimens were used in both the 8 selected patients and in the cohort.
The 8 selected patients developed grade 3 sensory neuropathy at a cumulative paclitaxel dose ≤ 800 mg/m^2 (400-800 mg/m^2). The neuropathy resulted in treatment suspension (50% of patients) or paclitaxel dose reduction (50% of patients) and continued with at least grade 2 intensity for 19-66 months after termination of paclitaxel treatment. Other causes of neuropathy such as diabetes mellitus, alcoholism, hepatic diseases, AIDS, and previous neuropathies were ruled out.
For the 228 patients in the cohort, the dose was reduced due to neuropathy in 2% (in 9% due to all causes) and treatment was suspended due to neuropathy in 7% (in 9% due to all causes). One or more additional risk factors for neuropathy (diabetes, high alcohol intake, restless-legs-syndrome) were present in 5.8% of the 226 patients for which data on risk factors were known.
Co-medication with influence on CYP3A4 was not excluded.
Potential confounders were accounted for by stratification.

Genotyping:
Coding sequence variants:
- 229x NM
- 7x IM (4x IM with inactive allele (*1/*20), 3x IM with reduced activity allele (1x *1/*8, 1x *1/*25, 1x *1/*27))

*22:
- 216x NM
- 15x IM

Results:
<table>
<tr><td colspan="4">Results for IM compared to NM:</td></tr>
<tr><td colspan="4">Coding sequence variants:</td></tr>
<tr><td>outcome</td><td>IM with inactive allele</td><td>IM with reduced activity allele</td><td>value for NM</td></tr>
<tr><td rowspan="2">% of patients with neuropathy grade 3</td><td>x 2.0 (S)</td><td>x 1.3 (NS)</td><td>51%</td></tr>
<tr><td colspan="2">S for (IM with inactive allele) versus (IM with reduced activity allele) versus NM</td></tr>
<tr><td>% of patients</td><td>x 6.9 (S)</td><td>x 3.0 (NS)</td><td>11%</td></tr>
</table>
</td>
<td>Author’s conclusion: “This is the first description of a genetic marker associated with paclitaxel treatment modifications caused by neuropathy. CYP3A4 defective variants may provide a basis for paclitaxel treatment individualization.”</td>
</tr>
</table>

<table>
<tr>
<td>ref. 5, continuation</td>
<td>IM: AA</td>
<td>
<table>
<tr><td>with paclitaxel dose reduction or cessation due to neuropathy</td><td>S for (IM with inactive allele) versus (IM with reduced activity allele) versus NM</td><td></td></tr>
<tr><td colspan="3">*22:</td></tr>
<tr><td>outcome</td><td>IM</td><td>value for NM</td></tr>
<tr><td>% of patients with neuropathy grade 1-3</td><td>NS</td><td>approxi-mately 82%</td></tr>
<tr><td>% of patients with paclitaxel dose reduction or cessation due to neuropathy</td><td>NS</td><td>approxi-mately 10%</td></tr>
<tr><td>% of patients with paclitaxel dose reduction or cessation due to all causes</td><td>trend for an increase (p = 0.066; NS)</td><td>approxi-mately 20%</td></tr>
</table>

Note: Genotyping in the 8 selected patients was by whole exome sequencing, so all coding region variants. Genotyping in the cohort was also for all coding region variants, and next to this for the intronic variant *22. These are the most important gene variants in this Spanish population.

Note: *25 and *27 are novel alleles. The authors showed that *25 and *27 have decreased stability in a transfec-ted human cell line.
</td>
<td></td>
</tr>
<tr>
<td>ref. 6
Assis J et al.
Influence of CYP3A4 genotypes in the outcome of serous ovarian cancer patients treated with first-line chemothera-py: implication of a CYP3A4 activity profile.
Int J Clin Exp Med 2013;6:552-61.
PubMed PMID: 23936594.</td>
<td>3

IM+PM: AA</td>
<td>99 women were treated with paclitaxel (175 mg/m^2) and cisplatin or carboplatin every three weeks for six cycles. The therapy was concluded when objective disease progression was observed or unacceptable toxicity appeared. Follow-up was more than 200 days. Relapse was analysed in 96 women.
Co-medication with influence on CYP3A4 was not exclu-ded.

Genotyping:
- 93x NM
- 6x IM+PM

Results:
<table>
<tr><td colspan="3">Results for IM+PM compared to NM:</td></tr>
<tr><td></td><td></td><td>value for NM</td></tr>
<tr><td>% of patients with relapse</td><td>NS</td><td>63.7%</td></tr>
<tr><td>% of patients alive with no evidence of cancer</td><td>NS</td><td>55.9%</td></tr>
</table>

Note: Genotyping was for *22. This is the most important gene variant in this European population.
</td>
<td>Author’s conclusion: “CYP3A4*22 might alter CYP3A4 activity and affect conse-quently dose require-ments, response and toxicity to drugs with a narrow therapeutic window as chemo-therapy agents.”</td>
</tr>
<tr>
<td>ref. 7
de Graan AJ et al.
CYP3A4*22 genotype and systemic exposure affect paclitaxel-induced neurotoxicity.
Clin Cancer Res 2013;19:3316-24.
PubMed PMID: 23640974.</td>
<td>4</td>
<td>254 patients (exploratory cohort; 52% male) and 237 patients (independent validation cohort; 54% male) were treated with paclitaxel containing therapy. In the explo-ratory cohort, the median paclitaxel dose during each cycle was 180 mg and the median cumulative dose was 975 mg. In the validation cohort, the median paclitaxel dose during each cycle was 165 mg and the median cumulative dose was 1,140 mg. Patients in both cohorts received paclitaxel weekly or every 3 weeks in different combination regimens. Also patients receiving chemo-therapy in combination with radiotherapy were included. These patients received a weekly dose of 50 mg/m^2.</td>
<td>Author’s conclusion: ‘In this study, female CYP3A4*22 carriers had increased risk of developing severe neurotoxicity during paclitaxel therapy.’</td>
</tr>
</table>

ref. 7, continuation

Paclitaxel pharmacokinetics was assessed using a validated limited sampling strategy. Individual pharmacokinetic parameters were calculated based on measured plasma samples and a previously developed population pharmacokinetic model for paclitaxel.
In the exploratory cohort, co-medication with CYP3A4 and CYP2C8 inducers or inhibitors was excluded.
To test the association between severity of neurotoxicity and CYP3A4*22 carrier status, logistic regression was performed. Multivariate analyses were not warranted in both cohorts because of the relatively low incidence of neurotoxicity grade 3, so correction for confounders was not possible.

Genotyping:

Exploratory cohort:	Validation cohort:
- 219x NM	- 211x NM
- 35x IM+PM	- 26x IM+PM

Results:

Results for IM+PM compared to NM:			
Exploratory cohort:			
outcome	gender		value for NM (gr = grade)
neurotoxicity score distribution	males	NS	gr 1: 21% gr 2: 4% gr 3: 0%
	females	S, gr 1: x 1.1 gr 2: x 3.1 gr 3: x 6.2	gr 1: 44% gr 2: 8% gr 3: 1%
AUC_{96h} of paclitaxel	males	NS	
	females	NS	
clearance paclitaxel	males	NS	
	females	NS	
maximum paclitaxel concentration	males	NS	
	females	NS	
time paclitaxel concentration > 0.05 µmol/L	males	NS	
	females	NS	
cumulative paclitaxel dose	males	NS	
	females	NS	
Validation cohort:			
outcome	gender		value for NM (gr = grade)
% of patients with neurotoxicity grade 3	all	OR = 19.1 (95% CI: 3.3-110) (S)	0.9%
		Results were similar when data of both cohorts were pooled, stratified for cumulative dose of paclitaxel and adjusted for cohort and gender: HR = 22.1 (95% CI: 4.7-105) (S)	0.7%
neurotoxi-	males	S,	

IM+PM: D

<table>
<tr>
<td>ref. 7, continuation</td>
<td></td>
<td>
<table>
<tr><td>city score distribution</td><td></td><td>gr 1: x 1.2
gr 2: x 0
gr 3: value = 14%</td><td>gr 1: 25%
gr 2: 4%
gr 3: 0%</td></tr>
<tr><td></td><td>females</td><td>S,
gr 1: x 0.6
gr 2: x 0
gr 3: x 8.1</td><td>gr 1: 54%
gr 2: 13%
gr 3: 2%</td></tr>
<tr><td>cumulative paclitaxel dose</td><td>males</td><td>NS</td><td></td></tr>
<tr><td></td><td>females</td><td>NS</td><td></td></tr>
</table>

Note: systemic exposure of paclitaxel was significantly associated with severity of neurotoxicity (only assessed in the exploratory cohort). Significantly more females than males developed neurotoxicity (both cohorts).

Note: Genotyping was for *22. This is the most important gene variant in this Dutch population.
</td>
<td></td>
</tr>
<tr>
<td>ref. 8
Nakajima Y et al. Impact of the haplotype CYP3A4*16B harboring the Thr185Ser substitution on paclitaxel metabolism in Japanese patients with cancer. Clin Pharmacol Ther 2006;80:179-91. PubMed PMID: 16890579.</td>
<td>3

IM: A</td>
<td>199 patients were treated with a continuous infusion of paclitaxel 175-210 mg/m^2 .
Co-medication with influence on CYP3A4 was not excluded.
Results were corrected for multiple comparisons by use of the nonparametric Dunn multiple comparisons test.

Genotyping:
- 180x NM
- 9x IM (7x *1/*16B, 1x *16B/*18B, 1x *1/*6)
- 10x *1/*18B

Results:
<table>
<tr><td colspan="4">Results compared to NM:</td></tr>
<tr><td></td><td>*1/*16B + *16B/ *18B</td><td>*1/*6</td><td>*1/*18B</td></tr>
<tr><td>median clearance of paclitaxel</td><td>NS</td><td>NS</td><td>NS</td></tr>
<tr><td>median AUC ratio of 3’-p-hydroxypaclitaxel/paclitaxel</td><td>x 0.8 (S)</td><td></td><td>NS</td></tr>
<tr><td>median AUC ratio of 6α-hydroxypaclitaxel/ paclitaxel</td><td>x 1.7 (S)</td><td>x 3.7</td><td>NS</td></tr>
<tr><td>median AUC ratio of 3’-p-hydroxypaclitaxel/6α-hydroxypaclitaxel</td><td>x 0.4 (S)</td><td>x 0.2</td><td>NS</td></tr>
</table>

Note: The effect of the *18B-variant is not clear and might be substrate-specific. The effect of *6 is not indicated on the PharmVar-website, but this gene variant results in a frameshift from amino acid 277 and is thus likely to be deficient.

Note: A patient group (n = 30) receiving a paclitaxel dose of 80-100 mg/m^2, showed a 2-fold lower median paclitaxel clearance than the high-dose group described above. Thus, paclitaxel displayed non-linear pharmacokinetics. The authors indicated that the nonlinearity of paclitaxel pharmacokinetics can be attributed to the presence of polyoxyethyleenglyceroltriricinoleaat 35, an additive in the paclitaxel injection, which solubilizes paclitaxel into micelles.

Note: Genotyping was by sequencing (i.e. for all variants)</td>
<td>Authors’ conclusion: “Our results suggest that CYP3A4*16B is associated with both reduced 3’-p-hydroxylation of paclitaxel and probably increased levels of 6α-hydroxypaclitaxel.”</td>
</tr>
</table>

<table>
<tr><td>ref. 8, continuation</td><td></td><td>in 45% of patients, and for *6, *11, *16B, and *18B in the remaining 55%. These are the most important gene variants in this Japanese population. *11 was not present in this patient group.</td><td></td></tr>
<tr><td>ref. 9
Nakajima M et al. Pharmacokinetics of paclitaxel in ovarian cancer patients and genetic polymorphisms of CYP2C8, CYP3A4, and MDR1. J Clin Pharmacol 2005;45:674-82. PubMed PMID: 15901749.</td><td>3

IM: AA</td><td>23 women were treated with a 3-hour infusion of paclitaxel 180 mg/m^2, followed by carboplatin.
The mean AUC of paclitaxel was 20,839 nM.h/L. The mean clearance of paclitaxel was 16.7 L/h.
Co-medication with influence on CYP3A4 was not excluded. No pharmacokinetic interactions have been reported between paclitaxel and carboplatin at standard doses.

Genotyping:
- 21x NM
- 2x IM

Results:
<table>
<tr><td>Results for IM compared to NM:</td><td></td></tr>
<tr><td>AUC of paclitaxel</td><td>NS</td></tr>
<tr><td>Clearance of paclitaxel</td><td>NS</td></tr>
<tr><td>AUC of 3’-p-hydroxypaclitaxel</td><td>NS</td></tr>
<tr><td>AUC of 6α-hydroxypaclitaxel</td><td>NS</td></tr>
</table>
Note: Genotyping was for *6, *16, and *17. These are the most important gene variants in these Japanese population. *6 and *17 were not detected in this patient group.

Note: The effect of *6 is not indicated on the PharmVar website, but this gene variant results in a frameshift from amino acid 277 and is thus likely to be deficient.</td><td>Author’s conclusion: “Genotyping of the CYP2C8, CYP3A4, and MDR1 genes might not be essential to predict adverse effects of paclitaxel in Japanese patients.”</td></tr>
</table>

Risk group	-

Comments:

- Studies were only included in the risk analysis if they investigated CYP3A4 gene variants known to result in altered CYP3A4 activity (based on the PharmVar-website or shown by the authors). For this reason, studies and results for the variants *1B and *3, and genotyping results for *4 and *5 and the *1-subvariants *1A, *1G, *1H, *1J and *1S, were not included. Studies in which only part of the analyzed patient group used paclitaxel were not included in the risk analysis. Studies with variants not known to affect CYP3A4 activity and studies with only part of the analysed patients using paclitaxel do not add enough to the evidence on the CYP3A4-paclitaxel interaction.

Date of literature search: 19 September 2024.

	Phenotype	Code	Gene-drug interaction	Action	Date
KNMP Pharmacogenetics Working Group Decision	PM	4D	yes	no	27 January 2025
	IM	4D	yes	no	

Mechanism:

Paclitaxel is metabolized predominantly by CYP2C8 to 6α-hydroxypaclitaxel and to a lesser extent by CYP3A4 to 3’-p-hydroxypaclitaxel. Both metabolites are inactive and are further metabolised to 6α,3’-p-dihydroxypaclitaxel by CYP3A4 and CYP2C8 respectively.